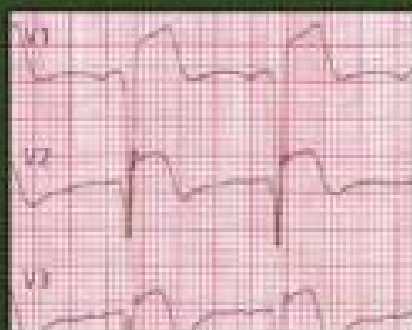
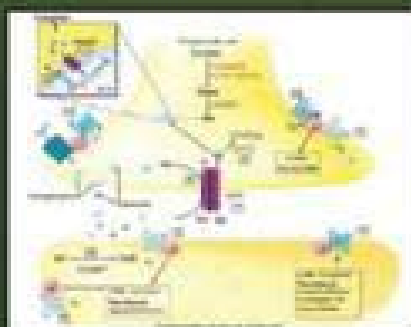
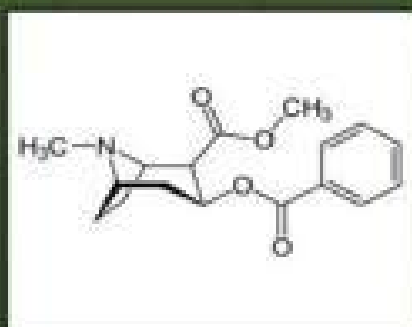


Goldfrank's **TOXICOLOGIC EMERGENCIES**

Tenth Edition



Robert S. Hoffman

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GOLDFRANK'S TOXICOLOGIC EMERGENCIES TENTH EDITION

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Neal E. Flomenbaum, MD, FACP, FACEP Editor Emeritus

With the publication of the ninth edition of Goldfrank's Toxicologic Emergencies, Neal Flomenbaum informed us of his decision to step down as an editor in order to be able to devote more time to his growing interests in geriatric emergency medicine and prehospital care, while continuing to fulfill his clinical and administrative responsibilities as Chief of Emergency Medicine at New York Presbyterian Hospital-Weill Cornell Medical Center and as Medical Director of its extensive prehospital care system.



In 1979, Dr. Flomenbaum accepted an offer from Lewis Goldfrank to join him at New York University Bellevue Hospital as Associate Director of Emergency Services and Consultant (later, Chief Consultant) to the New York City Poison Control Center, and their subsequent collaborations resulted in many of the outstanding features of this textbook. Frequently, ideas and concepts Neal and Lewis developed for presenting clinical toxicology were recognized for their value to the textbook and then developed further by both, with considerable input and efforts by Neal Lewin, Richard Weisman, Mary Ann Howland, Robert Hoffman, and Lewis Nelson. Thus, an idea for a 1984 review article entitled “Newer Antidotes and Controversies in Antidotal Therapy,” written to familiarize clinicians with the appropriate use of antidotes in patient management, became “Antidotes in Depth,” a signature feature of this book.

Similarly, the idea for an organ system track in the NYU postgraduate toxicology courses that Neal and Lewis codirected in the early 1980s became “The Pathophysiologic Basis of Medical Toxicology: The Organ System Approach” in the textbook. This section, in turn, suggested another section entitled “The Biochemical and Molecular Basis of Medical Toxicology.”

Additional ideas followed for making Goldfrank's Toxicologic Emergencies more accessible both as a teaching and a reference resource. A monthly case-based consultants' meeting at the New York City Poison Control Center was modeled after the successful format originated in the first edition of this book, and many of the cases discussed there were adapted for the text and related review books. Placing essential reference tables on the inside front and back covers of the textbook proved to be another useful feature, and Neal is particularly proud of the unique way the textbook acknowledges previous authors at the end of chapters. In addition to his ideas and his organizational and editorial contributions, Neal has written, coauthored, or contributed to dozens of chapters since 1982, including those on salicylates, rodenticides, and managing the acutely poisoned or overdosed patient.

Neal Flomenbaum first became interested in medical toxicology because of the clinical challenges it presented to emergency physicians, internists, and pediatricians, and he has remained focused on these clinical aspects. His creative energies, talents, and contributions to the second through ninth editions of this book have helped transform a case-based introduction to clinical toxicology into the 2000 page textbook it is today, and these contributions will remain an important part of future editions.

Erythroxylum coca, the source of cocaine, is renowned in toxicology and medicine for its ritual use by ancient cultures, traditional use by modern indigenous peoples, role as the first pharmaceutical local anesthetic, and notorious use as an illicit drug of abuse. The molecule benzoylmethylecgonine (cocaine) highlights the complex structure of a plant alkaloid. At the cellular level, cocaine is a remarkable drug that blocks the reuptake of neurotransmitters (dopamine, norepinephrine, epinephrine, and serotonin), blocks neuronal and cardiac sodium channels, and causes vasoconstriction. The cardiotoxic effects are demonstrated on the electrocardiogram, which shows a classic ST segment anterior wall myocardial infarction in a young person who recently used cocaine. Although a true antidote to cocaine toxicity has yet to be developed, the vial represents the benzodiazepines, which have become the mainstay of therapy for psychomotor agitation that results from typical cocaine overdose.

DEDICATION

To the staffs of our hospitals, emergency departments, intensive care units, and outpatient venues, who have worked with remarkable courage, concern, compassion, and understanding in treating the patients discussed in this text and many thousands more like them

To the staff of the New York City Poison Center, who have quietly and conscientiously integrated their skills with ours to serve these patients and prevent many patients from ever needing a hospital visit

To all the faculty, fellows, residents, and students who have studied toxicology with us, whose inquisitiveness has helped us continually strive to understand complex and evolving problems and develop methods to teach them to others

To my wife Ali; my children Casey and Jesse; my parents; and my friends, family, and colleagues for their never-ending patience and forgiveness for the time I have spent away from them (R.H.)

To my husband Bob; to my children Robert, and Marcy and Doug; to my mother and to the loving memory of my father; and to family, friends, colleagues, and students for all their help and continuing inspiration (M.A.H.)

To my wife Gail Miller, my sons Dr. Jesse Miller Lewin, Dr. Justin Miller Lewin, and Dr. Alana Amarosa Lewin, and in memory of my parents. To all my patients, students, residents, fellows, and colleagues who constantly stimulate my being a perpetual student (N.L.)

To my wife Laura for her unwavering support; to my children Daniel, Adina, and Benjamin for their fresh perspective, youthful insight, and boundless energy; to my parents Myrna of blessed memory and Dr. Irwin Nelson for the foundation they provided; and to my family, friends, and colleagues who keep me focused on what is important in life (L.N.)

To my children Rebecca and Ryan, Jennifer, Andrew and Joan, Michelle and James; to my grandchildren Benjamin, Adam, Sarah, Kay, Samantha, Herbert, and Jonah who have kept me acutely aware of the ready availability of possible poisons; and to my wife, partner, and best friend Susan whose support was essential and whose contributions will be found throughout the text (L.G.)

ANTIDOTES IN DEPTH

Editor: Mary Ann Howland

Associate Editor: Silas W. Smith

Readers of previous editions of Goldfrank's Toxicologic Emergencies are undoubtedly aware that the editors have always felt that an emphasis on general management of patients who are poisoned or overdosed coupled with sound medical management is as important as the selection and use of a specific antidote in the vast majority of cases. Nevertheless, there are some instances when nothing other than the timely use of a specific antidote is an essential lifesaving intervention. For this reason, and also because the use of such strategies may be problematic, controversial, or unfamiliar to the practitioner as new therapeutic approaches continue to emerge and old standards are reevaluated, we have included a section (or sections) at the end of each chapter where an in-depth discussion of such material is relevant.

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Michael A. Darracq and Richard F. Clark

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Mary Ann Howland

BENZODIAZEPINES

Robert S. Hoffman, Lewis S. Nelson, and Mary Ann Howland

BOTULINUM ANTITOXIN

Silas W. Smith and Howard L. Geyer

CALCIUM

Mary Ann Howland

L-CARNITINE

Mary Ann Howland

DANTROLENE SODIUM

Kenneth M. Sutin

DEFEROXAMINE

Mary Ann Howland

DIGOXIN-SPECIFIC ANTIBODY FRAGMENTS

Mary Ann Howland

DEXTROSE (D-Glucose)

Larissa I. Velez and Kathleen A. Delaney

DIMERCAPROL (BRITISH ANTI-LEWISITE OR BAL)

Mary Ann Howland

EDETATE CALCIUM DISODIUM (CaNa₂EDTA)

Mary Ann Howland

ETHANOL

Mary Ann Howland

FLUMAZENIL

Mary Ann Howland

FOLATES: LEUCOVORIN (FOLINIC ACID) AND FOLIC ACID⁶⁹³

Mary Ann Howland

FOMEPIZOLE

Mary Ann Howland

GLUCAGON

Mary Ann Howland

GLUCARPIDASE (CARBOXYPEPTIDASE G₂)

Silas W. Smith

HIGH-DOSE INSULIN EUGLYCEMIA

Samuel J. Stellpflug and William Kerns, II

HYDROXOCOBALAMIN

Mary Ann Howland

HYPERBARIC OXYGEN

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INTRAVENOUS FAT EMULSION

Theodore C. Bania

METHYLENE BLUE

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N-ACETYLCYSTEINE

Robert G. Hendrickson and Mary Ann Howland

OCTREOTIDE

Mary Ann Howland and Silas W. Smith

OPIOID ANTAGONISTS

Lewis S. Nelson and Mary Ann Howland

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Mary Ann Howland

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Joseph G. Rella

PRALIDOXIME

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PROTAMINE

Mary Ann Howland

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Mary Ann Howland

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Silas W. Smith and Mary Ann Howland

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PREFACE

Goldfrank's Toxicologic Emergencies is a multiauthored text of approximately 2000 pages prepared by using the educational and management principles we apply at the New York City Poison Center and at our clinical sites. In this tenth edition of Goldfrank's Toxicologic Emergencies, we proudly offer readers an approach to medical toxicology using evidence-based principles viewed through the lens of an active bedside clinical practice.

Some would ask why create textbooks and e-books in an era when podcasts and blogs appear so successful. We still believe that the slow, thoughtful, rigorous development by a team of authors and editors that is required to create and revise this text is necessary to appropriately analyze the most complex problems that challenge our daily practices. Although in our field we have made great progress, the level of uncertainty remains substantial. We have attempted to integrate the collaborative wisdom of many experts from diverse backgrounds into the text to provide the most up to date information. We offer our readers the evidence, shared thoughts, and commitments necessary to arrive at a decision. Evidence is created not only with randomized clinical trials, observational studies, case control studies, and case reports, but also with the insights of five toxicologists who have worked together for decades, along with the gifted scholars we selected as authors. We have worked together defining and redefining the scope and context of chapters, Antidotes in Depth, and Special Considerations. We then shared our ideas with many respected toxicologists, thus creating new chapters that these toxicologists have revised by adding information that has come to light over the last 4 years. In this way, knowledge from their work in toxicology and related disciplines is merged with ours, allowing us to create chapters that represent our collective thoughts. This iterative process is continued until the authors and editors are satisfied that we have closely approximated the best strategy to evaluate and care for poisoned or overdosed patients. This is a fascinating process. Because we occasionally disagree, we then reread, research, look for special cases, and reflect on a final version with our authors. By reviewing the quality of each chapter, we thus create, recreate, and reformat.

In this edition, we have reintroduced the patient into the text. These are the patients who wake us up at night. Such patients, whose signs and symptoms might be related to the whole book or to several chapters, serve to return us to focus on the unknown, the differential diagnosis, and problem solving and include cases representative of our work. Patients with a pesticide exposure, bradycardia, metabolic acidosis, medication error, seizures, as well as coma or agitation and hyperthermia, are offered as examples for contemplation. We believe that analyzing the care of these complex, undifferentiated patients will help you as much as they have helped us and those who read the first edition of this book. These cases act as the building blocks for chapters in this edition and represent provocative introductions to several sections of this text. We have demonstrated our thought processes so that you can read, think, criticize, and communicate. This classic Socratic development of knowledge and improvement of clinical decision making will foster problem solving, initiate creative investigation, and improve care. We hope to facilitate your participation in the intellectual process that we believe to be essential in order to create a fine book for thoughtful readers who must render exceptional attention to their patients. The cases serve as the transition between the patient and population. You can switch your role from the medical or clinical toxicologist at the bedside to the toxicologist serving the public needs of a community. Our hope is that these cases recreate the clinicians experience of the thinking that occurs before the action.

The other major change in this edition has occurred in one of our most valued sections—the Antidotes in Depth. Mary Ann Howland, PharmD, has worked on improving the presentation of each of the Antidotes in Depth with an even more rigorous format. Her wisdom in this area is unmatched, as she has nurtured these key toxicologic elements since the third edition of this textbook. In this tenth edition, Silas W. Smith, MD, has collaborated with her as an Associate Editor for the Antidotes in Depth section. We are sure that you will appreciate the reorganization of this section, which will enhance your ability to use the material the Antidotes in Depth provide. Their collaboration should be a great asset to the reader.

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The many letters and verbal communications we have received with the reviews of the previous editions of this book continue to improve our efforts. We are deeply indebted to our friends, associates, and students, who stimulated us to begin this book with their questions and then faithfully criticized our answers.

We thank the many volunteers, students, librarians, and particularly the St. John's University College of Pharmacy students and drug information staff who provide us with vital technical assistance in our daily attempts to deal with toxicologic emergencies.

Mary Ann Howland, PharmD, gratefully acknowledges the helpful comments of Parshotam Madam, PhD, Department of Pharmaceutical Sciences, St. John's University College of Pharmacy and Health Sciences in the preparation of her chapter on Pharmacokinetic and Toxicokinetic Principles.

No words can adequately express our indebtedness to the many authors who worked on earlier editions of many of the chapters in this book. As different authors write and rewrite topics with each new edition, we recognize that without the foundation work of their predecessors this book would not be what it is today.

We appreciate the creative and rigorous advances in design and scientific art that the McGraw-Hill team, led by Armen Ovsepyan, have added to the text. The devotion to the creation of high-quality art graphics and tables is greatly appreciated. The support for excellence in this edition was facilitated by the constant vigilance of Executive Editor, Michael Weitz.

We appreciate the calm, thoughtful, and cooperative spirit of Karen Edmonson at McGraw-Hill. Her intelligence and ever vigilant commitment to our efforts has been wonderful. We are pleased with the creative developmental editorial efforts of Christie Naglieri. The organized project management by Tania Andrabi has found errors hiding throughout our pages. Her carefully posed questions have facilitated the process of correcting the text. It has been a pleasure to have her assistance. We greatly appreciate the compulsion and rigor that Michael Ferreira has applied to make this edition's index one of unique value. We appreciate the work of Catherine Saggese in ensuring the quality of production in the finished work.

1 HISTORICAL PRINCIPLES AND PERSPECTIVES

Paul M. Wax

The term poison first appeared in the English literature around the year 1225 A.D. to describe a potion or draught that was prepared with deadly ingredients.^{8,147} The history of poisons and poisoning, however, dates back thousands of years. Throughout the millennia, poisons have played an important role in human history—from political assassination in Roman times, to weapons of war, to contemporary environmental concerns, and to weapons of terrorism.

This chapter offers a perspective on the impact of poisons and poisoning on history. It also provides a historic overview of human understanding of poisons and the development of toxicology from antiquity to the present. The development of the modern poison center, the genesis of the field of medical toxicology, and the recent increasing focus on medication errors are examined. [Chapter 2](#) describes poison plagues and unintentional disasters throughout history and examines the societal consequences of these unfortunate events. An appreciation of past failures and mistakes in dealing with poisons and poisoning promotes a keener insight and a more critical evaluation of present-day toxicologic issues and helps in the assessment and management of future toxicologic problems.

POISONS, POISONERS, AND ANTIDOTES OF ANTIQUITY

The earliest poisons consisted of plant extracts, animal venoms, and minerals. They were used for hunting, waging war, and sanctioned and unsanctioned executions. The Ebers Papyrus, an ancient Egyptian text written circa 1500 B.C. that is considered to be among the earliest medical texts, describes many ancient poisons, including aconite, antimony, arsenic, cyanogenic glycosides, hemlock, lead, mandrake, opium, and wormwood.^{97,147} These poisons were thought to have mystical properties, and their use was surrounded by superstition and intrigue. Some agents, such as the Calabar bean (*Physostigma venenosum*) containing physostigmine, were referred to as “ordeal poisons.” Ingestion of these substances was believed to be lethal to the guilty and harmless to the innocent.¹²³ The “penalty of the peach” involved the administration of peach pits, which we now know contain the cyanide precursor amygdalin, as an ordeal poison. Magicians, sorcerers, and religious figures were the toxicologists of antiquity. The Sumerians, in circa 4500 B.C., were said to worship the deity Gula, who was known as the “mistress of charms and spells” and the “controller of noxious poisons” ([Table 1–1](#)).¹⁴⁷

TABLE 1–1. Important Early Figures in the History of Toxicology

<i>Person</i>	<i>Date</i>	<i>Importance</i>
Gula	ca. 4500 B.C.	First deity associated with poisons
Shen Nung	ca. 2000 B.C.	Chinese emperor who experimented with poisons and antidotes and wrote treatise on herbal medicine
Homer	ca. 850 B.C.	Wrote how Ulysses anointed arrows with the venom of serpents
Aristotle	384–322 B.C.	Described the preparation and use of arrow poisons
Theophrastus	ca. 370–286 B.C.	Referred to poisonous plants in <i>De Historia Plantarum</i>
Socrates	ca. 470–399 B.C.	Executed by poison hemlock
Nicander	204–135 B.C.	Wrote two poems, <i>Theriaca</i> and <i>Alexipharmaca</i> , that are among the earliest works on poisons
King Mithridates VI	ca. 132–63 B.C.	Fanatical fear of poisons; developed mithradatum, one of the first universal antidotes
Sulla	81 B.C.	Issued <i>Lex Cornelia</i> , the first antipoisoning law
Cleopatra	69–30 B.C.	Committed suicide with deliberate cobra envenomation
Andromachus	37–68 A.D.	Refined mithradatum; known as the Theriac of Andromachus
Dioscorides	40–80 A.D.	Wrote <i>Materia Medica</i> , which classified poisons by animal, vegetable, and mineral
Galen	ca. 129–200 A.D.	Prepared “nut theriac” for Roman emperors, a remedy against bites, stings, and poisons; wrote <i>De Antidotis I</i> and <i>II</i> , which provided recipes for different antidotes, including mithradatum and panacea
Ibn Wahshiya	9th century	Famed Arab toxicologist; wrote toxicology treatise <i>Book on Poisons</i> , combining contemporary science, magic, and astrology
Moses Maimonides	1135–1204	Wrote <i>Treatise on Poisons and Their Antidotes</i>
Petrus Abbonus	1250–1315	Wrote <i>De Venenis</i> , major work on poisoning

Arrow and Dart Poisons

The prehistoric Masai hunters of Kenya, who lived 18,000 years ago, used arrow and dart poisons to increase the lethality of their weapons.²⁰ One of these poisons appears to have consisted of extracts of *Strophanthus* species, an indigenous plant that contains strophanthin, a digitalislike substance.⁹⁷ Cave paintings of arrowheads and spearheads reveal that these weapons were crafted with small depressions at the end to hold the poison.¹⁴⁸ In fact, the term toxicology is derived from the Greek terms *toxikos* (“bow”) and *toxikon* (“poison into which arrowheads are dipped”).^{6,148}

References to arrow poisons are cited in a number of other important literary works. The ancient Indian text *Rig Veda*, written in the 12th century B.C., refers to the use of *Aconitum* species for arrow poisons.²⁰ In the *Odyssey*, Homer (ca. 850 B.C.) wrote that Ulysses anointed his arrows with a variety of poisons, including extracts of *Helleborus orientalis* and snake venoms. The writings of Ovid (43 B.C.–18 A.D.), describe weapons poisoned with the blood of serpents.¹⁵⁵

Classification of Poisons

The first attempts at poison identification and classification and the introduction of the first antidotes took place during Greek and Roman times. An early categorization of poisons divided them into fast poisons, such as strychnine, and slow poisons, such as arsenic. In his treatise, *Materia Medica*, the Greek physician Dioscorides (40–80 A.D.) categorized poisons by their origin—animal, vegetable, or mineral.¹⁴⁸ This categorization remained the standard classification for the next 1500 years.¹⁴⁸

Animal Poisons. Animal poisons usually referred to the venom from poisonous animals. Although the venom from poisonous snakes has always been among the most commonly feared poisons, poisons from toads, salamanders, jellyfish, stingrays, and sea hares are often as lethal. Nicander of Colophon (204–135 B.C.), a Greek poet and physician who is considered to be one of the earliest toxicologists, experimented with animal poisons on condemned criminals.¹³⁴ Nicander's poems *Theriaca* and *Alexipharmaca* are considered to be the earliest extant Greek toxicologic texts, describing the presentations and treatment of poisonings from animal xenobiotics.¹⁴⁷ A notable fatality from the effects of an animal xenobiotic was Cleopatra (69–30 B.C.), who reportedly committed suicide by deliberately falling on an asp.⁷⁵

Vegetable Poisons. Theophrastus (ca. 370–286 B.C.) described vegetable poisons in his treatise *De Historia Plantarum*.⁷⁶ Notorious poisonous plants included *Aconitum* species (monkshood aconite), *Conium maculatum* (poison hemlock), *Hyoscyamus niger* (henbane), *Mandragora officinarum* (mandrake), *Papaver somniferum* (opium poppy), and *Veratrum album* (hellebore). Aconite was among the most frequently encountered poisonous plants and was described as the “queen mother of poisons.”¹⁴⁷ Hemlock was the official poison used by the Greeks and was used in the execution of Socrates (ca. 470–399 B.C.) and many others.¹³⁶ Poisonous plants used in India at this time included *Cannabis indica* (marijuana), *Croton tiglium* (croton oil), and *Strychnos nux vomica* (poison nut, strychnine).⁷⁶

Mineral Poisons. The mineral poisons of antiquity consisted of the metals antimony, arsenic, lead, and mercury. Undoubtedly, the most famous of these was lead. Lead was discovered as early as 3500 B.C. Although controversy continues about whether an epidemic of lead poisoning among the Roman aristocracy contributed to the fall of the Roman Empire, lead was certainly used extensively during this period.^{55,112} In addition to its considerable use in plumbing, lead was also used in the production of food and drink containers.⁶² It was common practice to add lead directly to wine or to intentionally prepare the wine in a lead kettle to improve its taste. Not surprisingly, chronic lead poisoning became widespread. Nicander described the first case of lead poisoning in the 2nd century B.C.¹⁵¹ Dioscorides, writing in the 1st century A.D., noted that fortified wine was “most hurtful to the nerves.”¹⁵¹ Lead-induced gout (“saturnine gout”) may have also been widespread among the Roman elite.¹¹²

Gases. Although not animal, vegetable, or mineral in origin, the toxic effects of gases were also appreciated during antiquity. In the 3rd century B.C., Aristotle commented that “coal fumes (carbon monoxide) lead to a heavy head and death,”⁷³ and Cicero (106–43 B.C.) referred to the use of coal fumes in suicides and executions.

Poisoners of Antiquity

Given the increasing awareness of the toxic properties of some naturally occurring xenobiotics and the lack of analytical detection techniques, homicidal poisoning was common during Roman times. During this period, members of the aristocracy commonly used “tasters” to shield themselves from potential poisoners, a practice also in vogue during the reign of Louis XIV in 16th century France.¹⁵⁵

One of the most infamous poisoners of ancient Rome was Locusta, who was known to experiment on slaves with poisons that included aconite, arsenic, belladonna, henbane, and poisonous fungi. In 54 A.D., Nero's mother, Agrippina, hired Locusta to poison Emperor Claudius (Agrippina's husband and Nero's stepfather) as part of a scheme to make Nero emperor. As a result of these activities, Claudius, who was a great lover of mushrooms, died from *Amanita phalloides* poisoning.¹⁸ and in the next year, Britannicus (Nero's stepbrother) also became one of Locusta's victims. In his case, Locusta managed to fool the taster by preparing unusually hot soup that required additional cooling after the soup had been officially tasted. At the time of cooling, the poison was surreptitiously slipped into the soup. Almost immediately after drinking the soup, Britannicus collapsed and died. The exact poison remains in doubt, although some authorities suggest that it was a cyanogenic glycoside.¹³⁹

Early Quests for the Universal Antidote

The recognition, classification, and use of poisons in ancient Greece and Rome were accompanied by an intensive search for a universal antidote. In fact, many of the physicians of this period devoted significant parts of their careers to this endeavor.¹⁴⁷ Mystery and superstition surrounded the origins and sources of these proposed antidotes. One of the earliest specific references to a protective agent can be found in Homer's *Odyssey*, when Ulysses is advised to protect himself by taking the antidote “moli.” Recent speculation suggests that moli referred to *Galanthus nivalis*, which contains a cholinesterase inhibitor. This agent could have been used as an antidote against poisonous plants such as *Datura stramonium* (jimsonweed) that contain the anticholinergic alkaloids scopolamine, atropine, and hyoscyamine.¹²⁰

Theriaks and the Mithradatum. The Greeks referred to the universal antidote as the alexipharmaca or theriac.^{77,147} The term alexipharmaca was derived from the words alexipharmakos (“which keeps off poison”) and antipharmakon (“antidote”). Over the years, alexipharmaca was increasingly used to refer to a method of treatment, such as the induction of emesis by using a feather. Theriac, which originally had referred to poisonous reptiles or wild beasts, was later used to refer to the antidotes. Consumption of the early theriacs (ca. 200 B.C.) was reputed to make people “poison-proof” against bites of all venomous animals except the asp. Their ingredients included aniseed, anmi, apoponax, fennel, meru, parsley, and wild thyme.¹⁴⁷

The quest for the universal antidote was epitomized by the work of King Mithradates VI of Pontus (132–63 B.C.).⁷⁴ After repeatedly being subjected to poisoning attempts by his enemies during his youth, Mithradates sought protection by the development of universal antidotes. To find the best antidote, he performed acute toxicity experiments on criminals and slaves. The theriac he concocted, known as the “mithradatum,” contained a minimum of 36 ingredients and was thought to be protective against aconite, scorpions, sea slugs, spiders, vipers, and all other poisonous substances. Mithradates took his concoction every day. Ironically, when an old man, Mithradates attempted suicide by poison but supposedly was unsuccessful because he had become poison-proof. Having failed at self-poisoning, Mithradates was compelled to have a soldier kill him with a sword. Galen described Mithradates’ experiences in a series of three books: *De Antidotis I*, *De Antidotis II*, and *De Theriaca ad Pisonem*.^{74,152}

The Theriac of Andromachus, also known as the “Venice treacle” or “galene,” is probably the most well known theriac.⁶⁴ According to Galen, this preparation, formulated during the 1st century A.D., was considered an improvement over the mithradatum.¹⁴⁶ It was prepared by Andromachus (37–68 A.D.), physician to Emperor Nero. Andromachus added to the mithradatum ingredients such as the flesh of vipers, squills, and generous amounts of opium.¹⁵⁸ Other ingredients were removed. Altogether, 73 ingredients were required. It was advocated to “counteract all poisons and bites of venomous animals,” as well as a host of other medical problems, such as colic, dropsy, and jaundice, and it was used both therapeutically and prophylactically.^{147,152} As evidence of its efficacy, Galen demonstrated that fowl receiving poison followed by theriac had a higher survival rate than fowl receiving poison alone.¹⁴⁷ It is likely, however, that the scientific rigor and methodology used differed from current scientific practice.

By the Middle Ages, the Theriac of Andromachus contained more than 100 ingredients. Its synthesis was quite elaborate; the initial phase of production lasted months followed by an aging process that lasted years, somewhat similar to that of vintage wine.⁹² The final product was often more solid than liquid in consistency.

Other theriac preparations were named after famous physicians (Damocrates, Nicolaus, Amando, Arnould, and Abano) who contributed additional ingredients to the original formulation. Over the centuries, certain localities were celebrated for their own peculiar brand of theriac. Notable centers of theriac production included Bologna, Cairo, Florence, Genoa, Istanbul, and Venice. At times, theriac production was accompanied by great fanfare. For example, in Bologna, the mixing of the theriac could take place only under the direction of the medical professors at the university.¹⁴⁷

Whether these preparations were of actual benefit is uncertain. Some suggest that the theriac may have had an antiseptic effect on the gastrointestinal (GI) tract, but others state that the sole benefit of the theriac derived from its formulation with opium.⁹² Theriacs remained in vogue throughout the Middle Ages and Renaissance, and it was not until 1745 that their efficacy was finally questioned by William Heberden in *Antitheriaka: An Essay on Mithradatum and Theriaca*.⁷⁴ Nonetheless, pharmacopeias in France, Spain, and Germany continued to list these agents until the last quarter of the 19th century, and theriac was still available in Italy and Turkey in the early 20th century.^{19,92}

Sacred Earth. Beginning in the 5th century B.C., an adsorbent agent called terra sigillata was promoted as a universal antidote. This xenobiotic, also known as the “sacred sealed earth,” consisted of red clay that could be found on only one particular hill on the Greek island of Lemnos. Perhaps somewhat akin to the 20th-century “universal antidote,” it was advocated as effective in counteracting all poisons.¹⁴⁷ With great ceremony, once per year, the terra sigillata was retrieved from this hill and prepared for subsequent use. According to Dioscorides, this clay was formulated with goat’s blood to make it into a paste. At one time, it was included as part of the Theriac of Andromachus. Demand for terra sigillata continued into the 15th century. Similar antidotal clays were found in England, Italy, Malta, and Silesia.¹⁴⁷

Charms. Charms, such as toadstones, snakestones, unicorn horns, and bezoar stones, were also promoted as universal antidotes. Toadstones, found in the heads of old toads, were reputed to have the capability to extract poison from the site of a venomous bite or sting. In addition, the toadstone was supposedly able to detect the mere presence of poison by producing a sensation of heat upon contact with a poisonous substance.¹⁴⁷

Similarly, snakestones extracted from the heads of cobras (known as piedras della cobra de Capelos) were also reported to have magical qualities.¹⁴ The 17th-century Italian philosopher Athanasius Kircher (1602–1680) became an enthusiastic supporter of snakestone therapy for the treatment of snakebite after conducting experiments demonstrating the antidotal attributes of these charms “in front of amazed spectators.” Kircher attributed the efficacy of the snakestone to the theory of “attraction of like substances.” Francesco Redi (1626–1698), a court physician and contemporary of Kircher, debunked this quixotic approach. A harbinger of future experimental toxicologists, Redi was unwilling to accept isolated

case reports and field demonstrations as proof of the utility of the snakestone. Using a considerably more rigorous approach, *provando et riprovando* (by testing and retesting), Redi assessed the antidotal efficacy of snakestone on different animal species and different xenobiotics and failed to confirm any benefit.¹⁴

Much lore has surrounded the antidotal effects of the mythical unicorn horn. Ctesias, writing in 390 B.C., was the first to chronicle the wonders of the unicorn horn, claiming that drinking water or wine from the “horn of the unicorn” would protect against poison.¹⁴⁷ The horns were usually narwhal tusks or rhinoceros horns, and during the Middle Ages, the unicorn horn may have been worth as much as 10 times the price of gold. Similar to the toadstone, the unicorn horn was used both to detect poisons and to neutralize them. Supposedly, a cup made of unicorn horn would sweat if a poisonous substance was placed in it.⁹⁰ To give further credence to its use, a 1593 study on arsenic-poisoned dogs reportedly showed that the horn was protective.⁹⁰

Bezoar stones, also touted as universal antidotes, consisted of stomach or intestinal calculi formed by the deposition of calcium phosphate around a hair, fruit pit, or gallstone. They were removed from wild goats, cows, and apes and administered orally to humans. The Persian name for the bezoar stone was *pad zahr* (“expeller of poisons”); the ancient Hebrews referred to the bezoar stone as *bel Zaard* (“every cure for poisons”). Over the years, regional variations of bezoar stones were popularized, including an Asian variety from wild goat of Persia, an Occidental variety from llamas of Peru, and a European variety from chamois of the Swiss mountains.^{50,147}

OPIUM, COCA, CANNABIS, AND HALLUCINOGENS IN ANTIQUITY

Although it was not until the mid-19th century that the true perils of opiate addiction were first recognized, juice from the *Papaver somniferum* was known for its medicinal value in Egypt at least as early as the writing of the Ebers Papyrus in 1500 B.C. Egyptian pharmacologists of that time reportedly recommended opium poppy extract as a pacifier for children who exhibited incessant crying.¹³³ In Ancient Greece, Dioscorides and Galen were early advocates of opium as a therapeutic xenobiotic. During this time, it was also used as a means of suicide. Mithradates’ lack of success in his own attempted suicide by poisoning may have been the result of an opium tolerance that had developed from previous repetitive use.¹³³ One of the earliest descriptions of the abuse potential of opium is attributed to Epistratos (304–257 B.C.), who criticized the use of opium for earache because it “dulled the sight and is a narcotic.”¹³³

Cocaine use dates back to at least 300 B.C., when South American Indians reportedly chewed coca leaves during religious ceremonies.¹⁰⁶ Chewing coca to increase work efficacy and to elevate mood has remained commonplace in some South American societies for thousands of years. An Egyptian mummy from about 950 B.C. revealed significant amounts of cocaine in the stomach and liver, suggesting oral use of cocaine occurred during this time period.¹¹⁰ Large amounts of tetrahydrocannabinol (THC) were also found in the lung and muscle of the same mummy. Another investigation of 11 Egyptian (1079 B.C.–395 A.D.) and 72 Peruvian (200–1500 A.D.) mummies found cocaine, thought to be indigenous only to South America, and hashish, thought to be indigenous only to Asia, in both groups.¹¹⁹

Cannabis use in China dates back even further, to around 2700 B.C., when it was known as the “liberator of sin.”¹⁰⁶ In India and Iran, cannabis was used as early as 1000 B.C. as an xenobiotic known as *bang*.¹⁰⁹ Other currently abused xenobiotics that were known to the ancients include cannabis, hallucinogenic mushrooms, nutmeg, and peyote. As early as 1300 B.C., Peruvian Indian tribal ceremonies included the use of mescaline-containing San Pedro cacti.¹⁰⁶ The hallucinogenic mushroom *Amanita muscaria*, known as “fly agaric,” was used as a ritual drug and may have been known in India as “soma” around 2000 B.C.

EARLY ATTEMPTS AT GASTROINTESTINAL DECONTAMINATION

Nicander’s *Alexipharmaca* (Antidotes for Poisons) recommended induction of emesis by one of several methods: (a) ingesting warm linseed oil, (b) tickling the hypopharynx with a feather, or (c) “emptying the gullet with a small twisted and curved paper.”⁹² Nicander also advocated the use of suction to limit envenomation.¹⁴⁸ The Romans referred to the feather as the “vomiting feather” or “pinna.” Most commonly, the feather was used after a hearty feast to avoid the GI discomfort associated with overeating. At times, the pinna was dipped into a nauseating mixture to increase its efficacy.⁹⁵

TOXICOLOGY DURING THE MEDIEVAL AND RENAISSANCE PERIODS

After Galen (ca. A.D. 129–200), there is relatively little documented attention to the subject of poisons until the works of Ibn Wahshiya in the 9th century. Citing Greek, Persian, and Indian texts, Wahshiya’s work, titled *Book of Poisons*, combined contemporary science, magic, and astrology during his discussion of poison mechanisms (as they were understood at that time), symptomatology, antidotes (including his own recommendation for a universal antidote), and prophylaxis. He categorized poisons as lethal by sight, smell, touch, and sound, as well as by drinking and eating. For

victims of an aconite-containing dart arrow, Ibn Wahshiya recommended excision followed by cauterization and topical treatment with onion and salt.⁸⁷

Another significant medieval contribution to toxicology can be found in Moses Maimonides’ (1135–1204) *Treatise on Poisons and Their Antidotes* (1198). In part one of this treatise, Maimonides discussed the bites of snakes and mad dogs and the stings of bees, wasps, spiders, and scorpions.¹³¹ He also discussed the use of cupping glasses for bites (a progenitor of the modern suctioning device) and was one of the first to differentiate the hematotoxic (hot) from the neurotoxic (cold) effects of poison. In part two, he discussed mineral and vegetable poisons and their antidotes. He described belladonna poisoning as causing a “redness and a sort of excitation.”¹³¹ He suggested that emesis should be induced by hot water, *Anethum graveolens* (dill), and oil followed by fresh milk, butter, and honey. Although he rejected some of the popular treatments of the day, he advocated the use of the great theriac and the mithradatum as first- and second-line xenobiotics in the management of snakebite.¹³¹

On the subject of oleander poisoning, Petrus Abbonus (1250–1315) wrote that those who drink the juice, spines, or bark of oleander will develop anxiety, palpitations, and syncope.²² He described the clinical presentation of opium overdose as someone who “will be dull, lazy, and sleepy, without feeling, and he will neither understand nor feel anything, and if he does not receive succor, he will die.” Although this “succor” is not defined, he recommended that treatment of opium intoxication include drinking the strongest wine, rubbing the extremities with alkali and soap, and olfactory stimulation with pepper. To treat snakebite, Abbonus suggested the immediate application of a tourniquet, as well as oral suctioning of the bite wound, preferably performed by a servant. Interesting from a 21st-century perspective, Abbonus also suggested that St. John’s wort had the magical power to free anything from poisons and attributed this virtue to the influence of the stars.²²

The Scientists

Paracelsus’ (1493–1541) study on the dose–response relationship is usually considered the beginning of the scientific approach to toxicology (Table 1–2). He was the first to emphasize the chemical nature of toxic xenobiotics.¹¹⁷ Paracelsus stressed the need for proper observation and experimentation regarding the true response to xenobiotics. He underscored the need to differentiate between the therapeutic and toxic properties of chemicals when he stated in his Third Defense, “What is there that is not poison? All things are poison and nothing [is] without poison. Solely, the dose determines that a thing is not a poison.”⁴³

TABLE 1–2. Important Contributors to Toxicology

<i>Person</i>	<i>Date</i>	<i>Importance</i>
Paracelsus	1493–1541	Introduced the dose–response concept to toxicology
Ambroise Pare	1510–1590	Spoke out against unicorn horns and bezoars as antidotes
William Piso	1611–1678	First to study emetic qualities of ipecacuanha
Bernardino Ramazzini	1633–1714	Father of occupational medicine; wrote <i>De Morbis Artificum Diatriba</i>
Richard Mead	1673–1754	Wrote English-language book about poisoning
Percivall Pott	1714–1788	Wrote the first description of occupational cancer, relating the chimney sweep occupation to scrotal cancer
Felice Fontana	1730–1805	First scientific study of venomous snakes
Philip Physick	1767–1837	Early advocate of orogastric lavage to remove poisons
Baron Guillaume Dupuytren	1777–1835	Early advocate of orogastric lavage to remove poisons
Francois Magendie	1783–1855	Discovered emetine and studied the mechanisms of cyanide and strychnine
Bonaventure Orfila	1787–1853	Father of modern toxicology; wrote <i>Traite des Poisons</i> ; first to isolate arsenic from humans organs
James Marsh	1794–1846	Developed reduction test for arsenic
Robert Christison	1797–1882	Wrote <i>Treatise on Poisons</i> , one of the most influential texts of the early 19th century
Grand Marshall Bertrand	1813	Demonstrated the efficacy of activated charcoal in arsenic ingestion

Claude Bernard	1813–1878	Studied the mechanisms of toxicity of carbon monoxide and curare
Edward Jukes	1820	Self-experimented with orogastric lavage apparatus known as Jukes' syringe
Theodore Wormley	1826–1897	Wrote <i>Micro-Chemistry of Poisons</i> , the first American book devoted exclusively to toxicology
Pierre Touery	1831	Demonstrated the efficacy of activated charcoal in strychnine ingestion
Hugo Reinsch	1842–1884	Developed qualitative tests for arsenic and mercury
Alfred Garrod	1846	Conducted the first systematic study of activated charcoal in an animal model
Max Gutzeit	1847–1915	Developed method to quantitate small amounts of arsenic
Benjamin Howard Rand	1848	Conducted the first study of the efficacy of activated charcoal in humans
O.H. Costill	1848	Wrote the first book on symptoms and treatment of poisoning
Louis Lewin	1850–1929	Studied many toxins, including methanol, chloroform, snake venom, carbon monoxide, lead, opioids, and hallucinogenic plants
Rudolf Kobert	1854–1918	Studied digitalis and ergot alkaloids
Albert Niemann	1860	Isolated cocaine alkaloid
Alice Hamilton	1869–1970	Conducted landmark investigations associating worksite chemical hazards with disease; led reform movement to improve worker safety

Although Paracelsus is the best known Renaissance toxicologist, Ambroise Pare (1510–1590) and William Piso (1611–1678) also contributed to the field. Pare argued against the use of the unicorn horn and bezoar stone.⁹⁴ He also wrote an early treatise on carbon monoxide poisoning. Piso is credited as one of the first to recognize the emetic properties of ipecacuanha.¹²⁸

Medieval and Renaissance Poisoners

Along with these advances in toxicologic knowledge, the Renaissance is mainly remembered as the age of the poisoner, a time when the art of poisoning reached new heights (Table 1–3). In fact, poisoning was so rampant during this time that in 1531, King Henry VIII decreed that convicted poisoners should be boiled alive.⁵² From the 15th to 17th centuries, schools of poisoning existed in Venice and Rome. In Venice, poisoning services were provided by a group called the Council of Ten, whose members were hired to perform murder by poison.¹⁵⁵

TABLE 1–3. Notable Poisoners from Antiquity to the Present

<i>Poisoner</i>	<i>Date</i>	<i>Victim(s)</i>	<i>Poison(s)</i>
Locusta	54–55 A.D.	Claudius and Britannicus	<i>Amanita phalloides</i> , cyanide
Cesare Borgia	1400s	Cardinals and kings	La Cantarella (arsenic and phosphorus)
Catherine de Medici	1519–1589	Poor, sick, criminals	Unknown
Hieronyma Spara	Died 1659	Taught women how to poison their husbands	Mana of St. Nicholas of Bari (arsenic trioxide)
Marchioness de Brinvilliers	Died 1676	Hospitalized patients, husband, father	Antimony, arsenic, copper, lead, mercury
Catherine Deshayes	Died 1680	>2000 infants, many husbands	La poudre de succession (arsenic mixed with aconite, belladonna, and opium)
Madame Giulia Toffana	Died 1719	>600 people	Agua toffana (arsenic trioxide)
Mary Blandy	1752	Father	Arsenic
Anna Maria Zvanizer	1807	Random people	Antimony, arsenic
Marie Lefarge	1839	Husband	Arsenic (first use of Marsh test)
John Tawell	1845	Mistress	Cyanide
William Palmer, MD	1855	Fellow gambler	Strychnine
Madeline Smith (acquitted)	1857	Lover	Arsenic
Edmond de la Pommerai, MD	1863	Patient and mistress	Digitalis
Edward William Pritchard, MD	1865	Wife and mother-in-law	Antimony
George Henry Lamson, MD	1881	Brother-in-law	Aconite
Adelaide Bartlett (acquitted)	1886	Husband	Chloroform
Florence Maybrick	1889	Husband	Arsenic
Thomas Neville Cream, MD	1891	Prostitutes	Strychnine
Johann Hoch	1892–1905	Serial wives	Arsenic
Cordelia Botkin	1898	Rival woman	Arsenic (in chocolate candy)
Roland Molineux	1898	Acquaintance	Cyanide of mercury
Hawley Harvey Crippen, MD	1910	Wife	Hyoscine

Frederick Henry Seddon	1911	Boarder	Arsenic (fly paper)
Henri Girard Landru	1912	Acquaintances	<i>Amanita phalloides</i>
Robert Armstrong	1921	Wife	Arsenic (weed killer)
Landru	1922	Many women	Cyanide

Suzanne Fazekas	1929	Supplied poison to 100 wives to kill husbands	Arsenic
Sadamichi Hirasawa	1948	Bank employees	Potassium cyanide
Christa Ambros-Lehmaen	1954	Friend, husband, father-in-law	E-605 (parathion)
Nannie Doss	1954	11 relatives, including five husbands	Arsenic
Carl Coppolino, MD	1965	Wife	Succinylcholine
Graham Frederick Young	1971	Stepmother, coworkers	Antimony, thallium
Judas V. Buonoano	1971	Husband, son	Arsenic
Ronald Clark O'Bryan	1974	Son and neighborhood children	Cyanide (in Halloween candy)
Governmental	1978	Georgi Markov, Bulgarian dissident	Ricin
Jim Jones	1978	>900 people in mass suicide	Cyanide
Harold Shipman, MD	1974–1998	>100 patients	Heroin
Unidentified	1982	Seven random people	Extra Strength Tylenol mixed with cyanide
Donald Harvey	1983–1987	Patients	Arsenic
George Trepal	1988	Neighbors	Thallium
Michael Swango, MD	1980s–1990s	Hospitalized patients	Arsenic, potassium chloride, succinylcholine
Charles Cullen, RN	1990s–2003	Hospitalized patients	Digoxin
Governmental	2004	Viktor Yushchenko, Ukrainian presidential candidate	Dioxin
Governmental	2006	Alexander Litvinenko	Polonium-210

Members of the infamous Borgia family were considered to be responsible for many poisonings during this period. They preferred to use a poison called “La Cantarella,” a mixture of arsenic and phosphorus.¹⁴⁹ Rodrigo Borgia (1431–1503), who became Pope Alexander VI, and his son, Cesare Borgia, were reportedly responsible for the poisoning of cardinals and kings.

In the late 16th century, Catherine de Medici, wife of Henry II of France, introduced Italian poisoning techniques to France. She experimented on the poor, the sick, and the criminal. By analyzing the subsequent complaints of her victims, she is said to have learned the site of action and time of onset, the clinical signs and symptoms, and the efficacy of poisons.⁵⁶

Murder by poison remained quite popular during the latter half of the 17th and the early part of the 18th centuries in Italy and France.

The Marchioness de Brinvilliers (1630–1676) tested her poison concoctions on hospitalized patients and on her servants and allegedly murdered her husband, father, and two siblings.^{54,139} Among the favorite poisons of the Marchioness were arsenic, copper sulfate, corrosive sublimate (mercury bichloride), lead, and tartar emetic (antimony potassium tartrate).¹⁴⁹ Catherine Deshayes (1640–1680), a fortuneteller and sorceress, was one of the last “poisoners for hire” and was implicated in countless poisonings, including the killing of more than 2000 infants.⁵⁶ Better known as “La Voisine,” she reportedly sold poisons to women wishing to rid themselves of their husbands. Her particular brand of poison was a concoction of aconite, arsenic, belladonna, and opium known as la poudre de succession.¹⁴⁹ Ultimately, de Brinvilliers was beheaded and Deshayes was burned alive for their crimes. In an attempt to curtail these rampant poisonings, Louis XIV issued a decree in 1662 banning the sale of arsenic, mercury, and other poisons to customers not known to apothecaries and requiring buyers to sign a register declaring the purpose for their purchase.¹³⁹

A major center for poison practitioners was Naples, the home of the notorious Madame Giulia Toffana. She reportedly poisoned more than 600 people, preferring a particular solution of white arsenic (arsenic trioxide), better known as “aqua toffana,” and dispensed under the guise of a cosmetic. Eventually convicted of poisoning, Madame Toffana was executed in 1719.²¹

EIGHTEENTH-AND NINETEENTH-CENTURY DEVELOPMENTS IN

TOXICOLOGY

The development of toxicology as a distinct specialty began during the 18th and 19th centuries (Table 1–2).¹¹⁸ The mythological and magical mystique of poisoners began to be gradually replaced by an increasingly rational, scientific, and experimental approach to these agents. Much of the poison lore that had survived for almost 2000 years was finally debunked and discarded. The 18th-century Italian Felice Fontana was one of the first to usher in the modern age. He was an early experimental toxicologist who studied the venom of the European viper and wrote the classic text *Traite sur le Venin de la Vipere* in 1781.⁷⁹ Through his exacting experimental study on the effects of venom, Fontana brought a scientific insight to toxicology previously lacking and demonstrated that clinical symptoms resulted from the poison (venom) acting on specific target organs. During the 18th and 19th centuries, attention focused on the detection of poisons and the study of toxic effects of xenobiotics in animals.¹¹¹ Issues relating to adverse effects of industrialization and unintentional poisoning in the workplace and home environment were raised. Also during this time, early experience and experimentation with methods of GI decontamination took place.

Development of Analytical Toxicology and the Study of Poisons

The French physician Bonaventure Orfila (1787–1853) is often called the father of modern toxicology.¹¹¹ He emphasized toxicology as a distinct, scientific discipline, separate from clinical medicine and pharmacology.¹¹ He was also an early medical-legal expert who championed the use of chemical analysis and autopsy material as evidence to prove that a poisoning had occurred. His treatise *Traite des Poisons* (1814)¹¹⁶ evolved over five editions and was regarded as the foundation of experimental and forensic toxicology.¹⁵⁴ This text classified poisons into six groups: acrids, astringents, corrosives, narcoticoacrids, septic and putrefiants, and stupeficients and narcotics.

A number of other landmark works on poisoning also appeared during this period. In 1829, Robert Christison (1797–1882), a professor of medical jurisprudence and Orfila's student, wrote *A Treatise on Poisons*.³² This work simplified Orfila's poison classification schema by categorizing poisons into three groups: irritants, narcotics, and narcoticoacrids. Less concerned with jurisprudence than with clinical toxicology, O.H. Costill's *A Practical Treatise on Poisons*, published in 1848, was the first modern clinically oriented text to emphasize the symptoms and treatment of poisoning.³⁶ In 1867, Theodore Wormley (1826–1897) published the first American book written exclusively on poisons titled *Micro-Chemistry of Poisons*.^{48,157}

During this time, important breakthroughs in the chemical analysis of poisons resulted from the search for a more reliable assay for arsenic. Arsenic was widely available and was the suspected cause of a large number of deaths. In one study, arsenic was used in 31% of 679 homicidal poisonings.¹⁴⁹ A reliable means of detecting arsenic was much needed by the courts.

Until the 19th century, poisoning was mainly diagnosed by its resultant symptoms rather than by analytic tests. The first use of a chemical test as evidence in a poisoning trial occurred in the 1752 trial of Mary Blandy, who was accused of poisoning her father with arsenic.⁹⁹ Although Blandy was convicted and hanged publicly, the test used in this case was not very sensitive and depended in part on eliciting a garlic odor upon heating the gruel that the accused had fed to her father.

During the 19th century, James Marsh (1794–1846), Hugo Reinsch (1842–1884), and Max Gutzeit (1847–1915) each worked on this problem. Assays bearing their names are important contributions to the early history of analytic toxicology.^{100,111} The “Marsh test” to detect arsenic was first used in a criminal case in 1839 during the trial of Marie Lefarge, who was accused of using arsenic to murder her husband.¹³⁹ Orfila's trial testimony that the victim's viscera contained minute amounts of arsenic helped to convict the defendant, although subsequent debate suggested that contamination of the forensic specimen may have also played a role.

In a further attempt to curtail criminal poisoning by arsenic, the British Parliament passed the Arsenic Act in 1851. This bill, which was one of the first modern laws to regulate the sale of poisons, required that the retail sale of arsenic be restricted to chemists, druggists, and apothecaries and that a poison book be maintained to record all arsenic sales.¹⁵

Homicidal poisonings remained common during the 19th century and early 20th century. Infamous poisoners of that time included William Palmer, Edward Pritchard, Harvey Crippen, and Frederick Seddon.¹⁴⁹ Many of these poisoners were physicians who used their knowledge of medicine and toxicology in an attempt to solve their domestic and financial difficulties by committing the “perfect” murder. Some of the poisons used were aconitine (by Lamson, who was a classmate of Christison), *Amanita phalloides* (by Girard), arsenic (by Maybrick, Seddon, and others), antimony (by Pritchard), cyanide (by Molineux and Tawell), digitalis (by Pommerais), hyoscine (by Crippen), and strychnine (by Palmer and Cream) (Table 1–3).^{24,86,147,149}

In the early 20th century, forensic investigation into suspicious deaths, including poisonings, was significantly advanced with the development of the medical examiner system replacing the much-flawed coroner system that was subject to widespread corruption. In 1918, the first centrally controlled medical examiner system was established in New York City. Alexander Gettler, considered the father of forensic toxicology in the United States, established a toxicology laboratory

within the newly created New York City Medical Examiner's Office. Gettler pioneered new techniques for the detection of a variety of substances in biologic fluids, including carbon monoxide, chloroform, cyanide, and heavy metals.^{49,111}

Systematic investigation into the underlying mechanisms of toxic substances also commenced during the 19th century. Francois Magendie (1783–1855) studied the mechanisms of toxicity and sites of action of cyanide, emetine, and strychnine.⁴⁷ Claude Bernard (1813–1878), a pioneering physiologist and a student of Magendie, made important contributions to the understanding of the toxicity of carbon monoxide and curare.⁸⁵ Rudolf Kobert (1854–1918) studied digitalis and ergot alkaloids and authored a textbook on toxicology for physicians and students.^{83,114} Louis Lewin (1850–1929) was the first person to intensively study the differences between the pharmacologic and toxicologic actions of xenobiotics. Lewin studied chronic opium intoxication, as well as the toxicity of carbon monoxide, chloroform, lead, methanol, and snake venom. He also developed a classification system for psychoactive drugs, dividing them into euphorics, phantastics, inebriants, hypnotics, and excitants.⁹³

The Origin of Occupational Toxicology

The origins of occupational toxicology can be traced to the early 18th century and to the contributions of Bernardino Ramazzini (1633–1714). Considered the father of occupational medicine, Ramazzini wrote *De Morbis Artificum Diatriba* (Diseases of Workers) in 1700, which was the first comprehensive text discussing the relationship between disease and workplace hazards.⁵³ Ramazzini's essential contribution to patient care is epitomized by the addition of a standard question to a patient's medical history: "What occupation does the patient follow?"⁵¹ Altogether Ramazzini described diseases associated with 54 occupations, including hydrocarbon poisoning in painters, mercury poisoning in mirror makers, and pulmonary diseases in miners.

In 1775, Sir Percivall Pott proposed the first association between workplace exposure and cancer when he noticed a high incidence of scrotal cancer in English chimney sweeps. Pott's belief that the scrotal cancer was caused by prolonged exposure to tar and soot was confirmed by further investigation in the 1920s, indicating the carcinogenic nature of the polycyclic aromatic hydrocarbons contained in coal tar (including benzo[a]pyrene).⁷²

Dr. Alice Hamilton (1869–1970) was another pioneer in occupational toxicology whose rigorous scientific inquiry had a profound impact on linking chemical xenobiotics with human disease. A physician, scientist, humanitarian, and social reformer, Hamilton became the first female professor at Harvard University and conducted groundbreaking studies of many different occupational exposures and problems, including carbon monoxide poisoning in steelworkers, mercury poisoning in hatters, and wrist drop in lead workers. Hamilton's overriding concerns about these "dangerous trades" and her commitment to improving the health of workers led to extensive voluntary and regulatory reforms in the workplace.^{60,65}

Advances in Gastrointestinal Decontamination

Using gastric lavage and activated charcoal to treat poisoned patients was introduced in the late 18th and early 19th century. A stomach pump was first designed by Munro Secundus in 1769 to administer neutralizing substances to sheep and cattle for the treatment of bloat.²⁴ The American surgeon Philip Physick (1768–1837) and the French surgeon Baron Guillaume Dupuytren (1777–1835) were two of the first physicians to advocate gastric lavage for the removal of poisons.²⁵ As early as 1805, Physick demonstrated the use of a "stomach tube" for this purpose. Using brandy and water as the irrigation fluid, he performed stomach washings in twins to wash out excessive doses of tincture of opium.²⁵ Dupuytren performed gastric emptying by first introducing warm water into the stomach via a large syringe attached to a long flexible sound and then withdrawing the "same water charged with poison."²⁵ Edward Jukes, a British surgeon, was another early advocate of poison removal by gastric lavage. Jukes first experimented on animals, performing gastric lavage after the oral administration of tincture of opium. Attempting to gain human experience, he experimented on himself, by first ingesting 10 drams (600 g) of tincture of opium and then performing gastric lavage using a 25-inch-long, 0.5-inch-diameter tube, which became known as Jukes' syringe.¹⁰⁵ Other than some nausea and a 3-hour sleep, he suffered no ill effects, and the experiment was deemed a success.

The principle of using activated charcoal to adsorb xenobiotics was first described by Scheele (1773) and Lowitz (1785), but the medicinal use of activated charcoal dates to ancient times.³⁵ The earliest reference to the medicinal uses of activated charcoal is found in Egyptian papyrus from about 1500 B.C.³⁵ The activated charcoal used during Greek and Roman times, referred to as "wood charcoal," was used to treat those with anthrax, chlorosis, epilepsy, and vertigo. By the late 18th century, topical application of activated charcoal was recommended for gangrenous skin ulcers, and internal use of an activated charcoal-water suspension was recommended for use as a mouthwash and in the treatment of bilious conditions.³⁵

The first hint that activated charcoal might have a role in the treatment of poisoning came from a series of courageous self-experiments in France during the early 19th century. In 1813, the French chemist Bertrand publicly demonstrated the antidotal properties of activated charcoal by surviving a 5 g ingestion of arsenic trioxide that had been mixed with

activated charcoal.⁶⁸ Eighteen years later, before the French Academy of Medicine, the pharmacist Touery survived an ingestion consisting of 10 times the lethal dose of strychnine mixed with 15 g of activated charcoal.⁶⁸ One of the first reports of activated charcoal used in a poisoned patient was in 1834 by the American Hort, who successfully treated a mercury bichloride–poisoned patient with large amounts of powdered activated charcoal.³

In the 1840s, Garrod performed the first controlled study of activated charcoal when he examined its utility on a variety of poisons in animal models.⁶⁸ Garrod used dogs, cats, guinea pigs, and rabbits to demonstrate the potential benefits of activated charcoal in the management of strychnine poisoning. He also emphasized the importance of early use of activated charcoal and the proper ratio of activated charcoal to poison. Other toxic substances, such as aconite, hemlock, mercury bichloride, and morphine, were also studied during this period. The first activated charcoal efficacy studies in humans were performed by the American physician B. Rand in 1848.⁶⁸

But it was not until the early 20th century that an activation process was added to the manufacture of activated charcoal to increase its effectiveness. In 1900, the Russian Ostrejko demonstrated that treating activated charcoal with superheated steam significantly enhanced its adsorbing power.³⁵ Despite this improvement and the favorable reports mentioned, activated charcoal was only occasionally used in GI decontamination until the early 1960s, when Holt and Holz repopularized its use.⁶³

The Increasing Recognition of the Perils of Drug Abuse

Opioids. Although the medical use of opium was promoted by Paracelsus in the 16th century, the popularity of this agent was given a significant boost when the distinguished British physician Thomas Sydenham (1624–1689) formulated laudanum, which was a tincture of opium containing cinnamon, cloves, saffron, and sherry. Sydenham also formulated a different opium concoction known as “syrup of poppies.”⁸² A third opium preparation called Dover’s powder was designed by Sydenham’s protégé, Thomas Dover; this preparation contained syrup of ipecac, licorice, opium, salt-peter, and tartaric acid.

John Jones, the author of the 18th century text *The Mysteries of Opium Revealed*, was another enthusiastic advocate of its “medicinal” uses.⁸² A well-known opium user himself, Jones provided one of the earliest descriptions of opioid addiction. He insisted that opium offered many benefits if the dose was moderate but that discontinuation or a decrease in dose, particularly after “leaving off after long and lavish use,” would result in such symptoms as sweating, itching, diarrhea, and melancholy. His recommendation for the treatment of these withdrawal symptoms included decreasing the dose of opium by 1% each day until the drug was totally withdrawn. During this period, the number of English writers who became well-known opium addicts included Elizabeth Barrett Browning, Samuel Taylor Coleridge, and Thomas De Quincey. De Quincey, author of *Confessions of an English Opium Eater*, was an early advocate of the recreational use of opiates. The famed Coleridge poem *Kubla Khan* referred to opium as the “milk of paradise,” and De Quincey’s *Confessions* suggested that opium held the “key to paradise.” In many of these cases, the initiation of opium use for medical reasons led to recreational use, tolerance, and dependence.⁸²

Although opium was first introduced to Asian societies by Arab physicians some time after the fall of the Roman Empire, the use of opium in Asian countries grew considerably during the 18th and 19th centuries. China’s growing dependence on opium was spurred on by the English desire to establish and profit from a flourishing drug trade.¹³³ Opium was grown in India and exported east. Despite Chinese protests and edicts against this practice, the importation of opium persisted throughout the 19th century, with the British going to war twice in order to maintain their right to sell opium. Not surprisingly, by the beginning of the 20th century, opium abuse in China was endemic.

In England, opium use continued to increase during the first half of the 19th century. During this period, opium was legal and freely available from the neighborhood grocer. To many, its use was considered no more problematic than alcohol use.⁵⁸ The Chinese usually self-administered opium by smoking, a custom that was brought to the United States by Chinese immigrants in the mid-19th century; the English use of opium was more often by ingestion, that is, “opium eating.”

The liberal use of opioids as infant-soothing agents was one of the most unfortunate aspects of this period of unregulated opioid use.⁸³ Godfrey’s Cordial, Mother’s Friend, Mrs. Winslow’s Soothing Syrup, and Quietness were among the most popular opioids for children.⁸⁸ They were advertised as producing a natural sleep and recommended for teething and bowel regulation, as well as for crying. Because of the wide availability of opioids during this period, the number of acute opioid overdoses in children was consequential and would remain problematic until these unsavory remedies were condemned and removed from the market.

With the discovery of morphine in 1805 and Alexander Wood’s invention of the hypodermic syringe in 1853, parenteral administration of morphine became the preferred route of opioid administration for therapeutic use and abuse.⁷⁰ A legacy of the generous use of opium and morphine during the United States Civil War was “soldiers’ disease,” referring to a rather large veteran population that returned from the war with a lingering opioid habit.¹²⁵ One hundred years later, opioid abuse and addiction would again become common among the US military serving during the Vietnam War. Surveys indicated that as many as 20% of American soldiers in Vietnam were addicted to opioids during the war, partly because of its

widespread availability and high purity there.¹³⁰

Growing concerns about opioid abuse in England led to the passing of the Pharmacy Act of 1868, which restricted the sale of opium to registered chemists. But in 1898, the Bayer Pharmaceutical Company of Germany synthesized heroin from opium (Bayer also introduced aspirin that same year).¹⁴⁰ Although initially touted as a nonaddictive morphine substitute, problems with heroin use quickly became evident in the United States. Illicit heroin use reached epidemic proportions after World War II and again in the late 1960s.⁷¹ Although heroin use appeared to have leveled off by the end of the 20th century, an epidemic of prescription opioid abuse exploded during the first decade of the 21st century.⁹⁶

Cocaine. Ironically, during the later part of the 19th century, Sigmund Freud and Robert Christison, among others, promoted cocaine as a treatment for opiate addiction. After Albert Niemann's isolation of cocaine alkaloid from coca leaf in 1860, growing enthusiasm for cocaine as a panacea ensued.⁷⁸ Some of the most important medical figures of the time, including William Halsted, the famed Johns Hopkins surgeon, also extolled the virtues of cocaine use. Halsted championed the anesthetic properties of this drug, although his own use of cocaine and subsequent morphine use in an attempt to overcome his cocaine dependency would later take a considerable toll.¹¹⁵ In 1884, Freud wrote *Über Cocaine*,²⁷ advocating cocaine as a cure for opium and morphine addiction and as a treatment for fatigue and hysteria.

During the last third of the 19th century, cocaine was added to many popular nonprescription tonics. In 1863, Angelo Mariani, a Frenchman, introduced a new wine, "Vin Mariani," that consisted of a mixture of cocaine and wine (6 mg of cocaine alkaloid per ounce) and was sold as a digestive aid and restorative.¹⁰⁶ In direct competition with the French tonic was the American-made Coca-Cola, developed by J.S. Pemberton. It was originally formulated with coca and caffeine and marketed as a headache remedy and invigorator. With the public demand for cocaine increasing, patent medication manufacturers were adding cocaine to thousands of products. One such asthma remedy was "Dr. Tucker's Asthma Specific," which contained 420 mg of cocaine per ounce and was applied directly to the nasal mucosa.⁷⁸ By the end of the 19th century, the first American cocaine epidemic was underway.¹⁰⁸

Similar to the medical and societal adversities associated with opiate use, the increasing use of cocaine led to a growing concern about comparable adverse effects. In 1886, the first reports of cocaine-related cardiac arrest and stroke were published.¹²⁶ Reports of cocaine habituation occurring in patients using cocaine to treat their underlying opiate addiction also began to appear. In 1902, a popular book *Eight Years in Cocaine Hell* described some of these problems. *Century Magazine* called cocaine "the most harmful of all habit-forming drugs," and a report in *The New York Times* stated that cocaine was destroying "its victims more swiftly and surely than opium."⁴² In 1910, President William Taft proclaimed cocaine to be "public enemy number one."

In an attempt to curb the increasing problems associated with drug abuse and addiction, the 1914 Harrison Narcotics Act mandated stringent control over the sale and distribution of narcotics (defined as opium, opium derivatives, and cocaine).⁴² It was the first federal law in the United States to criminalize the nonmedical use of drugs. The bill required doctors, pharmacists, and others who prescribed narcotics to register and to pay a tax. A similar law, the Dangerous Drugs Act, was passed in the United Kingdom in 1920.⁵⁸ To help enforce these drug laws in the United States, the Narcotics Division of the Prohibition Unit of the Internal Revenue Service (a progenitor of the Drug Enforcement Agency) was established in 1920. In 1924, the Harrison Act was further strengthened with the passage of new legislation that banned the importation of opium for the purpose of manufacturing heroin, essentially outlawing the medicinal uses of heroin. With the legal venues to purchase these drugs now eliminated, users were forced to buy from illegal street dealers, creating a burgeoning black market that still exists today.

Sedative-Hypnotics. The introduction to medical practice of the anesthetic agents nitrous oxide, ether, and chloroform during the 19th century was accompanied by the recreational use of these agents and the first reports of volatile substance abuse. Chloroform "jags," ether "frolics," and nitrous parties became a new type of entertainment. Humphrey Davies was an early self-experimenter with the exhilarating effects associated with nitrous oxide inhalation. In certain Irish towns, especially where the temperance movement was strong, ether drinking became quite popular.¹⁰² Horace Wells, the American dentist who introduced chloroform as an anesthetic, became dependent on this volatile solvent and later committed suicide.

Until the last half of the 19th century, aconite, alcohol, hemlock, opium, and prussic acid (cyanide) were the primary agents used for sedation.³³ During the 1860s, new, more specific sedative-hypnotics, such as chloral hydrate and potassium bromide, were introduced into medical practice. In particular, chloral hydrate was hailed as a wonder drug that was relatively safe compared with opium and was recommended for insomnia, anxiety, and delirium tremens, as well as for scarlet fever, asthma, and cancer. But within a few years, problems with acute toxicity of chloral hydrate, as well as its potential to produce tolerance and physical dependence, became apparent.³³ Mixing chloral hydrate with ethanol, both of which inhibit each other's metabolism by competing with alcohol dehydrogenase, was noted to produce a rather powerful "knockout" combination that would become known as a "Mickey Finn" allegedly named after a Chicago saloon proprietor.¹⁶ Abuse of chloral hydrate, as well as other new sedatives such as potassium bromide, would prove to be a harbinger of 20th-century sedative-hypnotic abuse.

Absinthe, an ethanol-containing beverage that was manufactured with an extract from wormwood (*Artemisia absinthium*), was very popular during the last half of the 19th century.⁸⁴ This emerald-colored, very bitter drink was memorialized in the paintings of Degas, Toulouse-Lautrec, and Van Gogh and was a staple of French society during this period.¹² α -Thujone, a psychoactive component of wormwood and a noncompetitive γ -aminobutyric acid type A GABA_A blocker, is thought to be responsible for the pleasant feelings, hyperexcitability, and significant neurotoxicity associated with this drink.⁶⁷ Van Gogh’s debilitating episodes of psychosis were likely exacerbated by absinthe drinking.¹⁴⁴ Because of the medical problems associated with its use, absinthe was banned throughout most of Europe by the early 20th century.

Hallucinogens. Native Americans used peyote in religious ceremonies since at least the 17th century. Hallucinogenic mushrooms, particularly *Psilocybe* mushrooms, were also used in the religious life of Native Americans. These were called “teonanacatl,” which means “God’s sacred mushrooms” or “God’s flesh.”¹²¹ Interest in the recreational use of cannabis also accelerated during the 19th century after Napoleon’s troops brought the drug back from Egypt, where its use among the lower classes was widespread. In 1843, several French Romantics, including Balzac, Baudelaire, Gautier, and Hugo, formed a hashish club called “Le Club des Hachichins” in the Parisian apartment of a young French painter. Fitz Hugh Ludlow’s *The Hasheesh Eater*, published in 1857, was an early American text espousing the virtues of marijuana.⁹¹

A more recent event that had significant impact on modern-day hallucinogen use was the synthesis of lysergic acid diethylamide (LSD) by Albert Hofmann in 1938.⁶⁶ Working for Sandoz Pharmaceutical Company, Hofmann synthesized LSD while investigating the pharmacologic properties of ergot alkaloids. Subsequent self-experimentation by Hofmann led to the first description of its hallucinogenic effects and stimulated research into the therapeutic use of LSD. Hofmann is also credited with isolating psilocybin as the active ingredient in *Psilocybe mexicana* mushrooms in 1958.¹⁰⁶

TWENTIETH-CENTURY EVENTS

Early Regulatory Initiatives

The development of medical toxicology as a medical subspecialty and the important role of poison control centers began shortly after World War II. Before then, serious attention to the problem of household poisonings in the United States had been limited to a few federal legislative antipoisoning initiatives (Table 1–4). The 1906 Pure Food and Drug Act was the first federal legislation that sought to protect the public from problematic and potentially unsafe drugs and food. The driving force behind this reform was Harvey Wiley, the chief chemist at the Department of Agriculture. Beginning in the 1880s, Wiley investigated the problems of contaminated food. In 1902, he organized the “poison squad,” which consisted of a group of volunteers who did self-experiments with food preservatives.⁴ Revelations from the “poison squad,” as well as the publication of Upton Sinclair’s muckraking novel *The Jungle*¹³⁸ in 1906, exposed unhygienic practices of the meatpacking industry and led to growing support for legislative intervention. Samuel Hopkins Adams’ reports about the patent medicine industry revealed that some drug manufacturers added opiates to soothing syrups for infants and led to the call for reform.¹²⁷ Although the 1906 regulations were mostly concerned with protecting the public from adulterated food, regulations protecting against misbranded patent medications were also included.

TABLE 1–4. Protecting Our Health: Important US Regulatory Initiatives Pertaining to Xenobiotics

<i>Date</i>	<i>Federal Legislation</i>	<i>Intent</i>
1906	Pure Food and Drug Act	Early regulatory initiative. Prohibits interstate commerce of misbranded and adulterated foods and drugs.
1914	Harrison Narcotics Act	First federal law to criminalize the nonmedical use of drugs. Taxed and regulated distribution and sale of narcotics (opium, opium derivatives, and cocaine).
1927	Federal Caustic Poison Act	Mandated labeling of concentrated caustics.
1930	Food and Drug Administration (FDA)	Established successor to the Bureau of Chemistry; promulgation of food and drug regulations.
1937	Marijuana Tax Act	Applied controls to marijuana similar to those applied to narcotics.
1938	Federal Food, Drug, and Cosmetic Act	Required toxicity testing of pharmaceuticals before marketing.
1948	Federal Insecticide, Fungicide, and Rodenticide Act	Provided federal control for pesticide sale, distribution, and use.
1951	Durham-Humphrey Amendment	Restricted many therapeutic drugs to sale by prescription only.
1960	Federal Hazardous Substances Labeling Act	Mandated prominent labeling warnings on hazardous household chemical products.
1962	Kefauver-Harris Drug Amendments	Required drug manufacturers to demonstrate efficacy before marketing.
1963	Clean Air Act	Regulated air emissions by setting maximum pollutant standards.
1966	Child Protection Act	Banned hazardous toys when adequate label warnings could not be written.
1970	Comprehensive Drug Abuse and Control Act	Replaced and updated all previous laws concerning narcotics and other dangerous drugs.
1970	Environmental Protection Agency (EPA)	Established and enforced environmental protection standards.
1970	Occupational Safety and Health Act (OSHA)	Enacted to improve worker and workplace safety. Created National Institute for Occupational Safety and Health (NIOSH) as research institution for OSHA.
1970	Poison Prevention Packaging Act	Mandated child-resistant safety caps on certain pharmaceutical preparations to decrease unintentional childhood poisoning.
1972	Clean Water Act	Regulated discharge of pollutants into US waters.
1972	Consumer Product Safety Act	Established Consumer Product Safety Commission to reduce injuries and deaths from consumer products.

1972	Hazardous Material Transportation Act	Authorized the Department of Transportation to develop, promulgate, and enforce regulations for the safe transportation of hazardous materials.
1973	Drug Enforcement Administration (DEA)	Successor to the Bureau of Narcotics and Dangerous Drugs; charged with enforcing federal drug laws.
1973	Lead-based Paint Poison Prevention Act	Regulated the use of lead in residential paint. Lead in some paints was banned by Congress in 1978.

1974	Safe Drinking Water Act	Set safe standards for water purity.
1976	Resource Conservation and Recovery Act (RCRA)	Authorized EPA to control hazardous waste from the "cradle-to-grave," including the generation, transportation, treatment, storage, and disposal of hazardous waste.
1976	Toxic Substance Control Act	Emphasis on law enforcement. Authorized EPA to track 75,000 industrial chemicals produced or imported into the United States. Required testing of chemicals that pose environmental or human health risk.
1980	Comprehensive Environmental Response Compensation and Liability Act (CERCLA)	Set controls for hazardous waste sites. Established trust fund (Superfund) to provide cleanup for these sites. Agency for Toxic Substances and Disease Registry (ATSDR) created.
1983	Federal Anti-Tampering Act	Response to cyanide laced Tylenol deaths. Outlawed tampering with packaged consumer products.
1986	Controlled Substance Analogue Enforcement Act	Instituted legal controls on analog (designer) drugs with chemical structures similar to controlled substances.
1986	Drug-Free Federal Workplace Program	Executive order mandating drug testing of federal employees in sensitive positions.
1986	Superfund Amendments and Reauthorization Act (SARA)	Amendment to CERCLA. Increased funding for the research and cleanup of hazardous waste (SARA) sites.
1988	Labeling of Hazardous Art Materials Act	Required review of all art materials to determine hazard potential and mandated warning labels for hazardous materials.
1994	Dietary Supplement Health and Education Act	Permitted dietary supplements including many herbal preparations to bypass FDA scrutiny.
1997	FDA Modernization Act	Accelerated FDA reviews, regulated advertising of unapproved uses of approved drugs.
2002	The Public Health Security and Bioterrorism Preparedness and Response Act	Tightened control on biologic agents and toxins; increased safety of the US food and drug supply, and drinking water; and strengthened the Strategic National Stockpile.
2005	Combat Methamphetamine Epidemic Act	Part of the Patriot Act, this legislation restricted nonprescription sale of the methamphetamine precursor drugs ephedrine and pseudoephedrine used in the home production of methamphetamine.
2009	Family Smoking Prevention and Tobacco Control Act	Empowered FDA to set standards for tobacco products.

The Federal Caustic Poison Act of 1927 was the first federal legislation to specifically address household poisoning. As early as 1859, bottles clearly demarcated “poison” were manufactured in response to a rash of unfortunate dispensing errors that occurred when oxalic acid was unintentionally substituted for a similarly appearing Epsom salts solution.²⁸ Before 1927, however, “poison” warning labels were not required on chemical containers, regardless of toxicity or availability. The 1927 Caustic Act was spearheaded by the efforts of Chevalier Jackson, an otolaryngologist, who showed that unintentional exposures to household caustic agents were an increasingly frequent cause of severe oropharyngeal and GI burns. Under this statute, for the first time, alkali- and acid-containing products had to clearly display a “poison” warning label.¹⁴⁶

The most pivotal regulatory initiative the United States before World War II—and perhaps the most significant American toxicologic regulation of the 20th century—was the Federal Food, Drug, and Cosmetic Act of 1938. Although the Food and Drug Administration (FDA) had been established in 1930 and legislation to strengthen the 1906 Pure Food and Drug Act was considered by Congress in 1933, the proposed revisions still had not been passed by 1938. Then the elixir of sulfanilamide tragedy in 1938 ([Chap. 2](#)) claimed the lives of 105 people who had ingested a prescribed liquid preparation of the antibiotic sulfanilamide inappropriately dissolved in diethylene glycol. This event finally provided the catalyst for legislative intervention.^{104,153} Before the elixir disaster, proposed legislation called only for the banning of false and misleading drug labeling and for the outlawing of dangerous drugs without mandatory drug safety testing. After the tragedy, the proposal was strengthened to require assessment of drug safety before marketing, and the legislation was ultimately passed.

The Development of Poison Centers

World War II led to the rapid proliferation of new drugs and chemicals in the marketplace and in the household.³⁹ At the same time, suicide was recognized as a leading cause of death from these xenobiotics.⁹ Both of these factors led the medical community to develop a response to the serious problems of unintentional and intentional poisonings. In Europe during the late 1940s, special toxicology wards were organized in Copenhagen and Budapest,⁵⁹ and a poison information service was begun in the Netherlands ([Table 1–5](#)).¹⁵⁰ A 1952 American Academy of Pediatrics study revealed that more than 50% of childhood “accidents” in the United States were the result of unintentional poisonings.⁶¹ This study led Edward Press to open the first US poison center in Chicago in 1953.¹²² Press believed that it had become extremely difficult for

individual physicians to keep abreast of product information, toxicity, and treatment for the rapidly increasing number of potentially poisonous household products. His initial center was organized as a cooperative effort among the departments of pediatrics at several Chicago medical schools, with the goal of collecting and disseminating product information to inquiring physicians, mainly pediatricians.¹²⁴

TABLE 1–5. Milestones in the Development of Medical Toxicology in the United States

<i>Year</i>	<i>Milestone</i>
1952	American Academy of Pediatrics study shows that 51% of children's "accidents" are the result of the ingestion of potential poisons
1953	First US poison control center opens in Chicago
1957	National Clearinghouse for Poison Control Centers established
1958	American Association of Poison Control Centers (AAPCC) founded
1961	First Poison Prevention Week
1963	Initial call for development of regional Poison Control Centers (PCCs)
1964	Creation of European Association for PCCs
1968	American Academy of Clinical Toxicology (AACT) established
1972	Introduction of microfiche technology to poison information
1974	American Board of Medical Toxicology (ABMT) established
1978	AAPCC introduces standards of regional designation
1983	First examination given for Specialist in Poison Information (SPI)
1985	American Board of Applied Toxicology (ABAT) established
1992	Medical Toxicology recognized by American Board of Medical Specialties (ABMS)
1994	First ABMS examination in Medical Toxicology
2000	Accreditation Council for Graduate Medical Education (ACGME) approval of residency training programs in Medical Toxicology
2000	Poison Control Center Enhancement and Awareness Act
2004	Institute of Medicine (IOM) Report on the future of poison centers is released, calling for a greater integration between public health sector and poison control services

By 1957, 17 poison centers were operating in the United States.³⁹ With the Chicago center serving as a model, these early centers responded to physician callers by providing ingredient and toxicity information about drug and household products and making treatment recommendations. Records were kept of the calls, and preventive strategies were introduced into the community. As more poison centers opened, a second important function, providing information to calls from the general public, became increasingly common. The physician pioneers in poison prevention and poison treatment were predominantly pediatricians who focused on unintentional childhood ingestions.¹²⁹

During these early years in the development of poison centers, each center had to collect its own product information, which was a laborious and often redundant task.³⁸ In an effort to coordinate its operations and to avoid unnecessary duplication, Surgeon General James Goddard responded to the recommendation of the American Public Health Service and established the National Clearinghouse for Poison Control Centers in 1957.¹⁰¹ This organization, placed under the Bureau of Product Safety of the Food and Drug Administration, disseminated 5-inch by 8-inch index cards containing poison information to each center to help standardize poison center information resources. The Clearinghouse also collected and

tabulated poison data from each of the centers.

Between 1953 and 1972, a rapid, uncoordinated proliferation of poison centers occurred in the United States.⁹⁸ In 1962, there were 462 poison centers. By 1970, this number had risen to 590,⁸⁹ and by 1978, there were 661 poison centers in the United States, including 100 centers in the state of Illinois alone.¹³⁵ The nature of calls to centers changed as lay public-generated calls began to outnumber physician-generated calls. Recognizing the public relations value and strong popular support associated with poison centers, some hospitals started poison centers without adequately recognizing or providing for the associated responsibilities. Unfortunately, many of these centers offered no more than a part-time telephone service located in the back of the emergency department or pharmacy staffed by poorly trained personnel.¹³⁵

Despite the “growing pains” of these poison services during this period, many significant achievements were made. A dedicated group of physicians and other health care professionals began devoting an increasing proportion of their time to poison-related matters. In 1958, the American Association of Poison Control Centers (AAPCC) was founded to promote closer cooperation between poison centers, to establish uniform standards, and to develop educational programs for the general public and health care professionals.⁶¹ Annual research meetings were held, and important legislative initiatives were stimulated by the organization’s efforts.¹⁰¹ Examples of such legislation include the Federal Hazardous Substances Labeling Act of 1960, which improved product labeling; the Child Protection Act of 1966, which extended labeling statutes to pesticides and other hazardous substances; and the Poison Prevention Packaging Act of 1970, which mandated safety packaging. In 1961, in an attempt to heighten public awareness of the dangers of unintentional poisoning, the third week of March was designated as the Annual National Poison Prevention Week.

Another organization that would become important, the American Academy of Clinical Toxicology (AACT), was founded in 1968 by a diverse group of toxicologists.³⁴ This group was “interested in applying principles of rational toxicology to patient treatment” and in improving the standards of care on a national basis.¹³² The first modern textbooks of clinical toxicology began to appear in the mid-1950s with the publication of Dreisbach’s *Handbook of Poisoning* (1955)⁴⁵; Gleason, Gosselin, and Hodge’s *Clinical Toxicology of Commercial Products* (1957)⁵⁷; and Arena’s *Poisoning* (1963).¹⁰ Major advancements in the storage and retrieval of poison information were also instituted during these years. Information as noted above on consumer products initially appeared on index cards distributed regularly to poison centers by the National Clearinghouse, and by 1978, more than 16,000 individual product cards had been issued.¹³⁵ The introduction of microfiche technology in 1972 enabled the storage of much larger amounts of data in much smaller spaces at the individual poison centers. Toxifile and POISINDEX, two large drug and poison databases using microfiche technology, were introduced and gradually replaced the much more limited index card system.¹³⁵ During the 1980s, POISINDEX, which had become the standard database, was made more accessible by using CD-ROM technology. Sophisticated information about the most obscure xenobiotics was now instantaneously available by computer at every poison center.

In 1978, the poison center movement entered an important new stage in its development when the AAPCC introduced standards for regional poison center designation.⁹⁸ By defining strict criteria, the AAPCC sought to upgrade poison center operations significantly and to offer a national standard of service. These criteria included using poison specialists dedicated exclusively to operating the poison center 24 hours per day and serving a catchment area of between 1 and 10 million people. Not surprisingly, this professionalization of the poison center movement led to a rapid consolidation of services. An AAPCC credentialing examination for poison information specialists was inaugurated in 1983 to help ensure the quality and standards of poison center staff.⁷

In 2000, the Poison Control Center Enhancement and Awareness Act was passed by Congress and signed into law by President Clinton. For the first time, federal funding became available to provide assistance for poison prevention and to stabilize the funding of regional poison centers. This federal assistance permitted the establishment of a single nationwide toll-free phone number (800-222-1222) to access poison centers. At present, 57 centers contribute data to a National Poison Database System (NPDS) which from 1983 to 2006 was known as Toxic Exposure Surveillance System (TESS). Recently, the Centers for Disease Control and Prevention (CDC) has been collaborating with the AAPCC to conduct real-time surveillance of this data to help facilitate the early detection of chemical exposures of public health importance.¹⁵⁶

A poison center movement has also grown and evolved in Europe over the past 35 years, but unlike the movement in the United States, it focused from the beginning on establishing strong centralized toxicology treatment centers. In the late 1950s, Gaultier in Paris developed an inpatient unit dedicated to the care of poisoned patients.⁵⁹ In the United Kingdom, the National Poison Information Service developed at Guys Hospital in 1963 under Roy Goulding. Henry Matthew initiated a regional poisoning treatment center in Edinburgh about the same time.¹²⁴ In 1964, the European Association for Poison Control Centers was formed in Tours, France.⁵⁹

The Rise of Environmental Toxicology and Further Regulatory Protection from Toxic Substances

The rise of the environmental movement during the 1960s can be traced, in part, to the publication of Rachel Carson’s

Silent Spring in 1962, which revealed the perils of an increasingly toxic environment.²⁹ The movement also benefited from the new awareness by those involved with the poison movement of the growing menace of xenobiotics in the home environment.²⁶ Battery casing fume poisoning, resulting from the burning of discarded lead battery cases, and acrodynia, resulting from exposure to a variety of mercury-containing products,⁴¹ both demonstrated that young children are particularly vulnerable to low-dose exposures from certain xenobiotics. Worries about the persistence of pesticides in the ecosystem and the increasing number of chemicals introduced into the environment added to concerns of the environment as a potential source of illness, heralding a drive for additional regulatory protection.

Starting with the Clean Air Act in 1963, laws were passed to help reduce the toxic burden on our environment (Table 1–4). The establishment of the Environmental Protection Agency (EPA) in 1970 spearheaded this attempt at protecting our environment, and during the next 10 years, numerous protective regulations were introduced. Among the most important initiatives was the Occupational Safety and Health Act of 1970, which established the Occupational Safety and Health Administration (OSHA). This act mandates that employers provide safe work conditions for their employees. Specific exposure limits to toxic chemicals in the workplace were promulgated. The Consumer Product Safety Commission was created in 1972 to protect the public from consumer products that posed an unreasonable risk of illness or injury. Cancer-producing substances, such as asbestos, benzene, and vinyl chloride, were banned from consumer products as a result of these new regulations. Toxic waste disasters such as those at Love Canal, New York, and Times Beach, Missouri, led to the passing of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, also known as the Superfund) in 1980. This fund is designed to help pay for cleanup of hazardous substance releases posing a potential threat to public health. The Superfund legislation also led to the creation of the Agency for Toxic Substances and Disease Registry (ATSDR), a federal public health agency charged with determining the nature and extent of health problems at Superfund sites and advising the US EPA and state health and environmental agencies on the need for cleanup and other actions to protect the public's health. In 2003, the ATSDR became part of the National Center for Environmental Health of the CDC.

Medical Toxicology Comes of Age

Over the past 25 years, the primary specialties of medical toxicologists have changed. The development of emergency medicine and preventive medicine as medical specialties led to the training of more physicians with a dedicated interest in toxicology. By the early 1990s, emergency physicians accounted for more than half the number of practicing medical toxicologists. The increased diversity of medical toxicologists with primary training in emergency medicine, pediatrics, preventive medicine, or internal medicine has helped broaden the goals of poison centers and medical toxicologists beyond the treatment of acute unintentional childhood ingestions. The scope of medical toxicology now includes a much wider array of toxic exposures, including acute and chronic, adult and pediatric, unintentional and intentional, and occupational and environmental exposures.

The development of medical toxicology as a medical subspecialty began in 1974, when the AACT created the American Board of Medical Toxicology (ABMT) to recognize physician practitioners of medical toxicology.⁵ From 1974 to 1992, 209 physicians obtained board certification, and formal subspecialty recognition of medical toxicology by the American Board of Medical Specialties (ABMS) was granted in 1992. In that year, a conjoint subboard with representatives from the American Board of Emergency Medicine, American Board of Pediatrics, and American Board of Preventive Medicine was established, and the first ABMS-sanctioned examination in medical toxicology was offered in 1994. By 2013, a total of more than 450 physicians were board certified in medical toxicology. The American College of Medical Toxicology (ACMT) was founded in 1994 as a physician-based organization designed to advance clinical, educational, and research goals in medical toxicology. In 1999, the Accreditation Council of Graduate Medical Education (ACGME) in the United States formally recognized postgraduate education in medical toxicology, and by 2013, 29 fellowship training programs had been approved.

During the 1990s in the United States, some medical toxicologists began to work on establishing regional toxicology treatment centers. Adapting the European model, such toxicology treatment centers could serve as referral centers for patients requiring advanced toxicologic evaluation and treatment. Goals of such inpatient regional centers included enhancing care of poisoned patients, strengthening toxicology training, and facilitating research. The evaluation of the clinical efficacy and fiscal viability of such programs is ongoing.

The professional maturation of advanced practice pharmacists and nurses with primary interests in clinical toxicology has also taken place over the past 2 decades. In 1985, the AACT established the American Board of Applied Toxicology (ABAT) to administer certifying examinations for nonphysician practitioners of medical toxicology who meet their rigorous standards.⁴ By 2013, more than 85 toxicologists, who mostly held either a PharmD or a PhD in pharmacology or toxicology, were certified by this board.

Recent Poisonings and Poisoners

Although accounting for just a tiny fraction of all homicidal deaths (0.16% in the United States), notorious lethal poisonings

continued throughout the 20th century (Table 1–3).¹

In England, Graham Frederick Young developed a macabre fascination with poisons.³⁰ In 1971, at age 14 years, he killed his stepmother and other family members with arsenic and antimony. Sent away to a psychiatric hospital, he was released at age 24 years, when he was no longer considered to be a threat to society. Within months of his release, he again engaged in lethal poisonings, killing several of his coworkers with thallium. Ultimately, he died in prison in 1990.

In 1978, Georgi Markov, a Bulgarian defector living in London, developed multisystem failure and died 4 days after having been stabbed by an umbrella carried by an unknown assailant. The postmortem examination revealed a pinhead-sized metal sphere embedded in his thigh where he had been stabbed. Investigators hypothesized that this sphere had most likely carried a lethal dose of ricin into the victim.³⁷ This theory was greatly supported when ricin was isolated from the pellet of a second victim who was stabbed under similar circumstances.

In 1982, deliberate tampering of nonprescription Tylenol preparations with potassium cyanide caused seven deaths in Chicago.⁴⁶ Because of this tragedy, packaging of nonprescription medications was changed to decrease the possibility of future product tampering.¹⁰⁷ The perpetrator(s) were never apprehended, and other deaths from nonprescription product tampering were reported in 1991.³¹

In 1998, Judias Buenoano, known as the “black widow,” was executed for murdering her husband with arsenic in 1971 to collect insurance money. She was the first woman executed in Florida in 150 years. The fatal poisoning had remained undetected until 1983, when Buenoano was accused of trying to murder her fiancé with arsenic and by car bombing. Exhumation of the husband’s body, 12 years after he died, revealed substantial amounts of arsenic in the remains.²

Health care providers have been implicated in several poisoning homicides as well. An epidemic of mysterious cardiopulmonary arrests at the Ann Arbor Veterans Administration Hospital in Michigan in July and August 1975 was attributed to the homicidal use of pancuronium by two nurses.¹⁴⁵ Intentional digoxin poisoning by hospital personnel may have explained some of the increased number of deaths on a cardiology ward of a Toronto pediatric hospital in 1981, but the cause of the high mortality rate remained unclear.²³ In 2000, an English general practitioner Harold Shipman was convicted of murdering 15 women patients with heroin and may have murdered as many as 297 patients during his 24-year career. These recent revelations prompted calls for strengthening the death certification process, improving preservation of case records, and developing better procedures to monitor controlled drugs.⁶⁹

Also in 2000, Michael Swango, an American physician, pleaded guilty to the charge of poisoning a number of patients under his care during his residency training. Succinylcholine, potassium chloride, and arsenic were used to kill his patients.¹⁴³ Attention to more careful physician credentialing and to maintenance of a national physician database arose from this case because the poisonings occurred at multiple hospitals across the country. Continuing concerns about health care providers acting as serial killers is highlighted by a recent case in New Jersey in which a nurse, Charles Cullen, was found responsible for killing patients with digoxin.¹⁷

By the end of the 20th century, 24 centuries after Socrates was executed by poison hemlock, the means of implementing capital punishment had come full circle. Government-sanctioned execution in the United States again favored the use of a “state” poison—this time, the combination of sodium thiopental, pancuronium, and potassium chloride.

The use of a poison to achieve political ends has again resurfaced in several incidents from the former Soviet Union. In December 2004, it was announced that the Ukrainian presidential candidate Viktor Yushchenko was poisoned with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a potent dioxin.¹⁴¹ The dramatic development of chloracne over the face of this public person during the previous several months suggested dioxin as a possibly culprit. Given the paucity of reports of acute dioxin poisoning, however, it was not until laboratory tests confirmed that Yushenko’s dioxin concentrations were more than 6000 times normal that this diagnosis was confirmed. In another case, a former KGB agent and Russian dissident Alexander Litvinenko was murdered with polonium-210. Initially thought to be a possible case of heavy metal poisoning, Litvinenko developed acute radiation syndrome manifested by acute GI symptoms followed by alopecia and pancytopenia before he died.¹⁰³

Other Developments

Medical Errors. Beginning in the 1980s, several highly publicized medication errors received considerable public attention and provided a stimulus for the initiation of change in policies and systems. Ironically, all of the cases occurred at nationally preeminent university teaching hospitals. In 1984, 18 year-old Libby Zion died from severe hyperthermia soon after hospital admission. Although the cause of her death was likely multifactorial, drug–drug interactions and the failure to recognize and appropriately treat her agitated delirium also contributed to her death.¹³ State and national guidelines for closer house staff supervision, improved working conditions, and a heightened awareness of consequential drug–drug interactions resulted from the medical, legislative, and legal issues of this case. In 1994, a prominent health journalist for the Boston Globe, Betsy Lehman, was the unfortunate victim of another preventable dosing error when she inadvertently received four times the dose of the chemotherapeutic cyclophosphamide as part of an experimental protocol.⁸⁰ Despite treatment at a world-renowned cancer center, multiple physicians, nurses, and pharmacists failed to notice this erroneous

medication order. An overhaul of the medication-ordering system was implemented at that institution after this tragic event.

Another highly publicized death occurred in 1999 when 18-year-old Jesse Gelsinger died after enrolling in an experimental gene-therapy study. Gelsinger, who had ornithine transcarbamylase deficiency, died from multiorgan failure 4 days after receiving, by hepatic infusion, the first dose of an engineered adenovirus containing the normal gene. Although this unexpected death was not the direct result of a dosing or drug–drug interaction error, the FDA review concluded that major research violations had occurred, including failure to report adverse effects with this therapy in animals and earlier clinical trials and to properly obtain informed consent.¹³⁷ In 2001, Ellen Roche, a 24 year-old healthy volunteer in an asthma study at John Hopkins University, developed a progressive pulmonary illness and died one month after receiving 1 g of hexamethonium by inhalation as part of the study protocol.¹⁴² Hexamethonium, a ganglionic blocker, was once used to treat hypertension but was removed from the market in 1972. The investigators were cited for failing to indicate on the consent form that hexamethonium was experimental and not FDA approved. Calls for additional safeguards to protect patients in research studies resulted from these cases.

In late 1999, the problems of medical errors finally received the high visibility and deserved attention in the United States with the publication and subsequent reaction to an Institute of Medicine (IOM) report suggesting that 44,000 to 98,000 fatalities each year were the result of medical errors.⁸¹ Many of these errors were attributed to preventable medication errors. The IOM report focused on its findings that errors usually resulted from system faults and not solely from the carelessness of individuals.

Toxicology in the Twenty-First Century

As new challenges and opportunities arise in the 21st century, two new toxicologic disciplines have emerged: toxicogenomics and nanotoxicology.^{40,44,113} These nascent fields constitute the toxicologic responses to rapid advances in genetics and material sciences. Toxicogenomics combines toxicology with genomics dealing with how genes and proteins respond to toxic substances. The study of toxicogenomics attempts to better decipher the molecular events underlying toxicologic mechanisms, develop predictors of toxicity through the establishment of better molecular biomarkers, and better understand genetic susceptibilities that pertain to toxic substances such as unanticipated idiosyncratic drug reactions.

Nanotoxicology refers to the toxicology of engineered tiny particles, usually smaller than 100 nm. Given the extremely small size of nanoparticles, typical barriers at portals of entry may not prevent absorption or may themselves be adversely affected by the nanoparticles. Ongoing studies focus on the translocation of these particles to sensitive target sites such as the central nervous system or bone marrow (Chap. 129).¹¹³

SUMMARY

- Since the dawn of recorded history, toxicology has impacted greatly on human events and our ecosystem.
- Over the millennia, although the important poisons of the day have changed to some degree, toxic substances continue to challenge our safety.
- The era of poisoners for hire may have long ago reached its pinnacle, but problems with drug abuse, intentional self-poisoning, and exposure to environmental chemicals continue to challenge us.
- Knowledge acquired by one generation is often forgotten or discarded inappropriately by the next generation, leading to a cyclical historic course.

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2 TOXICOLOGIC MISFORTUNES AND CATASTROPHES IN HISTORY

Paul M. Wax

Throughout history, mass poisonings have caused suffering and misfortune. From the ergot epidemics of the Middle Ages to contemporary industrial disasters, these mass events have had great political, economic, social, and environmental ramifications. Particularly within the past 100 years, as the number of toxins and potential toxins has risen dramatically, toxic disasters have become an increasingly common event. The sites of some of these events—Bhopal (India), Chernobyl (Ukraine), Jonestown (Guyana), Love Canal (New York), Minamata Bay (Japan), Seveso (Italy), West Bengal (India)—have come to symbolize our increasing potential for toxicity in our environment. Globalization has led to the proliferation of toxic chemicals throughout the world and their rapid distribution. Many chemical factories that store large amounts of potentially lethal chemicals are not secure. Given the increasing attention to terrorism preparedness, an appreciation of chemicals as agents of opportunity for terrorists has suddenly assumed great importance. This chapter provides an overview of some of the most consequential and historically important toxin-associated mass poisonings that represent human and environmental disasters.

GAS DISASTERS

Inhalation of toxic gases and oral ingestions resulting in food poisoning tend to subject the greatest number of people to adverse consequences of a toxic exposure. Toxic gas exposures may be the result of a natural disaster (volcanic eruption), industrial mishap (fire, chemical release), chemical warfare, or an intentional homicidal or genocidal endeavor (concentration camp gas chamber). Depending on the toxin, the clinical presentation may be acute, with a rapid onset of toxicity (cyanide), or subacute or chronic, with a gradual onset of toxicity (air pollution).

One of the earliest recorded toxic gas disasters resulted from the eruption of Mount Vesuvius near Pompeii, Italy, in 79 A.D. (Table 2–1). Poisonous gases generated from the volcanic activity reportedly killed thousands of people.³⁴ A much more recent natural disaster occurred in 1986 in Cameroon when excessive amounts of carbon dioxide spontaneously erupted from Lake Nyos, a volcanic crater lake.¹⁹ Approximately 1700 human and countless animal fatalities resulted from exposure to this asphyxiant.

TABLE 2–1. Gas Disasters

<i>Xenobiotic</i>	<i>Location</i>	<i>Date</i>	<i>Significance</i>
Poisonous gas	Pompeii, Italy	79 A.D.	>2000 deaths from eruption of Mt. Vesuvius
Smog (SO ₂)	London, England	1873	268 deaths from bronchitis
NO ₂ , CO, CN	Cleveland Clinic, Cleveland, OH	1929	Fire in radiology department; 125 deaths
Smog (SO ₂)	Meuse Valley, Belgium	1930	64 deaths
CO, CN	Cocoanut Grove Night Club, Boston	1942	498 deaths from fire
CO	Salerno, Italy	1944	>500 deaths on a train stalled in a tunnel
Smog (SO ₂)	Donora, PA	1948	20 deaths; thousands ill
Smog (SO ₂)	London, England	1952	4000 deaths attributed to the fog and smog
Dioxin	Seveso, Italy	1976	Unintentional industrial release of dioxin into environment; chloracne
Methyl isocyanate	Bhopal, India	1984	>2000 deaths; 200,000 injuries
Carbon dioxide	Cameroon, Africa	1986	>1700 deaths from release of gas from Lake Nyos
Hydrofluoric acid	Texas City, TX	1987	Atmospheric release; 94 hospitalized
CO, CN	Happy Land Social Club, Bronx, NY	1990	87 deaths in fire from toxic smoke
Hydrogen sulfide	Xiaoying, China	2003	243 deaths and 10,000 became ill from gas poisoning after a gas well exploded
CO, CN	West Warwick, RI	2003	98 deaths in fire

A toxic gas leak at the Union Carbide pesticide plant in Bhopal, India, in 1984 resulted in one of the greatest civilian toxic disasters in modern history.¹²⁹ An unintended exothermic reaction at this carbaryl-producing plant caused the release of more than 24,000 kg of methyl isocyanate. This gas was quickly dispersed through the air over the densely populated area surrounding the factory where many of the workers lived, resulting in at least 2500 deaths and 200,000 injuries.⁸⁰ The initial response to this disaster was greatly limited by a lack of pertinent information about the toxicity of this chemical as well as the poverty of the residents. A follow-up study 10 years later showed persistence of small airway obstructive disease among survivors as well as chronic eye problems.³⁰ Calls for improvement in disaster preparedness and strengthened “right-to-know” laws regarding potential toxic exposures resulted from this tragedy.^{48,129}

The release into the atmosphere of 26 tons of hydrofluoric acid at a petrochemical plant in Texas in October 1987 resulted in 939 people seeking medical attention at nearby hospitals. Ninety-four people were hospitalized, but there were no deaths.¹³⁷

More than any other single toxin, carbon monoxide has been involved in the largest number of toxic disasters. Catastrophic fires, such as the Cocoanut Grove Nightclub fire in 1943, have caused hundreds of deaths at a time, many of them from carbon monoxide poisoning.³⁶ A 1990 fire deliberately started at the Happy Land Social Club in the Bronx, New York, claimed 87 victims, including a large number of nonburn deaths,⁷² and the 2003 fire at the Station nightclub in West Warwick, Rhode Island, killed 98 people.¹¹⁵ Carbon monoxide poisoning was a major determinant in many of these deaths, although hydrogen cyanide gas and simple asphyxiation may have also contributed to the overall mortality.

Another notable toxic gas disaster involving a fire occurred at the Cleveland Clinic in Cleveland, Ohio, in 1929, where a fire in the radiology department resulted in 125 deaths.³³ The burning of nitrocellulose radiographs produced nitrogen

dioxide, cyanide, and carbon monoxide gases held responsible for many of the fatalities. In 2003, at least 243 people died and 10,000 became ill after a drilling well exploded in Gaogiao, China, releasing hydrogen sulfide and natural gas into the air.¹⁴² A toxic gas cloud covered 25 square kilometers. Ninety percent of the villagers who lived in the village adjoining the gas well died.

The release of a dioxin-containing chemical cloud into the atmosphere from an explosion at a hexachlorophene production factory in Seveso, Italy, in 1976 resulted in one of the most serious exposures to dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin).⁴⁷ The lethality of this xenobiotic in animals has caused considerable concern for acute and latent injury from human exposure. Despite this apprehension, chloracne was the only significant clinical finding related to the dioxin exposure at 5-year follow-up.⁹

Air pollution is another source of toxic gases that causes significant disease and death. Complaints about smoky air date back to at least 1272, when King Edward I banned the burning of sea coal.¹²⁷ By the 19th century, the era of rapid industrialization in England, winter “fogs” became increasingly problematic. An 1873 London fog was responsible for 268 deaths from bronchitis. Excessive smog in the Meuse Valley of Belgium in 1930 and in Donora, Pennsylvania, in 1948 was also blamed for excess morbidity and mortality. In 1952, another dense sulfur dioxide–laden smog in London was responsible for 4000 deaths.⁶⁹ Both the initiation of long-overdue air pollution reform in England and Parliament’s passing of the 1956 Clean Air Act resulted from this latter “fog.”

WARFARE AND TERRORISM

Exposure to xenobiotics with the deliberate intent to inflict harm claimed an extraordinary number of victims during the 20th century (Table 2–2). During World War I, chlorine, phosgene, and the liquid vesicant mustard were used as battlefield weapons, with mustard causing approximately 80% of the chemical casualties.¹¹⁷ Reportedly, 100,000 deaths and 1.2 million casualties were attributable to these chemical attacks.³⁴ The toxic exposures resulted in severe airway irritation, acute respiratory distress syndrome, hemorrhagic pneumonitis, skin blistering, and ocular damage. Chemical weapons were used again in the 1980s during the war between Iran and Iraq.

TABLE 2–2. Warfare and Terrorism Disasters

Toxin	Location	Date	Significance
Chlorine, mustard gas, phosgene	Ypres, Belgium	1915–1918	100,000 dead and 1.2 million casualties from chemicals during World War I
CN, CO	Europe	1939–1945	Millions murdered by Zyklon-B (HCN) gas
Agent Orange	Vietnam	1960s	Contains dioxin; excess skin cancer
Mustard gas	Iraq–Iran	1982	New cycle of war gas casualties
Possible toxin	Persian Gulf	1991	Gulf War syndrome
Sarin	Matsumoto, Japan	1994	First terrorist attack in Japan using sarin
Sarin	Tokyo, Japan	1995	Subway exposure; 5510 people sought medical attention
Dust and other particulates	New York, NY	2001	World Trade Center collapse from terrorist air strike
Fentanyl derivative	Moscow, Russia	2002	Used by the Russian military to subdue terrorists in Moscow theater
Ricin	Washington, DC	2004	Detected in Dirksen Senate Office Building; no illness reported
Chlorine	Iraq	2007	Used against US troops and Iraqi civilians

The Nazis used poisonous gases during World War II to commit mass murder. Initially, the Nazis used carbon monoxide to kill. To expedite the killing process, Nazi scientists developed Zyklon-B gas (hydrogen cyanide gas). As many as 10,000 people per day were killed by the rapidly acting cyanide, and millions of deaths were attributable to the use of these gases.

Agent Orange was widely used as a defoliant during the Vietnam War. This herbicide consisted of a mixture of 2,4,5-trichlorophenoxy-acetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D), as well as small amounts of a contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), better known as dioxin. Over the years, a large number of adverse health effects have been attributed to Agent Orange exposure. A 2002 Institute of Medicine study concluded that among Vietnam veterans, there is sufficient evidence to demonstrate an association between this herbicide exposure and

chronic lymphocytic leukemia, soft tissue sarcomas, non-Hodgkin lymphomas, Hodgkin disease, and chloracne.⁵³

Mass exposure to the very potent organic phosphorus compound sarin occurred in March 1995 when terrorists released this chemical warfare agent in three separate Tokyo subway lines.⁹⁶ Eleven people were killed, and 5510 people sought emergency medical evaluation at more than 200 hospitals and clinics in the area.¹¹⁸ This calamity introduced the spectra of terrorism to the modern emergency medical services system, resulting in a greater emphasis on hospital preparedness, including planning for the psychological consequences of such events. Sarin exposure also resulted in several deaths and hundreds of casualties in Matsumoto, Japan, in June 1994.^{85,93}

After the terrorist attacks on New York City on September 11, 2001, that resulted in the collapse of World Trade Center, persistent cough and increased bronchial responsiveness were noted among 8% of New York City Fire Department workers who were exposed to large amounts of dust and other particulates during the clean-up.^{102,103} This condition, known as World Trade Center cough syndrome, is characterized by upper airway (chronic rhinosinusitis) and lower airway findings (bronchitis, asthma, or both) as well as, at times, gastroesophageal reflux dysfunction. The risk of development of hyperreactivity and reactive airways dysfunction was clearly associated with the intensity of exposure.¹⁶ A World Trade Center health registry has been established to investigate if those exposed workers may be at increased risk for development of cancer and other chronic diseases.^{68,90} Registry data suggest that some workers appear to be at an increased risk of developing sarcoidosis.⁵⁵

The Russian military used a mysterious “gas” to incapacitate Chechen rebels at a Moscow theatre in 2002, resulting in the deaths of more than 120 hostages. Although never publically indentified, the gas may have consisted of a highly potent aerosolized fentanyl derivative such as carfentanil and an inhalational anesthetic such as halothane. Better preparation of the rescuers with suitable amounts of naloxone may have helped prevent many of these seemingly unanticipated casualties.¹³¹

Ricin was found in several government buildings, including a mail- processing plant in Greenville, South Carolina, in 2003 and the Dirksen Senate Office Building in Washington, DC, in 2004. Although no cases of ricin-associated illness ensued, increased concern was generated because the method of delivery was thought to be the mail, and irradiation procedures designed to kill microbials such as anthrax would not inactivate chemical toxins such as ricin.^{14,111}

FOOD DISASTERS

Unintentional contamination of food and drink has led to numerous toxic disasters (Table 2–3). Ergot, produced by the fungus *Claviceps purpurea*, caused epidemic ergotism as the result of eating breads and cereals made from rye contaminated by *C. purpurea*. In some epidemics, convulsive manifestations predominated, and in others, gangrenous manifestations predominated.⁸² Ergot-induced severe vasospasm was thought to be responsible for both presentations.⁸¹ In 994 A.D., 40,000 people died in Aquitania, France, in one such epidemic.⁶⁶ Convulsive ergotism was initially described as a “fire which twisted the people,” and the term “St. Anthony’s fire” (*ignis sacer*) was used to refer to the excruciating burning pain experienced in the extremities that is an early manifestation of gangrenous ergotism. The events surrounding the Salem, Massachusetts, witchcraft trials have also been attributed to the ingestion of contaminated rye. The bizarre neuropsychiatric manifestations exhibited by some of the individuals associated with this event may have been caused by the hallucinogenic properties of ergotamine, a lysergic acid diethylamide (LSD) precursor.^{22,78}

TABLE 2–3. Food Disasters

<i>Toxin/Contaminant</i>	<i>Location</i>	<i>Date</i>	<i>Significance</i>
Ergot	Aquitania, France	994 A.D.	40,000 died in the epidemic
Ergot	Salem, MA	1692	Neuropsychiatric symptoms may be attributable to ergot
Lead	Devonshire, England	1700s	Colic from cider contaminated during production
Arsenious acid	France	1828	40,000 cases of polyneuropathy from contaminated wine and bread
Lead	Canada	1846	134 men died during the Franklin expedition, possibly because of contamination of food stored in lead cans
Arsenic	Staffordshire, England	1900	Contaminated sugar used in beer production
Cadmium	Japan	1939–1954	Itai-itai ("ouch-ouch") disease
Hexachlorobenzene	Turkey	1956	4000 cases of porphyria cutanea tarda
Methyl mercury	Minamata Bay, Japan	1950s	Consumption of organic mercury poisoned fish
Triorthocresyl phosphate	Meknes, Morocco	1959	Cooking oil adulterated with turbojet lubricant
Cobalt	Quebec City, Canada and others	1960s	Beer cardiomyopathy
Methylenedianiline	Epping, England	1965	Jaundice
Polychlorinated biphenyls	Japan	1968	Yusho ("rice oil disease")
Methyl mercury	Iraq	1971	>400 deaths from contaminated grain
Polybrominated biphenyls	Michigan	1973	92% of state contaminated through food chain
Polychlorinated biphenyls	Taiwan	1979	Yi-Cheng ("oil disease")
Rapeseed oil (denatured)	Spain	1981	Toxic oil syndrome affected 19,000 people
Arsenic	Buenos Aires	1987	Malicious contamination of meat; 61 people underwent chelation
Arsenic	Bangladesh and West Bengal, India	1990s–present	Contaminated ground water; millions exposed; 100,000s with symptoms; greatest mass poisoning in history
Tetramine	China	2002	Snacks deliberately contaminated, resulting in 42 deaths and 300 people with symptoms
Arsenic	Maine	2003	Intentional contamination of coffee; one death and 16 cases of illness
Nicotine	Michigan	2003	Deliberate contamination of ground beef; 92 people became ill
Melamine	China	2008	50,000 hospitalized from tainted infant formula

During the last half of the 20th century, unintentional mass poisoning from food and drink contaminated with toxic chemicals became all too common. One of the more unusual poisonings occurred in Turkey in 1956 when wheat seed intended for planting was treated with the fungicide hexachlorobenzene and then inadvertently used for human consumption. Approximately 4000 cases of porphyria cutanea tarda were attributed to the ingestion of this toxic wheat seed.¹¹²

Another example of chemical food poisoning took place in Epping, England, in 1965. In this incident, a sack of flour became contaminated with methylenedianiline when the chemical unintentionally spilled onto the flour during transport to a bakery. Subsequent ingestion of bread baked with the contaminated flour produced hepatitis in 84 people. This outbreak of toxic hepatitis became known as Epping jaundice.⁵⁹

The manufacture of polybrominated biphenyls (PBBs) in a factory that also produced food supplements for livestock resulted in the unintentional contamination of a large amount of livestock feed in Michigan in 1973.²³ Significant morbidity and mortality among the livestock population resulted, and increased human tissue concentrations of PBBs were reported,¹³⁸ although human toxicity seemed limited to vague constitutional symptoms and abnormal liver function test results.

The chemical contamination of rice oil in Japan in 1968 caused a syndrome called Yusho ("rice oil disease"). This occurred when heat-exchange fluid containing polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) leaked from a heating pipe into the rice oil. More than 1600 people developed chloracne, hyperpigmentation, an

increased incidence of liver cancer, or adverse reproductive effects. In 1979 in Taiwan, 2000 people developed similar clinical manifestations after ingesting another batch of PCB-contaminated rice oil. This latter epidemic was referred to as Yu-Cheng (“oil disease”).⁵⁴

In another oil contamination epidemic, consumption of illegally marketed cooking oil in Spain in 1981 was responsible for a mysterious poisoning epidemic that affected more than 19,000 people and resulted in at least 340 deaths. Exposed patients developed a multisystem disorder referred to as toxic oil syndrome (or toxic epidemic syndrome), characterized by pneumonitis, eosinophilia, pulmonary hypertension, scleroderma-like features, and neuromuscular changes. Although this syndrome was associated with the consumption of rapeseed oil denatured with 2% aniline, the exact etiology was not definitively identified at the time. Subsequent investigations suggest that the fatty acid oleyl anilide may have been the putative xenobiotic.^{56,57,100}

In 1999, an outbreak of health complaints related to consuming Coca Cola occurred in Belgium, when 943 people, mostly children, complained of gastrointestinal (GI) symptoms, malaise, headaches, and palpitations after drinking Coca Cola.⁹⁴ Many of those affected complained of an “off taste” or bad odor to the soft drink. In some of the Coca Cola bottles, the carbon dioxide was contaminated with small amounts of carbonyl sulfide, which hydrolyzes to hydrogen sulfide, and may have been responsible for odor-triggered reactions. Mass psychogenic illness may have contributed to the large number of medical complaints because the concentrations of the carbonyl sulfide and hydrogen sulfide were very low and unlikely to cause systemic toxicity.³⁸

Epidemics of heavy metal poisoning from contaminated food and drink have also occurred throughout history. Epidemic lead poisoning is associated with many different vehicles of transmission, including leaden bowls, kettles, and pipes. A famous 18th-century epidemic was known as the Devonshire colic. Although the exact etiology of this disorder was unknown for many years, later evidence suggested that the ingestion of lead-contaminated cider was responsible.¹³⁰

Intentional chemical contamination of food may also occur. Multiple cases of metal poisoning occurred in Buenos Aires in 1987, when vandals broke into a butcher’s shop and poured an unknown amount of a 45% sodium arsenite solution over 200 kg of partly minced meat.¹⁰⁸ The contaminated meat was purchased by 718 people. Of 307 meat purchasers who submitted to urine sampling, 49 had urine arsenic concentrations of 76 to 500 µg/dL, and 12 had urine arsenic concentrations above 500 µg/dL (normal urine arsenic is <50–100 µg/dL).

Cases of deliberate mass poisoning have heightened concerns about food safety and security. In China in 2002, a jealous food vendor adulterated fried dough sticks, sesame cakes, and rice prepared in a rival’s snack bar by surreptitiously putting a large amount of tetramine (tetramethylene disulfotetramine) into the raw pastry material. More than 300 people who consumed these adulterated snacks became ill, and 42 died.²⁹ In Maine in 2003, a disillusioned parishioner contaminated the communal coffee pot at a church bake sale with arsenic. One victim died within 12 hours, and five others developed hypotension.¹³⁹ In 2003 in Michigan, 92 people became ill after ingesting contaminated ground beef deliberately contaminated with a nicotine pesticide by a supermarket employee.⁶

At the end of the 20th century and beginning the 21st century, what may be the greatest mass poisoning in history is occurring in Bangladesh and India’s West Bengal State.^{32,87,104,121} (See Chap. 89.) In Bangladesh alone, 60 million people are routinely drinking arsenic-contaminated ground water and at least 220,000 inhabitants of India’s West Bengal have been diagnosed with arsenic poisoning.⁸⁶ Symptoms reported include melanosis, depigmentation, hyperkeratosis, hepatomegaly, splenomegaly, squamous cell carcinoma, intraepidermal carcinoma, and gangrene.³² In a country long plagued by dysentery, attempts to purify the water supply led to the drilling of millions of wells into the superficial water table. Unknown to the engineers, this water was naturally contaminated with arsenic, creating several thousand tube wells with extremely high concentrations of arsenic—up to 40 times the acceptable concentration. Although toxicity from arsenic-contaminated groundwater was previously reported from other areas of the world, including Argentina, China, Mexico, Taiwan (black foot disease), and Thailand, the number of people at risk in Bangladesh and West Bengal is by far the largest.

Methyl mercury is responsible for several poisoning epidemics in the past half century. During the 1950s, a Japanese chemical factory that manufactured vinyl chloride and acetaldehyde routinely discharged mercury into Minamata Bay, resulting in contamination of the aquatic food chain. An epidemic of methyl mercury poisoning ensued as the local people ate the poisoned fish.^{101,126} Chronic brain damage, tunnel vision, deafness, and severe congenital defects were associated with this mass poisoning.¹⁰¹ Another mass epidemic of methyl mercury poisoning occurred in Iraq in 1971, when the local population consumed homemade bread prepared from wheat seed treated with a methyl mercury fungicide.¹⁵ Six thousand hospital admissions and more than 400 deaths were associated with this mass poisoning. As was the case of the hexachlorobenzene exposure in Turkey 15 years previously, the treated grain, intended for use as seed, was instead used as food.

From 1939 to 1954, contamination of the local water supply with the wastewater runoff from a zinc–lead–cadmium mine in Japan was believed responsible for causing Itai-Itai (“ouch-ouch”) disease, an unusual chronic syndrome manifested by extreme bone pain and osteomalacia. The local water was used for drinking and irrigation of the rice fields. Approximately 200 people who lived along the banks of the Jintsu River developed these peculiar symptoms, which were

thought most likely to be caused by the cadmium.²

More than 50,000 infants were hospitalized in China in 2008 from the ill effects of melamine-contaminated powdered infant formulas.⁵² Melamine (1,3,5-triazine–2,4,6-triamine) is a component in many adhesives, glues, plastics, and laminated products (eg, plywood, cleaners, cement, cleansers, and fire-retardant paint). More than 20 Chinese companies produced the tainted formula. Analysis of these formulas found melamine concentrations as high as 2500 ppm. Clinically, exposure to high doses of melamine has been associated with the development of nephrolithiasis; obstructive uropathy; and in some cases, acute kidney failure. Melamine contamination of pet food resulting in deaths in dogs and cats had previously been reported.²¹ The melamine disaster also demonstrates that globalization and international agribusiness may facilitate worldwide distribution of contaminated foodstuffs. After the initial reports of melamine contamination in China, investigation in the United States revealed that certain brands of cookies, biscuits, candies, and milk sold in this country were also tainted with melamine, some of which was traced to an origin in China.⁵²

MEDICINAL DRUG DISASTERS

Illness and death as a consequence of therapeutic drug use occur as sporadic events, usually affecting individual patients, or as mass poisoning, affecting multiple (sometimes hundreds or thousands) patients. Sporadic single-patient medication-induced tragedies usually result from errors ([Chaps. 1 and 140](#)) or unforeseen idiosyncratic reactions. Mass therapeutic drug disasters have generally occurred secondary to poor safety testing, a lack of understanding of diluents and excipients, drug contamination, or problems with unanticipated drug–drug interactions or drug toxicity ([Table 2–4](#)).

TABLE 2–4. Medicinal Disasters

<i>Xenobiotic</i>	<i>Location</i>	<i>Date</i>	<i>Significance</i>
Thallium	US	1920s–1930s	Treatment of ringworm; 31 deaths
Diethylene glycol	US	1937	Elixir of sulfanilamide; kidney failure
Thorotrast	US	1930s–1950s	Hepatic angiosarcoma
Phenobarbital	US	1940–1941	Contaminated sulfathiazole; 82 deaths
Diethylstilbestrol (DES)	US, Europe	1940s–1970s	Vaginal adenocarcinoma in patients' daughters
Stalmon	France	1954	Severe neurotoxicity from triethyltin
Cloquinal	Japan	1955–1970	Subacute myelo-optic neuropathy (SMON); 10,000 symptomatic
Thalidomide	Europe	1960s	5000 cases of phocomelia
Isoproterenol 30%	Great Britain	1961–1967	3000 excess asthma deaths
Pentachlorophenol	US	1967	Used in hospital laundry; nine neonates ill, two deaths
Benzyl alcohol	US	1981	Neonatal gasping syndrome
Tylenol–cyanide	Chicago	1982	Tampering incident resulted in seven homicides
L-Tryptophan	US	1989	Eosinophilia myalgia syndrome
Diethylene glycol (DEG)	Haiti	1996	APAP elixir contaminated; kidney failure; >88 pediatric deaths
Diethylene glycol	Panama	2006	Contaminated cough preparation, causing 78 deaths
Diethylene glycol	Nigeria	2009	Contaminated teething formula, causing 84 deaths

In September and October 1937, more than 105 deaths were associated with the use of one of the early sulfa preparations—elixir of sulfanilamide–Massengill—that contained 72% diethylene glycol as the vehicle for drug delivery. Little was known about diethylene glycol toxicity at the time, and many cases of acute kidney failure and death occurred.⁴⁰ To avoid similar tragedies in the future, animal drug testing was mandated by the Food, Drug, and Cosmetic Act of 1938.¹³² Unfortunately, diethylene glycol continues to be sporadically used in other countries as a medicinal diluent, resulting in deaths in South Africa (1969), India (1986), Nigeria (1990), Bangladesh (1990–1992), and Haiti (1995–1996).¹³³ In 1996 in Haiti, at least 88 Haitian children died (case fatality rate of 98% for those who remained in Haiti) after ingesting an

acetaminophen (APAP) elixir formulated with diethylene glycol–contaminated glycerin.^{95,110} In Panama in 2006, glycerin contaminated with diethylene glycol found in prescription liquid cough syrup resulted in at least 121 cases of poisoning and 78 deaths (case fatality rate, 65.5%).^{18,106} Investigators of this last outbreak discovered that the contaminated glycerin was imported to Panama from China via a European broker, demonstrating that improprieties in pharmaceutical manufacturing may have worldwide implications. In Nigeria in 2009, a tainted teething formula was responsible for 84 deaths in children.⁷ The pharmaceutical manufacturers intended to purchase propylene glycol, a component of the teething formula, but had bought the diluent in a jerrycan instead of the original container, and the chemical contained diethylene glycol (Special Considerations: SC7).

A lesser known drug manufacturing event, also involving an early sulfa antimicrobial, occurred in 1940 to 1941, when at least 82 people died from the therapeutic use of sulfathiazole that was contaminated with phenobarbital (Luminal).¹²² The responsible pharmaceutical company, Winthrop Chemical, produced both sulfathiazole and phenobarbital, and the contamination likely occurred during the tableting process because the tableting machines for the two medications were adjacent to each other and were used interchangeably. Each contaminated sulfathiazole tablet contained about 350 mg of phenobarbital (and no sulfathiazole), and the typical sulfathiazole dosing regimen was several tablets within the first few hours of therapy. Twenty-nine percent of the production lot was contaminated. Food and Drug Administration (FDA) intervention was required to assist with the recovery of the tablets, although 22,000 contaminated tablets were never found.¹²²

In the early 1960s, one of the worst drug-related modern-day events occurred with the release of thalidomide as an antiemetic and sedative–hypnotic.³¹ Its use as a sedative–hypnotic by pregnant women caused about 5000 babies to be born with severe congenital limb anomalies.⁸² This tragedy was largely confined to Europe, Australia, and Canada, where the drug was initially marketed. The United States was spared because of the length of time required for review and the rigorous scrutiny of new drug applications by the FDA.⁷⁹

A major therapeutic drug event that did occur in the United States involved the recommended and subsequent widespread use of diethylstilbestrol (DES) for the treatment of threatened and habitual abortions. Despite the lack of convincing efficacy data, as many as 10 million Americans received DES during pregnancy or in utero during a 30-year period, until the drug was prohibited for use during pregnancy in 1971. Adverse health effects associated with DES use include increased risk for breast cancer in “DES mothers” and increased risk of a rare form of vaginal cancer, reproductive tract anomalies, and premature births in “DES daughters.”^{42,46}

Thorotrast (thorium dioxide 25%) is an intravenous radiologic contrast medium that was widely used between 1928 and 1955. Its use was associated with the delayed development of hepatic angiosarcomas, as well as skeletal sarcomas, leukemia, and “thorotrastomas” (malignancies at the site of extravasated thorotrast).^{120,134}

The use of thallium to treat ringworm infections in the 1920s and 1930s also led to needless morbidity and mortality.⁴³ Understanding that thallium caused alopecia, dermatologists and other physicians prescribed thallium acetate, both as pills and as a topical ointment (Koremlu), to remove the infected hair. A 1934 study found 692 cases of thallium toxicity after oral and topical application and 31 deaths after oral use.⁸⁹ “Medicinal” thallium was subsequently removed from the market.

The “Stalinon affair” in France in 1954 involved the unintentional contamination of a proprietary oral medication that was marketed for the treatment of staphylococcal skin infections, osteomyelitis, and anthrax. Although it was supposed to contain diethyltin diiodide and linoleic acid, triethyltin, a potent neurotoxin and the most toxic of organotin compounds, and trimethyltin were present as impurities. Of the approximately 1000 people who received this medication, 217 patients developed symptoms, and 102 patients died.^{10,17}

An unusual syndrome, featuring a constellation of abdominal symptoms (pain and diarrhea) followed by neurologic symptoms (peripheral neuropathy and visual disturbances, including blindness) was experienced by approximately 10,000 Japanese people between 1955 and 1970, resulting in several hundred deaths.⁶² This presentation, subsequently labeled subacute myelo-optic neuropathy (SMON), was associated with the use of the GI disinfectant clioquinol, known in the West as Entero-Vioform and most often used for the prevention of travelers’ diarrhea.⁹² In Japan, this drug was referred to as sei-cho-zai (“active in normalizing intestinal function”). It was incorporated into more than 100 nonprescription medications and was used by millions of people, often for weeks or months. The exact mechanism of toxicity has not been determined, but recent investigators theorize that clioquinol may enhance the cellular uptake of certain metals, particularly zinc, and that the clioquinol–zinc chelate may act as a mitochondrial toxin, causing this syndrome.¹³ New cases declined rapidly when clioquinol was banned in Japan.

In 1981, a number of premature neonates died with a “gasping syndrome,” manifested by severe metabolic acidosis, respiratory depression with gasping, and encephalopathy.⁴¹ Before the development of these findings, the infants had all received multiple injections of heparinized bacteriostatic sodium chloride solution (to flush their indwelling catheters) and bacteriostatic water (to mix medications), both of which contained 0.9% benzyl alcohol. Accumulation of large amounts of benzyl alcohol and its metabolite benzoic acid in the blood was thought to be responsible for this syndrome.⁴¹

In 1989 and 1990, eosinophilia-myalgia syndrome, a debilitating syndrome somewhat similar to toxic oil syndrome, developed in more than 1500 people who had used the dietary supplement L-tryptophan.¹²⁸ These patients presented with disabling myalgias and eosinophilia, often accompanied by extremity edema, dyspnea, and arthralgias. Skin changes, neuropathy, and weight loss sometimes developed. Intensive investigation revealed that all affected patients had ingested L-tryptophan produced by a single manufacturer that had recently introduced a new process involving genetically altered bacteria to improve L-tryptophan production. A contaminant produced by this process probably was responsible for this syndrome.²⁰ The banning of L-tryptophan by the FDA set in motion the passage of the Dietary Supplement Health and Education Act of 1994. This legislation, which attempted to regulate an uncontrolled industry, facilitated industry marketing of dietary supplements bypassing FDA scrutiny. In 2001, the FDA loosened the restrictions on the marketing of tryptophan, which is now sold through some compounding pharmacies.

A number of pharmaceuticals previously approved by the FDA have been withdrawn from the market because of concerns about health risks.¹⁴¹ Many more drugs have been given “black box warnings” by the FDA because of their propensity to cause serious or life-threatening adverse effects.⁷⁷ Some of the withdrawn drugs had been responsible for causing serious drug–drug interactions (astemizole, cisapride, mibefradil, terfenadine).⁸⁸ Other drugs were withdrawn because of a propensity to cause hepatotoxicity (troglitazone), anaphylaxis (bromfenac sodium), valvular heart disease (fenfluramine, dexfenfluramine), rhabdomyolysis (cerivastatin), hemorrhagic stroke (phenylpropanolamine), and other adverse cardiac and neurologic effects (ephedra, rofecoxib). One of the more disconcerting drug problems to arise was the development of cardiac valvulopathy and pulmonary hypertension in patients taking the weight-loss drug combination fenfluramine and phentermine (fen-phen) or dexfenfluramine.^{27,116} The histopathologic features observed with this condition were similar to the valvular lesions associated with ergotamine and carcinoid syndrome. Interestingly, appetite suppressant medications, as well as ergotamine and carcinoid, all increase available serotonin.

ALCOHOL AND ILLICIT DRUG DISASTERS

Unintended toxic disasters have also involved the use of alcohol and other drugs of abuse (Table 2–5). Arsenical neuropathy developed in an estimated 40,000 people in France in 1828, when wine and bread were unintentionally contaminated by arsenious acid.⁷⁶ The use of arsenic-contaminated sugar in the production of beer in England in 1900 resulted in at least 6000 cases of peripheral neuropathy and 70 deaths (Staffordshire beer epidemic).⁵

TABLE 2–5. Alcohol and Illicit Drug Disasters

<i>Xenobiotic</i>	<i>Location</i>	<i>Date</i>	<i>Significance</i>
Triorthocresyl phosphate	US	1930–1931	Ginger Jake paralysis
Methanol	Atlanta, GA	1951	Epidemic from ingesting bootleg whiskey
Methanol	Jackson, MI	1979	Occurred in a prison
MPTP	San Jose, CA	1982	Illicit meperidine manufacturing resulting in drug-induced parkinsonism
Heroin heated on aluminum foil	Netherlands	1982	Spongiform leukoencephalopathy
3-Methyl fentanyl	Pittsburgh, PA	1988	“China-white” epidemic
Methanol	Baroda, India	1989	Moonshine contamination; 100 deaths
Fentanyl	New York City	1990	“Tango and Cash” epidemic
Methanol	New Delhi, India	1991	Antidiarrheal medication contaminated with methanol; >200 deaths
Methanol	Cuttack, India	1992	Methanol-tainted liquor; 162 deaths
Scopolamine	US East Coast	1995–1996	325 cases of anticholinergic poisoning in heroin users
Methanol	Cambodia	1998	>60 deaths
Methanol	Nicaragua	2006	800 became ill, 15 blind, 45 deaths
Methanol	India	2011	>143 deaths

MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

During the early 20th century, particularly during Prohibition, the ethanolic extract of Jamaican ginger (sold as “the

Jake”) was a popular ethanol substitute in the southern and midwestern United States.⁸³ It was sold legally because it was considered a medical supplement to treat headaches and aid digestion and was not subject to Prohibition. For years, the Jake was sold adulterated with castor oil, but in 1930, as the price of castor oil rose, the Jake was reformulated with an alternative adulterant, triorthocresyl phosphate (TOCP). Little was previously known about the toxicity of this compound, and TOCP proved to be a potent neurotoxin. From 1930 to 1931, at least 50,000 people who drank the Jake developed TOCP poisoning, manifested by upper and lower extremity weakness (“ginger Jake paralysis”) and gait impairment (“Jake walk” or “Jake leg”).⁸³ A quarter century later, in Morocco, the dilution of cooking oil with a turbojet lubricant containing TOCP caused an additional 10,000 cases of TOCP-induced paralysis.¹¹⁹

In the 1960s, cobalt was added to several brands of beer as a foam stabilizer. Certain local breweries in Quebec City, Canada; Minneapolis, Minnesota; Omaha, Nebraska; and Louvain, Belgium added 0.5–5.5 ppm cobalt to their beer. This resulted in epidemics of fulminant heart failure among heavy beer drinkers (named cobalt–beer cardiomyopathy).^{1,84}

Epidemic methanol poisoning among those seeking ethanol and other inebriants is well described. In one such incident in Atlanta, Georgia, in 1951, the ingestion of methanol-contaminated bootleg whiskey caused 323 cases of methanol poisoning, including 41 deaths. In another epidemic in 1979, 46 prisoners became ill after ingesting a methanol-containing diluent used in copy machines.¹²³

In recent years, major mass methanol poisonings have continued to occur in developing countries, where store-bought alcohol is often prohibitively expensive. In Baroda, India, in 1989, at least 100 people died and another 200 became ill after drinking a homemade liquor that was contaminated with methanol.⁴ In New Delhi, India, in 1991, an inexpensive antidiarrheal medicine, advertised to contain large amounts of ethanol, was instead contaminated with methanol, causing more than 200 deaths.²⁶ The following year, in Cuttack, India, 162 people died and an additional 448 were hospitalized after drinking methanol-tainted liquor.¹¹ A major epidemic of methanol poisoning occurred in 1998 in Cambodia, when rice wine was contaminated with methanol.³ At least 60 deaths and 400 cases of illness were attributed to the methanol. In 2011 in Sangrampur, India, more than 143 died from drinking methanol tainted bootleg alcohol.⁷¹

So-called “designer drugs” are responsible for several toxicologic disasters. In 1982, several injection drug users living in San Jose, California, who were attempting to use a meperidine analog MPPP (1-methyl-4-phenyl-4-propionyloxy-piperidine) developed a peculiar, irreversible neurologic disease closely resembling Parkinson disease.⁶⁴ Investigation revealed that these patients had unknowingly injected trace amounts of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which was present as an inadvertent product of the clandestine MPPP synthesis. The subsequent metabolism of MPTP to MPP⁺ resulted in a toxic compound that selectively destroyed cells in the substantia nigra depleting dopamine stores or products causing severe and irreversible parkinsonism. The vigorous pursuit of the cause of this disaster led to a better understanding of the pathophysiology of parkinsonism.

Another example of a “designer drug” poisoning occurred in the New York City metropolitan area in 1991, when a sudden epidemic of opioid overdoses occurred among heroin users who bought envelopes labeled “Tango and Cash.”³⁷ Expecting to receive a new brand of heroin, the drug users instead purchased the much more potent fentanyl. Increased and unpredictable toxicity resulted from the inability of the dealer to adjust (“cut”) the fentanyl dose properly. Some purchasers presumably received little or no fentanyl, but others received potentially lethal doses. A similar epidemic involving 3-methylfentanyl occurred in 1988 in Pittsburgh, Pennsylvania and continue to occur in the United States in the 21st Century.⁷⁴

At least 325 cases of anticholinergic poisoning occurred among heroin users in New York City; Newark, New Jersey; Philadelphia, Pennsylvania; and Baltimore, Maryland from 1995 to 1996.⁸ The “street drug” used in these cases was adulterated with scopolamine. Whereas naloxone treatment was associated with increased agitation and hallucinations, physostigmine administration resulted in resolution of symptoms. Why the heroin was adulterated was unknown, although the use of an opiate–scopolamine mixture was reminiscent of the morphine–scopolamine combination therapy known as “twilight sleep” that was extensively used in obstetric anesthesia during the early 20th century.⁹⁸ Another unexpected complication of heroin use was observed in the Netherlands in the 1980s, when 47 heroin users developed mutism and spastic quadriparesis that was pathologically documented to be spongiform leukoencephalopathy.¹⁴⁰ In these and subsequent cases in Europe and the United States, the users inhaled heroin vapors after the heroin powder had been heated on aluminum foil, a drug administration technique known as “chasing the dragon.”^{60,140} The exact toxic mechanism has not been elucidated.

OCCUPATION-RELATED CHEMICAL DISASTERS

Unfortunately, occupation-related toxic epidemics have become increasingly common (Table 2–6). Such poisoning syndromes tend to have an insidious onset and may not be recognized clinically until years after the exposure. A specific xenobiotic may cause myriad problems, among the most worrisome being the carcinogenic and mutagenic potentials.

TABLE 2–6. Occupational Disasters

<i>Xenobiotic</i>	<i>Location</i>	<i>Date</i>	<i>Significance</i>
Polycyclic aromatic hydrocarbons	England	1700s	Scrotal cancer among chimney sweeps; first description of hydrocarbons occupational cancer
Mercury	New Jersey	Mid to late 1800s	Outbreak of mercurialism in hatters
White phosphorus	Europe	Mid to late 1800s	Phossy jaw in matchmakers
β -Naphthylamine	Worldwide	Early 1900s	Bladder cancer in dye makers
Benzene	Newark, NJ	1916–1928	Aplastic anemia among artificial leather manufacturers
Asbestos	Worldwide	20th century	Millions at risk for asbestos-related disease
Vinyl chloride	Louisville, KY	1960s–1970s	Hepatic angiosarcoma among plastics workers
Chlordecone	James River, VA	1973–1975	Neurologic abnormalities among insecticide workers
1,2-Dibromochloropropane	California	1974	Infertility among pesticide makers

Although the 18th-century observations of Ramazzini and Pott introduced the concept of certain diseases as a direct result of toxic exposures in the workplace, it was not until the height of the 19th-century industrial revolution that the problems associated with the increasingly hazardous workplace became apparent.⁵¹ During the 1860s, a peculiar disorder, attributed to the effects of inhaling mercury vapor, was described among manufacturers of felt hats in New Jersey.¹³⁵ Mercury nitrate was used as an essential part of the felting process at the time. “Hatter’s shakes” refers to the tremor that developed in an estimated 10% to 60% of hatters surveyed.¹³⁵ Extreme shyness, another manifestation of mercurialism, also developed in many hatters in later studies. Five percent of hatters during this period died from kidney failure.

Other notable 19th-century and early 20th-century occupational tragedies included an increased incidence of mandibular necrosis (phossy jaw) among workers in the matchmaking industry who were exposed to white phosphorus,⁴⁹ an increased incidence of bladder tumors among synthetic dye makers who used β -naphthylamine,⁴⁴ and an increased incidence of aplastic anemia among artificial leather manufacturers who used benzene.¹¹⁴ The epidemic of phossy jaw among matchmakers had a latency period of 5 years and a mortality rate of 20% and has been called the “greatest tragedy in the whole story of occupational disease.”²⁴ The problem continued in the United States until Congress passed the White Phosphorus Match Act in 1912, which established a prohibitive tax on white phosphorus matches.

Since antiquity, occupational lead poisoning has been a constant threat. Workplace exposure to lead was particularly problematic during the 19th century and early 20th century because of the large number of industries that relied heavily on lead. One of the most notorious of the “lead trades” was the actual production of white lead and lead oxides. Palsies, encephalopathy, and death from severe poisoning were reported.⁴⁵ Other occupations that resulted in dangerous lead exposures included pottery glazing, rubber manufacturing, pigment manufacturing, painting, printing, and plumbing.⁷³ Given the increasing awareness of harm suffered in the workplace, the British Factory and Workshop Act of 1895 required governmental notification of occupational diseases caused by lead, mercury, and phosphorus poisoning, as well as of occupational diseases caused by anthrax.⁶⁵

Exposures to asbestos during the 20th century have resulted in continuing extremely consequential occupational and environmental disasters.^{28,91} Even though the first case of asbestosis was reported in 1907, asbestos was heavily used in the shipbuilding industries in the 1940s as an insulating and fireproofing material. Since the early 1940s, 8 to 11 million individuals were occupationally exposed to asbestos,⁶⁷ including 4.5 million individuals who worked in the shipyards. Asbestos-related diseases include mesothelioma, lung cancer, and pulmonary fibrosis (asbestosis). A threefold excess of cancer deaths, primarily of excess lung cancer deaths, has been observed in asbestos-exposed insulation workers.¹¹³

The manufacture and use of a variety of newly synthesized chemicals has also resulted in mass occupational poisonings. In Louisville, Kentucky in 1974, an increased incidence of angiosarcoma of the liver was first noticed among polyvinyl chloride polymerization workers who were exposed to vinyl chloride monomer.³⁵ In 1975, chemical factory workers exposed to the organochlorine insecticide chlordecone (Kepone) experienced a high incidence of neurologic abnormalities, including tremor and chaotic eye movements.¹²⁴ An increased incidence of infertility among male Californian pesticide workers exposed to 1,2-dibromochloropropane (DBCP) was noted in 1977.¹³⁶

RADIATION DISASTERS

A discussion of mass poisonings is incomplete without mention of the large number of radiation disasters that have

characterized the 20th century (Table 2–7). The first significant mass exposure to radiation occurred among several thousand teenage girls and young women employed in the dial-painting industry.²⁵ These workers painted luminous numbers on watch and instrument dials with paint that contained radium. Exposure occurred by licking the paint brushes and inhaling radium-laden dust. Studies showed an increase in bone-related cancers, as well as aplastic anemia and leukemia, in exposed workers.^{75,99}

TABLE 2–7. Radiation Disasters

<i>Xenobiotic</i>	<i>Location</i>	<i>Date</i>	<i>Significance</i>
Radium	Orange, NJ	1910s–1920s	Increase in bone cancer in dial-painting workers
Radium	US	1920s	“Radithor” (radioactive water) sold as radium-containing patent medication
Radiation	Hiroshima and Nagasaki, Japan	1945	First atomic bombs dropped at the end of World War II; clinical effects still evident today
Radiation	Chernobyl, Ukraine	1986	Unintentional radioactive release; acute radiation sickness
Cesium	Goiania, Brazil	1987	Acute radiation sickness and radiation burns
Cesium, iodine	Fukushima, Japan	2011	Unintentional radioactive release after earthquake and tsunami

At the time of the “watch” disaster, radium was also being sold as a nostrum touted to cure all sorts of ailments, including rheumatism, syphilis, multiple sclerosis, and sexual dysfunction. Referred to as “mild radium therapy” to differentiate it from the higher dose radium that was used in the treatment of cancer at that time, such particle-emitting isotopes were hailed as powerful natural elixirs that acted as metabolic catalysts to deliver direct energy transfusions.⁷⁰

During the 1920s, dozens of patent medications containing small doses of radium were sold as radioactive tablets, liniments, or liquids. One of the most infamous preparations was Radithor. Each half-ounce bottle contained slightly more than one curie of radium-228 and radium-226. This radioactive water was sold all over the world “as harmless in every respect” and was heavily promoted as a sexual stimulant and aphrodisiac, taking on the glamour of a recreational drug for the wealthy.⁷⁰ More than 400,000 bottles were sold. The 1932 death of Eben Byers, a Radithor connoisseur, from chronic radiation poisoning drew increased public and governmental scrutiny to this unregulated radium industry and helped end the era of radioactive patent medications.⁷⁰

Concerns about the health effects of radiation have continued to escalate since the dawn of the nuclear age in 1945. Long-term follow-up studies 50 years after the atomic bombings at Hiroshima and Nagasaki demonstrate an increased incidence of leukemia, other cancers, radiation cataracts, hyperparathyroidism, delayed growth and development, and chromosomal anomalies in exposed individuals.⁵⁸

The unintentional nuclear disaster at Chernobyl, Ukraine, in April 1986 again forced the world to confront the medical consequences of 20th-century scientific advances that created the atomic age.³⁹ The release of radioactive material resulted in 31 deaths and the hospitalization of more than 200 people for acute radiation sickness. By 2003, the predominant long-term effects of the event appeared to be childhood thyroid cancer and psychological consequences.¹⁰⁵ In some areas of heavy contamination, the increase in childhood thyroid cancer has increased 100-fold.¹⁰⁹

Another serious radiation event occurred in Goiania, Brazil, in 1987 when an abandoned radiotherapy unit was opened in a junkyard and 244 people were exposed to cesium-137. Of those exposed, 104 showed evidence of internal contamination, 28 had local radiation injuries, and eight developed acute radiation syndrome. There were at least four deaths.^{97,107}

In September 1999, a nuclear event at a uranium-processing plant in Japan set off an uncontrolled chain reaction, exposing 49 people to radiation.⁶¹ Radiation measured outside the facility reached 4000 times the normal ambient level. Two workers died from the effects of the radiation.

A 9.0 magnitude earthquake and tsunami in Japan in March 2011 caused equipment failure at the Fukushima Daiichi nuclear plant resulted in a release of radioactive material into the atmosphere and seawater. Nearby foodstuff and drinking

water were contaminated with Cesium-137 and Iodine-131.¹²⁵

MASS SUICIDE BY POISON

Mass poisonings have also manifested themselves as events of mass suicide. In 1978 in Jonestown, Guyana, 911 members of the Peoples Temple died after drinking a beverage containing cyanide.¹² In 1997, phenobarbital and ethanol (sometimes assisted by physical asphyxiation) was the suicidal method favored by 39 members of the Heavens Gate cult in Rancho Santa Fe, California, a means of suicide recommended in the book *Final Exit*.⁵⁰ Apparently, the cult members committed suicide to shed their bodies in hopes of hopping aboard an alien spaceship they believed was in the wake of the Hale-Bopp comet.⁶³

SUMMARY

- There are significant lessons to be learned from mass poisonings.
- An understanding of the pathogenesis of these mass poisonings pertaining to drug, food, and occupational safety is critically important to prevent future disasters.
- Such events make us aware that many of the toxic xenobiotics involved are potential agents of opportunity for terrorists and others who invoke harm.
- Given the practical and ethical limitations in studying the effects of many specific xenobiotics in humans, lessons from these unfortunate tragedies must be fully mastered and retained for future generations.

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PART A

**THE GENERAL APPROACH TO MEDICAL
TOXICOLOGY**

3 INITIAL EVALUATION OF THE PATIENT: VITAL SIGNS AND TOXIC SYNDROMES

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For more than 200 years, American health care providers have attempted to standardize their approach to the assessment of patients. At the New York Hospital in 1865, pulse rate, respiratory rate, and temperature were incorporated into the bedside chart and called “vital signs.”⁶ It was not until the early part of the 20th century, however, that blood pressure determination also became routine. Additional components of the standard emergency assessment, such as oxygen saturation by pulse oximetry, capillary blood glucose, and pain severity, are now also beginning to be considered vital signs. Although assessment of oxygen saturation, capillary glucose, and pain severity are essential components of the clinical evaluation and are important considerations throughout this text, they are not discussed in this chapter.

In the practice of medical toxicology, vital signs play an important role beyond assessing and monitoring the overall status of a patient because they frequently provide valuable physiologic clues to the toxicologic etiology and severity of an illness. The vital signs also are a valuable parameter, which are used to assess and monitor a patient’s response to supportive treatment and antidotal therapy.

Table 3–1 presents the normal vital signs for various age groups. However, this broad range of values considered normal should serve merely as a guide. Only a complete assessment of a patient can determine whether or not a particular vital sign is truly clinically normal. This table of normal vital signs is useful in assessing children because normal values for children vary considerably with age, and knowing the range of normal variation is essential. Normal rectal temperature is defined as 95° to 100.4°F (35°–38°C).

TABLE 3–1. Normal Vital Signs by Age^{a,b}

Age	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats/min)	Respirations (breaths/min) ^b
Adult	≤120	<80	60–100	16–24
16 years	≤120	<80	80	16–30
12 years	119	76	85	16–30
10 years	115	74	90	16–30
6 years	107	69	100	20–30
4 years	104	65	110	20–30
4 months	90	50	145	30–35
2 months	85	50	145	30–35
Newborn	65	50	145	35–40

^aThe normal rectal temperature is defined as 95°F to 100.4°F (35°–38°C) for all ages. For children one year of age or younger, these values are the mean values for the 50th percentile. For older children, these values represent the 90th percentile at a specific age for the 50th percentile of weight in that age group. ^bThese values were determined in the emergency department and may be environment and situation dependent.

BP = blood pressure.

The difficulty in defining what constitutes “normal” vital signs in an emergency setting is inadequately addressed and may prove to be an impossible undertaking. Published normal values may have little relevance for an acutely ill or anxious

patient in the emergency setting, yet that is precisely the environment in which we must define abnormal vital signs and address them accordingly. Even in nonemergent situations, “normalcy” of vital signs depends on the clinical condition of the patient. A sleeping or comatose patient may have physiologic bradycardia; a slow heart rate appropriate for his or her low energy requiring state. For these reasons, descriptions of vital signs as “normal” or “stable” are too nonspecific to be meaningful and therefore should never be accepted as defining normalcy in an individual patient. Conversely, no patient should be considered too agitated, too young, or too gravely ill to obtain a complete set of vital signs; indeed, these patients urgently need a thorough evaluation that includes all of the vital signs. Also, the vital signs must be recorded as accurately as possible first in the prehospital setting, again with precision and accuracy as soon as a patient arrives in the emergency department (ED), and serially thereafter as clinically indicated.

Many xenobiotics affect the autonomic nervous system, which, in turn, affects the vital signs via the sympathetic pathway, the parasympathetic pathway, or both. Meticulous attention to both the initial and repeated determinations of vital signs is of extreme importance in identifying a pattern of changes suggesting a particular xenobiotic or group of xenobiotics. The value of serial monitoring of the vital signs is demonstrated by the patient who presents with an anticholinergic overdose who is then given the antidote, physostigmine. In this situation, it is important to recognize when tachycardia becomes bradycardia (ie, anticholinergic syndrome followed by physostigmine excess). Meticulous attention to these changes ensures that the therapeutic interventions can be modified or adjusted accordingly.

Similarly, consider the course of a patient who has opioid-induced bradypnea (a decreased rate of breathing) and then develops tachypnea (an increased rate of breathing) after the administration of the opioid antagonist naloxone. The analysis becomes exceedingly complicated when that patient may have been exposed to two or more xenobiotics, such as an opioid combined with cocaine. In this situation, the effects of cocaine may be “unmasked” by the naloxone used to counteract the opioid, and the clinician must then be forced to differentiate naloxone-induced opioid withdrawal from cocaine toxicity. The assessment starts by analyzing diverse information, including vital signs, history, and physical examination.

Table 3–2 describes the most typical toxic syndromes. This table includes only vital signs that are thought to be characteristically abnormal or pathognomonic and directly related to the toxicologic effect of the xenobiotic. The primary purpose of the table, however, is to include many findings, in addition to the vital signs, that together constitute a toxic syndrome. Mofenson and Greensher⁵ coined the term toxidromes from the words toxic syndromes to describe the groups of signs and symptoms that consistently result from particular toxins. These syndromes are usually best described by a combination of the vital signs and clinically apparent end-organ manifestations. The signs that prove most clinically useful are those involving the central nervous system (CNS; mental status), ophthalmic system (pupil size), gastrointestinal system (peristalsis), dermatologic system (skin dryness versus diaphoresis), mucous membranes (moistness versus dryness), and genitourinary system (urinary retention versus incontinence). Table 3–2 includes some of the most important signs and symptoms and the xenobiotics most commonly responsible for these manifestations. A detailed analysis of each sign, symptom, and toxic syndrome can be found in the pertinent chapters throughout the text. In this chapter, the most typical toxic syndromes are considered to enable the appropriate assessment and differential diagnosis of a poisoned patient.

TABLE 3–2. Toxic Syndromes

Group	Vital Signs				Mental Status	Pupil Size	Peristalsis	Diaphoresis	Other
	BP	P	R	T					
Anticholinergics	–/↑	↑	±	↑	Delirium	↑	↓	↓	Dry mucous membranes, flush, urinary retention
Cholinergics	±	±	–/↑	–	Normal to depressed	±	↑	↑	Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative–hypnotics	↓	↓	↓	–/↓	Depressed, agitated	±	↓	–	Hyporeflexia, ataxia
Opioids	↓	↓	↓	↓	Depressed	↓	↓	–	Hyporeflexia
Sympathomimetics	↑	↑	↑	↑	Agitated	↑	–/↑	↑	Tremor, seizures
Withdrawal from ethanol or sedative–hypnotics	↑	↑	↑	↑	Agitated, disoriented, hallucinations	↑	↑	↑	Tremor, seizures
Withdrawal from opioids	↑	↑	–	–	Normal, anxious	↑	↑	↑	Vomiting, rhinorrhea, piloerection, diarrhea, yawning

↑ = increases; ↓ = decreases; ± = variable; – = change unlikely; BP = blood pressure; P = pulse; R = respirations; T = temperature.

In considering a toxic syndrome, the reader should always remember that the actual clinical manifestations of a poisoning are far more variable than the syndromes described in Table 3–2. The concept of the toxic syndrome is most

useful when thinking about a clinical presentation and formulating a framework for assessment. Although some patients may present as “classic” cases, others manifest partial toxic syndromes or formes frustes. These incomplete syndromes may still provide at least a clue to the correct diagnosis. It is important to understand that partial presentations (particularly in the presence of multiple xenobiotics) do not necessarily imply less severe disease and, therefore, are comparably important to appreciate.

In some instances, an unexpected combination of findings may be particularly helpful in identifying a xenobiotic or a combination of xenobiotics. For example, a dissociation between such typically paired changes as an increase in pulse with a decrease in blood pressure (cyclic antidepressants or phenothiazines), or the presentation of a decrease in pulse with an increase in blood pressure (ergot alkaloids) may be extremely helpful in diagnosing a toxic etiology. The use of these unexpected or atypical clinical findings is demonstrated in [Chap. 17](#).

BLOOD PRESSURE

Xenobiotics cause hypotension by four major mechanisms: decreased peripheral vascular resistance, decreased myocardial contractility, dysrhythmias, and depletion of intravascular volume. Many xenobiotics can initially cause orthostatic hypotension without marked supine hypotension, and any xenobiotic that affects autonomic control of the heart or peripheral capacitance vessels may lead to orthostatic hypotension ([Table 3–3](#)). Hypertension from xenobiotics may be caused by CNS sympathetic overactivity, increased myocardial contractility or increased peripheral vascular resistance, or a combination of these.

TABLE 3–3. Common Xenobiotics That Affect the Blood Pressure^a

<i>Hypotension</i>	<i>Hypertension</i>
α_1 -Adrenergic antagonists	α_1 -Adrenergic agonists
α_2 -Adrenergic agonists	α_2 -Adrenergic antagonists
β -Adrenergic antagonists	Ergot alkaloids
Angiotensin-converting enzyme inhibitors	Lead (chronic)
Angiotensin receptor blockers	Monoamine oxidase inhibitors (overdose early and drug–food interaction)
Antidysrhythmics	Nicotine (early)
Calcium channel blockers	Phencyclidine
Cyanide	Sympathomimetics
Cyclic antidepressants	
Ethanol and other alcohols	
Iron	
Methylxanthines	
Nitrates and nitrites	
Nitroprusside	
Opioids	
Phenothiazines	
Phosphodiesterase-5 inhibitors	
Sedative–hypnotics	

^aChapter 17 lists additional xenobiotics that affect hemodynamic function.

Blood pressure and pulse rate may vary significantly as a result of changes in receptor responsiveness, degree of physical fitness, and degree of atherosclerosis. Changing patterns of blood pressure often assist in the diagnostic evaluation: overdose with a monoamine oxidase inhibitor (MAOI) characteristically causes an initial normal blood pressure, to be followed by hypertension, which, in turn, may be followed abruptly by severe hypotension ([Chap. 73](#)).

PULSE RATE

Extremely useful clinical information can be obtained by evaluating the pulse rate ([Table 3–4](#) and [Chap. 17](#)). Although the carotid artery is usually easily palpable, for reasons of both safety and reliability, the brachial artery is preferred in infants and in adults older than 60 years. The normal heart rate for adults was defined by consensus more than 50 years ago as a regular rate greater than 60 beats/min and less than 100 beats/min. More recent studies^{7,8} suggest that 95% of the population

has bradycardia and tachycardia thresholds of 50 beats/min and 90 beats/min, respectively. In our text, we have chosen to retain the consensus values.

TABLE 3–4. Common Xenobiotics That Affect the Pulse^a

<i>Bradycardia</i>	<i>Tachycardia</i>
α ₂ -Adrenergic agonists	Anticholinergics
β-Adrenergic antagonists	Antipsychotics
Baclofen	Cyclic antidepressants
Calcium channel blockers	Disulfiram-ethanol interaction
Cardioactive steroids	Ethanol and sedative-hypnotic withdrawal
Ciguatoxin	Iron
Ergot alkaloids	Methylxanthines
γ-Hydroxybutyric acid	Phencyclidine
Opioids	Sympathomimetics
Organic phosphorus compounds	Thyroid hormone
	Yohimbine

^aChapter 17 lists additional xenobiotics that affect the heart rate.

Because pulse rate is the net result of a balance between sympathetic (adrenergic) and parasympathetic (muscarinic and nicotinic) tone, many xenobiotics that exert therapeutic or toxic effects or cause pain syndromes, hyperthermia, or volume depletion also affect the pulse rate. With respect to temperature, there is a direct correlation between pulse rate and temperature in that pulse rate increases approximately 8 beats/min for each 1.8°F (1°C) elevation in temperature.⁴

The inability to differentiate easily between sympathomimetic and anticholinergic xenobiotic effects by vital signs alone illustrates the principle that no single vital sign abnormality can definitively establish a toxicologic diagnosis. In trying to differentiate between a sympathomimetic and anticholinergic toxic syndrome, it should be understood that although tachycardia commonly results from both sympathomimetic and anticholinergic xenobiotics, when tachycardia is accompanied by diaphoresis or increased bowel sounds, adrenergic toxicity is suggested, but when tachycardia is accompanied by decreased sweating, absent bowel sounds, and urinary retention, anticholinergic toxicity is likely.

RESPIRATIONS

Establishment of an airway and evaluation of respiratory status are the initial priorities in patient stabilization. Although respirations are typically assessed initially for rate alone, careful observation of the depth and pattern is essential (Table 3–5) for establishing the etiology of a systemic illness or toxicity.¹ Unfortunately, very few investigators have actually measured the respiratory rate in large populations of normal people, let alone in ED patients. Two papers^{2,3} investigating respiratory rates in ED patients differ substantially in their determinations of normal ranges from the remainder of the literature. The combined results of these investigations suggest “normal” respiratory rates are 16 to 24 breaths/min in adults with more rapid rates that are inversely related to age in children.

TABLE 3–5. Common Xenobiotics That Affect Respiration^a

<i>Bradypnea</i>	<i>Tachypnea</i>
α_2 -Adrenergic agonists	Cyanide
Botulinum toxin	Dinitrophenol and congeners
Elapidae venom	Epinephrine
Ethanol and other alcohols	Ethylene glycol
γ -Hydroxybutyric acid	Hydrogen sulfide
Neuromuscular blockers	Methanol
Opioids	Methemoglobin producers
Organic phosphorus compounds	Methylxanthines
Sedative-hypnotics	Nicotine (early)
	Pulmonary irritants
	Salicylates
	Sympathomimetics

^aChapter 29 lists additional xenobiotics affecting respiratory rate.

The term hyperventilation may mean tachypnea (an increase in ventilatory rate), hyperpnea (an increase in tidal volume), or both ([Chap. 29](#)). When hyperventilation results solely or predominantly from hyperpnea, clinicians may miss this important finding entirely, instead erroneously describing such a hyperventilating patient as normally ventilating or even hypoventilating if bradypnea is also present. The ventilatory status of the patient must be viewed in the context of the patient's physiologic condition.

Hyperventilation may result from the direct effect of a CNS stimulant, such as the direct effect of salicylates, on the brainstem. However, salicylate poisoning characteristically produces hyperventilation by tachypnea, but it also produces hyperpnea with or without tachypnea. Pulmonary injury from any source, including aspiration of gastric contents, may lead to hypoxemia with a resultant tachypnea. Later, tachypnea may change to bradypnea, hypopnea (shallow breathing), or both. Bradypnea may occur when a CNS depressant acts on the brainstem. A progression from fast to slow breathing may also occur in a patient exposed to increasing concentrations of cyanide or carbon monoxide.

TEMPERATURE

Temperature evaluation and control are critical. However, temperature assessment can be done only if safe and reliable equipment is used. The risks of inaccuracy are substantial when an oral temperature is taken in a tachypneic patient, an axillary temperature or a temporal artery temperature is taken in any patient (especially those found outdoors), or a tympanic temperature is taken in a patient with cerumen impaction. Obtaining rectal temperatures using a nonglass probe is essential for safe and accurate temperature determinations in agitated individuals and is considered the standard method of temperature determination in this text.

The core temperature or deep internal temperature (T) is relatively stable ($98.6^\circ \pm 1.08^\circ\text{F}$; $37^\circ \pm 0.6^\circ\text{C}$) under normal physiologic circumstances. Hypothermia ($T < 95^\circ\text{F}$; $< 35^\circ\text{C}$) and hyperthermia ($T > 100.4^\circ\text{F}$; $> 38^\circ\text{C}$) are common manifestations of toxicity. Severe or significant hypothermia and hyperthermia, unless immediately recognized and managed appropriately, may result in grave complications and inappropriate or inadequate resuscitative efforts. Life-threatening hyperthermia ($T > 106^\circ\text{F}$; $> 41.1^\circ\text{C}$) from any cause may lead to extensive rhabdomyolysis, myoglobinuric kidney failure, and direct liver and brain injury and must therefore be identified and corrected immediately.

Hyperthermia may result from a distinct neurologic response to a signal demanding thermal “upregulation.” This signal can be from internal generation of heat beyond the capacity of the body to cool, such as occurs in association with agitation or mitochondrial uncoupling, or from an externally imposed physical or environmental factor, such as the environmental conditions causing heat stroke or the excessive swaddling in clothing causing hyperthermia in infants. Fever, or pyrexia, is hyperthermia caused by an elevation in the hypothalamic thermoregulatory setpoint.

Regardless of etiology, core temperatures higher than 106°F (41.1°C) are extremely rare unless normal feedback mechanisms are overwhelmed. Hyperthermia of this extreme nature is usually attributed to environmental heat stroke; extreme psychomotor agitation; or xenobiotic-related temperature disturbances such as malignant hyperthermia, serotonin toxicity, or the neuroleptic malignant syndrome.

A common xenobiotic-related hyperthermia pattern that frequently occurs in the ED is defervescence after an acute temperature elevation resulting from agitation or a grand mal seizure. [Table 3–6](#) is a representative list of xenobiotics that affect body temperature. ([Chapter 30](#) provides greater detail.)

TABLE 3–6. Common Xenobiotics^a

<i>Hyperthermia</i>	<i>Hypothermia</i>
Anticholinergics	α_2 -Adrenergic agonists
Chlorophenoxy herbicides	Carbon monoxide
Dinitrophenol and congeners	Ethanol
Malignant hyperthermia	γ -Hydroxybutyric acid
Monoamine oxidase inhibitors	Hypoglycemics
Neuroleptic malignant syndrome	Opioids
Phencyclidine	Sedative–hypnotics
Salicylates	Thiamine deficiency
Sedative–hypnotic or ethanol withdrawal	
Serotonin toxicity	
Sympathomimetics	
Thyroid hormone	

^aChapter 30 lists additional xenobiotics that affect temperature.

Hypothermia is probably less of an immediate threat to life than hyperthermia, but it requires rapid appreciation, accurate diagnosis, and skilled management. Hypothermia impairs the metabolism of many xenobiotics, leading to unpredictable delayed and/or prolonged toxicologic effects when the patient is warmed. Many xenobiotics that lead to an alteration of mental status place patients at great risk for becoming hypothermic from exposure to cold climates. Most important, a hypothermic patient should never be declared dead without both an extensive assessment and a full resuscitative effort of adequate duration, taking into consideration the difficulties in resuscitating cold but living patients. This is true whenever the body temperature remains less than 95°F (35°C) ([Chap. 30](#)).

SUMMARY

- Early, accurate determinations followed by serial monitoring of the vital signs are as essential in medical toxicology as in any other type of emergency or critical care medicine.
- Careful observation of the vital signs helps to determine appropriate therapeutic interventions and guide the clinician in making necessary adjustments to initial and subsequent therapeutic interventions.
- When pathognomonic clinical and laboratory findings are combined with accurate initial and sometimes changing vital signs, a toxic syndrome may become evident, which will aid in both general supportive and specific antidotal treatment.
- Correct identification of toxic syndromes will also guide further diagnostic testing.

Acknowledgment

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4 PRINCIPLES OF MANAGING THE ACUTELY POISONED OR OVERDOSED PATIENT

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OVERVIEW

For over 5 decades, medical toxicologists and poison information specialists have used a clinical approach to poisoned or overdosed patients that emphasizes treating the patient rather than treating the poison.¹ Too often in the past, patients were initially all but neglected while attention was focused on the ingredients listed on the containers of the product(s) to which they presumably were exposed. Although the astute clinician must always be prepared to administer a specific antidote immediately in instances when nothing else will save a patient, such as cyanide poisoning, all poisoned or overdosed patients will benefit from an organized, rapid clinical management plan (Fig. 4–1).

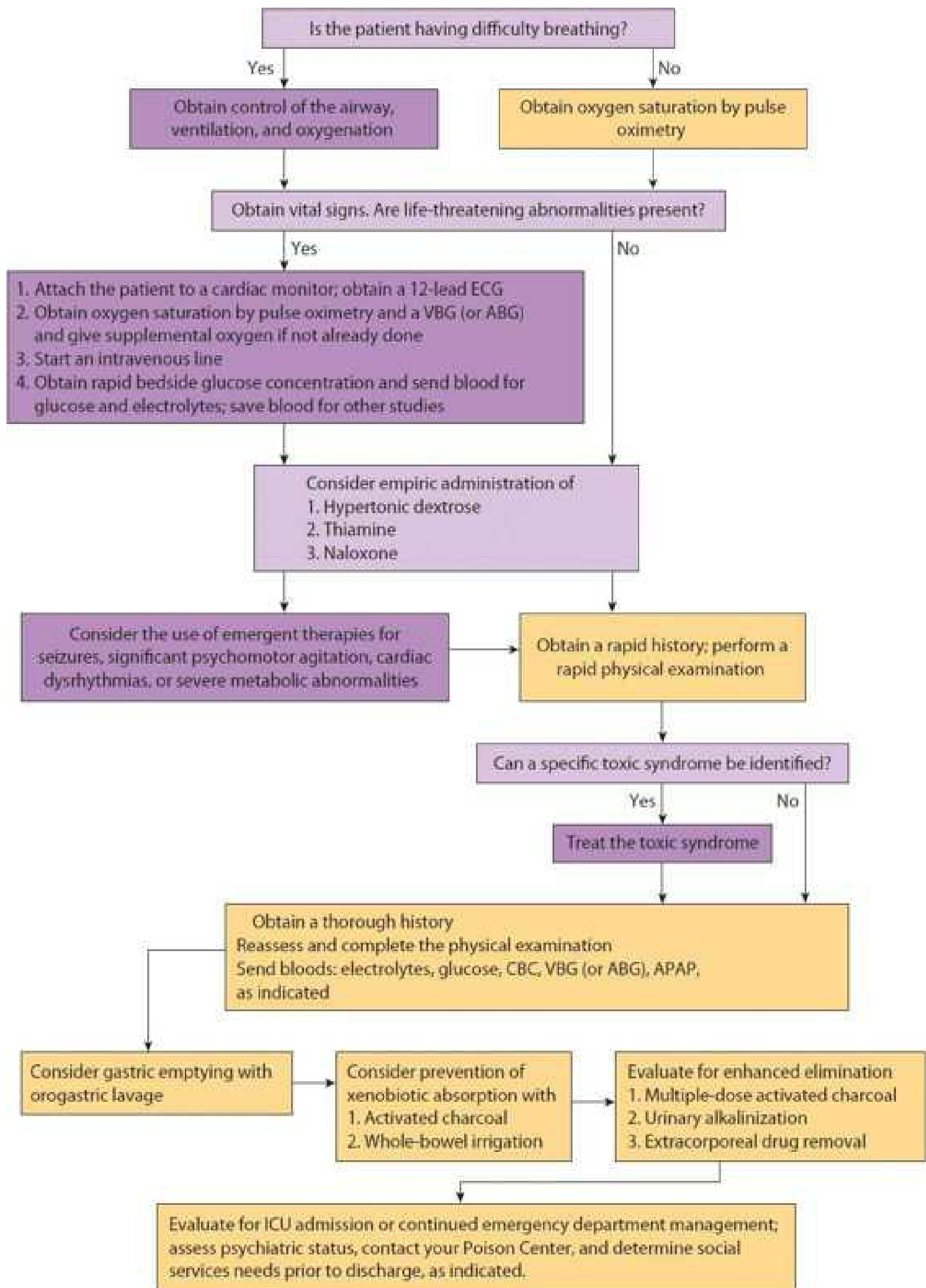


FIGURE 4–1. This algorithm is a basic guide to the management of poisoned patients. A more detailed description of the steps in management may be found in the accompanying text. This algorithm is only a guide to actual management, which must, of course, consider the patient’s clinical status. ABG = arterial blood gas; CBC = complete blood count; ICU = intensive care unit; VBG = venous blood gas.

Over the past 4 decades, some basic tenets and long-held beliefs regarding the initial therapeutic interventions in toxicologic management have been questioned and subjected to an “evidence-based” analysis. For example, in the mid-1970s, most medical toxicologists began to advocate a standardized approach to a comatose and possibly overdosed adult patient, typically calling for the intravenous (IV) administration of 50 mL of dextrose 50% in water (D₅₀W), 100 mg of thiamine, and 2 mg of naloxone along with 100% oxygen at high flow rates. The rationale for this approach was to compensate for the previously idiosyncratic style of overdose management encountered in different health care settings and for the unfortunate likelihood that omitting any one of these measures at the time that care was initiated in the emergency department (ED) would result in omitting it altogether. It was not unusual then to discover from a laboratory chemistry report more than one hour after a supposedly overdosed comatose patient had arrived in the ED that the initial blood glucose was 30 or 40 mg/dL—a critical delay in the management of unsuspected and consequently untreated hypoglycemic coma. Today, however, with the widespread availability of accurate rapid bedside testing for capillary glucose, pulse oximetry for oxygen saturation, and end-tidal CO₂ monitors coupled with a much greater appreciation by all physicians of what needs to be done for each suspected overdose patient, clinicians can safely provide a more rational, individualized approach to determine the need for, and in some instances more precise amounts of, dextrose, thiamine, naloxone, and oxygen.

A second major approach to providing more rational individualized early treatment for toxicologic emergencies involves a closer examination of the actual risks and benefits of various gastrointestinal (GI) emptying interventions. Appreciation of the potential for significant adverse effects associated with all types of GI emptying interventions and recognition of the absence of clear evidence-based support of efficacy have led to abandoning of syrup of ipecac-induced emesis, an almost complete elimination of orogastric lavage, and a significant reduction in the routine use of activated charcoal (AC). The value of whole-bowel irrigation (WBI) with polyethylene glycol electrolyte solution (PEG-ELS) appears to be much more specific and limited than originally thought, and some of the limitations and (uncommon) adverse effects of AC are now more widely recognized.

Similarly, interventions to eliminate absorbed xenobiotics from the body are now much more narrowly defined or, in some cases, abandoned. Multiple-dose activated charcoal (MDAC) is useful for select but not all xenobiotics. Ion trapping in the urine is only beneficial, achievable, and relatively safe when the urine can be maximally alkalinized after a significant salicylate or phenobarbital poisoning. Finally, the roles of hemodialysis, hemoperfusion, and other extracorporeal techniques are now much more specifically defined.² With the foregoing in mind, this chapter represents our current efforts to formulate a logical and effective approach to managing a patient with probable or actual toxic exposure.

Table 4–1 provides a recommended stock list of antidotes and therapeutics for the treatment of poisoned or overdosed patients.

TABLE 4–1. Antidotes and Therapeutics for the Treatment of Poisonings and Overdoses^a

Therapeutics ^a	Uses	Therapeutics ^a	Uses
Activated charcoal (p. 97)	Adjuvant antibiotics in the GI tract	Hydroxocobalamin (Cyanokit) (p. 1618)	Cyanide
Antivenom (<i>Centruroides</i> spp) (p. 1484)	Scorpion envenomation	Insulin (p. 851)	β -Adrenergic antagonists, CCBs, hyperglycemia
Antivenom (<i>Crotalinae</i>) (p. 1547)	Crotaline snake envenomations	Iodide (SSKI) (p. 1713)	Radioactive iodine (I^{131})
Antivenom (<i>Elopidre</i>) (p. 1547)	Coral snake envenomations	Ipecac, syrup of (p. 84)	Induces emesis
Antivenom (<i>Lutrodoctus mactans</i>) (p. 1489)	Black widow spider envenomations	Magnesium sulfate or magnesium citrate (p. 104)	Induces catharsis
Antivenom (<i>Synanceja</i> spp) (p. 1494)	Stonefish envenomation	Magnesium sulfate injection (p. 258)	Cardioactive steroids, hydrofluoric acid, hypomagnesemia, ethanol withdrawal, torsade de pointes
Atropine (p. 1425)	Bradycardias, cholinesterase inhibitors (organic phosphorus compounds, physostigmine) muscarinic mushrooms (<i>Clitocybe</i> , <i>Inocybe</i>) ingestions	Methylene blue (1% solution) (p. 1631)	Methemoglobinemia
Benzodiazepines (p. 1069)	Seizures, agitation, stimulants, ethanol and sedative-hypnotic withdrawal, cocaine, chloroquine, organic phosphorus compounds	N-acetylcysteine (Acetadote) (p. 465)	APAP and other causes of hepatotoxicity
Botulinum antitoxin (ABE-trivalent) (p. 559)	Botulism	Naloxone hydrochloride (Narcan) (p. 510)	Opioids, dantrolene
Calcium chloride, calcium gluconate (p. 1330)	Fluoride, hydrofluoric acid, ethylene glycol, CCBs, hypomagnesemia, β -adrenergic antagonists	Norepinephrine (Levophed) (p. 978)	Hypotension (preferred for cyclic antidepressants)
L-Carnitine (p. 657)	Valproic acid; hyperammonemia	Octreotide (Sandostatin) (p. 738)	Insulin secretagogues induced hypoglycemia
Cyanide kit (nitrites, p. 1612; sodium thiosulfate, p. 1615)	Cyanide	Oxygen (Hyperbaric) (p. 1594)	Carbon monoxide, cyanide, hydrogen sulfide
Cyproheptadine (p. 1023)	Serotonin toxicity	α -Penicillamine (Cuprimine) (p. 1215)	Copper
Dantrolene (p. 955)	Malignant hyperthermia	Phenobarbital (p. 1005)	Seizures, agitation, stimulants, ethanol and sedative-hypnotic withdrawal
Deferoxamine (Desferal) (p. 623)	Iron	Phentolamine (p. 1058)	Vasoconstriction: cocaine, MAOI interactions, epinephrine, and ergot alkaloids
Dextrose in water (50% adults; 20% pediatrics; 10% neonates) (p. 732)	Hypoglycemia	Physostigmine (Antilirium) (p. 905)	Anticholinergics
Digoxin-specific antibody fragments (p. 904)	Cardioactive steroids	Polyethylene glycol electrolyte solution (p. 104)	Decontamination
Dimercaprit (BAL, British anti-Lewisite) (p. 1181)	Arsenic, mercury, gold, lead	Pralidoxime chloride (2-PAM-chloride; Protopam) (p. 1429)	Acetylcholinesterase inhibitors (organic phosphorus compounds and carbamates)
Diphenhydramine (p. 663)	Dystonic reactions, allergic reactions	Protamine (p. 839)	Heparin anticoagulation
DTPA (p. 1717)	Radioactive isotopes	Prussian blue (Radiogardase) (p. 1283)	Thallium, cesium
Edetate calcium disodium (calcium disodium versenate, CaNa ₂ EDTA) (p. 1241)	Lead, other selected metals	Pyridoxine (vitamin B ₆) (p. 797)	Isoniazid, ethylene glycol, gyromitrin-containing mushrooms
Ethanol (p. 1369)	Methanol, ethylene glycol	Silibinin (p. 1515)	Amatoxin mushroom poisoning
Fat emulsion (Intralipid 20%) (p. 933)	Cardiac arrest; local anesthetics	Sodium bicarbonate (p. 528)	Ethylene glycol, methanol, salicylates, cyclic antidepressants, methotrexate, phenobarbital, quinidine, chlorpropamide, Class I antidysrhythmics, chlorophenyl herbicides
Flumazenil (Romazicon) (p. 1013)	Benzodiazepines	Starch (p. 1298)	Iodine
Folic acid (Leucovorin) (p. 693)	Methotrexate, methanol	Succimer (Chemet) (p. 1235)	Lead, mercury, arsenic
Fomepizole (Antizole) (p. 1364)	Ethylene glycol, methanol	Thiamine (vitamin B ₃) (p. 1094)	Thiamine deficiency, ethylene glycol, chronic ethanol consumption ("alcoholism")
Glucagon (p. 870)	β -Adrenergic antagonists, CCBs	Vitamin K ₁ (Aquamephyton) (p. 836)	Warfarin or rodenticide anticoagulants
Glucarpitase (p. 698)	Methotrexate	Whole-bowel irrigation (p. 104)	Induces catharsis

Each emergency department should have the vast majority of these antidotes immediately available; some of these antidotes may be stored in the pharmacy, and others may be available from the Centers for Disease Control and Prevention, but the precise mechanism for locating each one must be known by each staff member. ^aA detailed analysis of each of these agents is found in the Antidotes in Depth section on the page cited to the right of each antidote or therapeutic listed.

CCB = calcium channel blockers; DTPA = diethylenetriaminepentaacetic acid; DTPA = ethylenediamine tetraacetic acid; GI = gastrointestinal; MAOI = monoamine oxidase inhibitor; SSKI = saturated solution of potassium iodide.

MANAGING ACUTELY POISONED OR OVERDOSED PATIENTS

Rarely, if ever, are all of the circumstances involving a poisoned patient known. The history may be incomplete, unreliable, or unobtainable; multiple xenobiotics may be involved; and even when a xenobiotic etiology is identified, it may not be easy to determine whether the problem is an overdose, an allergic or idiosyncratic reaction, or a drug–drug interaction. Similarly, it is sometimes difficult or impossible to differentiate between the adverse effects of a correct dose of medication and the consequences of a deliberate or unintentional overdose. The patient’s presenting signs and symptoms may force an intervention at a time when there is almost no information available about the etiology of the patient’s condition (Table 4–2), and as a result, therapeutics must be thoughtfully chosen empirically to treat or diagnose a condition without exacerbating the situation.

TABLE 4–2. Clinical and Laboratory Findings in Poisoning and Overdose

Agitation	Anticholinergics, ^a hypoglycemia, phencyclidine, sympathomimetics, ^b withdrawal from ethanol and sedative-hypnotics
Alopecia	Alkylating agents, radiation, selenium, thallium
Ataxia	Benzodiazepines, carbamazepine, carbon monoxide, ethanol, hypoglycemia, lithium, mercury, nitrous oxide, phenytoin
Blindness or decreased visual acuity	Caustics (direct), cisplatin, cocaine, mercury, methanol, quinine, thallium
Blue skin	Amiodarone, FD&C #1 dye, methemoglobinemia, silver
Constipation	Anticholinergics, ^a botulism, lead, opioids, thallium (severe)
Deafness, tinnitus	Aminoglycosides, cisplatin, loop diuretics, metals, quinine, salicylates
Diaphoresis	Amphetamines, cholinergics, ^c hypoglycemia, opioid withdrawal, salicylates, serotonin syndrome, sympathomimetics, ^b withdrawal from ethanol and sedative-hypnotics
Diarrhea	Arsenic and other metals, boric acid (blue-green), botanical irritants, cathartics, cholinergics, ^c colchicine, iron, lithium, opioid withdrawal, radiation
Dysesthesias, paresthesias	Acrylamide, arsenic, ciguatera, cocaine, colchicine, thallium
Gum discoloration	Arsenic, bismuth, hypervitaminosis A, lead, mercury
Hallucination	Anticholinergics, ^a dopamine agonists, ergot alkaloids, ethanol, ethanol and sedative-hypnotic withdrawal, LSD, phencyclidine, sympathomimetics, ^b tryptamines
Headache	Carbon monoxide, hypoglycemia, monoamine oxidase inhibitor–food interaction (hypertensive crisis), serotonin toxicity
Metabolic acidosis (elevated anion gap)	Methanol, uremia, ketoacidosis (diabetic, starvation, alcoholic), paraldehyde, phenformin, metformin, iron, isoniazid, lactic acidosis, cyanide, protease inhibitors, ethylene glycol, salicylates, toluene
Miosis	Cholinergics, ^c clonidine, opioids, phencyclidine, phenothiazines
Mydriasis	Anticholinergics, ^a botulism, opioid withdrawal, sympathomimetics ^b
Nystagmus	Barbiturates, carbamazepine, carbon monoxide, ethanol, lithium, monoamine oxidase inhibitors, phencyclidine, phenytoin, quinine
Purpura	Anticoagulant rodenticides, clopidogrel, corticosteroids, heparin, pit viper venom, quinine, salicylates, warfarin
Radiopaque ingestion	Arsenic, halogenated hydrocarbons, metals (eg, iron, lead)
Red skin	Anticholinergics, ^a boric acid, disulfiram, hydroxocobalamin, scambroid, vancomycin
Rhabdomyolysis	Carbon monoxide, doxylamine, HMG-CoA reductase inhibitors, sympathomimetics, ^b <i>Tricholoma equestre</i> mushrooms
Salivation	Arsenic, caustics, cholinergics, ^c ketamine, mercury, phencyclidine, strychnine
Seizures	Bupropion, camphor, carbon monoxide, cyclic antidepressants, Gyromitra mushrooms, hypoglycemia, isoniazid, methylxanthines, ethanol and sedative-hypnotic withdrawal
Tremor	Antipsychotics, arsenic, carbon monoxide, cholinergics, ^c ethanol, lithium, mercury, methyl bromide, sympathomimetics, ^b thyroid replacement
Weakness	Botulism, diuretics, magnesium, paralytic shellfish, steroids, toluene
Yellow skin	APAP (late), pyrrolizidine alkaloids, β carotene, amatoxin mushrooms, dinitrophenol

^aAnticholinergics, including antihistamines, atropine, cyclic antidepressants, and scopolamine. ^bSympathomimetics, including adrenergic agonists, amphetamines, cocaine, and epinephrine. ^cCholinergics, including muscarinic mushrooms, organic phosphorus compounds, and carbamates, including select Alzheimer's disease drugs and physostigmine, and pilocarpine and other direct-acting cholinergics.

HMG-CoA = 3-hydroxy-3-methyl-glutaryl-CoA; LSD = lysergic acid diethylamide; MAOI = monoamine oxidase inhibitor.

Initial Management of Patients with a Suspected Exposure

Similar to the management of any seriously compromised patient, the clinical approach to the patient potentially exposed to a xenobiotic begins with the recognition and treatment of life-threatening conditions, including airway compromise, breathing difficulties, and circulatory problems such as hemodynamic instability and serious dysrhythmias. After the “ABCs” (airway, breathing, and circulation) have been addressed, the patient’s level of consciousness should be assessed because this helps determine the techniques to be used for further management of the exposure.

Management of Patients with Altered Mental Status

Altered mental status (AMS) is defined as the deviation of a patient's sensorium from normal. Although it is commonly construed as a depression in the patient's level of consciousness, a patient with agitation, delirium, psychosis, and other deviations from normal is also considered to have an AMS. After airway patency is established or secured, an initial bedside assessment should be made regarding the adequacy of breathing. If it is not possible to assess the depth and rate of ventilation, then at least the presence or absence of regular breathing should be determined. In this setting, any irregular or slow breathing pattern should be considered a possible sign of the incipient apnea, requiring ventilation with 100% oxygen by bag–valve–mask followed as soon as possible by endotracheal intubation and mechanical ventilation. Endotracheal intubation may be indicated for some cases of coma resulting from a toxic exposure to ensure and maintain control of the airway and to enable safe performance of procedures to prevent GI absorption or eliminate previously absorbed xenobiotics.

Although in many instances, the widespread availability of pulse oximetry to determine O₂ saturation and end-tidal CO₂ monitors have made arterial blood gas (ABG) analysis less of an immediate priority, these technical advances have not entirely eliminated the importance of blood gas analysis. An ABG determination will more accurately define the adequacy not only of oxygenation (PO₂, O₂ saturation) and ventilation (PCO₂) but may also alert the physician to possible toxic-metabolic etiologies of coma characterized by acid–base disturbances (pH, PCO₂) ([Chap. 19](#)). In addition, carboxyhemoglobin determinations are now available by point-of-care testing, and both carboxyhemoglobin and methemoglobin may be determined on either venous or arterial blood specimens ([Chaps. 125 and 127](#)). In every patient with an AMS, a bedside rapid capillary glucose concentration should be obtained as soon as possible.

After the patient's respiratory status has been assessed and managed appropriately, the strength, rate, and regularity of the pulse should be evaluated, the blood pressure determined, and a rectal temperature obtained. Both an initial 12-lead electrocardiogram (ECG) and continuous rhythm monitoring are essential. Monitoring will alert the clinician to dysrhythmias that are related to toxic exposures either directly or indirectly via hypoxemia or electrolyte imbalance. For example, a 12-lead ECG demonstrating QRS widening and a right axis deviation might indicate a life-threatening exposure to a cyclic antidepressant or another xenobiotic with sodium channel–blocking properties. In these cases, the physician can anticipate such serious sequelae as ventricular tachydysrhythmias, seizures, and cardiac arrest and consider both the early use of specific treatment (antidotes), such as IV sodium bicarbonate, and avoidance of medications, such as procainamide and other class IA and IC antidysrhythmics, which could exacerbate the situation.

Extremes of core body temperature must be addressed early in the evaluation and treatment of a comatose patient. Life-threatening hyperthermia (temperature >106°F; >41.1°C) is usually appreciated when the patient is touched (although the widespread use of gloves as part of universal precautions has made this less apparent than previously). Most individuals with severe hyperthermia, regardless of the etiology, should have their temperatures immediately reduced to about 101.5°F (38.7°C) by sedation if they are agitated or displaying muscle rigidity and by ice water immersion ([Chap. 30](#)). Hypothermia is probably easier to miss than hyperthermia, especially in northern regions during the winter months, when most arriving patients feel cold to the touch. Early recognition of hypothermia, however, helps to avoid administering a variety of medications that may be ineffective until the patient becomes relatively euthermic, which may cause iatrogenic toxicity as a result of a sudden response to xenobiotics previously administered.

For a hypotensive patient with clear lungs and an unknown overdose, a fluid challenge with IV 0.9% sodium chloride or lactated Ringer solution may be started. If the patient remains hypotensive or cannot tolerate fluids, an antidote, a vasopressor, or an inotropic agent may be indicated, as may more invasive monitoring.

At the time that the IV catheter is inserted, blood samples for glucose, electrolytes, blood urea nitrogen (BUN), a complete blood count (CBC), and any indicated toxicologic analyses can be obtained. A pregnancy test should be obtained in any woman with childbearing potential. If the patient has an AMS, there may be a temptation to send blood and urine specimens to identify any central nervous system (CNS) depressants or so-called drugs of abuse in addition to other medications. But the indiscriminate ordering of these tests rarely provides clinically useful information. For the potentially suicidal patient, an APAP concentration should be routinely requested along with tests affecting the management of any specific xenobiotic, such as carbon monoxide, lithium, theophylline, iron, salicylates, and digoxin (or other cardioactive steroids), as suggested by the patient's history, physical examination, or bedside diagnostic tests. In the vast majority of cases, the blood tests that are most useful in diagnosing toxicologic emergencies are not the toxicologic assays but rather the “nontoxicologic” routine metabolic profile tests such as BUN, glucose, electrolytes, and blood gas analysis.

Xenobiotic-related seizures may broadly be divided into three categories: (1) those that respond to standard anticonvulsant treatment (typically using a benzodiazepine); (2) those that either require specific antidotes to control seizure activity or that do not respond consistently to standard anticonvulsant treatment, such as isoniazid-induced seizures requiring pyridoxine administration; and (3) those that may appear to respond to initial treatment with cessation of tonic–clonic activity but that leave the patient exposed to the underlying, unidentified xenobiotic or to continued electrical seizure activity, as is the case with carbon monoxide poisoning and hypoglycemia.

Within the first 5 minutes of managing a patient with an AMS, four therapeutic interventions should be considered, and if indicated, administered:

1. High-flow oxygen (8–10 L/min) to treat a variety of xenobiotic-induced hypoxic conditions
2. Hypertonic dextrose: 0.5–1.0 g/kg of D₅₀W for an adult or a more dilute dextrose solution (D₁₀W or D₂₅W) for a child; the dextrose is administered as an IV bolus to diagnose and treat or exclude hypoglycemia
3. Thiamine (100 mg IV for an adult; usually unnecessary for a child) to prevent or treat Wernicke encephalopathy
4. Naloxone (0.04 mg IV with upward titration) for an adult or child with opioid-induced respiratory compromise

The clinician must consider that hypoglycemia may be the sole or contributing cause of coma even when the patient manifests focal neurologic findings; therefore, dextrose administration should only be omitted when hypoglycemia can be definitely excluded by accurate rapid bedside testing. Also, while examining a patient for clues to the etiology of a presumably toxic-metabolic form of AMS, it is important to search for any indication that trauma may have caused, contributed to, or resulted from the patient's condition. Conversely, the possibility of a concomitant drug ingestion or toxic metabolic disorder in a patient with obvious head trauma should also be considered.

The remainder of the physical examination should be performed rapidly but thoroughly. In addition to evaluating the patient's level of consciousness, the physician should note abnormal posturing (decorticate or decerebrate), abnormal or unilateral withdrawal responses, and pupil size and reactivity. Pinpoint pupils suggest exposure to opioids or organic phosphorus insecticides, and widely dilated pupils suggest anticholinergic or sympathomimetic poisoning. The presence or absence of nystagmus, abnormal reflexes, and any other focal neurologic findings may provide important clues to a structural cause of AMS. For clinicians accustomed to applying the Glasgow Coma Scale (GCS) to all patients with AMS, assigning a score to the overdosed or poisoned patient may provide a useful measure for assessing changes in neurologic status. However, in this situation, the GCS should never be used for prognostic purposes because despite a low GCS score, complete recovery from properly managed toxic-metabolic coma is the rule rather than the exception ([Chap. 24](#)).

Characteristic breath or skin odors may identify the etiology of coma. The fruity odor of ketones on the breath suggests diabetic or alcoholic ketoacidosis but also the possible ingestion of acetone or isopropyl alcohol, which is metabolized to acetone. The pungent, minty odor of oil of wintergreen on the breath or skin suggests methyl salicylate poisoning. The odors of other substances such as cyanide ("bitter almonds"), hydrogen sulfide ("rotten eggs"), and organic phosphorus compounds ("garlic") are described in detail in [Chap. 26](#) and summarized in [Table 26–1](#).

Further Evaluation of All Patients with Suspected Xenobiotic Exposures

Auscultation of breath sounds, particularly after a fluid challenge, helps to diagnose pulmonary edema, acute lung injury, or aspiration pneumonitis when present. Coupled with an abnormal breath odor of hydrocarbons or organic phosphorus compounds, for example, crackles and rhonchi may point to a toxic pulmonary etiology instead of a cardiac etiology; this is important because the administration of certain cardioactive medications may be inappropriate or dangerous in the former circumstances.

Heart murmurs in an injection drug user, especially when accompanied by fever, may indicate bacterial endocarditis. Dysrhythmias may suggest overdoses or inappropriate use of cardioactive xenobiotics, such as digoxin and other cardioactive steroids, β -adrenergic antagonists, calcium channel blockers, and cyclic antidepressants.

The abdominal examination may reveal signs of trauma or alcohol-related hepatic disease. The presence or absence of bowel sounds helps to exclude or to diagnose anticholinergic toxicity and is important in considering whether to manipulate the GI tract in an attempt to remove the toxin. A large palpable bladder may signal urinary retention as a further manifestation of anticholinergic toxicity.

Examination of the extremities might reveal clues to current or former drug use (track marks, skin-popping scars); metal poisoning (Mees lines, arsenical dermatitis); and the presence of cyanosis or edema suggesting preexisting cardiac, pulmonary, or kidney disease ([Chap. 29](#)).

Repeated evaluation of the patient suspected of an overdose is essential for identifying new or developing findings or toxic syndromes and for early identification and treatment of a deteriorating condition. Until the patient is completely recovered or considered no longer at risk for the consequences of a xenobiotic exposure, frequent reassessment must be provided even as the procedures described later are carried out. Toxicologic etiologies of abnormal vital signs and physical findings are summarized in [Tables 3–1 to 3–6](#). Toxic syndromes, sometimes called "toxidromes," are summarized in [Table 3–1](#).

Typically in the management of patients with toxicologic emergencies, there is both a necessity and an opportunity to obtain various diagnostic studies and ancillary tests interspersed with stabilizing the patient's condition, obtaining the history, and performing the physical examination. [Chapters 5, 6, and 16](#) discuss the timing and indications for diagnostic imaging procedures, qualitative and quantitative diagnostic laboratory studies, and the use and interpretation of the ECG in evaluating and managing poisoned or overdosed patients.

The Role of Gastrointestinal Evacuation

A series of highly individualized treatment decisions must now be made. As noted previously and as discussed in detail in [Chap. 8](#), the decision to evacuate the GI tract or administer AC can no longer be considered standard or routine toxicologic

care for most patients. Instead, the decision should be based on the type of ingestion, estimated quantity and size of pill or tablet, time since ingestion, concurrent ingestions, ancillary medical conditions, and age and size of the patient. The indications, contraindications, and procedures for performing orogastric lavage and for administering WBI, AC, MDAC, and cathartics are listed in [Tables 8–1 through 8–7](#) and are discussed in [Chap. 8](#) and in the specific Antidotes in Depth sections immediately following [Chap. 8](#).

Eliminating Absorbed Xenobiotics from the Body

After deciding whether or not an intervention to try to prevent absorption of a xenobiotic is indicated, the clinician must next consider the applicability of techniques available to eliminate xenobiotics already absorbed. Detailed discussions of the indications for and techniques of manipulating urinary pH (ion trapping), diuresis, hemodialysis, hemoperfusion, hemofiltration, and exchange transfusion are found in [Chap. 10](#). Briefly, patients who may benefit from these procedures are those who have systemically absorbed xenobiotics amenable to one of these techniques and whose clinical conditions are both serious (or potentially serious) and unresponsive to supportive care or whose physiologic route of elimination (liver–feces, kidney–urine) is impaired.

Alkalinization of the urinary pH for acidic xenobiotics has only limited applicability. Commonly, sodium bicarbonate can be used to alkalinize the urine (as well as the blood) and enhance salicylate elimination (other xenobiotics are discussed in [Chap. 10](#)), and sodium bicarbonate also prevents toxicity from methotrexate (Antidotes in Depth: A5). Acidifying the urine to hasten the elimination of alkaline substances is difficult to accomplish, probably useless, and possibly dangerous and therefore has no role in poison management. Forced diuresis also has no indication and may endanger the patient by causing pulmonary or cerebral edema.

If extracorporeal elimination is contemplated, hemodialysis should be considered for overdoses of salicylates, methanol, ethylene glycol, lithium, valproic acid, and xenobiotics that are both dialyzable and cause fluid and electrolyte problems. If available, hemoperfusion or high-flux hemodialysis should be considered for overdoses of theophylline, phenobarbital, and carbamazepine (although rarely, if ever, for the last two). When hemoperfusion is the method of choice (as for a theophylline overdose) but not available, hemodialysis is a logical, effective alternative and certainly preferable to delaying treatment until hemoperfusion becomes available. Peritoneal dialysis is too ineffective to be of practical utility, and hemodiafiltration is not as efficacious as hemodialysis or hemoperfusion, although it may play a role between multiple runs of dialysis or in hemodynamically compromised patients who cannot tolerate hemodialysis. In theory, both hemodialysis and hemoperfusion in series may be useful for a very few life-threatening overdoses such as thallium or salicylates. Plasmapheresis and exchange transfusion are used to eliminate xenobiotics with large molecular weights that are not dialyzable ([Chap. 10](#)).

AVOIDING PITFALLS

The history alone may not be a reliable indicator of which patients require naloxone, hypertonic dextrose, thiamine, and oxygen. Instead, these therapies should be considered (unless specifically contraindicated) only after a clinical assessment for all patients with AMS. The physical examination should be used to guide the use of naloxone. If dextrose or naloxone is indicated, sufficient amounts should be administered to exclude or treat hypoglycemia or opioid toxicity, respectively.

In a patient with a suspected but unknown overdose, the use of vasopressors should be avoided in the initial management of hypotension before administering fluids or assessing filling pressures.

Attributing an AMS to alcohol because of its odor on a patient's breath is potentially dangerous and misleading. Small amounts of alcohol and its congeners generally produce the same breath odor as do intoxicating amounts. Conversely, even when an extremely high blood ethanol concentration is confirmed by the laboratory, it is dangerous to ignore other possible causes of an AMS. Because individuals with chronic alcoholism may be awake and seemingly alert with ethanol concentrations in excess of 500 mg/dL, a concentration that would result in coma and possibly apnea and death in a nontolerant person, finding a high ethanol concentration does not eliminate the need for further search into the cause of a depressed level of consciousness.

The metabolism of ethanol is fairly constant at 15 to 30 mg/dL/h. Therefore, as a general rule, regardless of the initial blood alcohol concentration, a presumably “inebriated” comatose patient who is still unarousable 3 to 4 hours after initial assessment should be considered to have head trauma, a cerebrovascular accident, CNS infection, or another toxic-metabolic etiology for the alteration in consciousness, until proven otherwise. Careful neurologic evaluation of the completely undressed patient supplemented by a head computed tomography scan or a lumbar puncture is frequently indicated in such cases. This is especially important in dealing with a seemingly “intoxicated” patient who appears to have only a minor bruise because the early treatment of a subdural or epidural hematoma or subarachnoid hemorrhage is critical to a successful outcome.

ADDITIONAL CONSIDERATIONS IN MANAGING PATIENTS WITH A

NORMAL MENTAL STATUS

As in the case of the patient with AMS, vital signs must be obtained and recorded. Initially, an assumption may have been made that the patient was breathing adequately, and if the patient is alert, talking, and in no respiratory distress, all that remains to document are the respiratory rate and rhythm. Because the patient is alert, additional history should be obtained, keeping in mind that information regarding the number and types of xenobiotics ingested, time elapsed, prior vomiting, and other critical information may be unreliable, depending in part on whether the ingestion was intentional or unintentional.

When indicated for the potential benefit of the patient, another history should be privately and independently obtained from a friend or relative after the patient has been initially stabilized. Recent emphasis on compliance with the federal Health Insurance Portability and Accountability Act (HIPAA) may inappropriately discourage clinicians from attempting to obtain information necessary to evaluate and treat patients. Obtaining such information from a friend or relative without unnecessarily giving that person information about the patient may be the key to successfully helping such a patient without violating confidentiality.

Speaking to a friend or relative of the patient may provide an opportunity to learn useful and reliable information regarding the ingestion, the patient's frame of mind, a history of previous ingestions, and the type of support that is available if the patient is discharged from the ED. At times, it may be essential to initially separate the patient from any relatives or friends to obtain greater cooperation from the patient and avoid violating confidentiality and because their anxiety may interfere with therapy. Even if the history obtained from a patient with an overdose proves to be unreliable, it may nevertheless provide clues to an overlooked possibility of a second ingestant or reveal the patient's mental and emotional condition. As is often true of the history, physical examination, or laboratory assessment in other clinical situations, the information obtained may confirm but never exclude possible causes.

At this point in the management of a conscious patient, a focused physical examination should be performed, concentrating on the pulmonary, cardiac, and abdominal examinations. A neurologic survey should emphasize reflexes and any focal findings.

APPROACHING PATIENTS WITH INTENTIONAL EXPOSURES

Initial efforts at establishing rapport with the patient by indicating to the patient concern about the problems that led to the ingestion and the availability of help after the xenobiotic is removed (if such procedures are planned) often facilitates management. If GI decontamination is deemed necessary, the reason for and nature of the procedure should be clearly explained to the patient together with reassurance that after the procedure is completed, there will be ample time to discuss related problems and provide additional care. These considerations are especially important in managing the patient with an intentional overdose who may be seeking psychiatric help or emotional support. In deciding on the necessity of GI decontamination, it is important to consider that a resistant patient may transform a procedure of only potential value into one with predictable adverse consequences.

SPECIAL CONSIDERATIONS FOR MANAGING PREGNANT PATIENTS

In general, a successful outcome for both the mother and fetus depends on optimum management of the mother, and proven effective treatment for a potentially serious toxic exposure to the mother should never be withheld based on theoretical concerns regarding the fetus ([Chap. 31](#)).

Physiologic Factors

A pregnant woman's total blood volume and cardiac output are elevated through the second trimester and into the later stages of the third trimester. This means that signs of hypoperfusion and hypotension manifest later than they would in a woman who is not pregnant, and when they do, uterine blood flow may already be compromised. For these reasons, the possibility of hypotension in a pregnant woman must be more aggressively sought and, if found, more rapidly treated. Maintaining the patient in the left-lateral decubitus position helps prevent supine hypotension resulting from impairment of systemic venous return by compression of the inferior vena cava. The left lateral decubitus position is also the preferred position for orogastric lavage if this procedure is deemed necessary.

Because the tidal volume is increased in pregnancy, the baseline PCO₂ will normally be lower by approximately 10 mm Hg. Appropriate adjustment for this effect should be made when interpreting blood gas results.

Use of Antidotes

Limited data are available on the use of antidotes in pregnancy. In general, antidotes should not be used if the indications for use are equivocal. On the other hand, antidotes should not be withheld if their use may reduce potential morbidity and mortality. Risks and benefits of either decision must be considered. For example, reversal of opioid-induced respiratory depression calls for the use of naloxone, but in an opioid-dependent woman, the naloxone can precipitate acute opioid

withdrawal, including uterine contractions and possible induction of labor. Very slow, careful, IV titration starting with 0.04 mg naloxone may be indicated unless apnea is present, cessation of breathing appears imminent, or the PO₂ or O₂ saturation is already compromised. In these instances, naloxone may have to be administered in higher doses (ie, 0.4–2.0 mg) or assisted ventilation provided or a combination of assisted ventilation and small doses of naloxone used.

An APAP overdose is a serious maternal problem when it occurs at any stage of pregnancy, but the fetus is at greatest risk in the third trimester. Although APAP crosses the placenta easily, N-acetylcysteine has somewhat diminished transplacental passage. During the third trimester, when both the mother and the fetus may be at substantial risk from a significant APAP overdose with manifest hepatotoxicity, immediate delivery of a mature or viable fetus may need to be considered.

In contrast to the situation with APAP, the fetal risk from iron poisoning is less than the maternal risk. Because deferoxamine is a large charged molecule with little transplacental transport, deferoxamine should never be withheld out of unwarranted concern for fetal toxicity when indicated to treat the mother.

Carbon monoxide (CO) poisoning is particularly threatening to fetal survival. The normal PO₂ of the fetal blood is approximately 15 to 20 mm Hg. Oxygen delivery to fetal tissues is impaired by the presence of carboxyhemoglobin, which shifts the oxyhemoglobin dissociation curve to the left, potentially compromising an already tenuous balance. For this reason, hyperbaric oxygen is recommended for much lower carboxyhemoglobin concentrations in a pregnant compared with a nonpregnant woman ([Chap. 125](#) and Antidotes in Depth: A38). Early notification of the obstetrician and close cooperation among involved physicians are essential for the best results in all of these instances.

MANAGEMENT OF PATIENTS WITH CUTANEOUS EXPOSURE

The xenobiotics that people are commonly exposed to externally include household cleaning materials; organic phosphorus or carbamate insecticides from crop dusting, gardening, or pest extermination; acids from leaking or exploding batteries; alkalis, such as lye; and lacrimating agents that are used in crowd control. In all of these cases, the principles of management are as follows:

1. Avoid secondary exposures by wearing protective (rubber or plastic) gowns, gloves, and shoe covers. Cases of serious secondary poisoning have occurred in emergency personnel after contact with xenobiotics such as organic phosphorus compounds on the victim's skin or clothing.
2. Remove the patient's clothing, place it in plastic bags, and then seal the bags.
3. Wash the patient with soap and copious amounts of water twice regardless of how much time has elapsed since the exposure.
4. Make no attempt to neutralize an acid with a base or a base with an acid. Further tissue damage may result from the heat generated by this reaction.
5. Avoid using any greases or creams because they will only keep the xenobiotic in close contact with the skin and ultimately make removal more difficult.

[Chapter 18](#) discusses the principles of managing cutaneous exposures.

MANAGEMENT OF PATIENTS WITH OPHTHALMIC EXPOSURES

Although the vast majority of toxicologic emergencies result from ingestion, injection, or inhalation, the eyes are occasionally the routes of systemic absorption or are the organs at risk for ophthalmic exposures. The eyes should be irrigated with the eyelids fully retracted for no less than 20 minutes. To facilitate irrigation, a drop of an anesthetic (eg, proparacaine) in each eye should be used, and the eyelids should be kept open with an eyelid retractor. An adequate irrigation stream may be obtained by running 1 L of 0.9% sodium chloride through regular IV tubing held a few inches from the eye or by using an irrigating lens. Checking the eyelid fornices with pH paper strips is important to ensure adequate irrigation; the pH should normally be 6.5 to 7.6 if accurately tested, although when using paper test strips, the measurement will often be near 8.0. [Chapter 25](#) describes the management of toxic ophthalmic exposures in more detail.

IDENTIFYING PATIENTS WITH NONTOXIC EXPOSURES

There is a risk of needlessly subjecting a patient to potential harm when a patient with a nontoxic exposure is treated aggressively with GI evacuation techniques and other forms of management indicated for serious exposures. More than 40% of exposures reported to poison centers annually are judged to be nontoxic or minimally toxic. The following general guidelines^{3,4} for considering an exposure nontoxic or minimally toxic will assist clinical decision making:

1. Identification of the product and its ingredients is possible.
2. None of the US Consumer Product Safety Commission's "signal words" (CAUTION, WARNING, or DANGER) appear on the product label.

3. The history permits the route(s) of exposure to be determined.
4. The history permits a reliable approximation of the maximum quantity involved with the exposure.
5. Based on the available medical literature and clinical experience, the potential effects related to the exposure are expected to be at most benign and self-limited and do not require referral to a clinician.^{3,4}
6. The patient is asymptomatic or has developed the expected benign self-limited toxicity.

ENSURING OPTIMAL OUTCOME

The best way to ensure an optimal outcome for the patient with a suspected toxic exposure is to apply the principles of basic and advanced life support in conjunction with a planned and stepwise approach, always bearing in mind that a toxicologic etiology or co-etiology for any abnormal conditions necessitates modifying whatever standard approach is brought to the bedside of a severely ill patient. For example, it is extremely important to recognize that xenobiotic-induced dysrhythmias or cardiac instability require alterations in standard protocols that assume a primary cardiac or nontoxicologic etiology ([Chaps. 16 and 17](#)).

Typically, only some of the xenobiotics to which a patient is exposed will ever be confirmed by laboratory analysis. The thoughtful combination of stabilization, general management principles, and specific treatment when indicated will result in successful outcomes in the vast majority of patients with actual or suspected exposures.

SUMMARY

- Patients with a suspected overdose or poisoning and an AMS present some of the most serious initial challenges.
- Conscious patients, asymptomatic patients, and pregnant patients with possible xenobiotic exposures raise additional management issues, as do the victims of toxic cutaneous or ophthalmic exposures.
- One of the most frequent toxicologic emergencies that clinicians must address is a patient with a suspected toxic exposure to an unidentified xenobiotic (medication or substance), sometimes referred to as an unknown overdose.
- Consider not only patients who have an AMS but also those who are suicidal, those who use illicit drugs, and those who are exposed to xenobiotics of which they are unaware.

Acknowledgment

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5 DIAGNOSTIC IMAGING

David T. Schwartz

Diagnostic imaging can play a significant role in the management of many patients with toxicologic emergencies. Radiography can confirm a diagnosis (eg, by visualizing the xenobiotic), assist in therapeutic interventions such as monitoring gastrointestinal (GI) decontamination, and detect complications of the xenobiotic exposure (Table 5–1).¹⁸⁰

TABLE 5–1. Xenobiotics with Diagnostic Imaging Findings

<i>Xenobiotic</i>	<i>Imaging Study*</i>	<i>Finding</i>
Amiodarone	Chest	Phospholipidosis (interstitial and alveolar filling), pulmonary fibrosis
Asbestos	Chest	Interstitial fibrosis (asbestosis), calcified pleural plaques, mesothelioma
Beryllium	Chest	Acute: Airspace filling; chronic: hilar adenopathy
Biphosphonates	Skeletal	Increase bone density, insufficiency fractures femoral shaft
Body packer	Upper GI series or abdominal CT	Ingested packets, ileus, bowel obstruction
Carbon monoxide	Head CT, MRI SPECT, PET	Bilateral basal ganglia lucencies, white matter demyelination, cerebral dysfunction
Gastric ingestion	Enteric contrast	Esophageal perforation or stricture
Chemotherapeutics (busulfan, bleomycin)	Chest	Interstitial pneumonitis
Cholinergics	Chest	Diffuse airspace filling (bronchorrhea)
Cocaine	Chest, abdominal Noncontrast head CT, MRI, TEE, SPECT, PET	Diffuse airspace filling, perianomedastinum, pneumothorax, aortic dissection, perforation SAH, intracerebral hemorrhage, infarction, cerebral dysfunction, dopamine receptor downregulation
Corticosteroids	Skeletal	Avascular necrosis (femoral head)
Ethanol	Chest, Head CT, MRI, SPECT, PET	Dilated cardiomyopathy, aspiration pneumonitis, rib fractures, cortical atrophy, cerebellar atrophy, SDH (head trauma), cerebellar and cortical dysfunction
Fluorosis	Skeletal	Osteodensosis, osteophytosis, ligament calcification
Hydrocarbons (low viscosity)	Chest	Aspiration pneumonitis
Inhaled allergens	Chest	Hypersensitivity pneumonitis
Iron	Abdominal	Radiopaque tablets
Irritant gases	Chest	Diffuse airspace filling
Lead	Skeletal Abdominal	Metaphyseal bands in children (proximal tibia, distal radius), bullets (dissolution near joints); ingested leaded paint chips or other leaded compounds
Manganese	Brain MRI	Basal ganglia and midbrain hyperintensity
Mercury (elemental)	Abdominal, skeletal, or chest	Ingested, injected, or embolic deposits
Metals (Pb, Tl, As)	Abdominal	Ingested xenobiotic
Nitrofurantoin	Chest	Hypersensitivity pneumonitis
Opioids	Chest Abdominal	Acute respiratory distress syndrome Ileus
Phenytoin	Chest	Hilar lymphadenopathy
Procainamide, INH, hydralazine	Chest	Pleural and pericardial effusions (xenobiotic-induced lupus syndrome)
Salicylates	Chest	Acute respiratory distress syndrome
Silica, coal dust	Chest	Interstitial fibrosis, hilar adenopathy (egg-shell calcification)
Thorium dioxide	Abdominal	Hepatic and splenic deposition

*Conventional radiography unless otherwise stated.

CT = computed tomography; INH = isoniazid; MRI = magnetic resonance imaging; PET = positron emission tomography; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; SPECT = single-photon emission tomography.

Conventional radiography is readily available in the emergency department (ED) and is the imaging modality most frequently used in acute patient management. Other imaging modalities are used in certain other toxicologic emergencies, including computed tomography (CT); enteric and intravascular contrast studies; ultrasonography; transesophageal

echocardiography (TEE); magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA); and nuclear scintigraphy, including positron emission tomography (PET) and single-photon emission tomography (SPECT).

VISUALIZING THE XENOBIOTIC

A number of xenobiotics are radiopaque and can potentially be detected by conventional radiography. Radiography is most useful when a substance that is known to be radiopaque is ingested or injected. When the identity of the xenobiotic is unknown, the usefulness of radiography is very limited. When ingested, a radiopaque xenobiotic may be seen on an abdominal radiograph. Injected radiopaque xenobiotics are also amenable to radiographic detection. If the toxic material itself is available for examination, it can be radiographed outside of the body to detect any radiopaque contents (Fig. 105–2).⁷⁶

RADIOACITY

The radiopacity of a xenobiotic is determined by several factors. First, the intrinsic radiopacity of a substance depends on its physical density (g/cm^3) and the atomic numbers of its constituent atoms. Biologic tissues are composed mostly of carbon, hydrogen, and oxygen and have an average atomic number of approximately 6. Substances that are more radiopaque than soft tissues include bone, which contains calcium (atomic number 20), radiocontrast agents containing iodine (atomic number 53) and barium (atomic number 56), iron (atomic number, 26), and lead (atomic number 82). Some xenobiotics have constituent atoms of high atomic number, such as chlorine (atomic number 17), potassium (atomic number 19), and sulfur (atomic number 16) that contribute to their radiopacity.

The thickness of an object also affects its radiopacity. Small particles of a moderately radiopaque xenobiotic are often not visible on a radiograph. Finally, the radiographic appearance of the surrounding area also affects the detectability of an object. A moderately radiopaque tablet is easily seen against a uniform background, but in a patient, overlying bone or bowel gas often obscures the tablet.

ULTRASONOGRAPHY

Compared with conventional radiography, ultrasonography theoretically is a useful tool for detecting ingested xenobiotics because it depends on echogenicity rather than radiopacity for visualization.³³ Solid pills within the fluid-filled stomach may have an appearance similar to gallstones within the gallbladder. In one in vitro study using a water-bath model, virtually all intact pills could be visualized.⁷ The authors were also successful at detecting pills within the stomachs of human volunteers who ingested pills. Nonetheless, reliably finding pills scattered throughout the GI tract, which often contains air and feces that block the ultrasound beam, is a formidable task. Ultrasonography, therefore, has limited clinical practicality.

INGESTION OF AN UNKNOWN XENOBIOTIC

Although a clinical policy issued by the American College of Emergency Physicians in 1995 suggested that an abdominal radiograph should be obtained in unresponsive overdosed patients in an attempt to identify the involved xenobiotic, the role of abdominal radiography in screening a patient who has ingested an unknown xenobiotic is questionable.⁶ The number of potentially ingested xenobiotics that are radiopaque is limited. In addition, the radiographic appearance of an ingested xenobiotic is not sufficiently distinctive to determine its identity (Fig. 5–1).²⁰⁵ However, when ingestion of a radiopaque xenobiotic such as ferrous sulfate tablets or another metal with a high atomic number is suspected, abdominal radiographs are helpful.⁵ In addition, knowledge of potentially radiopaque xenobiotics is useful in suggesting diagnostic possibilities when a radiopaque xenobiotic is discovered on an abdominal radiograph that was obtained for reasons other than suspected xenobiotic ingestion, such as in a patient with abdominal pain (Fig. 5–2).^{179,186}

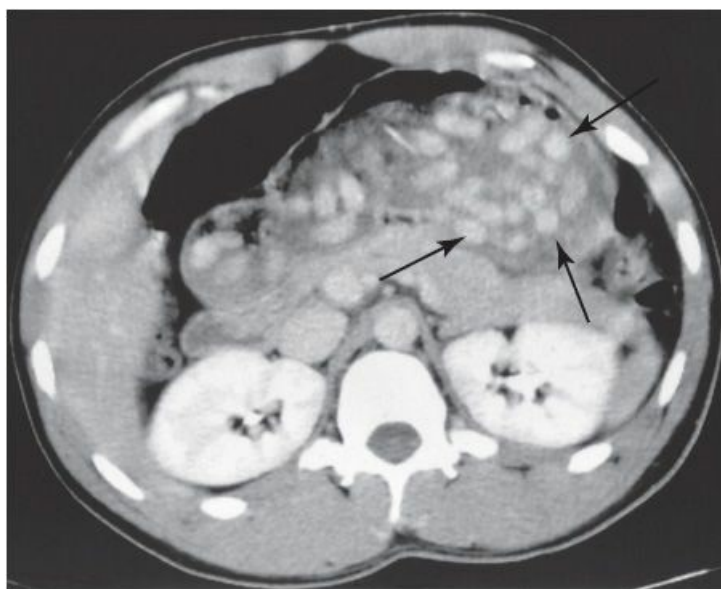


FIGURE 5–1. Ingestion of an unknown substance. A 46 year-old man presented to the emergency department with a depressed level of consciousness. Because he also complained of abdominal pain and mild diffuse abdominal tenderness, a CT scan of the abdomen was obtained. The CT scan revealed innumerable tablet-shaped densities within the stomach (arrows). The CT finding was suspicious for an overdose of an unknown xenobiotic. Orogastric lavage was attempted, and the patient vomited a large amount of whole navy beans. CT is able to detect small, nearly isodense structures such as these that cannot be seen using conventional radiography. (Used with permission of Dr. Earl J. Reisdorff, MD, Michigan State University, Lansing, MI.)



FIGURE 5–2. Detection of a radiopaque substance on an abdominal radiograph. An abdominal radiograph obtained on a patient with upper abdominal pain revealed radiopaque material throughout the intestinal tract (arrows). Further questioning of the patient revealed that he had been consuming bismuth subsalicylate (Pepto-Bismol) tablets to treat his peptic ulcer (bismuth; atomic number 83). The identification of radiopaque material does not allow determination of the nature of the substance.

Several investigators have studied the radiopacity of various medications.^{52,59,81,87,97,147,176,189,197} These investigators used an in vitro water-bath model to simulate the radiopacity of abdominal soft tissues.¹⁷⁶ The studies found that only a small number of medications exhibit some degree of radiopacity. A short list of the more consistently radiopaque xenobiotics is summarized in the mnemonic CHIPES—chloral hydrate, “heavy metals,” iron, phenothiazines, and enteric-

coated and sustained-release preparations.

The CHIPES mnemonic has several limitations.¹⁷⁶ It does not include all of the pills that are radiopaque in vitro such as acetazolamide and busulfan. Most radiopaque medications are only moderately radiopaque, and when ingested, they dissolve rapidly, becoming difficult or impossible to detect. “Psychotropic medications” include a wide variety of compounds of varying radiopacity.^{147,176} For example, whereas trifluoperazine (containing fluorine; atomic number 9) is radiopaque in vitro, chlorpromazine (containing chlorine; atomic number 17) is not.¹⁷⁶

Finally, sustained-release preparations and those with enteric coatings have variable composition and radiopacity. Pill formulations of fillers, binders, and coatings vary among manufacturers, and even a specific product can change depending on the date of manufacture. Furthermore, the insoluble matrix of some sustained-release preparations is radiopaque, and when seen on a radiograph, these tablets may no longer contain active medication. Some sustained-release cardiac medications such as verapamil and nifedipine have inconsistent radiopacity.^{119,188,199}

EXPOSURE TO A KNOWN XENOBIOTIC

When a xenobiotic that is known to be radiopaque is involved in an exposure, radiography plays an important role in patient care.⁵ Radiography can confirm the diagnosis of a radiopaque xenobiotic exposure, quantify the approximate amount of xenobiotic involved, and monitor its removal from the body. Examples include ferrous sulfate, sustained-release potassium chloride,¹⁹³ and heavy metals.

Iron Tablet Ingestion

Adult-strength ferrous sulfate tablets are readily detected radiographically because they are highly radiopaque and disintegrate slowly when ingested. Aside from confirming an iron tablet ingestion and quantifying the amount ingested, radiographs repeated after whole-bowel irrigation help to determine whether further GI decontamination is needed (Fig. 5–3).^{51,61,101,146,151,153,205} Nonetheless, caution must be exercised in using radiography to exclude an iron ingestion. Some iron preparations are not radiographically detectable. Liquid, chewable, or encapsulated (“Spansule”) iron preparations rapidly fragment and disperse after ingestion. Even when intact, these preparations are less radiopaque than ferrous sulfate tablets.⁵²

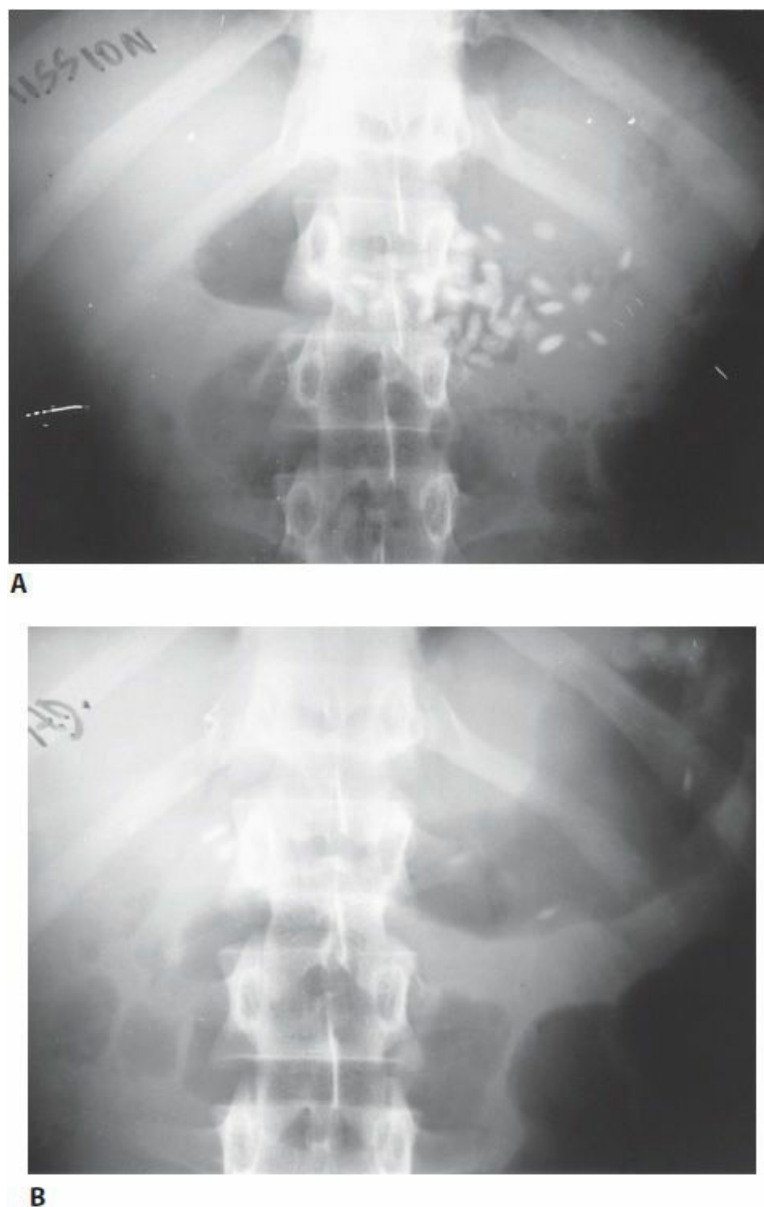


FIGURE 5-3. Iron tablet overdose. (A) Identification of the large amount of radiopaque tablets confirms the diagnosis in a patient with a suspected iron overdose and permits rough quantification of the amount ingested. (B) After emesis and whole-bowel irrigation, a second radiograph revealed some remaining tablets and indicated the need for further intestinal decontamination. (Used with permission of The Toxicology Fellowship of the New York City Poison Center.)

Metals

Metals, such as arsenic, cesium, lead, manganese, mercury, potassium, and thallium, can be detected radiographically. Examples of metal exposure include leaded ceramic glaze (Fig. 5-4),¹⁶⁸ paint chips containing lead (Fig. 96-6),^{112,133} mercuric oxide and elemental mercury (Fig. 98-1),¹²² thallium salts (atomic number 81),^{44,134} and zinc (atomic number 30).²³ Arsenic (Fig. 5-5)^{77,116,203} with a lower atomic number (atomic number 33) is also radiopaque.



FIGURE 5-4. An abdominal radiograph of a patient who intentionally ingested ceramic glaze containing 40% lead. (Used with permission of The Toxicology Fellowship of the New York City Poison Center.)

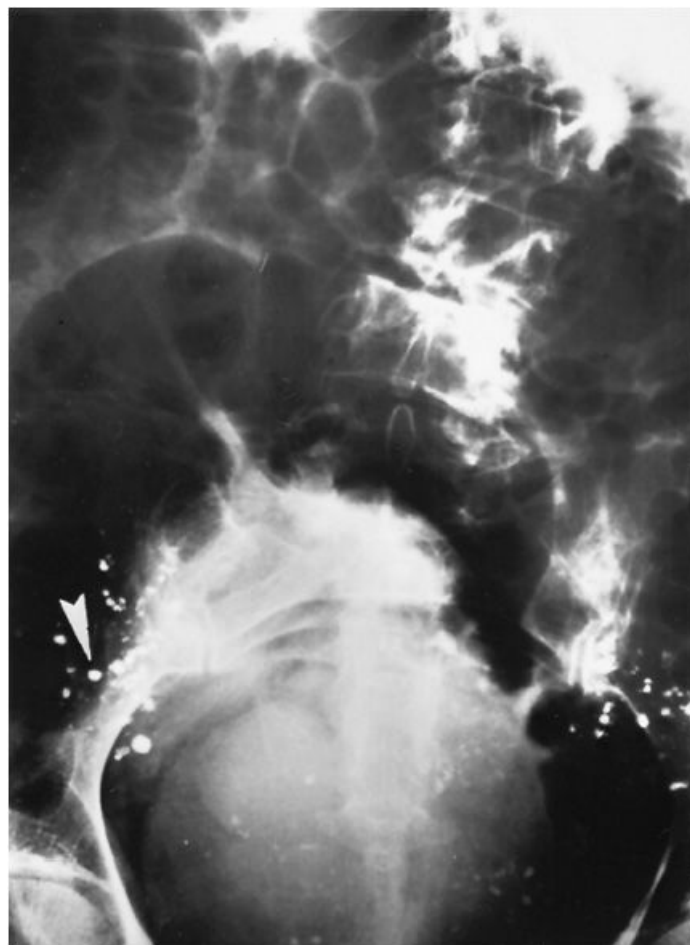


FIGURE 5-5. An abdominal radiograph in an elderly woman incidentally revealed radiopaque material in the pelvic region (arrowhead). This was residual from gluteal injection of antisypylis therapy she had received 35 to 40 years earlier. The injections may have contained an arsenical. (Used with permission of Dr. Emil J. Balthazar, Department of Radiology, Bellevue Hospital Center.)

Mercury. Unintentional ingestion of elemental mercury can occur when a glass thermometer or a long intestinal tube

with a mercury-containing balloon breaks. Liquid elemental mercury can be injected subcutaneously or intravenously. Radiographic studies assist débridement by detecting mercury that remains after the initial excision. Elemental mercury that is injected intravenously produces a dramatic radiographic picture of pulmonary embolization (Fig. 5–6).^{23,26,112,126,130,143}

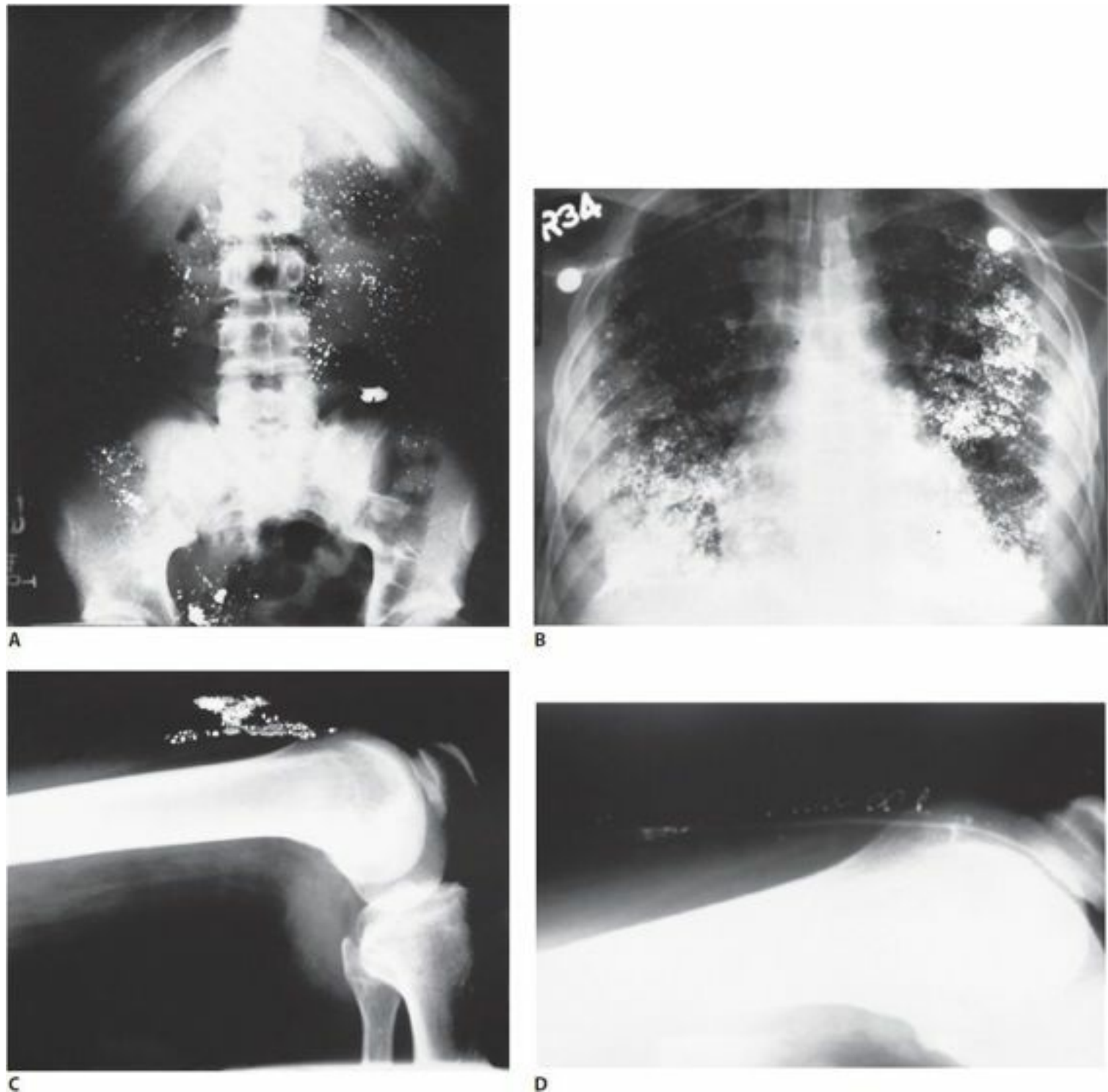


FIGURE 5–6. Elemental mercury exposures. (A) Unintentional rupture of a Cantor intestinal tube distributed mercury throughout the bowel. (B) The chest radiograph in a patient after intravenous injection of elemental mercury showing metallic pulmonary embolism. The patient developed respiratory failure, pleural effusions, and uremia and died despite aggressive therapeutic interventions. (C) Subcutaneous injection of liquid elemental mercury is readily detected radiographically. Because mercury is systemically absorbed from subcutaneous tissues, it must be removed by surgical excision. (D) A radiograph after surgical débridement reveals nearly complete removal of the mercury deposit. Surgical staples and a radiopaque drain are visible. (Image A used with permission of Dr. Richard Lefleur, Department of Radiology, Bellevue Hospital Center; image B used with permission of Dr. N. John Stewart, Department of Emergency Medicine, Palmetto Health, University of South Carolina School of Medicine; and images C and D used with permission of The Toxicology Fellowship of the New York City Poison Center.)

Lead. Ingested lead can be detected only by abdominal radiography, such as in a child with lead poisoning who has ingested paint chips (Fig. 96–6). Metallic lead (eg, a bullet) that is embedded in soft tissues is not usually systemically absorbed. However, when the bullet is in contact with an acidic environment such as synovial fluid or cerebrospinal fluid

(CSF), there may be significant absorption. Over many years, mechanical and chemical action within the joint causes the bullet to fragment and gradually dissolve.^{43,45,53,192,196} Radiography can confirm the source of lead poisoning by revealing metallic material in the joint or CSF (Fig. 5–7).

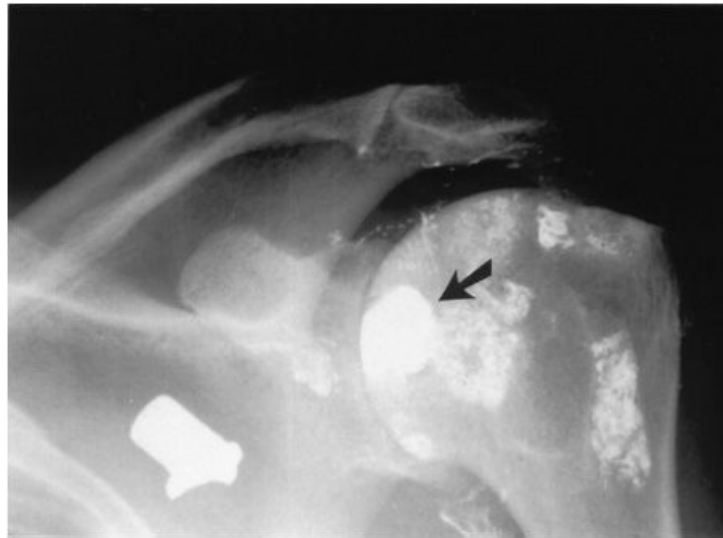


FIGURE 5–7. A “lead arthrogram” discovered many years after a bullet wound to the shoulder. At the time of the initial injury, the bullet was embedded in the articular surface of the humeral head (arrow). The portion of the bullet that protruded into the joint space was surgically removed, leaving a portion of the bullet exposed to the synovial space. A second bullet was embedded in the muscles of the scapula. Eight years after the injury, the patient presented with weakness and anemia. Extensive lead deposition throughout the synovium is seen. The blood lead concentration was 91 $\mu\text{g/dL}$. (Used with permission of The Toxicology Fellowship of the New York City Poison Center.)

Xenobiotics in Containers

In some circumstances, ingested xenobiotics can be seen even though they are of similar radiopacity to surrounding soft tissues. If a xenobiotic is ingested in a container, the container itself may be visible.

Body Packers. “Body packers” are individuals who smuggle large quantities of illicit drugs across international borders in securely sealed packets.^{3,15,16,25,36,56,95,109,125,132,156,181,183,201} The uniformly shaped, oblong packets can be seen on abdominal radiographs either because there is a thin layer of air or metallic foil within the container wall or because the packets are outlined by bowel gas (Fig. 5–8). In some cases, a “rosette” representing the knot at the end of the packet is seen.¹⁸³ Intraabdominal calcifications (pancreatic calcifications and bladder stones) have occasionally been misinterpreted as drug-containing packets.^{201,217}



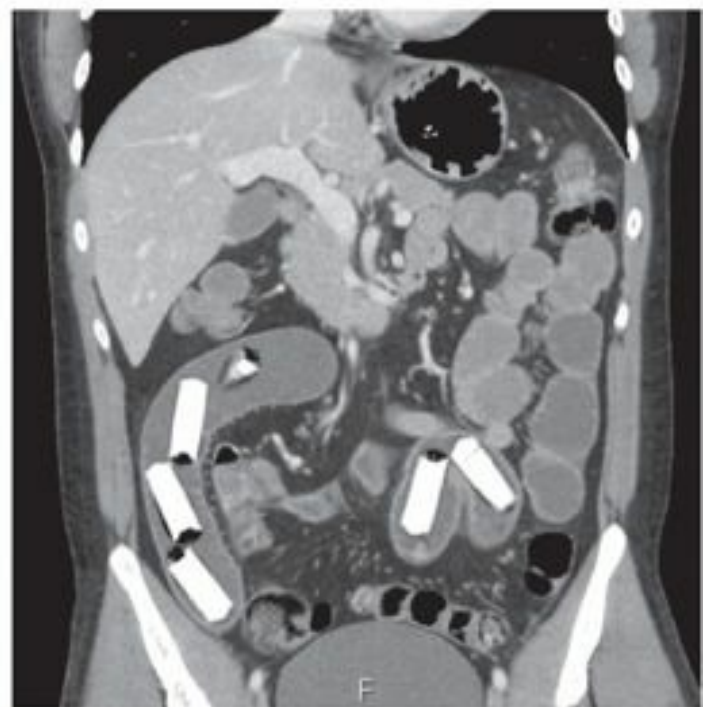
A



B



C



D

FIGURE 5–8. Three “body packers” showing the various appearances of drug packets. Drug smuggling is accomplished by packing the gastrointestinal tract with large numbers of manufactured, well-sealed containers. (A) Multiple oblong packages of uniform size and shape are seen throughout the bowel. (B) The packets are visible in this patient because they are surrounded by a thin layer of air within the wall of the packet. (C and D) Small bowel obstruction caused by drug packets in a man who developed abdominal pain and vomiting one day after arriving on a plane flight from Colombia. Computed tomography confirmed bowel obstruction, and the patient underwent laparotomy and removal of 15 packets through an enterotomy. (Images A and B used with permission of Dr. Emil J. Balthazar, Department of Radiology, Bellevue Hospital Center. Images C and D used with permission of The Toxicology Fellowship of the New York City Poison

Control Center.)

The sensitivity of abdominal radiography for such packets is high, in the range of 85% to 90%. The major role of radiography is as a rapid screening test to confirm the diagnosis in individuals suspected of smuggling drugs, such as persons being held by airport customs agents. However, because packets are occasionally not visualized and the rupture of even a single packet can be fatal, abdominal radiography should not be relied on to exclude the diagnosis of body packing. Ultrasonography has also been used to rapidly detect packets, although it also should not be relied on to exclude such a life-threatening ingestion.^{33,78,136} After intestinal decontamination, an upper GI series with oral contrast or CT with or without enteric contrast can reveal any remaining packets.^{80,91,148}

Body Stuffers. A “body stuffer” is an individual who, in an attempt to avoid imminent arrest, hurriedly ingests contraband in insecure packaging.¹⁷⁰ The risk of leakage from such haphazardly constructed containers is high. Unfortunately, radiographic studies cannot reliably confirm or exclude such ingestions.¹⁸⁷

Occasionally, a radiograph will demonstrate the ingested container (Fig. 5–9). If the drug is in a glass or in a hard-plastic crack vial, the container may be seen.⁹⁰ If the body stuffer swallows soft plastic bags containing the drug, the containers are not usually visible. However, in three reported cases, “baggies” were visualized by abdominal CT.^{37,48,83,85,105,157,180}

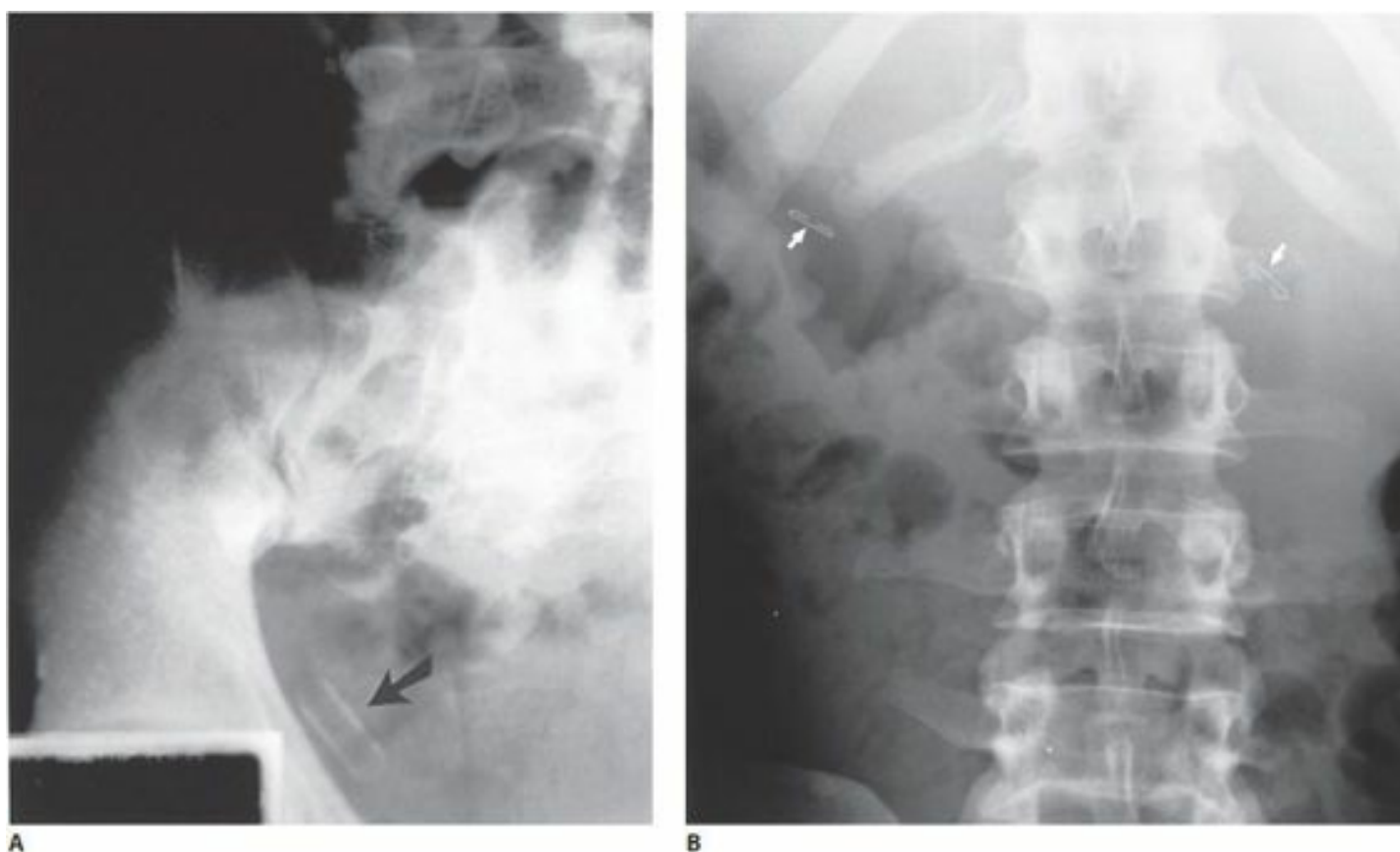


FIGURE 5–9. Two “body stuffers.” Radiography infrequently helps with the diagnosis. (A) An ingested glass crack vial is seen in the distal bowel (arrow). The patient had ingested his contraband several hours earlier at the time of a police raid. Only the tubular-shaped container, and not the xenobiotic, is visible radiographically. The patient did not develop signs of cocaine intoxication during 24 hours of observation. (B) Another patient in police custody was brought to the emergency department for allegedly ingesting his drugs. The patient repeatedly denied this. The radiographs revealed “nonsurgical” staples in his abdomen (arrows). When questioned again, the patient admitted that he had swallowed several plastic bags that were stapled closed. (Used with permission of The Toxicology Fellowship of the New York City Poison Center.)

Halogenated Hydrocarbons

Some halogenated hydrocarbons can be visualized radiographically.^{31,38} Radiopacity is proportionate to the number of chlorine atoms. Both carbon tetrachloride (CCl_4) and chloroform (CHCl_3) are radiopaque. Because these liquids are immiscible in water, a triple layer may be seen within the stomach on an upright abdominal radiograph—an uppermost air bubble, a middle radiopaque chlorinated hydrocarbon layer, and a lower gastric fluid layer. However, these ingestions are rare, and the quantity ingested is usually too small to show this effect. Other halogenated hydrocarbons such as methylene iodide are highly radiopaque.²¹⁶

Mothballs

Some types of mothballs can be visualized by radiography. Whereas relatively nontoxic paradichlorobenzene mothballs (containing chlorine; atomic number 17) are moderately radiopaque, more toxic naphthalene mothballs are radiolucent.¹⁹⁴ If the patient is known to have swallowed mothballs, the difference in radiopacity may help determine the type. However, if mothball ingestion is not already suspected, the more toxic naphthalene type may not be detected. Radiographs of mothballs outside of the patient can help distinguish these two types (Fig. 105–2).

Radiolucent Xenobiotics

A radiolucent xenobiotic may be visible because it is less radiopaque than surrounding soft tissues. Hydrocarbons such as gasoline are relatively radiolucent when embedded in soft tissues. The radiographic appearance resembles subcutaneous gas as seen in a necrotizing soft tissue infection (Fig. 5–10).



FIGURE 5–10. Subcutaneous injection of gasoline into the antecubital fossa. The radiolucent hydrocarbon mimics gas in the soft tissues that is seen with a necrotizing soft tissue infection such as necrotizing fasciitis or gas gangrene (arrows). (Used with permission of The Toxicology Fellowship of the New York City Poison Center.)

EXTRAVASATION OF INTRAVENOUS CONTRAST MATERIAL

Extravasation of intravenous (IV) radiographic contrast material is a common occurrence. In most cases, the volume extravasated is small, and there are no clinical sequelae.^{17,35,54,169} Rarely, a patient has an extravasation large enough to cause cutaneous necrosis and ulceration.

Recently, the incidence of sizable extravasations has increased because of the use of rapid-bolus automated power injectors for CT studies.²⁰⁸ Fortunately, nonionic low-osmolality contrast solutions are currently nearly always used for these studies. These solutions are far less toxic to soft tissues than older ionic high-osmolality contrast materials.

The treatment of contrast extravasation has not been studied in a large series of human subjects and is therefore controversial. Various strategies have been proposed. The affected extremity should be elevated to promote drainage. Although topical application of heat causes vasodilation and could theoretically promote absorption of extravasated contrast material, the intermittent application of ice packs has been shown to lower the incidence of ulceration.³⁵ Rarely, an extremely large volume of liquid is injected into the soft tissues, which requires surgical decompression when there are signs of a compartment syndrome. A radiograph of the extremity will demonstrate the extent of extravasation (Fig. 5–11).³⁵



FIGURE 5–11. Extravasation of intravenous contrast into the soft tissues of the upper extremity that occurred during a computed tomography contrast bolus administered by a power injector. Despite the extensive extravasation, the patient was successfully managed with limb elevation and cool compresses. (Used with permission of Mark Bernstein, MD, Department of Radiology, New York University School of Medicine.)

Precautions should be taken to prevent extravasation. A recently placed, well-running IV catheter should be used. The distal portions of the extremities (hands, wrist, and feet) should not be used as IV sites for injecting contrast. Patients who are more vulnerable to complications and those whose veins may be more fragile, such as infants, debilitated patients, and those with an impaired ability to communicate, must be closely monitored to prevent or determine if extravasation occurs.

Summary

Obtaining an abdominal radiograph in an attempt to identify pills or other xenobiotics in a patient with an unknown ingestion is unlikely to be helpful and is, in general, not warranted. Radiography is most useful when the suspected xenobiotic is known to be radiopaque, as is the case with iron tablets and heavy metals. The xenobiotic can be radiographed within the patient’s abdomen; elsewhere in the patient’s body; or, if the material is available, outside of the patient.

VISUALIZING THE EFFECTS OF A XENOBIOTIC ON THE BODY

The lungs, central nervous system (CNS), GI tract, and skeleton are the organ systems that are most amenable to diagnostic imaging. Disorders of the lungs and skeletal system are seen by plain radiography. For abdominal pathology, contrast studies and CT are more useful, although plain radiographs can diagnose intestinal obstruction, perforation, and radiopaque foreign bodies. Imaging of the CNS uses CT, MRI, and nuclear scintigraphy (PET and SPECT).

Skeletal Changes Caused by Xenobiotics

A number of xenobiotics affect bone mineralization. Toxicologic effects on bone result in either increased or decreased density (Table 5–2). Some xenobiotics produce characteristic radiographic pictures, although exact diagnoses usually depend on correlation with the clinical scenario.^{10,145} Furthermore, alterations in skeletal structure develop gradually and are usually not visible unless the exposure continues for at least 2 weeks.

TABLE 5–2. Xenobiotic Causes of Skeletal Abnormalities

<i>Increased Bone Density</i>	<i>Diminished Bone Density (Either Diffuse Osteoporosis or Focal Lesions)</i>
<p>Metaphyseal bands (children): Lead, bismuth, phosphorus: Chondrosclerosis caused by toxic effect on bone growth</p> <p>Diffuse increased bone density: Fluorosis: Osteosclerosis (hyperostosis deformans), osteophytosis, ligament calcification; usually involves the axial skeleton (vertebrae and pelvis) and may cause compression of the spinal cord and nerve roots</p> <p>Bisphosphonates: Increased bone density (inhibition of osteoclast activity) Atypical insufficiency fractures proximal femoral shaft and subtrochanteric region</p> <p>Hypervitaminosis A (pediatric): Cortical hyperostosis and subperiosteal new bone formation; diaphyses of long bones have an undulating appearance</p> <p>Hypervitaminosis D: Generalized osteosclerosis, cortical thickening, and metaphyseal bands</p>	<p>Corticosteroids: Osteoporosis: Diffuse Osteonecrosis: Focal lesions, eg, avascular necrosis of the femoral head; loss of volume with both increased and decreased bone density; osteonecrosis also occurs in alcoholism, bismuth arthropathy, Caisson disease (dysbarism), trauma</p> <p>Hypervitaminosis D: Focal or generalized osteoporosis</p> <p>Injection drug use: Osteomyelitis (focal lytic lesions) caused by septic emboli; usually affects vertebral bodies and sternomanubrial joint</p> <p>Vinyl chloride monomer: Acroosteolysis (distal phalanges)</p>

Increase in Bone Density

Lead poisoning. Skeletal radiography may suggest the diagnosis of chronic lead poisoning even before the blood lead concentration is obtained. With lead poisoning, the metaphyseal regions of rapidly growing long bones develop transverse bands of increased density along the growth plate (Fig. 5-12).^{21,160,163,174} Characteristic locations are the distal femur and proximal tibia. Flaring of the distal metaphysis also occurs. Such lead lines are also seen in the vertebral bodies and iliac crest. Detected in approximately 80% of children with a mean lead concentration of $49 \pm 17 \mu\text{g/dL}$, lead lines usually occur in children between the ages of 2 and 9 years.²¹ In most children, it takes several weeks for lead lines to appear, although in very young infants (2–4 months old), lead lines may develop within days of exposure.²²¹ After exposure ceases, lead lines diminish and may eventually disappear.

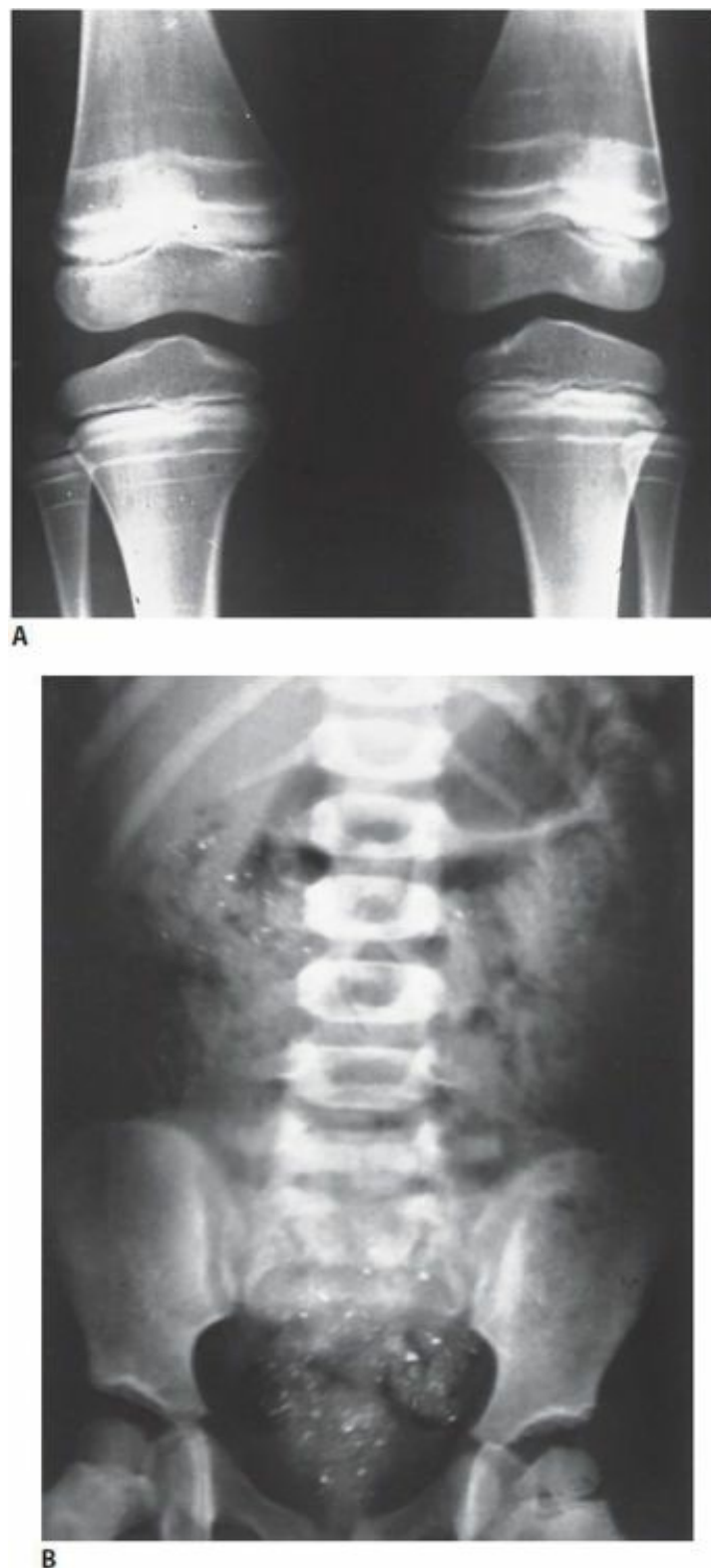


FIGURE 5-12. (A) A radiograph of the knees of a child with lead poisoning. The metaphyseal regions of the distal femur and proximal tibia have developed transverse bands representing bone growth abnormalities caused by lead toxicity. The multiplicity of lines implies repeated exposures to lead. (B) The abdominal radiograph of the child shows many radiopaque flakes of ingested leaded paint chips. Lead poisoning also caused abnormally increased cortical mineralization of the vertebral bodies, which gives them a boxlike appearance. (Used with permission of Dr. Nancy Genieser, Department of Radiology, Bellevue Hospital Center.)

Lead lines are caused by the toxic effect of lead on bone growth and do not represent deposition of lead in bone. Lead impedes resorption of calcified cartilage in the zone of provisional calcification adjacent to the growth plate. This is termed chondrosclerosis.^{21,47} Other xenobiotics that cause metaphyseal bands are yellow phosphorus ([Chap. 116](#)), bismuth ([Chap. 90](#)), and vitamin D ([Chap. 47](#)).

Fluorosis. Fluoride poisoning causes a diffuse increase in bone mineralization. Endemic fluorosis occurs where drinking water contains very high levels of fluoride (≥ 2 or more parts per million), as an occupational exposure among aluminum workers handling cryolite (sodium–aluminum fluoride), or with excessive tea drinking. The skeletal changes associated with fluorosis are osteosclerosis (hyperostosis deformans), osteophytosis, and ligament calcification ([Fig. 5-13](#)). Fluorosis primarily affects the axial skeleton, especially the vertebral column and pelvis. Thickening of the vertebral

column may cause compression of the spinal cord and nerve roots. Without a history of fluoride exposure, the clinical and radiographic findings can be mistaken for osteoblastic skeletal metastases. The diagnosis of fluorosis is confirmed by histologic examination of the bone and measurement of fluoride levels in the bone and urine.^{22,210}



FIGURE 5-13. Skeletal fluorosis. A 28 year-old man developed progressive muscle and joint pain over 3 to 4 weeks particularly involving his hands with thickening of his fingers. An evaluation for inflammatory rheumatologic disorders was negative. Radiographs of his hands showed exuberant periosteal new bone formation known as “periostitis deformans,” which is characteristic of skeletal fluorosis. Further questioning revealed that the patient had been “huffing” the propellant of “Dust Off”; 225 cans were found at his residence. The propellant is difluoroethane (Freon 152a). The hydrocarbon is dehalogenated in the liver and chronic exposure results in fluoride toxicity. (Used with permission of Dr. Eric Lavonas, Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, CO, and Dr. Shawn M. Varney, Department of Emergency Medicine, San Antonio Military Medical Center, TX.)

Bisphosphonates. Bisphosphonates such as alendronate (Fosamax) are commonly used to treat osteoporosis. They increase bone density by inhibiting osteoclast activity and decreasing bone resorption. However, by suppressing bone turnover and fracture healing, bisphosphonates are associated with accumulated microdamage to bone and skeletal weakening, which makes the bone vulnerable to fractures. Radiographically, there is thickening of the cortex of diaphyseal bone, typically the proximal femoral shaft. Such bone is associated with atypical proximal femoral shaft and subtrochanteric fractures after low-energy injuries such as a fall from standing. The fractures are transverse and have a characteristic “beaked” appearance caused by the cortical thickening (Fig. 5-14).



FIGURE 5–14. Biphosphonate (alendronate) associated proximal femoral shaft fracture. A 61 year-old woman tripped on the sidewalk, falling on to her right side. She had been taking alendronate (Fosamax) for 3 years for osteoporosis. There is diffuse cortical thickening of the femoral shaft and a transverse fracture in the subtrochanteric region with “beaking” of the fractured cortex on the medial side of the fracture.

Focal Loss of Bone Density. Skeletal disorders associated with focal diminished bone density (or mixed rarefaction and sclerosis) include osteonecrosis, osteomyelitis, and osteolysis. Osteonecrosis, also known as avascular necrosis, most often affects the femoral head, humeral head, and proximal tibia.¹²⁷ There are many causes of osteonecrosis. Xenobiotic causes include long-term corticosteroid use and alcoholism. Radiographically, focal skeletal lucencies and sclerosis are seen, ultimately with loss of bone volume and collapse (**Fig. 5–15A**).

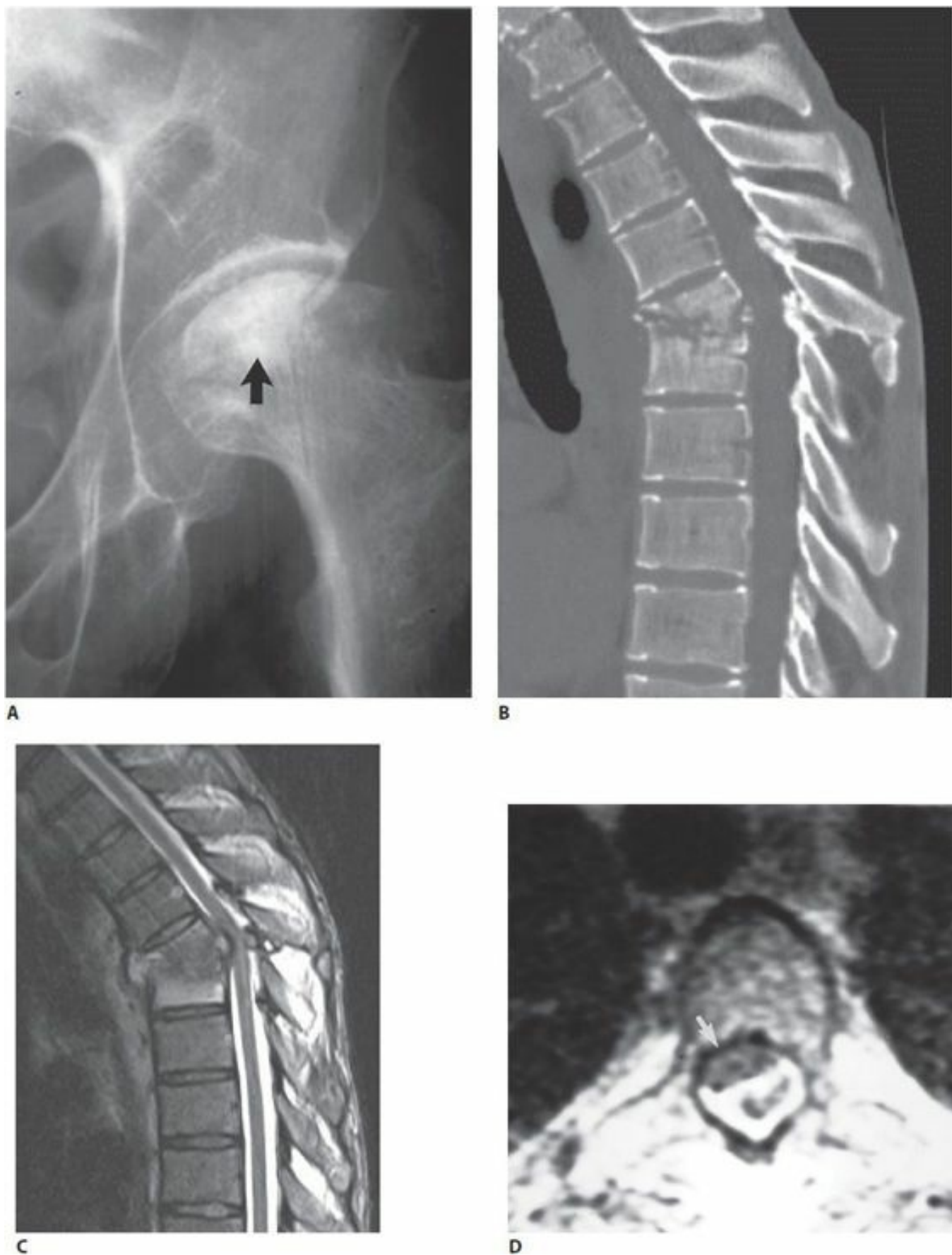


FIGURE 5-15. (A) Avascular necrosis causing collapse of the femoral head in a patient with long-standing steroid-dependent asthma (arrow). (B and C) Vertebral osteomyelitis in an injection drug user who presented with posterior thoracic pain for 2 weeks and then lower extremity weakness. As seen on CT, the infection begins in the intervertebral disk and then spreads to the adjacent vertebral bodies. Magnetic resonance image shows extension into the spinal canal causing spinal cord compression. (D) An injection drug user with thoracic back pain, leg weakness, and low-grade fever. Radiographic and CT findings of the spine were negative. Magnetic resonance image showing an epidural abscess (arrow) compressing the spinal cord. The cerebrospinal fluid in the compressed thecal sac is bright on this T2-weighted image. (From Levitan R: Thoracolumbar spine. In Schwartz, Reisdorff EJ, eds: Emergency Radiology. New York, McGraw-Hill; 2000:343, with permission.)

Acroosteolysis. Acroosteolysis is bone resorption of the distal phalanges and is associated with occupational exposure

to vinyl chloride monomer. Protective measures have reduced its incidence since it was first described in the early 1960s.¹⁶⁴

Osteomyelitis. Osteomyelitis is a serious complication of injection drug use. It usually affects the axial skeleton, especially the vertebral bodies, as well as the sternomanubrial and sternoclavicular joints (Figs. 5–15B and C).^{74,79} Back pain or neck pain in injection drug users warrants careful consideration. A spinal epidural abscess causing spinal cord compression may accompany vertebral osteomyelitis.^{92,125} Radiographic findings are negative early in the disease course before skeletal changes are visible and the diagnosis is confirmed by MRI or CT (Fig. 5–15D).

Soft Tissue Changes

Certain abnormalities in soft tissues, predominantly as a consequence of infectious complications of injection drug use, are amenable to radiographic diagnosis.^{74,75,79,99,198} In an injection drug user who presents with signs of local soft tissue infections, radiography is indicated to detect a retained metallic foreign body, such as a needle fragment, or subcutaneous gas, as may be seen in a necrotizing soft tissue infection such as necrotizing fasciitis. CT is more sensitive at detecting soft tissue gas than is conventional radiography. CT and ultrasonography can also detect subcutaneous or deeper abscesses that require surgical or percutaneous drainage.

Pulmonary and Other Thoracic Problems

Many xenobiotics that affect intrathoracic organs produce pathologic changes that can be detected on chest radiographs.^{9,12,24,49,63,75,140,172,219} The lungs are most often affected, resulting in dyspnea or cough, but the pleura, hilum, heart, and great vessels may also be involved.⁶ Patients with chest pain may have a pneumothorax, pneumomediastinum, or aortic dissection. Patients with fever, with or without respiratory symptoms, may have a focal infiltrate, pleural effusion, or hilar lymphadenopathy.

Chest radiographic findings may suggest certain diseases, although the diagnosis ultimately depends on a thorough clinical history. When a specific xenobiotic exposure is known or suspected, the chest radiograph can confirm the diagnosis and help in assessment. If a history of xenobiotic exposure is not obtained, a patient with an abnormal chest radiograph may initially be misdiagnosed as having pneumonia or another disorder that is more common than xenobiotic-mediated lung disease.¹⁶⁶ Therefore, patients with chest radiographic abnormalities should be carefully questioned regarding possible xenobiotic exposures at work or at home, as well as the use of medications or other drugs.

Many pulmonary disorders are radiographically detectable because they result in fluid accumulation within the normally air-filled lung. Fluid may accumulate within the alveolar spaces or interstitial tissues of the lung, producing the two major radiographic patterns of pulmonary disease: airspace filling and interstitial lung disease (Table 5–3). Most xenobiotics are widely distributed throughout the lungs and produce a diffuse rather than a focal radiographic abnormality.

TABLE 5–3. Chest Radiographic Findings in Toxicologic Emergencies

<i>Radiographic Finding</i>	<i>Responsible Xenobiotic</i>	<i>Disease Processes</i>
Diffuse airspace filling	Salicylates Opioids Paraquat Irritant gases: NO ₂ (silo filler's disease), phosgene (COCl ₂), Cl ₂ , H ₂ S Organic phosphorus compounds, carbamates Alcoholic cardiomyopathy, cocaine, doxorubicin, cobalt	Acute respiratory distress syndrome Cholinergic stimulation (bronchorrhea) Congestive heart failure
Focal airspace filling	Low-viscosity hydrocarbons Gastric contents aspiration: CNS depressants, alcohol, seizures	Aspiration pneumonia
Multifocal airspace filling	Injection drug user	Septic emboli
Interstitial patterns: Fine or coarse reticular or reticulonodular pattern Patchy airspace filling is seen in some cases	Inhaled organic allergens: Farmer's lung, pigeon breeder's lung Nitrofurantoin, penicillamine Antineoplastics: Busulfan, bleomycin, carmustine, cyclophosphamide, methotrexate Amiodarone Talcosis (illicit drug contaminant) Pneumoconiosis: Asbestosis, silicosis, coal dust, berylliosis (chronic)	Hypersensitivity pneumonitis Cytotoxic lung damage Phospholipidosis Injected particulates Inhaled inorganic particulates
Pleural effusion	Procainamide, hydralazine, INH, methyldopa	Drug-induced SLE
Pneumomediastinum Pneumothorax	"Crack" cocaine and marijuana (forceful inhalation), syrup of ipecac and alcoholism (forceful vomiting), subclavian vein injection puncture	Barotrauma
Pleural plaques (calcified)	Asbestos exposure	Fibrosis or asbestosis
Lymphadenopathy	Phenytoin, methotrexate (rare) Silicosis (eggshell calcification), berylliosis	Pseudolymphoma Pneumoconiosis
Cardiomegaly (chronic exposure)	Ethanol, doxorubicin, cocaine, cobalt amphetamine, ipecac syrup Drug-induced systemic lupus erythematosus (procainamide, hydralazine, INH)	Dilated cardiomyopathy Pericardial effusion
Aortic enlargement	Cocaine	Aortic dissection

CNS = central nervous system; INH = isoniazid; SLE = systemic lupus erythematosus.

Diffuse Airspace Filling. Overdose with various xenobiotics, including salicylates, opioids, and paraquat, may cause acute respiratory distress syndrome (ARDS) (formerly known as noncardiogenic pulmonary edema or acute lung injury) with or without diffuse alveolar damage and characterized by leaky capillaries (Fig. 5–16).^{75,85,89,123,184,191,218} There are, of course, many other causes of ARDS, including sepsis, anaphylaxis, and major trauma.²¹³ Other xenobiotic exposures that may result in diffuse airspace filling include inhalation of irritant gases that are of low water solubility such as phosgene (COCl₂), nitrogen dioxide (silo filler's disease), chlorine, hydrogen sulfide, and sulfur dioxide (Chaps. 124 and 126).^{79,102} Organic phosphorus insecticide poisoning causes cholinergic hyperstimulation, resulting in bronchorrhea (Chap. 113). Smoking "crack" cocaine is associated with diffuse alveolar hemorrhage (Chap. 78).^{60,75,79,165,219}

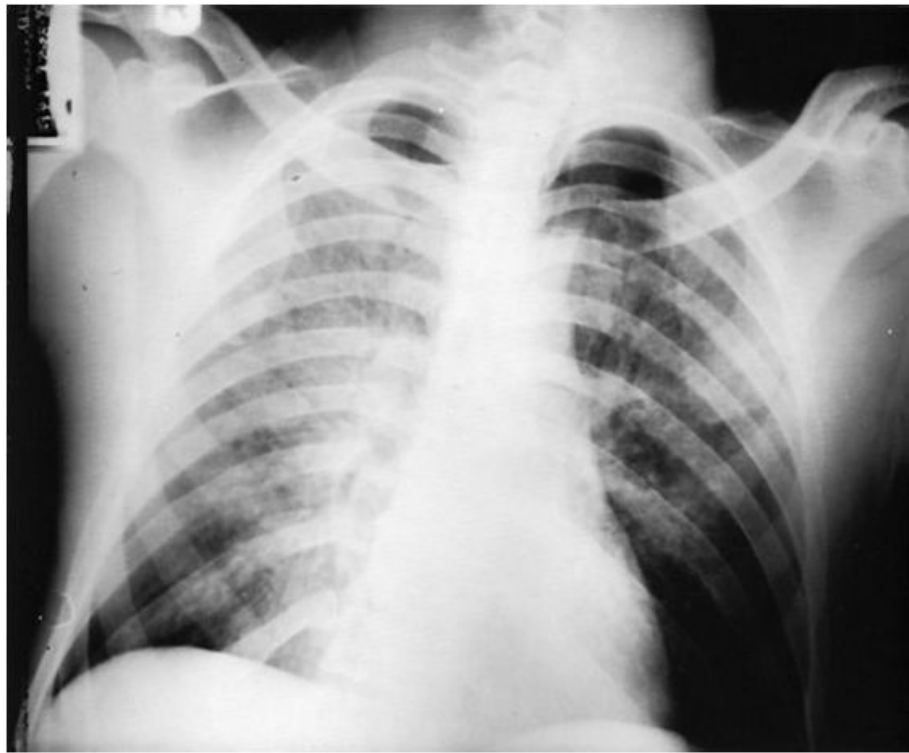


FIGURE 5–16. Diffuse airspace filling. The chest radiograph of a patient who had recently injected heroin intravenously presented with respiratory distress and acute respiratory distress syndrome. The heart size is normal.

Focal Airspace Filling. Focal infiltrates are usually caused by bacterial pneumonia, although aspiration of gastric contents also causes localized airspace disease.^{75,195} Aspiration may occur during sedative–hypnotic or alcohol intoxication or during a seizure. During ingestion, low-viscosity hydrocarbons often enter the lungs while they are being swallowed (Figs. 5–17 and 108–1). There may be a delay in the development of radiographic abnormalities, and the chest radiograph may not appear to be abnormal until 6 hours after the ingestion.⁸ During aspiration, the most dependent portions of the lung are affected. When the patient is upright at the time of aspiration, the lower lung segments are involved. When the patient is supine, the posterior segments of the upper and lower lobes are affected.⁶²

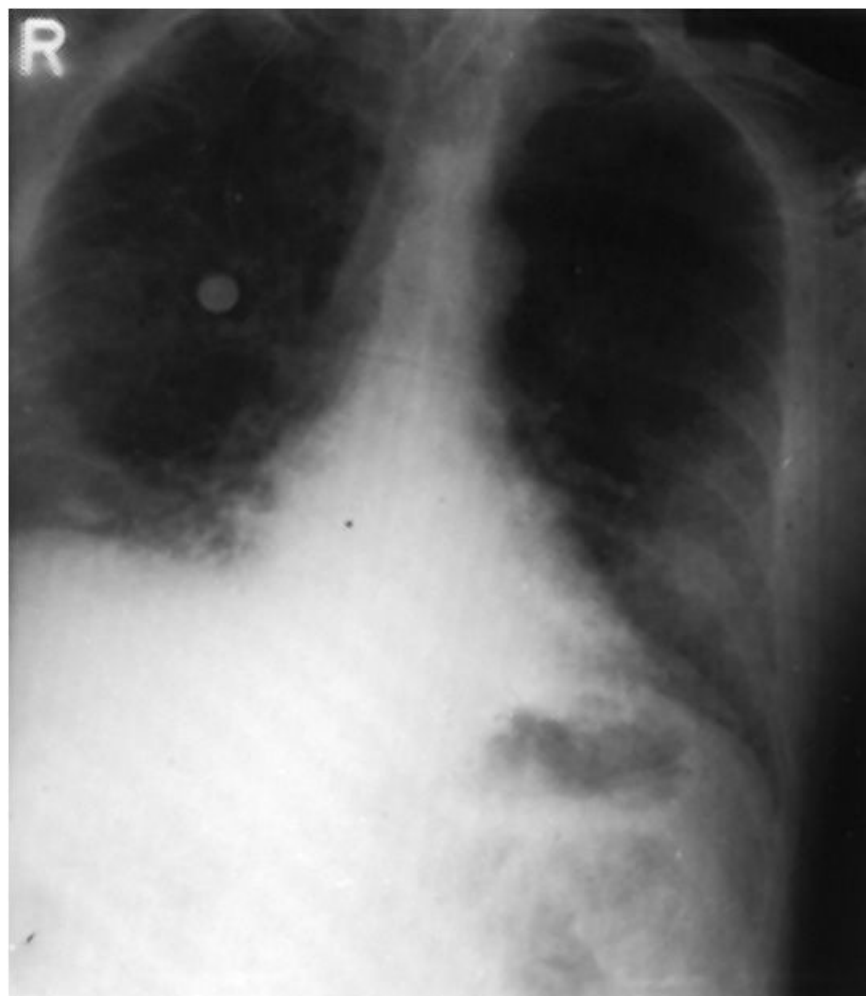


FIGURE 5–17. Focal airspace filling as a result of hydrocarbon aspiration. A 34 year-old man aspirated gasoline. The chest radiograph shows bilateral lower lobe infiltrates.

Multifocal Airspace Filling. Multifocal airspace filling occurs with septic pulmonary emboli, which is a complication of injection drug use and right-sided bacterial endocarditis. The foci of pulmonary infection often undergo necrosis and cavitation (Fig. 5–18).^{75,79}



FIGURE 5–18. Multifocal airspace filling. The chest radiograph in an injection drug user who presented with high fever but without pulmonary symptoms. Multiple ill-defined pulmonary opacities are seen throughout both lungs, which are characteristic of septic pulmonary emboli. His blood cultures grew *Staphylococcus aureus*.

Interstitial Lung Diseases. Toxicologic causes of interstitial lung disease include hypersensitivity pneumonitis, use of medications with direct pulmonary toxicity, and inhalation or injection of inorganic particulates.⁷⁵ Interstitial lung diseases may have an acute, subacute, or chronic course. On the chest radiograph, acute and subacute disorders cause a fine reticular or reticulonodular pattern (Fig. 5–19). Chronic interstitial disorders cause a coarse reticular “honeycomb” pattern.



FIGURE 5–19. Reticular interstitial pattern. The chest radiograph of a patient with cardiac disease who presented to the

ED with progressive dyspnea. The initial diagnostic impression was interstitial pulmonary edema. The patient was taking amiodarone for malignant ventricular dysrhythmias (note the implanted automatic defibrillator). The lack of response to diuretics and the high-resolution CT pattern suggested that this was toxicity to amiodarone. The medication was stopped, and there was partial clearing over several weeks. (Used with permission of Dr. Georgeann McGuinness, Department of Radiology, New York University.)

Hypersensitivity Pneumonitis. Hypersensitivity pneumonitis is a delayed-type hypersensitivity reaction to an inhaled or ingested allergen.^{40,96,166} Inhaled organic allergens such as those in moldy hay (farmer's lung) and bird droppings (pigeon breeder's lung) cause hypersensitivity pneumonitis in sensitized individuals. There are two clinical syndromes: an acute, recurrent illness and a chronic, progressive disease. The acute illness presents with fever and dyspnea. In these cases, the chest radiograph findings are normal or may show fine interstitial or alveolar infiltrates. Chronic hypersensitivity pneumonitis causes progressive dyspnea, and the radiograph shows interstitial fibrosis.

The most common medication causing hypersensitivity pneumonitis is nitrofurantoin. Respiratory symptoms occur after taking the medication for 1 to 2 weeks. Other medications that may cause hypersensitivity pneumonitis include sulfonamides and penicillins.

Chemotherapeutics. Various chemotherapeutic agents, such as busulfan, bleomycin, cyclophosphamide, and methotrexate, cause pulmonary injury by their direct cytotoxic effect on alveolar cells.^{39,65} The radiographic pattern is usually interstitial (reticular or nodular) but may include airspace filling or mixed patterns. The patient presents with dyspnea, fever, and pulmonary infiltrates that begin after several weeks of therapy. Other causes of these clinical and radiographic findings must be considered, including opportunistic infection, pulmonary carcinomatosis, pulmonary edema, and intraparenchymal hemorrhage. Symptoms usually resolve with discontinuation of the offending medication.

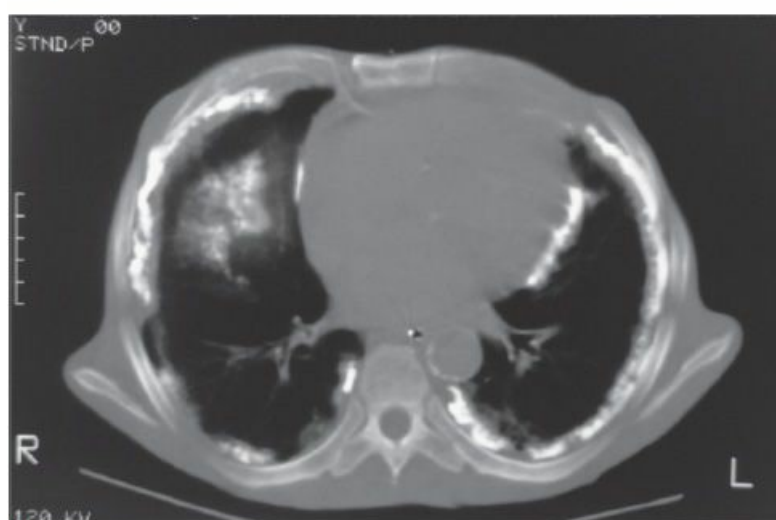
Amiodarone. Amiodarone toxicity causes phospholipid accumulation within alveolar cells and may result in pulmonary fibrosis. An interstitial radiographic pattern is seen, although airspace filling may also occur (Fig. 5–19) (Chap. 64).

Particulates. Inhaled inorganic particulates, such as asbestos, silica, and coal dust, cause pneumoconiosis. This is a chronic interstitial lung disease characterized by interstitial fibrosis and loss of lung volume.^{32,138,167,215} IV injection of illicit xenobiotics that have particulate contaminants, such as talc, causes a chronic interstitial lung disease known as talcosis.^{1,55,212}

Pleural Disorders. Asbestos-related calcified pleural plaques develop many years after asbestos exposure (Fig. 5–20). These lesions do not cause clinical symptoms and have only a minor association with malignancy and interstitial lung disease. Asbestos-related pleural plaques should not be called asbestosis because that term refers specifically to the interstitial lung disease caused by asbestos. Pleural plaques must be distinguished from mesotheliomas, which are not calcified, enlarge at a rapid rate, and erode into nearby structures such as the ribs.



A



B

FIGURE 5–20. (A) Calcified plaques typical of asbestos exposure are seen on the pleural surfaces of the lungs, diaphragm, and heart. The patient was asymptomatic; this was an incidental radiographic finding. (B) The CT scan demonstrates that the opacities seen on the chest radiograph do not involve the lung itself. A lower thoracic image shows calcified pleural plaques (the diaphragmatic plaque is seen on the right). The CT confirms that there is no interstitial lung disease (“asbestosis”).

Pleural effusions occur with drug-induced systemic lupus erythematosus (SLE).¹⁴⁰ The medications most frequently implicated are procainamide, hydralazine, isoniazid, and methyldopa. The patient presents with fever as well as other symptoms of SLE.

Pneumothorax and pneumomediastinum are associated with illicit drug use. These complications are related to the route of administration rather than to the particular drug. Barotrauma associated with the Valsalva maneuver or intense inhalation with breath holding during the smoking of “crack” cocaine or marijuana results in pneumomediastinum (Fig. 5–21A).^{20,50,75,150} Pneumomediastinum is one cause of cocaine-related chest pain that can be diagnosed by chest radiography. Forceful vomiting after ingestion of syrup of ipecac or alcohol may produce a Mallory-Weiss syndrome, pneumomediastinum, and mediastinitis (Boerhaave syndrome).²²⁰ IV drug users who attempt to inject into the subclavian and internal jugular veins may cause a pneumothorax.⁴⁶

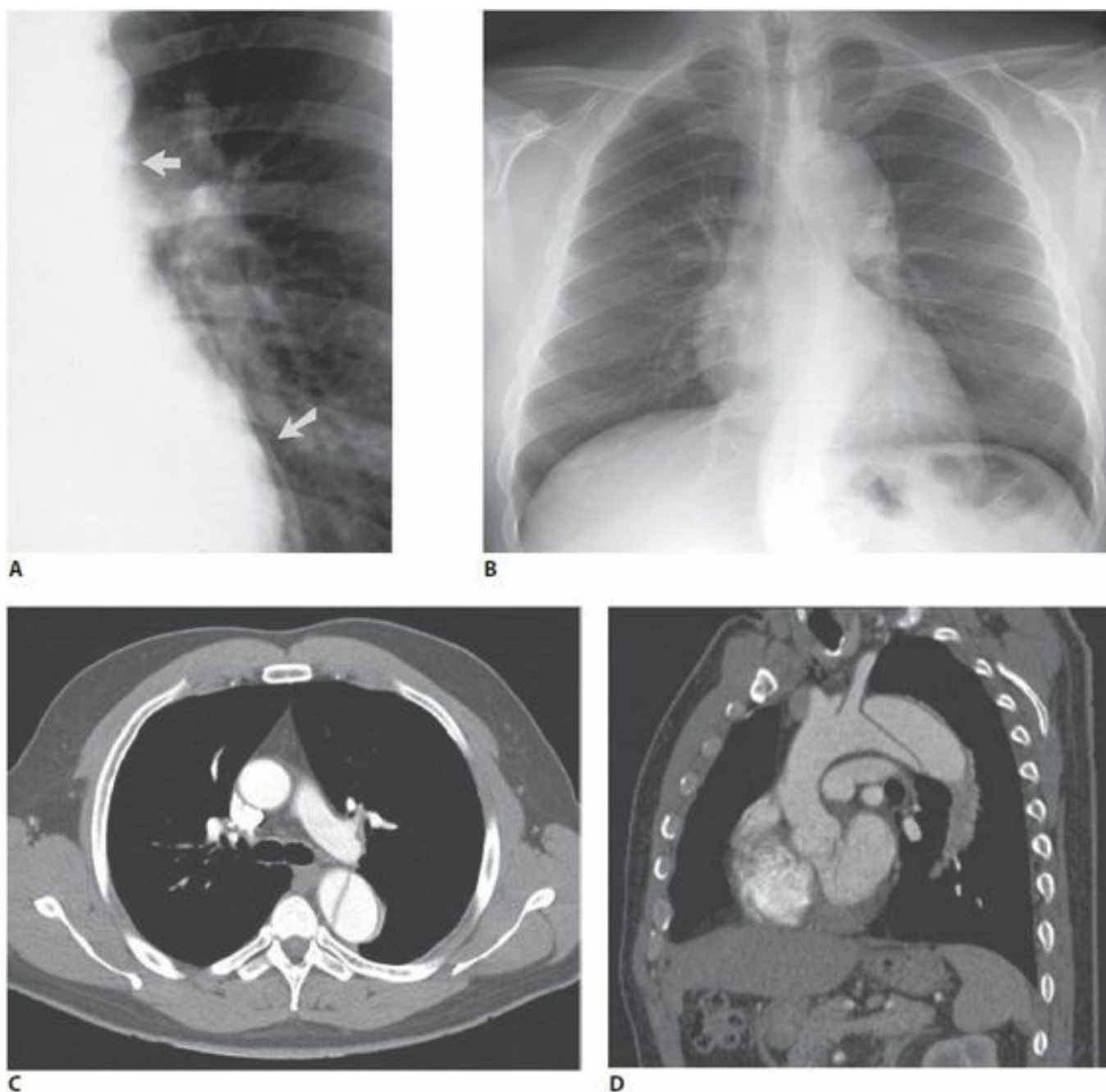


FIGURE 5-21. Two patients with chest pain after cocaine use. (A) Pneumomediastinum after forceful inhalation while smoking “crack” cocaine. A fine white line representing the pleura elevated from the mediastinal structures is seen (arrows). The patient’s chest pain resolved during a 24-hour period of observation. (B to D) Thoracic aortic dissection after cocaine use. The patient presented with chest pain radiating to the back. He had a history of hypertension and was noncompliant with medications. Chest radiography shows an enlarged aorta caused by aortic wall weakening secondary to his long-standing hypertension. Computed tomography angiography shows the intraluminal dissection flap originating at the left subclavian artery and extending into the descending aorta. (Image A used with permission of The Toxicology Fellowship of the New York City Poison Control Center.)

Lymphadenopathy. Phenytoin may cause drug-induced lymphoid hyperplasia with hilar lymphadenopathy.¹⁴⁰ Chronic beryllium exposure results in hilar lymphadenopathy that mimics sarcoidosis, with granulomatous changes in the lung parenchyma. Silicosis is associated with “eggshell” calcification of hilar lymph nodes.

Cardiovascular Abnormalities. Dilated cardiomyopathy occurs in chronic alcoholism and exposure to cardiotoxic medications such as doxorubicin (Adriamycin). Enlargement of the cardiac silhouette may also be caused by a pericardial effusion, which may accompany drug-induced SLE. Aortic dissection is associated with use of cocaine and amphetamines.^{66,75,114,152,162} The chest radiograph may show an enlarged or indistinct aortic knob and an ascending or descending aorta (Figs. 5-21B to D).

Abdominal Problems

Abdominal imaging modalities include conventional radiography, CT, GI contrast studies, and angiography.⁶⁸ Conventional radiography is limited in its ability to detect most intraabdominal pathology because most pathologic processes involve soft tissue structures that are not well seen. Plain radiography readily visualizes gas in the abdomen and is therefore usable to

diagnose pneumoperitoneum (free intraperitoneal air) and bowel distension caused by mechanical obstruction or diminished gut motility (adynamic ileus). Other abnormal gas collections, such as intramural gas associated with intestinal infarction, are seen infrequently (Table 5–4).^{73,120,128,137,186}

TABLE 5–4. Plain Abdominal Radiography in Toxicologic Emergencies

<i>Radiographic Finding</i>	<i>Xenobiotic</i>
Pneumoperitoneum (hollow viscus perforation)	Caustics: Iron, alkali, acids Cocaine GI decontamination (syrup of ipecac, lavage tube)
Mechanical obstruction intraluminal foreign body Intestinal gastric outlet } Upper GI esophageal } series	Foreign-body ingestion: Body packer, enteric-coated pills (bezoar)
Ileus (diminished gut motility)	Opioids Anticholinergics Cyclic antidepressants Mesenteric ischemia (cocaine, oral contraceptives, cardioactive steroids, hypokalemia, hypomagnesemia)
Intramural gas (intestinal infarction) Bowel wall thickening Hepatic portal venous gas (CT is more sensitive)	Cocaine Ergot alkaloids Oral contraceptives Calcium channel blockers Hypotension
Foreign-body ingestion	Iron pills Metals (As, Cs, Hg, Pb, Tl) Body packers and stuffers Bismuth subsalicylate Calcium carbonate Enteric-coated and sustained-release tablets Pica (calcareous clay)

Pneumoperitoneum. GI perforation is diagnosed by seeing free intraperitoneal air under the diaphragm on an upright chest radiograph. Peptic ulcer perforation is associated with crack cocaine use.^{2,29,107} Esophageal or gastric perforation (or tear) can be a complication of forceful emesis induced by syrup of ipecac or alcohol intoxication or attempted placement of a large-bore orogastric tube (Fig. 5–22).²²⁰ Esophageal and gastric perforation may also occur after the ingestion of caustics such as iron, alkali, or acid.¹⁰³ Esophageal perforation causes pneumomediastinum and mediastinitis.

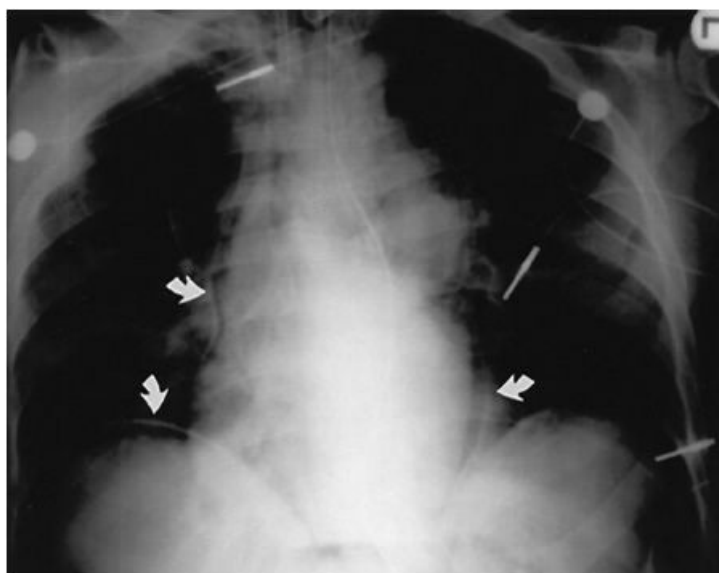


FIGURE 5–22. Gastrointestinal perforation after gastric lavage with a large-bore orogastric tube. The upright chest radiograph shows air under the right hemidiaphragm and pneumomediastinum (arrows). An esophagram with water-soluble contrast did not demonstrate the perforation. Laparotomy revealed perforation of the anterior wall of the stomach.

Obstruction and Ileus. Both mechanical bowel obstruction and adynamic ileus (diminished gut motility) cause bowel distension. With mechanical obstruction, there is a greater amount of intestinal distension proximal to the obstruction and a relative paucity of gas and intestinal collapse distal to the obstruction. In adynamic ileus, the bowel distension is relatively uniform throughout the entire intestinal tract. On the upright abdominal radiograph, both mechanical obstruction and adynamic ileus show air-fluid levels. In mechanical obstruction, air-fluid levels are seen at different heights and produce a “stepladder” appearance.

Mechanical bowel obstruction may be caused by large intraluminal foreign bodies such as a body packer’s packets or a medication bezoar.^{64,197} Adynamic ileus may result from the use of opioids, anticholinergics, and tricyclic antidepressants (Fig. 5–23).^{15,68} Because adynamic ileus occurs in many diseases, the radiographic finding of an ileus is not helpful diagnostically. When the distinction between obstruction and adynamic ileus cannot be made based on the abdominal radiographs, abdominal CT can clarify the diagnosis.¹³⁵

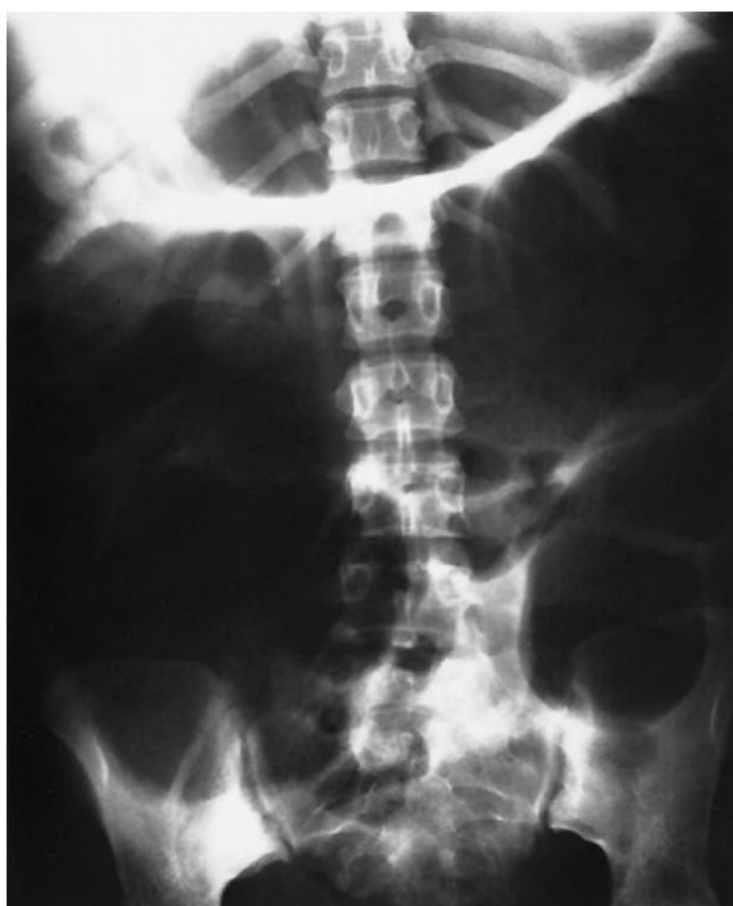


FIGURE 5–23. Methadone maintenance therapy causing marked abdominal distension. The radiograph reveals striking

large bowel dilatation, termed colonic ileus, caused by chronic opioid use. A similar radiographic picture is seen with anticholinergic poisoning. A contrast enema can clarify the diagnosis. (Used with permission of Dr. Emil J. Balthazar, Department of Radiology, Bellevue Hospital Center.)

Mesenteric Ischemia. In most patients with intestinal ischemia, plain abdominal radiographs show only a nonspecific or adynamic ileus pattern. In a small proportion of patients with ischemic bowel (5%), intramural gas is seen.¹⁵ Rarely, gas is also seen in the hepatic portal venous system. CT is better able to detect signs of mesenteric ischemia, particularly bowel wall thickening (Fig. 5–24).¹⁴

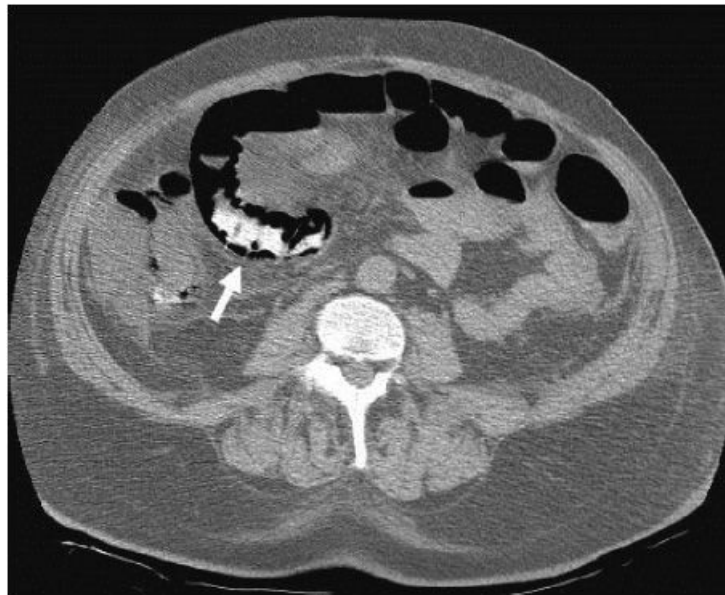


FIGURE 5–24. Bowel infarction in a 50 year-old man with an aspirin overdose. He presented with renal failure, hypotension, and altered mental status. The next day after hemodialysis and hemofiltration, he developed abdominal distension and fever. Abdominal computed tomography showed extensive intramural gas (arrow) caused by bowel infarction, and the patient underwent surgical bowel resection.

Intestinal ischemia and infarction may be caused by use of cocaine; other sympathomimetics; and the ergot alkaloids, all of which induce mesenteric vasoconstriction.^{79,110,130} Calcium channel blocker overdoses cause splanchnic vasodilation and hypotension that may result in intestinal ischemia. Superior mesenteric vein thrombosis may be caused by hypercoagulability associated with chronic oral contraceptive use.

Gastrointestinal Hemorrhage and Hepatotoxicity. Radiography is not usually helpful in the diagnosis of such common abdominal complications as GI bleeding and hepatotoxicity.

The now obsolete radiocontrast agent thorium dioxide (Thorotrast; thorium, atomic number 90) provides a unique example of pharmaceutical-induced hepatotoxicity. It was used as an angiographic contrast agent until 1947, when it was found to cause hepatic malignancies. The radioactive isotope of thorium has a half-life of 400 years. It accumulates within the reticuloendothelial system and remains there for the life of the patient. It had a characteristic radiographic appearance, with multiple punctate opacities in the liver, spleen, and lymph nodes (Fig. 5–25). Patients who received thorium before its removal from the market may still present with hepatic malignancies.^{18,204}

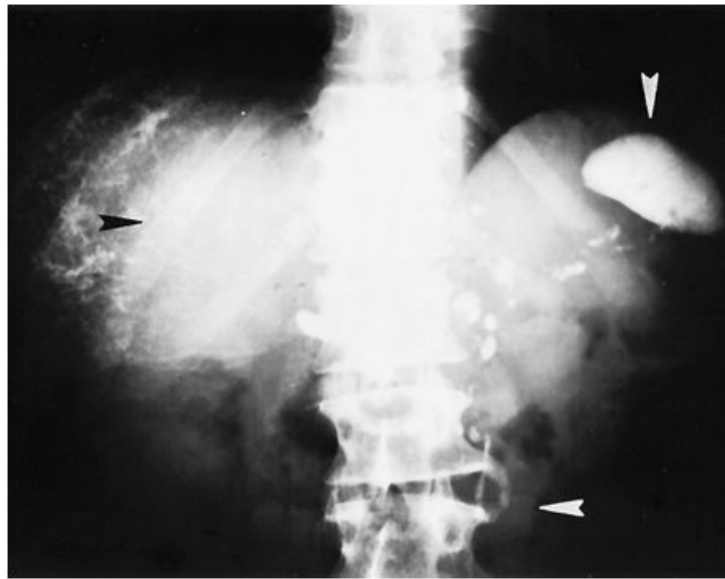


FIGURE 5–25. An abdominal radiograph of a patient who had received thorium dioxide (Thorotrast) for a radiocontrast study many years previously. The spleen (vertical white arrowhead), liver (horizontal black arrowhead), and lymph nodes (horizontal white arrowhead) are demarcated by thorium retained in the reticuloendothelial system. (Used with permission of Dr. Emil J. Balthazar, Department of Radiology, Bellevue Hospital Center.)

Contrast Esophagram and Upper Gastrointestinal Series. Ingestion of a caustic may cause severe damage to the mucosal lining of the esophagus. This can be demonstrated by a contrast esophagram. However, in the acute setting, upper endoscopy should be performed rather than an esophagram because it provides more information about the extent of injury and prognosis.¹¹¹ In addition, administration of barium will coat the mucosa, making endoscopy difficult. For later evaluation, a contrast esophagram identifies mucosal defects, scarring, and stricture formation (Figs. 5–26 and 106–4).¹²⁹

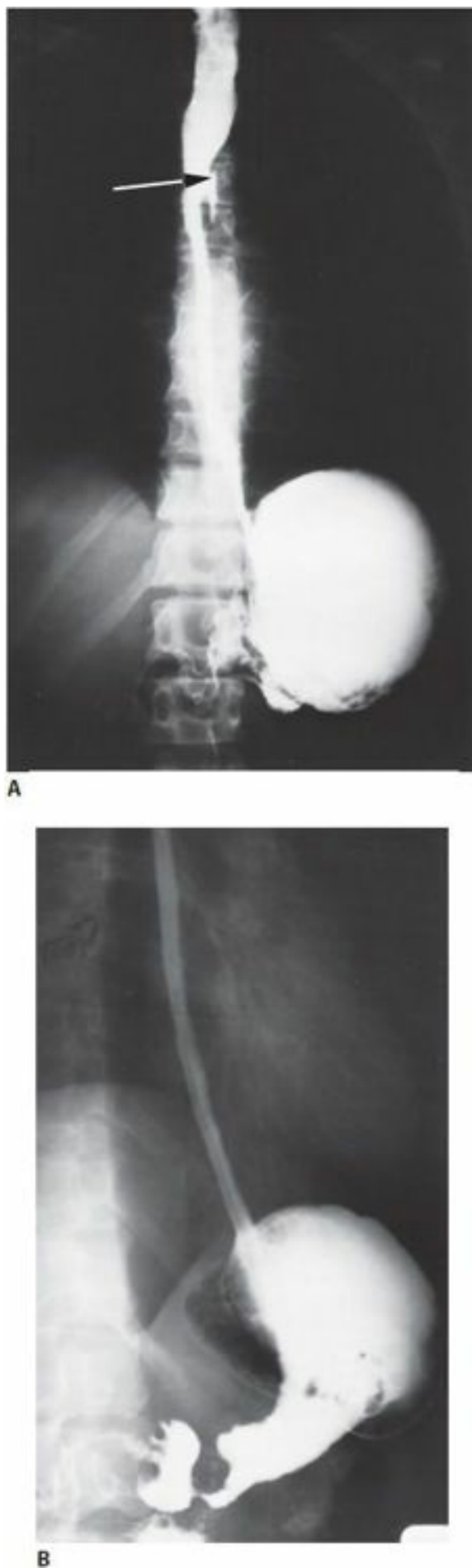


FIGURE 5–26. (A) A barium swallow performed several days after ingestion of liquid lye shows intramural dissection and extravasation of barium with early stricture formation. (B) At 3 weeks after ingestion, there is an absence of peristalsis, diffuse narrowing of the esophagus, and reduction in size of the fundus and antrum of the stomach as a result of scarring. (Used with permission of Dr. Emil J. Balthazar, Department of Radiology, Bellevue Hospital Center.)

The choice of radiographic contrast agent (barium or water-soluble material) depends on the clinical situation. If the esophagus is severely strictured and there is a risk of aspiration, barium should be used because water-soluble contrast material is damaging to the pulmonary parenchyma. If, on the other hand, esophageal or gastric perforation is suspected,

water-soluble contrast is safer because extravasated barium is highly irritating to mediastinal and peritoneal tissues, but extravasated water-soluble contrast is gradually absorbed into the circulation.

Ingested foreign bodies may cause esophageal and gastric outlet obstruction. Esophageal obstruction caused by a drug packet can be demonstrated by a contrast esophagram. Concretions of ingested material in the stomach may cause gastric outlet obstruction. This has been reported with potassium chloride tablets and enteric-coated aspirin.^{11,185}

Abdominal Computed Tomography. CT provides great anatomic definition of intraabdominal organs and plays an important role in the diagnosis of a wide variety of abdominal disorders. In most cases, both oral and IV contrast are administered. Oral contrast delineates the intestinal lumen. IV contrast is needed to reliably detect lesions in hepatic and splenic parenchyma, the kidneys, and the bowel wall.

Certain abdominal complications of poisonings are amenable to CT diagnosis. Intestinal ischemia causes bowel wall thickening; intramural hemorrhage; and at a later stage, intramural gas and hepatic portal venous gas (Fig. 5-24).¹⁴ Hepatic portal venous gas can also be seen after ingestion of 3% hydrogen peroxide. Splenic infarction and splenic and psoas abscesses are complications of IV drug use that may be diagnosed on CT.¹⁵ Radiopaque foreign substances such as intravenously injected elemental mercury may be detected and accurately localized by CT.¹²⁶ Radiolucent foreign bodies, such as a body packer's packets, may be detected by using enteric contrast.^{83,85}

Vascular Lesions. Angiography may detect such complications of injection drug use as venous thrombosis and arterial laceration causing pseudoaneurysm formation (Figs. 5-27 and 5-28). IV injection of amphetamine, cocaine, or ergotamine causes necrotizing angiitis that is associated with microaneurysms, segmental stenosis, and arterial thrombosis. These lesions are seen in the kidneys, small bowel, liver, pancreas, and cerebral circulation (Fig. 5-29).^{34,161} Complications include aneurysm rupture and visceral infarction. Renal lesions cause severe hypertension and acute kidney injury.¹⁷⁵

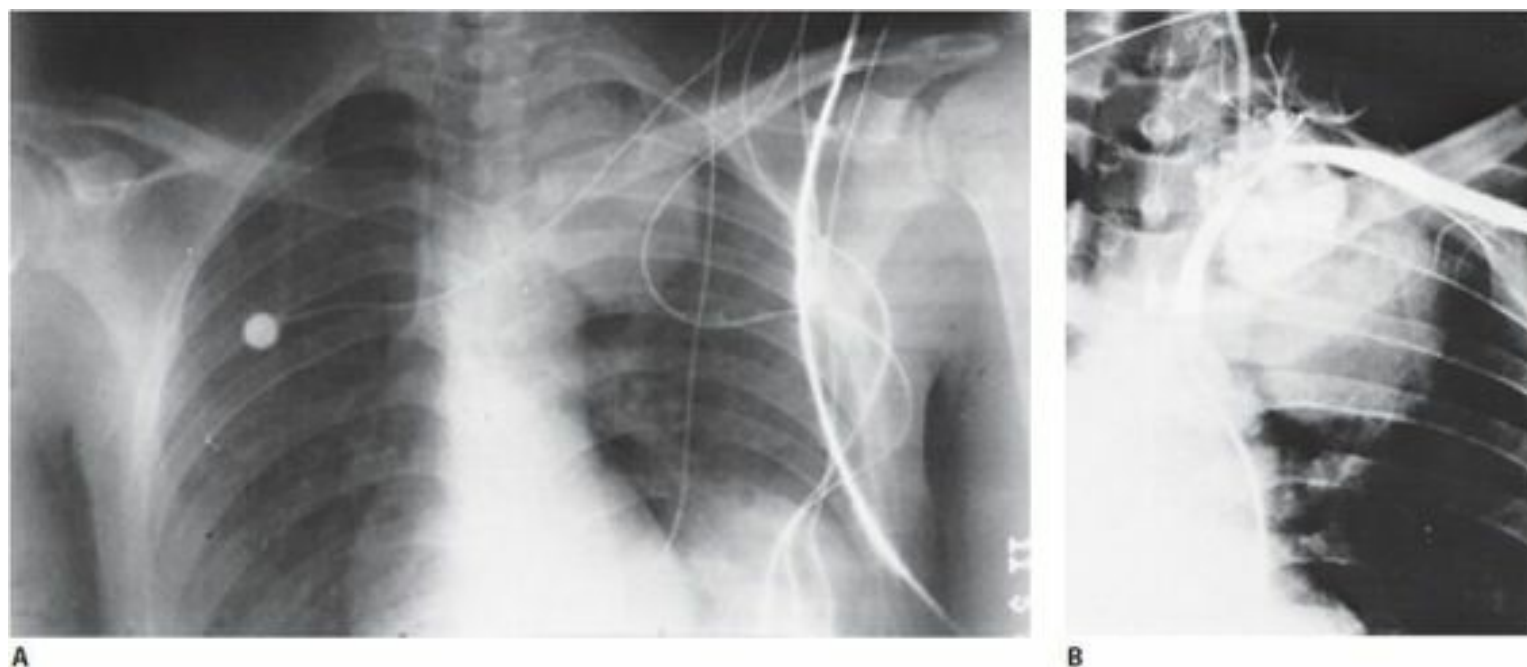


FIGURE 5-27. (A) Chest radiograph of a young drug abuser who used the supraclavicular approach for heroin injection. The large mass in the left chest was suspicious for a pseudoaneurysm. (B) An arch aortogram performed on the patient revealed a large pseudoaneurysm and hematoma subsequent to an arterial tear during attempted injection. Surgical repair was performed. (Used with permission of Dr. Richard Lefleur, Department of Radiology, Bellevue Hospital.)



FIGURE 5–28. Venogram of a 50 year-old patient who routinely injected heroin into his groin. Occlusion of the femoral vein (black arrowhead) with diffuse aneurysmal dilatation (small arrowhead) and extensive collaterals are shown. Incidental radiopaque materials are noted in the right buttock (double arrowheads). By history, this represents either bismuth or arsenicals he received as antisypilitic therapy. (Used with permission of Dr. Richard Lefleur, Department of Radiology, Bellevue Hospital.)



FIGURE 5–29. A selective renal angiogram in an injection methamphetamine user demonstrating multiple small and large aneurysms (arrowheads). (Used with permission of Dr. Richard Lefleur, Department of Radiology, Bellevue Hospital Center.)

Neurologic Problems

Diagnostic imaging studies have revolutionized the management of CNS disorders.^{57,71} Both acute brain lesions and chronic degenerative changes can be detected (Table 5–5).¹¹⁸ Some xenobiotics have a direct toxic effect on the CNS; others indirectly cause neurologic injury by causing hypoxia, hypotension, hypertension, cerebral vasoconstriction, head trauma,

or infection.

TABLE 5–5. Head Computed Tomography (Noncontrast) in Toxicologic Emergencies

<i>CT Finding</i>	<i>Brain Lesion</i>	<i>Xenobiotic Etiology</i>
Hemorrhage	Intraparenchymal hemorrhage	Sympathomimetics: cocaine (“crack”), amphetamine, phenylpropanolamine, phencyclidine, ephedrine, pseudoephedrine
	Subarachnoid hemorrhage	Mycotic aneurysm rupture (IDU)
	Subdural hematoma	Trauma secondary to ethanol, sedative-hypnotics, seizures Anticoagulants
Brain lucencies	Basal ganglia focal necrosis (also subcortical white matter lucencies)	Carbon monoxide, cyanide, hydrogen sulfide, methanol, manganese
	Stroke: Vasoconstriction	Sympathomimetics: cocaine (“crack”), amphetamine, phenylpropanolamine, phencyclidine, ephedrine, pseudoephedrine, ergotamine
	Mass lesion: tumor, abscess	Septic emboli, AIDS-related CNS toxoplasmosis or lymphoma
Loss of brain tissue	Atrophy: Cerebral, cerebellar	Alcoholism, toluene

CNS = central nervous system; CT = computed tomography; IDU = injection drug use.

Imaging Modalities. CT can directly visualize brain tissue and many intracranial lesions.⁷⁰ CT is the imaging study of choice in the emergency setting because it readily detects acute intracranial hemorrhage as well as parenchymal lesions that are causing mass effect. CT is fast, is widely available on an emergency basis, and can accommodate critical support and monitoring devices. Infusion of IV contrast further delineates intracerebral mass lesions such as tumors and abscesses.

MRI has largely supplanted CT in nonemergency neurodiagnosis. It offers better anatomic discrimination of brain tissues and areas of cerebral edema and demyelination. However, MRI is no better than CT in detecting acute blood collections or mass lesions. In the emergency setting, the disadvantages of MRI outweigh its strengths. MRI is usually not readily available on an emergency basis, image acquisition time is long, and critical care supportive and monitoring devices are often incompatible with MR scanning machines.¹²¹

Nuclear scintigraphy that uses CT technology (SPECT and PET) is being used as a tool to elucidate functional characteristics of the CNS. Examples include both immediate and long-term effects of various xenobiotics on regional brain metabolism, blood flow, and neurotransmitter function.^{115,154,207}

Emergency Head Computed Tomography Scanning. An emergency noncontrast head CT scan is obtained to detect acute intracranial hemorrhage and focal brain lesions causing cerebral edema and mass effect. Patients with these lesions present with focal neurologic deficits, seizures, headache, or altered mental status. Toxicologic causes of intraparenchymal and subarachnoid hemorrhage include cocaine and other sympathomimetics (Fig. 5–30).^{113,117} Cocaine-induced vasospasm may cause ischemic infarction, although this is not well seen by CT until 6 to 24 or more hours after onset of the neurologic deficit (Fig. 5–31). Drug-induced CNS depression, most commonly ethanol intoxication, predisposes the patient to head trauma, which may result in a subdural hematoma or cerebral contusion (Fig. 5–32). Toxicologic causes of intracerebral mass lesions include septic emboli complicating injection drug use and HIV-associated CNS toxoplasmosis and lymphoma (Fig. 5–33).^{19,74,79,149} On a contrast CT, such tumors and focal infections exhibit a pattern of “ring enhancement.”

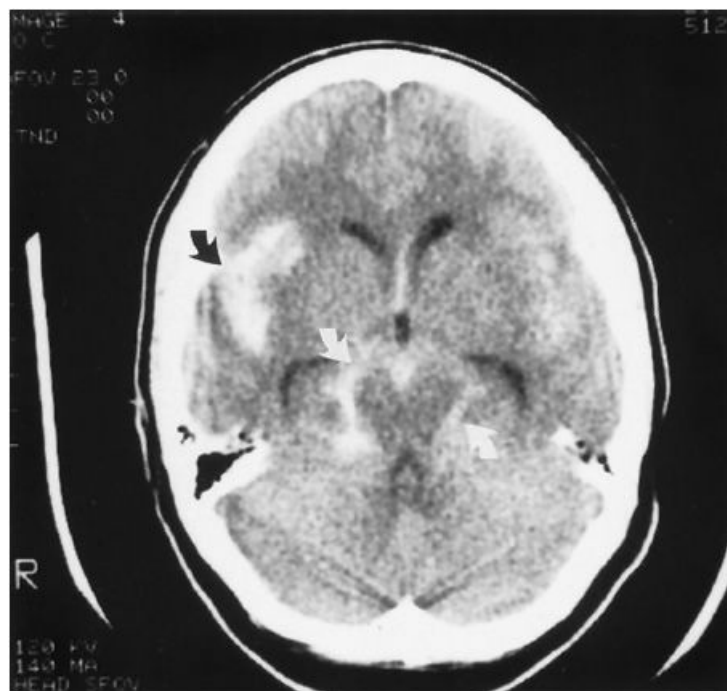


FIGURE 5–30. Subarachnoid hemorrhage after intravenous cocaine use. The patient had sudden severe headache followed by a generalized seizure. Extensive hemorrhage is seen surrounding the midbrain (white arrows) and in the right Sylvian fissure (black arrow). Angiography revealed an aneurysm at the origin of the right middle cerebral artery.

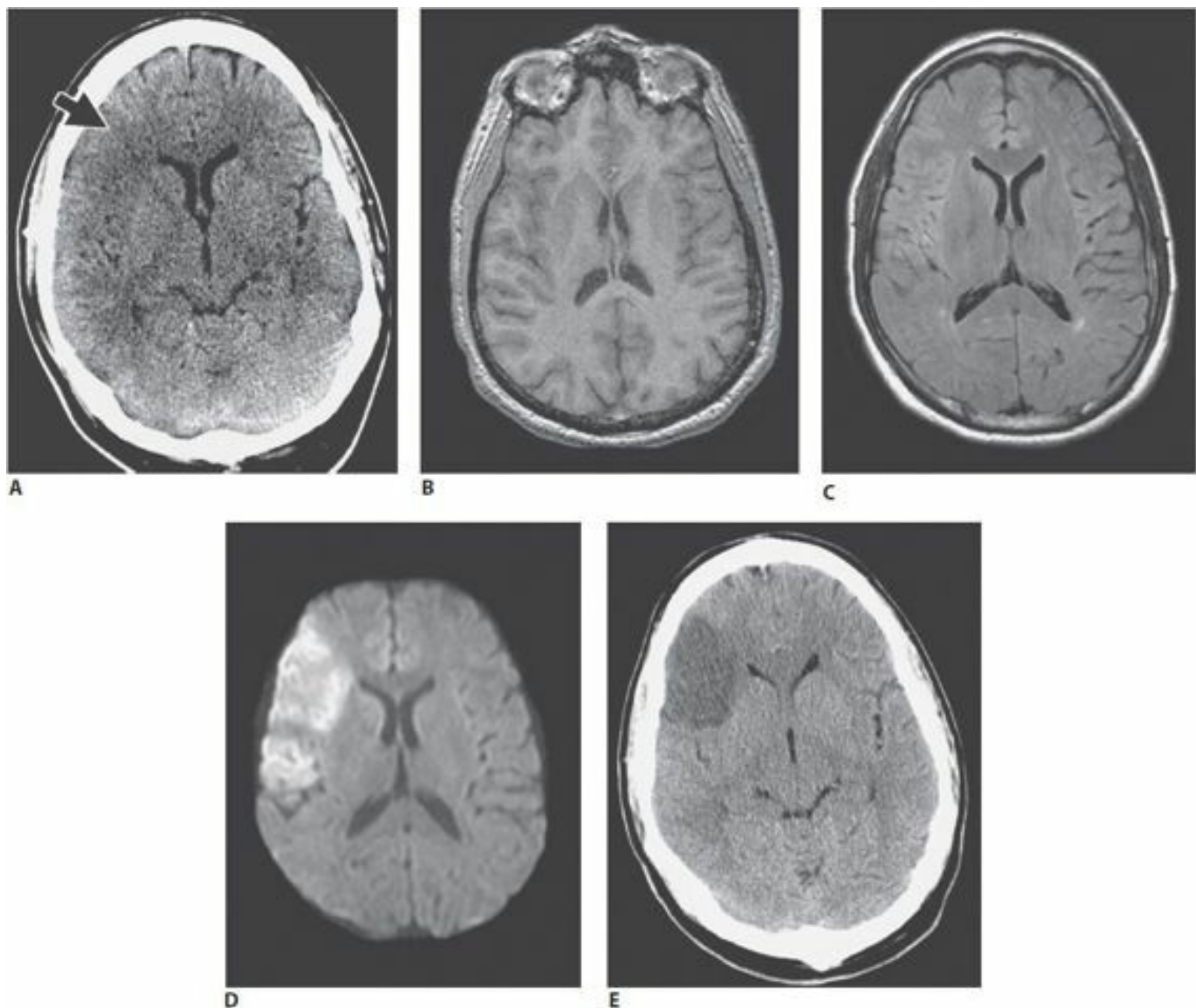


FIGURE 5–31. Acute stroke confirmed by diffusion-weighted magnetic resonance image (MRI). A 39 year-old man presented with left facial weakness that began 3 hours earlier after smoking crack cocaine. He also complained of left arm “tingling” but had normal examination findings. An emergency noncontrast computed tomography (CT) scan was obtained that was interpreted as normal (A), although in retrospect there was subtle loss of the normal gray–white differentiation (arrow). MRI was obtained to confirm that the facial palsy was a stroke and not a peripheral seventh cranial nerve palsy. Standard MRI sequence (T1-weighted, T2-weighted, and FLAIR) were normal in this early ischemic lesion (B and C). Diffusion-weighted imaging is able to show such early ischemic change—cytotoxic (intracellular) edema (D). The patient’s facial paresis improved but did not entirely resolve. A repeat CT scan 2 days later showed an evolving (subacute) infarction with vasogenic edema (E). Infarction was presumably caused by vasospasm because no carotid artery lesion or cardiac source of embolism was found. (From Schwartz DT: Emergency Radiology: Case Studies, New York, McGraw-Hill; 2008:517, with permission.)

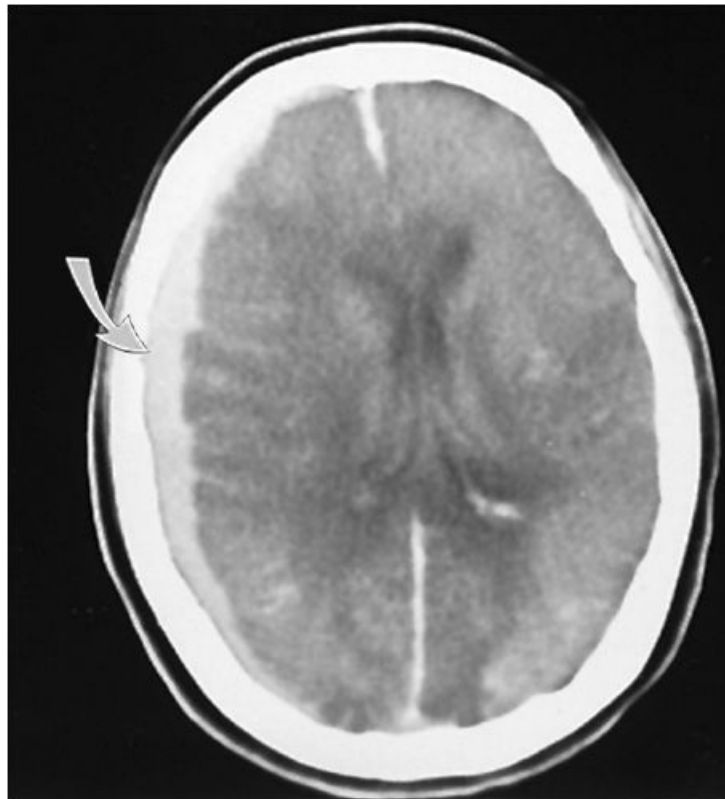


FIGURE 5–32. An acute subdural hematoma in a patient with alcoholism after an alcohol binge. A crescent-shaped blood collection is seen between the right cerebral convexity and the inner table of the skull (arrow).

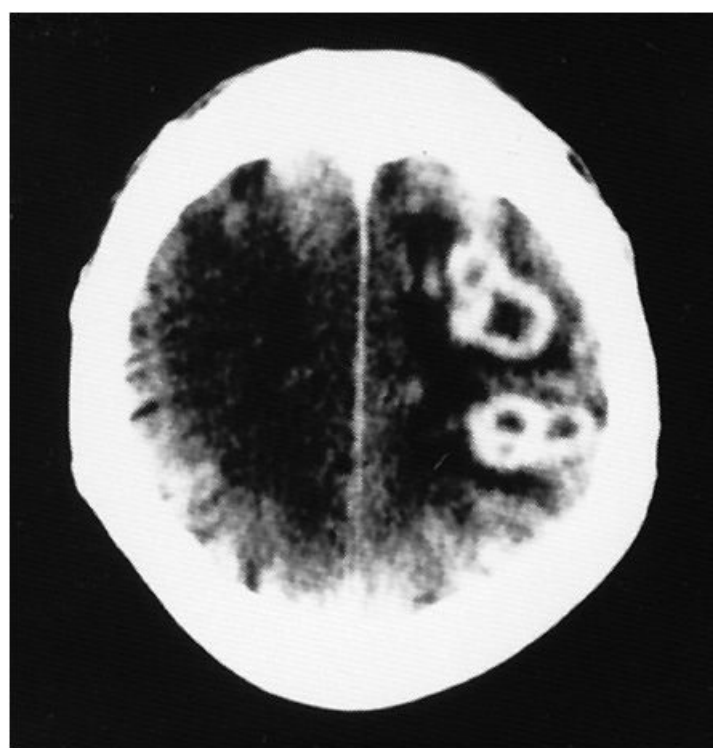


FIGURE 5–33. An injection drug user with ring-enhancing intracerebral lesions. The patient presented with fever and

altered mental status. In this patient, the lesions represent multiple septic emboli complicating acute *Staphylococcus aureus* bacterial endocarditis. A similar ring-enhancing appearance is seen with lesions caused by toxoplasmosis or primary central nervous system lymphoma in patients with AIDS. This patient was HIV negative.

Xenobiotic-Mediated Neurodegenerative Disorders. A number of xenobiotics directly damage brain tissue, producing morphologic changes that may be detectable using CT and MRI. Such changes include generalized atrophy, focal areas of neuronal loss, demyelination, and cerebral edema. Imaging abnormalities may help establish a diagnosis or predict prognosis in a patient with neurologic dysfunction after a xenobiotic exposure. In some cases, the imaging abnormality will suggest a toxicologic diagnosis in a patient with a neurologic disorder in whom a xenobiotic exposure was not suspected clinically.^{4,13,57,100,104,155,165,214}

Atrophy. Ethanol is the most widely used neurotoxin. With long-term ethanol use, there is a widespread loss of neurons and resultant atrophy. In some individuals with alcoholism, the loss of brain tissue is especially prominent in the cerebellum. However, the amount of cerebral or cerebellar atrophy does not always correlate with the extent of cognitive impairment or gait disturbance.^{42,67,84,86,106,209,211} Chronic solvent exposure, such as to toluene (occupational and illicit use), also causes diffuse cerebral atrophy.^{93,171}

Focal Degenerative Lesions. Carbon monoxide poisoning produces focal degenerative lesions in the brain. In about half of patients with severe neurologic dysfunction after carbon monoxide poisoning, CT scans show bilateral symmetrical lucencies in the basal ganglia, particularly the globus pallidus (**Figs. 5–34 and 125–1**).^{27,94,100,141,155,158,159,177,178,182,200,206} The basal ganglia are especially sensitive to hypoxic damage because of their limited blood supply and high metabolic requirements. Subcortical white matter lesions also occur after carbon monoxide poisoning. Although less frequent than lesions of the basal ganglia, white matter lesions are more clearly associated with a poor neurologic outcome. MRI is more sensitive than CT at detecting these white matter abnormalities.^{27,57,104,159,200}



FIGURE 5–34. A head computed tomography scan of a patient with mental status changes after carbon monoxide poisoning. The scan shows characteristic bilateral symmetrical lucencies of the globus pallidus (arrows). (Used with permission of Dr. Paul Blackburn, Maricopa Medical Center, AZ.)

Basal ganglion lucencies, white matter lesions, and atrophy are caused by other xenobiotics such as methanol,^{12,41,69,82,142,173} ethylene glycol, cyanide,^{58,139} hydrogen sulfide, inorganic and organic mercury,¹³¹ manganese,^{13,190} heroin,^{104,108} barbiturates, chemotherapeutic agents, solvents such as toluene,^{57,93,171,150,83,156} and podophyllin.^{28,144} Nontoxicologic disorders may cause similar imaging abnormalities, including hypoxia, hypoglycemia, and infectious encephalitis.^{82,88}

Nuclear Scintigraphy. Whereas both CT and MRI display cerebral anatomy, nuclear medicine studies provide functional information about the brain. Nuclear scintigraphy uses radioactive isotopes that are bound to carrier molecules (ligands). The choice of ligand depends on the biologic function being studied. Brain cells take up the radiolabeled ligand

in proportion to their physiologic activity or the regional blood flow. The radioactive emission from the isotope is detected by a scintigraphic camera, which produces an image showing the quantity and distribution of tracer. Better anatomic detail is provided by using CT techniques to generate cross-sectional images. There are two such technologies: SPECT and PET. These imaging modalities are used in the research and clinical settings to study the neurologic effects of particular xenobiotics and the mechanisms of xenobiotic-induced neurologic dysfunction.

SPECT uses conventional isotopes such as technetium-99m and iodine-123.¹¹⁵ These isotopes are bound to ligands that are taken up in the brain in proportion to regional blood flow, reflecting the local metabolic rate.

PET uses radioactive isotopes of biologic elements such as carbon-11, oxygen-15, nitrogen-13, and fluoride-18 (a substitute for hydrogen).¹⁵⁴ These radioisotopes have very short half-lives so that PET scanning requires an onsite cyclotron to produce the isotope. The isotopes are incorporated into molecules such as glucose, oxygen, water, various neurotransmitters, and drugs. Labeled glucose is taken up in proportion to the local metabolic rate for glucose. Uptake of labeled oxygen demonstrates the local metabolic rate for oxygen. Labeled neurotransmitters generate images reflecting their concentration and distribution within the brain.

Both PET and SPECT have been used to study the effects of various xenobiotics on cerebral function. For example, although both CT and MRI can detect cerebellar atrophy in individuals with chronic alcoholism, there is a poor correlation between the magnitude of cerebellar atrophy and the clinical signs of cerebellar dysfunction. PET scans may demonstrate diminished cerebellar metabolic rate for glucose, which correlates more accurately with the patient's clinical status.^{72,209}

In patients with severe neurologic dysfunction after carbon monoxide poisoning, SPECT regional blood flow measurements show diffuse hypometabolism in the frontal cortex.³⁰ In one patient, severe perfusion abnormalities improved slightly over several months in proportion to the patient's gradual clinical improvement.⁹⁸ In another patient treated with hyperbaric oxygen, a SPECT scan revealed increased blood flow in the frontal lobes, although the blood flow still remained significantly less than normal.¹²⁴

In patients who chronically use cocaine, SPECT blood flow scintigraphy demonstrates focal cortical perfusion defects. The extent of these perfusion defects correlates with the frequency of drug use. Focal perfusion defects probably represent local vasculitis or small areas of infarction.^{92,202} PET scanning has been used to demonstrate the effects of cocaine on cerebral blood flow and regional glucose metabolism. PET neurotransmitter studies show promise in elucidating potential mechanisms of action of cocaine. Using radiolabeled dopamine analogs, downregulation of dopamine (D₂) receptors has been noted after a cocaine binge. This finding may be responsible for cocaine craving that occurs during cocaine withdrawal. Using ¹¹C-labeled cocaine, uptake of cocaine can be demonstrated in the basal ganglia, a region rich in dopamine receptors.²⁰⁷

Much has been learned about these imaging modalities, and initial applications can be applied to patient care. These imaging modalities are capable of demonstrating abnormalities in many patients with xenobiotic exposures, although other patients with significant cerebral dysfunction have normal study findings.

SUMMARY

This chapter has highlighted a variety of situations in which diagnostic imaging studies are useful in toxicologic emergencies.

- Imaging can be an important tool in establishing a diagnosis, assisting in the treatment of patients, and detecting complications of a toxicologic emergency.
- The imaging modalities include plain radiography, CT, enteric and intravascular contrast studies, nuclear scintigraphy, and ultrasonography.
- However, effective use of a diagnostic test requires a precise understanding of the clinical situations in which each test can be useful, knowledge of the capabilities and limitations of the tests, and how the results should be applied to the care of an individual patient.

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6 LABORATORY PRINCIPLES

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Toxicology addresses harm caused by acute and chronic exposures to excessive amounts of a xenobiotic. Detecting the presence or measuring the concentration of toxic xenobiotics is the primary activity of the analytical toxicology laboratory. Such testing is closely intertwined with therapeutic drug monitoring, in which drug concentrations are measured as an aid to optimizing drug dosing regimens. The toxicology laboratory is frequently viewed in much the same way as other clinical laboratories often are—as a “black box” that converts orders into test results. Because toxicology testing volumes are relatively low and menus are extensive, testing is not as highly automated as in other clinical laboratories. Many results may be “handmade the old-fashioned way.” A downside of this may be somewhat longer turnaround times. But the upside is that toxicology laboratory personnel have the incentive and flexibility to develop substantial expertise. Clinicians who understand how toxicology testing is done will be able to order more judiciously and apply the results more effectively.

RECOMMENDATIONS FOR ROUTINELY AVAILABLE TOXICOLOGY TESTS

Despite a common focus, there is remarkable variability in the range of tests offered by analytical toxicology laboratories. Test menus may range from once-daily testing for routinely monitored drugs and common drugs of abuse to around-the-clock availability of a broad array of assays with the theoretical potential to identify several thousand compounds. Consensus statements have recommended tests that should be available to support management of poisoned patients presenting to emergency departments.^{21,32} These guidelines make specific recommendations but recognize that no set of recommendations will be universally appropriate and that it is impossible for a clinical laboratory to offer a full spectrum of toxicology testing in real time.

Decisions on the menu of tests to be offered by any specific laboratory should be decided by the laboratory director in consultation with the medical toxicologists and other clinicians who will use the service and should take into account regional patterns of use of licit and illicit drugs and exposure to environmental toxins, as well as resources available and competing priorities.

The recommendations in [Table 6–1](#) were developed by the National Academy of Clinical Biochemists (NACB) from a consensus process that involved clinical biochemists, medical toxicologists, forensic toxicologists, and emergency physicians.³² Although these tests should be readily available in the clinical laboratory, they should not be considered as a test panel for possibly poisoned patients. As with all laboratory tests, they should be selectively ordered based on the patient’s history, clinical presentation, or other relevant factors. Suggested turnaround time for reporting serum concentrations of the drugs listed in [Table 6–1](#) was one hour or less. Quantitative tests for serum methanol and ethylene glycol were also recommended, with the reservations that these tests are not needed in all settings and that a realistic turnaround time is 2 to 4 hours. Serum cholinesterase testing with a turnaround time of less than 4 hours was proposed by some participants but did not achieve a general consensus. In the United Kingdom, the National Poisons Information Service and the Association of Clinical Biochemists have recommended a nearly identical list of tests, omitting the anticonvulsants.²¹

TABLE 6–1. Toxicology Assays Recommended by the National Academy of Clinical Biochemists

<i>Quantitative Serum Assays</i>	<i>Qualitative Urine Assays</i>
Acetaminophen (APAP)	Amphetamines
Carbamazepine	Barbiturates
Cooximetry (carboxyhemoglobin, methemoglobin, oxygen saturation)	Cocaine
Digoxin	Opiates
Ethanol	Propoxyphene
Iron (plus transferrin or iron-binding capacity)	Phencyclidine
Lithium	Tricyclic antidepressants (TCAs)
Phenobarbital	
Salicylates	
Theophylline	
Valproic acid	

Although the consensus for the menu of serum assays was generally excellent, there was less agreement as to the need for qualitative urine assays. This was largely a result of issues of poor sensitivity and specificity, poor correlation with clinical effects, and infrequent alteration of patient management. Although these were potential issues for all of the urine drug tests, they led to explicit omission of tests for tetrahydrocannabinol (THC) and benzodiazepines from the recommended list despite their widespread use. THC results were thought to have little value in managing patients with acute problems, and tests for benzodiazepines were believed to have an inadequate spectrum of detection. Testing for amphetamines, propoxyphene, and phencyclidine (PCP) were only recommended in areas where use was prevalent. It was also suggested that diagnosis of tricyclic antidepressant (TCA) toxicity not be based solely on the results of a urine screening immunoassay because a number of other drugs may cross-react. The significance of TCA results should always be correlated with electrocardiographic and clinical findings. The only urine test included in the United Kingdom guidelines was a spot test for paraquat.²¹ Paraquat testing was omitted in the NACB guidelines because of a very low incidence of paraquat exposure in North America.³²

The NACB guidelines also recommend the availability of broad-spectrum toxicology testing in addition to the tests in Table 6–1 to be used for selected patients with presentations compatible with poisoning but who remain undiagnosed and who are not improving. In general, such testing should not be ordered until the patient is stabilized and input has been obtained from a medical toxicologist or poison center. This second level of testing may be provided directly by the local laboratory or by referral to a reference laboratory or a regional toxicology center.

Many physicians order a broad-spectrum toxicology screen for a poisoned patient if one is readily available, but only approximately 2% of clinical laboratories provide relatively comprehensive toxicology services (as estimated from proficiency testing data³). Although broad-spectrum toxicology screens can identify most drugs present in overdosed patients, the results of broad-spectrum screens infrequently have altered management or outcomes.^{13,14,20,22,29}

The extent to which the NACB recommendations are being followed may be estimated from the numbers of laboratories participating in various types of proficiency testing. Result summaries from the 2011 series of proficiency surveys administered by the College of American Pathologists suggest that among laboratories that offer routine clinical testing, 50% to 60% offer quantitative assays for APAP, carbamazepine, ethanol, lithium, phenobarbital, salicylates, theophylline, and valproic acid; 60% to 70% offer digoxin, iron, and transferrin or iron-binding capacity; and 70% to 80% offer carboxyhemoglobin and methemoglobin. About half of these laboratories offer screening tests for drugs of abuse in urine.³

About 2% of laboratories participated in proficiency testing for a full range of toxicology services. These full-service laboratories typically offer quantitative assays for additional therapeutic drugs, particularly TCAs, as well as assays that are designated as broad-spectrum or comprehensive toxicology screens. About 80% of these full-service toxicology laboratories offer testing for volatile alcohols other than ethanol, and half offer testing for ethylene glycol.⁴

Although relatively few laboratories offer a wide range of in-house testing, most laboratories send out specimens to reference laboratories that offer large toxicology menus. The turnaround time for such “send-out” tests ranges from a few hours to several days, depending on the proximity of the reference laboratory and the type of test requested.

Even in full-service toxicology laboratories, the test menu may vary substantially from institution to institution. Larger laboratories typically offer one or more broad-spectrum testing choices, often referred to as “tox screens.” There is as much variety in the range of xenobiotics detected by various toxicologic screens as there is in the total menu of toxicologic tests. Routinely available tests are usually listed in a printed or online laboratory manual. Laboratories with comprehensive services may be able to offer ad hoc chromatographic assays for additional xenobiotics that are not listed. Testing that is sent to a reference laboratory is often not listed in the laboratory manual. The best way to determine if a particular

xenobiotic can be detected or quantitated is to ask the director or supervisor of the toxicology or clinical chemistry section because laboratory clerical staff may only be aware of tests listed in the manual.

USING THE TOXICOLOGY LABORATORY

There are many reasons for toxicologic testing. The most common function is to confirm or exclude suspected toxic exposures. A laboratory result provides a level of confidence not readily obtained otherwise and may avert other unproductive diagnostic investigations driven by the desire for completeness and medical certainty. Testing increased diagnostic certainty in more than half of cases,^{2,13,14} and in some instances, a diagnosis may be based primarily on the results of testing. This can be particularly important in poisonings with xenobiotics having delayed onset of clinical toxicity, such as APAP, or in patients with ingestion of multiple xenobiotics. In these instances, characteristic clinical findings may not have developed at the time of presentation or may be obscured or altered by the effects of coingestants.

Testing can provide two key parameters that will have a major impact on the clinical course, namely, the xenobiotic involved and the intensity of the exposure. This information can assist in triage decisions and can facilitate management decisions, such as use of specific antidotes or interventions to hasten elimination. Well-defined exposure information can also facilitate provision of optimum advice by poison centers. Finally, positive findings for ethanol or drugs of abuse in trauma patients may serve as an indication for substance use intervention as well as a risk marker for the likelihood of future trauma.¹³

The confirmation of a clinical diagnosis of poisoning provides an important feedback function, whereby the physician may evaluate the diagnosis against a “gold standard.” Another important benefit is reassurance that an unintentional ingestion did not result in absorption of a toxic amount of xenobiotic. This reassurance may allow a physician to avoid spending excessive time with patients who are relatively stable. It may also allow admissions to be made and interventions undertaken more confidently and efficiently than would be likely based solely on a clinical diagnosis. Testing may also be indicated for medicolegal reasons to establish a diagnosis “beyond a reasonable doubt.”

The key to optimal use of the toxicology laboratory is communication. This begins with learning the laboratory’s capabilities, including the xenobiotics on its menus, which can be quantitated and which merely detected, and the anticipated turnaround times. For screening assays, one should know which xenobiotics are routinely detected, which ones can be detected if specifically requested, and which ones cannot be detected even when present at concentrations that typically result in toxicity.

One should know specimen type that is appropriate for the test requested. A general rule is that quantitative tests require serum (red stopper) or heparinized plasma (green stopper) but not ethylenediamine tetraacetic acid (EDTA) plasma (lavender stopper) or citrate plasma (light-blue stopper). EDTA and citrate bind divalent cations that may serve as cofactors for enzymes used as reagents or labels in various assays. Additionally, liquid EDTA and citrate anticoagulants dilute the specimen. Serum or plasma separator tubes (identifiable by the separator gel at the bottom of the tube) are also acceptable, provided that prolonged gel contact before testing is avoided. Some hydrophobic drugs may diffuse slowly into the gel, leading to falsely low results after several hours. A random, clean urine specimen is generally preferred for toxicology screens because the higher drug concentrations usually found in urine can compensate for the lower sensitivity of the broadly focused screening techniques. A urine specimen of 20 mL is usually optimal. Requirements for all specimens may vary from laboratory to laboratory.

When requesting a screening test, an important—and often overlooked—item of communication is specifying any xenobiotics of particular concern. This may allow faster results and a greater likelihood of detection.

Most full-service toxicology laboratories welcome consultation on puzzling cases or results that appear inconsistent with the clinical presentation. The laboratory will be familiar with the capabilities and limitations of their testing methods, as well as common sources of discrepant results.

METHODS USED IN THE TOXICOLOGY LABORATORY

Most tests in the toxicology laboratory are directed toward the identification or quantitation of xenobiotics. The primary techniques used include spot tests, spectrochemical tests, immunoassays, and chromatographic techniques. Mass spectrometry may also be used, usually in conjunction with gas chromatography (GS) or liquid chromatography. [Table 6–2](#) compares the basic features of these methodologies. Other methodologies include ion-selective electrode measurements of lithium, atomic absorption spectroscopy or inductively coupled plasma mass spectroscopy for lithium and heavy metals, and anodic stripping methods for heavy metals. Many adjunctive tests, including glucose, creatinine, electrolytes, osmolality, metabolic products, and enzyme activities, may also be useful in the management of poisoned patients. The focus here is on the major methods used for directly measuring xenobiotics.

TABLE 6–2. Relative Comparison of Toxicology Methods

Method	Sensitivity	Specificity	Quantitation	Analyte Range	Speed	Cost
Spot test	+	±	No	Few	Fast	\$
Spectrochemical	+	+	Yes	Few	Medium	\$
Immunoassay	++	++	Yes	Moderate	Variable	\$\$
TLC	+	++	No	Broad	Slow	\$\$
HPLC	++	++	Yes	Broad	Medium	\$\$
GC	++	++	Yes	Broad	Medium	\$\$
GC/MS	+++	+++	Yes	Broad	Slow	\$\$\$
LC/MS/MS	+++	+++	Yes	Broad	Medium	\$\$\$\$

\$ = very low; \$\$\$\$ = very high cost; GC = gas chromatography; GC/MS = gas chromatography/mass spectroscopy; HPLC = high-performance liquid chromatography; LC/MS/MS = liquid chromatography/tandem mass spectroscopy; TLC = thin-layer chromatography.

Spot Tests

The simplest tests are spot tests. These rely on the rapid reaction of a xenobiotic with a chemical reagent to produce a colored product (eg, the formation of a colored complex between salicylate and ferric ions) that is visually assessed in a semiquantitative manner. Because the reagents may cause precipitation of serum proteins, spot tests are more commonly performed on urine specimens or gastric aspirates. Such tests were once a mainstay of toxicologic testing. Because of the poor selectivity of chemical reagents, as well as substantial variability in visual interpretation, these assays suffer from fairly frequent false-positive results and occasional false-negative results and are rarely used today.

Spectrochemical Tests

Spectrochemical tests rely on measurement of a light-absorbing substance. Some analytes that are intrinsically light absorbing may be directly measured. Cooximetry (also known as hemoximetry) represents a sophisticated application of spectrophotometry to the measurement of various forms of hemoglobin in a hemolyzed blood sample. Measurement of light absorbance at multiple wavelengths allows several hemoglobin species to be simultaneously quantitated. For mathematical reasons, the number of wavelengths used must be greater than the number of different types of hemoglobin present. This is why classic pulse oximetry, which uses only two wavelengths, yields spurious results in the presence of significant amounts of methemoglobin or carboxyhemoglobin ([Chaps. 29, 125, and 127](#)). Cooximetry is relatively free of interferences because the concentrations of the hemoglobins are so much higher than other substances in the blood. However, the presence of intensely colored substances (eg, methylene blue) may cause spurious increases or decreases in the apparent percentages of the hemoglobins. Modern instruments are often able to recognize a significantly atypical pattern of absorbance and generate an error message in addition to or instead of a result.

Most analytes are neither as deeply colored nor as highly concentrated as hemoglobin species. Their detection requires a chemical reaction to produce an intensely light-absorbing product that is quantitatively measured at a specific wavelength in a spectrophotometer. Because spectrophotometers can also measure ultraviolet and infrared light, it is not necessary for the product to have a visible color. Early spectrochemical assays typically measured the absorbance after conversion of all of the analyte to the light-absorbing product. Modern assays usually use rate spectrophotometry, taking multiple absorbance measurements over time to determine the rate of change in light absorbance as the reaction proceeds. During the initial phase of the reaction, this rate is constant and proportional to the initial concentration of the analyte. This significantly reduces the time needed to obtain a result because it is not necessary for the reaction to go to completion, and it allows the averaging of multiple measurements, improving precision. Furthermore, it is unaffected by nonreacting substances that absorb light at the test wavelength because the absorbance of the nonreacting substances is constant and does not contribute to the rate of change in the absorbance.

Rate spectrophotometry remains subject to interference by substances that react to produce light-absorbing products, thereby falsely increasing the apparent concentration. Substances that inhibit the assay reaction or that consume reagents without producing a light-absorbing product give falsely low results. For example, ascorbic acid produces negative interference in many spectrophotometric assays that use oxidation reactions to generate colored products.

One way to improve the selectivity of a spectrochemical assay is to increase the selectivity of the reaction that generates the light-absorbing product. Enzymes, which can catalyze highly selective reactions, are often used for this purpose. For example, many assays for ethanol use alcohol dehydrogenase (ADH) to catalyze the oxidation of ethanol to acetaldehyde, with concomitant reduction of the cofactor NAD⁺ (oxidized form of nicotinamide adenine dinucleotide) to NADH (reduced form of nicotinamide adenine dinucleotide). The initial rate of increase in light absorption produced by

the conversion of NAD^+ to NADH is proportional to the concentration of ethanol. Although other alcohols, such as isopropanol and methanol, can also be oxidized by ADH, they are much poorer substrates for ADH with low rates of reaction and correspondingly low levels of interference.

Many other enzymatic assays also rely on measuring the change in light absorption at 340 nm when NAD^+ is converted to NADH or vice versa. These include enzymatic assays for ethylene glycol, as well as some enzyme-linked immunoassays, such as EMIT (enzyme-multiplied immunoassay technique) assays. All such assays are potentially subject to interference by specimens with high concentrations of lactate. Lactate dehydrogenase, which is naturally present in serum, will oxidize this lactate to pyruvate if NAD^+ becomes available for simultaneous reduction to NADH. When a serum specimen with high lactate is mixed with assay reagents that contain NAD^+ , oxidation of the lactate contributes to the total rate of NADH production. The increased rate of NADH production results in a false increase in the measured concentration of the target analyte.

Some enzymatic reactions do not produce a colored product. Enzymes such as glucose oxidase or lactate oxidase couple oxidation of the substrate to reduction of oxygen to hydrogen peroxide, which is colorless. A coupled second reaction is then necessary using the peroxide to convert a colorless dye to a colored one. Oxidase-based reactions may be subject to interference by compounds with high structural similarity to the target analyte. For example, glycolate, a toxic metabolite of ethylene glycol, is an excellent substrate for lactate oxidase and will give falsely high lactate results when it is present.

Immunoassays

The need to measure very low concentrations of an analyte with a high degree of specificity led to the development of immunoassays. The combination of high affinity and high selectivity makes antibodies excellent assay reagents. There are two common types of immunoassays: noncompetitive and competitive. In noncompetitive immunoassays, the analyte is sandwiched between two antibodies, each of which recognizes a different epitope on the analyte. In competitive immunoassays, analyte from the patient's specimen competes for a limited number of antibody binding sites with a labeled version of the analyte provided in the reaction mixture. Because most drugs are too small to have two distinct antibody binding sites, drug immunoassays are usually competitive.

In competitive immunoassays, increasing the concentration of xenobiotic in the specimen results in increased displacement of labeled xenobiotic from the antibodies. The amount of xenobiotic in the specimen can be determined by measuring either the amount of label remaining bound to the assay antibodies or the amount of label free in solution. In the earliest immunoassays, the label was a radioisotope, typically iodine-125, tritium, or carbon-14. Today, radioimmunoassays are relatively uncommon because of problems associated with handling and disposal of radioactivity. Nonisotopic immunoassays are currently the most widely used methodologies for the measurement of drugs. They offer high selectivity and good precision and are readily adapted to automated analyzers, thereby decreasing both the cost and the turnaround time of the assays. The xenobiotics for which immunoassays are available are limited to those for which there is a high demand, such as widely monitored therapeutic drugs and the drugs of abuse included in workplace drug screening. However, because production costs are relatively low, these tests are widely distributed at reasonable prices.

The most widely used nonisotopic drug immunoassays are in the category of homogenous immunoassays. Homogenous immunoassays measure differences in the properties of bound and free labels rather than directly measuring one or the other after their physical separation. Avoiding a separation step allows homogenous immunoassays to be readily adapted to automated analysis. Homogenous techniques that are in wide use include EMIT (Fig. 6-1), kinetic inhibition of microparticles in solution (KIMS), and cloned enzyme donor immunoassay (CEDIA).

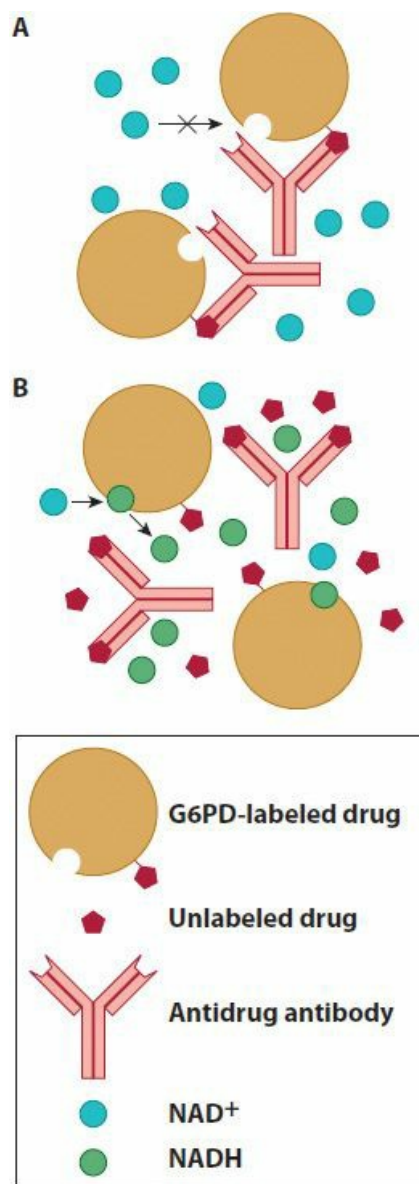


FIGURE 6–1. Enzyme-multiplied immunoassay technique (EMIT) immunoassay. The drug to be measured is labeled by being attached to the enzyme glucose-6-phosphate dehydrogenase (G6PD) near the active site. **(A)** Binding of the enzyme-labeled drug to the assay antibody blocks the active site, inhibiting conversion of NAD^+ (oxidized form of nicotinamide adenine dinucleotide) to NADH (reduced form of nicotinamide adenine dinucleotide). **(B)** Unlabeled drug from the specimen can displace the drug–enzyme conjugate from the antibody, thereby unblocking the active site and increasing the rate of reaction.

Many of the newest automated immunoassays are again using physical separation techniques. In these assays, the detection antibody is physically attached to a solid support, and separation occurs by a simple wash step. This wash step removes the patient's serum along with many potentially interfering substances. Older assays of this type used antibodies bound to large plastic beads or wells of microtiter plates and required long incubation steps because of substantial times required for diffusion of the reactants to the antibodies. Newer assays typically use latex microparticles that have very high total surface areas, allowing rapid equilibration and short assay times.

Figure 6–2 shows a schematic magnetic microparticle enzyme-labeled chemiluminescent competitive immunoassay. A single enzyme label can generate many photons, allowing high signal amplification. Coupled with a background luminescence that is essentially zero, such assays can measure concentrations below the nanomolar level. Many variations of this approach are in use. Enzyme substrates may be used that result in fluorescent or colored products. Enzymes other than alkaline phosphatase may be used as labels, or nonenzymatic fluorescent, chemiluminescent, or electroluminescent labels may be used. These new techniques are readily automated and have higher sensitivities than homogenous immunoassays.

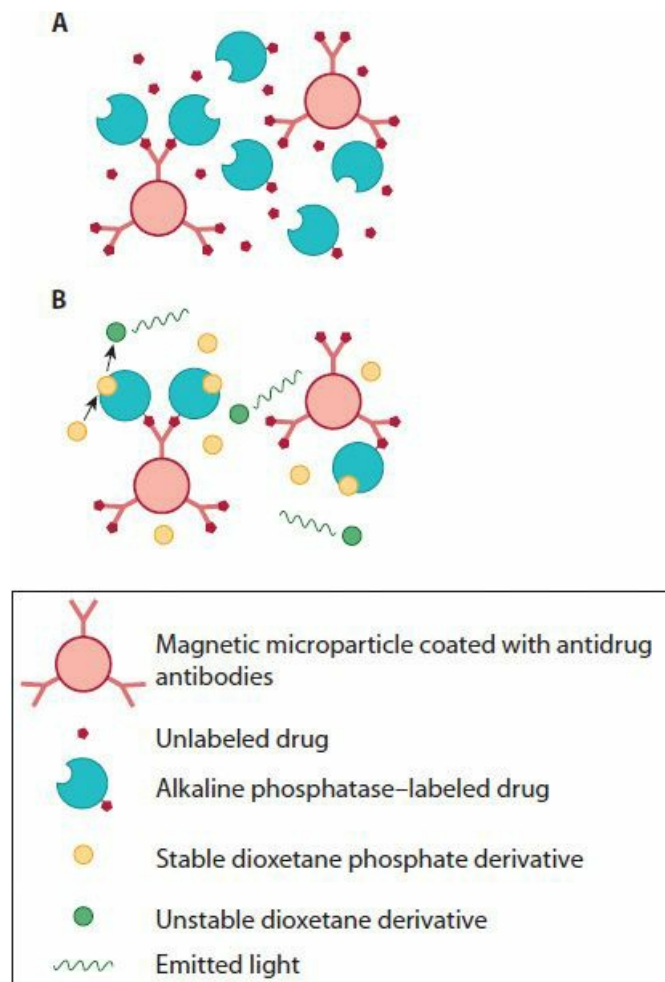


FIGURE 6–2. Magnetic microparticle chemiluminescent competitive immunoassay. **(A)** Unlabeled drug from the specimen competes with alkaline phosphatase–labeled drug for binding to antibody-coated magnetic microparticles. The microparticles are then held by a magnetic field while unbound material is washed away. **(B)** A dioxetane phosphate derivative is added and is dephosphorylated by microparticle-bound alkaline phosphatase to give an unstable dioxetane product that spontaneously decomposes with emission of light. The rate of light production is directly proportional to the amount of alkaline phosphatase bound to the microparticles and inversely proportional to the concentration of competing unlabeled drug from the specimen.

Microparticle capture assays are a type of qualitative competitive immunoassay that have become very popular, especially for urine drug screening tests. The use of either colored latex or colloidal gold microparticles enables the result to be read visually as the presence or absence of a colored band, with no special instrumentation required. Competitive binding occurs as the assay mixture is drawn by capillary action through a porous membrane. This design feature is responsible for alternate names for the technique: lateral flow immunoassay or immunochromatography.

The simplest microparticle capture design uses an antidrug antibody bound to colored microparticles and a capture zone consisting of immobilized drug (Fig. 6–3). If the specimen is xenobiotic free, the beads will bind to the immobilized analyte, forming a colored band. When the amount of drug in the patient specimen exceeds the detection limit, all of the antibody sites will be occupied by drug from the specimen, and no labeled antibody will be retained in the capture zone. The use of multiple antibodies and discrete capture zones with different immobilized analytes can allow several xenobiotics to be detected with a single device.

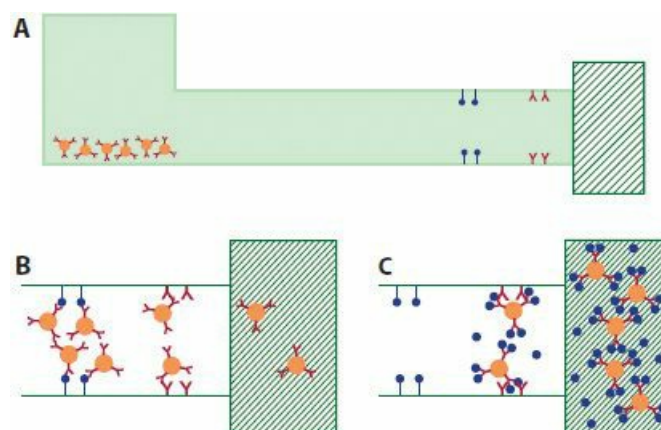


FIGURE 6-3. Microparticle capture immunoassay. (A) Diagram of a device before specimen addition. Colored microbeads (about the size of red blood cells) coated with antidrug antibodies (Y) are in the specimen well. At the far end of a porous strip are capture zones with immobilized drug molecules (•) and a control zone with antibodies recognizing the antibodies that coat the microbeads. (B) Adding the urine specimen suspends the microbeads, which are drawn by capillary action through the porous strip and into an absorbent reservoir (hatched area) at the far end of the strip. In the absence of drug in the urine, the antibodies will bind the beads to the capture zone containing the immobilized drug and form a colored band. Excess beads will be bound by antibody–antibody interactions in the control zone, forming a second colored band that verifies the integrity of the antibodies in the device. (C) If the urine contains the drug (•) in concentrations exceeding the detection limit, all of the antibodies on the microbeads will be occupied by drug from the specimen, and the microbeads will not be retained by the immobilized drug in the capture zone. No colored band will form. However, the beads will be bound and form a band in the control zone.

A disadvantage of this design is the potential for causing confusion because a positive test result is indicated by the absence of a band. More complex (and more expensive) variations have been developed in which a colored band denotes a positive test result.

Although immunoassays have a high degree of sensitivity and selectivity, they are also subject to interferences and problems with cross-reactivity. Cross-reactivity refers to the ability of the assay antibody to bind to xenobiotics other than the target analyte. Xenobiotics with similar chemical structures may be efficiently bound, which can lead to falsely elevated results. In some situations, cross-reactivity can be beneficially exploited. For example, some immunoassays effectively detect classes of drugs rather than one specific drug. Immunoassays for opioids use antibodies to morphine that cross-react to varying degrees with structurally related substances, including codeine, hydrocodone, and hydromorphone. Oxycodone typically has low cross-reactivity, and higher concentrations are required to give a positive result. The cross-reactivity of non-morphine opiates varies with manufacturer. Consult with your lab for the relative sensitivities of the immunoassay it uses. Structurally unrelated synthetic opioids, such as meperidine and methadone, have little or no cross-reactivity and are not detected by opiate immunoassays. Immunoassays for the benzodiazepine class react with a wide variety of benzodiazepines but with varying degrees of sensitivity.^{12,16} Because of the highly variable response of immunoassays to the various opiates and benzodiazepines, methods based on mass spectrometry should be used for definitive results.

Class specificity can be a two-edged sword. Assays for the TCA family have similar reactivity with amitriptyline, nortriptyline, imipramine, and desipramine and can be used to provide an estimate of the total concentration of any combination of these drugs. To account for nonuniform cross-reactivity, such results of these assays are usually reported as concentration ranges (eg, <100 ng/mL, 100–300 ng/mL). A large number of other drugs with tricyclic structures, including carbamazepine, many phenothiazines, and diphenhydramine, also cross-react and generate a signal, particularly at concentrations found in patients who overdose. Qualitative tests, such as microparticle capture assays, may then yield false-positive results if the signal generated by the cross-reacting drug (eg, carbamazepine) exceeds the detection limit of the immunoassay. With quantitative or semiquantitative assays, however, the apparent concentration produced by a cross-reacting drug is generally well below TCA concentrations associated with toxicity.

Even when an antibody is selected to be specific to a single drug, it is common that metabolites of the target drug show some cross-reactivity. This, too, may be beneficial. When the metabolite is an active one (eg, carbamazepine epoxide), the contribution of its cross-reactivity may yield results that correlate better with the drug effect than the true concentration of the parent drug alone.

Immunoassays are also subject to interference by substances that impair detection of the label. Elevated lactate concentrations may lead to spuriously increased drug concentrations in specimens tested by EMIT, as described earlier. Immunoassays that rely on enzyme labels are particularly sensitive to nonspecific interference because enzyme activity is highly dependent on reaction conditions. A number of substances that can inhibit the enzyme reaction in EMIT assays are used to adulterate urine submitted for drug abuse testing with the intent of producing false-negative results (see the discussion of drug-abuse screening tests under “Special Considerations for Drug Abuse Screening Tests” later). Such adulteration may be detected when the rate of reaction is lower than the rate observed with a drug-free control.

Chromatography

Chromatography encompasses several related techniques in which analyte specificity is achieved by physical separation. The unifying mechanism for separation is the partition of the analytes between a stationary phase and a moving phase (mobile phase). In most instances, the stationary phase consists of very fine particles arranged in a thin layer or enclosed within a column. The mobile phase flows through the spaces between the particles. Analytes are in a rapid equilibrium between solution in the mobile phase and adsorption to the surfaces of the particles. They move when in the mobile phase and stop when adsorbed to the stationary phase. The average velocity of the analyte xenobiotics depends on the relative time spent in the moving versus stationary phase. Xenobiotics that partition primarily into the mobile phase have average velocities slightly lower than the mobile phase velocity. Average velocity decreases as the proportion of time adsorbed to the stationary phase increases. Under controlled conditions, these average velocities are highly reproducible. Xenobiotics

may be provisionally identified based on their characteristic velocity, as measured by the amount of time required to traverse the length of a chromatography column (retention time). Chromatography is a separation method and must be combined with a detection method to allow identification and measurement of the separated substances.

Chromatographic behavior is sufficiently reproducible that the failure to detect a signal at the retention time characteristic of a compound effectively excludes the presence of that compound in amounts greater than the detection limit. On the other hand, a number of different substances may have migration velocities that are identical or nearly so. A positive finding is therefore not completely specific. Definitive identification depends on having additional information, which may be obtained through selective detection techniques or by confirmatory testing using a second method. The sensitivity of chromatographic methods depends on both the amount of specimen available and the sensitivity of the detection method. A major advantage of chromatographic techniques is that multiple xenobiotics may be detected and measured in a single procedure. Nor is it necessary to know in advance the specific xenobiotic to be looked for. For this reason, chromatographic techniques have a major role in screening for multiple xenobiotics.

Most chromatographic procedures require extraction and concentration of the xenobiotics to be analyzed before the chromatography is done. Extraction results in removal of salts, proteins, and other materials that may exhibit unfavorable interactions with either of the chromatographic phases. Concentration allows the substances to be introduced in a narrow “band,” so that compounds with slightly different relative mobilities become completely resolved, or separated from one another, rather than overlapping. This also results in a more intense signal as a band passes through the detector and increases sensitivity.

Extraction of drugs is most commonly done with organic solvents, but “solid-phase extraction” is also very popular.¹¹ Solid-phase extraction is itself a modified chromatographic procedure in which a urine or serum specimen is passed through a short chromatography column with a hydrophobic stationary phase. Most drugs are sufficiently hydrophobic to partition almost completely into the stationary phase and are retained on the column. Subsequently, the retained xenobiotics are eluted with an organic solvent. The organic solvents from either extraction technique are evaporated to concentrate the extract. The extraction process allows the analyte from a large volume of specimen to be concentrated. Detection sensitivity can thereby be increased provided large-volume specimens can be readily obtained, as is true with urine.

Often a preextraction treatment is used to increase the hydrophobicity of the substances to be extracted. The most common manipulation is pH adjustment, either upward or downward, to convert charged forms of drugs into uncharged, hydrophobic, and therefore extractable ones. In other instances, enzymatic or chemical hydrolysis may be used to convert water-soluble glucuronide metabolites back to their more readily extracted parent compounds, for example, conversion of morphine glucuronide to morphine.

In the technique of high-performance liquid chromatography (HPLC), a stationary phase is packed into a column and the mobile phase is pumped through under high pressure (Fig. 6–4). This allows good flow rates to be achieved even when solid phases with very small particle sizes are used. Smaller particle size increases surface area, decreases diffusion distances, and improves resolution, but the spaces between the particles are also smaller, increasing the resistance to flow. The use of high pressure and small particles allows good separations while keeping assay time short.

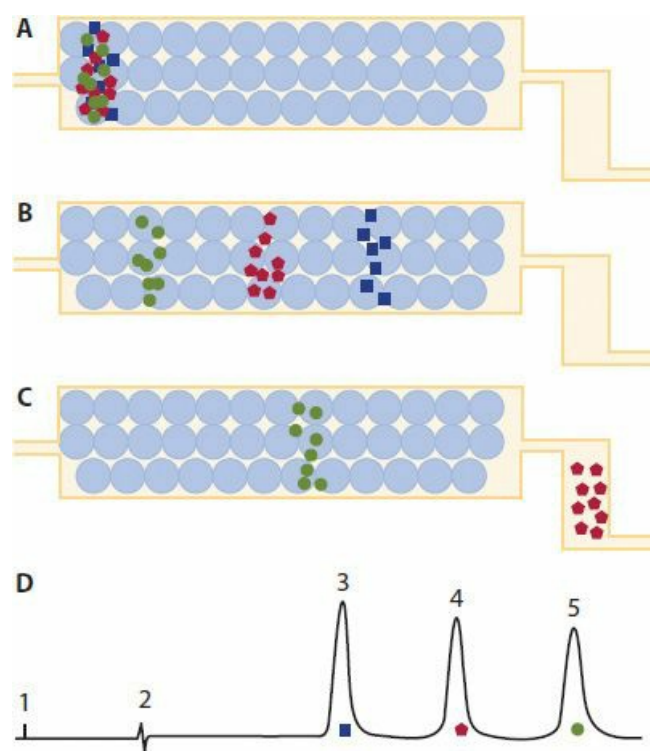


FIGURE 6–4. High-performance liquid chromatography (HPLC). HPLC is schematically shown. (A) A mixture of three compounds (■) (●) (●) is injected into a column filled with a spherical reversed-phase packing. (B) The compounds move

through the column at characteristic speeds. The most hydrophilic compound (■) moves most quickly, and the most hydrophobic compound (●) moves most slowly. (C) The compound of intermediate polarity (●) has reached the detection cell, where it absorbs light directed through the cell and generates a signal proportional to its concentration. (D) Illustration of the HPLC tracing that might result: 1 indicates the time of injection. The artifact at 2 results when the injection solvent reaches the detector and indicates the retention time of a completely unretained compound. The peaks at 3, 4, and 5 correspond to the separated compounds. For example, peak 4 might be amitriptyline, peak 3 might be the more polar metabolite, nortriptyline, and peak 5 could be the more hydrophobic internal standard N-ethylnortriptyline. Later-emerging peaks are typically wider and shorter because of more time for diffusive forces to spread out the molecules

HPLC drug assays typically use “reverse-phase” chromatography. Early chromatographic techniques typically used relatively polar silica gel particles as the stationary phase, with organic solvent mobile phases. Reverse-phase chromatography uses stationary phases consisting of silica gel particles that have had hydrocarbon molecules covalently linked to the outer surface. This coats the particles with a permanently bonded oil-like layer. Mobile phases are primarily aqueous with varying amounts of organic solvent. Because of these modifications, hydrophobic xenobiotics are more strongly adsorbed by the stationary phase, but hydrophilic ones tend to remain in the mobile phase. This results in an order of elution from the column that is approximately the reverse of that seen with unmodified silica gel and organic solvents. Thus, the term reverse-phase chromatography is used. HPLC can be done using either “normal-phase” or “reverse-phase” conditions, but reverse-phase conditions are much more commonly used. A variety of hydrocarbons can be used to derivatize the silica gel. By far, the most common reverse-phase columns use an octadecyl hydrocarbon as the outer coating and are often referred to as C-18 columns.

In HPLC, the xenobiotics are detected after they exit the chromatographic column. In this case, they are identified by their retention time (the characteristic time required to traverse the column). Because most xenobiotics absorb ultraviolet light, detection is commonly by ultraviolet spectroscopy using specially designed flow-through cuvettes. Measuring light absorbance at a selected wavelength allows the amount of the xenobiotic to be determined. Accuracy is often enhanced by comparing the absorbance of the target analyte with absorbance of an internal standard (ie, a compound with a different retention time that is added in a fixed amount to all specimens). The ratio of the drug absorbance to the internal standard absorbance is proportional to the drug concentration in the specimen.

Although most HPLC detectors allow a selection of the detection wavelength, only one wavelength is commonly used during a given run. Some detectors, however, allow absorbance at multiple wavelengths to be determined by breaking white light into its component wavelengths after it has passed through the detection cuvette and then making measurements at multiple wavelengths simultaneously using a light-sensitive chip similar to those used in digital cameras. This allows the absorbance spectrum of a compound to be determined as it elutes from the column. This information can supplement the retention time and allow more specific identifications to be made.

HPLC is often the method of choice for measuring serum concentrations of xenobiotics for which no immunoassay is available. However, it is limited by an inability to analyze drugs with a wide range of polarities in a single assay or to fully resolve substances with very similar polarity, both of which limit its usefulness as a broad drug-screening technique.

GC is similar in principle to HPLC except that the moving phase is a gas, usually the inert gas helium but occasionally nitrogen. The schematic illustration of HPLC in Fig. 6–4 is also applicable to GC. The low flow resistance of gas allows high flow rates that make possible substantially longer columns than are used in HPLC. This offers the dual advantages of high resolution and fast analysis. As was true in HPLC, most GC assays incorporate an internal standard to increase precision.

Because the inert carrier gas does not engage in intermolecular interactions, partition of the analytes into the moving gas phase depends primarily on their natural volatility. Elevated column temperatures are required to achieve sufficient volatility for analysis of most xenobiotics. The use of a temperature gradient (the column temperature is programmed to increase throughout the course of the analysis) can allow xenobiotics with a wide range of volatility to be analyzed in a single run. This feature, coupled with excellent resolution, makes GC suitable for screening assays that encompass a broad range of drugs.

GC is limited to xenobiotics that are reasonably volatile at temperatures below 572°F (300°C), above which the stationary phase may begin to break down. Two principal attributes of a xenobiotic limit its volatility: its size and its ability to form hydrogen bonds. Xenobiotics that form hydrogen bonds via amino, hydroxyl, and carboxylate moieties can be made more volatile by replacing hydrogens on oxygen and nitrogen atoms with a nonbonding, preferably large, substituent. (Large substituents sterically hinder access to the acceptor electron pairs on the nitrogen and oxygen atoms.) A number of derivatizing agents can be used to add appropriate substituents. The most common derivatives involve the trimethylsilyl (TMS) group. Although derivatization with TMS substantially increases the molecular weight, the resulting derivative is much more volatile as a consequence of the loss of hydrogen bonding.

In traditional packed-column GC, the packing may consist of inert support particles with a thin coating of nonvolatile, high-molecular-weight oil that comprises the stationary phase. It is increasingly common for the stationary phase to be covalently bonded to the support particles. A highly useful variant of GC is capillary chromatography. A long, thin capillary tube of fused silica is coated on the inside with a covalently bonded stationary phase. The mobile gas phase flows

through the tiny channel in the middle. These capillaries are flexible, allowing very long columns (≥ 10 m) to be coiled into a small space. The long column length, coupled with highly uniform conditions throughout the column, results in extremely high resolution. The small diameter of the column allows rapid thermal equilibration and the use of steep temperature gradients that can speed analysis. The major drawback to capillary chromatography is a very limited column capacity. Special techniques are needed to restrict the amount of material introduced into the column and thereby to avoid overloading it. High-sensitivity detectors are required to measure the small quantities that can be chromatographed.

A number of detectors are available for GC. The most common detector, particularly for packed columns, is the flame ionization detector. This involves directing the outflow of the column into a hydrogen flame. Organic molecules emerging from the column are burned, creating charged combustion intermediates that can be measured as a current. The amount of current flow is largely determined by the mass of carbon that is being burned. Nitrogen–phosphorus detectors are also widely used in drug analysis. In this modification of a flame ionization detector, a heated bead coated with an alkali metal salt is used to selectively generate ions from xenobiotics containing nitrogen or phosphorus. These devices detect broad ranges of substances but do not identify them. The identity of the compounds detected must be inferred from the retention time.

The mass spectrometer can serve as a highly sensitive GC detector and possesses the ability to generate highly characteristic mass spectra from the compounds it is detecting. A special requirement of the mass spectrometer is that it requires a high vacuum to prevent the ionic particles that it creates from interacting with other molecules or ions. This requires removal of the inert carrier gas and is easiest when there is a low total gas flow, such as occurs with capillary GC. The mass spectrometer in turn provides good sensitivity for the small amounts of analyte that can be accommodated in capillary GC.

The detection process begins by generating ions from the analyte. This is usually done using electron impact ionization. The gas phase analyte is separated from the bulk of the carrier gas and introduced into an ionization chamber, where it is bombarded by a stream of electrons. Electron impact can dislodge an electron from the analyte, creating a positively charged ion and frequently imparting sufficient energy to the ion to break it into pieces. If fragmentation occurs, conservation of charge requires that one of the resulting fragments be a positively charged ion. The fragments into which a molecular ion can break are characteristic of the xenobiotic as are the relative probabilities that any given fragment will carry the positive charge.

The mass spectrometer then uses electromagnetic filtering to direct only ions of a specified mass-to-charge (m/z) ratio to a detector. Because most of the ions produced have a single positive charge, the observed peaks generally correspond to the mass of the ions. The detector has sufficient electronic amplification that a single ion could theoretically be detected, accounting for the high sensitivity of mass spectrometric detection. By rapidly scanning through a range of masses that are sequentially allowed to reach the detector, a mass spectrum may be generated. The mass spectrum records the masses of the pieces produced by fragmentation of the parent ion, as well as the relative frequency with which these fragments are produced and detected. The highest mass observed in the spectrum usually corresponds to the mass of intact parent ions generated from collisions that were not energetic enough to cause fragmentation.

Figure 6–5 shows the mass spectrum obtained from a gas chromatograph at a time when the TMS derivative of the cocaine metabolite benzoylecgonine was emerging from the capillary column. The mass spectrum of any compound is highly distinctive and usually unique. The primary exception involves optical enantiomers, both of which have the same mass spectrum. Toxicologically significant examples of enantiomers include D-methamphetamine, a drug of abuse, and L-methamphetamine, which is found in decongestant inhalers. It is also important to distinguish dextrophan, the major metabolite of the cough suppressant dextromethorphan, and levorphan (levorphanol), a controlled substance.

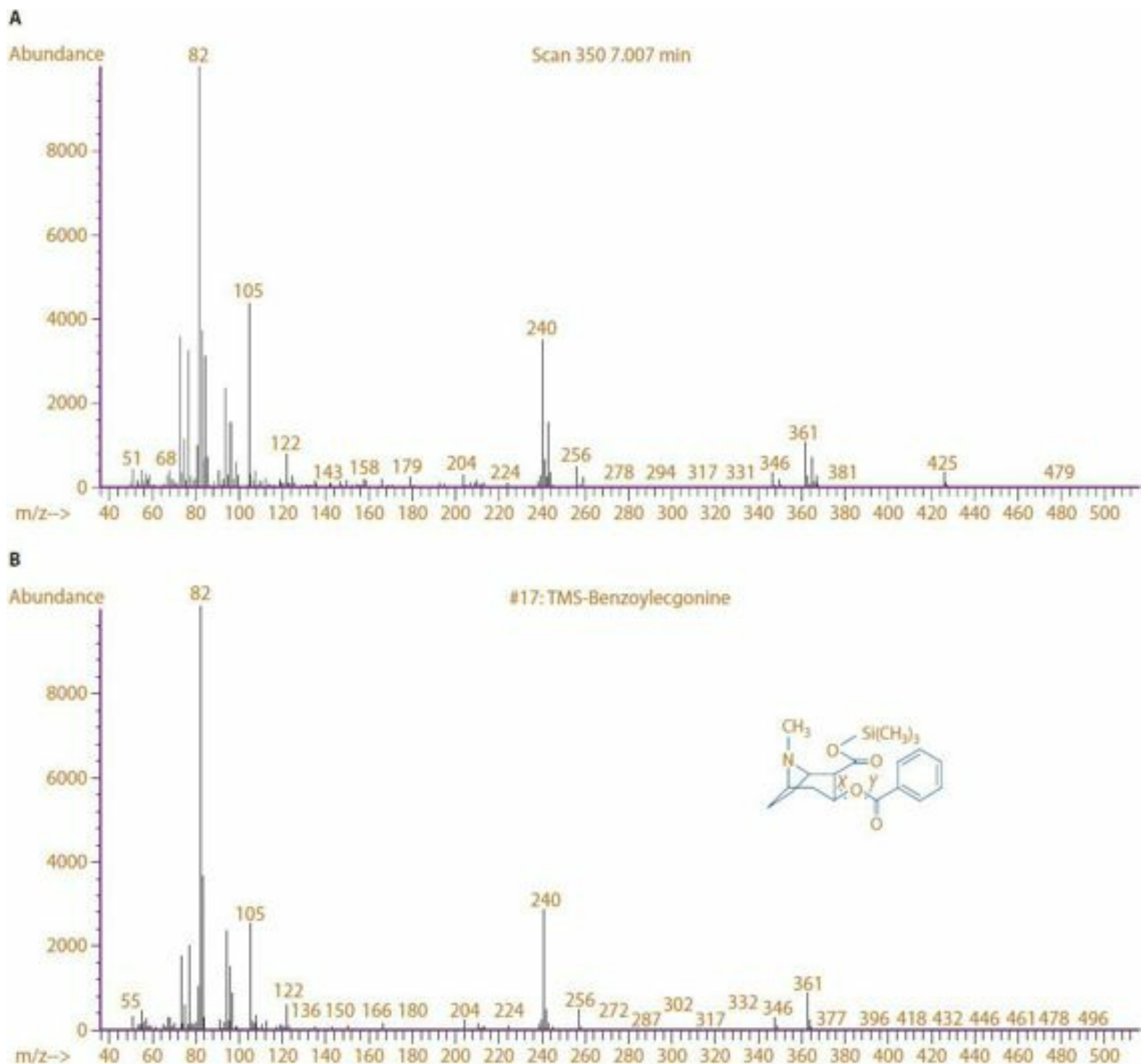


FIGURE 6-5. Mass spectrum of the trimethylsilyl derivative of benzoyllecgonine (TMS-BE). (A) Mass spectrum of effluent from a gas chromatography (GC) column at the retention time of TMS-BE. The unfragmented parent ion of TMS-BE is at a mass-to-charge (m/z) ratio of 361. The two fragment peaks at m/z 243 and 259 result from fracture of the bonds at X and Y, respectively, in structure of TMS-BE (inset in B). Additional peaks at m/z 243, 259, and 364 are derived from trideuterated TMS-BZE (d_3 -TMS-BE) added as an internal standard. The mass spectrometer can identify and quantify TMS-BE and d_3 -TMS-BE independently of one another by measuring the heights of the peaks unique for each compound. The peak at m/z 425 is from a coeluting contaminant. (B) Mass spectrum of pure TMS-BE.

To avoid the need to scan the full range of masses in a typical mass spectrum, selected ion monitoring is often used. Here, the mass spectrometer is typically programmed to filter and detect only three of the larger and more characteristic peaks in the mass spectrum. In the case of TMS-benzoyllecgonine (TMS-BE), the peaks at m/z 240, 256, and 361 are used. The concentration of TMS-BE in the specimen is determined from the ratio of the peak height at m/z 240 to height of a peak at m/z 243 that results from a corresponding fragment of the internal standard, which is TMS-BE that is labeled with three deuterium atoms (d_3 -TMS-BE) to give it a mass distinct from that of TMS-BE from the specimen (Fig. 6-5). The specificity of the identification is verified by finding peaks at m/z 256 and m/z 361, with peak height ratios to the peak at m/z 240 comparable to the ratios seen with authentic TMS-BE. The detection at the correct retention time of a xenobiotic producing all three peaks in the correct ratios produces an extremely specific identification.

The high sensitivity and specificity afforded by GS/mass spectrometry is being further extended by the related hybrid technique of liquid chromatography/tandem mass spectrometry, often abbreviated as LC/MS/MS.¹⁸ This technique is being

used in an increasing number of toxicology laboratories. In LC/MS/MS, a tandem mass spectrometer is used as the detector for liquid chromatography system. The initial ionization is done under conditions that do not promote fragmentation and is commonly achieved by adding or removing a proton rather than forcefully dislodging an electron. The resulting ions have a mass that differs from that of the parent molecule by one mass unit ($[M+H]^+$ or $[M-H]^-$). The first mass spectrometer is used to selectively filter only unfragmented ions with the expected molecular mass. As the selected ions exit the first mass spectrometer at high speed, they are allowed to collide with molecules of an inert gas. These collisions cause the ions to break apart to create the fragment mass spectrum that is detected by the second mass spectrometer. The additional selection step provided by the first mass spectrometer greatly enhances specificity and reduces background signal, enhancing sensitivity.

QUANTITATIVE DRUG MEASUREMENTS

When properly used to guide dosing adjustments, drug concentration measurements improve medical outcomes.⁹ However, many therapeutic drug measurements are drawn at inappropriate times or are made without an appropriate therapeutic question in mind. An essential requirement for interpretation of xenobiotic concentrations is that the relationship between concentrations and effects must be known. Such knowledge is available for routinely monitored xenobiotics and is often encapsulated in published ranges of therapeutic concentrations and toxic concentrations. Concentrations designated as “toxic” are usually higher than the upper end of the therapeutic range and typically represent concentrations at which toxicity is acute and potentially serious (see back cover).

For most xenobiotics, the relationships between toxic concentrations and effects cannot be systematically studied in humans and consequently are often incompletely defined. These relationships are largely inferred from data provided in overdose case reports and case series. The measurement of xenobiotic concentrations in overdose cases in which concentration–effect relationships are not well defined may contribute more to the management of future overdosed patients than to the management of the patient in whom the measurements were made.

For toxicologists, xenobiotic concentrations are especially useful in two ways. For xenobiotics whose toxicity is delayed or is clinically inapparent during the early phases of an overdose, concentrations may have substantial prognostic value and facilitate anticipatory management. These concentrations may also be used to make decisions regarding the use of antidotes or of interventions to hasten drug elimination, such as hemodialysis.

Quantitative xenobiotic measurements are subject to various interferences, but these are less problematic than in qualitative assays. Signals generated by cross-reacting substances are weaker than those from the target analyte and are relatively unlikely to lead to a false diagnosis of toxicity, particularly if the target analyte is absent. Such cross-reactivity can be exploited in some instances to provide confirmatory evidence of a poison for which no specific assay is immediately available. For example, the immunoassay finding of apparent subtoxic concentrations of TCAs can help confirm a diphenhydramine overdose, and the finding of a measurable digoxin concentration in an unexposed patient may suggest poisoning with other cardioactive steroids of plant or animal origin. Negative interferences are much less frequent. Interferences in chromatographic methods usually result from the presence of other compounds with migration rates similar to the target analyte. Because the migration rates are rarely exactly the same, the laboratory can often recognize the presence of the interference as an overlapping peak when both compounds are present. In such instances, the interference may impair accurate measurement of the drug concentration. When no target xenobiotic is present, misidentification of the interfering peak as the target becomes much more likely because a single peak is seen at approximately the expected position. Because interferences in chromatographic methods are generally unique to a specific method, information about these interferences should be obtained by asking the laboratory.

Xenobiotic measurements are unlike most other laboratory measurements in that the concentrations are highly dependent on the timing of the measurement. Knowledge of the pharmacokinetics of a xenobiotic can substantially enhance the ability to draw meaningful conclusions from a measured concentration. Some xenobiotics alter their pharmacokinetic behavior at very high concentrations. These changes in pharmacokinetics may be predictable from the mechanisms of drug clearance and the extent of binding to plasma proteins and to tissues (Chap. 9).

Knowledge of the relationship between xenobiotic concentrations and effects, or pharmacodynamics, is also important. Effects depend on local concentrations at the site of action, typically at cell membrane receptors or intracellular locations. Serum or plasma concentrations can be correlated with effects only when these concentrations are in equilibrium with concentrations at the site of action. During the absorption and distribution phases, the concentration ratio will be higher than its equilibrium value, yet often the only xenobiotic concentration measured after an acute overdose is one obtained while absorption and distribution are still ongoing. This effect may explain some observations of apparent poor correlation between measured concentrations and toxic effects.

For xenobiotics that bind significantly to plasma proteins, it is the concentration of xenobiotic that is not bound to proteins (the free-xenobiotic concentration) that is in equilibrium with concentrations at the site of action. For most drugs at therapeutic concentrations, the free-drug concentration is an approximately constant percentage of the total drug concentration. The total concentration is what is usually measured in the laboratory. Under these conditions, the ratio of

total concentration to active site concentration is approximately constant, and a reasonable correlation between total concentration and effects can be expected.

A major change in the free fraction occurs after treatment of digoxin toxicity with digoxin specific antibody fragments when the free digoxin concentration falls from approximately 75% of the total concentration to less than 1% as a consequence of digoxin binding by the antidigoxin antibody fragments. At the same time, there is extensive redistribution of digoxin from tissues to plasma, leading to substantial increases in total digoxin concentration. This situation may be further complicated by complex digoxin specific antibody fragments interference in many digoxin immunoassays.

Measurement of free-drug concentrations can clarify such situations.¹⁵ Assays for free phenytoin are available in many laboratories. Assays for other free-drug concentrations may require special arrangements. The availability and expected turnaround time can be provided by the laboratory. For example, for patients treated with digoxin specific antibody fragments, newer immunoassays that use antibodies attached to microparticles or glass fibers give results that can be used to set an upper bound on free-digoxin concentrations and thereby verify adequacy of treatment.²³

Toxicology Screening

A test unique to the toxicology laboratory is the toxicology screen, or “tox screen.” Depending on the laboratory, this term may refer to a single testing methodology with the ability to detect multiple xenobiotics, such as GC/MS; it may refer to a panel of individual tests, such as a drug-abuse screen; or it may be a combination of broad-spectrum and individual tests. The widespread use of the term “tox screen” is unfortunate because this inappropriately implies for many physicians the availability of a test that can confirm or exclude poisoning as a diagnosis. Although there are many more toxic xenobiotics in the world than there are named diseases, most serious poisonings involve a relatively limited number of xenobiotics. Comprehensive drug screens can identify many of these agents but may miss recently introduced therapeutic agents or new designer drugs, such as components of “bath salts.” Moreover, comprehensive toxicology screens typically do not detect ionic substances, including bromide, cyanide, lithium, iron, lead, and other heavy metals, and may miss substances that are toxic at extremely low concentrations, such as digoxin and synthetic cannabinoids. Designer drugs are a problem because for any drug, authentic material must be available to establish its behavior in the assay system. By the time a particular drug is added to the system, it has often been largely supplanted in users by something new. It should be apparent that a negative toxicology screen result cannot exclude poisoning. It is equally true that a positive finding does not necessarily confirm a diagnosis of poisoning. For assays that detect only the presence of a xenobiotic, it is not possible to distinguish benign or therapeutic concentrations from toxic ones. Quantitative tests may falsely suggest toxicity when drug concentrations are measured during the drug’s distribution phase, which may extend for several hours with drugs such as digoxin and lithium. Moreover, the phenomenon of tolerance may allow chronic drug users to be relatively unaffected by concentrations that would be quite toxic to a non-using individual. Because comprehensive drug screens may differ widely among institutions and patterns of exposure also show substantial regional variation, there is limited ability to draw meaningful conclusions from any study of the sensitivity and specificity of such screens for detecting or excluding poisoning.

The predictive power of the result of a toxicology screen depends on a number of factors, including the likelihood of poisoning before receiving the test results (the prior probability or the prevalence), the range of xenobiotics effectively detected, and the frequency of false-positive results. It should be noted that false-positive and false-negative results may be either analytical or clinical in origin. A clinical false-positive result occurs when a xenobiotic is detected that is not contributing to the medical problem (eg, a therapeutic amount of APAP). A clinical false-negative result may occur when the wrong test is ordered (eg, a screen for drugs of abuse for a patient with APAP poisoning).

Although only approximately 2% of laboratories offer comprehensive toxicology screening,⁴ most laboratories offer some sort of testing in response to a request for a toxicology screen. This may vary from a panel of immunoassays for drugs of abuse to a comprehensive screening test performed at a reference laboratory. Other laboratories may offer a focused panel of tests rather than a comprehensive screening analysis. Larger laboratories may have several types of “tox screens” available for use in different situations. Among laboratories that do not limit their tests exclusively to commercially available methods, it is likely that no two will have exactly the same menu of drugs that can be reliably detected. Given the trends toward increasing automation and decreasing personnel in clinical laboratories, it is relevant to ask what benefits may be derived from such testing. Studies show that comprehensive toxicologic screening has the potential to provide significant information, with utility varying with the indication for testing. The prevalence of positive results has ranged from 34% to 86% of specimens submitted for testing. When drug exposure, as predicted from the patient’s history and physical examination, was compared with screening results, clinically unsuspected substances were found in 7% to 48% of the cases, and clinically suspected xenobiotics were not found in 9% to 25%.^{13,14,24} However, limited utility is suggested by studies showing that the results of comprehensive screening affect management in fewer than 5% of cases.^{13,14,20,22,28} A survey of emergency physicians found that more than 75% were not fully aware of the range of drugs detected and not detected by their laboratory’s toxicology screen. The majority believed that the screen was more comprehensive than it actually was.¹⁰

One reason for a limited effect on management is the substantial time delay before the results of comprehensive screening are typically available. Generally, more than 3 hours is required for the report of a negative result, and an even

longer time may be required for confirmation of a positive finding. By this time, most consequential management decisions have been implemented. Another possible explanation for the limited utility of screening is that comprehensive screening is largely available only in major medical centers, where consultation from a medical or clinical toxicologist is more likely to be available. Such experts may be more able to make correct diagnoses and initiate appropriate management relying on clinical findings alone.

Several point-of-care devices are capable of rapidly screening urine for the presence of drugs of abuse, as well as TCAs. Results are typically available in 5 to 20 minutes. The accuracy of these devices is typically less than that of laboratory testing.³⁰ In a small study of one such device, diagnosis was believed to have been aided in 82% of cases, and clinical management was changed in 25%.² Additional studies are needed to ascertain the utility of point-of-care drug screening in emergency toxicology.³¹

A useful alternative to the toxicology screen is the toxicology hold. This is a set of serum or urine (or both serum and urine) specimens drawn at the time of presentation, when xenobiotic concentrations are likely to be near maximum concentrations, and initially held refrigerated or frozen without testing. This allows a specimen to remain available for subsequent testing if needed. Most laboratories hold such specimens for several days.

SPECIAL CONSIDERATIONS FOR DRUG ABUSE SCREENING TESTS

Testing for drugs of abuse is a significant component of medical toxicology testing. These tests are widely used in the evaluation of potential poisonings and are assuming an increasing role in assuring the appropriate use of pain medications.⁷ Initial testing is usually done with a screening immunoassay. Although drug-screening immunoassays were initially developed for use in workplace drug-screening programs and are not always optimal for medical purposes, their wide availability, low cost, and ease of use led to their nearly universal adoption in clinical laboratories. Growth of the market for medical drug screening has led to the development of point-of-care tests specifically for medical use, but these devices largely retain the deficiencies of their predecessors. Drug abuse testing for nonmedical reasons is generally considered to be forensic testing, and confirmation of immunoassay results is considered mandatory in such circumstances. Confirmatory testing can compensate for some immunoassay shortcomings but is frequently not done when screening tests are used for medical purposes. Despite the widespread use of drug-screening immunoassays in medical practice, studies suggest that many physicians do not fully understand the capabilities and limitations of these tests.²⁵

The most commonly tested-for drugs are amphetamines, cannabinoids, cocaine, opioids, and PCP. These are often referred to as the NIDA five because they are the five drugs that were recommended in 1988 by the National Institute on Drug Abuse (NIDA) for drug screening of federal employees. (Responsibility for recommendations for federal drug testing now lies with the Substance Abuse and Mental Health Services Administration {SAMHSA}.) Drug-screening immunoassays are also frequently done for methadone and benzodiazepines and less frequently for oxycodone and hydrocodone. Drug-screening devices intended primarily for medical use may also include tests for APAP or TCAs. [Table 6–3](#) lists some of the general characteristics of these tests. Commercial urine immunoassays are also available for buprenorphine, lysergic acid diethylamide, methaqualone, methylenedioxymethamphetamine (MDMA), and oxycodone. Drug-screening immunoassays are available in a number of formats, which may differ in performance. Almost all of them are designed to be used with urine specimens because these can be obtained noninvasively and generally have higher concentrations than serum, enhancing the sensitivity of the test.

TABLE 6–3. Performance Characteristics of Common Drug Abuse Screening Immunoassays^a

Drug/Class	Detection Limits ^a	Confirmation Limits ^a	Detection Interval ^b	Comments
Amphetamines	1000 ng/mL	500 ng/mL amphetamine or MDMA	1–2 days (2–4 days)	Decongestants, ephedrine, L-methamphetamine, selegiline, and bupropion metabolites may give false-positive test results. MDA and MDMA are variably detected. Confirmation of methamphetamine requires detection of >500 ng/mL with >200 ng/mL of metabolite, amphetamine.
Barbiturates	200 ng/mL Secobarbital		2–4 days	Phenobarbital may be detected for up to 4 weeks.
Benzodiazepines	100–300 ng/mL		1–30 days	Benzodiazepines vary in reactivity and potency. Hydrolysis of glucuronides increases sensitivity. False-positive test results may be seen with oxaprozin.
Cannabinoids	50 ng/mL; 20 ng/mL; 25 ng/mL; 100 ng/mL THCA	15 ng/mL THCA	1–3 days (>1 month)	Screening assays detect inactive and active cannabinoids; confirmatory assay detects inactive metabolite THCA. Duration of positivity is highly dependent on screening assay detection limits.
Cocaine	300 ng/mL BE	150 ng/mL BE	2 days (1 wk)	Screening and confirmatory assays detect inactive metabolite BE. False-positive test results due to cross-reactive compounds are unlikely.
Opiates	2000 ng/mL; 300 ng/mL	2000 ng/mL; morphine or codeine	1–2 days; 2–4 days (<1 week)	>10 ng/mL of heroin metabolite 6-monacetyl morphine is also confirmatory. Semisynthetic opioids derived from morphine show variable cross-reactivity. Fully synthetic opioids (eg, fentanyl, meperidine, methadone, propoxyphene, tramadol) have minimal cross-reactivity. Quinolones may cross-react.
Methadone	300 ng/mL		1–4 days	Doxylamine may cross-react.
Phencyclidine	25 ng/mL	25 ng/mL	4–7 days (>1 month)	Dextromethorphan, diphenhydramine, ketamine, and venlafaxine may cross-react.
Propoxyphene	300 ng/mL		3–10 days	Duration of positivity depends on cross-reactivity of metabolite norpropoxyphene.

^aPerformance characteristics vary with manufacturer and may change over time. For the most accurate information, consult the package insert of the current lot or contact the manufacturer. ^bSubstance Abuse and Mental Health Services Administration recommendations¹ are shown as the first value for amphetamines, cannabinoids, cocaine, opiates, and phencyclidine immunoassays and as only values for confirmatory assays. Other commercial immunoassay cutoffs are also listed. Other gas spectrometry cutoffs are set by the laboratory. ^cValues are after typical use; values in parentheses are after heavy or prolonged use.

BE = benzoylecgonine; MDA = methylmethoxyamphetamine; MDMA = methylenedioxyamphetamine; THCA = tetrahydrocannabinolic acid.

The drug-screening tests for cannabinoids and cocaine are directed toward drug metabolites rather than the parent compound. The parent drugs, cocaine and THC, are both short lived and persist for no more than a few hours after use. The metabolites remain present substantially longer. Detection of the metabolites increases the ability to detect any recent drug use. However, this limits the utility of the assays for determining whether a patient is currently under the influence of the drug. Because the metabolites are rapidly formed, a negative test result generally excludes toxicity, but a positive test result indicates only use in the recent past, not current toxicity.

To increase sensitivity for detection of less recent drug use, substrates other than urine can be used for drug screening, including hair and meconium. The latter is used to document intrauterine drug exposure ([Chap. 31](#)). SAMHSA is planning to develop regulations governing the use of hair, saliva, and sweat specimens for federal workplace testing after their performance characteristics have been adequately studied. This can be expected to increase the availability of clinical testing using these substrates. However, testing performed on hair and sweat is unlikely to offer advantages over testing of serum and urine for the management of toxicologic emergencies.

The stigma attached to a positive test result for an abused drug requires that special care be exercised in performing and reporting the test results. To protect citizens' rights, many states have legislated specific requirements for workplace drug screening. In some states, the requirements apply only to screening in the workplace, exempting testing for medical purposes. Laws in other states might apply to all drug screening. Although they are not always legally required, some workplace drug-screening practices have been widely applied to all drug screening.

The use of specific cutoff concentrations is nearly universal. Test results are considered positive only when the concentration of drugs in the specimen exceeds a predetermined threshold. This threshold should be set sufficiently high that false-positive results as a consequence of analytic variability or cross-reactivity are extremely infrequent. They should also be low enough to give consistent positive results in persons who are regularly using drugs. Cutoff concentrations used

vary with the drug or drug class under investigation. In some drug-screening immunoassays, the laboratory has the option of selecting from several cutoff values.

The use of cutoff values sometimes creates confusion when a patient who is known to have recently used a drug has a negative result reported on a drug screen. In such instances, the drug is usually present but at a concentration below the cutoff value. A quantitative confirmatory test (see below) is usually able to demonstrate the presence of the drug or its metabolites under such circumstances. Another potential problem occurs when a patient's drug-screening test result is positive after previously having become negative. This is usually interpreted as indicating renewed drug use, but it may actually be an artifact. Urine drug concentrations are directly proportional to the serum drug concentrations but inversely proportional to the rate of urine production. The rate of the urine flow may vary up to 100-fold, with a resulting possible 100-fold change in the urine drug concentration. This effect is often exploited by individuals who drink large quantities of water before taking a urine drug test to increase urine flow and decrease urine drug concentrations. In contrast, a decrease in the rate of urine production may result in a positive test result after a negative one despite no new drug exposure. A similar effect may be produced by changes in urine pH. Drugs containing a basic nitrogen may demonstrate ionic trapping, with increasing concentrations as urine pH decreases. Similarly, excretion of an anionic drug (eg, phenobarbital) may increase with increasing urine pH. Another widely used practice is the confirmation of positive screening results using an analytical methodology different from that used in the screen, such as an immunoassay screen followed by mass spectrometry based confirmation. The possibility of simultaneous false-positive results by two distinct methods is quite low. Clinical laboratories may differ in their policies with regard to confirmatory testing. Some may confirm all positive results from screening immunoassays, but others may not provide any confirmatory testing unless it is explicitly requested.

The most common confirmatory method is gas chromatography/mass spectrometry (GC/MS). The high specificity afforded by the combination of the retention time and the mass spectrum makes false-positive results extremely unlikely. GC/MS also has greater sensitivity than the screening immunoassays, minimizing failed confirmations because of a drug concentration below the sensitivity of the confirmatory assay. Some states require GC/MS confirmation for workplace drug screening, and it may be legally required for all drug screening.

Immunoassay results can generally be obtained within one hour. Confirmatory testing usually requires at least several hours. This can create a problem when confirmation of initial immunoassay results is considered mandatory. Most laboratories provide a verbal report of a presumptive positive result to facilitate medical management but may not enter the result into a permanent record, such as the laboratory computer, until after confirmation has been completed.

Confirmatory testing is less critical in an emergency department setting because a positive finding infrequently has consequences that extend beyond the medical management of the patient. An exception may occur when results of testing performed on motor vehicle crash victims can be subsequently subpoenaed as evidence in legal proceedings. Confirmatory testing also becomes more important in drug abuse testing associated with chronic pain management programs, in which unexpected findings (whether positive or negative) may result in termination of care.

One workplace drug-screening practice that is not widely followed in medical toxicology is maintenance of a chain of custody. Employers generally insist on chain of custody for workplace testing because actions taken in response to a positive result may be contested in court. A chain of custody provides results that are readily defended in court. Laboratories providing testing for medical purposes rarely keep a chain of custody because it is quite expensive and does not benefit the patient. Additionally, the medical personnel responsible for obtaining the specimens are rarely trained in collection requirements for a chain of custody.

Another practice common in workplace testing but rare in medical laboratories is testing for specimen validity. It is common for individuals to try to "beat" a workplace drug test through a variety of means, including diluting the specimen (either physiologically by water ingestion or by direct addition of water to the specimen), substituting "clean" urine obtained from another individual, or adding various substances that will either destroy drugs in the specimen or inactivate the enzymes or antibodies used in the screening immunoassays. Such substances include acids, bases, oxidizing agents (bleach, nitrite, peroxide, peroxidase, iodine, chromate), glutaraldehyde, pyridine, niacin, detergents, and soap. SAMHSA requires validity testing for all specimens in federal workplace testing, including measurement of urinary pH, specific gravity, and creatinine concentration, as well as tests for the presence of adulterants.⁸ Dipsticks are available that detect the most common adulterants. However, manipulation or adulteration is rarely a problem in specimens obtained for emergency medical management, and clinical laboratories may not provide validity testing.

A rapidly expanding epidemic of misuse of opioid analgesics and accompanying deaths due to unintentional overdoses has led to the issuance of extensive recommendations, and often regulations, for managing chronic opioid therapy for noncancer pain. The use of periodic urine drug tests to monitor compliance with prescribed medications, as well as to detect use of illicit or unprescribed drugs, is consistently a feature of such recommendations, although there is currently very little evidence that this practice reduces misuse or diversion of prescribed drugs or improves outcomes for patients.⁶ There is evidence that the results of urine drug monitoring are inconsistent with the agreed-upon pain management plan in a very substantial fraction of patients so tested.⁶

The objectives of urine drug testing in chronic pain patients are more complex than either testing during possible toxicologic emergencies or workplace drug testing in that negative results could signal misuse or diversion of a prescribed

opioid, but positive results may indicate illicit drug use. The opioids screening immunoassay is not capable of this task and must be assisted by follow-up testing with a mass spectrometry–based assay capable of distinguishing and quantitating prescription opiates and opioids, as well as key metabolites. This may be done on specimens with a positive screening result to ensure that it is positive for the right reasons and for an unexpected negative result to address the possibility that the expected opioid or its metabolites are actually present but at concentrations too low to give a signal exceeding the cutoff value.

Because of the possible consequences of a positive result in workplace drug testing, all positive results are interpreted by a Medical Review Officer with special training in the pharmacology and metabolism of the tested drugs, as well as the performance characteristics of both the screening and confirmatory tests. No corresponding review is mandated for chronic pain testing, and the interpretation of the results may be left to the patient’s physician, who may not be well prepared for this task.

PERFORMANCE CHARACTERISTICS OF COMMON DRUG-SCREENING ASSAYS

Medical toxicologists, toxicology laboratory directors, and practicing physicians may frequently get questions about the significance of drug-screening assays, particularly about the causes of false-positive results. Often these questions come from an individual who recently had a positive test result. [Table 6–3](#) summarizes drug-screening test performance characteristics, which are discussed in more detail below.

There are problems with all summaries of performance characteristics of urine drug tests. There are multiple manufacturers of urine drug immunoassays. Each uses proprietary antibodies in a proprietary design and thus has unique performance characteristics, including reactivity with target drugs and cross-reactivity with interfering substances. Reviews and summaries often list performance characteristics, especially sources of false-positive results, without identifying the specific manufacturer of the assay. This can lead readers to assume that the interference applies to all immunoassays for the drug in question. Recent summaries that cite interferences described in earlier misleading summaries may further obscure the lack of generality for a reported source of false-positive results. Reformulation of assays can remedy problems that previously existed, but this does not stop older reports of false-positive results that are no longer valid from being recited in current articles. The interference of ibuprofen in a widely used assay for cannabinoids was corrected more than 20 years ago but continues to be cited in contemporary literature.²⁴ Adding further confusion, tabular summaries of interferences may use negative to mean either that the substance does not interfere or that the substance falsely lowers results. The best source of current information is the laboratory that is doing the testing or the manufacturer of a point-of-care device.

Immunoassays for opiates are directed toward morphine but have good cross-reactivity with many (but not all) structurally similar natural and semisynthetic opioids. The extent of cross-reactivity may vary among manufacturers. For example, oxycodone exhibits approximately 30% cross-reactivity relative to morphine in a fluorescence polarization immunoassay but less than 5% cross-reactivity in a number of other screening assays.^{16,27} A failure to appreciate the poor detection of oxycodone can create problems when opiate-screening immunoassays are used to confirm that patients receiving prescription oxycodone for chronic pain are indeed taking it rather than diverting it for illicit sale. If a low cross-reactivity assay is used, a patient taking oxycodone as prescribed might have a negative result, but another patient who is selling the oxycodone and using the proceeds to buy heroin would have a positive result. To address this problem, assays specific for oxycodone have been introduced. These assays are sensitive to therapeutic amounts of oxycodone but relatively insensitive to other opiates.

Synthetic opioids, such as dextromethorphan, fentanyl, meperidine, methadone, propoxyphene, and tramadol, show little or no cross-reactivity in opiate immunoassays. Urine immunoassays specific for meperidine, methadone, and propoxyphene are available. Given the increasing importance of buprenorphine as maintenance therapy for opioid dependency, it is worth noting that the combination of high potency and low cross-reactivity means that buprenorphine will generally not be detected by opiate immunoassays. Immunoassays for specific detection of buprenorphine have therefore been developed.

A positive immunoassay result may reflect multiple contributions from various opiates and opiate metabolites. Concentrations of morphine glucuronide in the urine may be up to 10-fold higher than the concentrations of unchanged morphine and can contribute substantially to positive results. A positive opiate result after the use of heroin (diacetylmorphine) is primarily a result of the morphine and morphine glucuronide that result from heroin metabolism. Distinguishing heroin from other opioids requires detection of 6-monoacetylmorphine, the heroin-specific metabolite. Small amounts of the metabolite may be detected by GC/MS for up to 24 hours after use. A half-life of 5 minutes means that unchanged heroin can only be found in the urine if sampling is done immediately after use.

The duration of positivity of an opiate immunoassay after last use depends on the identity and amount of the opiate used, the specific immunoassay, the cutoff value, and the pharmacokinetics of the individual. Currently, SAMHSA recommends a cutoff equivalent to 2000 ng/mL of morphine for workplace screening because poppy seeds can rarely produce transient positive results with the previously recommended cutoff of 300 ng/mL. However, most toxicology laboratories continue to

use a 300 ng/mL cutoff.

Drug-screening assays for “cocaine” are actually assays for the cocaine metabolite benzoylecgonine, which is eliminated more slowly than cocaine. This extends the duration of positivity after last use from a few hours to 2 days and sometimes to one week or longer after prolonged heavy use. Because the assay is directed toward a metabolite, positive results do not equate with toxicity but merely indicate recent exposure. The assay is highly specific for benzoylecgonine, and false-positive results due to an interfering substance are extremely uncommon (Chap. 78). Point-of-care devices may yield false-positive results because of device failure or operator error. False-positive results may also occur with misidentified specimens or (rarely) intentional specimen adulteration.

Immunoassays for cannabinoids are also directed toward a metabolite, in this case tetrahydrocannabinolic acid. These immunoassays exhibit cross-reactivity with other cannabinoids but little else. Because cannabinoids are structurally unique and occur only in plants of the genus *Cannabis*, false-positive results are uncommon (Chap. 77). It is unusual, although possible, to become exposed to sufficient “secondhand” or sidestream marijuana smoke to develop a positive urine test result.⁵ Legal hemp products include fiber, oil, and seedcake derived from *Cannabis* varieties with low concentrations of cannabinoids. Hemp food products contain insufficient amounts of THC to produce psychoactive effects and usually will not increase urinary cannabinoid concentrations above a 50 ng/mL screening threshold.^{12,25}

Interpretation of a positive result for cannabinoids can be problematic. Urine may be positive for up to 3 days after occasional recreational use. However, with heavy or prolonged use, there may be significant accumulation of cannabinoids in adipose tissue. These stored cannabinoids are slowly released into the bloodstream and can produce positive findings for one month or more. Consequently, little can be concluded from a positive finding in terms of current toxicity. Because positive results in the absence of toxicity are very common and because THC is rarely responsible for serious acute toxicity, NACB guidelines recommend against its routine inclusion in drug screening for patients with acute symptoms.³² Synthetic cannabinoids (found in “spice”) are generally not detected by cannabinoids assays, presumably because of a combination of very low concentrations in urine and limited cross-reactivity.

Amphetamine-screening tests have the greatest problems with false-positive results. A number of structurally related compounds may have significant cross-reactivity, including bupropion metabolites³ and nonprescription decongestants such as pseudoephedrine, as well as L-ephedrine, which is found in a variety of herbal preparations. Some nonprescription nasal inhalers contain L-methamphetamine, the less potent levorotary isomer of D-methamphetamine. It is particularly problematic because it not only cross-reacts in immunoassays but also cannot be distinguished from the D-isomer by mass spectrometry.¹¹ This cross-reactivity is beneficial from the point of view of the medical toxicologist because all of these compounds may produce serious stimulant toxicity. But it is problematic in drug abuse screening because of the widespread legitimate use of cold medications. Assays with greater selectivity for amphetamine or methamphetamine have been developed. Although these assays produce fewer false-positive results caused by decongestant cross-reactivity, they are also less sensitive for the detection of other abused amphetaminelike compounds, including methylenedioxymphetamine (MDA), MDMA, and phentermine. Cross-reactivity patterns vary from assay to assay.¹⁶ The manufacturer’s literature should be consulted for specific details. A number of designer phenethylamine derivatives (such as those found in “bath salts”) might be expected to cross-react in amphetamine assays because of structural similarity. However, they are typically much more potent than amphetamine or methamphetamine and do not achieve high enough concentrations to give a signal exceeding the cutoff.

Testing for benzodiazepines is complicated by the wide array of benzodiazepines that differ substantially in their potency, cross-reactivity, and half-lives. There are also substantial differences in the detection patterns of the various immunoassays.^{12,16} This heterogeneity complicates the interpretation of benzodiazepine-screening assays. Screening results may be positive in persons using low therapeutic doses of diazepam but negative after an overdose of a highly potent benzodiazepine such as clonazepam. To improve the scope of detection, some assays use antibodies to oxazepam, which is a metabolite of a number of different benzodiazepines. These assays may have poor sensitivity to benzodiazepines that are not metabolized to oxazepam. False-negative results may occur for benzodiazepines that are excreted in the urine almost entirely as glucuronides that have poor cross-reactivity with antibodies directed toward an unmodified benzodiazepine. This is one reason for the poor detectability of lorazepam in some screening assays. The latter situation has led to the recommendation that specimens be treated with β -glucuronidase before analysis.¹⁹ Some assays now include β -glucuronidase in the reagent mixture or use antibodies directed toward glucuronidated metabolites. The frequency of false-negative results and the fact that benzodiazepines are relatively benign in overdose have led the NACB guidelines to withhold recommendation for routine screening of urine for benzodiazepines until these problems with the immunoassays are addressed.³²

Barbiturates are comparable to benzodiazepines in their heterogeneity of potency, cross-reactivity, and half-lives, although the differences are less substantial. Specific assays for serum phenobarbital can often help to clarify the significance of a positive barbiturate screen.

Some PCP screening assays may give positive results with dextromethorphan, ketamine, or diphenhydramine but only when these are used in amounts above usual therapeutic quantities. A positive result may serve as a clue to a possible

overdose with any of these substances. Furthermore, much of the illicit PCP actually consists of a mixture of various congeners and byproducts of synthesis. The cross-reactivity of these xenobiotics with the assay varies significantly and may result in false-negative assay results in patients who use PCP.

REGULATORY ISSUES AFFECTING TOXICOLOGY TESTING

Since 1992, medical laboratory testing has been governed by federal regulations (42 CFR part 405 et seq) issued under the authority of the Clinical Laboratory Improvement Amendments of 1988 (often referred to as CLIA-88 or simply CLIA). These regulations apply to all laboratory testing of human specimens for medical purposes regardless of site. They include the universal requirement for possession of an appropriate certificate to perform even the simplest of tests. The remaining requirements depend on the complexity of the test. These regulations become important to the clinician whenever testing is done at the bedside, whether using spot tests or commercial point-of-care devices such as dipsticks, glucose meters, or urine drug-screening devices.

The regulations divide testing into three categories: waived, moderate complexity, and high complexity. Waived tests include a number of specifically designated simple tests, including urine dipsticks, urine pregnancy tests, urine drug-screening immunoassay devices, and blood glucose measurements with a handheld monitor. The only legal requirement for performing waived testing are the possession of an appropriate CLIA certificate (certificate of waiver or higher) and performance of the test in accordance with the manufacturer’s instructions.

There are substantial additional requirements for both moderate and highly complex testing, most of which simply represent good laboratory practice. Table 6–4 lists the most significant of these requirements. Most assays performed with commercial kits or devices are classified as belonging to the moderately complex category. All tests not specifically classified as waived or moderately complex are considered highly complex. This includes essentially all noncommercial tests, including spot tests, because the testing materials have not been subject to review and approval by the Food and Drug Administration.

TABLE 6–4. Major Clinical Laboratory Improvement Amendments (CLIA) Requirements for Laboratory Testing

Waived Tests

- Certificate of waiver
- Follow manufacturer’s instructions exactly

Moderate-Complexity Tests

- CLIA certificate
- Record keeping
- Test method verification
- Written procedures
- Qualified laboratory director
- Personnel educational requirements
- Documented training of all testing personnel
- Annual competency testing of all personnel
- Two levels of controls daily
- Participate in proficiency testing every 4 months
- Verify calibration and reportable range at least every 6 months
- Quality assessment program
- Biennial inspection and certification

High-Complexity Tests

- All moderate-complexity requirements plus
- Qualified onsite supervisor or
- Daily review of all results by qualified supervisor

These regulations have had a substantial impact in all areas of laboratory testing. Some of the most significant effects have been on bedside testing, including spot tests and point-of-care devices. Although clinical laboratories had been following most required practices before the implementation of the regulations, this was usually not the case for testing done at other sites. Most institutions have now established point-of-care testing programs to facilitate compliance with the

regulations, as well as with additional requirements of accrediting agencies, such as The Joint Commission. Any toxicologic or other testing done at the point of care should be set up in consultation with the institutional program. Often, all point-of-care testing is done under a CLIA certificate held by the program. There is frequently a point-of-care testing coordinator who may make recommendations or personally assist in efficiently addressing the assorted requirements.

Table 6–4 lists only the most significant requirements of the regulations implementing CLIA. These regulations continue to evolve. Many states also have laws regulating medical testing. Accrediting agencies such as The Joint Commission may have additional requirements. Consultation with the clinical laboratory or with an institutional point-of-care coordinator is recommended before implementing any testing.

Personnel unaccustomed to quality control and assessment practices may find the CLIA requirements initially burdensome. Nonetheless, compliance is important. Following these practices may lead to a threefold reduction in incorrect results,²⁷ thereby greatly improving the quality of care provided to patients. Moreover, noncompliant testing is illegal under federal law and may also be illegal under state law. Any untoward outcome associated with illegal testing creates a major risk management liability for both the institution and the individual. Additionally, billing for any testing that is not CLIA compliant may be considered fraudulent.

Another area in which the CLIA regulations have impacted toxicology testing is in the provision of infrequently requested tests. Meeting regulatory requirements involves a substantial labor investment even when few patient specimens are being tested. Mounting pressures to reduce laboratory costs make it less likely that laboratories will continue to maintain such assays.

Another important regulation, although not part of CLIA regulations, requires that the medical reason for ordering a test be provided with the order. Federal regulations require that the ordering physician provide the diagnosis that establishes the medical necessity for the test, either by name or by diagnostic code (CPT code). Laboratories may not use a “best guess” to assign codes to undocumented test requests.

SUMMARY

- Although broad spectrum toxicology screens can identify most drugs present in overdosed patients, the results of broad spectrum screens infrequently have altered management outcomes.
- When requesting a screening test, an important and often overlooked item of communication is specifying any xenobiotics of particular concern.
- Xenobiotic concentrations may be useful to make decisions regarding the use of antidotes or if interventions to hasten drug elimination, such as hemodialysis are indicated.
- The predictive power of the result of a toxicology screen depends on a number of factors, including the likelihood of poisoning before receiving the test results (the prior probability or the prevalence), the range of xenobiotics effectively detected, and the frequency of false positive test results.

FOR MORE INFORMATION

Additional information about clinical toxicology laboratories, including topics not covered in this chapter, may be found in contemporary textbooks.^{17,26}

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7 MEDICOLEGAL INTERPRETIVE TOXICOLOGY

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One of the potential areas of collaboration for toxicologists is the medicolegal setting. This includes working with forensic toxicologists, medical examiners, law enforcement, lawyers, and regulators. In this arena, interpretive toxicology, whether based on analytical findings or theoretical concepts, is routinely used or required to explain issues in criminal and civil proceedings and as the basis for policy making. Often, the concepts associated with forensic interpretive toxicology are presumed to be associated with deceased individuals. In practice, the preponderance of cases involving toxicologic interpretation involves living people and includes specialty testing such as human performance toxicology. Regardless, interpreting the role, or potential role, of xenobiotics in an adverse outcome is typically not straightforward. For example, the use of generally applied pharmacokinetic equations is usually inappropriate, especially in the postmortem setting, yet such is in widespread practice by individuals unfamiliar with the nuances of case-related issues.²⁷ Rarely is any given case accurately interpreted solely based on toxicologic assessment. As such, forensic interpretive toxicology generally involves an integrative approach that draws on an understanding of case history in addition to analytical, toxicologic, pathophysiologic, and specimen-related issues. Individuals called on to interpret the role of xenobiotics in any given case must understand the factors that affect such interpretations and associated limitations. Furthermore, although difficult in many situations, they should attempt to have their opinions firmly supported by science. Other chapters in this text (Chaps. 6 and 34, Special Considerations: SC2 and SC6) cover much of the basic science associated with interpretive issues. This section is meant to focus on specific issues as they relate to medicolegal (forensic) interpretive toxicology.

CASE HISTORY

It has been reported that case history plays a role in interpreting toxicologic findings in about 70% of cases.²⁴ A number of specific aspects of a case history will lead a seasoned toxicologist in a direction that narrows the scientific investigative focus and avoids a shotgun approach to deciphering the role of toxicology in an adverse outcome. Table 7–1 lists some of the more important aspects of the case history that should be considered from the outset to begin the interpretive process. Detailed information about the individual should optimally include anthropomorphic information, vocation, hobbies, medical history, timing of events to the extent possible, and other contextual information.¹⁷ As an example of the importance of this information, consider a case in which an individual suspected of drunk driving worked at a company that manufactured chemicals. One of the chemicals known to be handled by the individual was a substance that coeluted with ethyl alcohol in the gas chromatographic assay used to quantitate the blood alcohol concentration. Without his employment history, the potential for an incorrect interpretation of the data might have occurred.

TABLE 7–1. Important Aspects of Case History Related to Interpretation of Analytical Findings^{17,29}

<i>Aspect</i>	<i>Examples of Information to Be Gathered</i>
Individual history	Age, gender, weight, nationality, habitus, vocation, hobbies, smoking status, drug abuse history
Medical history	Disease processes, known medications, recent treatments or surgeries, resuscitative efforts, history of snoring (important for cases involving opioids)
Recent activity	Last known activity of the individual; description of behaviors; observations of friends, family, acquaintances and coworkers
Timing	When did an event occur? How much time between event and specimen collection? When was the patient last seen?
Cohabitants	Vocations, hobbies, medications
Scene	Description (kempt or unkempt) Search results of cabinets, trash cans, pill vials collected, ambient temperature, odors, plants or fungi, recent Internet searches, unusual books or literature, heating pads or hot water bottles
Position and description of body, if found unresponsive	Clothing, covered or uncovered, body temperature, vomitus
Notes or journals	Indications of intent, mindset

Unfortunately, toxicology is often not initially considered with respect to field investigation of a case. Therefore, important information is often lost, especially in the case of purposeful poisonings. The longer the time between suspicion of a toxicologic aspect to a case and proper investigation, the greater the chance of lost evidence for explaining the situation. The toxicologist can play a key role in mitigating this hindrance. As a significant point of contact with the poisoned or intoxicated individual, the toxicologist has the opportunity to not only ask the individual questions if he or she is conscious but to also ask police, paramedics, and others questions that could assist in not only treatment of the patient, but also address serious questions that often later arise.

Unlike the confidence in the medical diagnosis of poisoning supported by clinical findings or analytical data, it should be recognized that there is rarely surety in the use of toxicologic analysis for medicolegal purposes. Reasonable degree of certainty, the phrase often used as a measure of acceptability in interpretive toxicology, can only be attained through the weaving of multiple pieces of information into a coherent explanation of events.

PREANALYTICAL ISSUES

Ample evidence exists that the major source of error in analytical toxicology is based not on laboratory error, but on preanalytical issues.^{18,39} Preanalytical issues can be defined as those things that can affect an analytical result prior to the specimen(s) arriving at the laboratory. In accordance with ISO (International Organization for Standardization) requirements, mathematical uncertainty should be able to be determined by the analytical testing laboratory.²⁶ It has become an expectation in certain areas of toxicologic testing that such errors be reported for acceptance into legal proceedings.³¹ Although laboratory error can usually be relatively easily quantified, the error associated with issues surrounding samples before arrival at the laboratory is not so easily measured. The myriad of potential preanalytical factors is summarized in Table 7–2.

TABLE 7–2. Preanalytical Factors That Can Affect Interpretation of Findings^{11,61}

<i>Preanalytical Factor</i>	<i>Specific Issue</i>	<i>Potential Effect</i>
Specimen source	Site of collection (eg, collection near site of drug administration)	Falsely elevated results
Specimens	Collection tubes or containers to include preservative or anticoagulants used, storage conditions (temperature, humidity), mislabeling	Inability to detect specific analytes Analyte stability Wrong sample tested Addition of analytes not originally present
Contamination issues	Use of inappropriate collection techniques (eg, ethanol-based swabs, lack of metal-free devices and containers)	Introduction of unintended analytes, potential misassignment of poisoning
Postmortem-specific issues	Specimen collection techniques (eg, anatomical source of blood, nonspecified part of a solid organ, collection of only partial amount of gastric contents)	Falsely elevated or depressed analyte concentrations

Clinical Specimens

With respect to living individuals, where and how specimens are collected from patients, in addition to specimen storage, can adversely affect not only the analytical test but its interpretation as well.⁵¹ For example, although perhaps not protocol, occasionally samples for analysis are collected proximate to the site where they are administered, such as close to an indwelling antecubital fossa catheter. Contamination of such specimens cannot be excluded and can lead to misinterpretation of findings. Although the treatment of patients is the primary concern during medical emergencies, consideration of potential medicolegal issues should be part of the treating professional's assessment, especially in cases involving children, victims of drug-facilitated sexual assault, motor vehicle operation, workplace incidents, suspected poisoning, and other ill-defined situations. Adequate analysis requires that specimen collection be performed appropriately and consideration given to the types of preservatives used in the collection device. Not all collection devices fit the need for all xenobiotics. For example, although fluoride-containing tubes may work well to prevent microorganism-induced ethanol formation, this same preservative may lead to degradation of some organic phosphorus pesticides and make the sample totally useless in cases of suspected fluoride poisoning.^{1,47} In general, it is good practice to collect both preserved and unpreserved blood samples. Serum samples are generally a good choice from living individuals, but this is analyte specific and certainly not preferred for xenobiotics sequestered in red blood cells. Perhaps the most important precaution in this respect is the collection of specimens for legal blood alcohol determination. Not only are tubes containing fluoride (1%–5% w/v) and oxalate (anticoagulant) necessary, but skin cleansing swabs containing ethanol should be avoided.² Specimen storage conditions can significantly adversely affect analyte stability and specimen integrity. Except for specimens such as hair and nail clippings, specimens for toxicologic analysis should not be maintained at room temperature. Minimally, refrigeration is required, but if it is anticipated that a delay between sample collection and testing will occur, then freezing the samples at –20° or –60°C (the choice of temperature being analyte specific) should be considered, making sure to take precautions to prevent tube cracking.¹¹ It is recommended that if a specific xenobiotic or class of xenobiotics is suspected that laboratory personnel should be contacted before specimen collection for guidance on proper collection, preservation, and storage of specimens. Hospitals should have in place a mechanism that ensures retention of specimens beyond the routine time frame for suspect cases. Typically, hospitals maintain specimens from a few days to a few weeks after use compared to up to one year or longer in most forensic cases.^{44,58} In this regard, all available specimens should be maintained. This is especially important in cases in which death is preceded by a relatively long clinical course. Although it cannot be expected that a hospital maintain specimens under a legal chain of custody, maintaining tubes with original identifier labels often suffices for this purpose.¹⁹

Postmortem Specimens

In postmortem situations, the potential for sample contamination is substantial, especially in the face of significant trauma. For example, the spread of gastric or intestinal contents containing xenobiotics of interest can contaminate sources of blood collection and visceral organs.¹⁷ Additionally, other postmortem phenomena can mitigate the potential value of laboratory-based testing (Table 7–3) for interpretation purposes (see the Postmortem Redistribution section later). Specimen

collection should be done by an experienced pathologist who understands the intricacies of site-specific sample collection. Postmortem blood can be obtained from two broadly categorized sources, central (eg, heart) and peripheral sites (eg, femoral and subclavian veins). Not all peripheral sites have the same interpretive value.⁵³ “Blind stick” samples should not be considered appropriate surrogates for proper dissection and visualization of the specimen source.⁴⁰ For example, heart blood should be collected from the right atrium after opening of the pericardial sack, removal of the pericardium, and drying of the heart.^{11,62} Although there is no ideal postmortem specimen, femoral vein blood tends to better reflect circulating concentrations of xenobiotics closer to the time of death, but this is not always the case. It is realized today that even femoral blood may be subject to the same issues as other blood sources (eg, postmortem redistribution {PMR}). Whenever possible, both cardiac and femoral blood should be collected. Because of postmortem changes, heart blood tends to contain higher concentrations of xenobiotics than peripheral blood sites, thus making it a valuable screening specimen but limiting its actual interpretive value. To properly collect femoral vein blood, a dissection and visualization of the femoral vein followed by ligation or clamping of the vessel above the point of collection is recommended to avoid contamination by iliac blood, the latter seemingly representing a cross between peripheral and central blood.¹¹ Visceral organ specimens can be of value in the interpretation of the meaning of blood concentrations in certain situations.^{5,41} Although a plethora of data exist regarding toxicologic findings in blood, there tends to be less data regarding tissues. Nevertheless, certain organs can be of substantial value when considering specific xenobiotics (Table 7–4). Specimen collection tubes and storage conditions, although similar to those described with clinical specimens, tend to be more important with postmortem specimens because of continuous postmortem changes in blood pH, autolysis, and cell lysis, which can affect analyte stability, recovery, and interpretation.⁶¹

TABLE 7–3. Postmortem Phenomena That Can Affect Interpretation of Toxicologic Laboratory Results

<i>Phenomenon</i>	<i>Potential Effect</i>
Analyte stability	Can lead to increased or decreased concentrations of analytes (eg, ethanol and cyanide can both form and degrade in specimens); will affect interpretation of results by assuming too much or too little analyte present
Degree and type of decomposition	Can lead to analytical difficulties in recovery of xenobiotics; bacterial metabolism of xenobiotics can alter preexisting concentrations
Embalming	Can destroy or form xenobiotics or metabolites (eg, cyanide can be destroyed by embalming chemicals; methylation of desmethyl metabolites can occur; can lead to misinterpretation of results)
Entomologic factors	Insect invasion can lead to decreased or altered concentrations of xenobiotics; insects can also be useful to detect xenobiotics in badly decomposed bodies
Plasma vs. postmortem blood distribution differences	Blood and plasma concentrations of xenobiotics may differ widely, so reliance on kinetic data in living persons may not be comparable to postmortem blood findings; postmortem blood is not the same as whole blood in living individuals
Postmortem redistribution or diffusion	Can lead to elevated or decreased concentrations of xenobiotics; misinterpretation of findings
Toxicogenetics	Can lead to unpredictable effects on metabolism; analysis for metabolic status may not be useful because genotype may not equate to phenotype

TABLE 7–4. Potential Value of Postmortem Traditional and Alternative Specimens

Specimen	Value	Issues with Specimen
Bile	Accumulates xenobiotics, eliminated fecally (eg, opiates); therefore, xenobiotics may remain in bile after cleared from blood	Lack of interpretive data; presence of a xenobiotic may not provide temporal information for exposure
Blood	Largest amount of comparative data; easily obtained	Subject to PMR, diffusion, contamination; blind sticks are suboptimal; xenobiotic concentrations can be a combination of acute and chronic exposure, thus hampering interpretation; back calculation to dose ill advised
Brain	For certain xenobiotics, some correlation to effects	Very difficult specimen to handle analytically because of fat content
Gastric contents	Assessment of overdose; investigative purposes in tracking pill source; potential high concentrations of xenobiotics	Time dependent; lack of homogeneity of specimen; can be difficult analytically because of food and other xenobiotics
Hair	Provides exposure history data	Delay between exposure and appearance in hair (~1 week); may prevent acute exposure assessment; external contamination; contamination from sweat and sebum
Kidney	High concentrations of xenobiotics cleared renally allows for ease of detection	Lack of interpretive data; xenobiotics can accumulate because of specific and nonspecific binding, potentially hampering interpretability
Liver	Contains high concentrations of xenobiotics cleared hepatically; can aid in determination of overdose	Xenobiotics accumulate in liver over time, potentially hampering interpretability; can be affected by both PMR and diffusion; xenobiotics not distributed evenly throughout liver
Urine	Xenobiotics (and metabolites) eliminated renally accumulate in urine; may protect xenobiotics from postmortem degradation	Not always present; not always an indicator of acute exposure; analytical issues (deconjugation); no correlation with effects; no back calculation to dose possible
Vitreous humor	Some protection from compositional changes; ethanol determination; postmortem glucose determination	Delay between appearance of xenobiotic in blood versus vitreous

PMR = postmortem redistribution.

Data from Davis GL. Recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *J Med Toxicol* 2012; Oct 17:317-32-76.³

Hair collection should be considered in practically all cases of toxicologic concern, especially in those involving children because this specimen can circumvent arguments of incidental exposure and other issues.⁴⁵ This specimen, after being collected, requires no special storage conditions and can reflect exposure history for the length of hair growth (~1 cm/mo). Controversy regarding external contamination of hair leading to positive findings, although of some concern, does not outweigh the value of this specimen.^{25,33}

Last, iatrogenic toxicologic injury or death, whether unintentional or purposeful, are often not considered or poorly investigated. The involvement of hospital-based risk management often occurs late and valuable evidence that can either incriminate or exculpate individuals gets destroyed before collection and preservation. Protocols in suspicious cases should exist for the area where the individual was located to be considered a “crime scene.” That is, potential useful evidence, including devices and medications, should be gathered and stored.⁵⁵

SPECIAL LABORATORY CONSIDERATIONS

Testing for xenobiotics of interest is varied and inconsistent among laboratories. Hospital-based laboratories tend to be limited in scope compared with toxicology reference laboratories. Even in this latter group, wide variances exist with respect to capability and scope. No interpretation of toxicologic findings should take place without a complete understanding of the testing performed and its limitations in addition to a review of the analytical data by a competent toxicologist. With the development of robust, widely available analytical tools, insufficient testing with respect to medicolegal interpretive matters should no longer occur.

Ideally, all toxicologic analyses are performed under chain of custody, and all findings are confirmed by a separate and distinct analytical test, with at least one, such as mass spectrometry, that provides specific molecular identification.⁴⁶ This process reduces uncertainty in the utility of a finding for interpretive purposes. For example, the use of gas chromatography to identify ethylene glycol in a hospital-based laboratory led to the wrongful conviction and jailing of a mother for poisoning her infant son. The gas chromatographic peak was actually propionic acid. Remarkably, the reporting of ethylene glycol was duplicated by another laboratory. Postconviction analysis determined the misidentification of the peak. In this case, the propionic acid resulted from the inborn error of metabolism disease, methylmalonic acidemia. It has also been determined that 2,3-butanediol also coelutes with ethylene glycol in some gas chromatographic systems.^{15,60}

It is uncommon for hospital-based drug testing to be analytically confirmed. However, a positive screen using an immunoassay is rarely sufficient for medicolegal purposes given the general cross-reactivity of these tests. Most hospital laboratory reports include a disclaimer to this effect. Also, most of this testing is performed using urine, so such screening

tests are neither quantitative nor interpretable with respect to effects on a given individual.

Today, advanced toxicology laboratories use a combination of tools to help identify xenobiotics of toxicological concern. Many of these tests are performed rapidly and, in some sense, inexpensively compared with the offered breadth of testing. Instruments such as liquid chromatography time of flight (LC-TOF) have revolutionized broad-based toxicology testing. This technique allows for the rapid screening of a patient sample in minutes covering hundreds of chemically dissimilar compounds with identification using exact mass.²³ Liquid chromatography/tandem mass spectrometry (LC-MS/MS), although somewhat less amenable to broad-based screening, has a similar utility with an easier approach, in general, to quantitative analysis.⁴² Both devices are appearing in hospital-based laboratories and should help the toxicologist significantly in evaluating potentially poisoned patients.²² Other instruments, such as inductively coupled plasma mass spectrometry and inductively coupled plasma optical emission spectroscopy used for the analysis of the majority of metals, are still generally found in specialty laboratories and most likely will not be cost effective in the hospital laboratory ([Chap. 6](#)). In all cases, however, the toxicologist should understand the limitations of these devices that can lead to false-positive and false-negative findings.

CORRELATING FINDINGS OR THEORY TO CASE-RELATED ISSUES

Ultimately, the toxicologist's role in forensic interpretive toxicology is to correlate analytical findings or theory to an adverse outcome. Although explanations abound, both in concept and practice, plausible explanations are often few. It is rare that findings can simply be taken at face value. For example, it is common for identical findings in two different cases to have two completely distinct interpretations, which should not be surprising or disconcerting. Toxicology has been described as both science and art, with the interpretive aspect based in science, knowledge, and experience.²⁰ Many of the following factors need to be considered in rendering rational opinions.

Analytical Surprises

It is not uncommon for individuals to render toxicologic opinions without careful review of the analytical data that help form the basis of the opinions. Simple acceptance of reported results can be a fundamental flaw in medicolegal interpretations. It is helpful to review all available information that led to a reported result before interpretation. [Table 7–5](#) lists some of the important facets of analytical data review that can lead to incorrectly reported results. Although there is no expectation that the toxicologist be an expert in analytical chemistry, familiarity with the key elements that can lead to false-positive, false-negative, or poorly quantified findings should become part of the review process. Errors ranging from the wrong patient number on the analytical data to poor control and calibration of an analytical run to poorly integrated chromatographic peaks are all examples of errors that can invalidate any given finding.

TABLE 7–5. Important Aspects of Laboratory Data Leading to Reporting of Inaccurate Results

<i>Issue</i>	<i>Examples</i>	<i>Effects</i>
Inappropriate method validation	Unable to define limit of detection, limit of quantitation, analytical bias and precision, specificity, analyte and analytical stability, potential interferences	No confidence in the ability to produce a defensible result
No or poor analytical method	No written method to follow	Irreproducibility of results; lack of consistent direction to analysts
Lack of proper calibration or control	No controls included in analytical run, reporting results outside of the analytical measurement range, calibrators and controls prepared from the same stock solution	Unreliable results
Analytical characteristics	Poor chromatography, lack of proper internal standard, poor mass spectral characteristics, improper integration of peaks, improper baseline acceptance	Unreliable results
Administrative errors	Wrong demographics, case numbers, dates, etc. assigned to the data; improper chain of custody	No confidence that correct patient specimens were tested
Failure to follow standard operating procedures	Specified steps in either administrative or technical standard operating procedures were not followed	Lack of confidence in correct patient specimen tested or in analytical results

Postmortem Redistribution

There are many factors related to postmortem changes that complicate the interpretation of well-performed toxicologic test results.^{16,17,38,61} Many of these factors are discussed in [Chap. 34](#). However, the importance of PMR, a long-established principle in forensic toxicology, cannot be ignored or underestimated. Although recognized in the early 1980s, Prouty and Anderson authored the first codified report of this phenomenon in 1990.⁵⁴ Succinctly, PMR is the term given to changes in site-specific xenobiotic concentrations after death.⁵⁰ These xenobiotic movements postmortem generally result in elevated concentrations in common collection sites such as heart blood. The elevation for some substances can be dramatic, giving the appearance of overdose when no such conclusion is supported by other evidence, including analysis of sites of blood collection where PMR may occur to a lesser degree, such as femoral blood. Although instructed to do otherwise, many pathologists still collect heart blood as a sole source of postmortem blood. In attempting to assist in such situations, investigators often publish ratios of heart blood concentrations to femoral blood concentrations over a series of cases from a given laboratory. The common observation is a widespread range of values often encompassing three- to fivefold or greater differences in magnitude.⁸ The use of such ratios to convert a heart blood concentration to a femoral blood concentration, and by further analogy to a premortem circulating blood concentration, should not be performed. The greatest use of such ratios is to give an idea of the likelihood of PMR for any given xenobiotic based on the mean and range of ratios.⁴³ Because it cannot be predicted if PMR occurred in any given case and if so to what degree and over what time period, such calculations have no basis for antemortem blood concentration determination. Another confounder to the use of ratios is the possibility that site-specific differences are not due to PMR but merely a reflection of incomplete distribution before death.¹⁷ It is unclear how many of the reported ratios of heart blood to femoral blood actually reflect this process as opposed to true PMR. The proposed mechanisms and influencing factors resulting in PMR are varied and are listed in [Table 7–6](#). It is most likely a combination of factors that lead to PMR in any given case. Interestingly, as noted earlier, PMR is also reported to take place in femoral blood; thus, it should not be taken at face value that any postmortem blood concentration accurately reflects that circulating at and around the time of death.

TABLE 7–6. Factors Affecting Postmortem Redistribution^{16,50}

<i>Factor</i>	<i>Issue or Potential Effect</i>
Volume of distribution	Xenobiotics with high volumes of distribution often correlate with a greater degree of PMR; can lead to falsely elevated concentrations in postmortem fluids and tissues
pH of blood	pH of blood changes postmortem becoming more acidic; can alter ionization of xenobiotics and promote or hinder PMR
Drug reservoirs	Organs of high blood content or flow, tissues that specifically or nonspecifically retain analytes (eg, liver, kidney), and holding vessels (eg, GI organs) can facilitate movement to blood vessels and neighboring organs
Resuscitative efforts	Some demonstration that xenobiotics move in vivo as a result of resuscitative efforts
Breakdown of barriers	Cellular structural changes may cause leaking of xenobiotics from one site to another, including from intracellular sequestration sites
Release of xenobiotics from proteins	Will alter the free to bound ratio, potentially leading to an unreliable reliance on free xenobiotic concentrations
Postmortem metabolism	Can lead to decreased or increased concentrations of xenobiotics postmortem

GI = gastrointestinal; PMR = postmortem redistribution.

At one time it was believed that PMR was associated with basic xenobiotics with a large volume of distribution. Seemingly, however, most xenobiotics, including acidic and neutral xenobiotics, undergoes PMR. Furthermore, PMR occurs for xenobiotics with wide-ranging volumes of distribution. Still other xenobiotics that would be predicted to undergo PMR have experimental evidence to the contrary.⁵⁰ Thus, a priori predictions of PMR for any given xenobiotic without experimental evidence should explicitly state the caveats associated with such a conclusion. It must be stated, however, that PMR does not preclude the interpretation of findings for cause of death determination because the findings represent only one piece of data in a potential myriad of other relevant information.

Another similarly related phenomenon is postmortem diffusion of xenobiotics. In this situation, diffusion of xenobiotics from an area of high concentration to that of a lower concentration occurs. This is most noted when the gastric contents contain a substantial amount of a xenobiotic that migrates across the wall of the stomach into neighboring tissues and blood sources, such as abdominal aorta and iliac vessels. Additionally, perimortem aspiration of gastric contents can lead to significant esophageal, tracheal, and lung concentrations of a xenobiotic, further facilitating diffusion processes.^{10,52}

Alternative Matrices

Although most discussions regarding interpretive toxicology tend to focus on blood concentrations of xenobiotics, clearly in both the living and the dead, alternative matrices have become extremely valuable. It should be recognized that there is no perfect specimen to assess exposure or provide analytical findings in support of impairment. In the living, alternative specimens including hair, oral fluid (OF), and breath are useful. Hair gives a longer window of detection than most other easily obtained specimens.⁶² Analytical precautions, such as rinsing procedures, can be used to minimize some concerns with hair testing.⁵⁶ The utility of hair should not be underestimated, and despite some of its limitations, it can represent the best suited specimen in some cases, such as drug-facilitated sexual assault, especially when more than 24 to 48 hours passed before specimen collection from the time of event, thus often limiting the value of urine or blood testing.³⁵ In such cases, waiting 1 to 3 months before collecting hair will capture the potential exposure period in growing hair. It is especially useful in children to demonstrate acute versus chronic exposure to xenobiotics.⁴⁵ Collection of hair should be from the posterior vertex of the head, which can be easily approximated by drawing an imaginary line over the head connecting the tops of both ears and a line from the bridge of the nose to the nape of the neck.^{11,56} Where the two lines meet in the back of the head provides hair that grows most consistently on the head.³⁴ About a pencil thickness worth of hair should be clipped as closely to scalp as possible.¹² The root ends should be identified either by tying with string or wrapping in foil.¹¹ Virtually any other source of hair can be tested as well, such as pubic and axillary hair, although practical reasons and shorter growth rates tend to make such samples less suitable for testing.

Oral fluid (OF) is gaining ground as a viable specimen type to assess exposure and impairment because obtaining it is noninvasive, and it can be collected at the site of an event, thus eliminating time delays.⁴ Such delays can result in

clearance of a xenobiotic from other specimen types before collection. OF is composed of secretions from the parotid, submaxillary, sublingual, and other smaller glands. Numerous specimen collection devices exist today that circumvent the need to expectorate, which is not a desirable means of specimen collection.⁴⁸ For the most part, non-protein-bound parent compounds appear in OF, although there are exceptions (eg, benzoylecgonine).¹³ Factors that affect how much of a xenobiotic gets into OF include pH of the blood and OF, the pKa of the xenobiotic, and the degree of protein binding. In general, basic xenobiotics get into OF easier than acidic xenobiotics.⁶⁵ OF has been used for therapeutic drug monitoring purposes (eg, theophylline and digoxin).⁶ Although some correlations between blood concentrations and a number of xenobiotics have been made, it must be remembered that OF is susceptible to contamination from residual drug in the oral cavity, smoked drugs, and passive exposure.^{4,13} Despite its promise, there is variability in OF concentrations of xenobiotics not only within the same individual but also among individuals based on influencing factors that facilitate or inhibit secretion of a xenobiotic into OF.⁴ Last, based on the relatively small specimen volumes after OF collection, specialized testing, including tandem mass spectrometry, is often needed to detect the concentrations of xenobiotics present.

Breath testing for alcohol is a mature subject matter, yet when it comes to impairment, there is a current trend for states to move back to blood alcohol determinations. Legal arguments have been the force behind some of this movement.⁴⁹ Breath testing for other xenobiotics is still in its fledgling state. Despite this, the future holds promise for the detection of other xenobiotics in breath with the possibility of roadside breath drug-testing devices.³ The major advantage of this specimen is its lack of invasive collection technique and rapid screening capability.

Alternative matrices from decedents are varied and have included virtually all fluids and tissues (Table 7-4). Practically speaking, however, other than providing qualitative information, for most matrices, there is little data to support utility of a measured concentration to either allow for independent interpretation or correlation to blood concentrations. Although numerous studies exist that suggest such correlations, rarely is there consistency between studies. Even so, situational use of alternative matrices is sometimes warranted (eg, the use of fat or brain to detect volatiles). A specific exception is vitreous humor (vitreous), a specimen that is often extremely valuable postmortem. Vitreous electrolyte measurements provide data that cannot be gleaned from virtually any other specimen type (Table 7-7).⁷ For most xenobiotics, vitreous concentrations lag behind blood concentrations by about 1 or 2 hours. Thereafter, some correlations have been made between vitreous concentrations and those in blood, with the greatest example being ethanol, where there is an approximately 1:1 correlation when equilibrium is reached. Vitreous represents a relatively pristine specimen during decomposition, embalming, exsanguinations, severe peritoneal trauma, and other less ideal situations.²¹

TABLE 7-7. Valuable Vitreous Chemistries

Analyte	Reported Value	Reported Reference Range (mmol/L)
Chloride	Dehydration, water intoxication	105–135
Potassium	Postmortem interval	<15
Sodium	Dehydration, water intoxication	135–150
Urea nitrogen	Dehydration, renal-related problems (eg, azotemia)	8–20
Glucose	Hyperglycemia, DKA, hyperosmolar coma	<200
Ketones	Fasting or starvation, DKA, isopropanol exposure	None detected

DKA = diabetic ketoacidosis.

Data from Collins K: Postmortem Vitreous Analyses. Medscape Reference (accessed July 16, 2013, at <http://emedicine.medscape.com/article/1966150-overview>).⁷

Toxicokinetics and Toxicodynamics

The basics of toxicokinetics (TK) and toxicodynamics (TD) are covered in Chap. 9. The large and unpredictable degree of interindividual variability places practical limits on the use of TK and TD in postmortem interpretation. These same variations affect the pharmacologic response in living patients. Multiple elements related to TK and TD affect the ability to render interpretive opinions of xenobiotics related to an adverse outcome (Table 7-8). Many of these issues are covered elsewhere; however, the use of pharmaco- and toxicokinetic equations warrants special attention.

TABLE 7-8. Factors Affecting the Utility of Toxicokinetic and Toxicodynamic Principles in Interpretive Toxicology^{14,16,17,27}

<i>Criterion</i>	<i>Potential Effect</i>
Xenobiotic–xenobiotic interactions	Can lead to increased or decreased concentrations of analytes, resulting in serious adverse effects; interactions can take place via increased or decreased metabolism or via competitive interactions at target sites (eg, receptors); can give the appearance of intentional overdose
Idiosyncratic response	There is little or no means of identifying an idiosyncratic response after the fact; can result in serious adverse effects, including fatalities
Pathology or pregnancy	Disease states can alter the toxicokinetic and toxicodynamic profiles for a given xenobiotic and resultant effects; pharmaco- and toxicokinetics change in pregnant women (eg, clearance)
Route of administration	Affects body burdens and speed of action of xenobiotics
Tolerance	Can lead to an overestimation of effect of a given xenobiotic concentration; there is no <i>a priori</i> means of determining tolerance
Toxicogenomics	Can lead to unpredictable effects on metabolism; analysis for metabolic status may not be useful because genotype may not equate to phenotype
Toxicokinetic variables	Prevents utility of classic pharmaco- or toxicokinetic equations; there is no <i>a priori</i> means of knowing the value for the necessary variables unique to an individual used in equations (eg, clearance)
Trauma or shock	Associated issues, including blood shunting and decreased organ perfusion, can alter toxicokinetic factors

Toxicologic emergencies and overdoses often lead to derangement of normal physiological functions. Distortions, especially in liver and kidney function, can significantly alter normal TK parameters.^{59,63} Coupled with pharmacogenetics, drug–drug or drug–xenobiotic interactions, pathophysiology, and other significant factors, the use of routine TK equations can lead to grossly under- or overestimates of a specific measured value. Nevertheless, in a living patient, TK equations can be useful to estimate certain parameters (eg, dose and, in part, form the basis of such useful tools as nomograms). Postmortem, because of PMR and postmortem diffusion alone, the use of TK formulas to predict premortem concentrations or dosing is not generally an acceptable practice. For example, the use of the following formulas will lead to either an absurd dose calculation or an inappropriate estimate of predicted concentration compared with that reported for compounds undergoing significant PMR:^{14,27}

$$\text{Dose} = \text{Reported concentration} \times \text{Volume of distribution} \times \text{Body mass}$$

$$\text{Concentration} = \frac{\text{Dose}}{\text{Volume of distribution} \times \text{Body mass}}$$

Nevertheless, such calculations, although ill advised, are routinely performed and can provide grossly misleading information. “Back extrapolating” from a postmortem concentration to some concentration earlier in time using half-life is fraught with the same perils in that the beginning assumption of an unchanged postmortem blood concentration can rarely be made.¹⁶ Additionally, it is never known how much of any measured blood concentration resulted from a single or multiple dosing. Despite these issues, the toxicologist may be pressured into providing dosing information or predicting a blood concentration during life. The safest avenue in this respect is not to accede to such pressures because the scientific underpinnings are shaky at best.

Assessing Impairment

There exist two broad areas of concern with respect to impairment, that from alcohol and that from other xenobiotics. Impairment caused by alcohol has been long studied, and general conclusions are usually reached with some confidence. The same cannot be stated for impairment caused by drugs. Ultimately, conclusions of drug impairment are based on physical examination by a trained clinician, dosing information, length of time taking a medication, co-administered medications, pathophysiology, observed behaviors, measured concentrations in blood or serum or plasma, and any other

useful information.³² The use of the term “consistent with” is common in assessing impairment in any given individual and might very well be the best opinion that can be offered. Mitigating factors, including tolerance, single versus multiple dosing, reason for the presence of the substance, timing and route of administration, and pathophysiology, all make firm conclusions difficult, especially when blood findings are the first indication of potential impairment (ie, no visible signs of impairment).^{28,57} Great care must be exercised in evaluating or predicting impairment from drugs given the implications of such conclusions. There is currently no scientific support for back extrapolation of drug concentrations based on blood findings. It cannot be stressed enough that urine findings should never be used to assess impairment because the predictive value is limited.⁶⁴ Similar to blood alcohol concentration, many states and countries have developed per se drug laws that presume guilt by the presence of certain drugs or metabolites over some prescribed reportable concentration, even in urine, thus mitigating the need for interpretation in most cases. For example, the presence of carboxy-tetrahydrocannabinol, an inactive metabolite of marijuana, is used to convict drivers of impaired driving; for clarity, this is a legal issue, not a scientific issue.^{30,36} Last, tables and texts that list xenobiotics and determined concentrations in blood and other specimens should only be used as a guide for interpretive purposes because every case is unique.

SUMMARY

- Toxicologists have the opportunity based on both contact with patients and as consultants to be involved with medicolegal cases.
- To properly assess such cases, a holistic approach should be taken that involves the following integration of detailed historical information: preanalytical issues and understanding of the analytical work performed (including its limitations), specimen-specific utility, and special aspects that can weaken or strengthen the ability to form medically and scientifically sound conclusions.
- It should be understood that the burden on the toxicologist is not generally “absolute certainty” because this is something that is rarely achievable. Reasonable medical or scientific certainty usually carries the day, and in civil cases, a greater than 50% probability is all that is generally required.
- Regardless, the purpose of the conclusions offered should not be lost, that is, to educate someone or a group of individuals who have to make difficult decisions, some of which infringe on civil liberties and freedoms. In that respect, the burden assumed by toxicologists should be recognized as significant and warrant the same attention to detail with medicolegal opinions as treatment and diagnosis of a poisoned patient.

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8 TECHNIQUES USED TO PREVENT GASTROINTESTINAL ABSORPTION

Lotte C. G. Hoegberg and Anne-Bolette Gude

Gastrointestinal (GI) decontamination is a highly controversial issue in medical toxicology. It can play an essential role in the initial management of orally poisoned patients and frequently is the only treatment available other than routine supportive care. Unfortunately, as is true in most areas of medical toxicology, rigorous studies that demonstrate the effects of GI decontamination on clinically meaningful endpoints are difficult to find. The heterogeneity of poisoned patients demands that very large randomized studies be performed because patients who present to an emergency department (ED) may have an unreliable history and a low-risk exposure.^{31,156} These factors, as well as other significant sources of bias, are often hidden in inclusion and exclusion criteria of the available studies. Numerous determinants contribute to the difficulties in designing and completing studies that provide sound evidence for or against a particular therapeutic option. Incontrovertible endpoints, such as complication-specific mortality, also demand exceptionally large studies because the overall morbidity and mortality of poisoned patients are quite low.³¹ Whereas other endpoints, such as the length of stay in the hospital or intensive care unit (ICU), change in xenobiotic concentration, the rate of secondary complications, and the need for specific treatments such as expensive antidotes, must be considered, these surrogate markers are not adequately rigorous and are inadequately precise measures of morbidity. In the science of GI decontamination, we are also faced with the dilemma that randomizing half of a group of potentially ill patients to no decontamination is a significant ethical concern—we rarely omit decontamination unless a minimally toxic exposure has occurred or an effective, safe, readily available, and inexpensive antidote exists. Because acetaminophen (APAP) meets many of these parameters, it has been used both as the xenobiotic of choice in volunteer overdose studies^{42,82,94,152,239} and in the evaluation of actually poisoned patients.⁵³ However, despite its widespread use as a model, the applicability of the management approach for APAP poisoning to other ingestions is limited.

As might be suspected, no available study provides adequate guidance for the management of a patient who has definitely ingested an unknown xenobiotic at an unknown time. Fortunately, in most cases, there is some component of the history or clinical presentation, such as vital signs, physical examination, and focused diagnostic studies such as an electrocardiogram and anion gap, that might offer insight into the nature of the ingested xenobiotic ([Chap. 3](#)).

For many, the ongoing controversy or debate on GI decontamination culminated in 1997 with the publication of the position statements on activated charcoal, orogastric lavage, syrup of ipecac-induced emesis, and whole-bowel irrigation (WBI) from the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT),^{43,124,208,224,225} and has evolved from very invasive to a less aggressive approach after subsequent revisions.^{44,125,209,226} Contrary to initial expectations of some, these excellent reviews failed to end the debate; they simply highlighted many shortcomings and ambiguities within this field. A 2000 study concluded that despite having the evidence reviewed and consensus recommendations made, poison specialists at North American poison centers still offered a wide variety of recommendations for GI decontamination.¹¹⁷ The study evaluated decontamination options for a theoretical patient with a serious potentially life-threatening overdose of enteric-coated aspirin. The recommendations made were often inconsistent with the published position statements, and in some cases, were frankly dangerous. Even toxicologists who made substantial contributions to the development of these consensus statements disagreed on certain aspects of the treatment, although to a lesser extent. In a similar study, when an interactive questionnaire was sent to 14 European Poison Centers, significant differences in the protocols for the recommended method of GI decontamination, timing, and intervention doses were found.⁸¹ These differences suggest that there is inadequate evidence available to produce a proper evidence-based answer for many of the decisions in question. In most of the clinical studies that provide evidence to form the basis for the consensus statements, either the proportion of patients with life-threatening ingestions is very small, or these specific patients were excluded from the study. Similarly, there are no studies for most drugs with modified release kinetics, for newly marketed drugs, for patients with mixed overdose, extremes of age, or with significant end-organ dysfunction. Thus, the clinician must often make decisions based on a theoretical approach emphasizing an understanding of basic principles rather than evidence with a substantial level of uncertainty.

More recent studies investigating the trends in GI decontamination in both the advice given by poison centers and the clinical setting demonstrate a considerable decline in the use of all methods of decontamination.^{31,44} One study specifically

evaluating orogastric lavage found that during the years 1993 to 1997, an average of 18.7% of all poisoned patients received orogastric lavage compared with an average of 10.3% of poisoned patients during the years 1998 to 2003. The decline in the use of GI decontamination after the publication of the position statements is also probably a result of the epidemiologic shift in the developed world away from overdoses of more lethal substances, such as salicylates, theophylline, barbiturates, and tricyclic antidepressants, toward benzodiazepines, prescription opioids, serotonergic reuptake inhibitors, and APAP with a natural resultant decrease in morbidity and mortality or the availability of an excellent antidote. Although true, for the Western world, studies in developing countries indicate a different pattern of poisonings with patients ingesting xenobiotics such as organic phosphorus compounds and other pesticides and herbicides with a more lethal toxicologic profile.⁶²

This chapter does not discuss details with regard to the evaluation of the amount and type of xenobiotic ingested or other strategies for managing a patient with an unknown overdose; these issues are discussed in [Chap. 4](#). Rather, the focus is on determining which decontamination technique or combination of techniques is preferred after an indication for GI decontamination has been established. The literature published since the previously mentioned position papers and previous edition of this book is emphasized, existing evidence is summarized, and areas necessitating further investigation are identified. Detailed discussions of activated charcoal and WBI can be found in the corresponding Antidotes in Depth sections, Activated Charcoal (A1) and Whole-Bowel Irrigation and Other Intestinal Evacuants (A2). A limited discussion on induced emesis is presented here because it is no longer considered an appropriate intervention. In addition, when the ingested xenobiotic is known, readers should also refer to the decontamination sections found in Chaps. 35 through 128, which will offer insight into xenobiotic-specific issues that may alter decontamination strategies.

GASTRIC EMPTYING

The principal theory governing gastric emptying is very simple: If a portion of xenobiotic with substantial toxic potential can be removed before absorption, this potential toxicity should be either prevented or minimized. From 1982 to 1995, several important clinical trials attempted to define the role of gastric emptying in poisoned patients.^{6,29,48,103,148,177,223} Although all of these studies were flawed because of the inclusion of a large number of low-risk patients, numerous restrictive exclusion criteria, and a variety of other biases, they clearly demonstrated that many patients can be successfully managed without aggressive gastric emptying. From 1995 until the present, few additional studies on gastric emptying have been published, and the series of updated position papers in 2004 and reviews further emphasized the limited need for aggressive gastric emptying in poisoned patients.^{7,125,134,226} The studies showed diverging opinions of gastric emptying and no clear evidence to support its clinical effectiveness.^{27,29,63,84,206,207} The clinical parameters listed in [Table 8–1](#) help to identify individuals for whom gastric emptying is usually not indicated based on a risk-to-benefit analysis. In contrast, for a small subset of patients ([Table 8–1](#)), gastric emptying may still be indicated. A thorough understanding of this risk analysis is essential when deciding whether gastric emptying is appropriate for a patient who has ingested a xenobiotic.

TABLE 8–1. Risk Assessment: When to Consider Gastric Emptying	
Gastric Emptying Is Usually Not Indicated If*	Gastric Emptying May Be Indicated If*
<p>The xenobiotic has limited toxicity at almost any dose.</p> <p>Although the xenobiotic ingested is potentially toxic, the dose ingested is likely less than that expected to produce significant illness.</p> <p>The ingested xenobiotic is well adsorbed by activated charcoal, and the amount ingested is not expected to exceed the adsorptive capacity of activated charcoal.</p> <p>Significant spontaneous emesis has occurred.</p> <p>The patient presents many hours postingestion and has minimal signs or symptoms of poisoning.</p> <p>The ingested xenobiotic has a highly efficient antidote (eg, APAP and <i>N</i>-acetylcysteine).</p>	<p>The ingested xenobiotic is known to produce serious toxicity or the patient has obvious signs or symptoms of life-threatening toxicity and</p> <ul style="list-style-type: none">• There is reason to believe that, given the time of ingestion, a significant amount of the ingested xenobiotic is still present in the stomach or• The ingested xenobiotic is not adsorbed by activated charcoal or activated charcoal is unavailable or• Although the ingested xenobiotic is adsorbed by activated charcoal, the amount ingested exceeds the activated charcoal-to-xenobiotic ratio of 10:1 even when using a dose of activated charcoal that is twice the standard dose recommended and• The patient has not had spontaneous emesis or• No highly effective specific antidote exists or alternative therapies (eg, hemodialysis) pose a significant risk to the patient.
<p>*Patients who fulfill these criteria can be decontaminated safely with activated charcoal alone or may require no decontamination at all. *Patients who fulfill these criteria should be considered candidates for gastric emptying if there are no contraindications. For individuals who meet some of these criteria but who are judged not to be candidates for gastric emptying, single- or multiple-dose activated charcoal or whole-bowel irrigation (or both) should be considered.</p>	

Time is an important consideration because for gastric emptying to be beneficial, a consequential amount of xenobiotic must still be present in the stomach. Demographic studies have found that very few poisoned patients arrive at the ED within 1 to 2 hours after ingestion. In most studies, the average time from ingestion to presentation was approximately 3 to 4 hours, with significant variations.^{118,125,126,211} This delay diminishes the likelihood of recovering a large percentage of the xenobiotic from the stomach unless the patient has ingested a xenobiotic that slows gastric emptying rates. As is discussed in more depth in the section on orogastric lavage later in this chapter, many authors advise against interventions beyond one hour after ingestion. Actual analysis of the data highlights the arbitrary nature of this limitation. One human volunteer study evaluated the pharmacokinetic effects of diphenhydramine and oxycodone in a simulated APAP overdose.⁹⁰ This model is relevant because of the rapid absorption of APAP and the presence of many such combination products in the marketplace.

Whereas diphenhydramine did not delay gastric emptying significantly, oxycodone delayed the time to peak APAP concentration by approximately one hour. Although GI decontamination was not part of the study protocol, it can be inferred that APAP was available for GI decontamination for a longer time than the one-hour guideline suggests. Case reports frequently demonstrate that poisoned patients still have xenobiotics in their stomach (as confirmed by computed tomography or gastroscopy) as residuals or pharmacobezoars, from 5 hours up to several days after ingestion and even on autopsy.^{60,121}

In fact, markedly prolonged gastric emptying half-lives and gastric hypomotility were demonstrated using gastric scintigraphy in a prospective study of 85 poisoned patients.¹ Remarkably, these findings occurred with ingestions such as APAP, which are not typically expected to prolong gastric emptying. Patients who underwent orogastric lavage did not have significantly different gastric emptying half-lives, suggesting that the procedure itself was not the cause of the gastroparesis, and likewise there was no evidence that activated charcoal affected gastric emptying rates. The authors speculated that stress in an overdosed patient might be part of the etiology of the hypomotility observed and that the management of patients should not be based on the assumption that GI motility is normal.

Assessment of whether or not gastric emptying is appropriate for a patient continues with an evaluation for potential contraindications (Table 8–2). Regardless of the severity of the ingestion and other contributing factors, such as time, there must be no contraindication to gastric emptying procedures. Because the demonstrable benefit of emptying after ingestion of an unidentified xenobiotic is marginal at best, even relative contraindications usually dictate that the procedure should not be attempted. However, the clinical benefit could be sizable if the ingested dose places the patient on the steep portion of the dose–response curve (Chap. 9). Under these circumstances, a small reduction in dose might translate into a significant reduction in toxicity.

TABLE 8–2. Orogastric Lavage: Indications and Contraindications

Indications	Contraindications
The patient meets criteria for gastric emptying (Table 8–1).	The patient does not meet criteria for gastric emptying (Table 8–1).
The benefits of gastric emptying outweigh the risks.	The patient has lost or will likely lose his or her airway protective reflexes and has not been intubated. (After the patient has been intubated, orogastric lavage can be performed if otherwise indicated).
	Ingestion of a xenobiotic with a high aspiration potential (eg, a hydrocarbon) in the absence of endotracheal intubation
	Ingestion of an alkaline caustic
	Ingestion of a foreign body (eg, a drug packet)
	The patient is at risk of hemorrhage or gastrointestinal perforation because of underlying pathology, recent surgery, or other medical condition that could be further compromised by the use of orogastric lavage.
	Ingestion of a xenobiotic in a form known to be too large to fit into the lumen of the lavage tube (eg, many modified-release preparations)

Orogastric Lavage

Many authors have adopted the consensus approach that orogastric lavage should not be considered unless a patient has ingested a potentially life-threatening amount of a xenobiotic and the procedure can be undertaken within 60 minutes of ingestion.¹⁸¹ Since the publication of the clinical studies cited in the 9th edition of this book, studies of orogastric lavage have been scarce.^{3,24,39,72,86,91,125,146,156,177,181} The previous studies observed a modest, varied, and unreliable effect of orogastric lavage.^{83,84,129,130,187} Gastric lavage was shown to be effective in the treatment of few specific xenobiotic poisoning (tetramine rodenticides), where fatality rate was lowered in the patient group that received gastric lavage compared to patients not lavaged.²³⁵ Use of combination therapies with administration of activated charcoal before gastric lavage was described by several,^{3,4,11,25,33,69,72,111,114,132,146,172,180,217,227} but the procedure was not more effective than activated charcoal alone^{26,42,129} and sometimes resulted in increased xenobiotic concentration and worsened clinical outcome.¹¹ In some cases, gastric lavage delays activated charcoal administration further, and considerations to eliminate gastric lavage and only administer activated charcoal should be made in order to initiate the fastest decontamination procedure. The trend in using gastric lavage continually declines.¹³¹ The frequency of gastric lavage procedure varies from lowest frequency (percent compared with total decontaminations using activated charcoal, gastric lavage, syrup of ipecac,

and WBI) in North America (5.7%)³¹ and Scandinavia (7.9%–9%; Denmark and Norway),^{137,237} in Mediterranean countries (30%–32%; Spain and Palestine),^{11,132,192} to the highest frequency in Asia and South American countries, India (34%–>50%),^{24,153} Nepal (43%),³³ and Bolivia (96%).⁷⁰ The frequency tends to correlate with the type of xenobiotic ingested, with highest frequency of lavage in regions where insecticides such as organic phosphorus compounds and carbamates are more commonly ingested.^{24,33,70}

It is important to highlight the differences between volunteer studies using therapeutic doses of drugs and actual patients with clinically significant overdoses. The most important aspect of this comparison is a bias against gastric emptying and toward a benefit with activated charcoal. The drugs used in volunteer studies are typically well adsorbed by activated charcoal, and the doses of activated charcoal are significantly in excess of the activated charcoal:drug ratios that can be achieved in clinically significant overdoses. Larger overdoses, as might occur in patients with clinically important ingestions, are likely to saturate activated charcoal. An additional bias is introduced against gastric emptying because the small amounts of any study drug used are unlikely to alter gastric motility, and thus the drugs may pass through the pylorus before orogastric lavage can occur. A synthesis of available data can be used to develop indications for orogastric lavage (Table 8–2). This procedure should always be performed by trained health care professionals and in health care settings. When deciding whether to actually perform orogastric lavage on a poisoned patient, these indications, contraindications, and potential adverse effects must be considered. Table 8–3 summarizes the technique of orogastric lavage.

TABLE 8–3. The Technique of Performing Orogastric Lavage

Select the correct tube size

Adults and adolescents: 36–40 French

Children: 22–28 French

Procedure

1. If there is potential airway compromise, endotracheal intubation should precede orogastric lavage.
2. The patient should be kept in the left lateral decubitus position. Because the pylorus points upward in this orientation, this positioning theoretically helps prevent the xenobiotic from passing through the pylorus during the procedure.
3. Before insertion, the proper length of tubing to be passed should be measured and marked on the tube. The length should allow the most proximal tube opening to be passed beyond the lower esophageal sphincter.
4. After the tube is inserted, it is essential to confirm that the distal end of the tube is in the stomach.
5. Any material present in the stomach should be withdrawn and immediate instillation of activated charcoal should be considered for large ingestions of xenobiotics that are known to be adsorbed by activated charcoal.
6. In adults, 250-mL aliquots of a room temperature saline lavage solution is instilled via a funnel or lavage syringe. In children, aliquots should be 10 to 15 mL/kg to a maximum of 250 mL.
7. Orogastric lavage should continue for at least several liters in an adult and for at least 0.5 to 1.0 L in a child or until no particulate matter returns and the effluent lavage solution is clear.
8. After orogastric lavage, the same tube should be used to instill activated charcoal if indicated.

Reported adverse effects of orogastric lavage include injury to the esophagus^{34,85} and stomach,⁵⁷ as well as significant decreases in serum calcium,⁸⁰ ionized calcium,⁸⁰ and magnesium⁸⁰; severe hyponatremia¹⁴⁹; and leukocytosis.¹¹¹ Hyponatremia resulted from a lavage that was performed using 12 L of hypertonic saline.¹⁴⁹ An observational case series studying 14 consecutive gastric lavages performed in a resource-poor location found three deaths directly related to the procedure, all of which seemed to have resulted from inadequate airway protection.⁶⁴ These cases, as well as other well-known complications such as respiratory events, including need for mechanical ventilation,¹¹² hypoxemia,¹¹² respiratory failure,²³⁴ and higher frequency of aspiration pneumonitis,^{112,224,226,234} demonstrate that orogastric lavage is not risk free and should only be considered based on the rigorous indications for gastric emptying listed in Table 8–1.

Syrup of Ipecac

Syrup of ipecac-induced emesis is no longer a recommended approach for gastric emptying in the treatment of poisoning. Clinical benefit for the use of syrup of ipecac as a gastric emptying technique has never been proven,^{27,86,101,125} and gastric content may be forced beyond the pylorus, increasing the amount of xenobiotic available for absorption.¹⁸⁷ Since the position statement from AAPCC/EAPCCT in 1997,¹²⁴ the frequency of syrup of ipecac use has declined steadily.³¹ Furthermore, as the benefits of activated charcoal are recognized and the time to its administration evaluated, it has become evident that the administration of syrup of ipecac delays the administration of activated charcoal¹²³ and possibly oral antidotes.

PREVENTION OF XENOBIOTIC ABSORPTION

Activated Charcoal

Activated charcoal continues to be recognized as an effective method for reducing the systemic absorption of many xenobiotics.^{2,7,16,20,77,86,110,119,160,166} For certain xenobiotics, it also enhances elimination through interruption of either the enterohepatic or enteroenteric cycle.⁴⁹ Its superb adsorptive properties theoretically make it the single most useful management strategy for diverse patients with acute oral overdoses.^{12-14,26,42,49,50,79,102,173,174} However, as is true for the other methods of GI decontamination, there is a lack of sound evidence of its benefits as defined by clinically meaningful endpoints. This opinion is reflected both in the consensus statements and reviews and in the overall trend toward not performing decontamination as shown in poison center data^{7,31,44,110,147} (Chap. 136). The consensus opinion concluded that a single dose of activated charcoal should not be administered routinely in the management of poisoned patients and, based on volunteer studies, the effectiveness of activated charcoal decreased with time, providing the greatest benefit in severely poisoned patients if dosed within one hour of ingestion. There was no evidence that the administration of a single dose of activated charcoal improved clinical outcome. These opinions are unfortunately biased by the fact that most “routinely” poisoned patients have low-risk exposures and do well with minimal intervention. Additionally, it is generally accepted that unless either airway protective reflexes are intact (and expected to remain so) or the patient’s airway has been protected, the administration of activated charcoal is contraindicated.⁴⁴ Despite little scientific basis or support from clinical trials, less severely poisoned patients might benefit from activated charcoal in terms of reduced need for life support, monitoring, and antidotes.¹¹⁰

Theoretically, the early administration of activated charcoal to patients presenting with a significant oral overdose of a potentially toxic xenobiotic would lower systemic exposure to that xenobiotic and thus be of benefit to the patient. Surprisingly, this intuitive result has been difficult to demonstrate using clinically relevant endpoints in large unselected populations of poisoned patients, again most likely as a result of inclusion of large numbers of minimally exposed low-risk individuals.

A randomized, controlled clinical trial of all orally overdosed patients (n = 327) presenting to the ED of a large hospital in an urban setting during 16 consecutive months found no difference in clinical endpoints such as length of stay or other outcomes between patients treated with a single dose of activated charcoal compared with no decontamination. The study excluded seven severely poisoned patients who all arrived within one hour of ingestion; the majority of the patients in the trial (nearly 60%) arrived within 2 hours postingestion. The most common xenobiotics ingested were APAP, benzodiazepines, and newer antidepressants all of which have low case-fatality rates.⁵⁴

A larger trial (n = 4629) studying self-poisoned patients from a rural and resource-poor location found no difference in mortality rates between those who received no activated charcoal, single-dose activated charcoal, or multiple-dose activated charcoal (MDAC). The patients primarily ingested pesticides and yellow oleander (*Thevetia peruviana*) seeds, both xenobiotics having very different kinetic properties compared to pharmaceuticals. It is important to note that the first 1904 patients in the control group actually received orogastric lavage, as was the case for all patients presenting within 2 hours of ingestion of substantial amounts of pesticides or potentially toxic xenobiotics because of pressure from the national doctors’ union. Although the authors claim that logistic regression analysis found no influence of lavage on their results, the data are not presented.⁶⁵ Furthermore, in an article on compliance related to activated charcoal, nested within this randomized, controlled trial, it is stated that a large number of patients included in the trial had undergone gastric emptying in some form before being transferred from peripheral hospitals.¹⁵⁰ The results of this trial are probably valid for the authors’ particular setting and patient profiles but cannot be generalized to developed nations. In contrast with the lack of effect on clinical endpoints such as death, a pharmacokinetic analysis from another subset of patients (n = 104) from this large trial found a significant increase in plasma clearance of the *Thevetia peruviana* cardenolides in patients administered both single-dose activated charcoal and MDAC. There was no difference between groups in mortality, but given the absolute numbers of two to three deaths per group, this could be related to a lack of power in the study design.¹⁸²

Mechanism. The entire effect of activated charcoal takes place in the GI tract. Oral activated charcoal is not absorbed through the GI wall but passes straight through the gut unchanged. Administration of xenobiotics may happen by a variety of routes, and these xenobiotics enter or are transported into the GI tract by different mechanisms determined by the specific physical-chemical properties of the individual xenobiotic. To be adsorbed to activated charcoal, the xenobiotic must be dissolved in the GI liquid phase and be in physical contact to the activated charcoal. The surface (internal and external) of activated charcoal is manufactured to possess a chemical nature that attracts certain molecules (xenobiotics). The possible sites of adsorption are indicated in Fig. 8–1. Activated charcoal forms an equilibrium between free xenobiotic and xenobiotic that is adsorbed to it through relatively weak intermolecular forces.

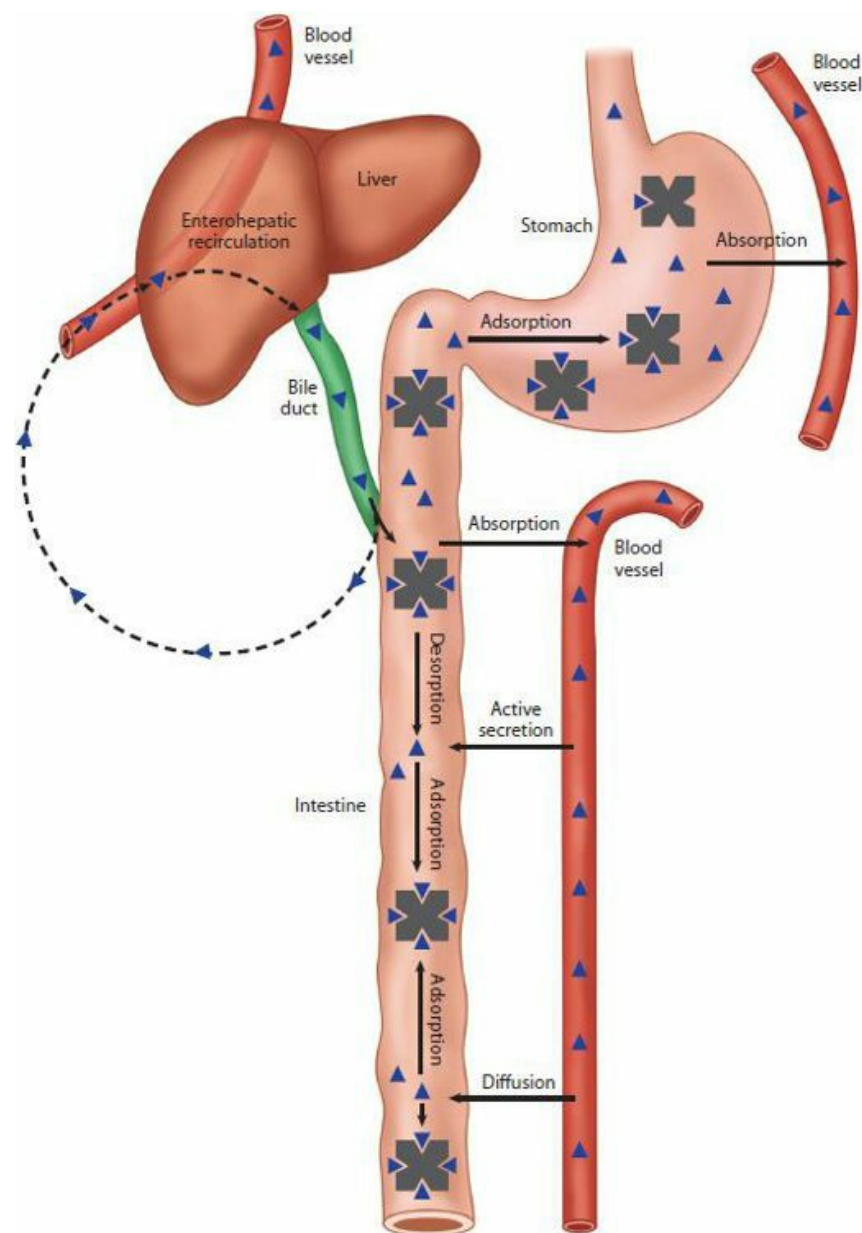


FIGURE 8–1. Mechanism of xenobiotic removal by activated charcoal in the luminal space of the gastrointestinal tract. The position of systemic xenobiotic absorption depends on the physical chemical characteristics of the xenobiotic and takes place from stomach, intestine, or both. Xenobiotic reentry into the luminal space can take place by enterohepatic recirculation and enteroenteric recirculation by active secretion and passive diffusion. Excess and continued supply of activated charcoal facilitates adsorption of recycled xenobiotic and favors continued active and passive diffusion of xenobiotic to the luminal space and adsorption of xenobiotic.

Free xenobiotic + Activated charcoal \rightleftharpoons Xenobiotic/Activated charcoal complex

Desorption of the adsorbed xenobiotic may occur, but if sufficient activated charcoal is present (see dosing below), the equilibrium will be shifted toward the xenobiotic–activated charcoal complex. The effect is a low free xenobiotic concentration in the liquid phase and reduced xenobiotic absorption.⁴⁹

Time Factors. The general statement in the literature is that administration of a single dose of activated charcoal should be considered if a patient has ingested a potentially toxic amount of a xenobiotic that is known to be adsorbed to activated charcoal in the previous hour. This position was chosen based primarily on case reports and volunteer studies using nontoxic doses of xenobiotics because it was believed that there were insufficient data to support or exclude the use of single-dose activated charcoal therapy more than one hour beyond ingestion.^{43,44} However, the efficacy of activated charcoal administered more than one hour after xenobiotic ingestion has been evaluated in several studies. These investigations confirm enhanced effect of activated charcoal if dosed as early as possible but also demonstrate a significant effect if dosing is delayed up to 4 hours after the xenobiotic ingestion.^{75,106,109,110,116,152,202} In fact, a few studies suggest efficacy up to 6 hours after ingestion.^{116,236} Furthermore, prolonged gastric emptying time caused by massive xenobiotic ingestion or specific properties of an ingested xenobiotic or bezoar formation possibly increase the time frame when activated charcoal might effectively adsorb the xenobiotic.^{1,121} The studies below emphasize this concept.

In volunteers, the effect of activated charcoal administered 2 and 4 hours after ingestion of acetaminophen demonstrated no significant difference in plasma acetaminophen concentration compared with control participants. In contrast, when

administered one hour after a simulated acetaminophen ingestion, activated charcoal reduced serum acetaminophen concentrations significantly.²³⁹ Likewise, when the effectiveness of activated charcoal administered 1, 2, and 3 hours after xenobiotic ingestion was determined, only the one-hour group had a pharmacokinetic profile that differed from the control group.⁸² Although these data do not support the administration of activated charcoal as a GI strategy more than one hour after an overdose, the applicability of these results to actual overdosed patients has not been adequately evaluated. The method in this volunteer study was an 8-hour fast followed by a small meal 1 hour before the administration of 3 to 4 g of acetaminophen.^{82,239} Considering the rapid absorption of acetaminophen, the small 3- to 4-g doses used, and the absence of food in the stomach, it is highly probable that little or no acetaminophen would be left in the GI tract to be adsorbed by activated charcoal, limiting the potential time to benefit from activated charcoal to approximately one hour.

In contrast, activated charcoal given 3 hours after an overdose was investigated in vivo, again using acetaminophen and a larger-than-standard dose (ie, 75 g) of activated charcoal. The results demonstrated some benefit in administering activated charcoal 3 hours after an overdose because there were significantly lower serum acetaminophen concentrations in the activated charcoal group than in the control group, 23% lower at 4 hours and 62% lower at 7 hours after ingestion.¹⁹¹ In a similar study, activated charcoal was effective in reducing the systemic absorption of acetaminophen when administered both 1 and 2 hours after ingestion, although the effect of the 2-hour intervention was substantially less than at one hour, reemphasizing the importance of early intervention.⁴²

The efficacy of activated charcoal was studied in 53 patients following 63 episodes of citalopram overdose.⁷⁵ When activated charcoal was administered between 0.5 and 4 hours to 17 patients who had ingested potentially toxic doses of citalopram, there was a 72% increase in clearance and a 22% decrease in bioavailability. In most patients, the activated charcoal was dosed more than one hour after ingestion. Only one patient received activated charcoal within one hour, nine patients received activated charcoal within 1 to 2 hours, and seven patients received activated charcoal within 2 to 4 hours.

Despite a delay to activated charcoal of 0.5 to 6.0 hours after a quetiapine overdose, a significant benefit for a single dose of activated charcoal was demonstrated. Activated charcoal decreased the fraction absorbed of quetiapine by 35%. No apparent effect on clearance was demonstrated.¹⁰⁷ In a later study by the same investigators, only early use (<2 hours) of activated charcoal was able to reduce the probability of intubation in quetiapine overdose patients. Activated charcoal administered between 2 and 4 hours did not reduce the probability of intubation. The study included 286 patients overdosed with quetiapine alone or in combination with other drugs. However, only a total of 42 patients (15%) received activated charcoal based on unknown criteria, four patients (1%) received activated charcoal within 1 hour but were excluded from analysis, 19 patients (7%) received activated charcoal within 2 hours, and 36 patients (13%) received activated charcoal within 4 hours from quetiapine ingestion.¹⁰⁹

A meta-analysis was performed to evaluate the effect of activated charcoal on xenobiotic absorption during the first 6 hours after ingestion. Data were obtained from 64 controlled studies in which activated charcoal was compared with placebo up to 6 hours after drug ingestion in volunteers. Additional considerations were given to assess the influence of physical and pharmacologic properties and the activated charcoal-to-drug ratio. The authors concluded that activated charcoal was most effective when administered immediately after xenobiotic ingestion. However, even with a delay of 4 hours after ingestion, 25% of the participants achieved at least a 32% reduction in absorption, especially when activated charcoal was given with large activated charcoal-to-drug ratios.¹¹⁶

Similarly, when aminotransferase elevations (>1000 IU/L) were measured in patients with acetaminophen overdose who presented more than 4 hours after ingestion, patients who received activated charcoal along with N-acetylcysteine (NAC) had less elevation than those who received NAC alone. Although this study was limited by its observational methodology, the findings are both consistent with studies described earlier and are biologically plausible.²⁰²

Efforts to reduce time to activated charcoal administration have been evaluated using pre-arrival communication between a poison center and both emergency medical services and an ED.^{221,222} Both approaches reduced the time from overdose to activated charcoal dosing to less than one hour.

Thus, it should be clear that the use of a one-hour time frame should serve as a guideline rather than an absolute concept. It is only logical that if an intervention is effective at 59 minutes, it will also be beneficial at 61 minutes. Although it is logical that efficacy decreases as time from ingestion increases, in certain cases, some benefit may be derived many hours after ingestion. Because after massive life-threatening ingestions, the absorption of xenobiotics may be prolonged, there is no exact time limit for activated charcoal use.¹⁵⁷ As discussed earlier, good data from patients with actual ingestions demonstrate that a significant amount of xenobiotic can be found in the stomach beyond this arbitrary one-hour time frame. Activated charcoal should therefore be considered to prevent absorption in poisoned patients even when they present late to medical care. Additional benefits on enhanced elimination are discussed below.

Prehospital Use. Adherence to the recommendation that activated charcoal should be administered within one hour of ingestion limits the potential to treat most poisoned patients. A study over a 6-month period identifying 63 patients who had taken potentially serious overdoses demonstrated a median time of arrival to health care of 136 minutes after the overdose. Only 15 patients presented within 1 hour, and only four of 10 patients who qualified actually received activated charcoal within 1 hour. The results demonstrate not only the difficulty in clinically assessing patients before 1 hour but also the

difficulty in adhering to the principle of treating patients with activated charcoal when they arrive within 1 hour unless activated charcoal could be safely administered to appropriate patients in the prehospitalization setting.¹¹⁸

Prehospital use of activated charcoal has not gained wide acceptance because of the concern that it would not be administered properly by the untrained lay public and that many children would refuse to drink the charcoal slurry. In fact, an 18 month consecutive case series demonstrated that activated charcoal can be administered successfully in the home by the lay public. Home use of activated charcoal significantly reduced the time to activated charcoal administration after xenobiotic ingestion from a mean of 73 ± 18.1 minutes for ED treatment to a mean of 38 ± 18.3 minutes for home treatment.²⁰¹ However, many authorities still recommend that activated charcoal should not be standard home treatment, but administration should only be carried out by health professionals.^{10,45,141,144,156,195,196}

A prospective follow-up study from Finland evaluated the adherence to a new protocol of administering activated charcoal in the prehospital setting. The protocol was implemented by either the first-response unit or paramedics. Activated charcoal was indicated in 722 of 2047 patients. Of these patients, 555 actually received activated charcoal at a mean of 88 minutes after ingestion. There were no adverse effects noted, although 72 patients refused to drink the activated charcoal. This study shows that it is feasible to administer activated charcoal in the prehospital setting, but its clinical implications are unknown.⁵

In reality, many factors, such as the presence of food in the stomach, sustained-release formulations, and co-ingestions that delay gastric emptying, can slow the rate of absorption of a xenobiotic. These factors increase the time frame for possible adsorption to activated charcoal. This increased effect of activated charcoal was demonstrated in a randomized, crossover study in which volunteers were administered acetaminophen in either the presence or absence of the anticholinergic drug atropine and subsequently given a single dose of activated charcoal 1 hour later. Activated charcoal was more effective in reducing acetaminophen bioavailability in the presence of atropine.⁸³

Dosing. The optimal dose of oral activated charcoal has never been fully established. Since the beginning of its clinical use as a GI decontaminant, various factors have been recommended for determining the optimal dose of activated charcoal. Two factors commonly discussed are the patient's weight and the quantity of the xenobiotic ingested. The problem in using the quantity of the xenobiotic as a basis for activated charcoal dosing is that the amount is usually unknown, and there is an implication that nothing else in the GI tract will occupy binding sites on activated charcoal. Additionally, the xenobiotic is often unknown, and xenobiotics vary enormously in their toxicities, rate of absorption, and the clinical effects they produce (eg, respiratory depression, convulsions, and effect on gastric emptying rate). Some xenobiotics are well adsorbed to activated charcoal, but others are not.⁴⁹ Because of variables such as the physical properties of the formulation ingested (liquid, solid, or sustained-release tablet), the volume and pH of gastric and intestinal fluids, and the presence of other xenobiotics adsorbed by activated charcoal,^{14,18,92,95,133,162,164} the optimal dose cannot be known with certainty in any given patient.

Information concerning the maximum adsorptive capacity of activated charcoal for the particular xenobiotic ingested permits a theoretical calculation of an adequate dose,^{8,12,17,19,40,50,158,159,162,163,183,184,186,199,214,219} assuming that the amount of xenobiotic ingested is known. However, clinicians must remain cognizant of the risk of approaching or exceeding the adsorptive capacity of the standard dose of approximately 1 g/kg of body weight of activated charcoal. This possibility has been investigated in some studies.^{8,19,36,95,104,155,186,231}

Thus, the idea that a fixed activated charcoal-to-xenobiotic ratio is appropriate for all xenobiotics is clearly imperfect. It is possible, however, to develop a logical approach to dosing based on available data. The effect of the activated charcoal:xenobiotic ratio is such that theoretically increasing the ratio enhances the completeness of adsorption corresponding to a higher percentage of adsorption and total amount of adsorbed xenobiotic (Fig. 8–2).¹⁵⁷ This was confirmed by Jürgens et al., demonstrating an increasing effect of activated charcoal with increasing activated charcoal–xenobiotic dose, up to a 40:1 ratio.¹¹⁶ The optimal activated charcoal dose is theoretically the minimum dose that completely adsorbs the ingested xenobiotic and, if relevant, that maximizes enhanced elimination. The results of in vitro studies show that the ideal activated charcoal:xenobiotic ratio varies widely, but a common recommendation is to deliver an activated charcoal:xenobiotic ratio of 10:1, or 50 to 100 g of activated charcoal to adult patients, whichever is greater. From a theoretical perspective, this amount will adsorb 5 to 10 g of a xenobiotic, which should be adequate for most poisonings.^{12,13,44,49,163} In human volunteers, the acetaminophen clearance was increased with increasing doses of activated charcoal.⁸⁷ Fixed doses of 50, 25, or 5 g activated charcoal were administered 1 hour after 50 mg/kg of acetaminophen was given. The apparent half-life of acetaminophen was significantly reduced from 2.5 hours for the 5 g activated charcoal dose to 1.9 hours and 1.6 hours for the 25 and 50 g doses, respectively.⁸⁷ The effect of larger doses of activated charcoal, adsorbing larger amounts of xenobiotics was supported by the meta-analysis mentioned earlier.¹¹⁶ Based on available data from in vivo and in vitro studies, the actual recommended dosing regimen for activated charcoal is 50 to 100 g in adults (1 g/kg of body weight) and 0.5 to 1.0 g/kg of body weight in children.^{44,49} These recommendations are generally based more on activated charcoal tolerance than on efficacy. When calculation of a 10:1 ratio exceeds these recommendations, either gastric emptying or MDAC therapy should be considered.

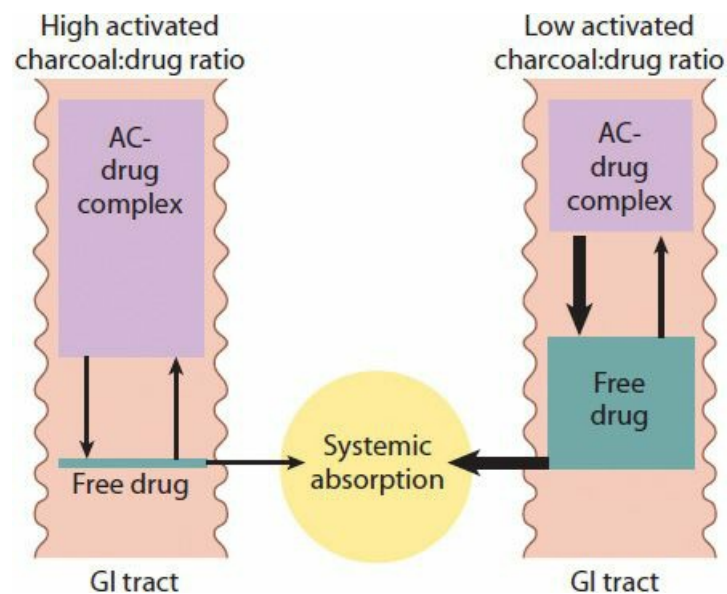


FIGURE 8–2. The effect of high and low ratios of activated charcoal to xenobiotic in the gastrointestinal tract is shown. The reduced systemic absorption achieved when the activated charcoal–xenobiotic ratio is high (left) compared with the increased systemic absorption at a low activated charcoal–xenobiotic ratio (right).

For example, consider a patient who intentionally overdosed by ingesting 30 (0.25-mg) digoxin tablets (total dose, 7.5 mg). Achieving a 10:1 ratio is quite easy, and a standard dose of 1 g/kg might exceed a 10,000:1 ratio. In comparison, consider a patient who intentionally ingests 30 (325-mg) aspirin tablets (total dose, 9.75 g). In this case, obtaining a 10:1 activated charcoal:xenobiotic ratio is quite difficult and is even less likely if a patient ingests 60 or 100 of the aspirin tablets. Poisoning with a combination of xenobiotics may also approach or exceed the maximum adsorptive capacity for the standard dose of activated charcoal, and increasing the dose to reach a higher activated charcoal:xenobiotic ratio might be necessary to consider in multiple-xenobiotic poisonings.⁹⁵

Methods to Increase the Palatability of Activated Charcoal. Activated charcoal has a pronounced gritty texture, and it immediately sticks in the throat because it adheres to the mucosal surfaces and begins to cake.⁴⁹ In addition, the black appearance and insipid taste of activated charcoal make it less attractive.

There have been numerous attempts at making activated charcoal more appealing by providing flavors, including jam,⁵⁸ chocolate syrup,^{142,154} cherry extract or syrup,^{88,168,238} cookie,¹²² juice,¹⁶⁸ sorbitol,^{51,55,143} saccharin,⁵² strawberry flavor,¹⁶⁷ orange or peppermint oil,⁴⁹ melted milk chocolate,^{66,67} chocolate milk,^{39,88,168} soda,^{39,88,168,179} yogurt,⁹⁴ and ice cream.^{40,93,210} The general recommendation, however, remains that activated charcoal should be mixed with water.^{10,115} Because activated charcoal adsorbs the flavoring agents, the palatable taste from added flavors often disappears within minutes after mixing.^{49,51,52,58} However, in cases in which the activated charcoal does not completely adsorb the flavoring agents, they provided a pleasant taste without significantly reducing the adsorptive properties of the activated charcoal.^{49,51,52,93,94}

Effect on Oral Therapeutics. The nonspecific nature and high adsorptive capacity of activated charcoal raises concerns about the simultaneous use of orally administered therapeutics. It would be expected that therapeutics administered shortly before or simultaneously with activated charcoal would be extensively adsorbed, greatly reducing therapeutic efficacy. Restored utility of a therapeutic would be as complex and would depend on all of the factors that influence the efficacy of activated charcoal. Although there is some concern over activated charcoal limiting the efficacy of common oral antidotes such as NAC and succimer, additional concerns arise regarding the administration of oral maintenance medications. For example, activated charcoal might alter the kinetics of the new oral anticoagulants (dabigatran, apixaban, and rivaroxaban).¹⁹⁷ The issue is described to a limited extent and not in the context of poisoning.^{178,203}

Contraindications and Complications. Few clinically significant adverse effects are associated with the use of activated charcoal for poisoned patients.^{49,178} Adverse GI effects are most commonly described, but the frequency varies,¹⁷⁸ and it might be difficult to differentiate from adverse effects resulting from the ingested xenobiotic.¹⁹⁰ In a study of 24 volunteers, mild adverse effects such as abdominal fullness or constipation (46%) and nausea (17%) were most common.¹⁹⁰ In a randomized clinical trial, vomiting was not more frequent in patients treated with activated charcoal compared with the control group, which received no activated charcoal.⁵⁴ Similarly, although vomiting was observed in 22% of patients in a randomized controlled trial of 1103 patients with intentional poisoning, a nonsignificant difference in incidence was reported between patients who had or had not received GI emptying procedures.¹⁵⁰ A prospective cohort study estimating the incidence of vomiting subsequent to the therapeutic administration of activated charcoal to poisoned children younger than 18 years of age showed that one of five of these children vomited. Children with previous vomiting or nasogastric tube administration were at highest risk.¹⁶⁹ This incidence of vomiting appears to be greater when activated charcoal is

administered with sorbitol²²⁵ and after rapid ingestion of larger doses.¹⁵⁷

Pulmonary aspiration of gastric contents containing activated charcoal and inadvertent direct instillation of activated charcoal into the lungs from a misplaced nasogastric tube are rare but severe incidents^{54,74,198} that might lead to airway obstruction, bronchospasm, hypoxemia, aspiration, permanent lung injury, and even death.^{161,166} Administration of activated charcoal to already intubated patients is associated with a low incidence of aspiration pneumonia.¹⁵¹ In fact, pulmonary complications associated with activated charcoal aspiration might be primarily related to the aspiration of acidic gastric contents and not directly related to aspiration of activated charcoal.¹⁸⁵ A retrospective study found that only 1.6% of unselected overdose patients aspirated and that administration of activated charcoal was not found to be an associated risk factor.¹⁰⁶ Pulmonary aspiration in overdose patients who have received activated charcoal is more easily documented because activated charcoal is a very identifiable marker.

Although relatively few reports of clinically significant emesis and pulmonary aspiration resulting from the administration of activated charcoal exist, the severity of these complications is clear. Consequently, it is important to evaluate, particularly in patients determined to be at limited risk from their exposures, whether single-dose activated charcoal therapy is likely to be beneficial based on the indications and contraindications listed in Table 8–4. This is especially true in small children, in whom the risks of nasogastric tube use might outweigh the benefits of activated charcoal.

TABLE 8–4. Single-Dose Activated Charcoal Therapy without Gastric Emptying: Indications and Contraindications

<i>Indications</i>	<i>Contraindications</i>
The patient does not meet criteria for gastric emptying (Table 8–1) or gastric emptying is likely to be harmful.	Activated charcoal is known not to adsorb a clinically meaningful amount of the ingested xenobiotic.
The patient has ingested a potentially toxic amount of a xenobiotic that is well adsorbed by activated charcoal.	Airway protective reflexes are absent or expected to be lost, and the patient is not intubated.
The ingestion has occurred within a time frame amenable to adsorption by activated charcoal or clinical factors are present that suggest that not all of the xenobiotic has already been systemically absorbed.	Gastrointestinal perforation is likely as in cases of caustic ingestions.
Patients with potentially life-threatening toxicity regardless of the time since ingestion as long as no absolute contraindications exist.	Therapy may increase the risk and severity of aspiration, such as in the presence of hydrocarbons with a high aspiration potential.
	Endoscopy will be an essential diagnostic modality (caustics).

MULTIPLE-DOSE ACTIVATED CHARCOAL

MDAC is typically defined as at least two sequential doses of activated charcoal.²²⁵ In many cases, the actual number of doses administered is substantially greater. This technique serves two purposes: (1) to prevent ongoing absorption of a xenobiotic that persists in the GI tract (usually in the form of a modified-release preparation) and (2) to enhance elimination in the postabsorptive phase by either disrupting enterohepatic recirculation or enteroenteric recirculation (“gut dialysis”).

The 1999 position statement of the AACT and the EAPCCT concluded that based on clinical studies, MDAC should be considered only if a patient has ingested a potentially life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Although data have confirmed enhanced elimination of these drugs, no controlled studies have demonstrated clinical benefit after their ingestion. Volunteer studies demonstrate that MDAC increases the elimination of amitriptyline, dextropropoxyphene, digitoxin, digoxin, disopyramide, nadolol, phenylbutazone, phenytoin, piroxicam, and sotalol, but there are insufficient clinical data to support or exclude the use of MDAC in these patients.²²⁵ A possibly beneficial effect of MDAC has recently been shown in poisonings including *Amanita phalloides* and other *Amanita* spp,^{38,79,113,176} amiodarone,²⁰⁵ carbamazepine,²²⁷ dosulepin,¹⁴⁵ duloxetine,⁶⁹ diquat,²¹⁸ lamotrigine,⁶⁹ phenobarbital,⁴⁶ theophylline,³⁷ valproic acid,²²⁹ and verapamil.¹⁹³ Furthermore, MDAC is recommended in severe poisonings, including with colchicine²⁸ and quinine.¹¹¹ Although technically correct, the preceding statements suffer from a lack of high quality evidence. Because the clinical studies used to formulate this opinion all lack sufficient numbers of significantly poisoned patients, they induce a bias against any benefit of MDAC. Additionally, none of the studies included a detailed analysis of sustained- or extended-release formulations, which are widely used today. Finally, it is noteworthy that the definition of

“life threatening” is highly subjective. Endpoints such as decreased morbidity or rigorously determined lengths of stay should be considered essential in any study design. Three studies with these clinical endpoints were previously discussed.⁸⁷ Unfortunately, their results were discordant, highlighting the difficulties within this field of study.^{30,59,65}

Dosing. Various MDAC regimens were evaluated to optimize the efficacy of activated charcoal.^{105,119} Reduced xenobiotic absorption and enhanced elimination were demonstrated compared with either single-dose activated charcoal or control without activated charcoal.¹¹⁹ The effect of MDAC on elimination was studied in volunteers who were dosed with lamotrigine and oxcarbazepine in therapeutic doses.¹¹⁹ The MDAC dose regimen was 25 g activated charcoal at 6, 12, 24, 36, 48, and 72 hours after a 100 mg lamotrigine dose or 20 g activated charcoal at 12, 24, 36, and 48 hours after a 300 mg oxcarbazepine dose. Each regimen was compared to control subjects with no activated charcoal and one single dose of 50 g activated charcoal at 30 minutes after lamotrigine or oxcarbazepine ingestion, respectively. Pharmacokinetic parameters were evaluated from the serum concentrations of lamotrigine and oxcarbazepine (by measuring the active metabolite 10-hydroxy-carbazepine). Both activated charcoal regimens significantly reduced the total systemic xenobiotic load compared with control subjects with reductions of 51% for lamotrigine and 41% for 10-hydroxy-carbazepine. The elimination half-life for both xenobiotics was significantly shortened with MDAC; 11±3.5 hours (MDAC) versus 25±4.3 hours (control) for lamotrigine, and 9.0±1.5 (MDAC) versus 20±12 hours (control) for 10-hydroxy-carbazepine.¹¹⁹

Intravenous administration of a xenobiotic is an ideal method to evaluate the ability of different MDAC dose regimens to enhance elimination of a xenobiotic in the postabsorptive phase. A total dose of 150 g activated charcoal given as a loading dose of 50 g and the remaining 100 g divided in either 12.5 g every hour, 25.0 g every 2 hours, or 50.0 g every 4 hours during a total time of 8 hours was equally effective in reducing the mean area under the concentration versus time curve (AUC) in volunteers receiving 8 mg/kg of aminophylline intravenously over a period of 60 minutes.¹⁰⁵

Contraindications and Complications. Similar to single-dose activated charcoal, MDAC can produce emesis, with subsequent pulmonary aspiration of gastric contents containing activated charcoal. It is intuitive that these risks are greater with MDAC than with single-dose therapy. One retrospective study attempted to determine the frequency of complications associated with the use of MDAC.⁶¹ The authors identified nearly 900 patients who had received MDAC and found that only 0.6% of patients had clinically significant pulmonary aspiration. Although no patients developed GI obstruction, 9% had hypernatremia or hypermagnesemia without any clinical consequences noted. The authors did not specify whether the multiple-dose regimens administered included the use of cathartics, but the profile of the adverse reactions suggests that these electrolyte abnormalities were probably from cathartic use. Despite the obvious limitations, this study demonstrates a reasonably low rate of complications associated with MDAC.

Table 8–5 summarizes the indications and contraindications for MDAC therapy. Because the optimal doses and intervals for MDAC have not been established, recommendations are based more on amounts that can be tolerated than on amounts that might be considered pharmacologically appropriate. Table 8–6 lists typical dosing regimens. Larger doses and shorter intervals should be used for patients with more severe toxicity. It is reasonable to base endpoints either on the patient’s clinical condition or on xenobiotic concentrations when they are easily measured.

TABLE 8–5. Multiple-Dose Activated Charcoal Therapy: Indications and Contraindications	
Indications	Contraindications
Ingestion of a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, salicylates or theophylline	Any contraindication to single-dose activated charcoal
Ingestion of a life-threatening amount of another xenobiotic that undergoes entero-hepatic or enteroenteric recirculation and that is adsorbed to activated charcoal	The presence of an ileus or other causes of diminished peristalsis
Ingestion of a significant amount of any slowly released xenobiotic or of a xenobiotic known to form concretions or bezoars	

TABLE 8–6. Technique of Administering Multiple-Dose Activated Charcoal Therapy

Initial dose orally or via orogastric or nasogastric tube:

Adults and children: 1 g/kg of body weight or a 10:1 ratio of activated charcoal to xenobiotic, whichever is greater. After massive ingestions, 2 g/kg of body weight might be indicated if such a large dose can be easily administered and tolerated.

Repeat doses orally or via orogastric or nasogastric tube:

Adults and children: 0.5 g/kg of body weight every 4–6 hours for 12–24 hours in accordance with the dose and dosage form of xenobiotic ingested (larger doses or shorter dosing intervals may occasionally be indicated).

Procedure:

1. Add eight parts of water to the selected amount of powdered form. All formulations, including prepacked slurries, should be shaken well for at least one minute to form a transiently stable suspension before the patient drinks it or it is instilled via orogastric or nasogastric tube.
2. Activated charcoal can be administered with a cathartic for the first dose only when indicated. Cathartics should never be administered routinely and never be repeated with subsequent doses of activated charcoal.
3. If the patient vomits the dose of activated charcoal, it should be repeated. Smaller, more frequent doses or continuous nasogastric administration may be better tolerated. An antiemetic may be needed.
4. If a nasogastric or orogastric tube is used for MDAC administration, time should be allowed for the last dose to pass through the stomach before the tube is removed. Suctioning the tube itself before removal may prevent subsequent activated charcoal aspiration.

MDAC = multiple-dose activated charcoal.

Further clinical and toxicokinetic studies concerning MDAC are needed to establish an optimal dosing regimen and to confirm an effect on relevant endpoints. From available data discussed earlier, the dosing and most appropriate dosing intervals should be considered in each individual overdose case including compliance and clinical challenges from complications (eg, emesis and vomiting). Readers are referred to *Antidotes in Depth: A1* for a more detailed discussion of single-dose activated charcoal and MDAC therapy.

WHOLE-BOWEL IRRIGATION

Whole-bowel irrigation represents a method of purging the GI tract in an attempt to expeditiously achieve gut clearance and prevent further absorption of xenobiotics. This is achieved through the oral or nasogastric administration of large amounts of an osmotically balanced polyethylene glycol electrolyte lavage solution (PEG-ELS). WBI was subjected to a thorough literature review, which was published as a revised position statement in 2004.²⁰⁸ The position statement was unable to establish a clear set of evidence-based indications for the use of WBI because no clinical outcome studies have ever been performed. When experimental, theoretical, and anecdotal human experience is considered, the use of WBI with PEG-ELS can be supported for patients with potentially toxic ingestions of sustained-release pharmaceuticals and substantial amounts of metals. Other indications include the ingestion of large amounts of a xenobiotic with a slow absorptive phase in which morbidity is expected to be high, the ingested xenobiotic is not adsorbed by activated charcoal, and other methods of GI decontamination are unlikely to be either safe or beneficial.²⁰⁸ The removal of packets of xenobiotics from body packers can be considered a unique indication for WBI.^{22,215}

Whole-bowel irrigation cannot be applied safely if the GI tract is not intact; there is an adynamic or obstructive ileus; in the presence of significant GI hemorrhage; or in patients with inadequate airway protection, uncontrolled vomiting, or consequential hemodynamic instability that compromises GI function or integrity.^{56,208} Compliance may be an issue because 1 to 2 L/h of PEG-ELS is required for rapid cleansing. These large volumes can be facilitated when the solution is administered via a nasogastric tube.¹³⁶ Additionally, in vitro, the combination of WBI and activated charcoal decreases the adsorptive capacity of activated charcoal or increases the desorption of xenobiotic from activated charcoal,^{17,99,139} especially when the WBI solution is premixed with activated charcoal.¹³⁹ Activated charcoal should therefore be administered immediately after the WBI procedure, rather than simultaneously.

Results from volunteer studies often offer extreme variability in results,^{127-129,138} and significant variations are noted when individual subjects are simultaneously given three different sustained release xenobiotics.¹²⁹ In one study, nine volunteers took sustained-release preparations of 200 mg of carbamazepine, 200 mg of theophylline, and 120 mg of verapamil, and 1 hour after ingestion, they were assigned to 25 g of activated charcoal followed by WBI, 1 L/h PEG-ELS, 25 g of activated charcoal, or water (200 mL). When the combination therapy was compared with activated charcoal alone, it was not more efficient at reducing pharmacokinetic parameters such as AUC (0–24 hours) and C_{\max} (maximum concentration) for carbamazepine and theophylline, but for verapamil, the combination therapy was more effective than activated charcoal alone.¹²⁹ WBI could not be demonstrated to significantly reduce the AUC for sustained-release acetaminophen (75 mg/kg) compared with control participants in a volunteer study in which WBI was initiated 30 minutes after drug ingestion.¹³⁸ In this study, a capsule containing radiopaque markers, which was given simultaneously with acetaminophen, reached colon more rapidly and in a “collected cluster” on the day of WBI administration compared with the control when the markers were spread throughout the GI tract.

In both of these studies, therapeutic or nontoxic doses of pharmaceuticals were used as marker xenobiotics. In actual

overdoses, the pharmacokinetic properties of pharmaceuticals and the effects of decontamination may differ substantially. As mentioned earlier, study designs using activated charcoal and small doses of xenobiotics tend to bias the study toward a benefit of activated charcoal. In an overdose scenario, when the adsorptive capacity of activated charcoal may be exceeded, it is intuitive that the benefits of other modalities would be more evident.

Pharmacokinetic and pharmacodynamic evaluation in venlafaxine-overdosed patients showed that compared with activated charcoal alone, combination therapy of WBI and activated charcoal might be more beneficial based on decreased venlafaxine bioavailability (29% reduction), increased venlafaxine clearance (35% increase), and lower venlafaxine peak concentrations¹²⁸ and resulted in a decreased probability of venlafaxine-induced seizures (odds ratio {OR}, 0.25 for the combination therapy vs 0.48 for activated charcoal alone).¹²⁷

A small, retrospective, descriptive case series of 16 body packers treated with WBI supports the safety of WBI for body packers. Although the complication rate was reported as 12.5% (two of 16), these complications were not serious. One case of mild cocaine toxicity resulted from leakage, and one heroin body packer had to undergo surgery because of retained packages. There was no correlation between the dose of PEG-ELS, drug type, or packet quantity and length of hospital stay. Because there was no control group, it is not possible to evaluate whether WBI influenced any clinical outcome.⁷¹ Clearance of cocaine packets was performed using PEG-ELS WBI in 33% of 61 verified body packers judged not to be able to clear the packets from their gut. A dosage regimen of 1.5 L/h PEG-ELS was continued until all packets had passed, and there was no limit on the total volume given.²²

Whole-bowel irrigation has been used to treat overdoses in pregnant women and children. Two such cases involved iron overdoses in women during the second and third trimesters of pregnancy; both women were treated successfully and without complications.^{220,228} Pediatric case reports describe combined WBI with succimer therapy⁴⁷ and eventually colonoscopic removal of ingested lead pellets.^{47,91} Abdominal radiographs showed two small lead pellets, which WBI failed to remove, therefore requiring endoscopic removal.⁴⁷ Seven days of WBI, however, was ineffective in the removal of approximately 800 ingested lead pellets, which necessitated removal by colonoscopy.⁹¹ Several reports support the use of WBI in children, including an intentional ingestion of mercury,¹⁸⁹ two pediatric body packers,²¹⁶ and a 16 month-old boy who had ingested a significant amount of iron.²³² In the latter case, despite WBI, the iron bezoar was not removed, treatment was eventually stopped, and the bezoar was expelled after a normal diet was resumed.²³²

The current evidence for the clinical efficacy of WBI is divergent, depending on the xenobiotic and its formulation. Additional case reports and series demonstrate the overall safety of WBI as well as some beneficial effects on secondary endpoints, but the benefits remain generally theoretical. The evidence for simultaneous administration of activated charcoal with WBI is contradictory. Although there is little doubt that PEG-ELS reduces the adsorptive capacity of activated charcoal in vitro, it is unclear if this effect has any clinical significance.

The indications for WBI with PEG-ELS are patients with potentially toxic ingestions of sustained-release pharmaceuticals, xenobiotic ingestions with slow absorptive phases when morbidity is expected to be high, and foreign body ingestions. The combination of WBI and activated charcoal should be considered when adsorption of the ingested xenobiotic to activated charcoal is expected to be high. Other uses of WBI remain theoretical because the only support for the efficacy comes from surrogate markers and anecdotal experience. Table 8–7 summarizes the indications and contraindications for WBI.

TABLE 8–7. Whole-Bowel Irrigation: Indications and Contraindications

<i>Indications</i>	<i>Contraindications</i>
Potentially toxic ingestions of sustained-release drugs	Airway protective reflexes are absent or expected to become so in a patient who has not been intubated.
Ingestion of a toxic amount of a xenobiotic that is not adsorbed to activated charcoal when other methods of GI decontamination are not possible or not efficacious	GI tract is not intact. There are signs of ileus, obstruction, significant GI hemorrhage, or hemodynamic instability that might compromise GI motility.
Removal of illicit drug packets from body packers	Persistent vomiting Signs of leakage from cocaine packets (indication for surgical removal)

GI = gastrointestinal.

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CATHARTICS

At present, there is no indication for the routine use of cathartics as a method of either limiting absorption or enhancing elimination. A single dose can be given as an adjunct to activated charcoal therapy when there are no contraindications and constipation or an increased GI transit time is expected. Multiple-dose cathartics should never be used, and magnesium-containing cathartics should be avoided in patients with kidney disease (Antidotes in Depth: A2).

SURGERY AND ENDOSCOPY

Surgery and endoscopy are occasionally indicated for decontamination of poisoned patients. As might be expected, no controlled studies have been conducted, and potential indications are based largely on case reports and case series. A prospective, uncontrolled series of 50 patients with cocaine packet ingestion was published more than 20 years ago.³⁵ The patients were conservatively managed and only underwent surgery if there were signs of leakage or mechanical bowel obstruction. Bowel obstruction occurred in three patients, who promptly underwent successful emergency laparotomy; another six patients chose elective surgery. The authors concluded that body packers should be treated conservatively and only operated on for xenobiotic leakage or bowel obstruction.³⁵ A similar study performed a 16-year retrospective analysis of all body packers treated in a single center.¹⁹⁴ Of the 2880 body packers who were identified, 63 (2.2%) developed symptoms of severe cocaine toxicity after rupture of a package, 43 of the 63 symptomatic patients (68%) died before surgery could be initiated, and 20 (32%) underwent emergency laparotomy to remove the drug packets and survived. A more recent report described two body packers who successfully underwent surgery to remove drug packets. In one case, the indications were rupture and signs of cocaine toxicity. In the other case, the indication for surgery was bowel obstruction.¹⁶⁵ Because most packages do not spontaneously rupture, mechanical obstruction is probably the most common reason for surgical removal of ingested drug packets.²¹⁵ Leakage from heroin-containing packages can usually be managed by naloxone infusion, but the lack of antidote when cocaine packages rupture necessitates surgery (Special Considerations: SC5).²¹⁵

Over the years, a few case reports have presented mixed results for the endoscopic removal of drug packets or pharmacobezoars from the stomach.^{41,60,200,204,215} At present, this method is not commonly recommended because of concerns about packet rupture. However, under exceptional circumstances, there is certainly a precedent for attempting this procedure in a highly controlled setting such as an ICU or operating room.

In rare cases of massive iron overdoses when emesis, orogastric lavage, and gastroscopy failed or were estimated to result in an insufficient treatment outcome, gastrotomy was performed. The significant clinical improvement and postoperative recovery indicated that surgery in these particular cases was the correct approach.^{73,89,171} In a case of zinc toxicity resulting from massive chronic coin ingestion, laparotomy and gastrotomy proved essential to remove the more than 270 coins ingested¹⁷⁰ (Chap. 103).

OTHER ADJUNCTIVE METHODS USED FOR GASTROINTESTINAL DECONTAMINATION

Other xenobiotics, such as cholecystokinin, have been considered as adjuncts to standard measures for GI decontamination.^{68,97} Pharmaceuticals that either speed up GI passage or slow down gastric emptying have been administered in an attempt to minimize the absorption of a xenobiotic. In all cases, the results have been negligible, and the potential risks of administering additional pharmacologically active xenobiotics to an already poisoned patient seem to outweigh any benefit.^{9,233} Interventions that reduce the absorption of xenobiotics from the GI tract other than activated charcoal have also been studied, including sodium polystyrene sulphonate for lithium^{23,78,138-140,181,213} or thallium overdose.¹⁰⁰ Human studies showed minimal decreased absorption and increased clearance of lithium when sodium polystyrene sulphonate was administered.^{78,181} Likewise, case reports describe the use of the lipid-lowering resins cholestyramine and colestipol to interrupt the enterohepatic circulation of digoxin, digitoxin, and chlordane to increase elimination.^{21,76,120,175} With the increased use of activated charcoal and availability of digoxin-specific Fab fragments, indications for lipid-lowering resins for cardioactive steroid ingestions seem obsolete. Studies on clay products in vitro have demonstrated a lower efficacy compared with activated charcoal and activated charcoal-kaolin products in the adsorption of Nerium oleander toxins.²¹²

GENERAL GUIDANCE

Only a few studies provide guidance based on meaningful clinical endpoints for GI decontamination. Pharmacokinetic and pharmacodynamic parameters were introduced and systematically evaluated in human venlafaxine, citalopram,

escitalopram, and quetiapine overdose cases,^{107-109,127,128} increasingly popular pharmaceuticals known to cause central nervous system and cardiac toxicity. Cohort studies^{107-109,127,128} have recently evaluated the effect of GI decontamination with the aim to predict cardiotoxicity and the effects of the GI decontamination method chosen in real-life situations that are often inconsistent with the recommendations of the position papers.^{43,125,209,225,226} In a cohort of 436 venlafaxine overdose occasions, activated charcoal increased venlafaxine clearance and decreased the probability of seizures.^{127,128} Similarly, 77 escitalopram patient overdoses were used to develop a pharmacokinetic–pharmacodynamic model that predicted the probability of having abnormal QT as a surrogate for torsade de pointes.²³⁰ In this model, activated charcoal decreased the bioavailability by 31% and reduced the relative risk reduction of prolonged QT interval by 35% after the ingestion of 200 mg of escitalopram or more.²³⁰

The trends in GI decontamination have dramatically shifted toward less intervention over the years. In 2011, of the 2,334,004 human exposure reported to the American Association of Poison Control Centers,³¹ it is remarkable that only 64,866 patients were given single-dose activated charcoal, 1904 were given MDAC, 4126 underwent lavage, and 2040 received WBI. Similar trends are reported elsewhere with no apparent worsening of outcome.¹⁵ These trends in practice noted reflect the overall combined philosophy of the position statements, which are applicable to the vast majority of poisoned patients. They highlight the benign nature of many exposures and the benefits of good supportive care in the typical patient in whom the interventions of decontamination represent more risk than benefit. In contrast, the survey mentioned on the first page of this chapter of recommendations for a theoretical patient with a serious enteric-coated aspirin overdose reveals less consensus in that 36 different courses of action were proposed for the same patient—a situation in which nonintervention may have greater risk to the patient than decontamination. Most of the poison centers and toxicologists did, however, recommend at least one dose of activated charcoal.¹¹⁷ This distinction serves as a reminder that the existing studies and consensus statements cannot be applied to all cases and that a lack of data produces significant uncertainty in choices for GI decontamination in either atypical or severely poisoned patients.⁹⁸

It is essential to note that only one study has ever demonstrated a survival advantage for any form of GI decontamination of poisoned patients.⁵⁹ Its unique design, involving a cohort of patients with life-threatening toxicity, forces a reassessment of all previous and subsequent literature and confirms that the principles of decontamination are sound. It also suggests that the failure of most studies to demonstrate a benefit results not from a failure of the techniques used but from applying decontamination techniques to subsets of patients who were likely to have good outcomes regardless of intervention.

SUMMARY

- The approach to GI decontamination needs to be more individualized than previously thought. No decontamination method is completely free of risks. The indications and contraindications for GI decontamination must be well defined for each patient, and the method of choice must depend largely on what was ingested, how much was ingested, who ingested it, and when it was ingested.
- Evidence now points away from the routine GI decontamination of most patients presenting to an ED with an oral pharmaceutical drug overdose.
- A single dose of activated charcoal alone will be sufficient in moderate-risk patients, and only in a small subset of exceptionally high-risk patients will the benefit of orogastric lavage outweigh the risks.
- Orogastric lavage as a single intervention is reserved for cases in which the ingested xenobiotic is not adsorbed by activated charcoal and there is reason to believe that the ingested xenobiotic is both life threatening and still in the stomach.
- MDAC and WBI have narrowly defined indications, which may broaden in the future as more studies focus on subsets of significantly poisoned patients.
- The absolute time frame for when decontamination is indicated depends on many factors, such as the rate of gastric emptying, the rate of xenobiotic absorption, and the possibility of enterohepatic and enteroenteric recirculation. The commonly stated short time frame of up to 1 hour postingestion for intervention is most likely an artificially constructed evidence-free time limitation and the potential benefits associated with GI decontamination after a potentially serious ingestion.

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A1 ANTIDOTES IN DEPTH

Activated Charcoal

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INTRODUCTION

Activated charcoal (AC) is an excellent nonspecific adsorbent. Understanding AC's role in poison management is established by the integration of pharmacologic data, controlled volunteer trials, studies in heterogeneous patients with overdose or poisoning, and clinical experience.²⁴ AC should be considered for a poisoned or overdosed patient after a risk-to-benefit assessment of the presumed ingested substance and patient-specific factors and circumstances.¹¹ Benefits include preventing absorption or enterohepatic recirculation of a potentially toxic xenobiotic; risks include vomiting and subsequent aspiration pneumonitis. A detailed discussion of the merits of AC as a decontamination strategy is presented in Chap. 8.

HISTORY

Activated charcoal, a fine, black, odorless powder, has been recognized for more than two centuries as an effective adsorbent of many substances. Organic chemist Scheele's first use of charcoal to absorb gases in 1773 was followed by Lowitz's use of charcoal with colored liquids in 1791.^{6,84} In 1830, the French pharmacist Touery demonstrated AC's powerful adsorbent qualities by ingesting several lethal doses of strychnine mixed with AC in front of colleagues, suffering no ill effects.⁶ An American physician, Holt, first used AC to save a patient from mercury bichloride poisoning in 1834.^{6,84} However, it was not until the 1940s that Andersen began to systematically investigate the adsorbency of AC and unquestionably demonstrate that AC is an excellent, broad-spectrum gastrointestinal (GI) adsorbent.⁶⁻⁸

PHARMACOLOGY

Chemistry and Preparation

Activated charcoal is produced in a two-step process, beginning with the pyrolysis of various carbonaceous materials such as wood, coconut, petroleum, or peat. This processing is followed by treatment at high temperatures (600°–900°C) with a variety of oxidizing (activating) agents such as steam, carbon dioxide, or acids to increase adsorptive capacity through formation of an internal maze of pores.^{26,56,112} Typical AC surface areas average 800 to 1200 m²/g.¹¹⁰

Mechanism of Action

The actual adsorption of a xenobiotic by AC is believed to rely on hydrogen bonding, ion–ion, dipole, and van der Waals forces, suggesting that most xenobiotics are best adsorbed by AC in their dissolved, nonionized form.²⁶

Pharmacokinetics

Activated charcoal is pharmacologically inert and unabsorbed. Its GI transit time is influenced by the type and quantity of an ingested xenobiotic, fasting and hydration status, muscarinic and opioid receptor xenobiotic properties, perfusion, and the use of associated cathartics or evacuants, among other factors. In six volunteers acting as their own controls, AC alone or administered with sodium chloride, sodium sulfate, magnesium sulfate, or a proprietary cathartic “salt” (36.7% anhydrous citric acid, 17.65% magnesium sulfate, and 45.6% sodium bicarbonate), the GI transit times to fecal evacuation were 29.3 ± 1.2 hours, 24.4 ± 1.2 hours, 15.4 ± 3.0 hours, 17.3 ± 1.9 hours, and 17.5 ± 2.3 hours, respectively.¹¹¹ In 59 overdose patients ingesting acetaminophen (APAP), carbamazepine, cyclic antidepressants, opioid–APAP combinations, and phenytoin who were administered 25 to 50 g of AC with 70% sorbitol solution, median half-lives for gastric emptying, small intestinal transit, and orocecal transit were 82 minutes, 180 minutes, and 210 minutes, respectively.² When these patients are compared with historical controls given AC without sorbitol,¹ the gastric emptying times (158 vs. 58 minutes), small intestinal transit times (218 vs. 75 minutes), and orocecal transit times (300 vs. 90 minutes) in carbamazepine

ingestions and small intestinal transit times (180 vs. 135 minutes) and orocecal transit times (240 vs. 180 minutes) in APAP ingestions were significantly reduced. These subgroups helped power a statistically significant decrease in orocecal transit times from 270 to 210 minutes for the entire overdose group when 70% sorbitol was added to AC.

Pharmacodynamics

The adsorption rate to AC depends on external surface area, and the adsorptive capacity depends on the far larger internal surface area.^{26,27,104} The adsorptive capacity may be modified by altering the size of the pores. Current AC products have pore sizes that range from 10 to 1000 angstroms (Å), with most of the internal surface area created by 10- to 20-Å-sized pores.^{26,28} Most xenobiotics are of moderate molecular weight (100–800 Da) and adsorb well to pores in the range of 10 to 20 Å. Mesoporous charcoals with a pore size of 20 to 200 Å have a greater capacity to adsorb larger xenobiotics as well as those in their larger hydrated forms.⁸¹

When the AC surface area is large, the adsorptive capacity is increased, but affinity is decreased because van der Waals forces and hydrophobic forces diminish.¹⁴³ According to the Henderson-Hasselbalch equation, weak bases are best adsorbed at basic pHs, and weak acids are best adsorbed at acidic pHs. For example, cocaine, a weak base, binds to AC with a maximum adsorptive capacity of 273 mg of cocaine per gram of AC at a pH of 7.0; this capacity is reduced to 212 mg of cocaine per gram of AC at a pH of 1.2.⁸⁰ AC binds amitriptyline hydrochloride with adsorption capacities of 120 and 100 mg per gram of AC in simulated gastric and intestinal fluids, respectively.¹⁴² The adsorption to AC of a weakly dissociated metallic salt such as mercuric chloride (HgCl₂) decreases with decreasing pH because the number of complex ions of the type HgCl₃ and HgCl₄ increases, and the number of electroneutral molecules (HgCl₂) is reduced.⁷ Nonpolar, poorly water-soluble organic substances are more likely to be adsorbed from an aqueous solution than polar, water-soluble substances.²⁶ Among the organic molecules, aromatics are better adsorbed than aliphatics; molecules with branched chains are better adsorbed than those with straight chains; and molecules containing nitro groups are better adsorbed than those containing hydroxyl, amino, or sulfonic groups.²⁶

Activated charcoal decreases the systemic absorption of most xenobiotics, including APAP, aspirin, barbiturates, cyclic antidepressants, glutethimide, phenytoin, theophylline, and most inorganic and organic materials.^{41,100,114} Notable xenobiotics not amenable to AC are the alcohols, acids and alkalis, iron, lithium, magnesium, potassium, and sodium salts.⁴⁵ Although AC's binding to cyanide is less than 4%, the toxic dose is small, and 50 g of AC would theoretically be able to bind more than 10 lethal doses of potassium cyanide. AC is capable of rapidly removing volatile anesthetic gases such as isoflurane, sevoflurane, and desflurane from anesthetic breathing circuits, which is potentially important in patients who are susceptible to or develop malignant hyperthermia.¹⁵

Activated charcoal's efficacy is directly related to the quantity administered. The effect of the AC-to-drug ratio on adsorption was demonstrated both in vitro and in vivo with para-aminosalicylate (PAS). In vitro, the fraction of unadsorbed PAS decreased from 55% to 3% as the AC-to-PAS ratio increased from 1:1 to 10:1 at a pH of 1.2.¹⁰⁸ This study provides the best scientific basis for the 10:1 AC-to-drug ratio dose typically recommended. In human volunteers, as the AC-to-PAS ratio increased from 2.5:1 to 50:1, the total 48-hour urinary excretion decreased from 37% to 4%.¹⁰⁸ Presumably this occurred because more of the PAS was adsorbed by AC in the lumen of the GI tract rather than being absorbed systemically. These same studies demonstrate AC saturation at low ratios of AC to drug and argue for a 10:1 ratio of AC to xenobiotic.

In a meta-analysis of 64 controlled volunteer studies, a sigmoid dose–response curve described the percentage reduction in drug exposure provided by AC: reduction of drug exposure (%) = $8.95 + [86.79 / (1 + 10^{(0.9861 - \log AC/drug)})]$.⁶⁴ According to this formula, AC:drug ratios of 1:1, 5:1, 10:1, 20:1, 25:1, and 50:1 would reduce drug exposures by 9.0%, 30.2%, 44.6%, 58.9%, 62.9%, and 73.0%, respectively. In a subsequent study of volunteers ingesting 50 mg/kg of APAP, reducing a 1-hour postingestion 50-g AC dose to 25 or 5 g caused the APAP area under the concentration versus time curve (AUC) to increase by 23.6% and 59.0%, respectively.⁴⁸

In vitro studies demonstrate that adsorption begins within about 1 minute of AC administration but may not achieve equilibrium for 10 to 25 minutes.^{27,100} AC's clinical efficacy is inversely related to the time elapsed after ingestion and depends largely on the rate of absorption of the xenobiotic. According to a meta-analysis of volunteer studies, the median reductions of drug exposure when AC was administered at 0 to 5 minutes, 30 minutes, 60 minutes, 120 minutes, 180 minutes, 240 minutes, and 360 minutes after ingestion were 88.4%, 48.5%, 38.4%, 24.4%, 13.6%, 27.4%, and 11%, respectively.⁶⁴ Early AC administration is more important with rapidly absorbed xenobiotics, in which AC functions to prevent xenobiotic absorption by achieving rapid adsorption in the GI tract. After a xenobiotic is systemically absorbed or parenterally administered, AC may still enhance elimination through a mechanism referred to as GI dialysis.

Desorption (drug dissociation from AC) may occur, especially for weak acids, as the AC–drug complex transits the stomach and intestine and as the pH changes from acidic to basic.^{42,107,139} Whereas strongly ionized and dissociated salts, such as sodium chloride and potassium chloride, are poorly adsorbed, nonionized or weakly dissociated salts, such as

iodine and mercuric chloride, respectively, are adsorbed. Binding of γ -hydroxybutyrate (800 mg) to AC (10 g) decreased from 84.3% to 23.3% when exchanging simulated gastric for intestinal fluid.⁹⁹ Diminished AC adsorptive capacity in the intestinal lumen may also occur because of AC's rapid adsorption of intestinal fatty acids, which cover rapidly the surface of carbon granules.⁸⁴ Desorption may lead to ongoing systemic xenobiotic absorption over days. In this case, the apparent elimination half-life of the xenobiotic increases, but peak concentrations remain unaffected.¹⁰⁵ The clinical effects of desorption can be minimized by providing sufficient AC to overcome the decreased affinity of the xenobiotic secondary to pH change, such as by using multiple-dose AC.^{68,90,103,115,132} Although ethanol and other solvents such as polyethylene glycol (PEG) are minimally adsorbed by AC, they may decrease AC adsorptive capacity for a co-ingested xenobiotic by competing for AC binding.^{12,105,107,109}

Concomitant Administration of Activated Charcoal with Cathartics or Evacuants

Cathartics are often used with AC; however, evidence suggests that AC alone is comparably effective to AC plus a single dose of cathartic (sorbitol or magnesium citrate).^{3,68,85,86,90,98,104,113} If a cathartic is used, it should be used only once. Repeated doses of magnesium-containing cathartics are associated with hypermagnesemia,^{94,134} and repeated doses of any cathartic are associated with dehydration, hypotension, and severe or fatal fluid and electrolyte derangements.⁴⁰ AC with sorbitol is not recommended for children younger than one year of age.¹¹²

Whole-bowel irrigation (WBI) with PEG electrolyte lavage solution may significantly decrease the in vitro and in vivo adsorptive capacity of AC,⁵⁴ depending on the individual xenobiotic and its formulation.^{10,74} The most likely explanation is competition by PEG for the surface of the AC for solute adsorption.

Related Agents

A superactivated charcoal with a surface area approximately double the current AC formulations is demonstrated in both in vitro and in vivo studies to have greater maximum adsorptive capacity.^{27,124} Endogenous enteric uremic toxins such as indoxyl sulfate are adsorbed by porous carbon microsphere compounds (eg, AST-120) to mitigate glomerular hypertrophy, interstitial fibrosis, and progressive chronic kidney disease.¹²⁹

ROLE OF ACTIVATED CHARCOAL IN GASTROINTESTINAL DECONTAMINATION

Single-Dose Activated Charcoal

It is difficult to assess the efficacy of single-dose AC (SDAC) in a large, single-institution, prospective study involving consecutive adults receiving 50 g of AC for self-poisonings. This study which excluded lithium, iron, heavy metals, monoamine oxidase inhibitors, digoxin, formaldehyde, mushrooms, APAP, methanol, or sustained-release products because SDAC was used in all symptomatic patients, who also received some form of GI intervention.⁹² Not surprisingly, a beneficial effect of SDAC on outcome measures could not be demonstrated in asymptomatic patients. Similarly, a study of routine SDAC administration after oral overdose consisting primarily of benzodiazepines, APAP, and selective serotonin reuptake inhibitors could not demonstrate differences in mortality, length of stay, vomiting, or intensive care admissions.²⁹ A prospective trial of 876 patients comparing SDAC alone with SDAC plus gastric emptying was unable to demonstrate a difference in outcomes, with the exception of patients presenting within one hour of ingestion, although this difference was not sustained after being adjusted for severity.¹¹⁸ However, when evaluating SDAC alone, a meta-analysis of 64 controlled volunteer studies found significant reductions in ingested xenobiotic amounts when SDAC was provided in appropriate quantity (eg, 10:1) and within 240 minutes of exposure.⁶⁴

Research subsequent to this meta-analysis has sustained SDAC's primarily pharmacokinetic advantage, although some improvement in clinically important endpoints has been demonstrated. A healthy volunteer study in 12 patients in which SDAC was provided 15 minutes after supratherapeutic APAP ingestions (60 mg/kg) reduced APAP absorption by a mean of 41%.¹⁴⁵ In nine human volunteers ingesting 5 g of APAP and 0.5 mg/kg of oxycodone, 50 g of SDAC at 1, 2, or 3 hours reduced the APAP AUC by 43%, 22%, and 15%, respectively.⁹⁷ Concentrations of lamotrigine (100 mg), oxcarbazepine (600 mg), and oxcarbazepine's active metabolite, 10,11-dihydro-10-hydroxy-carbamazepine in six volunteers were reduced by 42%, 97.2%, and 95.8%, respectively, by 50 g of AC provided 30 minutes after ingestion.⁶⁹

In a pharmacokinetics and pharmacodynamics evaluation of escitalopram overdose patients, SDAC reduced the absorbed fraction by 31% and reduced the risk of QT prolongation by approximately 35% for escitalopram doses above 200 mg.¹⁴⁴ In 319 patients with 436 venlafaxine overdoses, SDAC or SDAC with WBI significantly decreased the odds of seizure to 0.48 and 0.25, respectively, compared with no decontamination.⁷³ In 176 patients presenting with 286 separate quetiapine overdoses, SDAC administration within 2 hours reduced the probability of intubation by 7% for a 2-g ingestion

and by 17% for a 10-g ingestion, although time to extubation was unaffected.⁶²

Multiple-Dose Activated Charcoal

Multiple-dose AC (MDAC) functions to prevent the absorption of xenobiotics that are slowly absorbed from the GI tract and to enhance the elimination of suitable xenobiotics that have already been absorbed. MDAC decreases xenobiotic absorption when large amounts of xenobiotics are ingested and dissolution is delayed (eg, masses, bezoars), when xenobiotic formulations exhibit a delayed or prolonged release phase (eg, enteric coated, extended release), when GI motility is impaired because of co-ingestants, or when reabsorption can be prevented (eg, enterohepatic circulation of active xenobiotic, active metabolites, or conjugated xenobiotic hydrolyzed by gut bacteria to active xenobiotic).

MDAC's ability to enhance elimination after absorption had already occurred was first reported in 1982.¹³ This report concluded that orally administered MDAC enhanced the total body clearance (nonrenal clearance) of six healthy volunteers given 2.85 mg/kg of body weight of intravenous (IV) phenobarbital.¹³ The serum half-life of phenobarbital decreased from 110 ± 8 to 45 ± 6 hours. An editorial suggested that MDAC enhanced the diffusion of phenobarbital from the blood into the GI tract and trapped it there for later fecal excretion. In this manner, AC was said to perform as an "infinite sink," allowing for "gastrointestinal dialysis" to occur.⁷⁶ These findings were confirmed by studies in dogs and rats using IV aminophylline and shown to be independent of theophylline enterohepatic circulation.^{32,72,88} Subsequent studies using MDAC with IV aminophylline further extended these results to humans.⁵⁹ Using an isolated perfused rat small intestine, the concept of GI dialysis⁸⁸ was elegantly demonstrated because AC dramatically affected the pharmacokinetics of theophylline and produced a constant intestinal clearance that approximated intestinal blood flow.⁸⁸ In 114 hemodialysis patients who received a mean AC daily dose of 3.19 ± 0.81 g/day in three divided doses, mean serum phosphate concentrations decreased by 2.60 ± 0.11 mg/dL, further supporting the concept of "GI dialysis."¹⁴⁶

The toxicokinetic considerations underlying MDAC's ability to enhance elimination are similar to those involved in deciding whether hemodialysis would be appropriate for a given xenobiotic. Successful MDAC requires the xenobiotic to be in the blood compartment (low volume of distribution), have limited protein binding, and have prolonged endogenous clearance. Experimental evidence suggests a role for MDAC in the absence of available Prussian blue (Antidotes in Depth: A28) to treat thallium poisoning.⁵⁵ Although MDAC increases to varying degrees the elimination of amitriptyline, cyclosporine,⁵⁷ carbamazepine,^{16,18,147} dapsone,¹⁰² digitoxin,^{30,117} nadolol,³⁵ nortriptyline, phenobarbital,¹¹⁹ phenylbutazone,¹⁰¹ propoxyphene,⁶⁶ quinine,²⁴ salicylate,^{53,70} and theophylline,^{14,79,138} its clinical utility remains to be defined.^{24,67,137}

An analysis of 28 volunteer studies involving 17 xenobiotics was unable to correlate the physical chemical properties of a particular xenobiotic with MDAC's ability to decrease the plasma half-life of that xenobiotic.²¹ Although the half-life was not thought to be the best marker of enhanced elimination, it was the only parameter consistently evaluated in these exceptionally diverse studies. The xenobiotics with the longest intrinsic plasma half-lives seemed to demonstrate the largest percent reduction in plasma half-life when MDAC was used. A subsequent animal model with therapeutic doses of four simultaneously administered IV xenobiotics (APAP, digoxin, theophylline, and valproic acid) clarified the role of pharmacokinetics on MDAC's effectiveness.²³ Theophylline, APAP, and valproic acid all have small volumes of distribution. However, of the three, only valproic acid is highly protein bound at the doses used, which probably accounted for MDAC's inability to increase its clearance while increasing clearance of the three other xenobiotics. MDAC's most rapid and dramatic effect was on theophylline clearance. Large volumes of distribution alone may not exclude MDAC benefit. Although digoxin has a large volume of distribution, it requires several hours to distribute from the blood to the tissues. MDAC is beneficial as long as the digoxin remains in the blood compartment and distribution is incomplete. However, volunteer studies do not accurately reflect the overdose situation⁸⁹ in which saturation of plasma protein binding, saturation of first-pass metabolism, and acid-base disturbances may make more free xenobiotic available for an enteroenteric effect and therefore more amenable to MDAC use.

In one case series of infants with aminophylline and theophylline overdoses, MDAC appeared to reduce theophylline half-lives (2–12 hours) compared with historical values.¹³⁰ MDAC added as an adjunct to phototherapy in neonatal hyperbilirubinemia produced a significantly greater decline in bilirubin concentrations than in those receiving phototherapy alone.⁵ In a randomized clinical study, phenobarbital overdose patients were given SDAC or MDAC.¹¹⁹ Although the phenobarbital half-life was significantly decreased in the MDAC group (36 vs. 93 hours), the length of intubation time required by each group did not differ from one another. This study was criticized for small size, unevenly matched groups, and focus on a single endpoint (extubation) potentially dependent on factors other than patient condition (eg, the time of day). In 15 adult patients with supratherapeutic phenytoin concentrations, MDAC reduced the time to phenytoin concentration less than 25 mg/L from 41.1 to 19.3 hours, although clinical endpoints were again unchanged.¹³³ A compelling demonstration of MDAC's benefits in the overdose setting comes from a study performed in Sri Lanka in patients with severe cardiac toxicity caused by intentional overdose with yellow oleander seeds.³¹ An initial AC dose of 50 g was administered to all patients, who were then randomized to 50 g of AC every 6 hours for 3 days or placebo. There

were statistically fewer deaths and fewer life-threatening dysrhythmias in the MDAC group. Subsequent randomized, controlled trials further evaluated no AC, SDAC, and MDAC in self-poisoned patients. In 104 patients ingesting yellow oleander seeds, despite erratic and prolonged absorption, SDAC and MDAC significantly and equivalently reduced cardiac glycoside 24-hour mean residence time (which quantifies the time course of a xenobiotic through the body) from 11.21 ± 1.55 hours (no AC) to 10.36 ± 1.14 hours (SDAC) and 10.20 ± 0.99 hours (MDAC), respectively, and apparent terminal half-life from 62.9 hours (no AC) to 33.9 hours (SDAC) and 32.3 hours (MDAC), respectively.¹²³ Despite this, neither SDAC nor MDAC reduced the mortality rate among 4629 randomized, poisoned patients.³⁶ About one-third of the patients had ingested yellow oleander seeds, and slightly less than one-third ingested pesticides. It is unclear how these trials apply to management in developed countries, where the use of antidotes such as digoxin-specific antibody fragments for cardioactive steroid poisoning and atropine and pralidoxime for organic phosphorous pesticide poisoning routinely complement GI decontamination, and the absorption kinetics of most prescription medications differ from the substances ingested in the trial.⁶³ A systematic review concluded that MDAC could enhance phenobarbital or primidone elimination in severe poisonings, although supportive care is the relevant clinical intervention.¹²²

Ultimately, the decision to administer SDAC or MDAC will need to balance the particular ingested xenobiotic, its quantity and the formulation; the xenobiotic's dose-response curve; SDAC's or MDAC's impact on this curve; the time since ingestion; co-ingestants; available antidotes, therapies, and medical support; severity of presentation; anticipated sequelae; patient cooperativity; and other patient-specific factors (eg, age) against potential adverse effects.^{63,110,135}

ADVERSE EFFECTS AND SAFETY ISSUES

Contraindications to AC include presumed GI perforation and the need for endoscopic visualization (eg, caustic ingestion). To prevent aspiration pneumonitis from oral AC administration, an airway assessment must occur and potential airway compromise be excluded. Subsequently, a risk-to-benefit assessment with regard to the need for airway protection and the need for AC should be made. Other considerations include a determination of adequate GI motility (appropriate bowel sounds to ensure peristalsis) and normal abdominal examination findings, and absent distension or signs of an acute abdomen. With compromised bowel function, AC should be withheld or delayed until the stomach can be decompressed to decrease the risk of subsequent vomiting and aspiration.

Although the use of AC is relatively safe, emesis, which typically occurs after rapid administration; constipation; and diarrhea frequently occur after AC administration.¹⁰⁴ Constipation and diarrhea are more likely to result from the ingestion itself than from the AC. However, black stools that are negative for occult blood, black tongues, and darkened mucous membranes are frequently observed. Serious adverse effects of AC include pulmonary aspiration of AC with or without gastric contents, leading to airway obstruction, acute respiratory distress syndrome, bronchiolitis obliterans, and death;^{9,39,44,46,50-52,65,91,100,112,116,131} peritonitis from spillage of enteric contents, including AC, into the peritoneum after GI perforation;⁸³ and intestinal obstruction and pseudo-obstruction, especially after repeated AC doses in the presence of either dehydration or prior bowel adhesions.^{19,47,78,93,121,148} Although a significant number of patients aspirate gastric contents before endotracheal intubation and AC administration,^{95,125} the incidence of AC aspiration after endotracheal intubation was reported to vary from 4% to 25%, depending on the nature of the study. Another retrospective investigation demonstrated a 1.6% incidence of aspiration pneumonitis in unselected overdosed patients. Altered mental status, spontaneous emesis, and tricyclic antidepressant overdose were associated risk factors; AC was not in itself a risk factor.⁶¹ The package insert warns against administration in patients with a genetic intolerance to fructose.¹¹²

Adverse Effects of Multiple-Dose Activated Charcoal

Complications observed with SDAC increase with MDAC. Other adverse effects of MDAC include diarrhea when multiple sorbitol-containing charcoal preparations are used, constipation, vomiting with a subsequent risk of aspiration, intestinal obstruction, and a reduction of serum concentrations of therapeutically used xenobiotics.^{34,93,100,116} One retrospective review of 834 patients receiving MDAC found clinically significant pulmonary aspiration in 0.6%, hypernatremia in 6.0%, and hypermagnesemia in 3.1%.³⁴ Multiple sorbitol-containing charcoal preparations may produce dehydration, hypotension, and potentially fatal electrolyte derangements, especially in children.^{40,96}

PREGNANCY AND LACTATION

Activated charcoal's pregnancy category is undetermined. The benefit of preventing absorption with AC should outweigh the risk of administration to the pregnant patient. The underlying elevated prevalence of nausea and vomiting in pregnancy⁷¹ might predispose pregnant patients to a potentially higher rate of vomiting, although this is speculative. AC has been safely administered to pregnant patients as part of poisoning management.^{22,87,126} Murine and lapine studies have not demonstrated any teratogenic risk.¹¹²

Activated charcoal's lack of absorption would not predispose it to breast milk excretion, although definitive safety in lactation has not been established.¹¹²

DOSING AND ADMINISTRATION

Activated charcoal should not be routinely administered to all poisoned or overdosed patients. SDAC should be administered when a xenobiotic is still expected to be available for adsorption in the GI tract and the benefit of preventing absorption outweighs the risk. The optimal SDAC dose is unknown.²⁴ However, most authorities recommend a minimum AC dose of 1 g/kg of body weight or a 10:1 ratio of AC to xenobiotic, up to an amount that can be tolerated by the patient and safely administered if the dose is known, which usually represents 50 to 100 g in adults. For some ingestions (eg, salicylate or APAP), a 10:1 ratio would be impracticable to achieve, although the 1-g/kg dose may still be efficacious. This is supported by volunteer studies of supratherapeutic ingestions.^{48,64} AC that is not premixed is best administered as a slurry in a 1:8 ratio of AC to suitable liquid, such as water or cola.

Prehospital Administration

Prehospital AC administration by emergency medical technicians and paramedics may expedite the administration after overdose.^{4,149} However, the costs of implementation of such a program would have to be weighed against the small number of patients who would actually benefit.⁶⁰ In a study simulating home administration in 50 young children, 86% readily drank the AC–water slurry, and 76% of them consumed 95% to 100% of the total dose.²⁰ Of seven children in a simulated home environment administered AC in regular cola, three drank 1 g/kg, two drank about half of this therapeutic dose, and the other two drank very little.¹²⁷ A prospective poison center case series demonstrated successful home AC administration. In this series, the median age of the patients was 3 years, and the median AC dose ingested was 12 g.¹³⁶ However, other attempts at getting children to ingest AC were not as successful. Difficulty was noted in 70% of attempts to administer a standard AC dose to children in the home setting.³³ A review of AC in the home suggested variable success depending on the parent and child.³⁸ A retrospective review of poisoned children concluded that those who were preannounced to an emergency department by the poison center received AC earlier (59 ± 34 minutes) than patients without a referral (71 ± 43 minutes).¹⁴⁰

Hospital Administration

Administration may be facilitated by offering children an opaque, decorated, covered cup and a straw.¹⁵⁰ AC's black color and gritty nature has led to the development of many formulations to improve palatability and patient acceptance. Bentonite, carboxymethyl cellulose, and starch^{49,98,128} are used as thickening agents, and cherry syrup, chocolate syrup, sorbitol, sucrose, saccharin, and ice cream have been used as flavoring agents.^{27,77,82,151} Most additives do not decrease the adsorptive capacity; however, improvement in palatability and acceptance has been minimal or nonexistent with all of these formulations.²⁶ Although a milk chocolate AC formulation evaluated by children was rated superior in palatability to standard AC preparations,³⁷ it was never marketed in the United States. A marketed cherry-flavored AC product was rated by adult volunteers as preferable over plain AC, and a statistically significant larger quantity of the flavored AC was ingested.²⁵ This difference was not maintained in adult overdosed patients; most patients consumed the entire bottle of AC independent of cherry flavoring. Cold cola was used to enhance palatability in volunteer children and adults. Children preferred regular cola over diet cola. The adults rated the cola–charcoal combination preferable to the plain charcoal.^{120,127} Other studies in adult overdosed patients compared different AC brands without additives or flavoring to determine the AC quantity typically ingested.^{17,43} In one study, approximately half of the 50 g of AC offered was ingested, and 7% of the patients vomited.¹⁷ In the other study, 60 g of AC as Liqui-Char or CharcoAid G was offered, and approximately 95% of each formulation was consumed in 20 minutes. There was no difference in the amount consumed even though the palatability of the granular form of AC (CharcoAid G) was rated higher.⁴³

Multiple-Dose Activated Charcoal Administration

An initial AC loading dose should be administered to adults and children in an AC-to-xenobiotic ratio of 10:1 or 1 g/kg of body weight (if the xenobiotic exposure amount is unknown). The correct AC dose and interval for multiple dosing, when it is indicated, is best tailored to the amount and dosage form of the xenobiotic ingested, the severity of the overdose, the potential lethality of the xenobiotic, and the patient's ability to tolerate AC. Benefit should always be weighed against risk. Doses of AC for multiple dosing have varied considerably in the past, ranging from 0.25 to 0.5 g/kg of body weight every 1 to 6 hours to 20 to 60 g for adults every 1, 2, 4, or 6 hours. Some evidence suggests that the total dose administered may be more important than the frequency of administration.^{58,141} In some cases, continuous nasogastric administration of AC can be used, especially when vomiting is a problem.^{42,106,141} After the initial AC loading dose of 1 g/kg, subsequent doses of

0.5 g/kg (~25–50 g in adults) every 4 to 6 hours for up to 12 to 24 hours would appear to be an appropriate regimen in most circumstances.

FORMULATION AND ACQUISITION

Activated charcoal may be supplied in bottles or tubes as a ready-to-use aqueous suspension in multiple doses formulations (eg, suspensions of 15 g, 25 g, and 50 g of AC at a fixed concentration of 208 mg/mL AC).¹¹² The AC suspension may also be premixed with sorbitol (eg, 25 and 50 g AC with 48 or 96 g of sorbitol to yield 208 mg/mL of AC and 400 mg/mL of sorbitol).¹¹² When not premixed, it is recommended to create a slurry of AC in a 1:8 ratio of AC to suitable liquid (eg, water, cola).

SUMMARY

- AC is a very effective, nonspecific adsorbent.
- Absent contraindications, AC should be of benefit to a patient with a potentially life-threatening ingestion of a xenobiotic adsorbable by AC that is expected to be present in the GI tract at the time of administration.
- MDAC is useful to prevent systemic absorption of xenobiotics with a prolonged absorptive phases such as an extended-release formulations.
- In the postabsorptive phase, MDAC may decrease the elimination half-lives of certain xenobiotics.
- Care must be taken to avoid pulmonary aspiration and intestinal obstruction when administering AC and MDAC.
- Home availability of AC should be encouraged in remote locations where prehospital care is not immediately available.^{74,75}

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A2 ANTIDOTES IN DEPTH

Whole-Bowel Irrigation and Other Intestinal Evacuants

Silas W. Smith and Mary Ann Howland

INTRODUCTION

To alter xenobiotic pharmacokinetics, the approach to a poisoned patient may include administration of gastrointestinal (GI) evacuants. Selected patients may benefit from minimizing systemic exposure by decreasing GI transit time and increasing rectal expulsion. The most effective process of evacuating the GI tract in poisoned patients is referred to as whole-bowel irrigation (WBI). WBI is typically accomplished using polyethylene glycol with a balanced electrolyte lavage solution (PEG-ELS). A detailed discussion of the merits of WBI in the context of various decontamination strategies is provided in [Chap. 8](#).

HISTORY

In 1625 while endeavoring to recover from febrile “Hungarian disease,” Johann Glauber drank from a well from which he later isolated sal mirabile, now known as sodium sulfate, Na_2SO_4 .⁴⁷ He advocated its use as a purgative and determined a synthetic production method.⁴⁷ In 1675, Nehemiah Grew first observed the presence of a purgative salt in the springs at Epsom, later determined to be magnesium sulfate.¹¹³ Phosphate of soda, called “tasteless purging salt,” was found in the urine by Hellot in 1737 and introduced into clinical practice as a purgative by George Pearson some 50 years later.¹⁰⁷ In 1882 to 1883, Hay reported on a series of experiments that provided the basis for the understanding of the mechanism of action of the saline cathartics. He identified the viscus as the main source of bowel fluid, which was secretory in nature, and established a dose–response principle of decreased time to stool as salt concentrations were increased.^{43,44} PEG was introduced in 1957 as a nonabsorbable marker for the study of human fat, carbohydrate, and protein absorption.¹⁵ Experimental studies of intestinal lavage in normal human subjects appeared in 1968.⁷⁸ In 1973, Hewitt and colleagues reported on WBI in clinical practice, their method of “whole-gut irrigation” with a solution of sodium chloride, potassium chloride, and sodium bicarbonate in distilled water to prepare the large bowel for surgery.⁴⁶ WBI was used therapeutically for poisoning in 1976 in a patient ingesting 300 lead airgun pellets who was unresponsive to oral magnesium sulfate purgation.¹⁴⁷

PHARMACOLOGY

Nomenclature

Xenobiotics that promote intestinal evacuation are referred to as laxatives, cathartics, purgatives, promotility agents, and evacuants. Depending upon dose, the same xenobiotic may accomplish some or all of these tasks, with differing side effect profiles. Laxatives promote a soft-formed or semifluid stool within 6 hours to 3 days. Cathartics promote a rapid, watery evacuation within 1 to 3 hours.¹¹⁹ The term purgatives relates the force associated with bowel evacuation. Evacuants are commonly used for pre-procedural bowel cleansing, with an onset of action of as little as 30 to 60 minutes, but typically require 4 hours for a more complete effect. Promotility agents stimulate GI motor function via the enteric nervous system via acetylcholine, serotonin, motilin, or intestinal chloride channels.

Laxatives are further classified into categories of bulk forming, softener or emollient, lubricant, stimulant or irritant, saline, hyperosmotic, and evacuant. Bulk-forming agents include high-fiber products such as methylcellulose, polycarbophil, and psyllium; softeners or emollients include docusate calcium. Mineral oil is the sole lubricant. None of these cathartics is used therapeutically in medical toxicology because their onset of action is delayed. Stimulant or irritant laxatives include anthraquinones (sennosides, aloe, and casanthranol), diphenylmethane (bisacodyl), and castor oil. Saline (meaning salt) cathartics, which include magnesium citrate, magnesium hydroxide, magnesium sulfate, sodium phosphate,

and sodium sulfate, are used infrequently. Hyperosmotic agents, generally nonabsorbable sugars and alcohols including sorbitol and lactulose, are occasionally considered in poisoned patients. The most common process of evacuating the intestinal tract in poisoned patients is WBI.

Chemistry and Preparation

Magnesium citrate ($C_6H_6MgO_7$) and magnesium sulfate ($MgSO_4$, “Epsom salt”) are water-soluble salts of magnesium; magnesium hydroxide ($Mg\{OH\}_2$, “milk of magnesia”) is insoluble.⁵⁶ Sodium sulfate can be prepared through purification of naturally occurring brine deposits or other manufacturing processes. Sodium phosphate is supplied as a combination of the monobasic monohydrate ($NaH_2PO_4 \cdot H_2O$) and dibasic anhydrous (Na_2HPO_4) forms. D-Sorbitol ($C_6H_{14}O_6$), an isomer of mannitol, is a hexitol naturally occurring in many fruits and is produced commercially by the reduction of glucose. Lactulose is a water-soluble, synthetic disaccharide, 4-O- β -D-galactopyranosyl-D-fructofuranose.

The addition reaction of ethylene oxide (C_2H_4O) to an ethylene glycol equivalent creates ethylene oxide polymerization into polyethylene glycol (PEG). The “n” in the molecular structure of PEG, $H-(OCH_2CH_2)_n-OH$ refers to the average number of repeating oxyethylene groups.⁶⁰ The number after PEG represents its average molecular weight (MW). PEG, also known as macrogol, has numerous medicinal applications. It can be conjugated to pharmaceuticals to delay vascular clearance (“PEGylation”), serve as a solvent in oral liquids and soft capsules, function as a nonalcohol solubilizer and diluent for liquid oral-dose medications, provide a base for medical ointment and cosmetics, and act as a base liquid for producing vapor in electronic cigarettes.¹⁰³ Low-molecular-weight PEG (eg, 300 or 400 Da), because of its advantageous solvent properties, is used to decontaminate phenol burns, although animal studies demonstrated the equal efficacy of copious (deluge) quantities of water.⁵¹ Higher-molecular-weight variants are used to promote laxation. Although PEG’s physical properties (eg, water solubility, hygroscopicity, vapor pressure, melting or freezing range, and viscosity) vary with MW and blending because of chain-length effects, the chemical properties are similar.¹³¹ PEG 3350 used in pharmaceutical, personal care, and food applications is water soluble. It has a MW range of 3015 to 3685 Da, an average number of 75.7 repeating oxyethylene units, a pH of a 5% aqueous solution of 4.5 to 7.5 at 25°C, a density of 1.09 g/cm³ at 60°C, a melting or freezing range between 53° and 57°C, a water solubility of 67% by weight at 20°C, and a viscosity of 90.8 centistokes at 100°C.^{130,132} PEG 3350 without electrolytes is sold for nonprescription use for short-term constipation treatment. WBI used in poison management is typically accomplished using PEG 3350 added to a balanced electrolyte lavage solution (PEG-ELS), which contains an isotonic mixture of sodium sulfate, sodium bicarbonate, sodium chloride, and potassium chloride.¹¹⁹

Mechanisms of Action

The effects of saline cathartics are largely attributed to their relatively nonabsorbable ions that establish an osmotic gradient and draw water into the gut.¹⁰⁴ The increased water leads to increased intestinal pressure and a subsequent increase in intestinal motility. Magnesium ions also lead to the release of cholecystokinin from the duodenal mucosa, which stimulates intestinal motor activity and alters fluid movement, contributing to catharsis.^{14,119,126} A lack of endogenous hydrolytic enzymes allows sorbitol and lactulose to reach the colon unchanged. Colonic bacteria metabolize sorbitol into acetic and other short chain fatty acids and lactulose into lactic acid and small amounts of formic and acetic acids. This results in a slight acidification of colonic contents, an increase in osmotic pressure that draws water into the lumen, and stimulation of colonic propulsive motility.¹¹⁹

Long-chain PEGs (eg, MW ~3350 Da) are nonabsorbable, isoosmotic, indigestible molecules that remain in the colon together with the water diluent, resulting in WBI primarily by the mechanical effect of large-volume lavage. The added balanced electrolyte solution practically eliminates electrolyte abnormalities and helps preclude fluid shifts across the GI mucosa. Sodium sulfate in many preparations reduces sodium absorption in the small intestine because of the absence of chloride, the accompanying anion necessary for active absorption against the electrochemical gradient.⁸³

Promotility agents such as metoclopramide and erythromycin stimulate gut motor function. Metoclopramide mediates GI 5-HT₄ receptor agonist and D₂ receptor antagonist activity, which both result in increased acetylcholine release and GI motility. Erythromycin also stimulates gut motor function but via direct stimulation of GI motilin receptors.¹³⁹ Lubiprostone is a promotility drug that stimulates chloride secretion and enhances the contraction of gastric and colonic musculature.⁶¹ Although lubiprostone has been used with WBI for the treatment of constipation, their combined use has not yet been reported in poisoned patients.

Pharmacokinetics

Absorption of magnesium, phosphate, and other electrolytes contained in hypertonic products is well described and may risk morbidity.^{27,98,104} In one prospective, nonrandomized study, nine of 14 patients developed elevated magnesium concentrations (2.2–5.0 mEq/L) after multiple doses of magnesium-containing cathartics for suspected drug overdose

despite normal blood urea nitrogen and creatinine values.¹²³ During the 24 hours after administration of oral sodium phosphate solution in seven healthy volunteers, serum phosphorus reached a mean peak of 7.6 mg/dL (range, 3.6–12.4 mg/dL), and ionized calcium reached a mean nadir 4.6 mg/dL (range, 4.4–5.2 mg/dL).²⁷

By virtue of its high osmotic nature long-chain PEG is poorly absorbed, is retained in the lumen, and does not distribute. PEG is therefore eliminated unmetabolized in rectal effluent.

Pharmacodynamics

Patients ingesting 45 mL of an aqueous sodium phosphate preparation taken the evening before and the morning of a procedure initiated bowel activity within 1.7 hours of the first dose and within 0.7 hours of the second dose, with a mean duration of activity of 4.6 and 2.9 hours, respectively, and an end of bowel activity within 4 to 5 hours.⁷⁴ In six volunteers, saline cathartics decreased activated charcoal (AC) mean GI transit time from 29.3±1.2 hours to 24.4±1.2 hours, 15.4±3.0 hours, 17.3±1.9 hours, and 17.5±2.3 hours with sodium chloride, sodium sulfate, magnesium sulfate, and a proprietary cathartic “salt” (36.7% anhydrous citric acid, 17.65% magnesium sulfate, and 45.6% sodium bicarbonate), respectively.¹⁰⁵ When different cathartics were compared with respect to time to first stool and number of stools,^{54,68,96,97,127} sorbitol produced 10 to 15 watery stools and the most abdominal cramping before catharsis. Sorbitol produced stools in the shortest amount of time, which also was associated with the highest incidence of nausea, vomiting, generated gas, and flatus.^{62,64,99} In one systematic review, mean transit times after administration of sorbitol, magnesium citrate, magnesium sulfate, and sodium sulfate were 0.9 to 8.5 hours, 3 to 14 hours, 9.3 hours, and 4.2 to 15.4 hours, respectively.⁵ In comparison, the first bowel movement typically occurs relatively quickly after the initiation of WBI with PEG-ELS. Patients ingesting GoLYTELY (1.2–1.8 L/h until the rectal effluent was clear) completed their colonic preparation within 1.5 to 3 hours after averaging a total of 5.5 L per patient (range, 3–8 L).³⁹

ROLE OF GASTROINTESTINAL EVACUATION IN POISONING MANAGEMENT

Although recommended for basic poison management for many years, cathartics should not be used routinely in the management of overdosed patients.⁵ Intuitively, the advantages of cathartics appear to result from their ability to decrease the potential for constipation or obstruction from AC and hasten the delivery of AC to the small intestine. However, these theoretical advantages have never been demonstrated clinically.

Studies demonstrate that when administered alone, cathartics such as sorbitol or sodium sulfate may decrease peak or total absorption of some xenobiotics, but no study of cathartics alone has achieved results comparable to that of AC alone.^{2,24,88,108,141} When comparing the efficacy of a single dose of AC alone with that of AC plus a single dose of cathartic, studies suggest the combination to be equal to,^{2,93,102,122} slightly better than,^{24,62} or even slightly worse than AC alone.^{88,141} WBI with PEG-ELS is currently advocated to hasten the elimination of poorly absorbed xenobiotics or sustained-release medications before they can be absorbed. This approach is theoretically sound and does not produce the fluid and electrolyte complications associated with cathartics. Unfortunately, evidence of efficacy is limited to anecdotal case reports and volunteer studies.

Many studies of WBI using PEG-ELS demonstrate patient acceptance, effectiveness, and safety when used for bowel preparation, its labeled indication.^{4,12,16,17,28,31,32,109,133,136} Animal models suggest that WBI may enhance systemic clearance via GI dialysis, similar to multiple-dose activated charcoal (MDAC).⁷³ In actuality, low flow rates, the typical delay in administering WBI in actual clinical situations, and the inconvenience of this procedure make it highly unlikely that enhanced systemic clearance can be achieved in humans. In human volunteer studies, WBI was more effective than AC with sorbitol for enteric-coated acetylsalicylic acid (ASA) when administered 4 hours after ingestion,⁶⁴ decreased peak lithium concentrations, and lithium AUC (area under the plasma drug concentration vs. time curve) compared with control participants;¹²⁴ decreased the bioavailability of two sustained-release medications;^{21,71} and propelled radiopaque markers through the gut more efficiently than control participants.⁸⁰ In a retrospective analysis of 59 acute-on-chronic lithium overdoses, those decontaminated at an early stage with sodium polystyrene sulfonate, WBI, or both achieved statistically significant and clinically relevant decreases in peak serum lithium concentrations compared with those with delayed (>12 hours) or no decontamination (2.39 vs. 4.08 mEq/L).¹⁸ A retrospective chart review of 176 pediatric cases in a state electronic database from 2000 and 2010 documented WBI use in 72 cases involving sustained- and delayed-release medications, such as nifedipine, bupropion, verapamil, diltiazem, and felodipine.⁷⁵ Abdominal radiographs were performed in 36 cases, of whom 16 had demonstrable radiopaque pills. Four of these had repeat abdominal radiographs, all of which demonstrated a decrease in opacities.

Not unexpectedly, WBI was inferior to AC with regard to prevention of absorption when administered after 650 mg of immediate-release aspirin.¹¹² Additionally, after the aspirin was absorbed, WBI was unable to enhance systemic

clearance.⁸⁷ Likewise, only a small, statistically insignificant effect of WBI could be demonstrated on the absorption of extended-release acetaminophen in a human volunteer study.⁸⁰ These findings highlight the limited utility of WBI to assist in the prevention of absorption of relatively rapidly absorbed xenobiotics. Reports have shown successful WBI use in the management of overdoses of iron,^{33,59,85,128,129} sustained-release theophylline,⁵⁵ sustained-release verapamil,¹⁹ modified-release fenfluramine,⁹⁵ zinc sulfate,²⁰ lead,^{92,94,116,147} arsenic trioxide,⁵³ arsenic-containing herbicide,⁷² mercuric oxide powder,⁸¹ strontium,⁶³ potassium chloride capsules,^{42,50} and clonidine and fentanyl transdermal patches^{36,52} and in body packers.^{49,134,138} Although some clinicians express enthusiasm for the use of WBI for a variety of ingestions, others question its efficacy.^{20,114} WBI for 5 hours after ingestion of 10 fluorescent coffee beans by each of seven volunteers removed an average of only four beans (range, 1–8).¹¹⁴ Similar failures are reported with jequirity beans,²⁰ iron,^{23,142} and button batteries.¹²⁸ It can be argued that because of physical characteristics (eg, density, solubility, size, or pharmacobezoar formation), these cases might not be representative of xenobiotics amenable to WBI.

Internal Drug Concealment

The approach to patients with internal concealment and enteral transport of illicit substances (eg, cocaine, heroin, amphetamines, and hashish) is comprehensively reviewed in Special Considerations: SC5. Close coordination with surgical services is advised because of the risks of obstruction, intestinal retention, or rupture. Mineral oil rapidly degrades latex condoms.¹⁴⁴ Use of mineral oil in evacuating drug packets, which may be constructed in this fashion, risks fatal rupture.¹⁴³ In a retrospective descriptive case series of 16 body packers, conservative management with WBI was successful in 14; a ruptured cocaine packet produced mild toxicity in one patient, and packets were retained in one of the heroin body packers.³⁵ In another retrospective analysis of 34 cocaine body stuffers who were asymptomatic on presentation, one received WBI alone, and 19 received WBI plus AC and remained asymptomatic and were discharged after 24 hours.⁵⁸ A review of 1250 confirmed body packers found the success rate of a conservative management strategy of WBI to be 98%.⁸⁴ All conservatively managed patients passed all of their packets within 5 days. WBI may not always evacuate all of the drug packets because of inadequate dosing, partial obstruction, or the nature of the procedure. In one case, prolonged WBI failed to clear a methamphetamine body stuffer who engaged in “parachuting.”⁴⁵ As a result of these failures, promotility agents were added to WBI and presumably successfully enhanced bowel evacuation in two body packers suspected of having ingested well-constructed drug packets.¹³⁵

ADVERSE EFFECTS AND SAFETY ISSUES

Potential adverse effects associated with various cathartics and promotility agents include dehydration, hypokalemia and metabolic alkalosis from dehydration, absorption of magnesium or other absorbable electrolytes, activation of the renin–angiotensin–aldosterone system, phosphate-induced nephropathy, and colonic fermentation of digestible sugars.^{22,37,121} Cathartic-induced rectal prolapse is reported in geriatric patients.⁶⁶ The use of repetitive doses of cathartics, either by design or unintentionally, has led to hypermagnesemia, altered mental status, and death.^{57,98,123,146} Hypocalcemia, hyperphosphatemia, and hypokalemia have accompanied the use of hypertonic phosphate enemas and oral sodium phosphate despite adherence to recommended dosing.^{29,37,41,77,86,110,125} Frail elderly patients, children, and those with decreased kidney function may be most susceptible to adverse effects.^{11,13}

Softeners may increase intestinal permeability and therefore increase the absorption of some xenobiotics.^{9,119} Mineral oil risks enhanced absorption of lipid-soluble xenobiotics, lipid pneumonia in the event of aspiration, and rupture of concealed drug packets packaged in latex.¹⁴³ Stimulant and irritant laxatives are rarely used today in medical toxicology because of their significant GI side effects, including abdominal discomfort, cramping, and tenesmus and with chronic administration, bowel habituation and intestinal tissue damage.

Contraindications to WBI include prior, current, or anticipated diarrhea; volume depletion; significant GI anatomical or functional compromise such as colitis, hemorrhage, ileus, obstruction, perforation, or toxic megacolon; an unprotected or compromised airway; and hemodynamic instability.^{6,128}

MDAC regimens containing 70% sorbitol used to enhance elimination resulted in severe cathartic-related adverse effects in several case reports.^{3,34,76,89} The potential for sorbitol-related adverse events from the unintentional use of repetitive AC dosing was emphasized by a survey revealing that 16% of hospitals surveyed only stocked AC premixed with sorbitol.¹⁴⁵ The retention of sorbitol after repetitive doses in an aperistaltic gut may lead to significant morbidity from gas formation and abdominal distention as a result of the digestive action of gut bacteria.⁷⁶

Adverse effects resulting from the use of WBI with PEG-ELS include vomiting, particularly after rapid administration, abdominal bloating, fullness, cramping, flatulence, and pruritus ani. Of the 176 pediatric cases detailed in the California Poison Control System electronic database, 16 vomited, and one experienced abdominal pain.⁷⁵ In an alternative administration strategy in which 46 children were provided 238 g of PEG-3350 mixed with 1.9 L of Gatorade, complaint

rates of nausea and vomiting, abdominal pain and cramping, and fatigue and weakness were 60%, 44%, and 40%, respectively.¹ Typically, patients need to remain near a commode for 4 to 6 hours to complete WBI therapy. Slow or low-volume administration of PEG-ELS results in sodium absorption. If a total of 500 mL of PEG-ELS was used instead of multiple liters, potentially 1.5 g of sodium may be absorbed.³⁰ This adverse effect might have resulted in the exacerbation of congestive heart failure in an unstable patient with cardiac and renal dysfunction.⁴⁰ An unusual complication of WBI is colonic perforation, which occurred in a patient with active diverticulitis.⁷⁰ Other adverse effects noted by the manufacturer include isolated reports of upper GI bleeding from a Mallory-Weiss tear, esophageal perforation, aspiration pneumonitis after vomiting, and ARDS. Rare cases of both hypo- and hypernatremia, leading to altered consciousness, seizures, cerebral edema, and death, are reported with PEG, alone or in combination with ELS.^{10,100,115}

Unintentional administration of PEG-ELS by other than the enteral route has occurred. A 4 year-old child inadvertently received 390 mL of PEG-ELS intravenously with no obvious adverse result.¹¹¹ In contrast, acute respiratory distress syndrome (ARDS) developed in an 11 year-old child administered PEG-ELS through a nasogastric tube inadvertently inserted in the trachea.¹⁰¹ In a similar case, a poorly placed nasogastric tube was responsible for PEG-ELS aspiration in a 3 year-old boy, with resultant hypoxia and hemodynamic instability requiring endotracheal intubation.³⁸ An 8 year-old girl with emesis during nasogastric infusion of 1 L of PEG-ELS experienced gagging, coughing, and emesis, and respiratory distress 2 hours after infusion, resulted in ARDS and requiring intubation and ventilatory support for 2 days.¹⁰⁶ A report of two cases suggests that vomiting and aspiration may be more frequent than previously recognized in hemodynamically unstable patients.²⁶ Presumably, a patient's hypotension results in GI hypoperfusion and ileus, which, with the continued administration of WBI in the presence of decreased GI motility, produces abdominal distention and vomiting.

For MiraLax to be useful in WBI, it would need to be administered at a dose of 2 L/h (8 heaping teaspoons in 2 L of water/h) in adults. This is not recommended for WBI because it does not contain any added electrolytes and could result in an electrolyte imbalance and shifts.

Activated Charcoal and Whole-Bowel Irrigation Interactions

Several in vitro studies (with cocaine, chlorpromazine, fluoxetine, salicylate, and theophylline) demonstrate that the addition of PEG-ELS to AC significantly decreases the adsorptive capacity of AC.^{7,8,48,65,82} Some interactions were affected by pH and magnified by high ratios of PEG-ELS to AC.^{8,65,82} The most likely explanation is competition with the AC surface for solute adsorption. Additionally, in an animal model, WBI appeared to have an adverse effect by washing the AC away from the sustained-release theophylline.²¹ One controlled study evaluated the effect of WBI added to 25 g of AC in nine healthy human volunteers simultaneously ingesting 200 mg of carbamazepine, 200 mg of theophylline, and 120 mg of verapamil.⁷¹ Compared with AC alone, WBI provided with AC significantly decreased verapamil peak concentration (C_{max}) and AUC but significantly increased carbamazepine C_{max} and AUC and nonsignificantly increased theophylline C_{max} and AUC. One case report documents rapid increases in carbamazepine concentrations temporally related to the initiation of WBI.⁷⁹ Although the patient had received MDAC and hemoperfusion, xenobiotic concentrations were increasing 58 hours after ingestion. It is possible that PEG-ELS competed for carbamazepine binding to AC, displacing some drug and making it available for absorption. A similar rapidly increasing drug concentration was noted after the initiation of WBI in a patient with a reported 10-g phenytoin overdose.²⁵ In this case, AC had not been given before the initiation of WBI. One possible explanation is that the massive dose of phenytoin prevented its own absorption by exceeding its solubility, but the administration of WBI provided sufficient diluent to allow phenytoin dissolution before GI emptying with subsequent absorption. One human study evaluated the influence of various decontamination strategies on the probability of seizures in 319 patients who overdosed on venlafaxine on 436 occasions.⁶⁹ WBI added to AC alone in a mean ingestion of 2100 mg further reduced the odds ratio (OR) of a seizure to 0.25 (0.08–0.62) compared with an OR of 0.48 (0.25–0.89) with AC alone. Most of these patients ingested extended-release venlafaxine. Their results demonstrated that combining AC and WBI provided a greater benefit than the sum of the independent effects of single-dose activated charcoal (SDAC) and WBI and argued against adverse clinical effects caused by desorption in venlafaxine ingestion.⁶⁹

PREGNANCY AND LACTATION

Commercial preparations of PEG-ELS are pregnancy category C.^{16,17,117,118} Animal reproduction studies have not been conducted with Colyte, GoLYTELY, NuLYTELY, or TriLyte.^{16,17,117,118} The underlying elevated prevalence of nausea and vomiting in pregnancy⁶⁷ might predispose pregnant patients to vomit more frequently, although this is speculative. WBI with large volumes of fluid has been used successfully in pregnant women at 26 and 38 weeks of gestation.^{137,140} The lack of absorption PEG-ELS would not predispose it to excretion in breast milk, although definitive safety in lactation is not established.

DOSING AND ADMINISTRATION

The usual nonprescription daily dose for the short-term treatment (2 weeks) of occasional constipation is 17 g of powder in 8 oz (240 mL) of water. The recommended dose of WBI with PEG-ELS solution is considerably larger: 0.5 L/h or 25 mL/kg/h for small children and 1.5 to 2.0 L/h or 20 to 30 mL/min for adolescents and adults. WBI solution may be administered orally or through a nasogastric tube for 4 to 6 hours or until the rectal effluent becomes clear. An antiemetic such as metoclopramide or a 5-HT₃ serotonin antagonist may be required for the treatment of nausea or vomiting. In select patients, promotility agents may serve as useful adjuncts.¹³⁵ If the xenobiotic being removed is radiopaque, a diagnostic imaging technique demonstrating the absence of the xenobiotic may serve as an initial clinical endpoint (Special Considerations: SC5).

FORMULATION AND ACQUISITION

The original WBI solution was GoLYTELY manufactured by Braintree. This solution contained PEG with electrolytes and sodium sulfate as an added laxative. Colyte is manufactured by Schwartz Pharma and is similar to GoLYTELY. Braintree later introduced NuLYTELY, a PEG formulation with 52% less total salt than GoLYTELY without added sodium sulfate. These changes decreased the salty taste and the risk of fluid- or electrolyte-related complications.⁹⁰ Many products are available with flavors. The available PEG-ELS products are prepared by filling the container to the 4-L (or 1-gal) mark with water and shaking vigorously several times to ensure dissolution. Lukewarm water facilitates dissolution, but subsequent chilling improves palatability. Chilled solutions are not recommended for infants because of hypothermia risk. Products are stable with refrigeration for 48 hours after reconstitution. Available PEG-ELS products (eg, GoLYTELY, Colyte, NuLYTELY, TriLyte) differ slightly in their composition. All contain PEG 3350 with varying amounts of sodium chloride, potassium chloride, sodium sulfate, and sodium bicarbonate, which upon reconstitution yield sodium, 65 to 125 mEq/L; potassium, 5 to 10 mEq/L; chloride, 35 to 53 mEq/L; bicarbonate, 17 to 20 mEq/L; and sulfate, 0 to 80 mEq/L.^{16,17,117,118}

MiraLax contains electrolyte-free PEG 3350 powder meant for oral administration after dissolution in water, juice, or soda. It is indicated for occasional constipation and not for poisoning management, with a recommended dose of 1 heaping teaspoon (17 g) in 8 oz (240 mL) of liquid per day. However, alternative WBI formulations using electrolyte-free PEG 3350 with Gatorade have been used clinically. One study of 139 patients comparing 4 L of PEG-ELS with electrolyte-free PEG combined with 1.9 L of Gatorade and found no differences in colonoscopy preparation scores, higher overall patient satisfaction scores with the Gatorade mixture, and fewer adverse effects (bloating and nausea).⁹¹ In 46 children provided PEG 3350 mixed with 1.9 L of Gatorade over a few hours, 93.5% completed the regimen, and 77% achieved effective colonic visualization.¹ In a retrospective evaluation of an endoscopic database analysis, patients undergoing bowel preparation using PEG 3350 without electrolytes (238 g of MiraLax in 64 oz of Gatorade) and four 5-mg bisacodyl tablets were more likely to achieve an excellent or good bowel cleansing compared with patients receiving a GoLyteLy preparation (93.3% vs. 89.3%), without any adverse events.¹²⁰

SUMMARY

- Cathartics are not considered part of routine management of poisoning and overdose in children or adults and should not be used as an AC substitute when xenobiotics known to be adsorbed to AC are involved.
- When MDAC is administered, if a cathartic is used at all, it should be provided only with the first dose. Sufficient oral fluids should always accompany cathartic administration to avoid dehydration and inspissation.
- AC should be given to patients for whom it is indicated, and if WBI is being performed in conjunction, a comparable dose of AC should be given after WBI to prevent or overcome the potential desorption and possible further systemic absorption of the xenobiotic.
- Unless contraindicated, WBI is preferable to repetitive dose cathartics for evacuation of sustained-release or poorly soluble xenobiotics not adsorbed to AC.
- WBI's precise role and the interactions between PEG-ELS and AC in overdosed patients remain ill defined. Absent controlled clinical studies to assess outcome, WBI may be considered in ingestions of sustained-release xenobiotics, xenobiotic ingestions with a slow absorptive phase and a high expectation of morbidity; xenobiotics not adsorbed by activated charcoal (eg, iron, lead, lithium); and foreign body ingestions, specifically drug packets in body packers.

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9 PHARMACOKINETIC AND TOXICOKINETIC PRINCIPLES

Mary Ann Howland

Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion of xenobiotics. Xenobiotics are substances that are foreign to the body and include natural or synthetic chemicals, drugs, pesticides, environmental agents, and industrial agents.⁴⁹ Mathematical models and equations are used to describe and to predict these phenomena. Pharmacodynamics is the term used to describe an investigation of the relationship of xenobiotic concentration to clinical effects. Toxicokinetics, which is analogous to pharmacokinetics, is the study of the absorption, distribution, metabolism, and excretion of a xenobiotic under circumstances that produce toxicity. Toxicodynamics, which is analogous to pharmacodynamics, is the study of the relationship of toxic concentrations of xenobiotics to clinical effects.

Overdoses provide many challenges to the mathematical precision of toxicokinetics and toxicodynamics because many of the variables, such as dose, time of ingestion, and presence of vomiting, that affect the result are often unknown. In contrast to the therapeutic setting, atypical solubility characteristics are noted, and saturation of enzymatic processes occurs. Intestinal or hepatic enzymatic saturation or alterations in transporters may lead to enhanced absorption through a decrease in first-pass effect. Metabolism before the xenobiotic reaches the blood is referred to as the first-pass effect.^{2,76} Saturation of plasma protein binding results in more free xenobiotic available in the plasma. Saturation of hepatic enzymes or active renal tubular secretion leads to prolonged elimination. In addition, age, obesity, gender, pharmacogenetics and pharmacogenomics, chronopharmacokinetics (diurnal variations), and the effects of illness and compromised organ perfusion all further inhibit attempts to achieve precise analyses.^{3,17,40,45,68,72} Furthermore, various treatments may alter one or more pharmacokinetic and toxicokinetic parameters. There are numerous approaches to recognizing these variables, such as obtaining historical information from the patient's family and friends, performing pill counts, procuring sequential serum concentrations during the phases of toxicity, and occasionally repeating a pharmacokinetic evaluation during therapeutic dosing of that same xenobiotic to obtain comparative data.

Although different, plasma concentration and serum concentration are terms often used interchangeably. When a reference or calculation is made with regard to a concentration in the body, it is actually a plasma concentration. When concentrations are measured in the laboratory, a serum concentration (clotted and centrifuged blood) is often determined. In reality, the laboratory measurements of most xenobiotics in serum or plasma are nearly equivalent. Frequently, this is not the case for whole-blood determination if the xenobiotic distributes into the erythrocyte, such as lead and most other heavy metals.

Despite all of the confounding and individual variability, toxicokinetic principles may nonetheless be applied to facilitate our understanding and to make certain predictions. These principles may be used to help evaluate whether a certain antidote or extracorporeal removal method is appropriate for use, when the serum concentration might be expected to decrease into the therapeutic range (if one exists), what ingested dose might be considered potentially toxic, what the onset and duration of toxicity might be, and what the importance is of a serum concentration. While considering all of these factors, the clinical status of the patient is paramount, and mathematical formulas and equations can never substitute for a sound clinical assessment. This chapter explains the principles and presents the mathematics in a user-friendly fashion.⁷⁹

ABSORPTION

Absorption is the process by which a xenobiotic enters the body. A xenobiotic must reach the bloodstream and then be distributed to the site or sites of action to cause a systemic effect. Both the rate (k_a) and extent of absorption (F) are measurable and important determinants of toxicity. The rate of absorption often predicts the onset of action and relies on dosage form, and the extent of absorption (bioavailability) often predicts the intensity of the effect and depends in part on first-pass effects.^{36,37} Figure 9–1 depicts how changes in the rate of absorption may affect toxicity when the bioavailability is held constant versus how toxicity may be affected by changes in bioavailability when the rate of absorption is held constant.

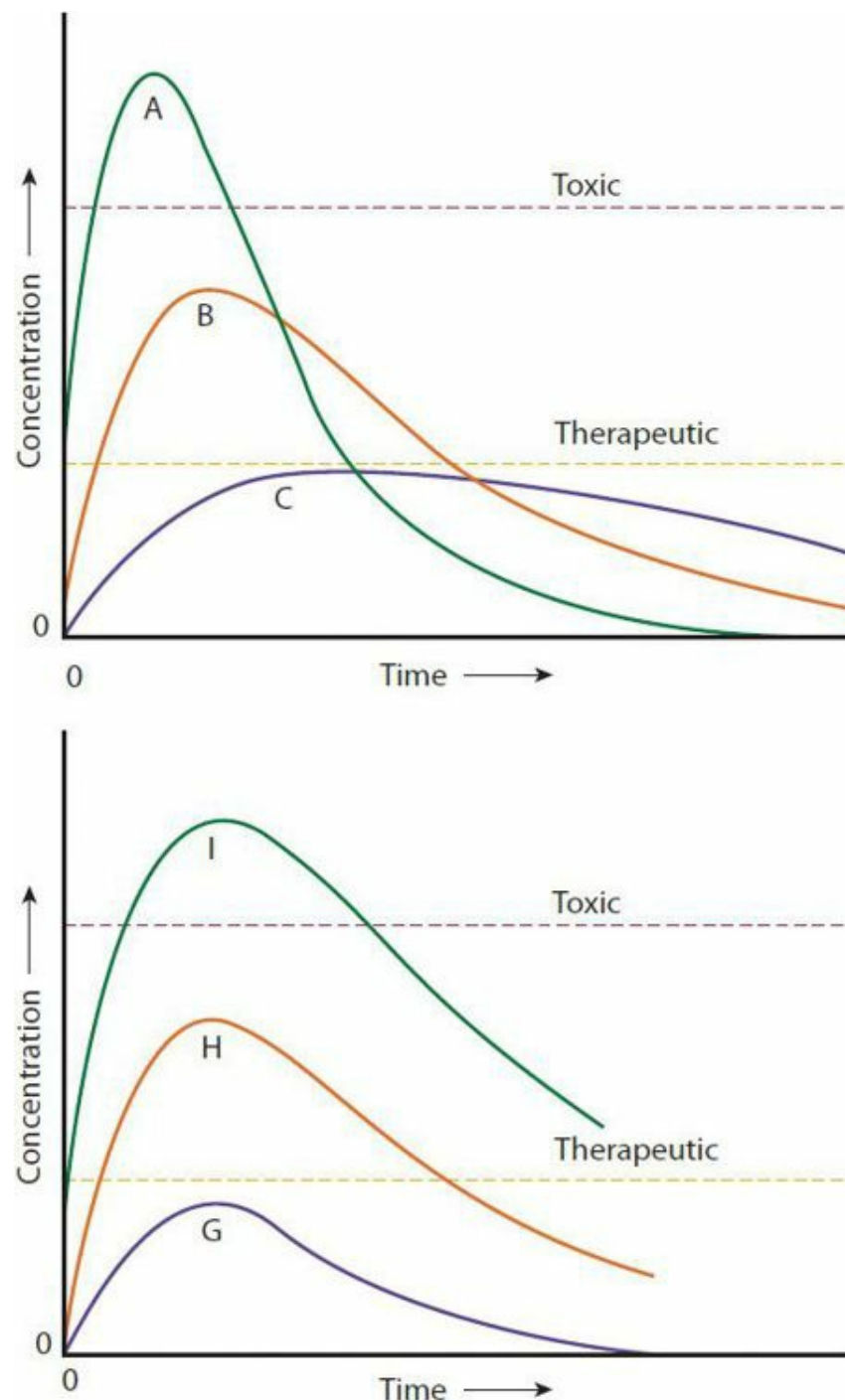


FIGURE 9-1. Effects of changes in k_a (rate of absorption) and F (bioavailability) on the blood concentration versus time graph and achieving a toxic threshold. In curves A, B, and C, F is constant as k_a decreases. In curves G, H, and I, k_a is constant as F increases from G to I.⁵⁴

The route by which the xenobiotic enters the body significantly affects both the rate and extent of absorption. As an approximation, the rate of absorption proceeds in the following order from fastest to slowest: intravenous (IV), inhalation > sublingual > intramuscular, subcutaneous, intranasal, oral > cutaneous, rectal. After the oral intake of 200 mg (0.59 mmole) of cocaine hydrochloride, the onset of action is 20 minutes, with an average peak concentration of 200 ng/mL.⁷¹ In marked contrast, smoking 200 mg (0.66 mmole) of cocaine freebase results in an onset of action of 8 seconds and a peak concentration of 640 ng/mL. When administered IV as 200 mg cocaine hydrochloride, it then has an onset of action of 30 seconds and a peak concentration of 1000 ng/mL.⁷¹

A xenobiotic must diffuse through a number of membranes before it can reach its site of action. Figure 9-2 shows the number of membranes through which a xenobiotic typically diffuses. Membranes are predominantly composed of phospholipids and cholesterol in addition to other lipid compounds.⁵⁴ A phospholipid is composed of a polar head and a fatty acid tail, which are arranged in membranes so that the fatty acid tails are inside and the polar heads face outward in a mirror image.⁵⁸ Proteins are found on both sides of the membranes and may traverse the membrane.⁵⁴ These proteins may function as receptors and channels. Pores are found throughout the membranes. The principles relating to diffusion apply to absorption, distribution, certain aspects of elimination, and each mechanism that permits a xenobiotic to be transported through a membrane.

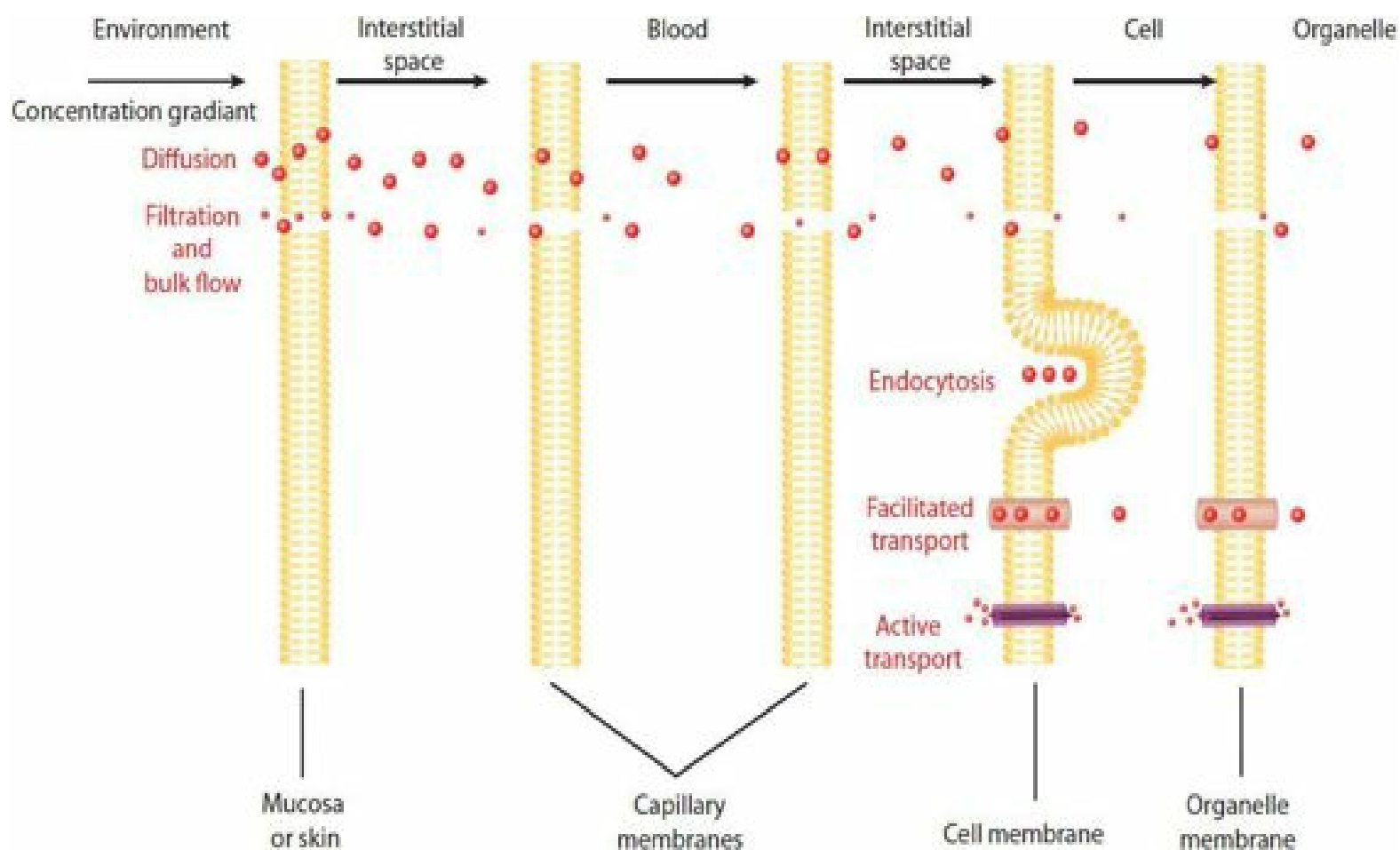


FIGURE 9-2. Illustration of the number of membranes encountered by a xenobiotic in the process of absorption and distribution and the transport mechanisms involved in the passage of xenobiotics across membranes. Examples include diffusion: nonelectrolytes (ethanol) and nonionized forms of weak acids (salicylic acid) and bases (amphetamines); endocytosis: Sabin polio virus vaccine; facilitated: 5-fluorouracil, lead, methyldopa, thallium; and active: thiamine and pyridoxine.

Transport through membranes occurs via (1) passive diffusion; (2) filtration or bulk flow, which is most important in renal and biliary secretion as the mechanism of transport associated with the movement of molecules with a molecular weight less than 100 Da, with water directly through aquapores; (3) carrier-mediated active or facilitated transport, which is saturable; and (4) rarely, endocytosis (Fig. 9-2). Most xenobiotics traverse membranes via simple passive diffusion. The rate of diffusion is determined by the Fick's law of diffusion (Equation 9-1):

$$\text{Rate of diffusion} = \frac{dQ}{dt} = \frac{DAK(C_1 - C_2)}{h} \quad (\text{Eq. 9-1})$$

Where:

D = diffusion coefficient

A = surface area of the membrane

h = membrane thickness

K = partition coefficient

$C_1 - C_2$ = difference in concentrations of the xenobiotic on each side of the membrane

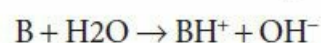
The driving force for passive diffusion is the difference between the concentrations of the xenobiotic on the opposing sides of the membrane. D is a constant for each xenobiotic and is derived when the difference in concentrations between the two sides of the membrane is one. The larger the surface area A, the higher the rate of diffusion. Most ingested xenobiotics are absorbed more rapidly in the small intestine than in the stomach because of the tremendous increase in surface area created by the presence of microvilli. The partition constant or ratio (previously called the coefficient) K_{ow} represents the lipid-to-water partitioning of the nonionized xenobiotic with pH adjustment to favor nonionized xenobiotic. To a substantial degree, the more lipid soluble a xenobiotic is, the more easily it crosses membranes. The logarithm of the K_{ow} is known as the log P. The distribution constant or ratio represents the lipid-to-water partitioning of the sum of the nonionized plus ionized in the octanol and water phase and is pH dependent. The logarithm of the distribution constant is called log D and is most useful when measured at physiologic pH. Membrane thickness (h) is inversely proportional to the rate at which a

xenobiotic diffuses through the membrane. Xenobiotics that are uncharged, nonpolar, of low molecular weight, and of the appropriate lipid solubility have the highest rates of passive diffusion.

The extent of ionization of weak electrolytes (weak acids and weak bases) affects their rate of passive diffusion. Nonpolar and uncharged molecules penetrate faster. The Henderson-Hasselbalch relationship is used to determine the degree of ionization. An acid (HA), by definition, gives up a proton, and a base (B) accepts a proton. Acids and bases can be nonionized (uncharged, molecular, free), positively charged (cationic), or negatively charged (anionic). Aspirin and phenobarbital are uncharged acids (RCOOH), and pseudoephedrine HCl is a cationic acid. Morphine, amphetamine, and amitriptyline are nonionized bases (RNH₂), and sodium valproate is an anionic base. The equilibrium dissociation constants K_a and K_b can then be described. $K_a \times K_b = K_w$, and K_w is the dissociation constant of water. Because these numbers are difficult to work with, they are transformed using logarithms. By Equations 9–2A and 9–2B:

$$\text{For weak acids: } HA = H^+ + A^- \quad K_a = \frac{[H^+][A^-]}{[HA]} \quad (\text{Eq. 9-2A})$$

$$\text{For weak bases: } BH^+ = B + H^+ \quad K_b = \frac{[H^+][B]}{[BH^+]} \quad (\text{Eq. 9-2B})$$



To work with these numbers in a more comfortable fashion, the negative log of both sides is determined. The results are given in Equations 9–3A and 9–3B.

$$\text{For weak acids: } -\log K_a = -\log[H^+] - \log \frac{[A^-]}{[HA]} \quad (\text{Eq. 9-3A})$$

$$\text{For weak bases: } -\log K_b = -\log[H^+] - \log \frac{[B]}{[BH^+]} \quad (\text{Eq. 9-3B})$$

By definition, the negative log of $[H^+]$ is expressed as pH, and the negative log of K_a is pK_a . Rearranging the equations gives the familiar forms of the Henderson-Hasselbalch equations, as shown in Equations 9–4A, 9–4B, and 9–4C:

$$pH = pK_a + \log \frac{\text{Unprotonated species}}{\text{Protonated species}} \quad (\text{Eq. 9-4A})$$

$$\text{For weak acids: } pH = pK_a + \log \frac{[A^-]}{[HA]} \quad (\text{Eq. 9-4B})$$

$$\text{For weak bases: } pH = pK_b + \log \frac{[B]}{[BH^+]} \quad (\text{Eq. 9-4C})$$

Because uncharged molecules traverse membranes more rapidly, it is understood that weak acids cross membranes more rapidly in an acidic environment, and weak bases move more rapidly in a basic environment. When the pH equals the pK_a , half of the xenobiotic is charged, and half is uncharged. An acid with a low pK_a is a strong acid, and a base with a low pK_a is a weak base. For an acid, a pH less than the pK_a favors the protonated or uncharged species facilitating membrane diffusion, and for a base, a pH greater than the pK_a achieves the same result. [Table 9–1](#) lists the pH of selected body fluids, and [Fig. 9–3](#) illustrates the extent of charged versus uncharged xenobiotic at different pH and pK_a and pK_b values.

TABLE 1 9–1. pH of Selected Body Fluids

Fluids	pH
Cerebrospinal	7.3
Gastric secretions	1–3
Large intestinal secretions	8
Ophthalmic (tears)	7–8
Plasma	7.4
Stool: Infants and children	7.2–12
Saliva	6.4–7.2
Small intestinal secretions: Duodenum	5–6
Small intestinal secretions: Ileum	8
Urine	4–8
Vaginal secretions	3.8–4.5

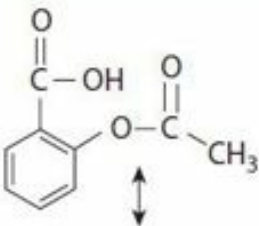
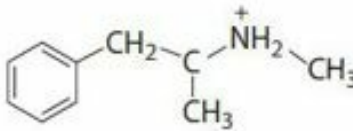
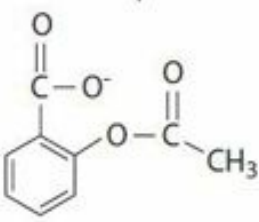
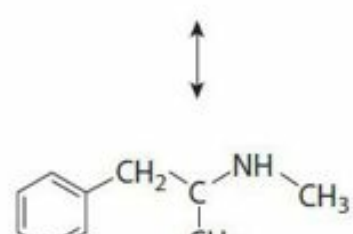


pH	Aspirin ($pK_a = 3.5$)	% Nonionized	Methamphetamine ($pK_a = 10$)	% Nonionized
1		99.7		0.001
2		97		
3		76		
3.5		50		
4		24		0.01
5		3		0.1
6		0.315		50
7		0.032		90.9
10				99
11				
12				

FIGURE 9–3. Effect of pH on the ionization of aspirin ($pK_a = 3.5$) and methamphetamine ($pK_a = 10$).

Lipid solubility and ionization each have a distinct influence on absorption. **Figure 9–4** demonstrates these characteristics for three different xenobiotics. Although the three xenobiotics have similar pK_a and pK_b values, their different partition constants result in different degrees of absorption from the stomach.

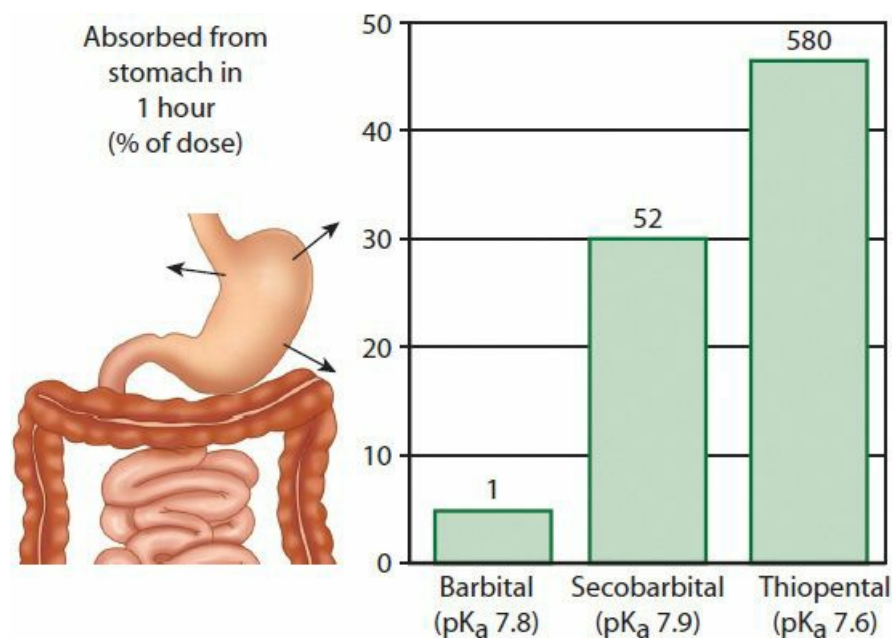


FIGURE 9-4. Influence of increasing lipid solubility on the amount of xenobiotic absorbed from the stomach for three xenobiotics with similar pK_a values. The number above each column is the oil/water equilibrium partition coefficient. (Reprinted with permission from Brody T: Absorption, distribution, metabolism, and elimination. In: Brody TM, Larner J, Minneman KP, Neu HP, eds: Human Pharmacology: Molecular to Clinical, 2nd ed. St. Louis, Mosby, 1994, p 50.)

Specialized transport mechanisms are either adenosine triphosphate (ATP) dependent to transport xenobiotics against a concentration gradient (ie, active transport) or ATP independent and lack the ability to transport against a concentration gradient (ie, facilitated transport). These transport mechanisms are of importance in numerous parts of the body, including the intestines, liver, lungs, kidneys, and biliary system. These same principles apply to a small number of lipid-insoluble molecules that resemble essential endogenous molecules.^{28,64} For example, 5-fluorouracil resembles pyrimidine and is transported by the same system, and thallium and lead are actively absorbed by the endogenous transport mechanisms that absorb and transport potassium and calcium, respectively. Filtration is generally considered to be of limited importance in the absorption of most xenobiotics but is substantially more important with regard to renal and biliary elimination. Endocytosis, which describes the encircling of a xenobiotic by a cellular membrane, is responsible for the absorption of large macromolecules such as the oral Sabin polio vaccine.⁶⁴

Gastrointestinal (GI) absorption is affected by xenobiotic-related characteristics such as dosage form, degree of ionization, partition constant, and patient factors (eg, GI blood flow; GI motility; and the presence or absence of food, ethanol, or other interfering substances such as calcium) (Fig. 9-5).

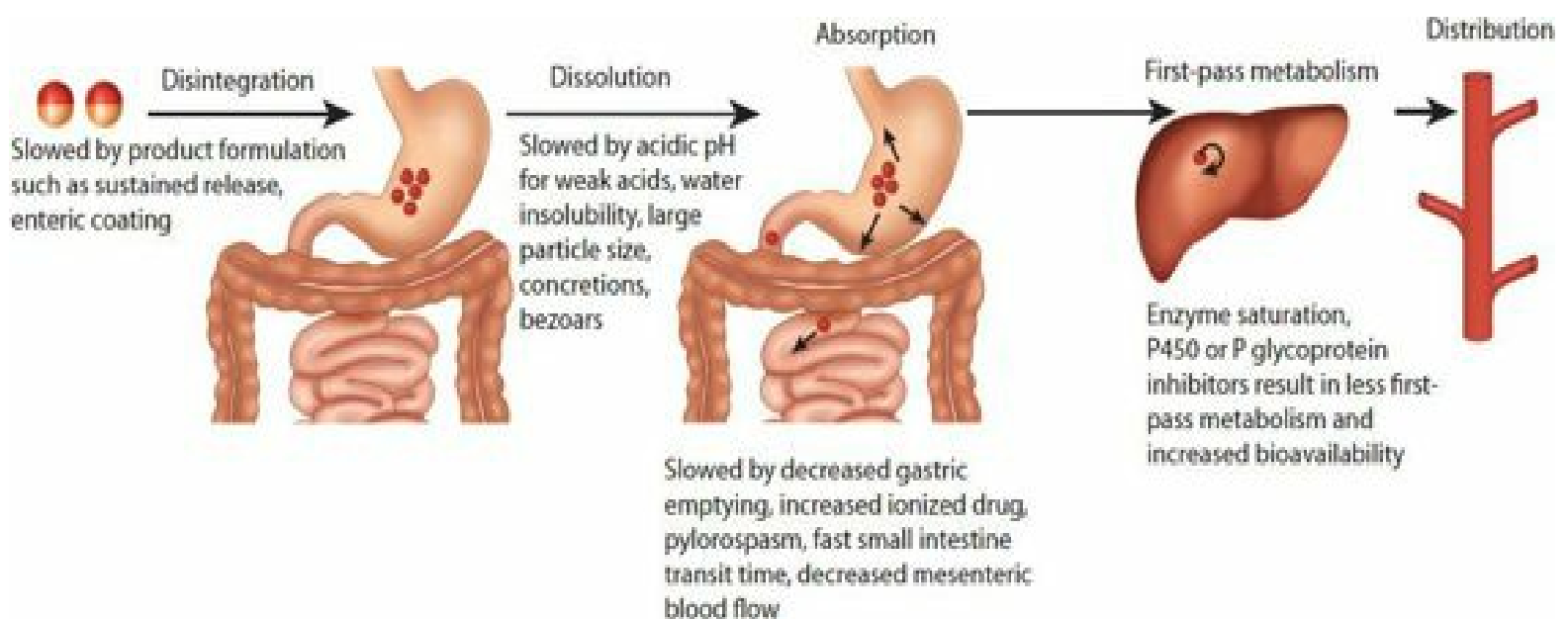


FIGURE 9-5. Determinants of absorption.

The formulation of a xenobiotic is extremely important in predicting GI absorption. Disintegration and dissolution must precede absorption. Disintegration is usually much more rapid than dissolution except for modified-release products. Modified release is a broad term that encompasses products that are delayed-release and extended-release formulations.

These modified-release formulations are designed to release the xenobiotic over a prolonged period of time to simulate the blood concentrations achieved with the use of a constant IV infusion. By definition, extended-release formulations decrease the frequency of drug administration by at least 50% compared with immediate-release formulations, and they include controlled-release, sustained-release, and prolonged-release formulations. These formulations minimize blood concentration fluctuations, reduce peak-related side effects, reduce dosing frequency, and improve patient compliance. A variety of products use different pharmaceutical strategies, including dissolution control (encapsulation or matrix; Feosol), diffusion control (membrane or matrix; Plendil ER), erosion (Sinemet CR), osmotic pump systems (Procardia XL, Glucotrol XL), and ion exchange resins (MS Contin suspension). Overdoses with modified-release formulations often result in a prolonged absorption phase, a delay to peak concentrations, and a prolonged duration of effect.⁷ Some delayed-release preparations are enteric coated and specifically designed to bypass the stomach and to release drug in the small intestine. Other delayed-release formulations (eg, Verelan PM) are designed to release the drug later but not specifically designed to bypass release in the stomach. Enteric-coated (acetylsalicylic acid {ASA}, divalproex sodium) formulations resist disintegration and delay the time to onset of effect.⁶ Dissolution is affected by ionization, solubility, and the partition coefficient. In the overdose setting, the formation of poorly soluble or adherent masses such as concretions of foreign material termed bezoars significantly delay the time to onset of toxicity (Table 9–2).^{4,11,29,30,60}

TABLE 9–2. Xenobiotics That Form Concretions or Bezoars, Delay Gastric Emptying, or Result in Pylorospasm

Anticholinergics	Meprobamate
Barbiturates	Methaqualone
Bromides	Opioids
Enteric-coated tablets	Phenytoin
Glutethimide	Salicylates
Iron	Verapamil

Most ingested xenobiotics are primarily absorbed in the small intestine as a result of the large surface area and extensive blood flow of the small intestines.⁵⁹ Critically ill patients who are hypotensive, have a reduced cardiac output, or are receiving vasopressors such as norepinephrine have a decreased perfusion of vital organs, including the GI tract, kidneys, and liver.³ Not only is absorption delayed, but elimination is also diminished.⁵⁷ Total GI transit time can be from 0.4 to 5 days, and small intestinal transit time is usually 3 to 4 hours. Extremely short GI transit times reduce absorption. This change in transit time is the unproven rationale for use of whole-bowel irrigation (WBI). Delays in emptying of the stomach impair absorption as a result of the delay in delivery to the small intestine. Delays in gastric emptying occur as a result of the presence of food, especially fatty meals; agents with anticholinergic, opioid, or antiserotonergic properties; ethanol; and any xenobiotic that results in pylorospasm (salicylates, iron).

Bioavailability is a measure of the amount of xenobiotic that reaches the systemic circulation unchanged (Equation 9–5).³⁸ The fractional absorption (F) of a xenobiotic is defined by the area under the plasma drug concentration versus time curve (AUC) of the designated route of absorption compared with the AUC of the IV route. The AUC for each route represents the amount absorbed.

$$F = \frac{(\text{AUC})_{\text{route under study}}}{(\text{AUC})_{\text{IV}}} \quad (\text{Eq. 9-5})$$

Gastric emptying and activated charcoal are used to decrease the bioavailability of ingested xenobiotics. The oral administration of certain chelators (deferoxamine, D-penicillamine) actually enhances the bioavailability of the complexed xenobiotic. The net effect of some chelators, such as succimer, is a reduction in body burden via enhanced urinary elimination even though absorption is enhanced.³¹

Presystemic metabolism may decrease or increase the bioavailability of a xenobiotic or a metabolite.⁵³ The GI tract contains microbial organisms that can metabolize or degrade xenobiotics such as digoxin and oral contraceptives and enzymes, such as peptidases, that metabolize insulin.⁵⁴ However, in rare cases, GI hydrolysis can convert a xenobiotic into a toxic metabolite, as occurs when amygdalin is enzymatically hydrolyzed to produce cyanide, a metabolic step that does not occur when amygdalin is administered intravenously.²⁷ Xenobiotic-metabolizing enzymes and influx and efflux transporters such as organic anion transporting polypeptides (OATP) and P-glycoprotein (P-gp), respectively, may also affect bioavailability. Xenobiotic-metabolizing enzymes are found in the lumen of the small intestine and can substantially decrease the absorption of a xenobiotic.^{44,73} Some of the xenobiotic that enters the cell can then be removed by the P-gp transporter from the cell and returned to the GI lumen and reexposed to the metabolizing enzymes.^{44,73} Venous drainage from the stomach and intestines delivers orally (and intraperitoneally) administered xenobiotics to the liver via the portal

vein and avoids direct delivery to the systemic circulation. This venous drainage allows hepatic metabolism to occur before the xenobiotic reaches the blood, and as previously mentioned, is referred to as the first-pass effect.^{2,76} The hepatic extraction ratio is the percentage of xenobiotic metabolized in one pass of blood through the liver.⁴⁷ Xenobiotics that undergo significant first-pass metabolism (eg, propranolol, verapamil) are used at much lower IV doses than oral doses. Some drugs, such as lidocaine and nitroglycerin, are not administered by the oral route because of significant first-pass effect.⁴ Instead, sublingual, transcutaneous (topical), and rectal administration of drugs are used to bypass the portal circulation and avoid first-pass metabolism.

In the overdose setting, presystemic metabolism may be saturated, leading to an increased bioavailability of xenobiotics such as cyclic antidepressants, phenothiazines, opioids, and many β -adrenergic antagonists.⁵⁶ Hepatic metabolism usually transforms the xenobiotic into a less active metabolite but occasionally results in the formation of a more toxic xenobiotic such as occurs with the transformation of parathion to paraoxon.⁵¹ Biliary excretion into the small intestine usually occurs for these transformed xenobiotics of molecular weights greater than 350 Da and may result in a xenobiotic appearing in the feces even though it had not been administered orally.^{34,54,67} Hepatic conjugated metabolites such as glucuronides may be hydrolyzed in the intestines to the parent form or to another active metabolite that can be reabsorbed by the enterohepatic circulation.^{41,49,52,54} The enterohepatic circulation may be responsible for what is termed a double-peak phenomenon after the administration of certain xenobiotics.⁶⁴ The double-peak phenomenon is characterized as a serum concentration that decreases and then increases again as xenobiotic is reabsorbed from the GI tract. Other causes include variability in stomach emptying, presence of food, or failure of a tablet dosage form.⁶⁴

DISTRIBUTION

After the xenobiotic reaches the systemic circulation, it is available for transport to peripheral tissue compartments and to the liver and kidney for elimination. Both the rate and extent of distribution depend on many of the same principles discussed with regard to diffusion. Additional factors include affinity of the xenobiotic for plasma (plasma protein binding) and tissue proteins, acid–base status of the patient (which affects ionization), drug transporters, and physiologic barriers to distribution (blood–brain barrier, placental transfer, blood–testis barrier).^{23,35,58} Blood flow, the percentage of free xenobiotic in the plasma, the activity of transporters account for the initial phase of distribution, and xenobiotic affinities determine the final distribution pattern. Whereas the adrenal glands, kidneys, liver, heart, and brain receive from 55 to 550 mL/min/100 g of tissue of blood flow, the skin, muscle, connective tissue, and fat receive 1 to 5 mL/min/100 g of tissue of blood flow.⁶² Hypoperfusion of the various organs in the critically ill and injured affects absorption, distribution, and elimination.⁷⁴

ATP-binding cassette (ABC) transporters are active ATP-dependent transmembrane protein carriers of which P-gp was the initial example discovered.⁹ Approximately 50 ABC transporters exist, and they are divided into subfamilies based on their similarities. Several members of the ABC superfamily, including P-gp, are under extensive investigation because of their role in controlling xenobiotic entry into, distribution in, and elimination from the body as well as their contributions to xenobiotic interactions.^{21,32,73} The discovery of P-gp resulted from an investigation into why certain tumors exhibit multidrug resistance to many antineoplastics. P-gp (ABCB1) as well as ABCC and ABCG2 are known to be efflux transporters located in the intestines, renal proximal tubules, hepatic bile canaliculi, placenta, and blood–brain barrier and are responsible for the intra- to extracellular transport of various xenobiotics.¹⁶ First-generation transport inhibitors such as amiodarone, ketoconazole, quinidine, and verapamil are responsible for increasing body concentrations of P-gp substrates such as digoxin, the protease inhibitors, vinca alkaloids, and paclitaxel. St. John's wort is a transport inducer, and it lowers serum concentrations of these same xenobiotics. Second- and third-generation xenobiotics that will affect transport with a higher affinity and specificity are in development.^{18,65} Many of the same xenobiotics that affect cytochrome P450 CYP3A4 also affect P-gp (Appendix Chap. 13: Cytochrome P450 Substrates Inhibitors and Inducers).

The organic anion transporting polypeptides (OATPs) are another group of transporters found in the liver, kidneys, intestines, brain, and placenta that affect the absorption, distribution, and elimination of many xenobiotics and contribute to xenobiotic interactions. They include the organic anion transporters (OATs) and the organic cation transporters (OCTs).¹⁸ For example, probenecid increases the serum concentrations of penicillin by inhibiting the OAT responsible for the active secretion of penicillin by the renal tubular cells, and cimetidine inhibits the OCT responsible for the renal elimination of procainamide and metformin. A variety of OAT inhibitors are being investigated to decrease the hepatic uptake of amatoxins¹⁸ (Chap. 120).

Volume of distribution (V_d) is the proportionality term used to relate the dose of the xenobiotic that the individual receives with the resultant plasma concentration. V_d is an apparent or theoretical volume into which a xenobiotic distributes. It is a measure of how much xenobiotic is located inside versus outside of the plasma compartment after administration of a xenobiotic. Because only the plasma compartment is routinely assayed, the amount that remains in the plasma can be used to calculate the movement out of the blood. In a 70-kg man, the total body water (TBW) is 60% of total

body weight, or 42 L, with two-thirds (28 L) of the fluid accounted for by intracellular fluid. Of the 14 L of extracellular fluid, 8 L is considered interstitial or between the cells; 3 L, or 0.04 L/kg, is plasma; and 6 L, or 0.08 L/kg, is blood. If 42 g of a xenobiotic is administered and remains in the plasma compartment ($V_d = 0.04$ L/kg), the concentration would be 15 g/L. If the distribution of the 42 g of xenobiotic approximated TBW (methanol; 0.6 L/kg), the concentration would be 1 g/L (usually reported as 100 mg/dL). These calculations can be performed by using Equation 9–6, where S equals the percent pure drug if a salt form is used.

$$Vd = \frac{S \times F \times \text{Dose (mg)}}{C_0}$$

(Eq. 9-6)

Experimental determination of V_d involves administering an IV dose of the xenobiotic and extrapolating the plasma concentration time curve back to time zero (C_0). If the determination takes place after steady state has been achieved, the volume of distribution is then referred to as the $V_{d_{ss}}$. For many xenobiotics, the V_d is known and readily available in the literature (Table 9–3). When the V_d and the dose ingested are known, a maximum predicted plasma concentration can be calculated after assuming all of the xenobiotic is absorbed and no elimination occurred. This assumption usually overestimates the plasma concentration. Distribution is complex, and differential affinities for various storage sites in the body, such as plasma proteins, liver, kidney, fat, and bone, determine where a xenobiotic ultimately resides.

TABLE 9–3. Pharmacokinetic Characteristics of Xenobiotics Associated with Significant Morbidity and Mortality

	<i>V_d</i> (L/kg)	<i>Protein Binding</i> (%)	<i>Renal Elimination</i> (% Unchanged)	<i>Hepatic Metabolism</i> (CYP)	<i>Active Metabolite</i>	<i>Enterohepatic</i>
Analgesics						
Acetaminophen (APAP)	0.8–1.0	5–20	2	95% 5–10% (2E1)	<i>N</i> -acetyl- <i>p</i> -benzoquinonimine Salicylic acid	27%–42% excreted in bile
Aspirin	0.15–0.20	50–80 (salicylic acid) saturable	10 (pH dependent)	Majority		None
Methadone	3.59	71–87	5–10	Majority (3A4, 2D6) <i>n</i> -Demethylation	None?	Yes
Morphine	3–4	35	<10		15% Morphine 6-glucuronide, 55% morphine 3-glucuronide	Yes
Oxycodone	2.6	45	19	>64% (3A4, 2D6) Noroxycodone	Oxymorphone	No?
Antidepressants						
Amitriptyline	8.3 ± 2	96	5	Yes (2C9)	Nortriptyline (2D6)	Yes
Bupropion	18.6	84	0	Yes (2B6)	Hydroxybupropion	No
Citalopram	12	80	0	Yes (3A4, 2C19)	Desmethylcitalopram	Yes
Desipramine	33–42	92	0.3–2.6	Yes (2D6)	None	Yes
Doxepin	20 ± 8	—	0	Yes	Desmethyldoxepin	Yes
Imipramine	15 ± 6	85	0–1.7	Yes (2D6)	Desipramine	Yes
Lithium	0.79	None	89–98	None	None	None
Cardiovascular						
Digoxin	5.1–7.4	20–25	50–80		Minor amount	Yes
Diltiazem	5.3	70–80	1–3	90% (3A)	Yes, many	No
Nifedipine	0.8–1.4	9–98	7	98% (3A4)	No	No
Propranolol	3.6	93	<0.5	>95% (2C19, 2D6)	No	No
Verapamil	4.7	83–92	3–4%	97% (3A4, 1A2, 2C9)	Norverapamil	No
Stimulants and Drugs of Abuse						
Amphetamine	6.11 (in drug dependent) 3.5–4.6 (in naive)	16	45 (pH dependent)	50%	<i>p</i> -Hydroxynorephedrine 0.3%; <i>p</i> -hydroxyamphetamine 2%–4%	No
Cocaine	1.96–2.7	8.7	9.5–20 (pH dependent)	5–10%	Norcocaine; (?) others	No
Heroin	25	40	Minor	Yes	Acetylmorphine, morphine	No
Methamphetamine	3.2–3.7	pH dependent			Amphetamine 4%–7%; <i>p</i> -hydroxymethamphetamine 15%	No
Sedative-Hypnotics						
Alprazolam	1–2	80	100%	None	None	No
Chloral hydrate	0.75	70–80	Minor	Alcohol dehydrogenase	Trichloroethanol	No
Phenobarbital	0.88	40–50	20–50 (pH dependent)	Yes (2C9, 2C19)	None	No
Quetiapine	10	83	0	Yes (3A4)	None	Yes
Alcohols						
Ethanol	0.5–0.6	None	Very little	95% Alcohol dehydrogenase	Acetaldehyde	No
Ethylene glycol	0.6–0.8	None	20	Alcohol dehydrogenase	Oxalic and glycolic acids	No
Methanol	0.6–0.7	None	3–5	95% alcohol dehydrogenase	Formic acid	No
Miscellaneous						
Cyanide	0.4	60	0		Thiocyanate	None
Theophylline	0.5	50–60	7	90% (1A2, 2E1 > 3A4)	1,3-Dimethylxanthine; caffeine (in neonates)	
Organic Phosphorus Compounds						
Malathion	NA	None		Microsomal enzymes	Malaoxon	No
Chlorpyrifos	NA	None		Yes	3,5,6-Trichloro-2 pyridinol	No
Rodenticides						
Brodifacoum	0.985 (rats)	None		Yes		Yes
Strychnine	13	None	10–20 in 24 hr	Yes		No

For the purposes of determining the utility of extracorporeal removal of a xenobiotic, a low V_d is often considered to be less than 1 L/kg. For some xenobiotics, such as digoxin ($V_d = 7$ L/kg) and the cyclic antidepressants ($V_d = 10\text{--}15$ L/kg), the V_d is much larger than the actual volume of the body. A large V_d indicates that the xenobiotic resides outside of the plasma compartment, but again, it does not describe the site of distribution.

The site of accumulation of a xenobiotic may or may not be a site of action or toxicity. If the site of accumulation is not a site of toxicity, then the storage depot may be relatively inactive, and the accumulation at that site may be theoretically protective to the animal or person.⁵⁸ Selective accumulation of xenobiotics occurs in certain areas of the body because of affinity for certain tissue-binding proteins. For example, the kidney contains metallothionein, which has a high affinity for metals such as cadmium, lead, and mercury.²³ The retina contains the pigment melanin, which binds and accumulates chlorpromazine, thioridazine, and chloroquine.²³ Other examples of xenobiotics accumulating at primary sites of toxicity are carbon monoxide binding to hemoglobin and myoglobin and paraquat distributing to type II alveolar cells in the lungs.⁵⁵ Dichlorodiphenyltrichloroethane (DDT), chlordane, and polychlorinated biphenyls are stored in fat and can be mobilized if malnutrition develops.⁷⁷ Lead sequestered in bone³³ is not immediately toxic, but mobilization of bone through an increase in osteoclast activity⁵⁸ (hyperparathyroidism, pregnancy, immobilization) may free lead for distribution to sites of toxicity in the central nervous system (CNS) or blood.

Several plasma proteins bind xenobiotics and act as carriers and storage depots. The percentage of protein binding varies among xenobiotics, as do their affinities and potential for reversibility. After it is bound to plasma protein, a xenobiotic with high binding affinity will remain largely confined to the plasma until elimination occurs. However, dissociation and reassociation may occur if another carrier is available with a higher binding affinity. Most plasma measurements of xenobiotic concentrations reflect total xenobiotic (bound plus unbound). Only the unbound xenobiotic is free to diffuse through membranes for distribution or for elimination. Albumin binds primarily to weakly acidic, poorly water-soluble xenobiotics, which include salicylates, phenytoin, and warfarin, as well as endogenous substances, including free fatty acids, cortisone, aldosterone, thyroxine, and unconjugated bilirubin.⁶² α_1 -Acid glyco-protein usually binds basic xenobiotics, including lidocaine, imipramine, and propranolol.⁶² Transferrin, a β_1 -globulin, transports iron, and ceruloplasmin carries copper.

Phenytoin is an example of a xenobiotic whose effects are significantly influenced by changes in concentration of plasma albumin because only free phenytoin is active. When albumin concentrations are in the normal range, approximately 90% of phenytoin is bound to albumin. As the albumin concentration decreases, more phenytoin is free for distribution, and a greater clinical response to the same serum phenytoin concentration is often observed. The free plasma phenytoin concentration can be calculated based on the albumin concentration. This achieves an appropriate interpretation (adjusted) of total phenytoin within the conventional therapeutic range of 10 to 20 mg/L of free plus bound phenytoin (Equation 9-7).

$$\text{Adjusted phenytoin concentration} = \frac{\text{Actual phenytoin concentration}}{(0.25 \times [\text{albumin}] + 0.1)} \quad (\text{Eq. 9-7})$$

The clinical implications are that a malnourished patient with an albumin of 2 g/dL receiving phenytoin can manifest toxicity with a plasma phenytoin concentration of 14 mg/L. This measurement is total phenytoin (bound + unbound). Because the patient has a reduced albumin concentration, this actually represents a substantially higher proportion and absolute amount of active unbound phenytoin. Substitution into the above equation of 14 mg/L for actual plasma phenytoin concentration and 2 g/dL for albumin gives an adjusted plasma phenytoin concentration of 23.3 mg/L (therapeutic range, 10–20 mg/L).

Although drug interactions are often attributed to the displacement of xenobiotics from plasma protein binding, concurrent metabolic interactions are usually more consequential. Displacement transiently increases the amount of unbound, active drug. This may result in an immediate increase in drug effect. This is followed by enhanced distribution and elimination of unbound drug. Gradually, the unbound plasma concentration returns to predisplacement concentrations.⁵⁹

Saturation of plasma proteins may occur in the therapeutic range for a drug such as valproic acid. Acute saturation of plasma protein binding after an overdose often leads to consequential adverse effects. Saturation of plasma protein binding with salicylates and iron after overdose increase distribution to the CNS (salicylates) or to the liver, heart, and other tissues (iron), increasing toxicity.

Specific therapeutic maneuvers in the overdose setting are designed to alter xenobiotic distribution by inactivating or enhancing elimination to limit toxicity. These therapeutic maneuvers include manipulation of serum or urine pH (salicylates), the use of chelators (lead), and the use of antibodies or antibody fragments (digoxin).

The V_d permits predictions about plasma concentrations and assists in defining whether an extracorporeal method of removal is beneficial for a particular toxin. If the V_d is large (>1 L/kg), it is unlikely that hemodialysis, hemoperfusion, or

exchange transfusion would be effective because most of the xenobiotic is outside of the plasma compartment. Plasma protein binding also influences this decision. If the xenobiotic is more tightly bound to plasma proteins than to activated charcoal, then hemoperfusion is unlikely to be beneficial even if the V_d of the xenobiotic is small. In addition, high plasma protein binding limits the effectiveness of hemodialysis because only unbound xenobiotic will freely cross the dialysis membrane. Exchange transfusion can be effective for a xenobiotic with a small V_d and substantial plasma protein binding because both bound and free xenobiotic are removed simultaneously.

ELIMINATION

Removal of a parent xenobiotic from the body (elimination) begins as soon as the xenobiotic is delivered to clearance organs such as the liver, kidneys, and lungs. Elimination includes biotransformation and excretion. Elimination begins immediately but may not be the predominant kinetic process until absorption and distribution are substantially completed. The functional integrity of the cardiovascular, pulmonary, renal, and hepatic systems are major determinants of the efficiency of xenobiotic removal and of therapeutically administered antidotes. The xenobiotics themselves may cause kidney or liver (eg, APAP) failure, subsequently compromising their own elimination. Other factors that influence elimination include older age (enzyme maturation), competition or inhibition of elimination processes by interacting xenobiotics, saturation of enzymatic processes, gender, pharmacogenetics and pharmacogenomics, obesity, and the physicochemical properties of the xenobiotic.⁴⁶

Elimination can be accomplished by biotransformation to one or more metabolites or by excretion from the body of unchanged xenobiotic. Excretion may occur via the kidneys, lungs, GI tract, and body secretions (sweat, tears, milk). Because of their water solubility, hydrophilic (polar) or charged xenobiotics and their metabolites are generally excreted via the kidney. The majority of xenobiotic metabolism occurs in the liver, but it also occurs in the blood, skin, GI tract, placenta, or kidneys. Lipophilic (uncharged or nonpolar) xenobiotics are usually metabolized in the liver to hydrophilic metabolites, which are then excreted by the kidneys.^{24,51} These metabolites are generally inactive, but if active, they may contribute to toxicity. Examples of active metabolites include nortriptyline (derived from amitriptyline), N-acetylprocainamide (derived from procainamide) and normeperidine (derived from meperidine).

Metabolic reactions catalyzed by enzymes, categorized as either phase I or phase II, may result in pharmacologically active metabolites; frequently, the latter have different toxicities than the parent compounds. Phase I (asynthetic), or preparative metabolism, which may or may not precede phase II, is responsible for introducing polar groups onto nonpolar xenobiotics by oxidation (hydroxylation, dealkylation, deamination), reduction (alcohol dehydrogenase, azo reduction), and hydrolysis (ester hydrolysis).^{22,49} Phase II, or synthetic, reactions conjugate the polar group with a glucuronide, sulfate, acetate, methyl or glutathione or amino acids such as glycine, taurine, and glutamic acid, creating more polar metabolites.^{14,22,49}

Comparatively, phase II reactions produce a much larger increase in hydrophilicity than phase I reactions. The enzymes involved in these reactions have low substrate specificity, and those in the liver are usually localized to either the endoplasmic reticulum (microsomes) or the soluble fraction of the cytoplasm (cytosol).⁴⁹ The location of the enzymes becomes important if they form reactive metabolites, which then concentrate at the site of metabolism and cause toxicity. For example, APAP causes centrilobular necrosis because the CYP2E1 enzymes, which form N-acetyl-p-benzoquinoneimine (NAPQI), the toxic metabolite, are located in their highest concentration in that zone of the liver.

The enzymes that metabolize the largest variety of xenobiotics are heme-containing proteins referred to as CYP monooxygenase enzymes.^{28,49} This group of enzymes, formerly called the mixed function oxidase system, is found in abundance in the microsomal endoplasmic reticulum of the liver. These cytochrome P450 metabolizing enzymes (CYPs) primarily catalyze the oxidation of xenobiotics. Cytochrome P450 in a reduced state (Fe^{2+}) binds carbon monoxide. Its discovery and initial name resulted from spectral identification of the colored CO-bound cytochrome P450, which absorbs light maximally at 450 nm. The cytochrome P450 system is composed of many enzymes grouped according to their respective gene families and subfamilies, of which approximately 57 of these functional human genes have been sequenced. Members of a gene family have more than 40% similarity of their amino acid sequencing, and subfamilies have more than 55% similarity. For example, the CYP2D6*1a gene encodes wild-type protein (enzyme) CYP2D6, where 2 represents the family, D the subfamily and 6 the individual gene, and *1a the mutant allele; CYP2D6.1 represents the most common or wild-type allele.

Toxicity may result from induction or inhibition of CYP enzymes by another xenobiotic, resulting in a consequential drug interaction (Chap. 13). Many of these interactions are predictable based on the known xenobiotic affinities and their capability to induce or inhibit the P450 system.^{12,42,49,50,66} However, polymorphism (individual genetic expression of enzymes),¹ stereoisomer variability⁷⁵ (enantiomers with different potencies and isoenzyme affinities), and the capability to metabolize a xenobiotic by alternate pathways contribute to unexpected metabolic outcomes. The pharmaceutical industry is now exploiting the concept of chiral switching (marketing a single enantiomer instead of the racemic mixture) to alter efficacy or side effect profiles. Enantiomers are named either according to the direction in which they rotate polarized light

(l or – for levorotatory, and d or + for dextrorotatory) or according to the absolute spatial orientation of the groups at the chiral center (S or R). Chiral means “hand” in Greek, and the latter designations refer to either sinister (left-handed) or rectus (right-handed). There is no direct correlation between levorotatory or dextrorotatory and S and R, which indicates the direction polarized light is rotated by a solution of the xenobiotic.⁷⁰

The liver reduces the oral bioavailability of xenobiotics with high extraction ratios. The bioavailabilities of xenobiotics with high extraction ratios are greatly affected by enzyme induction and enzyme inhibition; the reverse is true for xenobiotics with a low extraction ratio. After the xenobiotic is in the blood, the hepatic elimination is affected by blood flow to the liver, the intrinsic hepatic metabolism, and plasma protein binding. If the hepatic metabolism of a xenobiotic is very high, then the only limit to hepatic clearance is blood flow to the liver, and not protein binding. However, if the intrinsic hepatic metabolism for a xenobiotic is low, then blood flow to the liver is not consequential. Plasma protein binding becomes important because only unbound xenobiotics can be cleared by the liver. Because enzyme inhibition and induction greatly affect intrinsic hepatic metabolism, these factors are also important.

Excretion is primarily accomplished by the kidneys, with biliary, pulmonary, and body fluid secretions contributing to lesser degrees. Urinary excretion occurs through glomerular filtration, tubular secretion, and passive tubular reabsorption. The glomerulus filters unbound xenobiotics of a particular size and shape in a manner that is not saturable (but is subject to renal blood flow and perfusion). Passive tubular reabsorption accounts for the reabsorption of uncharged, lipid-soluble xenobiotics and is therefore influenced by the pH of the urine and the pK_a or pK_b of the xenobiotic. The principles of diffusion discussed earlier permit, for example, the ion trapping of salicylate ($pK_a = 3.5$) in the urine through urinary alkalization. Tubular secretion is an active process carried out by drug transporters (OATs, OCTs) and subject to saturation and drug interactions (Table 9–4).

TABLE 9–4. Xenobiotics Secreted by Renal Tubules

<i>Organic Anion Transport</i>	<i>Organic Cation Transport</i>
Acetazolamide	Acetylcholine
Bile salts	Amiodarone
Cephalosporins	Atropine
Indomethacin	Cimetidine
Hydrochlorothiazide	Digoxin
Furosemide	Diltiazem
Methotrexate	Dopamine
Penicillin G	Epinephrine
Probenecid	Morphine
Prostaglandins	Neostigmine
Salicylates	Procainamide
	Quinidine
	Quinine
	Triamterene
	Trimethoprim
	Verapamil

The effects of obesity on elimination are being studied. Obesity is the accumulation of adipose tissue far in excess of that which is considered normal for a person’s age and gender. The National Institutes of Health defines obesity as a body mass index (BMI) greater than 30 and overweight as a BMI between 25 and 29.9. The BMI is calculated by dividing a person’s weight in kilograms by the individual’s height in meters squared (m^2). By this criterion, about one-third of the adult US population is obese. Obesity poses problems in determining the correct loading dose and maintenance dose for therapeutic xenobiotics and for the estimation of serum concentrations and elimination times in the overdose setting.^{10,26,39,48} A number of formulas have been proposed to classify body size in addition to BMI, but none has been tested adequately in the obese population. Obese patients have not only an increase in adipose tissue but also an increase in lean body mass of 20% to 55%, which results in the alteration of the distribution of both lipophilic and hydrophilic xenobiotics. In general, the absorption of xenobiotics in obese patients does not appear to be affected, but distribution is affected. The effect of obesity on hepatic metabolism requires additional study, although some studies suggest a nonlinear increase in clearance. The glomerular filtration rate increases in obesity. For example, although aminoglycosides are hydrophilic, because of an increase in fat free mass in obese patients, a dosing weight correction of 40% is used to calculate both the loading dose and the maintenance dose ($\text{Dosing body weight} = 0.4 \times \{\text{Actual body weight} - \text{Ideal body weight}\} + \text{Ideal body weight}$). Preliminary studies with propofol, a very lipophilic drug, suggest that induction and maintenance doses correlate better with actual body weight. These equations are found in Table 9–5. One recent evaluation suggests using 40% of actual body weight instead of ideal body weight in the Cockcroft-Gault formula to estimate kidney

function in the obese.

TABLE 9–5. Equations for Determining Body Size

$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$
$\text{BSA (m}^2\text{)} = \frac{\sqrt{\text{Height (cm)} \times \text{Weight (kg)}}}{\sqrt{3600}}$
IBW: Males (kg) = 50 + 2.3 (Height > 60 in)
IBW: Females (kg) = 45.5 + 2.3 (Height > 60 in)
$\text{LBW}_{2005} \text{ : Males (kg)} = \frac{9270 \times \text{Weight (kg)}}{6680 + [(216 \times \text{BMI (kg/m}^2\text{)})]}$
$\text{LBW}_{2005} \text{ : Females (kg)} = \frac{9270 \times \text{Weight (kg)}}{8780 + [(244 \times \text{BMI (kg/m}^2\text{)})]}$

BMI = body mass index; BSA = body surface area; IBW = ideal body weight; LBW = lean body weight.

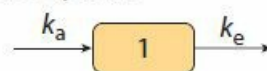
CLASSICAL VERSUS PHYSIOLOGIC COMPARTMENT TOXICOKINETICS

Models exist to study and describe the movement of xenobiotics in the body with mathematical equations. Traditional compartmental models (one or two compartments) are data based and assume that changes in plasma concentrations represent proportional changes in tissue concentrations (Fig. 9–6).⁴⁷ Advances in computer technology facilitate the use of the classic concepts developed in the late 1930s.⁶⁹ Physiologic models consider the unique movement characteristics of xenobiotics based on known or theoretical biologic processes. This allows the prediction of tissue concentrations while incorporating the effects of changing physiologic parameters and affording better extrapolation from laboratory animals.⁷⁹ Unfortunately, physiologic modeling is still in its infancy, and the mathematical modeling it entails is often very complex.¹⁹ The commonest mathematical equations used are based on traditional compartmental modeling.

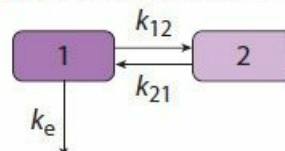
Model 1. One-compartment open model, IV injection.



Model 2. One-compartment open model with first-order absorption.



Model 3. Two-compartment open model, IV injection.



Model 4. Two-compartment open model with first-order absorption.

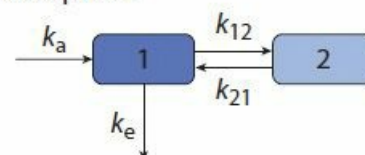


FIGURE 9–6. Various classical compartmental models. 1, plasma or central compartment; 2 = tissue compartment; IV,

intravenous; k_a = absorption rate constant; k_e = pharmacokinetic elimination rate constants; k_{12} = rate constant into tissue from plasma; k_{21} = rate constant into plasma from tissue.

The one-compartment model is the simplest approach for analytic purposes and is applied to xenobiotics that enter and rapidly distribute throughout the body. This model assumes that changes in plasma concentrations will result in and reflect proportional changes in tissue concentrations. Many xenobiotics, such as digoxin, lithium, and lidocaine, do not instantaneously equilibrate with the tissues and are better described by a two-compartment model. In the two-compartment or more than two-compartment model, a xenobiotic is distributed instantaneously to highly perfused tissues (central compartment) and then is secondarily, and more slowly, distributed to a peripheral compartment. Elimination is assumed to take place from the central compartment.

If the rate of a reaction is directly proportional to the concentration of xenobiotic, it is termed first order or linear. Processes that are capacity limited or saturable are termed nonlinear (not proportional to the concentration of xenobiotic) and are described by the Michaelis-Menten equation, which is derived from enzyme kinetics. Calculus is used to derive the first-order equation.⁷⁹ Rate is directly proportional to concentration of xenobiotic, as in Equation 9–8.

$$\text{Rate} \propto \text{concentration (C)} \quad (\text{Eq. 9-8})$$

An infinitesimal change in concentration of a xenobiotic (dC) with respect to an infinitesimal change in time (dt) is directly proportional to the concentration (C) of the xenobiotic as in Equation 9–9:

$$\frac{dC}{dt} \propto C \quad (\text{Eq. 9-9})$$

The proportionality constant k is added to the right side of the expression to mathematically allow the introduction of an equality sign. The constant k represents all of the bodily factors, such as metabolism and excretion, which contribute to the determination of concentration (Equation 9–10).

$$\frac{dC}{dt} = kC \quad (\text{Eq. 9-10})$$

Introducing a negative sign to the left-hand side of the equation describes the “decay” or decreasing xenobiotic concentration (Equation 9–11).

$$-\frac{dC}{dt} = kC \quad (\text{Eq. 9-11})$$

This equation is impractical because of the difficulty of measuring infinitesimal changes in C or t . Therefore, the use of calculus allows the integration or summing of all of the changes from one concentration to another beginning at time zero and terminating at time t . This relationship is mathematically represented by the integration sign (\int). The sign \int means to integrate the term from concentration at time zero (C_0) to concentration at a given time t (C_t). \int means the same with respect to time, where $t_0 = \text{zero}$. Before this application, the previous equation is first rearranged (Equation 9–12).

$$\begin{aligned} -\frac{dC}{C} &= k dt \\ \int_{C_0}^{C_t} -\frac{dC}{C} &= k \int_0^t dt \end{aligned} \quad (\text{Eq. 9-12})$$

The integration of dC divided by C is the natural logarithm of C ($\ln C$), and the integration of dt is t (Equation 9–13).

$$-\ln C \Big|_{C_0}^{C_t} = kt \Big|_{t_0}^t \quad (\text{Eq. 9-13})$$

The vertical straight lines proscribe the evaluation of the terms between those two limits. The following series of manipulations is then performed (Equation 9–14A–D).

$$-(\ln C_t - \ln C_0) = k(t - 0) \quad (\text{Eq. 9-14A})$$

$$-\ln C_t + \ln C_0 = kt \quad (\text{Eq. 9-14B})$$

$$-\ln C_t = -\ln C_0 + kt \quad (\text{Eq. 9-14C})$$

$$\begin{array}{ccc} -\ln C_t = & \ln C_0 - & kt \\ \text{Can be} & \text{Constant} & \text{Can be} \\ \text{measured} & & \text{selected} \end{array} \quad (\text{Eq. 9-14D})$$

Equation 9–14D can be recognized as taking the form of an equation of a straight line (Equation 9–15), where the slope is equal to the negative rate constant k and the intercept is C_0 .

$$y = b + mx \quad (\text{Eq. 9-15})$$

Instead of working with natural logarithms, an exponential form (the antilog) of Equation 9–14D may be used (Equation 9–16).

$$C_t = C_0 e^{-kt} \quad (\text{Eq. 9-16})$$

Graphing the \ln (natural logarithm) of the concentration of the xenobiotic at various times for a first-order reaction is a straight line. Equation 9–16 describes the events when only one first-order process occurs. This is appropriate for a one-compartment model (Fig. 9–7).

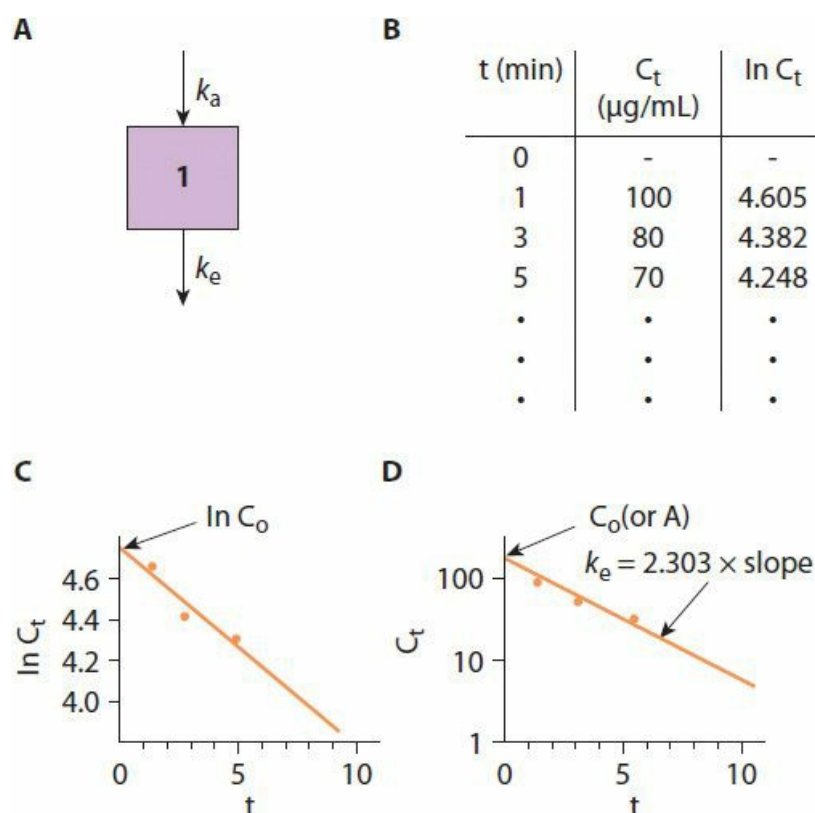


FIGURE 9–7. A one-compartment pharmacokinetic model demonstrating graphical illustration (A), hypothetical dataset (B), linear plot (C), and semilogarithmic plot (D).

In this model, regardless of the concentration of the xenobiotic, the rate (percentage) of decline is constant. The absolute amount of xenobiotic eliminated changes continuously while the percent eliminated remains constant. k is reported in h^{-1} . A k_e of 0.10 h^{-1} means that the xenobiotic is being processed (eliminated) at a rate of 10% per hour. k is often designated as k_e and referred to as the elimination rate constant. The time necessary for the xenobiotic concentration to be reduced by 50% is called the half-life. The half-life is determined by a rearrangement of Equation 9–14D whereby C_2 becomes C at time t_2 and C_1 becomes C at t_1 and by rearrangement giving Equation 9–17:

$$(t_1 - t_2) = \frac{(\ln C_1 - \ln C_2)}{k_e} \quad (\text{Eq. 9-17})$$

Substitution of 2 for C_1 and 1 for C_2 or 100 for C_1 and 50 for C_2 gives Equations 9–18A and 9–18B:

$$t_{1/2} = \frac{(\ln 2 - \ln 1)}{k_e} \quad (\text{Eq. 9-18A})$$

$$t_{1/2} = \frac{0.693}{k_e} \quad (\text{Eq. 9-18B})$$

The use of semilog paper facilitates graphing the first-order equation. If natural logs are used to calculate slope, then $k_e = -\text{slope}$, and if common logs are used to calculate slope, then $k_e = -2.303 \times \text{slope}$ (Fig. 9–7).

The mathematical modeling becomes more complex when more than one first-order process contributes to the overall elimination process. The equation that incorporates two first-order rates is used for a two-compartment model and is Equation 9–19.

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \quad (\text{Eq. 9-19})$$

Figure 9–8 demonstrates a two-compartment model where α often represents the distribution phase and β is the elimination phase.

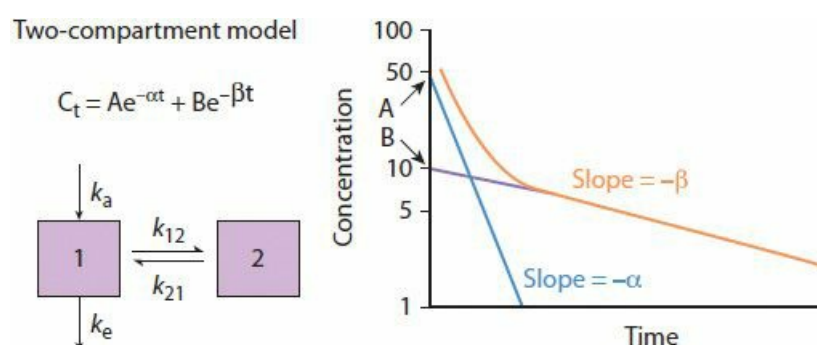


FIGURE 9–8. Mathematical and graphical forms of a two-compartment classical pharmacokinetic model. k_a represents the absorption rate constant, k_e represents the elimination rate constant, α represents the distribution phase, and β represents the elimination phase.

The rate of reaction of a saturable process is not linear (ie, not proportional to the concentration of xenobiotic) when saturation occurs (Fig. 9–9). This model is best described by the Michaelis-Menten equation used in enzyme kinetics (Equation 9–20) in which v is the velocity or rate of the enzymatic reaction, C is the concentration of the xenobiotic, V_{\max} is the maximum velocity of the reaction between the enzyme and the xenobiotic at high xenobiotic concentrations, and K_m is the substrate concentration at which the reaction rate is half of the V_{\max} .⁷⁹

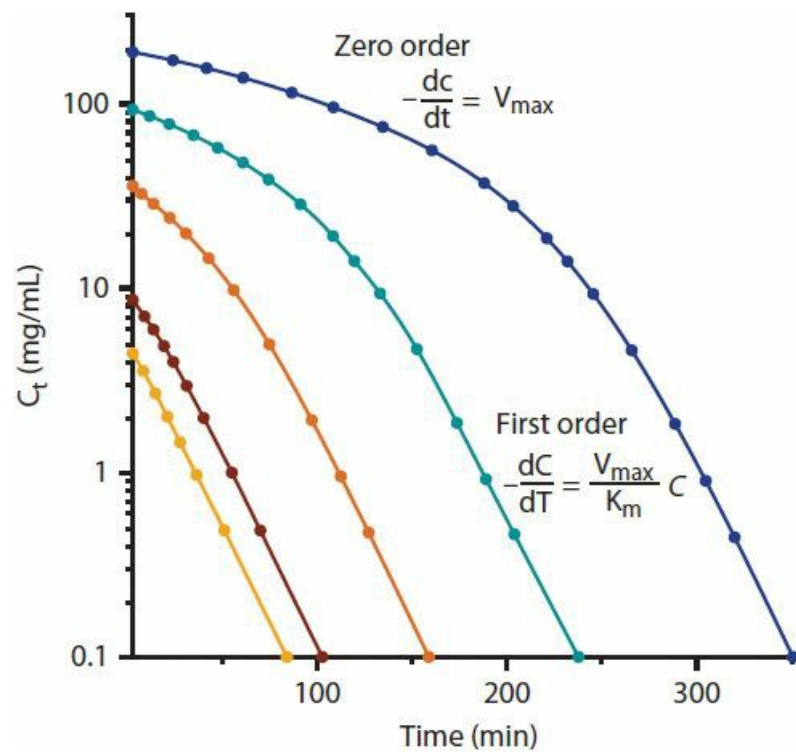


FIGURE 9-9. Concentration versus time curve for a xenobiotic showing nonlinear pharmacokinetics where concentrations below 10 mg/mL represent first-order elimination. C, concentration; K_m , affinity constant; v , velocity; V_{max} , maximum velocity.

$$v = \frac{V_{max} \times C}{K_m + C} \quad (\text{Eq. 9-20})$$

Application of this equation to toxicokinetics requires v to become the infinitesimal change in concentration of a xenobiotic (dC) with respect to an infinitesimal change in time (dt) as previously discussed (Equation 9-10). V_{max} and K_m both reflect the influences of diverse biologic processes. The Michaelis-Menten equation then becomes Equation 9-21, in which the negative sign again represents decay:

$$-\frac{dC}{dt} = \frac{V_{max} \times C}{K_m + C} \quad (\text{Eq. 9-21})$$

When the concentration of the xenobiotic is very low ($C \ll K_m$), it can be dropped from the bottom right of the equation because its contribution becomes negligible, and the resultant equation is described as a first-order process (Equation 9-22A and 9-22B). Conceptually, this is understandable because at a very low xenobiotic concentration, the process is not saturated.

$$-\frac{dC}{dt} = \frac{V_{max} \times C}{K_m} \quad (\text{Eq. 9-22A})$$

Because V_{max} divided by K_m is a constant, k , then:

$$-\frac{dC}{dt} = kC \quad (\text{Eq. 9-22B})$$

However, when the concentrations of the xenobiotic are extremely high and exceed the capacity of the system ($C \gg K_m$), the rate becomes fixed at a constant maximal rate regardless of the exact concentration of the xenobiotic, termed a zero-order reaction. [Tables 9-6A and 9-6B](#) compare a first-order reaction with a zero-order reaction. In this particular example, zero order is faster, but if the fraction of xenobiotic eliminated in the first-order example were 0.4, then the amount of xenobiotic in the body would decrease below 100 before the xenobiotic in the zero-order example. It is inappropriate to perform half-life calculations on a xenobiotic displaying zero-order behavior because the metabolic rates are continuously changing. Sometimes the term apparent half-life is used if it is unclear if the xenobiotic is exhibiting zero-order or first-order pharmacokinetics. After an overdose, enzyme saturation is a common occurrence because the capacity of enzyme systems is overwhelmed.

TABLE 9–6A. Illustration of 1000 mg of a Xenobiotic in the Body after First-Order Elimination

<i>Time after Administration (hour)</i>	<i>Amount in Body (mg)</i>	<i>Amount Eliminated over Preceding Hour (mg)</i>	<i>Fraction Eliminated over Preceding Hour</i>
0	1000	—	—
1	850	150	0.15
2	723	127	0.15
3	614	109	0.15
4	522	92	0.15
5	444	78	0.15
6	377	67	0.15

TABLE 9–6B. Illustration of 1000 mg of a Xenobiotic in the Body after Zero-Order Elimination

<i>Time after Drug Administration (hour)</i>	<i>Amount of Drug in Body (mg)</i>	<i>Amount of Drug Eliminated over Preceding Hour (mg)</i>	<i>Fraction of Drug Eliminated over Preceding Hour</i>
0	1000	—	—
1	850	150	0.15
2	700	150	0.18
3	550	150	0.21
4	400	150	0.27
5	250	150	0.38
6	100	150	0.60

CLEARANCE

Clearance (Cl) is the relationship between the rate of transfer or elimination of a xenobiotic from a reference fluid (usually plasma) to the plasma concentration (Cp) of the xenobiotic and is expressed in units of volume per unit time mL/min (Equation 9–23).^{25,47,61}

$$Cl = \frac{\text{Rate of elimination}}{C_p} \quad (\text{Eq. 9-23})$$

The determination of creatinine clearance is a well-known example of the concept of clearance. Creatinine clearance (Cl_{CR}) is determined by Equation 9–24:

$$Cl_{\text{creatinine}} = \frac{U \times V}{C_p} \quad (\text{Eq. 9-24})$$

in which U is the concentration of creatinine in urine (mg/mL), V is the volume flow of urine (mL/min), Cp is the plasma concentration of creatinine (mg/mL), and the units for clearance are milliliters per minute. A creatinine clearance of 100 mL/min means that 100 mL of plasma is completely cleared of creatinine every minute. Clearance for a particular eliminating organ or for extracorporeal elimination is calculated with Equation 9–25:

$$Cl = Q_b \times (ER) = Q_b \times \frac{(C_{in} - C_{out})}{C_{in}} \quad (\text{Eq. 9-25})$$

Cl = clearance for the eliminating organ or extracorporeal device

Q_b = blood flow to the organ or device

ER = extraction ratio

C_{in} = xenobiotic concentration in fluid (blood or serum) entering the organ or device

C_{out} = xenobiotic concentration in fluid (blood or serum) leaving the organ or device

Clearance can be applied to any elimination process independent of the precise mechanisms (ie, first order, Michaelis-Menten) and represents the sum total of all of the rate constants for xenobiotic elimination. Total body clearance ($Cl_{total\ body}$) is the sum of the clearances of each of the individual eliminating processes, as seen in Equation 9–26:

$$Cl_{total\ body} = Cl_{renal} + Cl_{hepatic} + Cl_{intestinal} + Cl_{chelation} + \dots \quad (\text{Eq. 9-26})$$

For a first-order process (one-compartment model), clearance is given by Equation 9–27:

$$Cl = k_e Vd \quad (\text{Eq. 9-27})$$

Experimentally, the clearance can be derived by examining the IV dose of xenobiotic in relation to the AUC from time zero to time t (Equation 9–28). The AUC is calculated using the trapezoidal rule or through integral calculus (units, eg, {mg \times hour}/mL) (Figs. 9–10 and 9–11).

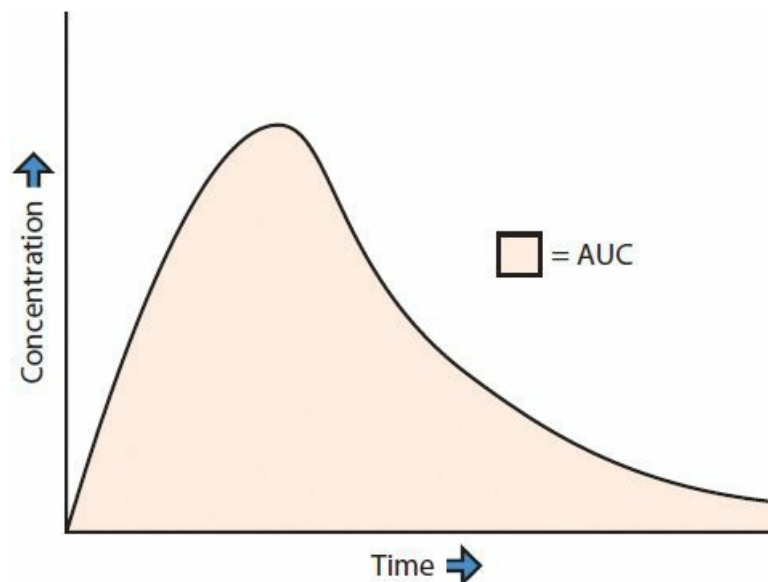


FIGURE 9–10. The area under the curve (AUC) profile obtained after extravascular administration of a xenobiotic.

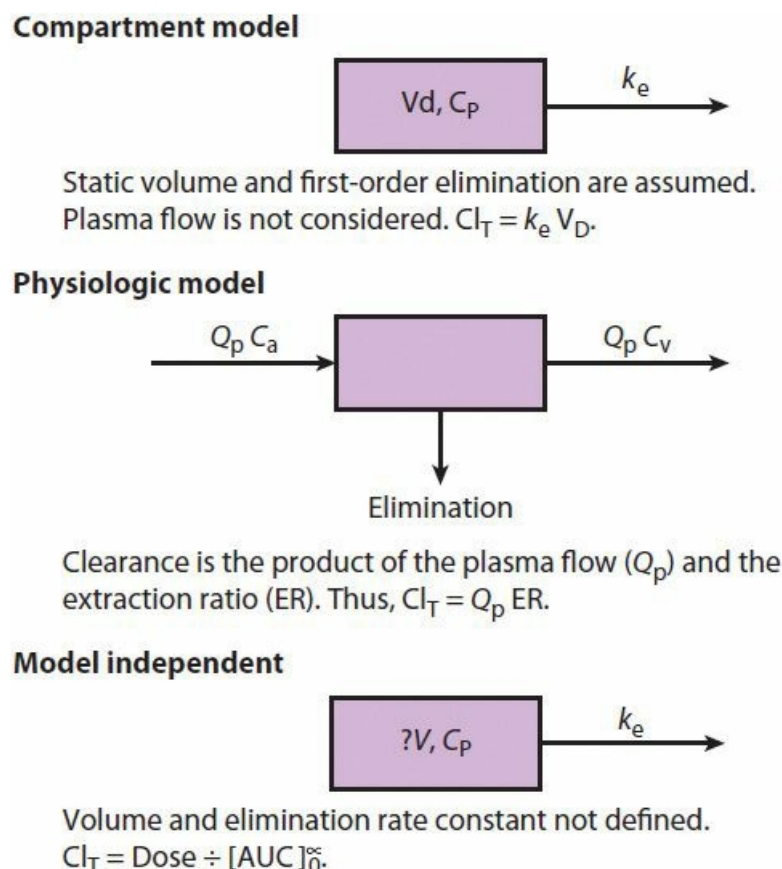


FIGURE 9–11. General approaches to clearance.

$$Cl = \frac{\text{dose}_{IV}}{AUC_{0-t}} \quad (\text{Eq. 9-28})$$

STEADY STATE

When exposure to a xenobiotic occurs at a fixed rate, the plasma concentration of the xenobiotic gradually achieves a plateau concentration at which the rate of absorption equals the rate of elimination and is termed steady state. The time to achieve 95% of steady-state concentration for a first-order process depends on the half-life and usually necessitates 5 half-lives. The concentration achieved at steady state depends on the V_d , the rate of exposure, and the half-life.

Iatrogenic toxicity may occur in the therapeutic setting when dosing decisions are based on serum concentrations determined before achieving a steady state. This adverse event is particularly common when using xenobiotics with long half-lives such as digoxin⁷⁸ and phenytoin.

PEAK PLASMA CONCENTRATIONS

Peak plasma concentrations (C_{\max}) of a xenobiotic occur at the time of peak absorption. At this point in time, the absorption rate is at least equal to the elimination rate. Thereafter, the elimination rate predominates, and plasma concentrations begin to decline. Whereas the C_{\max} depends on the dose, the rate of absorption (k_a), the rate of elimination (k_e), and the time to peak (t_{\max}) are independent of dose and only depend on the k_a and k_e . For the same dose of xenobiotic, if the k_e remains constant and the rate of absorption decreases, then the t_{\max} will occur later, and the C_{\max} will be slightly lower (Table 9–7). Controlled-release dosage forms and xenobiotics that form concretions and have a decreased rate of absorption may not achieve peak concentrations until many hours after an immediate-release preparation with rapid absorption. The AUC will remain the same. However, if the k_a remains constant and the k_e is increased, then the t_{\max} occurs sooner, the C_{\max} decreases, and the AUC decreases (Table 9–7).⁵² Values are based on a single oral dose (100 mg) that is 100% bioavailable ($F = 1$) and has an apparent V_d of 10 L. The drug follows a one-compartment open model. The AUC is calculated by the trapezoidal rule from 0 to 24 hours.

TABLE 9–7. Pharmacokinetic Effects of the Absorption Rate Constant and Elimination Rate Constant

Absorption Rate Constant k_a (h^{-1})	Elimination Rate Constant k_e (h^{-1})	t_{max} (h)	C_{max} ($\mu g/mL$)	AUC ($\mu g \cdot hr/mL$)
0.1	0.2	6.93	2.50	50
0.2	0.1	6.93	5.00	100
0.3	0.1	5.49	5.77	100
0.4	0.1	4.62	6.26	100
0.5	0.1	4.02	6.69	100
0.6	0.1	3.58	6.69	100
0.3	0.1	5.49	5.77	100
0.3	0.2	4.05	4.44	50
0.3	0.3	3.33	3.68	33.3
0.3	0.4	2.88	3.16	25
0.3	0.5	2.55	2.79	20

AUC = area under the (plasma drug concentration versus time) curve; C_{max} = peak xenobiotic concentration; t_{max} = time to peak plasma concentration.

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In the overdose setting, gastric emptying, single-dose activated charcoal, and WBI decrease k_a . Multiple-dose activated charcoal, manipulation of pH to promote ion trapping to facilitate elimination, and certain chelators (ie, succimer, deferoxamine) increase k_e and are likely to decrease C_{max} , t_{max} , and AUC.

INTERPRETATION OF SERUM CONCENTRATIONS

For serum concentrations to have significance, there must be an established relationship between effect and serum concentration. Many medications, such as valproic acid, digoxin, carbamazepine, lithium, and cyclosporine, have established therapeutic ranges. However, there are also many drugs (eg, diazepam, propranolol, verapamil) for which there is no established therapeutic range. Some xenobiotics (eg, physostigmine) exhibit hysteresis in which the effect increases as the serum concentration decreases. For many xenobiotics, very little information on toxicodynamics is available. Sequential serum concentrations often are collected for retrospective analysis in an attempt to correlate serum concentrations and toxicity. Tolerance to drugs, such as ethanol, also influences the interpretation of serum concentrations. Tolerance is an example of a pharmacodynamic or toxicodynamic effect as a result of cellular adaptation, and it occurs when larger doses of a xenobiotic are necessary to achieve the same clinical or pharmacologic result.

Other factors that influence the interpretation of serum concentrations include chronicity of dosing (a single dose vs. multiple doses); whether absorption is still ongoing and therefore concentrations are still increasing; whether distribution is still ongoing and therefore concentrations are uninterpretable (Fig. 9–12); or whether the value is a peak, trough, or steady-state concentration. Collection of accurate data for analysis requires at least 4 data points during at least 1 elimination half-life. Clinical examples in which interpretation is dependent on the dosing pattern of a single dose versus multiple doses include digoxin, lithium, vancomycin, and APAP. Controlled-release preparations and xenobiotics that delay gastric emptying or form concretions are expected to have prolonged absorptive phases and require serial serum concentrations to obtain a meaningful analysis of serum concentrations (Chap. 6). A combination of trough, peak, and minimum inhibitory concentrations is often consequential for monitoring antibiotics such as gentamicin.^{8,43}

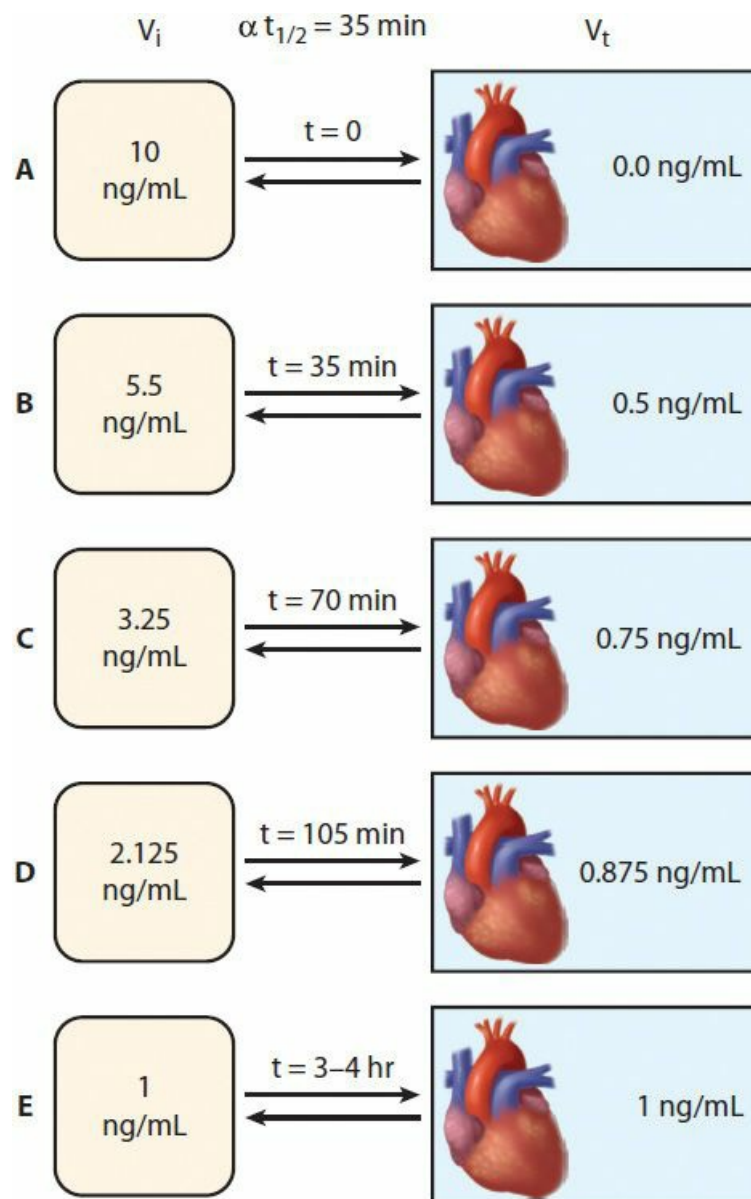


FIGURE 9-12. A theoretical two-compartment model for digoxin. Assume A to E represent the digoxin serum concentration equilibria at different t (time) intervals between the plasma compartment and the tissue compartment. V_i (initial volume of distribution) is smaller than V_t (tissue volume of distribution). The myocardium sits in V_t . E represents distribution at 5 half-lives and it is assumed that the plasma and tissue compartments are now in equilibrium.⁷⁸ (Reproduced with permission from Winter ME: Basic Clinical Pharmacokinetics, 5th edition. Vancouver, WA: Applied Therapeutics; 2010.)

Pitfalls in interpretation arise when the units for a particular serum concentration are not obtained or are unfamiliar (eg, mmol/L) to the clinician. The type of analysis generally applied clinically may not be appropriate to massive overdoses, and the laboratory may make errors in dilution, or errors can be inherent in the assay (Chap. 6). In these cases, the director of the laboratory should be consulted for advice with regard to the availability of a reference laboratory. The type of collection tube (eg, plasma or serum instead of whole blood for certain metals), the receptacle, or the conditions during delivery of the sample result in inaccurate or inadequate information. When in doubt, the laboratory toxicologist or chemist should be called before sample collection. The laboratory usually measures total xenobiotic (free plus bound), and for xenobiotics that are highly plasma protein bound, reductions in albumin increase free concentrations and alter the interpretation of the reported concentration (Equation 9-7). Active metabolites may contribute to toxicity and may not be measured.³⁷ During extracorporeal methods of elimination, ideal criteria for determining the amount removed require assay of the dialysate or activated charcoal cartridge or multiple simultaneous serum concentrations going into and out of the device rather than random serum concentrations (Chap. 10). Clearance calculations for drugs such as lithium that partition significantly into the red blood cells are more accurate when measurements are taken on whole blood.^{13,20} The patient's weight and height and, when indicated, hemoglobin, creatinine, albumin, and other parameters to assess elimination pathways may be helpful.

SUMMARY

- Pharmacokinetics and toxicokinetics are the study of the absorption, distribution, metabolism, and excretion of drugs in the therapeutic and overdose settings, respectively.
- Pharmacokinetics and toxicokinetics can help predict the onset and duration of toxicity when serum concentrations are related to therapeutic and toxic effects.
- Interpretation of serum concentrations relies on many factors dependent on the drugs (eg, dosage form, single versus multiple doses) and the patient (tolerance, genetic profile).

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10 PRINCIPLES AND TECHNIQUES APPLIED TO ENHANCE ELIMINATION

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Enhancing the elimination of a xenobiotic from a poisoned patient is a logical step after techniques to inhibit absorption such as orogastric lavage, activated charcoal, or whole-bowel irrigation have been considered. [Table 10–1](#) lists methods that might be used to enhance elimination. Some of these techniques are described in more detail in chapters that deal with specific xenobiotics. In this chapter, hemodialysis, hemoperfusion, and hemofiltration are considered extracorporeal treatments because xenobiotic removal occurs in a blood circuit outside the body. Currently, these methods are used infrequently because most poisonings are not amenable to removal by these methods. In addition, because these elimination techniques have associated adverse effects and complications, the risk-benefit analysis suggests a benefit in a relatively small proportion of patients.

TABLE 10–1. Potential Methods of Enhancing Elimination of Xenobiotics

<i>Occurring Inside the Body</i>	<i>Occurring Outside the Body (Extracorporeal)</i>
Cerebrospinal fluid replacement	Hemodialysis
Forced diuresis	Hemoperfusion (charcoal, resin)
Manipulation of urine pH	Hemofiltration/Hemodiafiltration
Metal chelators	Exchange transfusion
Multiple-dose activated charcoal	Plasmapheresis
Peritoneal dialysis	
Resins (Prussian blue, sodium polystyrene sulfonate, cholestyramine, colestipol)	

EPIDEMIOLOGY

Although undoubtedly an underestimate of true use, enhancement of elimination was used relatively infrequently in a cohort of approximately 2.4 million patients reported by the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) in 2011 ([Chap. 136](#)).¹² Alkalinization of the urine was reportedly used 10,843 times, multiple-dose activated charcoal (MDAC) 1904 times, hemodialysis 2323 times, and hemoperfusion 14 times. As in the past, there continue to be many instances of the use of extracorporeal treatments that we consider inappropriate, such as in the treatment of overdoses of cyclic antidepressants (CAs).¹²

Although data reporting remains important in comparing the most recent data with past reports ([Table 10–2](#)), there is a continued increase in the reported use of hemodialysis, paralleling a decline in reports of charcoal hemoperfusion ([Chap. 136](#)). Lithium and ethylene glycol were the most common xenobiotics for which hemodialysis was used between 1985 and 2005. Possible reasons for the decline in use of charcoal and resin hemoperfusion are described in the section Hemoperfusion below. Peritoneal dialysis (PD), a slower modality that should have little or no role in any poisoning, is no longer separately reported ([Chap. 136](#)). “Other extracorporeal procedures” in past AAPCC reports may include continuous modalities (discussed below in the section Continuous Hemofiltration and Hemodiafiltration), plasmapheresis, and PD.

TABLE 10–2. Changes in Use of Extracorporeal Therapies^a

	1986	1990	2001	2004	2007	2011
Hemodialysis	297	584	1280	1726	2106	2323
Charcoal hemoperfusion	99	111	45	20	16	14
Resin	23	37	—	—	—	—
Peritoneal dialysis	62	27	—	—	—	—
Other extracorporeal: CVVH, CVVHD, etc	—	—	26	33	24	26

^aData derived from American Association of Poison Control Centers annual reports (Chap. 136).

Very few prospective, randomized, controlled clinical trials have been conducted to determine which groups of patients actually benefit from enhanced elimination of various xenobiotics and which modalities are most efficacious. For most poisonings, it is unlikely that such studies will ever be performed, given the relative scarcity of appropriate cases of sufficient severity and because of the many variables that would hinder controlled comparisons. Thus, limited evidence predominates. We must therefore rely on an understanding of the principles of these methods to identify the individual patients for whom enhanced elimination is indicated. Isolated case reports in which the kinetics are studied before, during, and after enhanced elimination are also very useful in establishing the efficacy of a method. Fortunately, in the absence of robust evidence, consensus-based recommendations have now been published and are being developed to guide clinical decisions. The American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) published joint position papers on urine alkalinization and MDAC. The Extracorporeal Treatments in Poisoning (EXTRIP) work group, a collaboration of experts from diverse specialties (clinical toxicology, nephrology, pharmacology, critical care, emergency medicine) and represented by more than 30 international societies, is now reviewing the indications for dialysis and other treatments for overdose. Guidelines for several poisons are expected in 2014. See <http://extrip-workgroup.org>.

GENERAL INDICATIONS FOR ENHANCED ELIMINATION

Enhanced elimination may be indicated for several types of patients:

- Patients who fail to respond adequately to comprehensive supportive care. Such patients may have intractable hypotension, heart failure, seizures, metabolic acidosis, or dysrhythmias. Hemodialysis and hemoperfusion (although infrequently used) are much better tolerated than in the past and may represent potentially life-saving opportunities for patients with life-threatening toxicity caused by theophylline, lithium, salicylates, or toxic alcohols.
- Patients in whom the normal route of elimination of the xenobiotic is impaired. Such patients may have kidney or hepatic dysfunction, either preexisting or caused by the overdose. For example, a patient with chronic kidney disease associated with long-term lithium use is more likely to develop toxicity and require hemodialysis as treatment.
- Patients in whom the amount of xenobiotic absorbed or its high concentration in serum indicates that serious morbidity or mortality is likely. Such patients may not appear acutely ill on initial evaluation. Xenobiotics in this group may include ethylene glycol, lithium, methanol, paraquat, salicylates, and theophylline.
- Patients with concurrent disease or in an age group (very young or old) associated with increased risk of morbidity or mortality from the overdose. Such patients are intolerant of prolonged coma, immobility, and hemodynamic instability. An example is a patient with both severe underlying respiratory disease and chronic salicylate poisoning.
- Patients with concomitant electrolyte disorders that could be corrected with hemodialysis. An example is the metabolic acidosis with elevated lactate associated with metformin toxicity discussed in the Hemodialysis section of this chapter.

Ideally, these techniques will be applied to poisonings for which studies suggest an improvement in outcome in treated patients compared with patients not treated with extracorporeal removal. As previously mentioned, these data are rarely available.^{22,26}

The need for extracorporeal elimination is less clear for patients who are poisoned with xenobiotics that are known to be removed by the various modalities of treatment but that cause limited morbidity if supportive care is provided. Relatively high rates of endogenous clearance would also make extracorporeal elimination redundant. Examples of such xenobiotics include ethanol and some barbiturates. Both are subject to substantial rates of hepatic metabolism, and neither would be expected to lead to significant morbidity after the affected patient has had endotracheal intubation and is mechanically ventilated. There may be instances of severe toxicity from these two xenobiotics for which enhanced elimination will reduce the length of intensive care unit (ICU) stays and the associated nosocomial risks; extracorporeal elimination may then be a reasonable option.^{8,50} Dialysis should be avoided if other more effective modalities are

available. For example, a patient with an acetaminophen (APAP) overdose should be initially treated with N-acetylcysteine instead of hemodialysis.

CHARACTERISTICS OF XENOBIOTICS APPROPRIATE FOR EXTRACORPOREAL THERAPY

The appropriateness of any modality for increasing the elimination of a given xenobiotic depends on various properties of the molecules in question. Effective removal by the extracorporeal procedures and other methods listed in [Table 10–1](#) is limited by a large volume of distribution (Vd). The Vd relates to the concentration of the xenobiotic in the blood or serum to the total body burden. The Vd can be envisioned as the apparent volume in which a known total dose of drug is distributed before metabolism and excretion occur:

$$Vd \text{ (L/kg)} \times \text{patient weight (kg)} = \text{Dose (mg)} / \text{Concentration (mg/L)}$$

The larger the Vd, the less the xenobiotic is available in the blood compartment for elimination. A xenobiotic with a relatively small Vd, considered amenable to extracorporeal elimination, would distribute in an apparent volume not much larger than total body water (TBW). TBW is approximately 60% of total body weight, so a Vd equal to TBW is approximately 0.6 L/kg body weight.

Ethanol is an example of a xenobiotic with a small Vd approximately equal to TBW. A substantial fraction of a dose of ethanol could be removed by hemodialysis. In contrast, an insignificant fraction of digoxin with a large Vd (5–12 L/kg of body weight) would be removed by hemodialysis. Lipid-soluble xenobiotics have large volumes of distribution, which typically exceed TBW or even total body weight. These high apparent volumes of distribution imply that the xenobiotic is not available to extracorporeal removal because only a small portion would be in the blood and therefore the extracorporeal circuit. In addition to the alcohols, other xenobiotics with a relatively low Vd include phenobarbital, lithium, salicylates, valproic acid, bromide and fluoride ions, and theophylline. Conversely, those with a high Vd (≥ 1 L/kg of body weight), which would not be removed substantially by hemodialysis, include many β -adrenergic antagonists (with the possible exception of atenolol⁶⁰), diazepam, organic phosphorus compounds, phenothiazines, quinidine, and the CAs.

Pharmacokinetics also influence the ability to enhance elimination of a xenobiotic. Kinetic parameters after an overdose may differ from those after therapeutic or experimental doses. For instance, carrier- or enzyme-mediated elimination processes may be overwhelmed by higher concentrations of the xenobiotic in question, making extracorporeal removal potentially more useful. Similarly, plasma protein- and tissue-binding sites may all be saturated at higher concentrations, making extracorporeal removal feasible in instances in which it would have no role in less significant overdoses. An example is valproic acid, which may be poorly dialyzed at nontoxic concentrations because of high protein binding. However, at higher concentrations, protein-binding sites become saturated and lead to a higher proportion of the drug free in the serum, amenable to removal by hemodialysis at a clinically relevant rate.³⁴ Estimated endogenous elimination of a xenobiotic should be derived by proper toxicokinetic models and not by pharmacokinetic data after therapeutic doses.

When assessing the efficacy of any technique of enhanced elimination, a generally accepted principle is that the intervention is worthwhile only if a large portion of total body drug burden can be eliminated by extracorporeal removal or if total body clearance of the xenobiotic is increased by a factor of 2.⁴¹ This substantial increase is easier to achieve when the xenobiotic has a low endogenous clearance. Examples of xenobiotics with low endogenous clearances (<4 mL/min/kg) include valproic acid, lithium, paraquat, phenytoin, salicylate, and theophylline. Xenobiotics with high endogenous clearances include many β -adrenergic antagonists, lidocaine, opioids, nicotine, and CAs. Enhancement of elimination is expected to contribute more to overall clearance of the former group than to the latter.

The efficacy of any technique of elimination can be directly assessed by comparing the blood or serum concentrations of the xenobiotic at the beginning and the end of the procedure.⁶⁸ For example, a xenobiotic such as theophylline, with one-compartment kinetics, is essentially limited to the extracellular space. The difference between the theophylline concentration before the procedure, minus the concentration at the end of the procedure, divided by the concentration at the beginning, is the fraction of the body burden of the xenobiotic that is eliminated. However, this calculation would not be appropriate to estimate the effect of treatment on the total body burden of a xenobiotic that distributes in a larger Vd or with multicompartment kinetics because the changes in blood concentration may not reflect the effect of the treatment on the total amount in other compartments.

Certain xenobiotics, such as lithium, distribute in part to the intracellular compartment, and equilibrium is established between the intracellular and extracellular compartments. The latter compartment includes the blood from which xenobiotic elimination occurs and the interstitium. An increase in the elimination rate from the extracellular compartment, such as by hemodialysis, alters this equilibrium. The rate of redistribution of the xenobiotic from the intracellular compartment into the now-dialyzed extracellular compartment may be slower than the rate of clearance across the dialysis membrane. In that case, the serum concentration may become relatively low despite a substantial intracellular burden. This low serum concentration reduces the concentration gradient for diffusion from serum to dialysate so that dialysance (the dialysis

clearance) is reduced. Thus, although serum concentrations may decrease precipitously during the procedure, the total-body burden of the xenobiotic may not be affected significantly if it does not move from cells to the dialyzable extracellular volume. An example is a 60-kg patient who ingests 100 (25-mg) amitriptyline tablets, a CA.²² Assuming that the drug is fully absorbed, the 2500-mg distributes in an apparent volume of 40 L/kg of body weight to achieve a serum concentration of 1000 ng/mL, a potentially toxic concentration. If charcoal hemoperfusion is performed with a blood flow rate of 350 mL/min (plasma flow rate of 200 mL/min, assuming a hematocrit of approximately 43%) and the extraction ratio is 100% (see Charcoal Hemoperfusion later), the clearance of drug is 200 mL/min or 200 μ g/min. In 4 hours (240 minutes) of treatment, only 48 mg (48,000 μ g), or less than 2% of the amount ingested, will be removed. The treatment would not have affected toxicity.

Further evidence that a xenobiotic is in a slowly equilibrating compartment is provided by monitoring the serum concentrations after discontinuation of the procedure and demonstrating rebound. This rebound indicates postdialysis redistribution (Fig. 10–1). The magnitude of the rebound depends on total-body stores of the xenobiotic. A postdialysis increase in blood concentration may also result from ongoing absorption from the gastrointestinal (GI) tract.

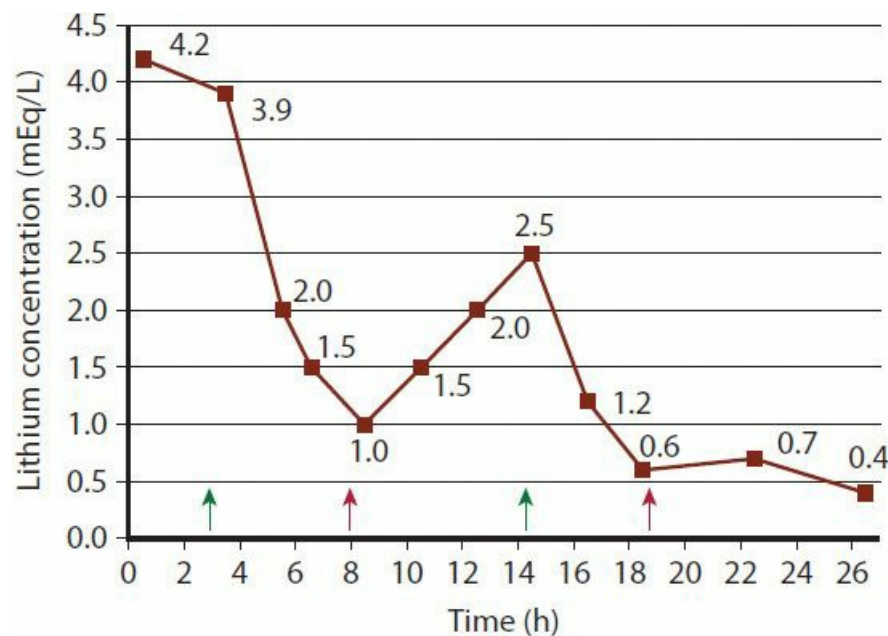


FIGURE 10–1. Repeated serum lithium concentrations after an acute ingestion. Arrows indicate beginning (green arrows) and end (red arrows) of hemodialysis. After a 5-hour hemodialysis treatment, a significant rebound in serum concentration occurred. An additional 4-hour hemodialysis treatment was then begun.

When assessing overall efficacy, the evidence of enhanced elimination must be considered in the context of the clinical response. In some instances, observed improvement is not predicted by the kinetics of the parent xenobiotic and may not result from the intervention. For example, in severe cases of CA poisoning, unexpected improvement during hemoperfusion could be fortuitous because the toxicity is manifested early and ameliorates rapidly during the initial distribution phase.

Beginning a procedure during the initial distribution phase may increase the fraction of the drug burden that can be removed. Later, after the xenobiotic has distributed into fat or has been bound by plasma or tissue proteins, administration of extracorporeal treatment may have much lower clearance rates and benefits.

The extent of xenobiotic removal by enhanced elimination is not necessarily correlated to clinical improvement. For example, enhanced elimination of phenobarbital by MDAC did not affect clinical outcomes compared with those of overdosed, untreated control subjects despite a decrease in their serum concentrations.⁵³ In another study, no difference was observed between patients with lithium poisoning for whom hemodialysis was done and those for whom it was recommended by a poison control center but not done.⁹ Unfortunately, the study was underpowered and limited by confounding by indication. Similarly, in APAP toxicity, the efficacy of administration of N-acetylcysteine makes extracorporeal removal usually unnecessary. Furthermore, although paraquat exhibits all the chemical characteristics necessary for high extracorporeal removal, the outcome of patients presenting late after paraquat ingestion remains dismal despite active elimination procedures.

Occasionally, there may be unanticipated evidence of improvement despite removal of marginal amounts of the xenobiotic and active metabolites. Some authors have attributed this surprising finding to removal of a critical amount of xenobiotic from a shallow “toxic effect” compartment. This theory has been advanced to explain the response to hemodialysis of patients overdosed with the antipsychotic chlorprothixene³⁹ or with a combination of diltiazem and metoprolol.³ Such effects may lead to transient improvements that are not sustained as drug redistributes from one pool to another, leading to early benefit but eventual recurrence of symptoms. Much of the relevant literature fails to provide long-

term follow-up to demonstrate prolongation of benefits after extracorporeal therapy is completed and xenobiotics have redistributed.

TECHNIQUES TO ENHANCE REMOVAL OF XENOBIOTICS

Although the efficacy of or need for removal of many xenobiotics remains controversial, consensus regarding the indications for a number of procedures has developed. This consensus has led to consistent application of several techniques of enhanced elimination for some toxic exposures that occur relatively more frequently. The techniques to enhance xenobiotic elimination most commonly applied over the past decade have been alkalization of the urine for salicylates and hemodialysis for methanol, ethylene glycol, lithium, and salicylates.

Multiple-Dose Activated Charcoal: “Gastrointestinal Dialysis”

Oral administration of multiple doses of activated charcoal increases elimination of some xenobiotics present in the blood. This modality is discussed in more detail in Antidotes in Depth: A1 and will not be discussed here.

Resins

Resins are sometimes used in poisoning management. They can reduce bioavailability of ingested drugs and act as decontaminants, similarly to activated charcoal. In addition, however, they can enhance elimination of certain xenobiotics by enhancing their back-diffusion from plasma to gut (GI dialysis) and interrupt enterohepatic recirculation.

The most commonly used resins are sodium polystyrene sulfonate (Kayexalate), cholestyramine, and Prussian blue. Sodium polystyrene sulfonate is an ion exchanger that is used regularly for hyperkalemia in patients with chronic kidney disease. Data now exist on its potential use in lithium poisoning, although treatment is limited by hypokalemia.^{25,43} Prussian blue is also an ion exchanger used for treatment of thallium poisoning (Antidotes in Depth: A28). Cholestyramine, a bile acid sequestrant, may bind several xenobiotics, including digoxin, ibuprofen, and mycophenolate mofetil, although its application in poisoning is doubtful (Chap. 65).

Forced Diuresis and Manipulation of Urinary pH

Forced diuresis by volume expansion with isotonic sodium-containing solutions, such as 0.9% sodium chloride and lactated Ringer (LR) solution with or without the addition of a diuretic, may increase renal clearance of some molecules. This therapy would theoretically be most useful for xenobiotics such as lithium for which the glomerular filtration rate (GFR), which is the volume of plasma filtered across the glomerular basement membrane per minute, is an important determinant of excretion. In people with normal extracellular fluid (ECF) volume who have not had loss of sodium via renal, GI, or other routes of excretion, the increase in GFR expected with plasma volume expansion is variable and unpredictable and may not lead to significant increases in xenobiotic elimination. The effect is potentially more important in patients who have had contraction of the ECF volume because of sodium loss. Loss of extracellular volume leads to a reduction of GFR partly as a result of decreased cardiac preload and cardiac output, which, in turn, reduces renal plasma flow. This circumstance is also accompanied by activation of angiotensin II, a small peptide that acts as a pressor and stimulates sodium reabsorption in the proximal tubule. Because small molecules such as lithium are both filtered at the glomerulus and reabsorbed by the proximal tubule, especially when sodium depletion has occurred and angiotensin II has been activated, repletion of ECF volume with 0.9% sodium chloride will increase GFR and suppress sodium reabsorption. The result is an increase in excretion of low-molecular-weight xenobiotics such as lithium. After the ECF volume is restored, the continued infusion of 0.9% sodium chloride or LR increases urine volume proportionally more than GFR, which may increase excretion of some small molecules such as urea, but which has little efficacy in the case of most poisonings.

The significant risk of excessive volume repletion is ECF volume overload, manifested by pulmonary and cerebral edema. This complication may be particularly likely in patients with long-standing lithium use in whom chronic tubulointerstitial disease may lead to chronic kidney disease that does not improve with fluid therapy. Other patients with acute kidney injury not mediated by ECF volume depletion are also at risk. Knowing the result of past serum creatinine concentrations may help distinguish acute from chronic kidney disease in such cases. Administration of diuretics such as furosemide along with saline may diminish the risk of ECF volume overload but may complicate the therapy, confuse the assessment of ECF volume, and increase the risk of metabolic alkalosis and hypokalemia. The unproven efficacy of forced diuresis in the management of any overdose has led most experts to abandon its use. On the other hand, the repletion of ECF volume when volume contraction is present, as determined by the history and physical examination, is, of course, appropriate.

Many xenobiotics are weak acids or bases that are ionized in aqueous solution to an extent that depends on the pK_a of the xenobiotic and the pH of the solution. Knowing these variables, the Henderson-Hasselbalch equation (Chap. 9) may be used to determine the relative proportions of the acids, bases, and buffer pairs. Whereas cell membranes are relatively

impermeable to ionized, or polar molecules (eg, an unprotonated salicylate anion), nonionized, nonpolar forms (eg, the protonated, noncharged salicylic acid) may cross more easily. As xenobiotics pass through the kidney, they may be filtered, secreted, and reabsorbed. If the urinary pH is manipulated to favor the formation of the ionized form in the tubular lumen, the xenobiotic is trapped in the tubular fluid and is not passively reabsorbed into the bloodstream. This is referred to as ion trapping. Hence, the rate and extent of its elimination can be increased. To make manipulation of urinary pH worthwhile, the renal excretion of the xenobiotic must be a major route of elimination. The 2004 position paper of the AACT and EAPCCT emphasizes that, as discussed above for extracorporeal therapies, enhanced removal does not necessarily translate into a clinical benefit with improved outcomes.⁵⁶

Alkalinization of the urine to enhance elimination of weak acids has a limited role for xenobiotics such as salicylates,⁴⁸ phenobarbital, chlorpropamide, formate, diflunisal, fluoride, methotrexate, and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). These weak acids are ionized at alkaline urine pH, and tubular reabsorption is thereby greatly reduced. Alkalinization is achieved by the intravenous administration of sodium bicarbonate (1 to 2 mEq/kg rapid initial infusion with additional dosing) to increase urinary pH to 7 to 8.

This degree of alkalinization may be difficult, if not impossible, if metabolic acidosis and acidemia are present, as often is the case in patients with salicylate poisoning. In this situation, bicarbonate (administered as the sodium salt, sodium bicarbonate) is consumed by titration of plasma protons before it can appear in the urine. On the other hand, salicylate poisoning often causes respiratory alkalosis as well. In that case, when the PCO₂ is low, raising serum bicarbonate, equivalent to the induction of metabolic alkalosis, may lead to profound, life-threatening alkalemia. Finally, the risk of ECF volume overload with sodium bicarbonate administration is the same as with the administration of 0.9% sodium chloride or LR. Hypernatremia may also occur after administration of hypertonic sodium bicarbonate. Bicarbonaturia is also associated with urinary potassium losses, so the patient's serum potassium concentration should be monitored frequently and KCl given liberally as long as GFR is not impaired. A further complication of alkalemia is a decrease of ionized calcium, which becomes bound by albumin as protons are titrated off serum proteins; in this event, tetany may occur.²¹ If these complications can be identified and dealt with judiciously and safely, the renal clearance of salicylate may increase fourfold as urine pH increases from 6.5 to 7.5 with alkalinization. Increasing urine pH by decreasing proximal tubular bicarbonate reabsorption via administration of carbonic anhydrase inhibitors such as acetazolamide is not recommended. Although elimination of a xenobiotic may be increased, metabolic acidosis will ensue unless ample sodium bicarbonate is also administered. In the case of salicylates, metabolic acidosis with acidemia increase distribution into the central nervous system. As with sodium bicarbonate administration, bicarbonaturia is accompanied by urinary potassium losses; hypokalemia may be profound. The role of urinary alkalinization in the management of patients with salicylate poisoning is discussed further in [Chap. 39](#).

Alkalinization is also used to increase the solubility of methotrexate and thereby prevents its precipitation in tubules when patients are given high-dose methotrexate.¹³ Precipitation of sulfonamide antibiotics with kidney stones or kidney failure may also be prevented by alkalinization. Administration of sodium bicarbonate, sodium chloride, or LR also protects the kidneys from the toxic effects of myoglobinuria in patients with extensive rhabdomyolysis. However, because patients with rhabdomyolysis may have acute kidney injury, sodium bicarbonate administration must be used before kidney injury occurs and may lead to ECF volume overload if its administration continues after kidney failure has developed.

Acidification of the urine by systemic administration of HCl or NH₄Cl to enhance elimination of weak bases, such as phencyclidine or the amphetamines, is not useful and is potentially dangerous. The technique has been abandoned because it does not significantly enhance removal of xenobiotics and is complicated by acidemia.

Peritoneal Dialysis

Theoretically, PD enhances the elimination of water-soluble, low-molecular-weight, non-protein-bound xenobiotics with a low V_d. Clearance of xenobiotics by PD is related to the number of exchanges, dwell time of dialysate, the surface area of the peritoneum, and the molecular weight of the compound. The highest clearances are achieved for xenobiotics with molecular weights below 500 Da. The efficacy of PD is markedly decreased when the patient is hypotensive.

Although PD is a relatively simple method to enhance xenobiotic elimination, it is too slow to be clinically useful. Consequently, PD is never the method of choice unless hemodialysis and hemoperfusion are unavailable and transfer to a center that can offer these techniques is not feasible. Besides exchange transfusion, it may be the only practical option in small children when experience with extracorporeal techniques in younger age groups is lacking or until a child can be transported to an appropriate center.

Hemodialysis

Hemodialysis has been employed for 100 years, ever since the discovery by John J. Abel and coworkers that dialysis could remove substantial amounts of salicylates from animals.¹ During conventional hemodialysis, blood and countercurrent dialysate are separated by a semipermeable membrane (dialyzer). Xenobiotics then diffuse across the membrane from blood into the dialysate down the concentration gradients ([Fig. 10–2](#)). Blood is pumped through one lumen of a temporary

dialysis catheter, passed through the machine, and returned to the venous circulation through the second lumen.

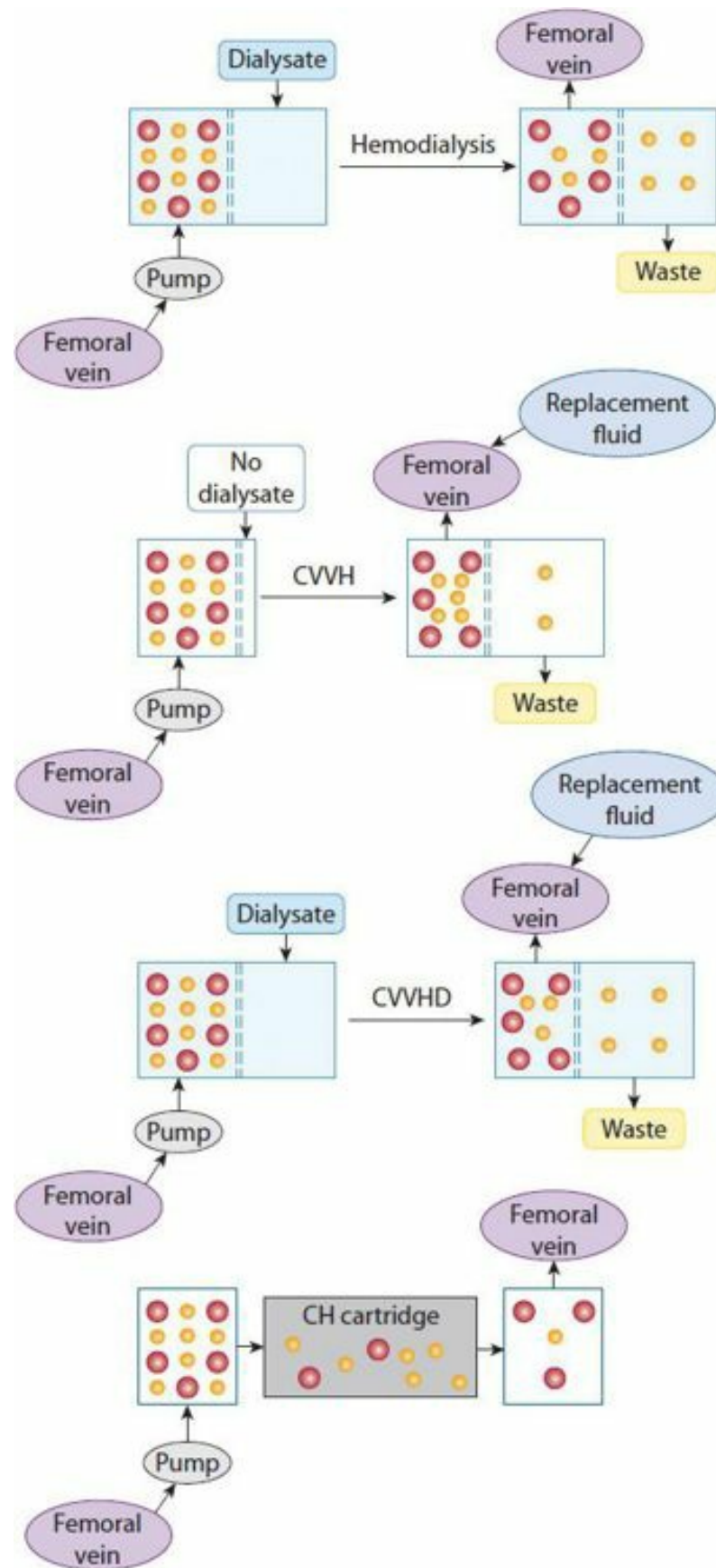


FIGURE 10–2. The comparative schematic layouts of hemodialysis (HD), continuous venovenous hemofiltration (CVVH), continuous venovenous hemofiltration with dialysis (CVVHD), and hemoperfusion (HP). Red circles ● are high molecular-weight (MW) xenobiotics, such as methotrexate, whose high MW makes them too large to be removed by HD; Yellow circles ● are low MW diffusible solutes such as urea or methanol. In dialysis, solute moves across a semipermeable membrane (dashed lines) from a solution in which it is present in a high concentration (blood) to one in which it is at a low concentration (dialysate). In CVVH and CVVHD, plasma moves across a similar membrane in response to hydrostatic pressures; replacement fluid must be provided. The latter also utilizes a dialysate to augment clearance. The availability of blood pumps has made arteriovenous modalities nearly obsolete. Charcoal hemoperfusion (CH) requires movement of blood through a sorbent-containing cartridge and does not include dialysis or hemofiltration.

The utility of hemodialysis for the treatment of patients with toxicity caused by lithium, toxic alcohols, salicylates, or theophylline is unquestionable and is not dealt with here; each of these xenobiotics is described in detail in separate chapters that also review their toxicity and indications for extracorporeal therapies. This section describes the hemodialysis procedure in general and its application to some newer situations.

Prompt consultation with a nephrologist is always indicated in the case of poisoning with a xenobiotic that might benefit from extracorporeal removal. Annual AAPCC data consistently suggest that some salicylate-related deaths, for example, could have been prevented if hemodialysis had been instituted earlier ([Chap. 136](#)).¹⁹ To perform hemodialysis, a nephrologist must be available along with a nurse or technician. The dialysis machine requires preparation, and a vascular access catheter must be inserted. A delay, ranging from one to several hours before hemodialysis can be instituted should be anticipated, particularly during hours when the hospital's dialysis unit, if there is one, is closed. If indicated, modalities of treatment such as fomepizole or ethanol for poisoning with toxic alcohols should be administered and other modalities to enhance elimination, such as urinary alkalization or oral MDAC, should be used when appropriate.

The technical details of performing hemodialysis for treatment of patients with poisonings do not differ markedly from those used in the treatment of patients with acute kidney failure. Several technologic advances have enabled improved xenobiotic clearance while limiting side effects and enabling better tolerance of dialysis.

Vascular access is obtained via a double-lumen catheter that is made of silicon, polyethylene, polyurethane, or Teflon. The catheter is usually inserted either via the femoral, the subclavian, or the jugular vein. The subclavian and internal jugular veins have the added risk of pneumothorax and necessitate radiographic confirmation of catheter position, whereas femoral catheters have increased blood recirculation (ie, lower efficacy of approximately 10% to 15%).⁴² Hemostasis after catheter removal is also more easily achieved at the femoral site. Bleeding or thrombosis at the site used for vascular access occur in approximately 5% of cases but can usually be addressed by adequate post-procedure tamponade of the catheter site. Ultrasonographic placement reduces the risk of complication for all sites and is now recommended in the United States. Larger catheters now permit blood flow rates that can be as high as 450 to 500 mL/min, although 350 mL/min may sometimes be the maximum rate achievable. Nosocomial bacteremia may occur when central catheters are indwelling but are exceedingly rare if they are in place for less than 3 days. This complication is therefore unusual in poisoning where extracorporeal treatment is necessary for a relatively short period of time. Femoral venous lines should always be removed in patients who are mobile and out of bed.

Because new dialysis membranes also have higher water permeability, computerized ultrafiltration control is necessary. These membranes, composed of polysulfone, polyamide, polyacrylonitrile, and other synthetic polymers, have better biocompatibility than older, cellulose-derived membranes. Biocompatibility is measured by the rate of activation or release, after exposure to the membrane, of inflammatory mediators that include white blood cells, platelets, complement, and cytokines. Better biocompatibility means less activation of these potentially damaging mechanisms compared with more bioincompatible membranes. The influence of biocompatibility on the outcomes of patients receiving long-term hemodialysis for chronic kidney failure is still being assessed. Patients with end-stage kidney failure are exposed to these membrane materials during at least three treatments a week for many years. It is unlikely that better biocompatibility will affect outcomes for dialysis of poisoned patients who require only one or two treatments.

Dialysis membrane composition has also continually evolved. The hollow-fiber dialyzer, almost universally used today, is composed of thousands of blood-filled capillary tubes held together in a bundle and bathed in the machine-generated dialysate. Older "conventional" dialyzers, much less frequently encountered today, are made of cellulose-derived polymers, most commonly called cuprophane. Hemodialysis efficacy for poisonings with low-molecular-weight xenobiotics should improve with the use of larger membranes with larger clearances. "High-flux," synthetic dialyzers have larger pores and increased surface area that allow greater clearance of larger molecules. With the use of high-flux and high-efficiency dialyzers, small molecule clearance has more than doubled, whereas clearance of larger molecules, such as β_2 -microglobulin (molecular weight, 11,800 Da) have increased by a factor of five. There are some instances in which high-flux dialyzers might be important in promoting clearance of larger molecules, such as vancomycin (molecular weight, 1449 Da), which are not readily removed by conventional low-flux membranes.²⁴ However, the indications for performing hemodialysis to enhance removal of vancomycin and other xenobiotics with higher molecular weights have not been delineated. Nonetheless, a sound pharmacologic basis for the efficacy of dialysis must still be present; no amount of increased clearance will eliminate a xenobiotic with a large V_d or significant protein or tissue binding. Although clearance rates reported in the literature of the 1970s and 1980s may significantly underestimate currently achievable clearance rates,⁵⁰ these data are still of interest given the relative paucity of more recent reports.

Patients undergoing hemodialysis experience much less hemodynamic instability than in the past; the blood lines and artificial kidney (the dialysis membrane) should be primed with an appropriate volume of fluid to reduce or avoid hypotension when the procedure is started. Furthermore, the source of base in dialysate is now routinely sodium bicarbonate rather than sodium acetate; the latter caused hypotension and decreased cardiac output. Computerized machines allow fine control of ultrafiltration rates to limit volume losses; in the past, imprecise calculations and manipulations led to frequent episodes of hypotension. As a result of such innovations, treatment can be delivered in more instances than was previously possible. Hypotension may still occur in critically ill patients but can often be corrected with 0.9% sodium

chloride, colloid, vasopressors, or inotropes.

Full anticoagulation with heparin is usually required to avoid clotting of the circuit. A typical adult heparin dose is 1000 to 5000 units as a bolus followed by 500 to 1000 units hourly, but lower doses can also be given. Alternatively, in patients at high risk of bleeding, periodic 0.9% sodium chloride flushes of the dialysis membrane may suffice. Use of a dialysate that contains citrate may be adequate for anticoagulation and may allow heparin to be avoided. These choices are particularly important when dialyzing patients for toxic alcohol and salicylate exposures who are at risk for increased intracerebral bleeding.

In poisoned patients, hemodialysis is usually performed for 4 to 8 hours. Some precautions are needed for the prescription of the dialysis parameters because poisoned patients have different characteristics than chronic kidney disease patients. In particular, serum potassium, phosphorus, and pH can be markedly different. Assuming that the patient's serum potassium concentration is normal, a standard bicarbonate-based dialysate with a potassium concentration of 3 or 4 mEq/L and a calcium concentration of 3 mEq/L, flowing at 600 to 800 mL/min, is sufficient. If dialysis is performed in a dialysis unit, the dialysate is a mix of a concentrate with sodium bicarbonate and highly purified water, usually derived by reverse osmosis or deionization. Phosphate can be added to the dialysate bath if needed. Ultrafiltration is rarely required unless oliguric acute kidney injury is present. Dialysis procedures done in ICUs should use portable reverse osmosis machines to generate the water for mixing. Although undesirable, tap water can be used if its chlorine content is less than 0.1 ppm.⁷

Complications specifically related to the dialysis procedure are rare. Furthermore, centers administering dialysis treatments are increasingly common today, and costs of the procedure are on the decline. For these reasons, if dialysis appears required for survival of a poisoned patient, it should usually be attempted.

Table 10–3 lists the characteristics of xenobiotics that make them amenable to hemodialysis. These requirements greatly reduce the number of xenobiotics that can be expected to be cleared by dialysis. During hemodialysis, clearance of a xenobiotic (Cl_x) can be calculated by:

TABLE 10–3. Characteristics of Xenobiotics That Allow Clearance by Hemodialysis, Hemoperfusion, and Hemofiltration

<i>For All Three Techniques</i>	<i>For Hemodialysis</i>	<i>For Hemoperfusion</i>	<i>For Hemofiltration</i>
Low Vd (<1 L/kg)	MW <5000 Da	Adsorption by activated charcoal	MW <40,000 Da
Single-compartment first order kinetics	Water soluble	Binding by plasma proteins does not preclude	
Low endogenous clearance (<4 mL/min/kg)	Not bound to plasma proteins		

MW = molecular weight; Vd = volume of distribution.

$$Cl_x = Q_p \times ER$$

where Q_p is the plasma flow rate and ER is the extraction ratio.

$$Q_p = Q_b \times (1 - Hct)$$

where Q_b is blood flow rate and Hct is hematocrit. The ER is a measure of the percentage of xenobiotic passing through the artificial kidney or charcoal hemoperfusion cartridge. This can be calculated as:

$$ER = \frac{C_{in} - C_{out}}{C_{in}} \times 100$$

where C_{in} is the concentration of the xenobiotic in blood entering the system and C_{out} is the concentration in blood leaving the system.

Thus:

$$Cl_x = [Q_p (C_{in} - C_{out})] / C_{in}$$

With the recent advances in dialysis therapy, there appears to be a role for high-flux hemodialysis in the clearance of certain xenobiotics that were previously thought to be effectively removed only by charcoal hemoperfusion.²³ The

situations in which these modalities are appropriate for these xenobiotics remain exceedingly rare. Because valproic acid is increasingly prescribed for neurologic and psychiatric disorders, the incidence of both intentional and unintentional overdoses of this drug will also increase.⁶⁷ As discussed previously, valproic acid is largely protein bound at therapeutic serum concentrations. Toxic concentrations saturate protein-binding sites, leading to a higher proportion of unbound drug in the serum and a lower apparent Vd, thereby making the drug more dialyzable. Indeed, several case reports have demonstrated that the clearance of valproic acid with high-flux hemodialysis is at least equivalent to, if not greater than, that of charcoal hemoperfusion.^{29,38} Although carbamazepine has a low molecular weight and a Vd that would allow for clearance by hemodialysis, its high protein binding and lack of water solubility are expected to impede the efficacy of hemodialysis. Nonetheless, carbamazepine is also effectively cleared by high-flux hemodialysis.⁶¹ In a patient who underwent high-flux hemodialysis followed by charcoal hemoperfusion for carbamazepine toxicity, removal rates were similar for the two modalities.⁶⁹ Unlike the case of valproic acid, the rationale for these anecdotal reports for enhanced carbamazepine elimination is unclear. Whether the pharmacokinetics of the drug are altered at toxic serum concentrations, as are those of valproic acid, is not known. Because of its potential efficacy and availability and its insignificant effect on cost and adverse events, high-flux hemodialysis should probably replace charcoal hemoperfusion as the treatment modality of choice when extracorporeal elimination is to be performed. As stated above, however, effective clearance is not necessarily a surrogate for improved outcomes.

In addition to removing xenobiotics, hemodialysis can correct acid–base and electrolyte abnormalities such as metabolic acidosis or alkalosis, hyperkalemia, and ECF volume overload. Consequently, hemodialysis is preferred, if not essential, for poisonings characterized by these disorders, especially when clearance rates resulting from hemoperfusion and hemodialysis are relatively similar. Examples include salicylate poisoning, which is often associated with metabolic acidosis,³² and propylene glycol toxicity, which is often associated with lactic acidosis, especially in the presence of renal or hepatic impairment.⁵² Valproic acid toxicity causes hyperammonemia, which is reduced by hemodialysis, possibly contributing to the benefit of the procedure.⁷⁰

A more controversial question is the role of dialysis in the treatment of metformin-associated lactic acidosis. Although debated, present evidence now suggests that metformin intoxication itself may induce metabolic acidosis with elevated lactate concentration without predisposing factors.^{2,55} Here, the small molecular weight and negligible plasma protein binding of metformin may allow for adequate drug removal despite a relatively large Vd. Endogenous clearance of metformin is quite high and dialysis has therefore less appeal in patients with intact kidney function. In addition, hemodialysis would rapidly correct acidosis via administration of sodium bicarbonate without the complication of volume overload. Clinical improvement with hemodialysis may result as much or more from rapid correction of the acidosis as from removal of the drug.

In addition, hemodialysis increases the elimination of some drugs administered therapeutically, such as folic acid and other water-soluble vitamins and xenobiotics. Doses of these drugs should be increased during dialysis or administered immediately afterward. Similarly, the rate of ethanol infusions used in the treatment of patients with toxic alcohol ingestions must be increased. Fomepizole also has a low molecular weight (molecular weight, 82.1 Da) and a low Vd (0.6–1.0 L/kg), so it can also be dialyzed. If necessary, it should be redosed after dialysis (Antidotes in Depth: A30). When fomepizole is not available, ethanol removal can be limited in such cases by enriching the dialysate with ethanol to a concentration of 100 mg/dL.¹⁴ Similarly, hypophosphatemia after more prolonged high-flux hemodialysis can be avoided by adding sodium phosphate salts (eg, Fleet Phospho-Soda) to the dialysate or by administering phosphate intravenously.

Hemoperfusion

During hemoperfusion, blood is pumped via a catheter through a cartridge containing a very large surface area of sorbent, either activated charcoal or a resin, on to which the xenobiotic can be directly adsorbed (Fig. 10–2). The activated charcoal sorbent is coated with a very thin layer of polymer membrane such as cellulose acetate (Adsorba: Gambro, Lakewood, CO), heparin-hydrogel (Biocompatible Hemoperfusion Systems: Clark, New Orleans, LA) or polyHEMA (2-hydroxyl methacrylate or Hemosorba: Asahi, Tokyo, Japan). The membrane prevents direct contact between blood and sorbent, improves biocompatibility, and helps prevent activated charcoal embolization. There may be a further theoretical advantage to the heparin–hydrogel coating to diminish platelet aggregation.

Other adsorptive resins were used for hemoperfusion in the past, such as the synthetic Amberlite XAD-2 and XAD-4 and anion exchange resins such as Dow 1X-2. None of these columns is currently approved or available for use in the United States, but remain available in other countries. The literature regarding their efficacy is scant and relatively anecdotal. Although in vitro evidence suggests that these resins may have greater adsorptive capacities than activated charcoal, there are few, if any, meaningful comparisons in a clinical setting.

The adsorptive capacity of the cartridge is reduced with use because of deposition of cellular debris and blood proteins and saturation of active sites by the xenobiotic in question. Hemoperfusion is usually performed for 4 to 6 hours at flow rates that can usually not exceed 350 mL/min because of the risk of hemolysis.⁵⁸ The technique can be used in adults¹⁵ or children.⁵¹

The characteristics of xenobiotics that make them amenable to hemoperfusion (Table 10–3) differ slightly from those for hemodialysis in that hemoperfusion is not as limited by plasma protein binding, although this is less true with the advent of new dialysis membranes which now permit removal of significant amounts of highly bound xenobiotics.²⁷ Some xenobiotics are poorly adsorbed by activated charcoal, including the alcohols, lithium, and many metals (Antidotes in Depth: A1), making hemoperfusion inappropriate in their management. Hemodialysis and hemoperfusion have been performed in series for procainamide, thallium, theophylline, and carbamazepine overdoses, with greater apparent clinical efficacy than with either procedure alone.^{10,17,37} In this technique, blood circulates first through the hemodialysis membrane and then through the activated charcoal cartridge. If blood traverses the dialysis membrane first, some of the xenobiotic is dialyzed, and the activated charcoal cartridge has less drug to adsorb.³¹

Added to the questionable benefits of hemoperfusion, multiple limitations make their use less attractive when compared to hemodialysis. A practical problem limiting the use of charcoal hemoperfusion is the availability of the cartridges. Many dialysis units do not currently stock these cartridges.⁶⁴ Activated charcoal cartridges were more available in hemodialysis units when they were more frequently needed for the treatment of patients with chronic aluminum toxicity. Saturation of the cartridge is apparent within 1 hour of use and markedly decreases absorptive capacity at 2 hours, whereas no such decreased performance is apparent with hemodialyzers. Compared with hemodialysis, patients must be anticoagulated with greater amounts of heparin. The cartridges are expensive (\$350–\$425 compared with the maximal cost for a high-flux dialysis membrane at about \$40–\$50), especially considering cartridges usually need to be replaced every 2 hours. Some have expiration dates, limiting their shelf life. Others, such as the Clark system, have an indefinite shelf life but must be autoclaved before use, which may affect their availability in an emergency. Complications of hemoperfusion are more common than with hemodialysis: thrombocytopenia, leukopenia, and hypocalcemia.⁶⁵ Finally, hemoperfusion cannot correct acid–base or electrolyte abnormalities and cannot provide ultrafiltration if volume overload occurs.

Although hemoperfusion has historically been considered the preferred method to enhance the elimination of carbamazepine, phenobarbital, phenytoin, and theophylline (Table 10–4), recent improvements in hemodialysis technology may make older comparisons of hemodialysis and hemoperfusion clearance rates obsolete. The most frequent indication for charcoal hemoperfusion in the past was theophylline toxicity, and theophylline is rarely used today in the treatment of obstructive lung disease and asthma and is consequently less often implicated in acute and chronic poisoning. Along with the rarity of aluminum toxicity in chronic hemodialysis patients, the infrequency of theophylline prescription accounts for the diminished availability of activated charcoal cartridges and the relative infrequency with which the procedure is performed. In a survey of New York City hospital dialysis units taking 911 calls, only 10 of 34 units had cartridges.⁶⁴ In a review of the AAPCC annual data, theophylline was the most common xenobiotic removed by hemoperfusion from 1985 to 2000, but carbamazepine became the most frequent xenobiotic removed by hemoperfusion during 2001 to 2005.³⁰ As in the case of hemodialysis, doses of drugs used therapeutically may need to be increased if they are removed by hemoperfusion.

TABLE 10–4. Properties of Xenobiotics Grouped by Benefit of Extracorporeal Techniques for Elimination

Xenobiotic	MW (Da)	Water Soluble	Vd (L/kg)	Protein Binding (%)	Endogenous Clearance (mL/min/kg)	Comments
Clinically Beneficial						
Bromide	35	Yes	0.7	0	0.1	Falsely elevated chloride measurement
Caffeine	194	Yes	0.6	36	1.3	
Ethylene glycol	62	Yes	0.6	0	2.0	May have osmolar, kidney failure
Diethylene glycol	106	Yes	0.5	0	NA	Renal failure
Isopropanol	60	Yes	0.6	0	1.2	No anion gap acidosis
Lithium	7	Yes	0.8	0	0.4	Cl ↓ in kidney failure
Methanol	32	Yes	0.6	0	0.7	Risk of CNS hemorrhage
Propylene glycol	76	Yes	0.6	0	1.7	Lactic acidosis, possible acute kidney injury
Salicylate	138	Yes	0.2	50	0.9	Cl and protein binding ↓, with ↑ dose; HD also corrects electrolytes, acid-base disturbance
Theophylline	180	Yes	0.5	56	0.7	HF and HD can also be combined
Valproic acid	144	Yes	0.2	90	0.1	↑ Concentrations associated with ↓ % protein binding
Possibly Clinically Beneficial						
Amatoxin	373–990	Yes	0.3	0	2.7–6.2	Possibly effective if performed within the first 24 hours of exposure
Aminoglycosides	>500	Yes	0.3	1.5	<10	Cl ↓ with kidney failure
Atenolol	255	Yes	1.0	2.5	<5	Useful if Cl ↓ caused by kidney failure
Carbamazepine	236	No	1.4	74	1.3	Cl ↑ in patients on long-term therapy
Disopyramide	340	No	0.6	1.2	90	Protein binding ↓ as concentration ↑
Fluoride	19	Yes	0.3	50	2.5	Hypocalcemia may be improved by HD; may add little if endogenous renal clearance is preserved
Methotrexate	454	Yes	0.6	50	1.5	Urine alkalinization is indicated
Paraquat	186	Yes	1.0	6	24.0	Tight tissue binding precludes efficacy unless initiated early
Phenobarbital	232	No	0.5	24	0.1	Only for prolonged coma
Phenytoin	252	No	0.6	90	0.3	Cl ↓, as dose ↑

Cl = clearance; HD = hemodialysis; HF = hemofiltration; HP = hemoperfusion; MW = molecular weight; NA = not available; Vd = volume of distribution.

Liver Dialysis

A newer concept for poisonings is that of liver dialysis. These procedures are currently available in the United States, mostly for the treatment of liver failure. Several techniques have been developed; the following three are the most common. (1) Single pass albumin dialysis (SPAD) is similar to hemodialysis but has albumin added to the dialysate in counter-directional flow and then discarded after passing through a filter. (2) The Molecular Adsorbents Recirculation System (MARS) is identical to SPAD, but the albumin-enhanced dialysate (with the adsorbed xenobiotics) is itself recycled after going through another dialysis circuit and through both resin and activated charcoal cartridges. (3) The Prometheus system is a device that combines albumin adsorption with high-flux hemodialysis after selective filtration of the albumin fraction through a polysulfone filter. In all of these techniques, the dialysate bathing the fibers contains human serum albumin that serves as a sorbent to bind the xenobiotic of interest and maintain concentrations of the free xenobiotic at zero. A steep concentration gradient from blood to dialysate is established so that even highly protein-bound xenobiotics can be removed

from the plasma. The membrane is impermeable to albumin, which remains in the dialysate.

These extracorporeal devices are all able to remove protein-bound xenobiotics, but their use in poisoning remains limited to rare case reports. These devices are mostly used in patients with hepatic encephalopathy and liver failure and as a bridge to hepatic transplantation.^{47,66} In toxicology, their use is mostly described in hepatic failure following toxicity of APAP or *Amanita* spp. exposure (Chap. 120). The reasons why the procedure might offer significant benefits are not completely understood, although it does remove both water-soluble and protein-bound compounds. It is not known which protein-bound molecules are removed from the blood, such as bile salts and aromatic amino acids, to account for the therapeutic advantage in hepatic failure. Specific uses for liver dialysis for elimination enhancement has been described in poisoning with phenytoin,⁶³ theophylline,⁴⁰ valproic acid,¹⁸ and *Amanita* mushrooms.³⁶ Whether this relatively expensive (in excess of \$4000 per treatment), complicated, and nonspecific procedure would offer benefit in a handful of instances in which protein-binding limits removal of xenobiotics is not known. The report of the initial use of a sorbent-based hemodiabsorption device in 10 cases of CA overdoses claimed benefit, although the limitations of extracorporeal therapy for this particular class of drugs are discussed above.⁶ Devices using powdered sorbent are not currently available in the United States.

Continuous Hemofiltration and Hemodiafiltration

Hemofiltration is the movement of plasma across a semipermeable membrane in response to hydrostatic pressure (convection). The addition of dialysate on the other side of the membrane further enhances elimination of xenobiotics or endogenous uremic toxins. A review of continuous modalities of dialytic therapy concluded that they are still relatively unproven for the treatment of poisoning.²⁸ These techniques find relatively widespread usage for the treatment of patients with acute kidney injury in the ICU, and in this context, they are referred to collectively as modalities of continuous renal replacement therapy (CRRT). The clearances of either urea or xenobiotics that are achieved with these techniques are significantly lower than those achieved with hemodialysis. But as continuous modalities, what they lack in clearance they can make up for in time.

There are several possible advantages of continuous modalities. One is the capability to continue therapy for 24 hours every day, permitting hemofiltration to be instituted after hemodialysis or hemoperfusion to further remove a xenobiotic after it redistributes from tissue to blood.⁴⁶ This is an attractive modality for slow, continuous removal of drugs, such as lithium, which distribute slowly from tissue-binding sites or from the intracellular compartment (Fig. 10–1). Other xenobiotics with volumes of distribution that are large enough to preclude use of dialysis or hemoperfusion might also be eliminated with longer courses.

Table 10–3 summarizes the properties of xenobiotics that make them amenable to hemofiltration. However, the rate of removal with this form of therapy may be insufficient to benefit critically ill patients. Patients who can tolerate slower clearance rates may not require this enhanced elimination therapy at all. Whether slow treatment to avoid redistribution of intracellularly distributed lithium, for example, is preferable to repeating conventional hemodialysis is unclear.^{45,71} Rebound of serum concentrations indicates that the drug is moving out of the intracellular compartment, where it is toxic, into the extracellular compartment, where it is susceptible to removal by hemodialysis. Therefore, although the continuous modalities are suggested to prevent rebound, the importance of this property, during which poison in the toxic compartment is actually decreasing while plasma concentrations actually increase, remains unproven and may in fact be desirable. Despite many case reports demonstrating significant xenobiotic clearance, no data have demonstrated that these continuous techniques affect prognosis or mortality in treatment of patients with xenobiotic toxicity. In most cases, hemodialysis should be considered the preferred initial mode of therapy.

The continuous modalities may be best suited for patients with hypotension who cannot tolerate conventional hemodialysis, although this situation is infrequent unless oliguric acute kidney injury is present.¹¹ These modalities may also have a role after hemodialysis to avoid the need for a repeat session after equilibration of the xenobiotics into plasma. The continuous modalities may also have a slight advantage over the use of high-flux hemodialysis membranes, in being able to clear larger molecules such as myoglobin (molecular weight, 17,000 Da). Growing evidence suggests that a significant part of the clearance of many molecules occurs because of adsorption of the molecule to synthetic membranes.¹⁶ However, quantification of the contribution of adsorption to total clearance is difficult and is not usually accomplished in published studies. Adsorption of molecules responsible for adverse effects is being studied as a potential benefit in the management of cytokines and liver failure and could be a property useful in the management of poisoning.⁵⁷ At present, this property is difficult to quantify and of uncertain benefit. Another practical advantage of CRRT is that the procedure is usually done now in ICUs by ICU nurses, and when available in such units, might not require dialysis personnel. Familiarity of ICU staff with the procedure is critical to its availability when needed; it is most likely to be used effectively in hospitals with higher incidence rates of acute kidney injury.

In pure hemofiltration, sometimes called slow continuous ultrafiltration (SCUF), there is no dialysate solution on the other side of the dialysis membrane (Fig. 10–2). Molecules are transported across the membrane with plasma water, a mechanism known as convective transport or bulk flow. The ECF volume status of the patient determines whether

replacement of all or some of the filtered plasma with physiologic electrolyte solution (LR or other commercially available preparations) is indicated. Although this technique can be done intermittently using a hemodialysis machine, it has been adapted for use in ICUs as a continuous form of treatment, particularly when removal of ECF is indicated. The clearance of low-molecular-weight solutes such as urea is relatively limited.

Solute clearance may be significantly enhanced by having a dialysate solution bathe the blood-filled capillaries running countercurrent to the blood flow, in order to add diffusion to convection. The combination of hemofiltration with dialysis is known as hemodiafiltration. Addition of dialysis also usually suffices to treat supervening acute kidney failure or preexisting chronic kidney failure. Hemodiafiltration, similar to hemodialysis, requires that blood perfuse hollow-fiber dialysis membranes made of synthetic plastics such as polysulfone or polyamide.²⁰ For all of these procedures, the patient usually must be fully anticoagulated, but some hemofilters are available that may not require anticoagulation. Anticoagulation may be achieved either with heparin or with citrate. The hydrostatic pressure required for hemofiltration is derived from a blood pump. Continuous venovenous hemofiltration (CVVH) uses a blood pump to maintain adequate flow rates and has replaced continuous arteriovenous hemofiltration (CAVH), which required arterial puncture with a large-bore catheter. However, the need for a blood pump also necessitates an experienced ICU team to be continuously present for more than the 4 to 6 hours needed for acute hemodialysis or hemoperfusion. Both the expense and the complexity of the xenobiotic-removal procedure are thereby increased. The addition of a dialysate bathing solution to the hemofiltration apparatus changes CVVH, or hemofiltration, to the augmented continuous venovenous hemodialysis (CVVHD), or, with greater convective volumes, hemodiafiltration (CVVHDF) (Fig. 10–2).

Ultrafiltrate flows of 100 to 6000 mL/h across the membrane can be achieved. Fluid and electrolyte losses must be replaced carefully. Depending on the filter, xenobiotics with a molecular weight of up to 40,000 Da, as well as water, urea, creatinine, and sodium, pass into the ultrafiltrate. Heparin, myoglobin, insulin, and vancomycin are examples of larger molecules cleared with relative efficiency.

Attention must be paid to the undesirable removal of therapeutic drugs such as antimicrobials via these continuous modalities. Drug clearances with different synthetic membranes are available in the literature; the doses necessary to maintain therapeutic drug concentrations can also be determined.⁵

Plasmapheresis and Exchange Transfusion

Plasmapheresis and exchange transfusion are intended to eliminate xenobiotics with large molecular weights that are not dialyzable. This includes xenobiotics and endogenous molecules with molecular weights greater than 150,000 Da typified by immunoglobulins. The xenobiotic to be eliminated should also have limited endogenous metabolism to make pheresis or exchange worthwhile.³⁵ By removing plasma proteins, both techniques offer the consequent potential benefit of removal of protein-bound molecules such as Amanita toxins,³⁰ thyroxine, vincristine, monoclonal antibodies, or complexes of digoxin and antidigoxin antibodies. However, there is little evidence that either technique affects the clinical course and prognosis of a patient poisoned by any of these or other xenobiotics.

Pheresis is particularly expensive, and both pheresis and exchange transfusion expose the patient to the risks of infection with plasma- or blood-borne diseases. Replacement of the removed plasma during plasmapheresis can be accomplished with fresh-frozen plasma, albumin, or combinations of both. The former is associated with hypersensitivity reactions, such as fever, urticaria, wheezing, and hypotension, in as many as 21% of cases.³⁵

A different setting in which exchange transfusion may be an appropriate technique is in the management of small infants or neonates in whom dialysis or hemoperfusion may be technically difficult or impossible. Anticoagulation and MDAC may be hazardous and therefore contraindicated in patients in the neonatal nursery, where the risk of intracerebral bleeding and necrotizing enterocolitis is high. In premature neonates, a single volume exchange appeared to alleviate manifestations of theophylline toxicity.⁴⁹ The therapy has been successfully used to treat other pediatric patients with poisonings, including severe salicylism.⁴⁴

OTHER TECHNIQUES TO ENHANCE ELIMINATION

Further discussions of some of the techniques to enhance elimination that are not discussed here may be found in Chap. 31 (exchange transfusion), Special Considerations: SC3 (cerebrospinal fluid drainage and replacement), Chap. 65 (toxin-specific antibodies), and Chap. 96 (chelation). All of these techniques have limited, very specific indications, and the effect of these interventions on the overall body burden of the xenobiotic is usually small.

TOXICOLOGY OF HEMODIALYSIS

Unlike patients who receive acute hemodialysis once or twice in the management of poisoning, patients with chronic kidney failure are repeatedly exposed to large volumes of water derived from municipal reservoirs during the course of their hemodialysis treatments. If an “average” regimen consists of three treatments of 4 hours each week, with dialysate flows of

800 mL/min, patients will be exposed to nearly 600 L of water separated from them only by a semipermeable membrane designed to allow solute passage in either direction. Problems with dialysate generation therefore have the potential to be lethal to this population by exposing them to significant quantities of toxins. There are two potential sources of dialysate contamination: the municipal reservoirs and water treatment plants and the dialysis unit.⁵⁴ The quality of water used for dialysate generation is regulated in the United States by the Association for the Advancement of Medical Instrumentation (AAMI).⁷ This organization regularly revises its guidelines to incorporate new technology and data.

Contamination of dialysate from the municipal water supply may occur as a result of xenobiotic runoff into reservoirs or as a result of inadvertent or intentional addition of a chemical by the municipality. Chlorine and chloramine are frequently added to municipal water supplies to control bacterial populations. However, chlorine may combine with nitrogenous compounds and form chloramine, which may cause nausea, vomiting, methemoglobinemia, and hemolytic anemia.⁷² Recently, chloramine was blamed for decreased bone marrow sensitivity to erythropoietin. Aluminum is present in some municipal water supplies, and before it was recognized as a problem, aluminum led to encephalopathy characterized by seizures, myoclonus, and dementia as well as osteomalacia and microcytic anemia.

Water from the municipal supply entering the dialysis unit is first treated with a water softener to remove calcium and magnesium. It is then run through an activated charcoal bed to adsorb chloramine. The potential toxicity (hemolysis and death) from this compound has caused AAMI to mandate a redundancy in the carbon beds; when the active sites in one carbon bed are exhausted, a second will ensure that no toxicity will occur. Most commonly, water for dialysate is then generated by reverse osmosis, a process that requires that water, in response to applied hydrostatic pressure (and against the osmotic gradient), cross a membrane that is relatively impermeable to solutes, leaving them behind. Alternatively, but less commonly, water can also be purified using deionization, a technique that runs water over an exchange resin, releasing hydroxyl ions in exchange for charged species in the water. Deionization is inferior to reverse osmosis for removal of aluminum and may be associated with release of lethal concentrations of fluoride when exchange sites are exhausted.⁴ General water chemistry testing is mandated annually; testing for chlorine and chloramine must be done before each dialysis shift.

Current requirements are that water be highly purified, but not sterile, because bacteria cannot cross from the dialysate into the blood. However, small quantities of endotoxin (molecular weight, 5–15,000 Da) can cross, particularly in situations that include the use of high-flux membranes. Endotoxin is suspected of contributing to activation of circulating cytokines, malnutrition, fever, and other syndromes such as carpal tunnel syndrome, which are associated with chronic inflammation. Recommendations for the frequency of testing for endotoxin and the maximum amounts of endotoxin tolerated are continually debated and continue to become more stringent. Water distribution systems are cleaned at least monthly with bleach, peracetic acid, or other sterilants. Care must be taken that all of these potential xenobiotics are thoroughly flushed from the system before dialysis is restarted. Other products of bacterial metabolism, such as volatile sulfur-containing compounds, generated on the dialysate side of the membrane may be responsible for symptoms in hemodialysis patients.⁶²

Unusual microbes have also been associated with serious toxicity. Untreated water at one center in Brazil demonstrated growth of Cyanobacteria (blue-green algae) and production of microcystins, cyclic peptides that cause serious hepatic toxicity; patients dialyzed with the contaminated water had a dramatic rate of death from liver failure.³³ Water contamination should especially be suspected when multiple dialysis patients experience similar symptoms nearly simultaneously. Dialysate distribution systems are always made of polyvinyl chloride (PVC) or other inert plastics, rather than copper, which may also leach into the water and cause hemolytic anemia.

Besides water for dialysate, another potential source of poisoning in hemodialysis units is the process of reusing dialysis membranes. Until recently, up to 70% of dialysis units in the United States reused membranes because of cost considerations. Reuse is becoming less common today, in part because the cost of dialyzers has continued to fall. Each dialysis membrane is sterilized with peracetic acid, formaldehyde, or glutaraldehyde. Careful quality assurance programs ensure that there is no significant exposure of the patients to these molecules during the dialysis procedure. Nonetheless, reuse programs are associated with a variety of syndromes such as pyrogenic reactions attributed to patient exposure to germicides or endotoxin caused by inadequate sterilization procedures.⁵⁹ Controversial data over the years have suggested, but not proven, higher mortality rates with reuse. Occupational exposure of dialysis personnel to the relevant sterilants has also been monitored closely.

SUMMARY

- Urinary alkalization and many of the other techniques listed in [Table 10–1](#) can be instituted quickly in the emergency department.
- The extracorporeal methods of xenobiotic removal, including hemodialysis, sorbent hemoperfusion, and continuous hemofiltration, all require consultation with a nephrologist or intensivist.
- Timely use of these techniques requires mobilization of a competent team and preparation of the requisite equipment.
- Rapid identification of a toxic exposure for which these techniques are appropriate and the presence of more ominous

prognostic features should lead to prompt notification of the appropriate consult services so that application of these techniques can proceed in an expeditious manner.

- The applicability of these techniques to new xenobiotics should be considered based on the principles discussed, so that these and newer treatment modalities are not used indiscriminately.
- The literature regarding these techniques in general, and for the treatment of specific xenobiotic exposures in particular, should be read critically and with appropriate skepticism.

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11 USE OF THE INTENSIVE CARE UNIT

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The practice of critical care medicine has its roots in the resuscitation of dying patients, and it focuses on the restoration of normal physiology without necessarily involving a complete understanding of a patient's chronic conditions. Over the past several decades, critical care has led to improved patient survival from many serious conditions. This is the direct result of noninvasive and invasive tools used to describe and correct pathophysiology.²⁹

Like many critically ill patients, the history of poisoned patients is often partial or incomplete, thereby confounding their care. The history is often unreliable regarding the xenobiotic ingested, time of ingestion, and amount ingested, even further complicating care. Additionally, the xenobiotic may have unknown or unpredictable effects at the exposure dose. Finally, the therapies, antidotes, and complications of acute poisoning may be unfamiliar to the intensive care unit (ICU) staff. These uncertainties challenge health care providers and influence decisions about admitting poisoned patients to the ICU.

In 2011, the American Association of Poison Control Centers (AAPCC) National Poison Database System (NPDS) reported 2,334,004 human exposures, of which 615,869 required health care facility management. Most patients did not require critical care, with only 7% of the total human exposures reporting moderate/major clinical outcomes or death and only 101,175 of the admitted patients admitted to critical care units; this represented only 4.3% of all human exposures reported that year.⁷ Most critically ill poisoned patients have acutely reversible conditions that will clearly benefit from an ICU intervention,⁶⁹ with a total attributable mortality of only 0.06%.

Unlike many patients with diseases managed in the ICU, poisoned patients are often admitted to the ICU for observation and monitoring, not for intervention.⁹³ Fewer than 25% of those hospitalized required specific treatments or antidotes other than gastrointestinal (GI) decontamination.^{6,93} Many physicians elect to observe poisoned patients in an ICU in anticipation of possible delayed, unrecognized life-threatening toxicity. The ICU provides necessary monitoring and individual nursing care that can help in the early recognition of developing toxicity. ICUs give health care providers the best opportunity to minimize morbidity and decrease mortality. However, ICU care is very expensive and has contributed significantly to the escalation of health care costs. In addition, critical care units struggle with overcrowding, requiring a justifiable decision-making process for each and every patient before committing these valuable resource.

The decision to admit a patient to a critical care unit is multifactorial. Patient characteristics, the need for acute reversal of physiologic abnormalities, and the characteristics of the exposure are all potential reasons for admission. Beyond managing the obvious end-organ toxicity requiring intervention, the ICU is especially useful for observing patients for the progression of end-organ effects that may require intervention. Because the natural course of a toxicologic emergency is often unpredictable, consideration must be given to patients at risk of deteriorating to the point that critical care interventions are required. Newer studies are attempting to define predictors of adverse events and risk quantification that will prove helpful in critical care admission decision making.^{23,49,57,88}

Given the degree of uncertainty that is typical for the poisoned patient, an informal "bedside risk assessment" is a helpful tool for decision making. In this case, "bedside risk assessment" is defined as the process of determining the likelihood of physiologic deterioration requiring critical care interventions for an individual after an exposure. This "bedside risk assessment" takes into account observed clinical effects, estimated dose, pharmacologic and toxicologic characteristics of the suspected xenobiotic, and characteristics of the exposed patient to help determine the need for ICU admission. It is intended to identify patients with conditions requiring meticulous supportive care, physiologic monitoring, or advanced technologic or pharmacologic therapies that can only be provided in the ICU. More importantly, it is needed to predict the likelihood of a patient deteriorating to the point of needing critical care interventions. This decision-making guide takes into account key clinical observations, current best available evidence from the medical literature, clinical experience, and preferences based on acceptable risks (Table 11–1).

TABLE 11–1. Key Parameters for Performing a Risk Assessment

Bedside observations for end-organ toxic effects
Evidence-based clinical criteria and severity of illness models
Need for specific monitoring or therapeutic interventions

Xenobiotic characteristics: toxicodynamic and toxicokinetic considerations

Patient factors that increase susceptibility to adverse outcomes

- At-risk populations

- Chronic and other comorbid medical conditions

Risk of life-threatening complications

- Anoxic brain injury

- Aspiration pneumonitis

- Rhabdomyolysis and compartment syndrome

The goal of this chapter is to encourage effective use of ICU resources without compromising patient care by proposing a structured approach to assessing risk. Effective utilization of ICU resources must take into consideration the unique characteristics of a xenobiotic, the capabilities of the hospital, and all realistic alternatives for managing and observing poisoned patients without compromising care. Current medical literature allows for the development of only very general recommendations. Future clinical studies addressing the use of health care resources for poisoned patients will allow refinement of these recommendations and could ultimately lead to clinical guidelines derived from their findings. Although it is impossible to be all inclusive, this chapter provides a risk-assessment strategy for most xenobiotics subsequently discussed in this text.

ASSESSING RISK USING CLINICAL OBSERVATIONS AS THE BASIS FOR ICU ADMISSION

The philosophy of “treating the patient and not the poison” may prove most helpful in the patient’s overall risk assessment. It seems reasonable to assume that a patient’s signs and symptoms can be used to decide the need for ICU admission.

Patients with serious central nervous system (CNS), respiratory, cardiovascular, or metabolic manifestations of poisoning need ICU interventions regardless of the exposure. For example, in a retrospective study⁶ of patients with respiratory failure requiring mechanical ventilation, hypotension or cardiac dysrhythmias requiring cardiovascular resuscitation, recurrent seizures requiring airway management and continuous anticonvulsant therapy, or agitation requiring high-dose sedation all clearly need ICU admission, and they are unlikely to be the subject of clinical research. Regardless of xenobiotic ingested, this study established that a patient’s initial signs and symptoms could be used as criteria to identify poisoned patients at risk of developing serious toxicity, thus needing ICU admission.⁶ Patients were classified as low risk when a set of high-risk clinical criteria were not observed in the emergency department (ED). None of the low-risk patients developed complications or required ICU interventions after admission. All patients developing high-risk complications such as hypoxia, respiratory failure, hypotension, or seizures after admission had other high-risk criteria in the ED.

In this study population, 70% of the low-risk patients were admitted to the ICU for observation. Because none of these patients developed complications or required ICU intervention, the authors postulated that applying their criteria would have eliminated 50% of the ICU days without compromising care. The limitations of this study are multifactorial: retrospective design, relatively small study population, and limited variety of xenobiotic exposures. Additionally, generalizing this study’s conclusions to today’s clinical environment is difficult. This study was published in 1987, and the spectrum of poisoning faced today is vastly different than previously studied. The main message of this study is that with some clinical judgment, many poisoned patients can be effectively triaged. Newer studies suggest that determining high-risk clinical criteria for predicting risk may be useful for triaging patients.^{43,47,48,50}

Patient Characteristics Influencing ICU Admission of Poisoned Patients

In addition to bedside observations, specific populations may be at higher risk for morbidity and mortality secondary to xenobiotic exposures. End-organ toxicity and specific monitoring or therapeutic interventions are the most important reasons to admit poisoned patients to the ICU. However, restricting ICU admission to those with only end-organ toxicity is inappropriate because the ICU is most capable of early recognition of delayed or worsening toxicity, potentially leading to catastrophic deterioration. Minimally symptomatic or asymptomatic patients may require ICU admission because other factors must be considered. In addition to end-organ toxicity, xenobiotic and specific patient characteristics should influence ICU admission decisions.

The patient’s comorbid medical conditions can increase the risk of developing complications related to the ingestion. Many patients who have chronic medical problems do not tolerate major physiologic stressors without significant compromise. For example, a patient with underlying cardiac disease could develop severe myocardial ischemia from a modest carbon monoxide exposure. An elderly or chronically ill or debilitated patient with chronic salicylism is more likely to have major respiratory or CNS complications than a younger, healthier patient. Conditions that alter xenobiotic metabolism or elimination, such as kidney or liver disease, may prolong toxicity or produce toxicity after lesser amounts

are ingested. For many of these reasons, the morbidity and mortality of acute poisoning are higher in elderly patients.⁵⁸

In addition, many toxicologic emergencies occur in young patients who are free of underlying disease. This increases the likelihood of surviving from significant insults such as prolonged hypotension or hypoxia. Indeed, one prospective trial involving 286 patients admitted to the ICU with nontraumatic coma found that 91% of the 101 xenobiotic-induced coma patients survived, a much higher rate than those patients whose cause of coma was hypoxia (33%), sepsis (28%), focal cerebral (26%), or a general cerebral insult (17%).²⁶ Despite negative predictors of outcome, aggressive resuscitation efforts may be justified for poisoned patients. Case reports of poisoning from barbiturates, cyclic antidepressants, baclofen, ethylene glycol, botulism, solvents, and sedative–hypnotics provide specific examples of this observation.^{3,65,80,86,91} Specifically, prolonged cardiac resuscitation should be provided for victims of cardiac arrest resulting from overdoses of cyclic antidepressants, β -adrenergic antagonists, or calcium channel blockers as well as for those with severe hypothermia.^{20,34,54,62,75}

There are situations in which knowledge of the patient's social and psychiatric state may prompt the need for ICU admission as well. For example, patients with physical dependency on ethanol, benzodiazepines, or barbiturates may be admitted to the hospital for acute withdrawal or, during hospitalization, go through a period of abstinence that results in an acute withdrawal syndrome. Withdrawal from ethanol and sedative–hypnotics can have serious consequences and complications. ICU management is frequently indicated because large doses of medications with respiratory depressant effects may be required for treatment. Similarly, the majority of recognized suicide attempts are associated with a psychiatric disorder and/or substance abuse and occur by overdose of medications. Acute complications of poisoning make it difficult to adequately assess suicidal risks. Patients have an increased rate of suicide after discharge from an ICU for drug overdose.⁷⁹ Until suicidal risks are adequately assessed, it must be assumed that overdosed patients need close observation.

Assessing Risk Using Severity of Illness Scoring Systems to Guide ICU Admission

Severity of illness scoring systems are designed to predict survival and length-of-stay using multiple key variables applied at the time of ICU admission or to risk adjust patient mortality based on data collected through the patient's hospitalization.¹⁹ This information helps the bedside clinician and patient's surrogate decision makers determine ICU care choices. These scoring systems serve additional administrative and research roles in comparing patient populations and hospitals.²⁹ It is important to note that these studies have primarily been performed to identify patients at risk for death as opposed to being used as a triage tool; this holds true for the studies presented in this section.

Scoring systems considering physiologic variables prospectively and administrative variables retrospectively are broadly used.¹⁹ Those based on physiologic variables are the most useful to the clinician at the bedside. There are five commonly used scoring systems: the Acute Physiology and Chronic Health Evaluation (APACHE II/III/IV), the Mortality Probability Model (MPM II/III), the Simplified Acute Physiology Score (SAPS II), and the Sequential Organ Failure Assessment (SOFA). For pediatric patients, the Pediatric Risk of Mortality (PRISM II/III) is widely used. All of these models are widely studied and generally accepted severity of illness models that score certain physiologic parameters and other factors to estimate risks and predict outcomes in critically ill individuals.^{14,78}

Clinical studies to validate such scoring systems have included patients with a variety of medical and surgical conditions, although few trials have validated these scoring systems in large cohorts of poisoned patients. The original APACHE II cohort of 5815 ICU admissions from 13 hospitals included only 153 patients admitted to the ICU with a diagnosis of “drug overdose.”³⁸ APACHE II is limited by its failure to distinguish between traumatic and nontraumatic causes of altered mental status, a fact of potentially vital import in cases of overdose. The development of APACHE III addressed this shortcoming of its predecessor. However, even this very complicated scoring system with proprietary mathematical modeling has limited value when applied to a wide range of poisoned patients. In fact, when APACHE III was used by its authors to screen a large independent database of almost 40,000 ICU admissions, including 1032 patients admitted with “drug overdose,” predicted and actual mortality statistics for these patients were vastly different.⁹² Seven deaths (0.7%) were predicted in this cohort, although the actual number turned out to be 25 (2.4%). The difference was statistically significant. APACHE IV has attempted to further address the shortcomings of its predecessor, but it still has relied on parameters collected over the first 24 hours in the ICU.⁷⁸ Additional articles addressing the usage of severity of illness scoring systems to identify high-risk overdose patients are lacking, although one review of 216 consecutive ICU admissions for intentional overdose found that admission APACHE II and Glasgow Coma Scale (GCS) were equally strong predictors of morbidity and mortality.³⁰ Specifically, a GCS of 12 or less was 88% sensitive and 92% specific in identifying patients at risk for developing morbidity requiring ICU admission. A recently published consortium study of 2755 poisoned patients admitted to an ICU in Finland predictably showed that the nonsurvivors had higher APACHE II and SOFA scores than survivors (APACHE II 27.2 versus 14.1 and SOFA 9.0 versus 4.7; $P < 0.001$). In multivariate regression, respiratory failure, kidney failure, and hypotension were key abnormalities that predicted prolonged ICU care and mortality.⁴⁴ A prospective study in 92 mixed ingestions presenting with coma showed that APACHE II, MAS (Modified APACHE II), and GCS all performed reasonably well in terms of discriminating survivors from nonsurvivors,

both at presentation and at 24 hours.¹⁷

Given the unique characteristics of individual xenobiotics, other authors have attempted to apply severity of illness models in specific instances. Within 24 hours of presentation, both SOFA and APACHE II scores showed promise as predictors of mortality when studied prospectively in acetaminophen (APAP)-induced acute liver failure, revealing similar power to predict a poor outcome when compared against the widely accepted King's College Criteria.^{11,56} Two studies evaluating organic phosphorus compound poisoning used APACHE II and SAPS II scores demonstrated that high scores were predictive of mortality.^{42,73} However, some clinical outcome predictors used in these scoring systems, such as neurologic outcome after cardiac arrest, are unreliable in poisoned patients.¹⁸ Patients with severe poisoning may have clinical characteristics that mimic brain death yet have a complete neurologic recovery.

Results of severity of illness models must be cautiously used.⁷⁸ These models lack individual prognostic application, and decisions about individual patients still require clinical judgment. Scores for these models need to be validated for the specific population for which they are to be used. A specific limitation of these models is lead-time bias (ie, pre-ICU care that influences mortality and in which the sole outcome measure is mortality). Additionally, some of these models use the most extreme values at 24 or 48 hours, and so when used at admission, they may underrepresent the patients' true predicted mortality.¹⁹ Therefore, severity of illness models to guide ICU care must be used cautiously when applied specifically to poisoned patients. More study is needed before any severity of illness model can be considered reliable in predicting which patients are at the highest risk of developing ICU-requiring morbidity or mortality.

Beyond illness scoring system literature, few studies specifically evaluate the use of the ICU for poisoned patients.^{6,27,31,33,39,79,83} Prospective studies focus on mortality rates, use of resources, or types of xenobiotics ingested; other studies, mostly retrospective ones, focus on patients exposed to a specific xenobiotic. Taken together, this suggests that physiologic risk assessment may be helpful to clinicians as an adjunct to other clinical factors and is an area where "triage" studies would provide the most useful new insight. Initiatives in the United States (American College of Medical Toxicology's Toxicology Investigators Consortium {ToxIC} and in Australia) have begun creating registries of patients directly treated by practicing medical toxicologists. These registries promise to capture high-quality clinical data that can advance our understanding of risk and potentially guide future clinical guideline development.^{85,87}

Ideally, clinical indicators for ICU care could be established for each xenobiotic, but these would be limited based on the uncertainty associated with the patient's presentation. Universal criteria cannot be applied to all poisoned patients because of the unique clinical course of some xenobiotics and the uncertainty regarding which xenobiotics were ingested. In one outcome study of elderly poisoned patients, the authors observed that each category of poisoning has its own special risk profile.⁵⁸ Until more specific predictors of outcome are developed for individual xenobiotics, nothing will be more useful than experience and good clinical judgment in predicting who may benefit from ICU admission. At present, withholding ICU care from poisoned patients based solely on a nonspecific "score" will not result in significant cost savings in the ICU but may increase the risk of morbidity and mortality.

Assessing Risk Using Xenobiotic Characteristics as a Basis for ICU Admission

Both the known and unknown characteristics of a xenobiotic will assist with ICU admission decisions. Some xenobiotics have proven their capability to cause harm or death to humans. Well-described, expected toxic effects assist in early recognition of poisoning. For other xenobiotics, the consequences after exposure are not yet reported.

ICU admission is warranted for patients with expected serious toxic effects from a xenobiotic. This is especially true for xenobiotics known to be deadly, such as calcium channel blockers, cyanide, cyclic antidepressants, and salicylates. For example, patients with calcium channel blocker poisoning who exhibit hemodynamic compromise require close attention and meticulous continuous treatment available only in critical care units.

Due to the availability of newer antidepressants in the past few years, poisoning from cyclic antidepressants is less common. However, the literature attempting to identify the clinical indicators of serious toxicity serves as an excellent case study. Indicators of toxicity should be identified for individual xenobiotics so that high-risk patients may be closely monitored and aggressively treated. Patients who have ingested cyclic antidepressants develop substantial morbidity and mortality and have been studied in great detail to determine indicators of toxicity. These studies demonstrate that a prolonged QRS complex on a 12-lead electrocardiogram (ECG) is predictive of serious complications such as seizures and dysrhythmias.^{4,60} Any patient manifesting ECG abnormalities (including QRS ≥ 0.10 seconds) or hypotension requires ICU monitoring.⁹ Unlike cyclic antidepressants, most xenobiotics do not have such an extensive literature to define high-risk patients.

Xenobiotics inducing liver injury have received some of the greatest attention in determining risk based on the known characteristics of the ingestion. For example, most APAP-poisoned patients can be safely managed outside of the ICU because they exhibit no end-organ toxicity and their hospital management entails only laboratory monitoring and antidotal therapy with N-acetylcysteine. However, APAP poisoning can be lethal, and at some point in the clinical course, manifestations of toxicity require close monitoring and treatments available only in the ICU. Predictors of poor outcome have been studied and can be useful guides for selecting patients who need ICU care. The King's College Criteria are well-

established indicators of impending hepatic failure and the need for evaluation for possible transplantation. Patients with abnormal clinical and laboratory data approaching these criteria are candidates for ICU admission or transfer to a specialized center with advanced ICU resources and transplantation services.⁶¹ In addition, the use of the discriminate function in risk adjusting for acute alcoholic hepatitis uses the patient's total bilirubin and prothrombin time. It has been used to predict severity, mortality, and indications for treatment following acute ingestion of alcohol.^{45,59,67}

Decisions can be challenging when the characteristics and clinical course of the xenobiotic are unknown. New pharmaceutical and industrial products are introduced every year with little data on toxic exposure doses or human health effects in overdose. Sometimes animal studies provide the only known toxicologic data, and preclinical trials for new xenobiotics may have excluded the populations at risk, such as infants, children, or the elderly. In these cases, clinicians must often make therapeutic decisions and anticipate potential toxicity with little or no reliable data. Because early recognition of serious toxicity may prevent an adverse outcome, expectant observation may be the only rational approach. For example, intentional and unintentional ingestions followed the introduction of fluoxetine. Because, at that time, clinicians lacked experience treating overdoses of this xenobiotic and had no data regarding the natural course and toxic dose, many patients were admitted to the ICU for observation of toxic effects. Now that clinicians have experience with this drug and studies are available demonstrating few severe manifestations, ICU resources are seldom needed to treat such patients.^{5,77}

Failure to appreciate the potential for serious, delayed toxic effects is a major pitfall in managing poisoned patients. An asymptomatic patient may be a "time bomb" with the potential to deteriorate rapidly. Delayed or continued absorption, slow tissue distribution, interference with cellular function, production of toxic metabolites, or depletion of target organ reserve capacity are causes of delayed onset of clinical effects.

Certain xenobiotics prolong GI absorption, delaying onset of toxicity.⁵³ Sustained-release pharmaceutical preparations and those with enteric coatings enhance patient compliance but, in overdose, may delay absorption and, in turn, make the onset of toxicity unpredictable.⁵⁵ Published cases of overdoses with sustained-release verapamil, diltiazem, and bupropion as well as long-acting opioids and enteric-coated aspirin report delayed onset of toxicity (>6 hours), with peak serum concentrations measured more than 24 hours after ingestion.^{21,76,90}

Serial xenobiotic concentrations are necessary to verify peaks and ensure decreasing concentrations. Serial concentrations may, if available, warn of increasing potential for serious toxic effects. However, when serum concentrations are unobtainable, extended observation, possibly in the ICU, is required for many patients with overdoses of sustained-release and enteric-coated medications.

Clinical effects may be delayed when toxicity depends on alteration of enzyme functions, cellular reproduction, or metabolic function. For example, toxicity from colchicine may not be apparent for many hours after an overdose but then may progress rapidly to severe toxicity such as cardiovascular collapse. Other xenobiotics may take days to exhibit their toxic effects. For example, methotrexate and other chemotherapeutics may cause life-threatening bone marrow suppression days after exposure. When there is potential for serious delayed toxicity, prolonged close patient monitoring, typically in an ICU setting, is necessary.

PHYSIOLOGIC MONITORING AND SPECIALIZED TREATMENT AS REQUIREMENTS FOR ICU ADMISSION

The medical toxicologist, prepared with a thorough understanding of pharmacokinetics, pharmacodynamics, and unique treatments for poisoning, can collaborate with the critical care specialist to optimize physiologic function. This combination provides the patient the greatest opportunity for a good clinical outcome.

One benefit of the ICU for the poisoned patient is the ability to rapidly respond to failing vital organs and to titrate therapies to restore normal physiology in the critically ill. This is achieved through a nurse-to-patient ratio that allows for frequent or continuous monitoring of basic physiologic parameters. These measurements of vital signs, neurologic status, and fluid intake and output measurements, along with continuous cardiac monitoring, make possible early detection of toxicity, recognition of conditions needing active intervention, and prevention of complications.²⁹ Medical technologic advances now provide a number of invasive and noninvasive capabilities that can signal or offer trends indicating risk of catastrophic deterioration or feedback on response to therapy.⁶⁴ For example, monitoring hemodynamic parameters are valuable for managing poisoned patients with hypotension, intravascular volume depletion, or respiratory failure from acute respiratory distress syndrome (ARDS). Most importantly, clinicians must recognize that no monitoring device improves clinical outcome unless coupled with a treatment that improves outcome.²⁸

Most critically ill poisoned patients have acute reversible conditions requiring supportive care measures (ie, ventilator support, vasopressor support, or both) and close monitoring that only ICUs are equipped to provide. Most often, supportive care measures improve the outcome of critically ill poisoned patients more than antidotes and specialized treatments. Focus on supportive care measures, such as maintaining a patent airway, preventing hypoxia with the administration of oxygen, and treatment of shock, decreased the mortality for patients with barbiturate overdoses from 20% in the 1930s to less than

2% in the 1950s.¹³ This approach seems equally important in this century to achieve desired patient outcomes in the critically ill. Studies in both adults and children report good outcomes in most critically ill poisoned patients treated with only mechanical ventilation, vasopressor support, and careful monitoring.^{18,39}

Many antidotes and specific treatments should be administered in the ED and the ICU settings. Although these treatments may possibly be life saving, they may have inherent risks. Because these treatments may be unfamiliar to staff, the ICU is the most appropriate environment to administer or continue such treatments. Whereas some antidotes are administered in unconventional doses, other familiar drugs should be avoided in treating patients with toxicologic emergencies. In toxicologic emergencies, a familiar drug may be an antidotal therapy that requires doses that far exceed conventional regimens or indications that deviate from common treatment protocols. High doses of atropine (ie, hundreds of milligrams) may be necessary for the treatment of patients with organic phosphorus insecticide poisoning.^{15,25,41} Vasopressors that are commonly used in medical hypotension, such as sepsis, should be avoided in most cases of xenobiotic-induced hypotension until specific antidotal therapy fails.

A false sense of security can result when an antidote reverses toxicity but has a shorter duration of effect than the xenobiotic. An example is a patient, comatose from an opioid overdose who responds to naloxone, awakens, and refuses further treatment. Sedation and possibly respiratory depression may reappear when the short duration of effect of naloxone allows opioid toxicity to recur. These patients must be closely observed for the possible need to readminister the antidote. In a retrospective review of patients presenting with opioid overdosage, 31% of 84 naloxone responders experienced resedation necessitating readministration.⁸⁴ Resedation is particularly problematic with long-acting opioids such as methadone and controlled-release preparations of oxycodone and morphine.³²

Extracorporeal methods of eliminating xenobiotics, such as hemodialysis and continuous venovenous hemofiltration, are ideally performed in the ICU.²² Invasive procedures, such as extracorporeal membrane oxygenation, cardiopulmonary bypass, and intraaortic balloon pump-assisted perfusion, are used successfully in resuscitating critically ill poisoned patients.^{34,40,74}

When the need for surgical intervention or specialized wound care is anticipated, patients with toxicologic emergencies are ideally managed in the ICU. Although transplantation becomes necessary in a minority of critically ill APAP-poisoned patients, this treatment can improve survival to discharge by as much as 75%.² Compartment syndrome, from muscle compression after prolonged xenobiotic-induced coma, is a rare but limb-threatening occurrence that sometimes results in the need for fasciotomy.²⁴ Any poisoned patient with significant rhabdomyolysis, whether localized or more widespread, is at risk for the development of compartment syndrome and acute kidney failure. If contemplating fasciotomy, monitoring and specialized postoperative care in an ICU is warranted. Plasmapheresis and specialized wound care in an ICU are necessary in cases of toxic epidermal necrolysis (TEN) secondary to xenobiotics. Mortality and morbidity may be reduced by early referral to a specialized burn center for conditions such as TEN or significant dermal burns from caustics.

LIFE-THREATENING COMPLICATIONS ASSOCIATED WITH POISONING

Poisoning produces both anticipated and unanticipated complications that can prolong ICU care and decrease survival. Serious complications of poisoning include pulmonary compromise, rhabdomyolysis, compartment syndrome, and anoxic brain injury. Complications such as acute kidney or liver failure also might prolong an ICU course.

Pulmonary compromise after toxic exposures often develops after several hours or days in the ICU. Pulmonary complications after a toxic exposure include aspiration pneumonitis and ARDS, leading to prolonged ICU stays, higher mortality, and substantial additional medical costs.⁶⁶ Aspiration of gastric contents is an uncommon but serious complication of poisoning, especially when a patient's mental status is altered and protective airway reflexes are lost.^{12,36} Poisoned patients may aspirate spontaneously while lying unresponsive before being discovered, from stomach dilation secondary to bag–valve–mask ventilation, from GI decontamination procedures such as orogastric lavage, or during insertion of endotracheal or nasogastric tubes.^{12,36} In a review of 4562 poisoning admissions, 71 patients clearly had aspiration pneumonitis, yielding a rate of 1.6%.³⁶ In logistic regression analysis, older age, a GCS below 15, spontaneous emesis, delayed presentation to the hospital, and ingestion of cyclic antidepressants were associated with aspiration pneumonitis. Not only were the rates of ICU admission and length of stay increased in the patients with aspiration pneumonitis, but mortality was also higher, with a rate of 8.5% compared with 0.4% for those without.

Poisoning may cause global cerebral anoxia from prolonged shock, respiratory failure, or direct toxic metabolic effects. Distinguishing anoxic cerebral injury from reversible encephalopathy can be difficult in poisoned patients. Coma and loss of brainstem reflexes after prolonged, severe cerebral hypoxia indicate a poor prognosis.^{80,89} Ancillary tests such as electroencephalography (EEG), computed tomography, cerebral angiography, magnetic resonance, and nuclear brain flow studies may be useful in assessing cerebral function and structural integrity. Results should be interpreted with caution when attempting to confirm brain death following drug overdose. EEG can be particularly misleading in certain overdoses, such as those involving benzodiazepines, barbiturates, or baclofen in which the lack of electrical brain activity is a direct effect of the xenobiotic.⁸⁰ Angiographic imaging via CT or direct arteriography may prove particularly useful in such cases,

although such tests can reveal continued blood flow when intracranial hypertension is absent despite severe axonal injury and brain death.⁵² Because clinical predictors of outcome may be unreliable when applied to poisoned patients, the diagnosis of brain death should be made cautiously. Cerebral edema is often a secondary effect of global cerebral anoxia, although some xenobiotics have direct cellular effects. Cerebral edema can be a complication of APAP-induced fulminant hepatic failure and the result of direct neuronal injury from salicylate and lead poisoning.^{51,68,81} Rigorous ICU care is preferred to treat patients with xenobiotic-induced cerebral injuries.

ALTERNATIVES TO ICU ADMISSION

Placing patients in the ICU solely for observation often is an ineffective use of this expensive resource. Patient placement decisions require balancing necessary health care resources with risk of adverse patient events. Until further clinical studies are available to define patients who are at risk for serious toxicity or life-threatening complications, many poisoned patients will be admitted to the ICU for observation. When information about the xenobiotic, the patient, and the capabilities of the medical unit are all considered, many patients can be safely observed outside the ICU. [Table 11–2](#) presents some items to consider when making disposition decisions.

TABLE 11–2. Considerations for Intensive Care Unit Admission

<i>Patient Characteristics</i>	<i>Xenobiotic Characteristics</i>	<i>Capabilities of the Inpatient/Observation Unit</i>
Does the patient have any signs of serious end-organ toxicity?	Are there known serious sequelae (eg, cyclic antidepressants, calcium channel blockers)?	Does the admitting health care team appreciate the potential seriousness of a toxicologic emergency?
Are the end-organ effects progressing?	Can the patient deteriorate rapidly from its toxic effects?	Is the nursing staff:
Are laboratory data suggestive of serious toxicity?	Is the onset of toxicity likely to be delayed (eg, sustained-release preparation, slowed GI motility, or delayed toxic effects)?	Familiar with this toxicologic emergency?
Is the patient a high risk for complications requiring ICU intervention?	Does the xenobiotic have effects that will require cardiac monitoring?	Familiar with the potential for serious complications?
Seizures	Is the amount ingested a potentially serious or potentially lethal dose?	Is the staffing adequate to monitor the patient?
Unresponsive to verbal stimuli	Are xenobiotic concentrations rising?	What is the ratio of nurses to patients?
Level of consciousness impaired to the point of potential airway compromise	Is the required or planned therapy unconventional (eg, large doses of atropine for treating overdoses of organic phosphorus insecticides)?	Are time-consuming nursing activities required and realistic?
PCO ₂ >45 mm Hg	Does the therapy have potentially serious adverse effects?	Can a safe environment be provided for a suicidal patient?
Systolic blood pressure <80 mm Hg (in an adult)	Is there insufficient literature to describe the potential human toxic effects?	Can a patient have suicide precautions and monitoring with a medical floor bed?
Cardiac dysrhythmias (ventricular dysrhythmias, high-grade conduction abnormalities)	Are potentially serious coingestants likely (must take into account the reliability of the history)?	Can a one-to-one observer be present in the room with the patient?
Abnormal ECG complexes and intervals (QRS duration ≥0.10 seconds; QT prolongation)		Can the patient be restrained?
Is the patient at high risk for complications such as aspiration pneumonia, anoxic brain injury, rhabdomyolysis, or compartment syndrome?		
Does the patient have preexisting medical conditions that could predispose to complications?		
Alcohol or drug dependence		
Liver disease		
Acute kidney injury or chronic kidney disease		
Heart disease		
Pregnancy: is the xenobiotic or the antidote teratogenic?		
Is the patient suicidal?		

Alternatives to ICU admission include an adult medical or pediatric floor bed, an intermediate care unit, a telemetry-monitored bed, a medical psychiatric unit, a hospital short stay unit, or an ED observation unit. Capabilities for managing poisoned patients may vary considerably between institutions and in different types of patient care areas. It is essential to understand the capabilities of the unit where a patient is being considered for admission. If the nursing staff is unfamiliar with the potential for rapid deterioration of the patient or the staffing pattern does not allow for close observation, the patient outcome can be severely compromised. For example, it is unrealistic to expect a nurse to perform/record frequent vital signs, make serial neuropsychiatric evaluations, and maintain a close watch for respiratory depression in a patient with altered mental status while caring for other patients.

ED observation may be an alternative for the care of select poisoned patients.^{8,35,70,71} An observation unit is dedicated

space, frequently located near the ED, providing focused care and observation to patients needing less than 24 hours of additional care but not yet ready to safely leave the hospital. Data projections suggest that using ED observation units saves significant dollars for the health care system.¹ These units are capable of frequent monitoring of vital signs, continuous cardiac monitoring, and maintaining a safe environment for suicidal patients.^{70,82} Patients with a low risk of serious toxicity or life-threatening complications who require only observation may be ideal candidates for ED observation units.

Many poisoned patients are placed in the ICU because they are suicide risks. Institutions differ on monitoring policies for suicidal patients not admitted on a psychiatric unit. Other than the ICU, many hospitals cannot provide an alternative for observing high-risk suicidal patients because one-on-one monitoring is cost prohibitive. Less costly alternatives are available, but they must ensure a safe environment for suicidal patients. An ED observation unit, an intermediate care unit, a medical psychiatric unit, or a one-on-one observer can safely monitor these patients.

Future studies must further define prognostic factors for poisoning complications. Patients can then be stratified into high- or low-risk groups. The limitations of current studies prevent generalizing the results to individual patients or certain subgroups. Unfortunately, many current policies now being used to regulate admission decisions to the ICU are clinical practice guidelines unlikely derived from the best and most recent evidence. Clinical guidelines should be based on sound evidence so they optimize the use of resources and minimize the risk of harm to patients.

CRITERIA FOR SAFE TRANSFER OUT OF THE ICU

After the acute toxic effects have resolved, most patients are safe to transfer out of the ICU. A good example for establishing safe criteria comes from past experiences with cyclic antidepressant overdoses. These patients were studied to determine when it was safe to discontinue monitoring. Concerns arose from case reports of patients developing sudden death as late as several days after a cyclic antidepressant overdose.^{9,53,72} In most cases, delayed complications developed in the setting of continued toxicity evidenced by lethargy or sinus tachycardia. Several subsequent studies demonstrate that dysrhythmias do not occur after signs of toxicity have resolved (ie, CNS and cardiac manifestations).^{10,63} The authors of these studies suggested cardiac monitoring for an additional 24 hours after normalization of the ECG and resolution of other signs of continued toxicity such as normalization of the mental status and blood pressure.¹⁰ This additional period of monitoring should occur after discontinuation of all specific forms of therapy, such as serum alkalization.

Most xenobiotics have not received the level of attention given to cyclic antidepressants, making clinical judgments the only basis for deciding when to discharge a patient from the ICU, pending further research and experience. For example, drug-induced QT interval prolongation may increase the risk of developing torsade de pointes.³⁷

Ongoing risk of complications or delayed deterioration may be pitfalls to a patient's safe discharge from an ICU. It is necessary to carefully consider discharge decisions about patients exposed to xenobiotics, such as colchicine, with serious delayed clinical effects. Clinicians should also be mindful that the duration of action of the xenobiotic may be longer than the duration of action of the specific treatment or antidote.

Finally, the patient's suicidal intent must be considered before transfer to a less closely monitored hospital unit. Transfer out of the ICU should occur only after assessment of suicide risk and other important psychosocial issues. Early involvement of psychiatric services, chemical dependency counseling, and social services can expedite ICU disposition. Disposition and treatment options may be considered at a time when the patient is still medically unstable by interviewing his or her family, friends, and outpatient counselors.

ICU-to-ICU Transfer

Poisoned patients may require ICU-to-ICU transfer in order to meet their critical care needs, but this poses a risk to the patient. Poison centers and medical toxicologists play a significant role in identifying clinical parameters that alert to impending deterioration, provide therapeutic advice to stabilize the patient until transferred, and can often facilitate rapid transfer to a higher level care facility with specialized capabilities. Although the etiology is not fully understood, there is an association between increasing mortality and distance traveled, medical complications, severity of illness, and subtype of illness.¹⁶ At one academic medical center, use of a structured instrument to guide communication between a transferring and a receiving ICU reduced the adjusted mortality. This suggests that individuals responsible for accepting patients for transfer should develop tools to systematize their process. In this study, one unique finding was the identification of three APAP overdoses who were not on N-acetylcysteine therapy at the transferring institution.⁴⁶

FUTURE DIRECTIONS

All of the health care components supporting patient care form a complex system facilitating the movement of the patient through the system, exchanging information, making critical decisions to optimize care, and aligning the necessary resources to treat critically ill poisoned patients. This complex system contains leverage points composed of those places where interventions may significantly influence patient outcomes and appropriately focus resources. To most influence the care of

future critically ill poisoned patients, the medical toxicologist should focus on studying this complex system, uncovering its leverage points and endeavoring to optimize it in as many directions as possible.

The medical toxicologist can enhance the care of critically ill poisoned patients by rapidly recognizing those patients most at risk for critical illness and finding those benefiting most from early specialized interventions. Additionally, the medical toxicologist augments the critical care specialist's ability to restore normal physiology to critically ill poisoned patients by sharing expert knowledge of early indicators of potentially severe toxicity and in-depth understanding of pharmacodynamics, pharmacokinetics, and specialized treatments.

Clearly identified clinical parameters, serving as clues or patterns predicting high risk for serious toxicity, can function as early warning detectors, decreasing reaction times to those critical actions that most benefit patient outcomes. Research discovering these key parameters could optimize this entire complex system supporting the care of critically ill poisoned patients. These patients have a much better chance of a positive outcome when clinicians define parameters which will inform them sufficiently quickly to recognize impending harmful consequences and leading to interventions that prevent or lessen harm. Such parameters allow poison centers and medical toxicologists to facilitate rapid transfer to a higher level care facility with specialized capabilities. With these parameters, physicians can select candidates for the ICU who are at highest risk of impending harm and can confidently and safely transfer those lower risk patients to alternative care sites outside of the ICU. Within the ICU, these parameters allow early recognition of impending deterioration, leading to interventions optimizing physiology, lessening harm, and preventing complications. Finally, they assist clinicians' ability to recognize the timing for a safe transfer from ICU care, streamlining the flow of patients for optimum use of these valuable resources.

SUMMARY

- Acute poisoning challenges the medical and nursing staff because of its unpredictable clinical course and unfamiliar therapies.
- Poisoned patients are especially problematic because their clinical history is incomplete and the medical literature is often limited. These potential unknowns create many uncertainties in management.
- Because the ICU offers the highest level of skilled staff and modern technology available, most seriously poisoned patients should be admitted there.
- Whether this is clinically justified or is an effective use of resources for a given patient remains a debated issue because admission of poisoned patients continues to be based mostly on clinical judgment and the best available information.

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PART B

THE FUNDAMENTAL PRINCIPLES OF MEDICAL
TOXICOLOGY

SECTION I

BIOCHEMICAL AND MOLECULAR BASIS

12 CHEMICAL PRINCIPLES

Stephen J. Traub and Lewis S. Nelson

Chemistry is the science of matter; it encompasses the structure, physical properties, and reactivities of atoms and their compounds. In many respects, toxicology is the science of the interactions of matter with living entities. Chemistry and toxicology are therefore intimately linked. The study of the principles of inorganic, organic, and biologic chemistry offers important insight into the mechanisms and clinical manifestations of xenobiotics and poisoning. This chapter reviews many of these tenets and provides relevance to the current practice of medical toxicology.

THE STRUCTURE OF MATTER

Basic Structure

Matter includes the substances of which everything is made. Elements are the foundation of matter, and all matter is made from one or more of the known elements. An atom is the smallest quantity of a given element that retains the properties of that element. Atoms consist of a nucleus, incorporating protons and neutrons, coupled with its orbiting electrons. The atomic number is the number of protons in the nucleus of an atom, and it is a whole number that is unique for each element. Thus, elements with 6 protons are always carbon, and all forms of carbon have exactly 6 protons. However, although the vast majority of carbon nuclei have 6 neutrons in addition to the protons, accounting for an atomic mass (protons plus neutrons) of 12 (^{12}C), a small proportion of naturally occurring carbon nuclei, called isotopes, have 8 neutrons and a mass number of (^{14}C). This is the reason that the atomic weight of carbon displayed on the periodic table is 12.011, and not 12, as it actually represents the average atomic masses of all isotopes found in nature weighted by their frequency of occurrence. Moreover, ^{14}C is actually a radioisotope, which is an isotope with an unstable nucleus that emits radiation (particles or rays) until it achieves a stable state ([Chap. 134](#)). The atomic weight, measured in grams per mole (g/mol), also indicates the molar mass of the element. That is, in one atomic weight (12.011 g for carbon) there is one mole (6.023×10^{23}) of atoms.

Elements combine chemically to form compounds, which generally have physical and chemical properties that differ from those of the constituent elements. The elements in a compound can be separated only by chemical means that destroy the original compound, as occurs during the burning (ie, oxidation) of a hydrocarbon, a process that releases the carbon principally as carbon dioxide and the hydrogen principally as water (H_2O). This important property differentiates compounds from mixtures, which are combinations of elements or compounds that can be separated by physical means such as the distillation of petroleum into its hydrocarbon components or the evaporation of seawater to separate water from sodium chloride and other substances. With notable exceptions, such as the elemental forms of many metals or halogens (eg, Cl_2), most xenobiotics are compounds or mixtures.

Dimitri Mendeleev, a Russian chemist in the mid-19th century, recognized that when all of the known elements were arranged in order of atomic weight, certain patterns of reactivity became apparent. The result of his work was the Periodic Table of the Elements ([Fig. 12-1](#)), which, with some minor alterations, is still an essential tool today. All of the currently recognized elements are represented; those heavier than uranium are known not to occur in nature. Many of the symbols used to identify the elements refer to the Latin name of the element. For example, silver is Ag, for argentum, and mercury is Hg, for hydrargyrum, literally “silver water.”

Periods	Rows/Groups																		Columns							
	IA Alkali metals		IIA Alkaline earth metals		Transition metals										IIIA		IVA		VA		VIA		VIIA Halogens		0 Inert gases	
	H		Li	Be											B	C	N	O	F	Ne						
	Na	Mg	IIIB		IVB	VB	VIB	VIIIB	VIII			IB	IIB	Al	Si	P	S	Cl	Ar							
	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr								
	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe								
	Cs	Ba	Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn								
	Fr	Ra	Lr	Rf	Db	Sg	Bh	Hs	Mt																	
Symbol		Name		Period		Group		Symbol		Name		Period		Group		Symbol		Name		Period		Group				

Ac	Actinium	89	227.0278
Al	Aluminum	13	26.9815
Am	Americium	95	243.06
Sb	Antimony	51	121.75
Ar	Argon	18	39.948
As	Arsenic	33	74.9216
At	Astatine	85	209.99
Ba	Barium	56	137.33
Bk	Berkelium	97	247.07
Be	Beryllium	4	9.0122
Bi	Bismuth	83	208.9804
Bh	Bohrium	107	262
B	Boron	5	10.81
Br	Bromine	35	79.904
Cd	Cadmium	48	112.41
Ca	Calcium	20	40.08
Cf	Californium	98	251.08
C	Carbon	6	12.011
Ce	Cerium	58	140.12
Cs	Cesium	55	132.9054
Cl	Chlorine	17	35.453
Cr	Chromium	24	51.996
Co	Cobalt	27	58.9332
Cu	Copper	29	63.546
Cm	Curium	96	247.07
Db	Dubnium	105	262
Dy	Dysprosium	66	162.5
Es	Einsteinium	99	252.08
Er	Erbium	68	167.26
Eu	Europium	63	157.26
Fl	Fermium	100	257.1
F	Fluorine	9	18.9984
Fr	Francium	87	223.02
Gd	Gadolinium	64	157.25
Ga	Gallium	31	69.72
Ge	Germanium	32	72.59
Au	Gold	79	196.9665

Hf	Hafnium	72	178.49
Hs	Hassium	108	265
He	Helium	2	4.0026
Ho	Holmium	67	164.9304
H	Hydrogen	1	1.0079
In	Indium	49	114.82
I	Iodine	53	126.9045
Ir	Iridium	77	192.22
Fe	Iron	26	55.847
Kr	Krypton	36	83.8
La	Lanthanum	57	138.9055
Lr	Lawrencium	103	260.11
Pb	Lead	82	207.2
Li	Lithium	3	6.941
Lu	Lutetium	71	174.97
Mg	Magnesium	12	24.305
Mn	Manganese	25	54.938
Mt	Mitlerium	109	266
Md	Mendelevium	101	258.1
Hg	Mercury	80	200.59
Mo	Molybdenum	42	95.94
Nd	Neodymium	60	144.24
Ne	Neon	10	20.179
Np	Neptunium	93	237.0482
Ni	Nickel	28	58.7
Nb	Niobium	41	92.9064
N	Nitrogen	7	14.0067
No	Nobelium	102	259.1
Os	Osmium	76	190.2
O	Oxygen	8	15.9994
Pd	Palladium	46	106.4
P	Phosphorus	15	30.9738
Pt	Platinum	78	195.09
Pu	Plutonium	94	244.06
Po	Polonium	84	208.98
K	Potassium	19	39.0983
Pr	Praseodymium	59	140.9077

Pm	Promethium	61	144.92
Pa	Protactinium	91	231.0359
Ra	Radium	88	226.0254
Rn	Radon	86	222.02
Rh	Rhenium	75	186.207
Rb	Rubidium	37	85.4678
Ru	Ruthenium	44	101.07
Rf	Rutherfordium	104	261
Sm	Samarium	62	150.4
Sc	Scandium	21	44.9559
Sg	Seaborgium	106	263
Se	Selenium	34	78.96
Si	Silicon	14	28.0855
Ag	Silver	47	107.868
Na	Sodium	11	22.98977
Sr	Strontium	38	87.62
S	Sulfur	16	32.06
Ta	Tantalum	73	180.9479
Tc	Technetium	43	98.906
Te	Tellurium	52	127.6
Tb	Terbium	65	158.9254
Tl	Thallium	81	204.37
Th	Thorium	90	232.0381
Tm	Thulium	69	168.9342
Sn	Tin	50	118.69
Ti	Titanium	22	47.9
W	Tungsten	74	183.85
U	Uranium	92	238.029
V	Vanadium	23	50.9414
Xe	Xenon	54	131.3
Yb	Ytterbium	70	173.04
Y	Yttrium	39	88.9059
Zn	Zinc	30	65.38
Zr	Zirconium	40	91.22

FIGURE 12–1. The Periodic Table of the Elements.

The reason for the periodicity of the table relates to the electrons that circle the nucleus in discrete orbitals. Although the details of quantum mechanics and electronic configuration are complex, it is important to review some aspects in order to predict chemical reactivity. Orbitals, or quantum shells, represent the energy levels in which electrons may exist around the nucleus. The orbitals are identified by various schemes, but the maximum number of electrons each orbital may contain is calculated as $2x^2$, where x represents the numerical rank order of the orbital. Thus, the first orbital may contain 2 electrons, the second orbital may contain 8, the third may contain 18, and so on. However, the outermost shell (designated by s, p, d nomenclature) of each orbital may only contain up to 8 electrons. This is irrelevant through element 20, calcium, because there is no need to fill the third-level or d shells. Even though the third orbital may contain 18 electrons, once 8 are present the 4s electrons dip below the 3d electrons in energy and this shell begins to fill. This occurs at element 21, scandium, and accounts for its chemical properties and those of the other transition elements. Transition elements are chemically defined as elements that form at least one ion with a partially filled subshell of d electrons. Also, because the inert gas elements, which are also known as noble gases, have complete outermost orbitals, they are unreactive under standard conditions.

In general, only electrons in unfilled shells, or valence shells, are involved in chemical reactions. This property relates to the fact that the most stable form of an element occurs when the configuration of its valence shell resembles that of the nearest noble gas, found in group 0 on the periodic table. This state can be obtained through the gaining, losing, or sharing of electrons with other elements and is the basis for virtually all chemical reactions.

INORGANIC CHEMISTRY

The Periodic Table

Chemical Reactivity. Broadly, the periodic table is divided into metals and nonmetals. Metals, in their elemental form, are typically malleable solids that conduct electricity, whereas nonmetals are usually dull, fragile, nonconductive compounds (C, N, P, O, S, Se, halogens). The metals are found on the left side of the periodic table, and account for the majority of the elements, whereas the nonmetals are on the right side. Separating the two groups are the metalloids, which fall on a jagged line starting with boron (B, Si, Ge, As, Sb, Te, At). Metalloids have chemical properties that are intermediate between the metals and the nonmetals. Each column of elements is termed a family or group, and each row is a period. Although conceived and organized in periods, trends in the chemical reactivity, and therefore toxicity, typically exist within the groups.

The ability of any particular element to produce toxicologic effects relates directly to one or more of its many physicochemical properties. These properties may, to some extent, be predicted by their location on the periodic table. For example, arsenate may substitute for phosphate in the mitochondrial production of adenosine triphosphate (ATP), creating adenosine diphosphate monoarsenate ([Chap. 13](#)). Because this compound is unstable and not useful as an energy source, energy production by the cell fails; in this manner arsenic interferes with oxidative phosphorylation. The existence of an interrelationship between Ca^{2+} and either Mg^{2+} or Ba^{2+} is predictable, although the actual effects are not. Under most circumstances Mg^{2+} is a Ca^{2+} antagonist, and patients with hypermagnesemia present with neuromuscular weakness caused by blockade of myocyte calcium channels. Alternatively, Ba^{2+} mimics Ca^{2+} and closes Ca^{2+} -dependent K^+ channels in myocytes, producing life-threatening hypokalemia. The physiologic relationships among the ions of lithium (Li^+), potassium (K^+), and sodium (Na^+) are also consistent with their chemical similarities (all alkali metals in Group IA). However, the clinical similarity between thallium (thallous) ion (Tl^+) and K^+ is not immediately predictable. Other than their monovalent nature (ie, +1 charge), it is difficult to predict the substitution of Tl^+ (Group IIIA, Period 6) for K^+ (Group IA, Period 4) in membrane ion channel functions, until the similarity of their ionic radii is known (Tl^+ , 1.47 Å; K^+ , 1.33 Å).

Alkali and Alkaline Earth Metals. Alkali metals (Group IA: Li, Na, K, Rb, Cs, Fr) and hydrogen (not an alkali metal on earth) have a single outer valence electron and lose this electron easily to form compounds with a valence of 1+. The alkaline earth metals (Group IIA: Be, Mg, Ca, Sr, Ba, Ra) (between the alkali and rare earth, Group IIIB) readily lose two electrons, and their cations have a 2+ charge. In their metallic form, members of both of these groups react violently with water to liberate strongly basic solutions accounting for their group names ($2\text{Na}^0 + 2\text{H}_2\text{O} \rightarrow 2\text{NaOH} + \text{H}_2$). The soluble ionic forms of sodium, potassium, or calcium, which are critical to survival, also produce life-threatening symptoms following excessive intake ([Chap. 19](#)). Xenobiotics may interfere with the physiologic role of these key electrolytes. Li^+ may mimic K^+ and enter neurons through K^+ channels, where it then serves as an inadequate substrate for the repolarizing of Na^+ - K^+ -ATPase. Thus, Li^+ interferes with cellular K^+ homeostasis and alters neuronal repolarization accounting for the neuroexcitability manifesting as tremor. Similarly, as noted previously, the molecular effects of Mg^{2+} and Ba^{2+} may supplant those of Ca^{2+} . More commonly, though, the consequential toxicities ascribed to alkali or alkaline earth salts actually relate to the anionic component. In the case of NaOH or $\text{Ca}(\text{OH})_2$, it is the hydroxide anion (not the hydroxyl

radical), while it is the CN^- anion in patients poisoned with potassium cyanide (KCN).

Transition Metals. Unlike the alkali and alkaline earth metals, most other metallic elements are neither soluble nor reactive. This includes the transition metals (Group IB to VIIIB), a large group that contains several ubiquitous metals such as iron (Fe) and copper (Cu). These elements, in their metallic form, are widely used in both industrial and household applications because of their high tensile strength, density, and melting point, which is partly a result of their ability to delocalize the electrons in the d orbital throughout the metallic lattice. Transition metals also form brightly colored salts that find widespread applications, including as pigments for paints or fireworks. The ionic forms, unlike the metallic forms, of these elements are typically highly reactive and toxicologically important. Chemically, the transition elements are elements that form at least one ion with a partially filled subshell of d electrons. Because the transition metals have partially filled valence shells, they are capable of obtaining several, usually positive, oxidation states. This important mechanism explains the role of transition metals in redox reactions generally as electron acceptors (see Reduction-Oxidation below). This reactivity is used by organisms in various physiologic, catalytic, and coordination roles, such as at the active sites of enzymes and in hemoglobin, respectively. As expected, the substantial reactivity of these transition metal elements is associated with cellular injury caused by several mechanisms, including the generation of reactive oxygen species (Fig. 12–2). For example, manganese ion exposure is implicated in the free radical damage of the basal ganglia causing parkinsonism.

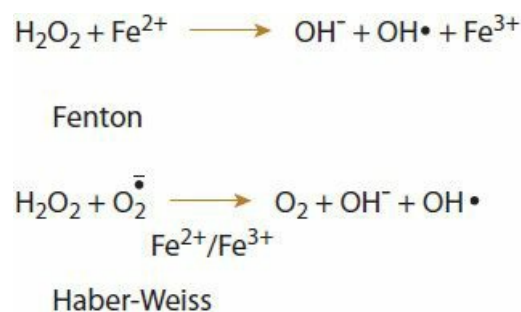


FIGURE 12–2. The Fenton and Haber-Weiss reactions, which are the two most important mechanisms to generate hydroxyl radicals, are both mediated by transition metals. Typical transition metals include iron (Fe^{2+} , shown) or copper (Cu^+).

Heavy Metals. Heavy metal is often loosely used to describe all metals of toxicologic significance, but in reality the term should be reserved to describe only those metals in the lower period of the periodic table, particularly those with atomic masses greater than 200 Da. The chemical properties and toxicologic predilection of this group vary among the elements, but their unifying toxicologic mechanism is electrophilic interference with nucleophilic sulfhydryl-containing enzymes. Some of the heavy metals also participate in the generation of free radicals through Fenton chemistry (Fig. 12–2). The likely determinant of the specific toxicologic effects produced by each metal is the tropism for various physiologic systems, enzymes, or microenvironments; thus lipophilicity, water solubility, ionic size, and other physicochemical parameters are undoubtedly critical. Also, because the chemistry of metals varies dramatically based on the chemical form (ie, organic, inorganic, or elemental), as well as the charge on the metal ion, prediction of the clinical effects of a particular metal is often difficult.

Mercury. Elemental mercury (Hg^0) is unique in that it is the only metal that exists in liquid form at room temperature and as such is capable of creating solid solutions, or amalgams, with other metals. Although it is relatively innocuous if ingested as a liquid, it is readily volatilized (ie, high vapor pressure), transforming it into a significant pulmonary mucosal irritant upon inhalation. In addition, this change in the route of exposure increases its systemic bioavailability. Absorbed, or incorporated, Hg^0 undergoes biotransformation in the erythrocyte and brain to the mercuric (Hg^{2+}) form, which has a high affinity for sulfhydryl-containing molecules, including proteins. This causes a depletion of glutathione in organs such as the kidney and also initiates lipid peroxidation. The mercurous form (Hg^+) is considerably less toxic than the mercuric (Hg^{2+}) form, perhaps because of its reduced water solubility, which limits absorption. Organic mercurial compounds, such as methylmercury and dimethylmercury, are environmentally formed by anaerobic bacteria containing the methylating compound methylcobalamin, a vitamin B_{12} analog (Chap. 98).

Thallium. Another toxicologically important member of the heavy metal group is thallium. Metallic thallium (Tl^0) is used in the production of electronic equipment and is itself minimally toxic. Thallium ions, however, have physicochemical properties that closely mimic potassium ions, allowing them to participate in, and potentially alter, the myriad physiologic activities related to potassium. This property is exploited during a thallium-stress test to assess for myocardial ischemia or infarction. Because ischemic myocardial cells lack adequate energy for normal Na^+/K^+ -ATPase function, they cannot exchange sodium for potassium (or in this scenario radioactive thallium), producing a “cold spot” in the ischemic areas on cardiac scintigraphy (Chap. 102).

Lead. Although lead is not very abundant in the Earth’s crust (only 0.002%), exposure may occur during the smelting

process or from one of its diverse commercial applications. Most of the useful lead compounds are inorganic plumbous (Pb^{2+}) salts, but plumbic (Pb^{4+}) compounds are also used. The Pb^{2+} compounds are typically ionizable, releasing Pb^{2+} when dissolved in a solvent, such as water. Pb^{2+} ions are absorbed in place of Ca^{2+} ions by the gastrointestinal tract and replace Ca^{2+} in certain physiologic processes. This mechanism is implicated in the neurotoxic effect of lead ions. Pb^{4+} compounds tend to be covalent compounds that do not ionize in water. Some of the Pb^{4+} compounds are oxidants. Although elemental lead is not itself toxic, it rapidly develops a coating of toxic lead oxide or lead carbonate on exposure to air or water (Chap. 96).

Metalloids. Although the metalloids (B, Si, Ge, As, Sb, Te, At) share many physical properties with the metals, they are differentiated by their propensity to form compounds with both metals and the nonmetals carbon, nitrogen, or oxygen. Thus, metalloids may be either oxidized or reduced in chemical reactions.

Arsenic. Toxicologically important inorganic arsenic compounds exist in either the pentavalent arsenite (As^{5+}) form or the trivalent arsenate (As^{3+}) form. The reduced water solubility of the arsenate compounds, such as arsenic pentoxide, accounts for its limited clinical toxicity when compared to trivalent arsenic trioxide. The trivalent form of arsenic is primarily a nucleophilic toxin, binding sulfhydryl groups and interfering with enzymatic function (Chaps. 13 and 89).

Nonmetals. The nonmetals (C, N, P, O, S, Se, halogens) are highly electronegative and, unlike the metals, may be toxic in either their compounded or their elemental form. The nonmetals with large electronegativity, such as O_2 or Cl_2 , generally oxidize other elements in chemical reactions. Those with lesser electronegativity, such as C, behave as reducing agents.

Halogens. In their highly reactive elemental form, which is a covalent dimer of halogen atoms, the halogens (F, Cl, Br, I, At) carry the suffix -ine (eg, Cl_2 , chlorine). Halogens require the addition of one electron to complete their valence shell; thus, halogens are strong oxidizing agents. Because they are highly electronegative, they form halides (eg, Cl^- , chloride) by abstracting electrons from less electronegative elements. Thus, the halogen ions, in their stable ionic form, generally carry a charge of -1 . The halides, although much less reactive than their respective elemental forms, are reducing agents. The hydrogen halides (eg, HCl, hydrogen chloride) are gases under standard conditions, but they ionize when dissolved in aqueous solution to form the hydrohalidic acids (eg, HCl, hydrochloric acid). All hydrogen halides except HF (hydrogen fluoride) ionize nearly completely in water to release H^+ and are considered strong acids. Because of its small ionic radius, lack of charge dispersion, and the intense electronegativity of the fluorine atom, HF ionizes poorly and is a weak acid. This specific property of HF has important toxicologic implications (Chap. 107).

Group 0: Inert Gases. Inert gases (He, Ne, Ar, Kr, Xe, Rn), also known as noble gases, maintain completed valence shells and are thus entirely unreactive except under extreme experimental conditions. However, despite their lack of chemical reactivity, the inert gases are toxicologically important as simple asphyxiants. That is, because they displace ambient oxygen from a confined space, hypoxia may occur (Chap. 124). During high-concentration exposure, inert gases may produce anesthesia, and xenon is used as an anesthetic agent. Radon, although a chemically unreactive gas, is radioactive, and prolonged exposure is associated with the development of lung cancer.

Bonds

Electrons are not generally shared evenly between atoms when they form a compound. Instead, unless the bond is between the same elements, as in Cl_2 , one of the elements exerts a larger attraction for the shared electrons. The degree to which an element draws the shared electron is determined by the electronegativity of the element (Fig. 12–3). The electronegativity of each element was catalogued by Linus Pauling and relates to the ionic radius, or the distance between the orbiting electron and the nucleus, and the shielding effects of the inner electrons. The electronegativity rises toward the right of the periodic table, corresponding with the expected charge obtained on an element when it forms a bond. Fluoride ion has the highest electronegativity of all elements, which explains many of its consequential toxicologic properties.

IA							0
H 2.20							He –
	IIA	IIIA	IVA	VA	VIA	VIIA	
Li 0.98	Be 1.57	B 2.04	C 2.55	N 3.04	O 3.44	F 3.98	Ne –
Na 0.93	Mg 1.31	Al 1.61	Si 1.90	P 2.19	S 2.58	Cl 3.16	Ar –
K 0.82	Ca 1.00			As 3.18	Se 2.55	Br 2.96	Kr –

FIGURE 12–3. Electronegativity of the common elements. Note that the inert gases are not reactive and thus do not have

electronegativity.

Several types of bonds exist between elements when they form compounds. When one element gains valence electrons and another loses them, the resulting elements are charged and attract one another in an ionic, or electrovalent, bond. An example is sodium chloride (NaCl), or table salt, in which the electronegativity difference between the elements is 1.9, or greater than the electronegativity of the sodium (Fig. 12–3). Thus, the chloride wrests control of the electrons in this bond. In solid form, ionic compounds exist in a crystalline lattice, but when put into solution, as in the serum, the elements may separate and form charged particles, or ions (Na^+ and Cl^-). The ions are stable in solution, however, because their valence shells contain eight electrons and are complete. The properties of ions differ from both the original atom from which the ion is derived and the noble gas with which it shares electronic structure.

It is important to recognize that when a mole of a salt, such as NaCl (molecular weight 58.45 g/mol), is put in aqueous solution, two moles of particles result. This is because NaCl essentially ionizes fully in water; that is, it produces one mole of Na^+ (23 g/mol) and one mole of Cl^- (35.5 g/mol). For salts that do not ionize completely, less than the intrinsic number of moles are released and the actual quantity liberated can be predicted based on the defined solubility of the compound, or the solubility product constant (K_{sp}). For ions that carry more than a single charge, the term equivalent is often used to denote the number of moles of other particles to which one mole of the substance will bind. Thus, an equivalent of calcium ion will typically bind two moles (or equivalents) of chloride ions (which are monovalent) because calcium ions are divalent. Alternatively stated, a 10% calcium chloride (CaCl_2) aqueous solution contains approximately 1.4 mEq/mL or 0.7 mmol/mL of Ca^{2+} .

Compounds formed by two elements of similar electronegativity have little ionic character because there is little impetus for separation of charge. Instead, these elements share pairs of valence electrons, a process known as covalence. The resultant molecule contains a covalent bond, which is typically very strong and generally requires a high-energy chemical reaction to disrupt it. There is wide variation in the extent to which the electrons are shared between the participants of a covalent bond, and the physicochemical and toxicologic properties of any particular molecule are in part determined by its nature. Rarely is sharing truly symmetric, as in oxygen (O_2) or chlorine (Cl_2). If sharing is asymmetric and the electrons thus exist to a greater degree around one of the component atoms, the bond is polar. However, the presence of a polar bond does not mean that the compound itself is polar. For example, methane contains a carbon atom that shares its valence electrons with four hydrogen atoms, in which there is a small charge separation between the elements (electronegativity {EN} difference = 0.40). However, because the molecule is configured in a tetrahedral formation, there is no notable polarity to the compound; this compound is nonpolar. The lack of polarity suggests that methane molecules have little affinity for other methane molecules and they are held together only by weak intermolecular bonds. This explains why methane is highly volatile under standard conditions and therefore exists as a gas under standard temperature and pressure.

Because the EN differences between hydrogen (EN = 2.20) and oxygen (EN = 3.44) are greater (EN difference = 1.24), the electrons in the hydrogen-oxygen bonds in water are drawn toward the oxygen atom, giving it a partial negative charge and the hydrogen a partial positive charge. Furthermore, because H_2O is angular, not linear or symmetric, water is a polar molecule. Water molecules are held together by hydrogen bonds, which are stronger than other intermolecular bonds (for example, van der Waals forces; see later). These hydrogen bonds have sufficient energy to open many ionic bonds and solvate the ions. In this process, the polar ends of the water molecule surround the charged particles of the dissolved salt. Thus, because there is little similarity between the nonpolar methane and the polar water molecules, methane is not water soluble. Similarly, salts cannot be solvated by nonpolar compounds, and thus a salt, such as sodium chloride, cannot dissolve in a nonpolar solvent, such as carbon tetrachloride.

Alternatively, the stability and irreversibility of the bond between an organic phosphorus insecticide and the cholinesterase enzyme are a result of covalent phosphorylation of an amino acid at the active site of the enzyme. The resulting bond is essentially irreversible in the absence of another chemical reaction (Fig. 113–3).

Compounds may share multiple pairs of electrons. For example, the two carbon atoms in acetylene ($\text{HC}\equiv\text{CH}$) share three pairs of electrons between them, and each shares one pair with a hydrogen. Carbon and nitrogen share three pairs of electrons in forming cyanide ($\text{C}\equiv\text{N}^-$), making this bond very stable and accounting for the large number of xenobiotics capable of liberating cyanide. Complex ions are covalently bonded groups of elements that behave as a single element. For example, hydroxide (OH^-) and sulfate (SO_4^{2-}) form sodium salts as if they were simply the ion of a single element (such as chloride).

Noncovalent bonds, such as hydrogen or ionic bonds, are important in the interaction between ligands and receptors as well as between ion channels and enzymes. These are low-energy bonds and easily broken. Van der Waals forces, also known as London dispersion forces, are intermolecular forces that arise from induced dipoles as a consequence of nonuniform distribution of the molecular electron cloud. These forces become stronger as the atom (or molecule) becomes larger because of the increased polarizability of the larger, more dispersed electron clouds. This accounts for the fact that under standard temperature and pressure, fluorine and chlorine are gases, whereas bromine is a liquid, and iodine is a

solid.

Reduction-Oxidation

Reduction-oxidation (redox) reactions involve the movement of electrons from one atom or molecule to another, and actually comprise two dependent reactions: reduction and oxidation. Reduction is the gain of electrons by an atom that is thereby reduced. The electrons derive from a reducing agent, which in the process becomes oxidized. Oxidation is the loss of electrons from an atom, which is, accordingly, oxidized. An oxidizing agent accepts electrons and, in the process, is reduced. By definition, these chemical reactions involve a change in the valence of an atom. It is also important to note that acid–base and electrolyte chemical reactions involve electrical charge interactions but no change in valence of any of the involved components. The implications of redox chemistry for toxicology are significant. For example, the oxidation of ferrous (Fe^{2+}) to ferric (Fe^{3+}) iron within the hemoglobin molecule creates the dysfunctional methemoglobin molecule (Chap. 127).

Also, elemental lead and mercury are both intrinsically harmless metals but when oxidized to their cationic forms, both produce devastating clinical effects. Additionally, the metabolism of ethanol to acetaldehyde involves a change in the oxidation state of the molecule. In this case, an enzyme, alcohol dehydrogenase, acting as a catalyst oxidizes (ie, removes electrons from) the C-O bond and delivers the electrons to oxidized nicotinamide adenine dinucleotide (NAD^+), reducing it to NADH. As in this last example, oxidation is occasionally used to signify the gain of oxygen by a substance. That is, when elemental iron (Fe^0) undergoes rusting to iron oxide (Fe_2O_3), it is said to oxidize. The use of this term is consistent because in the process of oxidation, oxygen derives electrons from the atom with which it is reacting and combining.

Reactive Oxygen Species. Free radicals are reactive molecules that contain one or more unpaired electrons and are typically neutral but may be anionic or cationic. However, because certain toxicologically important reactive molecules, such as hydrogen peroxide (H_2O_2) and ozone (O_3), do not contain unpaired electrons, the term reactive species is preferred. The reactivity of these molecules directly relates to their attempts to fill their outermost orbitals by receiving an electron; the result is oxidative stress on the biologic system. Molecular oxygen is actually a diradical with two unpaired electrons in the outer orbitals. However, its reactivity is less than that of the other radicals because the unpaired electrons have parallel spins, so catalysts (ie, enzymes or metals) are typically involved in the use of oxygen in biologic processes.

Reactive species are continuously generated as a consequence of endogenous metabolism, and there is an efficient detoxification system for their control. However, under conditions of either excessive endogenous generation or exposure to exogenous reactive species, the physiologic defenses against these toxic products are overwhelmed. When this occurs, reactive species induce direct cellular damage as well as initiate a cascade of oxidative reactions that perpetuate the toxic damage.

Intracellular organelles, particularly the mitochondria, may also be disrupted by various reactive species. This causes further injury to the cell as energy failure occurs. This initial damage is exacerbated by the activation of the host inflammatory response by chemokines that are released from cells in response to reactive species-induced damage. This inflammatory response aggravates cellular damage. The resultant membrane dysfunction or damage causes cellular apoptosis or necrosis.

The most important reactive oxygen species in medical toxicology are derived from oxygen, although those derived from nitrogen are also important. Table 12–1 lists some of the important reactive oxygen and nitrogen species.

TABLE 12–1. Structure of Important Reactive Species

Structure	
Reactive Oxygen Species	
<i>Free radicals</i>	
Hydroxyl radical	OH•
Alcoxyl radical	RO•
Peroxyl radical	ROO•
Superoxide radical	O ₂ • ⁻
<i>Nonradicals</i>	
Hydrogen peroxide	H ₂ O ₂
Hypochlorous acid	HOCl
Singlet oxygen	[O] or ¹ O ₂
Ozone	O ₃
Reactive Nitrogen Species	
<i>Free radicals</i>	
Nitric oxide	NO•
Nitrogen dioxide	NO ₂ •
<i>Nonradicals</i>	
Peroxynitrite anion	ONOO ⁻
Nitronium cation	NO ₂ ⁺

The biradical nature of oxygen explains both the physiologic and toxicologic importance of oxygen in biologic systems. Physiologically, the majority of oxygen is used by the body to serve as the ultimate electron acceptor in the mitochondrial electron transport chain. In this situation, four electrons are added to each molecule of oxygen to form two water molecules ($O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$).

Superoxide ($O_2^{\cdot-}$) is “mutated” from oxygen within neutrophil and macrophage lysosomes as part of the oxidative burst, which serves to help eliminate infectious agents and damaged cells. Superoxide may subsequently be enzymatically converted, or “dismutated,” into hydrogen peroxide by superoxide dismutase (SOD). Hydrogen peroxide may be subsequently converted into hypochlorous acid by the enzymatic addition of chloride by myeloperoxidase. Both hydrogen peroxide and hypochlorite ion are more potent reactive oxygen species than superoxide. However, this lysosomal protective system may also be responsible for tissue damage following poisoning as the innate inflammatory response attacks xenobiotic-damaged cells. Examples include acetaminophen (APAP)-induced hepatotoxicity ([Chap. 35](#)), carbon monoxide neurotoxicity ([Chap. 125](#)), and chlorine-induced pulmonary toxicity ([Chap. 124](#)), each of which may be altered, at least in experimental systems, by the addition of scavengers of reactive species.

Although superoxide and hydrogen peroxide are reactive species, it is their conversion into the hydroxyl radical (OH•) that accounts for their most consequential effects. The hydroxyl radical is generated by the Fenton reaction ([Fig. 12–2](#)), in which hydrogen peroxide is decomposed in the presence of a transition metal. This catalysis typically involves Fe^{2+} , Cu^+ , Cd^{2+} , Cr^{5+} , Ni^{2+} , or Mn^{2+} . The Haber-Weiss reaction ([Fig. 12–2](#)), in which a transition metal catalyzes the combination of superoxide and hydrogen peroxide, is the other important means of generating the hydroxyl radical. Alternatively, superoxide dismutase, within the erythrocyte, contains an ion of copper (Cu^{2+}) that participates in the catalytic reduction of superoxide to hydrogen peroxide and the subsequent detoxification of hydrogen peroxide by glutathione peroxidase or catalase.

Transition metal cations may bind to the cellular nucleus and locally generate reactive oxygen species, most importantly hydroxyl radicals. This results in DNA strand breaks and modification, accounting for the mutagenic effects of many transition metals. In addition to the important role that transition metal chemistry plays following iron or copper salt poisoning, the long-term consequences of chronic transition metal poisoning are exemplified by asbestos. The iron contained in asbestos is the origin of the Fenton-generated hydroxyl radicals that are responsible for the pulmonary fibrosis and cancers associated with long-term exposure.

The most important toxicologic effects of reactive oxygen species occur on the cell membrane, and are caused by the initiation by hydroxyl radicals of the lipid peroxidative cascade. The alteration of these lipid membranes ultimately causes membrane destruction. Identification of released oxidative products such as malondialdehyde is a common method of assessing lipid peroxidation.

Under normal conditions, there is a delicate balance between the formation and immediate detoxification of reactive oxygen species. For example, the conversion of the superoxide radical to hydrogen peroxide via SOD is rapidly followed

by the transformation of hydrogen peroxide to water by glutathione peroxidase or catalase. Furthermore, the fact that transition metals exist in “free” form in only minute quantities in biologic systems minimizes the formation of hydroxyl radicals; that is, cells have developed extensive systems by which transition metal ions can be sequestered and rendered harmless. Ferritin (binds iron), ceruloplasmin (binds copper), and metallothionein (binds cadmium) are all specialized proteins that safely sequester transition metal ions. Certain proteins and enzymes such as hemoglobin or SOD have critical biological functions associated with the transition metals at their active sites.

Detoxification of certain reactive species is difficult because of their extreme reactivity. Widespread antioxidant systems typically act to trap reactive species before tissue damage occurs. An example is the availability of glutathione, a reducing agent and nucleophile, which prevents both exogenous oxidants from producing hemolysis and the APAP metabolite N-acetyl-p-benzoquinoneimine (NAPQI) from damaging the hepatocyte ([Chap. 35](#)).

The key reactive nitrogen species is nitric oxide. At typical physiologic concentrations, this radical is responsible for vascular endothelial relaxation through stimulation of guanylate cyclase. However, during oxidative burst, high concentrations of nitric oxide are formed from L-arginine. At these concentrations, nitric oxide is directly damaging to tissue and also reacts with the superoxide radical to generate the peroxynitrite anion. This is particularly important because peroxynitrite may spontaneously degrade to form the hydroxyl radical. Peroxynitrite ion is implicated in both the delayed neurologic effects of carbon monoxide poisoning and the hepatic injury from APAP.

Redox cycling. Although transition metals are an important source of reactive species, certain xenobiotics are also capable of independently generating reactive species. Most do so through a process called redox cycling, in which a molecule accepts an electron from a reducing agent and subsequently transfers that electron to oxygen, generating the superoxide radical. At the same time, this second reaction regenerates the parent molecule, which itself can gain another electron and restart the process. The toxicity of paraquat ([Chap. 112](#)) is selectively localized to pulmonary endothelial cells. Its pulmonary toxicity results from redox cycling generation of reactive oxygen species ([Fig. 112–3](#)). A similar process, localized to the heart, occurs with anthracycline antineoplastics such as doxorubicin.

Acid–Base Chemistry

Water is amphoteric, which means that it can function as either an acid or a base, much the same way as the bicarbonate ion (HCO_3^-). In fact, because of the amphoteric nature of water, H^+ , despite the nomenclature, does not ever actually exist in aqueous solution; rather, it is covalently bound to a molecule of water to form the hydronium ion (H_3O^+). However, the term H^+ , or proton, is used for convenience.

Even in a neutral solution, a tiny proportion of water is always undergoing ionization to form both H^+ and OH^- in exactly equal amounts. By convention, however, it is the quantity of H^+ that is measured to determine the acidity or alkalinity of the solution. The units for this measurement are pH, which is $-\log[\text{H}^+]$. In a perfect system at equilibrium, the concentration of H^+ ions in water is precisely 0.0000001, or 10^{-7} , moles/L and that of OH^- is the same. The number of H^+ ions increases when an acid is added to the solution and falls when an alkali is added. The negative log of 10^{-7} is 7, and the pH of a neutral aqueous solution is thus 7. In actuality, the pH of water is approximately 6 because of dissolution of ambient carbon dioxide to form carbonic acid ($\text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{H}_2\text{CO}_3$), which ionizes to form H^+ and bicarbonate (HCO_3^-).

There are many definitions of acid and base. The three commonly used definitions are those advanced by (1) Svante Arrhenius, (2) Brønsted and Lowry, and (3) Lewis. Because the focus is on physiologic systems, which are aqueous, the original definition by the Swedish chemist Arrhenius is the most practical. In this view, an acid releases hydrogen ions, or protons (H^+), in water. Similarly, a base produces hydroxyl ions (OH^-) in water. Thus, hydrogen chloride (HCl), a neutral gas under standard conditions, dissolves in water to liberate H^+ and is therefore an acid.

For nonaqueous solutions, the Brønsted-Lowry definition is preferable. An acid, in this schema, is a substance that donates a proton and a base is one that accepts a proton. Thus, any molecule that has a hydrogen in the 1+ oxidation state is technically an acid, and any molecule with an unbound pair of valence electrons is a base. Because most of the acids or bases of toxicologic interest have ionizable protons or available electrons, respectively, the Brønsted-Lowry definition is most often considered when discussing acid–base chemistry (ie, $\text{HA} + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ + \text{A}^-$; $\text{B}^- + \text{H}_2\text{O} \rightarrow \text{HB} + \text{OH}^-$). However, this is not a defining property of all acids or bases.

The Lewis classification offers the least-restrictive definition of such substances. A Lewis acid is an electron acceptor and a Lewis base is an electron donor.

Simplistically, acids are sour and turn litmus paper red; bases feel slippery (due to the dissolution of skin), are bitter, and turn litmus paper blue. Of course, the tasting and tactile assessment of substances to determine their acid-base status is not recommended.

Because acidity and alkalinity are determined by the number of available H^+ ions, it is useful to classify chemicals by their effect on the H^+ concentration. Strong acids ionize almost completely in aqueous solution and very little of the parent compound remains. Thus, 0.001 (or 10^{-3}) mole of HCl, a strong acid, added to 1 L of water produces a solution with a pH

of 3. Weak acids, on the other hand, reach an equilibrium between parent and ionized forms, and thus do not alter the pH to the same degree as a similar quantity of a strong acid. This chemical notation defines the strength or weakness of an acid and should not be confused with the concentration of the acid. Thus, the pH of a dilute strong acid solution may be substantially less than that of a concentrated weak acid (Table 12–2).

TABLE 12–2. pH of 0.10 M Solutions of Common Acids and Bases Represents the Strength of the Acid or Base

<i>Acid/Base</i>	<i>pH</i>
HCl (hydrochloric acid)	1.1
H ₂ SO ₄ (sulfuric acid)	1.2
H ₂ SO ₃ (sulfurous acid)	1.5
H ₃ PO ₄ (phosphoric acid)	1.5
HF (hydrofluoric acid)	2.1
CH ₃ CO ₂ H (acetic acid)	2.9
H ₂ CO ₃ (carbonic acid)	3.8
H ₂ S (hydrogen sulfide)	4.1
NH ₄ Cl (ammonium chloride)	4.6
HCN (hydrocyanic acid)	5.1
NaHCO ₃ (sodium bicarbonate)	8.3
NaCH ₃ CO ₂ (sodium acetate)	8.9
Na ₂ HPO ₄ (sodium hydrogen phosphate)	9.3
Na ₂ SO ₃ (sodium sulfite)	9.8
NaCN (sodium cyanide)	11.0
NH ₄ OH (ammonium hydroxide)	11.1
Na ₂ CO ₃ (sodium carbonate)	11.6
Na ₃ PO ₄ (sodium phosphate)	12.0
NaOH (sodium hydroxide)	13.0

The degree of ionization of an acid is determined by the pK_a , or the negative log of the ionization constant, which represents the pH at which an acid is half dissociated in solution. The same relationship applies to the pK_b of an alkali, although pK_b is rarely used and the degree of ionization of bases is also expressed as pK_a (of note, $pK_a = 14 - pK_b$). The lower the pK_a , the stronger the acid; the higher the pK_a , the stronger the base. The pK of a strong acid is clinically irrelevant because it is nearly fully ionized under all but the most extremely acidic conditions. Importantly, knowledge of the pK_a does not itself denote the strength of an acid or an alkali. To some extent, this quality may be predicted by its chemical structure or reactivity, or it may be obtained through direct measurement or from a reference source.

Because only uncharged compounds cross lipid membranes spontaneously, the pK_a has strong clinical relevance. Salicylic acid, a weak acid with a pK_a of 3, is nonionized in the stomach (pH = 2) and passive absorption occurs (Fig. 9–3). Because it is predominantly in the ionized form (ie, salicylate) in blood, which has a pH of 7.4, little of the ionized blood-borne salicylate passively enters the tissues. However, because in overdose the serum salicylate rises considerably, enough enters the tissue to result in clinical toxicity. Salicylate is the conjugate base of a weak acid (and thus itself a strong base). It diffuses into the mitochondrial intermembrane space (between the inner and outer mitochondrial membrane), where abundant protons exist that have been transported there via the electron transport chain of this organelle (Fig. 13–3). Because salicylate is a strong base, it protonates easily in this environment. In this nonionized form, some of the salicylic acid may pass through the inner mitochondrial membrane, into the mitochondrial matrix, and again establish equilibrium by losing a proton. This is the uncoupling of oxidative phosphorylation, dispersing highly concentrated protons in the intermembrane space that are normally used to generate adenosine triphosphate (Chap. 13). Uncoupling produces a

metabolic acidosis, and this shifts the blood equilibrium of salicylate toward the nonionized, protonated form, enabling salicylic acid to cross the blood–brain barrier. Presumably, once in the brain, the salicylate uncouples the metabolic activity of neurons with the subsequent development of cerebral edema. This is the rationale for serum alkalization in patients with aspirin overdose (Chap. 39).

In a similar manner, alkalization of the patient’s urine prevents reabsorption by ionization of the urinary salicylate. Salicylate anion excreted into acidic urine may protonate, and the uncharged moiety may then back-diffuse across the renal tubular epithelium and re-enter the body. Alkalization of the urine “traps” salicylate in the deprotonated form, enhancing excretion. Conversely, because cyclic antidepressants are organic bases, alkalization of the urine reduces their ionization and actually decreases the urinary elimination of the drug. However, in the management of cyclic antidepressant poisoning, because the other beneficial effects of sodium bicarbonate on the sodium channel outweigh the negative effect on drug elimination, serum alkalization is recommended (Chap. 71).

ORGANIC CHEMISTRY

The study of carbon-based chemistry and the interaction of inorganic molecules with carbon-containing compounds is called organic chemistry, because the chemistry of living organisms is carbon based. Biochemistry (Chap. 13) is a subdivision of organic chemistry; it is the study of organic chemistry within biologic systems. This section reviews many of the salient points of organic chemistry, focusing on those with the most applicability to medicine and the study of toxicology: nomenclature, bonding, nucleophiles and electrophiles, stereochemistry, and functional groups.

Chemical Properties of Carbon

Carbon, atomic number 6, has a molecular weight of 12.011 g/mol. With few exceptions (notably cyanide ion and carbon monoxide), carbon forms four bonds in stable organic molecules. In organic compounds, carbon is commonly bonded to other carbon atoms, as well as to hydrogen, oxygen, nitrogen, or halides. Under certain circumstances, carbon can be bonded to metals, as is the case with methylmercury.

Nomenclature

The most systematic method to name organic compounds is in accordance with standards adopted by the International Union of Pure and Applied Chemistry (IUPAC); these names are infrequently used, especially for larger molecules, and alternative names are common. The complete details of the IUPAC naming system are beyond the scope of this text and can be reviewed elsewhere (www.iupac.org), but a brief description of the fundamentals of this system is included here.

The carbon backbone of a molecule serves as the basis of its chemical name. Once the carbon backbone has been identified and named, substituents (atoms or groups of atoms that substitute for hydrogen atoms) are identified, named, and numbered. The number refers to the carbon to which the substituent is attached. Some of the common substituents in organic chemistry are –OH (hydroxy), –NH₂ (amino), –Br (bromo), –Cl (chloro), and –F (fluoro). Substituents are then alphabetized and placed as prefixes to the carbon chain.

As an example, consider the molecule 2-bromo-2-chloro-1,1,1-trifluoroethane. The molecule has a two-carbon backbone (ethane), three fluoride atoms on the first carbon, a bromine atom on the second carbon, and a chlorine atom on the second carbon (Fig. 12–4A). A basic understanding of a few simple rules of nomenclature thus allows one to quickly generate the molecular structure of a familiar compound, halothane.

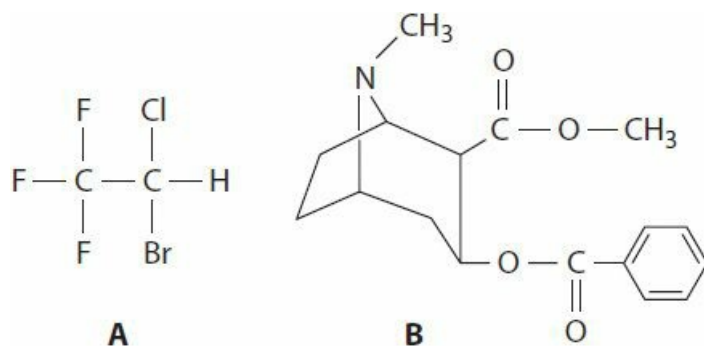


FIGURE 12–4. Nomenclature. (A) 2-Bromo-2-chloro-1,1,1-trifluoroethane, or halothane. (B) [1R-(exo,exo)]-3-(Benzoyloxy)-8-methyl-8-azabicyclo[3,2,1]-octane-2-carboxylic acid methyl ester, or cocaine.

Although the above mentioned rules suffice to name simple structures, they are inadequate to describe many others, such as molecules with complex branching or ring structures. The IUPAC rules for naming compounds such as [1R-(exo,exo)]-3-(benzoyloxy)-8-methyl-8-azabicyclo[3,2,1]octane-2-carboxylic acid methyl ester, for example, are too complex to include

here. Fortunately, many compounds with complex chemical names have simpler names for day-to-day use; as an example, this molecule is commonly referred to as cocaine (Fig. 12-4B).

Cocaine is an example of a common or trivial name; one without a systematic basis, but which is generally accepted as an alternative to frequently unwieldy proper chemical names. Common names may refer to the origin of the substance; for example, cocaine is derived from the coca leaf, and wood alcohol (methanol) can be prepared from wood. Alternatively, a common name may refer to the way in which a compound is used; rubbing alcohol is a common name for isopropanol. Common names are often imprecise and may generate some confusion, however, as evidenced by the fact that rubbing alcohol, when commercially marketed, may be either ethanol or isopropanol.

An even less precise system of nomenclature is the use of street names. A street name is a slang term for a drug of abuse, such as “blow” (cocaine), “weed” (marijuana), or “smack” (heroin). The street name ecstasy refers to the stimulant 3,4-methylenedioxymethamphetamine (MDMA), which is most frequently consumed in pill form. It would stand to reason that liquid ecstasy might refer to a solution of MDMA, but street names are not necessarily logical. Instead, liquid ecstasy refers to the drug γ -hydroxybutyrate, a sedative-hypnotic with a completely different pharmacologic and toxicologic profile. Furthermore, there are no standards for the content of ecstasy, and many street pills contain other chemicals.

A final consideration must be given to product names. Product names are trade names under which a given compound might be marketed, and are frequently different from both the chemical name and common name. Thus, the inhalational anesthetic in Fig. 12-4A with the chemical name 2-bromo-2-chloro-1,1,1-trifluoroethane has the common name halothane and the trade name Fluothane.

Bonding in Organic Chemistry

While much of the bonding in inorganic chemistry is ionic, the vast majority of bonding in organic molecules is covalent. Whereas electrons in ionic bonds are described as predominately “belonging” to one atom or another, electrons in covalent bonds are shared between two atoms; this type of bonding occurs when the difference in electronegativity between two atoms is insufficient for one atom to wrest control of an electron from another. Bonds are represented by lines between the atoms: one for a single bond, two for a double bond, and three for a triple bond.

Nucleophiles and Electrophiles

Many organic reactions of toxicologic importance can be described as the reactions of nucleophiles with electrophiles. Nucleophiles (literally, nucleus-loving) are species with increased electron density, frequently in the form of a lone pair of electrons (as in the cases of cyanide ion and carbon monoxide). Nucleophiles, by virtue of their increased electron density, have an affinity for atoms or molecules that are electron deficient; such moieties are called electrophiles (literally, electron-loving). The electron deficiency of electrophiles can be described as absolute or relative. Absolute electron deficiency occurs when an electrophile is charged, as is the case with cations such as Pb^{2+} and Hg^{2+} . Relative electron deficiency occurs when one atom or group of atoms shifts electrons away from a second atom, making the second atom relatively electron deficient. This is the case for the neurotoxin 2,5-hexanedione (Fig. 12-5); the electronegative oxygen of the carbon-oxygen double bond pulls electron density away from the second and fifth carbon atoms of this molecule, making these carbon atoms electrophilic.

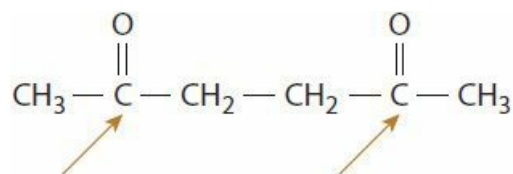


FIGURE 12-5. Chemical properties of 2,5-hexanedione. Arrows designate the electrophilic carbon atoms.

The reaction of a nucleophile with an electrophile involves the movement of electrons, by forming or breaking bonds. This movement of electrons is frequently denoted by the use of curved arrows, which better demonstrates how the nucleophile and electrophile interact. The interaction of acetylcholinesterase with acetylcholine, organic phosphorus pesticides, and pralidoxime hydrochloride provides an excellent example of the way in which nucleophiles and electrophiles interact, and of how the use of curved arrow notation can lead to better understanding of the reactions involved.

Under normal circumstances, the action of acetylcholine is terminated when the serine residue in the active site of acetylcholinesterase attacks this neurotransmitter, forming a transient serine-acetyl complex and liberating choline. This serine-acetyl complex is then rapidly hydrolyzed, producing an acetic acid molecule and regenerating the serine residue for another round of the reaction (Fig. 12-6A). In the presence of an organic phosphorus pesticide, however, this serine residue attacks the electrophilic phosphate atom, forming a stable serine-phosphate bond, which is not hydrolyzed (Fig. 12-6B). The enzyme, thus inactivated, can no longer break down acetylcholine, leading to an increase of this

neurotransmitter in the synapse and possibly a cholinergic crisis.

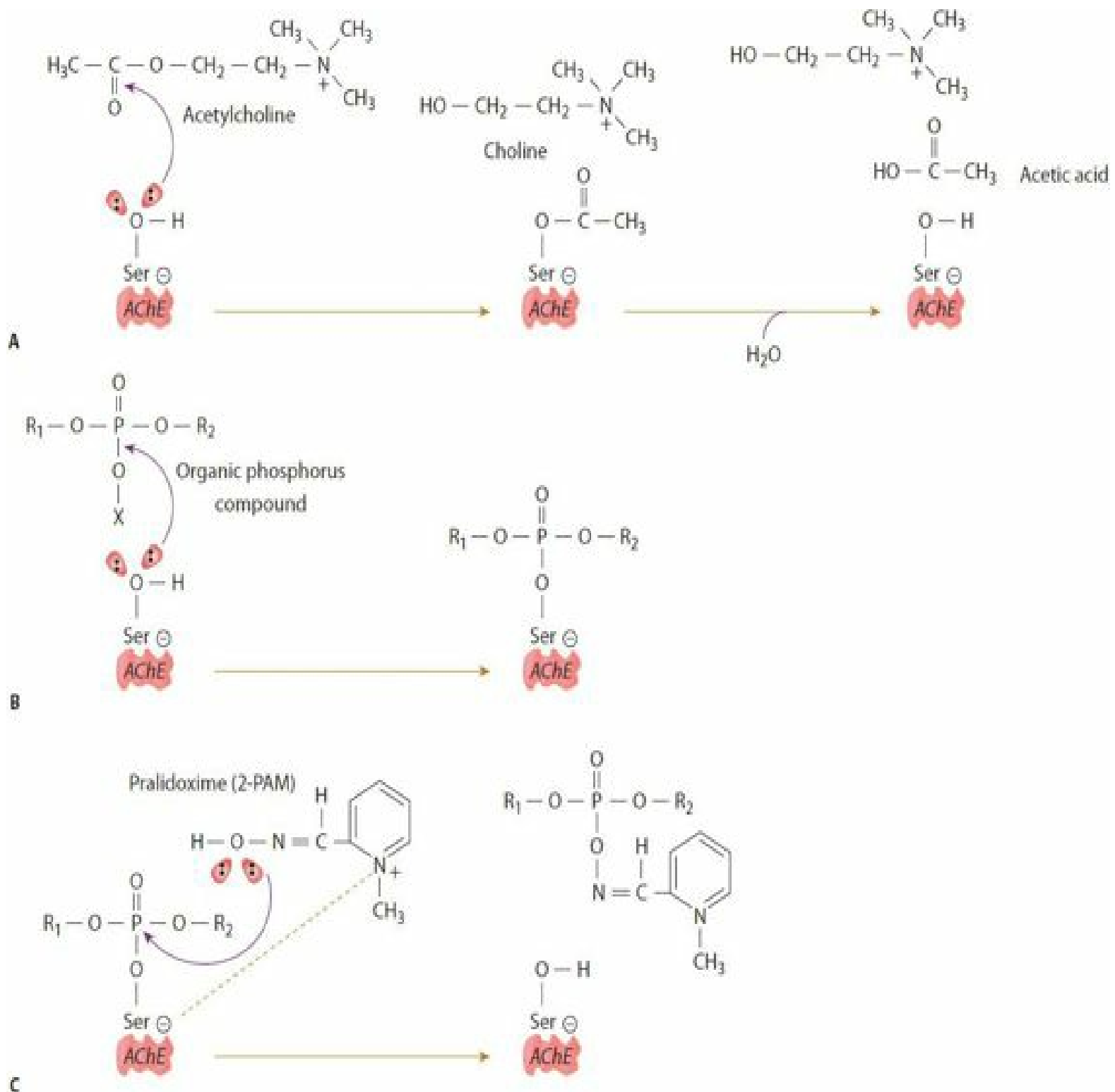


FIGURE 12-6. The reactions of acetylcholinesterase (AChE), organic phosphorus compounds, and pralidoxime hydrochloride (2-PAM). Curved arrows represent the movement of electrons as bonds are formed or broken. (A) Normal hydrolysis of acetylcholine by AChE. (B) Inactivation (phosphorylation) of AChE by organic phosphorus compound. (C) Reactivation by 2-PAM of functional AChE.

The enzyme can be reactivated, however, by the use of another nucleophile. Pralidoxime hydrochloride (2-PAM) is referred to as a site-directed nucleophile. Because part of its chemical structure (the charged nitrogen atom) is similar to the choline portion of acetylcholine, this antidote is directed to the active site of acetylcholinesterase. Once in position, the nucleophilic oxime moiety (-NOH) that is remote from the positive charge of 2-PAM attacks the electrophilic phosphate moiety. This displaces the serine residue, regenerating the enzyme (Fig. 12-6C). A further discussion of organic phosphorus compound toxicity and the use of 2-PAM can be found in Chap. 113 and Antidotes in Depth: A33, respectively.

A second toxicologically important electrophile is NAPQI (Fig. 12-7). NAPQI is formed when the endogenous detoxification pathways of APAP metabolism (glucuronidation and sulfation) are overwhelmed (Chap. 35). As a result of the electron configuration of NAPQI, the carbon atoms adjacent to the carbonyl carbon (a carbon that is double bonded to an oxygen) are very electrophilic; the sulfur groups of cysteine residues of hepatocyte proteins react with NAPQI to form a

characteristic adduct (formed when one compound is added to another), 3-(cystein-S-yl) APAP, in a multistep process. These adducts are released as hepatocytes die, and can be found in the blood of patients with APAP-related liver toxicity. **Figure 12–7** diagrams the mechanism of the protein–NAPQI reaction (**Chap. 35**).

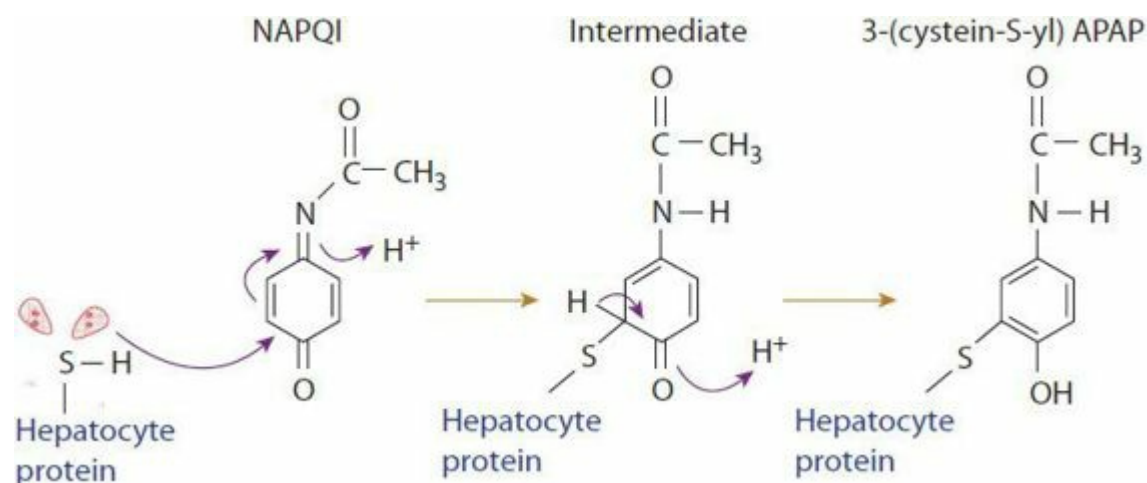


FIGURE 12–7. The reaction of cysteine residues on hepatocyte proteins with N-acetyl-p-benzoquinoneimine (NAPQI) to form the characteristic adducts 3-(cystein-S-yl) APAP.

Nucleophiles can be described by their strength, which by convention is related to the rate at which they react with the reference electrophile CH_3I . Of more use in pharmacology and toxicology, however, are the descriptive terms “hard” and “soft.” Although imprecise, the designations hard and soft help to predict, qualitatively, how nucleophiles and electrophiles interact with one another.

Hard species have a charge (or partial charge) that is highly localized; that is, their charge-to-radius ratio is high. Hard nucleophiles are molecules in which the electron density or lone pair is tightly held; fluoride, a small atom that cannot spread its electron density over a large area, is an example. Similarly, hard electrophiles are species in which the positive charge cannot be spread over a large area; ionized calcium, a small ion, is a hard electrophile.

Soft species, on the other hand, are capable of delocalizing their charge over a larger area. In this case the charge-to-mass ratio is low, either because the atom is large or because the charge can be spread over a number of atoms within a given molecule. Sulfur is the prototypical example of a soft nucleophile and the lead ion, Pb^{2+} , is a typical soft electrophile.

The utility of this classification lies in the observation that hard nucleophiles tend to react with hard electrophiles, and soft nucleophiles with soft electrophiles. For example, a principal toxicity of fluoride ion poisoning (**Chap. 107**) is hypocalcemia; this is because the fluoride ions (hard nucleophiles) readily react with calcium ions (hard electrophiles). On the other hand, the soft nucleophile lead is effectively chelated by soft electrophiles such as the sulfur atoms in the chelators dimercaprol (**Antidotes in Depth: A25**) and succimer (**Antidotes in Depth: A26**).

Isomerism

Isomerism describes the different ways in which molecules with the same chemical formula (ie, the same number and types of atoms) can be arranged to form different compounds. These different compounds are called isomers. Isomers always have the same chemical formula but differ either in the way that atoms are bonded to each other (constitutional isomers) or in the spatial arrangement of these atoms (geometric isomers or stereoisomers).

Constitutional isomers are conceptually the easiest to understand, because a quick glance shows them to be very different molecules. The chemical formula $\text{C}_2\text{H}_6\text{O}$, for example, can refer to either dimethyl ether or ethanol (**Fig. 12–8**). These molecules have very different physical and chemical characteristics, and they have little in common other than the number and type of their atomic constituents.



FIGURE 12–8. Two molecules with chemical formula $\text{C}_2\text{H}_6\text{O}$. (A) Dimethylether. (B) Ethanol (ethyl alcohol).

Stereoisomerism, also referred to as geometric isomerism, refers to the different ways in which atoms of a given molecule, with the same number and types of bonds, might be arranged. The most important type of stereoisomerism in pharmacology and toxicology is the stereochemistry around a stereogenic (sometimes called chiral) carbon.

Consider the two representations of halothane shown in **Fig. 12–9**. In this figure the straight solid lines and the atoms to which they are bonded exist in the plane of the paper, the solid triangle and the atom to which it is bonded are coming out of

the paper, and the dashed triangle and the atom to which it is bonded are receding into the paper. It is clear that, for the molecules in **Figs. 12–9A and B**, no amount of rotation or manipulation will make these molecules superimposable. They are, therefore, different compounds.

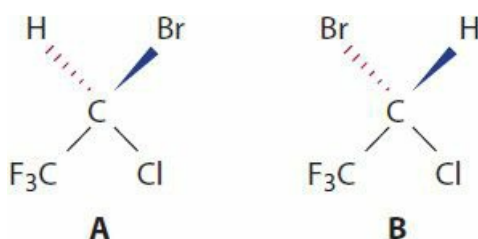


FIGURE 12–9. The graphic representation of the enantiomers of haloethane.

These molecules are enantiomers or optical isomers. They differ only in the way in which their atoms are bonded to a chiral carbon. It is important to define the stereochemical configuration of these two molecules, which can be done in one of two ways. In the first classification—the d(+)/l(–) system—molecules are named empirically based on the direction in which they rotate plane-polarized light. Each enantiomer will rotate plane-polarized light in one direction; the enantiomer that rotates light clockwise (to the right) is referred to as d(+), or dextrorotatory; the l(–), or levorotatory enantiomer rotates plane-polarized light in a counterclockwise fashion (to the left).

Alternatively, enantiomers can be named using an elaborate and formal set of rules known as Cahn-Ingold-Prelog. These rules establish priority for substituents, based primarily on molecular weight, and then use the arrangement of substituents to assign a configuration. To correctly assign configuration in this system, the molecule is rotated into a projection in which the chiral carbon is in the plane of the page, the lowest priority substituent is directly behind the chiral carbon (and therefore behind the plane of the page), and the other three substituents are arranged around the chiral carbon. **Figure 12–10** assigns Cahn-Ingold-Prelog priority to the haloethane enantiomers of **Fig. 12–9**, and rearranges the molecules in the appropriate projections.

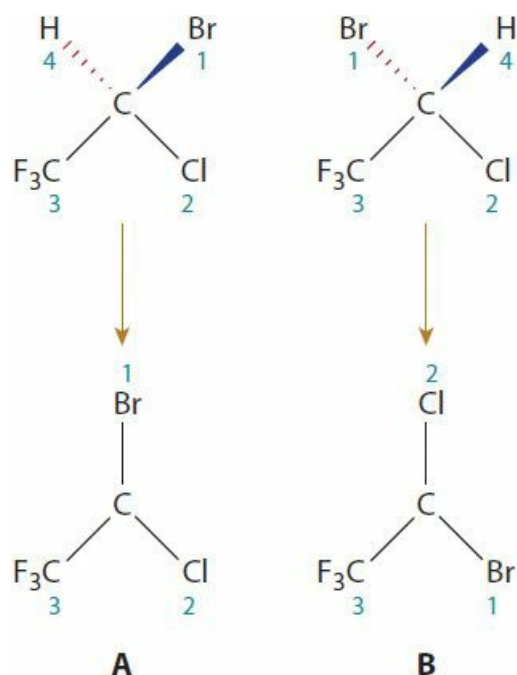


FIGURE 12–10. R and S enantiomers of haloethane. **(A)** The substituents increase in a clockwise fashion, so the configuration is R. **(B)** The substituents increase in a counterclockwise fashion, so the configuration is S. In this projection, hydrogen atoms are directly behind the carbon atoms.

If the priority of the substituents increases as one moves clockwise (to the right), the enantiomer is R (Latin, rectus = right); if it increases as one moves counterclockwise, the enantiomer is S (Latin, sinister = left). Thus, **Fig. 12–10A** is the R enantiomer of haloethane and **Fig. 12–10B** is the S enantiomer.

Enantiomers have identical physical properties, such as boiling point, melting point, and solubility in different solvents; they differ from each other in only two significant ways. The first, as mentioned before, is that enantiomers rotate plane-polarized light in opposite directions; this point has no practical toxicologic importance. The second is that enantiomers may interact in very different ways with other chiral structures (such as proteins and other cell receptors), which is of both pharmacologic and toxicologic significance.

The best analogy to explain the toxicologic and pharmacologic importance of stereochemistry is that of the way a hand

(analogous to a molecule of xenobiotic) fits into a glove (analogous to the biologic site of activity). Consider the left hand as the S enantiomer and the right hand as the R enantiomer. There are, qualitatively, three different ways in which the hand can fit into (interact with) a glove.

First, if the glove is pliable and relatively fluid (such as a disposable latex glove), it can accept either the left hand or the right hand without difficulty; this is the case for halothane, whose R and S enantiomers interact with cell membranes rather than specific receptors and possess equal activity. Second, if a glove is constructed with greater (but imperfect) specificity, one hand will fit well and the other poorly; this is the case for many substances, such as epinephrine and norepinephrine, whose naturally occurring levorotatory enantiomers are 10-fold more potent than the synthetic dextrorotatory enantiomers. Finally, a glove can be made with exquisite precision, such that one hand fits perfectly, while the other hand does not fit at all. This is the case for physostigmine, in which the (-) enantiomer is biologically active, whereas the (+) enantiomer is inactive.

Even the above analogy is oversimplified, however, because one enantiomer of a drug can be an agonist, while the other enantiomer is an antagonist. Dobutamine, for example, has one stereogenic carbon and thus two stereoisomers. At the α_1 receptor, l-dobutamine is a potent agonist and d-dobutamine is a potent antagonist. Because dobutamine is marketed as a racemic mixture (a racemic mixture is a 1:1 mixture of enantiomers), however, these effects cancel each other out. Interestingly, at the β_1 receptor, d- and l-dobutamine have unequal agonist effects, with d-dobutamine approximately 10 times more potent than l-dobutamine.

Functional Groups

There is perhaps no concept in organic chemistry as powerful as that of the functional group. Functional groups are atoms or groups of atoms that confer similar reactivity on a molecule; of less importance is the molecule to which it is attached. Alcohols, carboxylic acids, and thiols are functional groups; hydrocarbons are generally not considered functional groups per se, but rather are the structural backbone to which functional groups are attached. The functional groups discussed below are included to illustrate important principles, not because they represent an exhaustive list of important functional groups in toxicology.

Hydrocarbons, as their name implies, consist of only carbon and hydrogen. Alkanes are hydrocarbons that contain no multiple bonds; they may be straight chain, usually designated by the prefix n- butane [by the prefix n- as in n-butane (Fig. 12-11A) or iso- if branched, as in isobutane] (Fig. 12-11B). Alkenes contain carbon-carbon double bonds. Alkynes, which contain carbon-carbon triple bonds, are of limited toxicologic importance. Butane (lighter fluid) is an alkane, and gasoline is a mixture of alkanes.

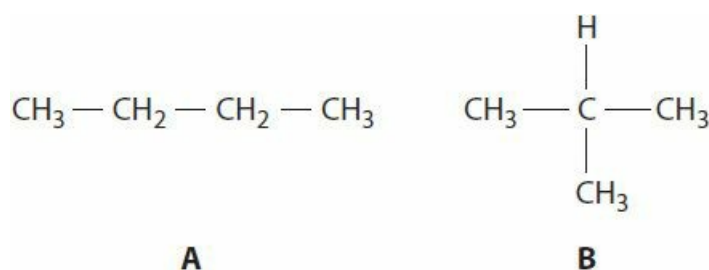


FIGURE 12-11. Two isomers of the four-carbon alkane, butane. (A) n-Butane. (B) Isobutane.

Hydrocarbons are of toxicologic importance for two reasons: they are widely abused as inhalational drugs for their central nervous system (CNS) depressant effects, and they can cause profound toxicity when aspirated. Although these effects are physiologically disparate, they are readily understood in the context of the chemical characteristics of the hydrocarbon functional group.

Hydrocarbons do not contain polar groups (ie, or groups that introduce full or partial charges into the molecule). As such, they interact readily with other nonpolar substances, such as lipids or lipophilic substances. Hydrocarbons readily interact with the myelin of the CNS, disrupting normal ion channel function and causing CNS depression. When aspirated, hydrocarbons interact with the fatty acid tail of surfactant, dissolving this protective substance and contributing to acute respiratory distress syndrome (Chap. 108).

Alcohols possess the hydroxyl (-OH) functional group, which adds polarity to the molecule and makes alcohols highly soluble in other polar substances, such as water. For example, ethane gas (CH₃CH₃) has negligible solubility in water, whereas ethanol (CH₃CH₂OH) is miscible, or infinitely soluble, in water. In biologic systems, alcohols are generally CNS depressants, but they can also act as nucleophiles. Ethanol may react with cocaine to form cocaethylene, a longer-acting and more vasoactive substance than cocaine itself (Fig. 12-12; Chap. 78).

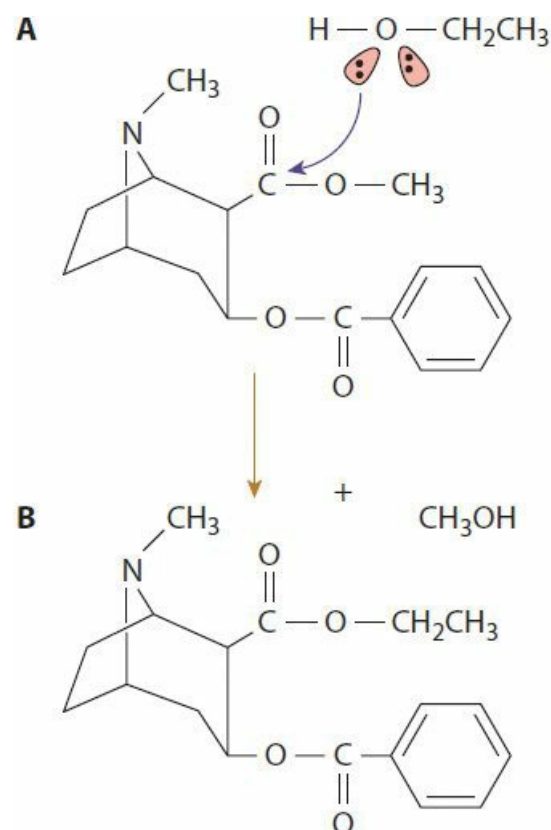


FIGURE 12–12. Transesterification reaction of cocaine with ethanol (A) to form cocaethylene and methanol (B).

Alcohols can be primary, secondary, or tertiary, in which the reference carbon is bonded to one, two, or three carbons in addition to the hydroxyl group. Methanol, in which the reference carbon is bonded to no other carbons, is not a primary alcohol per se but shares many of the reactivity patterns of primary alcohols. The difference between primary, secondary, and tertiary structures is important, because although the alcohol functional group imparts many qualities to the molecule, the degree of substitution can affect the chemical reactivity. Primary alcohols can undergo multistep oxidation to form carboxylic acids, whereas secondary alcohols generally undergo one-step metabolism to form ketones, and tertiary alcohols do not readily undergo oxidation. This is a point of significant toxicologic importance, and is discussed in more detail later.

Alcohols can be named in many ways; the most common is to add *-ol* or *-yl alcohol* to the appropriate prefix. If the alcohol group is bonded to an interior carbon, the number to which the carbon is bonded precedes the suffix.

Carboxylic acids contain the functional group *-COOH*. As their name implies, they are (weakly) acidic, and the pK_a of carboxylic acids is generally 4 or 5, depending on the substitution of the molecule. Small-molecular-weight carboxylic acids are capable of producing an elevated anion gap metabolic acidosis, which is true whether the acids are endogenous or exogenous. Examples of endogenous acids are β -hydroxybutyric acid and lactic acid; examples of exogenous acids are formic acid (produced by the metabolism of methanol) and glycolic, glyoxylic, and oxalic acids (produced by the metabolism of ethylene glycol). Carboxylic acids are named by adding *-oic acid* to the appropriate prefix; the four-carbon straight-chain carboxylic acid is thus butanoic acid.

Thiols contain a sulfur atom, which usually functions as a nucleophile. The sulfur atom of N-acetylcysteine can regenerate glutathione reductase and can also react directly with NAPQI to detoxify this electrophile. The sulfur atoms of many chelators, such as dimercaprol and succimer, are nucleophiles that are very effective at chelating electrophiles such as heavy metals. Thiols are generally named by adding the word *thiol* to the appropriate base. Thus, a two-carbon thiol is ethane thiol.

As noted above, molecules with a given functional group often have more in common with molecules with the same functional group than they have in common with the molecules from which they were derived. The alkanes methane, ethane, and propane are straight-chain hydrocarbons with similar properties. All are gases at room temperature, have almost no solubility in water, and have similar melting and boiling points. When these molecules are substituted with one or more hydroxide functional groups, they become alcohols: examples are methanol, ethanol, ethylene glycol (a glycol is a molecule that contains two alcohol functional groups), the primary alcohol 1-propanol, and the secondary alcohol 2-propanol (isopropanol). Each of these alcohols is a liquid at room temperature, and all are very water soluble. All have boiling points that are markedly different from the alkane from which they were derived, and quite close to each other.

In addition to conferring different physical properties on the molecule, the addition of the alcohol functional group also confers different chemical properties and reactivities. For example, methane, ethane, and propane are virtually incapable of undergoing oxidation in biologic systems. The alcohols formed by the addition of one or more hydroxyl groups, however, are readily oxidized by alcohol dehydrogenase (Fig. 12–13).

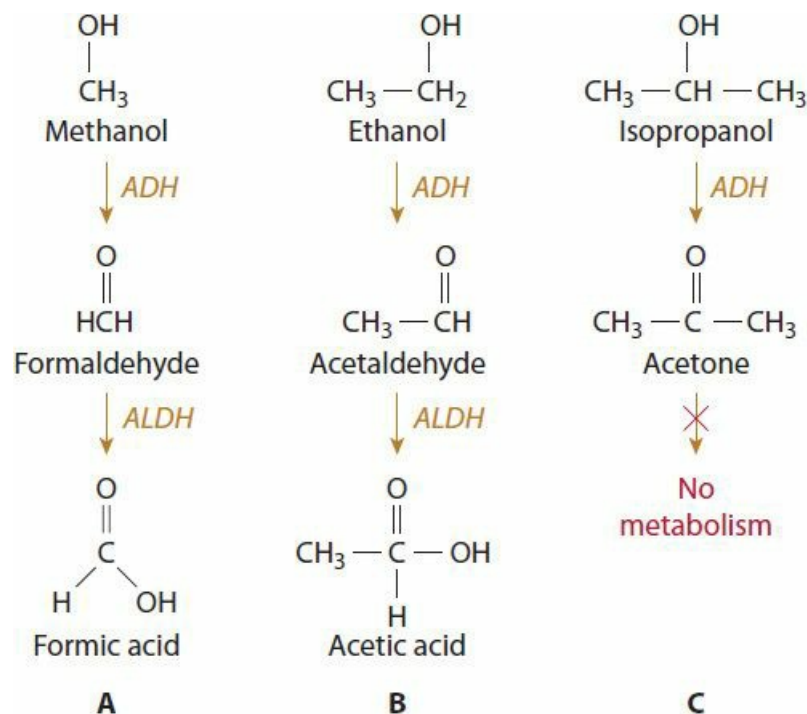


FIGURE 12–13. Oxidative metabolism of (A) methanol, (B) ethanol, and (C) isopropanol. Note that acetone does not undergo further oxidation in vivo. ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase.

As Fig. 12–13 indicates, the oxidation of the primary alcohols methanol and ethanol results in the formation of aldehydes (functional groups in which a carbon atom contains a double bond to oxygen and a single bond to hydrogen), whereas the oxidation of the secondary alcohol isopropanol results in the formation of a ketone (a functional group in which a carbon is double-bonded to an oxygen atom and single-bonded to two separate carbon atoms). Although both aldehydes and ketones contain the carbonyl group (a carbon-oxygen double bond), aldehydes and ketones are distinctly different functional groups, and they have different reactivity patterns. For instance, aldehydes can undergo enzymatic oxidation to carboxylic acids (Figs. 12–13A and B), whereas ketones cannot (Fig. 12–13C).

It is here that recognition of functional groups helps to understand the potential toxicity of an alcohol. Methanol, ethanol, and isopropanol are all alcohols; as such, their toxicity before metabolism is expected to be (and in fact is) quite similar to that of ethanol, producing CNS sedation. Because these toxins are primary and secondary alcohols, all can be metabolized to a carbonyl compound, either an aldehyde or a ketone. Here, however, the functional groups on the molecules have changed; whereas aldehydes can be metabolized to carboxylic acids (which can, in turn, cause an anion gap acidosis), ketones cannot. It is for this reason that methanol and ethylene glycol can cause an anion gap acidosis, and isopropanol cannot (Chap. 109).

The concept of functional groups, however useful, has limitations. For example, although both formic acid and oxalic acid are organic acids, they cause different patterns of organ system toxicity. Formic acid is a mitochondrial toxin and exerts effects primarily in areas (such as the retina or basal ganglia) that poorly tolerate an interruption in the energy supplied by oxidative phosphorylation. Conversely, oxalic acid readily precipitates calcium and is toxic to renal tubular cells, which accounts for the hypocalcemia and nephrotoxicity that are characteristic of severe ethylene glycol poisoning. The concept of the functional group is thus an aid to understanding chemical reactivity, but not a substitute for a working knowledge of the toxicokinetic or toxicodynamic effects of xenobiotics in living systems.

SUMMARY

- Understanding key principles of inorganic and organic chemistry provides insight into the mechanisms by which xenobiotics act.
- The periodic table forms the basis for inorganic chemistry and provides insight into the expected reactivity and to a large extent the clinical effects, of any element.
- A growing understanding of how reactive species are formed and how they interfere with physiologic processes has led to new insights in the pathogenesis and treatment of toxin-mediated diseases.
- Organic chemistry forms the basis of life, and is essential to an understanding of biochemistry and pharmacology.

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13 BIOCHEMICAL AND METABOLIC PRINCIPLES

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Xenobiotics are compounds that are foreign to a living system. Toxic xenobiotics interfere with critical metabolic processes, causing structural damage to cells or altering their cellular genetic material. The specific biochemical sites of actions that disrupt metabolic processes are well characterized for many xenobiotics although mechanisms of cellular injury are not. This chapter reviews the biochemical principles that are relevant to an understanding of the damaging effects of toxic xenobiotics and the biotransformation enzymes and their clinical implications.

XENOBIOTIC CHARACTERISTICS AND TOXICITY

The capacity of a xenobiotic to produce injury is affected by many factors, including its absorption, distribution, elimination, site of activation or detoxification, and site of action. This section focuses on how the route of exposure and the ability to cross membranes in order to access particular organs affect toxicity.

The route of exposure to a xenobiotic may confine damage primarily to one organ, for example, pulmonary injury that follows inhalation of an irritant gas or gastrointestinal (GI) injury that follows ingestion of a caustic. Hepatocellular injury results when a toxic xenobiotic is delivered to the liver, either by the portal venous system following ingestion or by the hepatic artery carrying blood containing xenobiotics absorbed from other sites of exposure.

Various factors affect the ability of a xenobiotic to access a particular organ. For example, many potentially toxic xenobiotics fail to produce central nervous system (CNS) injury because they cannot cross the blood–brain barrier. The negligible CNS effects of the mercuric salts when compared with organic mercury compounds are related to their relative inability to penetrate the CNS. Two potent biologic xenobiotics—ricin (from *Ricinus communis*) and α -amanitin (from *Amanita phalloides*)—block protein synthesis through the inhibition of RNA polymerase. However, they result in different clinical effects because they access different tissues. Ricin has a special binding protein that enables it to gain access to the endoplasmic reticulum in GI mucosal cells, where it inhibits cellular protein synthesis and causes severe diarrhea. α -Amanitin is transported into hepatocytes by bile salt transport systems, where inhibition of protein synthesis results in cell death. The electrical charge on a xenobiotic also affects its ability to enter a cell. Unlike the ionized (charged) form of a xenobiotic, the uncharged form is often lipophilic and passes through lipid cell membranes to enter the cells. The pK_a of an acidic xenobiotic ($HA \leftrightarrow A^- + H^+$) is the pH at which 50% of the molecules are charged (A^- form) and 50% is uncharged (HA form). A xenobiotic with a low pK_a is more likely to be absorbed in an acidic environment where the uncharged form predominates.

GENERAL ENZYME CONCEPTS

The capability to detoxify and eliminate both endogenous toxins and xenobiotics is crucial to the maintenance of physiologic homeostasis. A simple example is the detoxification of cyanide, a potent cellular poison that is common in the environment and is also a product of normal metabolism. Mammals have evolved the enzyme rhodanese, which combines cyanide with thiosulfate to create the less toxic, renally excreted compound thiocyanate.⁵

Most xenobiotics have lipophilic properties that facilitate absorption across cell membranes of organs that are portals of entry into the body: the skin, GI tract, and lungs. The liver has the highest concentration of enzymes that metabolize xenobiotics. Enzymes found in the cytosol of hepatocytes that are specific for alcohols, aldehydes, esters, or amines act on many different substrates within these broad chemical classes. Enzymes that act on more lipophilic xenobiotics, including the cytochrome P450 (CYP) enzymes, are embedded in the lipid membranes of the cytosol-based endoplasmic reticulum. Microsomes are the pieces of the endoplasmic reticulum that result when cells are disrupted. When cells are mechanically disrupted and centrifuged, these membrane-bound enzymes are found in the pellet, or microsomal fraction, hence they are called microsomal enzymes. Enzymes located in the liquid matrix of cells are called cytosolic enzymes and are found in the supernatant when disrupted cells are centrifuged.¹⁸

BIOTRANSFORMATION OVERVIEW

The study of xenobiotic metabolism was established as a scientific discipline by the seminal publication of Williams in 1949.⁹³ Biotransformation is the physiochemical alteration of a xenobiotic, usually as a result of enzyme action. Most definitions also include that this action converts lipophilic substances into more polar, excretable substances.^{52,83} Most xenobiotics undergo some biotransformation, the degree of which is affected by their chemical nature. The hydrophilic nature of ionized compounds such as carboxylic acids enables the kidneys to rapidly eliminate them. Very volatile compounds, such as enflurane, are expelled promptly via the lungs. Neither of these groups of xenobiotics undergo significant enzymatic metabolism.

Biotransformation usually results in “detoxification,” a reduction in the toxicity, by the conversion to hydrophilic metabolites of the xenobiotic that can be renally eliminated.⁵² However, this is not always the case. Many parent xenobiotics are inactive and must undergo “metabolic activation,” a classic concept introduced in 1947.⁵⁴ When metabolites are more toxic than the parent xenobiotic, biotransformation has resulted in “toxification.”⁸³ Biotransformation via acetylation or methylation enhances the lipophilicity of a xenobiotic. Biotransformation is done by impressively few enzymes, reflecting broad substrate specificity. The predominant pathway for the biotransformation of an individual xenobiotic is determined by many factors, including the availability of cofactors, changes in the concentration of the enzyme caused by induction, and the presence of inhibitors. The predominant pathway is also affected by the rate of substrate metabolism, reflected by the K_m (Michaelis-Menten dissociation constant) of the biotransformation enzyme⁸³ (Chap. 9).

Biotransformation is often divided into phase I and phase II reactions, terminology first introduced in 1959.⁹⁴ Phase I reactions prepare lipophilic xenobiotics for the addition of functional groups or actually add the groups, converting them into more chemically reactive metabolites. This is usually followed by phase II synthetic reactions that conjugate the reactive products of phase I with other molecules that render them more water soluble, further detoxifying the xenobiotics and facilitating renal elimination. However, since biotransformation often does not follow this stepwise process, it has been suggested that phase I and II terminology be eliminated.³⁹ Some xenobiotics undergo only a phase I or a phase II reaction prior to elimination. Additionally, phase II reactions can precede phase I. While virtually all phase II synthesis reactions cause inactivation, a classic exception is fluoroacetate being metabolized to fluorocitrate, a potent inhibitor of the tricarboxylic acid cycle (Chap. 115).⁶⁹

Biotransformed xenobiotics cannot be eliminated until they are moved back across cell membranes, out of the cells. Membrane transporters are proteins that move agents across the membranes without altering their chemical compositions, a process called a phase III reaction because it typically occurs after biotransformation.³⁹ However, membrane transport does not always occur after phase I or II reactions. Some parent compounds are transported across membranes without any biotransformation at all.

Phase I Biotransformation Reactions

Oxidation is the predominant phase I reaction, adding reactive functional groups suitable for synthetic conjugation during phase II. These groups include hydroxyl (–OH), sulfhydryl (–SH), amino (–NH₂), aldehyde (–CHO), or carboxyl (–COOH) moieties. Noncarbon elements such as nitrogen, sulfur, and phosphorus are also oxidized in phase I reactions. Other phase I reactions include hydrolysis (the splitting of a large molecule by the addition of water that is divided among the two products), hydration (incorporation of water into a complex molecule), hydroxylation (the attachment of –OH groups to carbon atoms), reduction, dehalogenation, dehydrogenation, and dealkylation.^{52,83}

The CYP enzymes are the most numerous and important of the phase I enzymes. A common oxidation reaction catalyzed by CYP enzymes is illustrated by the hydroxylation of a xenobiotic R–H to R–OH (Fig. 13–1).²⁴ Membrane-bound flavin monooxygenase (FMO), an NADPH-dependent oxidase located in the endoplasmic reticulum, is an important oxidizer of amines and other compounds containing nitrogen, sulfur, or phosphorus.⁵²

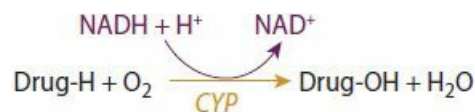


FIGURE 13–1. A common oxidation reaction catalyzed by CYP enzymes: the hydroxylation of Drug-H to Drug-OH.

The alcohol, aldehyde, and ketone oxidation systems use predominantly cytosolic enzymes that catalyze these reactions using NADH/NAD⁺ (Fig. 13–2).^{49,83} Two classic phase I oxidation reactions are the metabolism of ethanol to acetaldehyde by alcohol dehydrogenase (ADH) followed by the metabolism of acetaldehyde to acetic acid by aldehyde dehydrogenase (ALDH). Alcohol dehydrogenase, which oxidizes many different alcohols, is found in the liver, lungs, kidneys, and gastric mucosa.⁴⁹ Women have less ADH in their gastric mucosa than men. This results in decreased first-pass metabolism of alcohol and increased alcohol absorption. Some populations, particularly Asians, are deficient in ALDH, resulting in increased acetaldehyde concentrations and symptoms of the acetaldehyde syndrome⁴⁹ (Chap. 79).

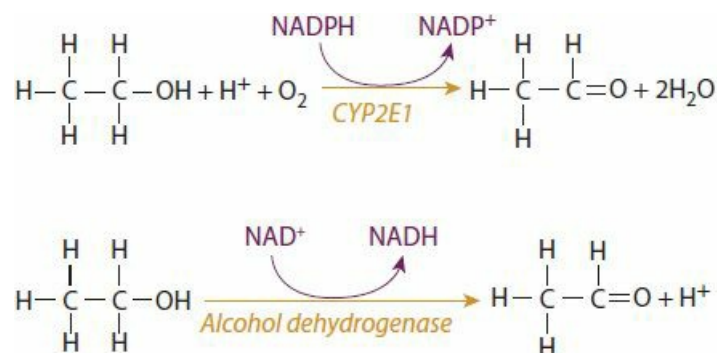


FIGURE 13–2. This is the conversion of ethanol to acetaldehyde by CYP2E1, using NADPH and oxygen, and by alcohol dehydrogenase, using NAD^+ . This illustrates how NAD and NADP can function in oxidation reactions in both their oxidized and reduced forms. Alcohol dehydrogenase has a low K_m for ethanol and is the predominant metabolic enzyme in moderate drinkers.

Oxidation Overview

Biotransformation often results in the oxidation or reduction of carbon. A substrate is oxidized when it transfers electrons to an electron-seeking (electrophilic or oxidizing) molecule, leading to reduction of the electrophilic molecule. These oxidation-reduction reactions are usually coupled to the cyclical oxidation and reduction of a cofactor, such as the pyridine nucleotides, nicotinamide adenine dinucleotide (NADH/NAD^+), or nicotinamide adenine dinucleotide phosphate ($\text{NADPH}/\text{NADP}^+$). The nucleotides alternate between their reduced (NADPH , NADH) and oxidized (NADP^+ , NAD^+) forms. Because xenobiotic oxidation is the most common phase I reaction, the newly created reduced cofactors must have a place to unload their electrons; otherwise, biotransformation ends. The electron transport chain serves as the major electron recipient.

Electrons resulting from the catabolism of energy sources are extracted primarily by NAD^+ , forming NADH . Within the mitochondria, NADH transports its electrons to the cytochrome-mediated electron transport chain. This results in the production of adenosine triphosphate (ATP), the reduction of molecular oxygen to water, and the regeneration of NAD^+ —all parts critical to the maintenance of oxidative metabolism. NADPH , created within the hexose monophosphate shunt, is used in the synthetic (anabolic) reactions of biosynthesis (especially fatty acid synthesis). NADPH is also the cofactor in the reduction of glutathione, a molecule vital to the protection of cells from oxidative damage.

The oxidation state of a specific carbon atom is determined by counting the number of hydrogen and carbon atoms to which it is connected. The more reduced a carbon, the higher the number of connections. For example, the carbon in methanol (CH_3OH) has three carbon–hydrogen bonds and is more reduced than the carbon in formaldehyde ($\text{H}_2\text{C}=\text{O}$), which has two. Carbon–carbon double bonds count as only one connection.

Cytochrome Enzymes—An Overview

Cytochromes are a class of hemoprotein enzymes whose function is electron transfer, using a cyclical transfer of electrons between oxidized (Fe^{3+}) or reduced (Fe^{2+}) forms of iron. One type of cytochrome is cytochrome P450 (CYP) whose nomenclature derives from the spectrophotometric characteristics of its associated heme molecule. When bound to carbon monoxide, the maximal absorption spectrum of the reduced CYP (Fe^{2+}) enzyme occurs at 450 nm.⁵⁹ CYP enzymes split the two oxygen atoms of an oxygen molecule, incorporating one into the substrate and one into water and thus are called mixed-function oxidases or monooxygenases. This differs from dioxygenases that incorporate both oxygen atoms into the substrate.^{59,83}

Cytochrome enzymes perform many functions. The biotransformation CYP enzymes are bound to the lipid membranes of the smooth endoplasmic reticulum. They execute 75% of all xenobiotic metabolism and most phase I oxidative biotransformations of xenobiotics.³² A second role for CYP enzymes is synthetic: biotransforming endobiotics (chemicals endogenous to the body) to cholesterol, steroids, bile acids, fatty acids, prostaglandins, and other important lipids. Cytochromes also act as electron transfer agents within the mitochondrial electron transport chain.^{33,59}

Although more than 6000 CYP genes exist in nature, the human genome project determined that the number of human CYP genes at 57.⁵⁹ CYP enzymes are categorized according to the similarities of their amino acid sequences. They are in the same “family” if they are more than 40% comparable and same “subfamily” if they are more than 55% similar. Families are designated by an Arabic numeral (n), subfamilies by a capital letter (X), and each individual enzyme by another numeral (m), resulting in the nomenclature CYPnXm for each enzyme. For example, CYP3A4 is enzyme number 4 of the CYP3 family and of the CYP3A subfamily.⁵⁶ Most xenobiotic metabolism is done by the CYP1, CYP2, and CYP3 families, with a small amount done by the CYP4 family.^{10,90} Although 15 CYP enzymes metabolize xenobiotics,⁶⁶ nearly 90% is done by 6 CYP enzymes: 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 (Table 13–1).⁵⁹

TABLE 13–1. Characteristics of Different Cytochrome P450 Enzymes^{1,10,20,23,47,57,62}

Enzyme	1A2	2C9	2C19	2D6	2E1	3A4
Percent of liver CYPs	2%	10%–20%	10%–20%	30%	7%	40%–55%
Contribution to enterocyte CYPs	Minor	Minor	Minor	Minor	Minor	70%
Organs other than liver with enzyme	Lung	Small intestine, nasal mucosa, heart	Small intestine, nasal mucosa, heart	Small intestine, kidney, lung, heart	Lung, small intestine, kidney	Much in small intestine; some in kidney, nasal mucosa, lung, stomach
Percent of metabolism of typically used drugs	2%–15%	10%–15%		25%–30%		50%–60%
Polymorphism ^a	No	Yes	Yes	Yes	No	No
Poor metabolizer						
African American	—	1%–2%	20%	2%–8%	—	—
Asian	—	1%–2%	15%–20%	>1%	—	—
White	—	1%–3%	3%–5%	5%–10%	—	—
Ultra extensive metabolizer						
Asian	—	—	—	1%	—	—
Ethiopian	—	—	—	30%	—	—
Northern Europeans	—	—	—	1%–2%	—	—
Southern Europeans	—	—	—	10%	—	—

^aEnzyme variations exist even in those listed as “No” for polymorphism.

Most CYP enzymes are found in the liver, where they comprise 2% of total microsomal protein.⁶⁶ High concentrations are also found in extrahepatic tissues, particularly the GI tract and kidney.^{20,60} The lungs,⁹⁶ heart,⁶⁴ and brain²¹ have the next highest amounts. Each tissue has a unique profile of CYP enzymes that determines its sensitivity to different xenobiotics.²⁰ The CYP enzymes in the enterocytes of the small intestine actually contribute significantly to “first-pass” metabolism of some xenobiotics.^{42,59} Corrected for tissue mass, the CYP enzyme system in the kidneys is as active as that in the liver. The activity of the renal CYP enzymes is decreased in patients with chronic kidney disease, with relative sparing of CYPs 1A2, 2C19, and 2D6 compared with 3A4 and 2C9.¹⁰

Cytochrome P450 Enzyme Specificity for Substrates

In vitro models are used to define the specificities of CYP enzymes for their substrates and inhibitors. However, activity in a test tube does not always correlate with that in a cell. These models use substrate and inhibitor concentrations that are much higher than would be encountered in vivo, and the mathematical models that extrapolate to clinically relevant processes yield conflicting results. This has resulted in discrepancies in reported substrates, inhibitors, and inducers of specific CYP enzymes.⁹²

Most CYP enzymes involved in xenobiotic biotransformation have broad substrate specificity and can metabolize many xenobiotics.³² This is fortunate because the number of xenobiotic substrates may exceed 200,000 and continues to grow.⁴⁸ Broad substrate specificity often results in multiple CYP enzymes being able to biotransform a xenobiotic. This enables the ongoing biotransformation despite an inhibition or deficiency of an enzyme. When a substrate can be biotransformed by more than one enzyme, the enzyme with the highest affinity for the substrate usually predominates at low substrate concentrations, whereas enzymes with lower affinity may be very important at high concentrations. This transition is usually concomitant with, but not dependent on, the saturation of the catalytic capacity of the primary enzyme as it reaches its maximum rate of activity.³² The K_m , which is defined as the concentration of substrate that results in 50% of maximal enzyme activity, describes this property of enzymes. For example, ADH in the liver has a very low K_m for ethanol, making it the primary metabolic enzyme for ethanol when concentrations are low.⁴⁹ Ethanol is also biotransformed by the CYP2E1 enzyme, which has a high K_m for ethanol and only functions when ethanol concentrations are high. The CYP2E1 enzyme metabolizes little ethanol in moderate drinkers but accounts for significantly more biotransformation in alcoholics. As another example, diazepam is metabolized by both CYP2C19 and CYP3A4 enzymes. However, the affinity of CYP3A4 for diazepam is so low (ie, the K_m is high) that most diazepam is metabolized by CYP2C19.³⁴

The substrate selectivity of some CYP enzymes is determined by molecular and physicochemical properties of the substrates. The CYP1A subfamily has greater specificity for planar polyaromatic substrates such as benzo[a]pyrene. The CYP2E enzyme subfamily targets low-molecular-weight hydrophilic xenobiotics, whereas the CYP3A4 enzyme has increased affinity for lipophilic compounds. Substrates of CYP2C9 are usually weakly acidic, whereas those of CYP2D6 are more basic.⁴⁸ High specificity can also result from key structural considerations such as stereoselectivity. Some xenobiotics are racemic mixtures of two stereoisomers that are substrates for different CYP enzymes and have distinct affinities for the enzymes, resulting in different rates of metabolism. For example, R-warfarin is biotransformed by CYP3A4 and CYP1A2, whereas S-warfarin is metabolized by CYP2C9.^{76,83}

The CYP enzymes that biotransform a specific xenobiotic cannot be predicted by its drug class. For example, fluoxetine and paroxetine are both major substrates and potent inhibitors of CYP2D6, but sertraline is not extensively metabolized by this enzyme and exhibits minimal interaction with other antidepressants.⁴ Most β -hydroxy- β -methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors are metabolized by CYP3A4 (lovastatin, simvastatin, and atorvastatin); however, fluvastatin is metabolized by CYP2D6 and pravastatin undergoes virtually no CYP enzyme metabolism at all.⁵¹ Among angiotensin-II receptor blockers, losartan and irbesartan are metabolized by CYP2C9, whereas valsartan, eprosartan, and candesartan are not substrates for any CYP enzyme. In addition, losartan is a prodrug whose active metabolite provides most of the pharmacologic activity, whereas irbesartan is the primary active compound. For these two drugs the inhibition of CYP2C9 is predicted to have opposite effects.²⁶

Cytochrome P450 and Drug–Drug/Drug–Chemical Interactions

Adverse reactions to medications and drug–drug interactions are common causes of morbidity and mortality, the risk of which increases with the number of drugs taken (Chaps. 139 and 140). Fifty percent of adverse reactions may be related to pharmacogenetic factors.²⁸ The most significant interactions are mediated by CYP enzymes.⁵⁹ The impacts of genetic polymorphism and enzyme induction or inhibition are addressed below.

CYP enzymes are involved in many types of drug interactions. The ability of potential new drugs to induce or inhibit enzymes is an important consideration of industry. Drug development focuses on the potential of new xenobiotics to induce or inhibit other drugs or enzymes during the drug discovery phase. Various in vitro models have been created to enable this early determination.⁵⁰

Many xenobiotics interact with the CYP enzymes. St. John's wort, an herb marketed as a natural antidepressant, induces multiple CYP enzymes, including 1A2, 2C9, and 3A4. The induction of CYP3A4 by St. John's wort is associated with a 57% decrease in effective serum concentrations of indinavir when given concomitantly.⁶⁷ Xenobiotics contained in grapefruit juice, such as naringin and furanocoumarins, are both substrates and inhibitors of CYP3A4. They inhibit the first-pass metabolism of CYP3A4 substrates by inhibiting CYP3A4 activity in both the GI tract and the liver.¹⁷ Polycyclic hydrocarbons found in charbroiled meats and in cigarette smoke induce CYP1A2. Thus, for smokers who drink coffee, concentrations of caffeine, a CYP1A2 substrate, will increase following a permanent cessation of smoking.²⁴

Genetic Polymorphism

The response to xenobiotics and to coadministration of inhibitory or inducing xenobiotics is highly variable. The translation of DNA sequences into proteins results in the phenotypic expression of the genes. When a genetic mutation occurs, the changed DNA may continue to exist, be eliminated, or propagate into a polymorphism. A polymorphism is a genetic change that exists in at least 1% of the human population.^{28,59} A polymorphism in a biotransformation enzyme may change its rate of activity. The heterogeneity of CYP enzymes contributes to the differences in metabolic activity between patients.²⁸ Differences in biotransformation capacity that lead to toxicity, once thought to be “idiosyncratic” drug reactions, are likely caused by these inherited differences in the genetic complement of individuals.

The normal catalytic speed of CYP enzyme activity is called extensive. There are two major metabolizer phenotypes due to polymorphism: poor (slow) and ultraextensive (rapid).^{28,56} The CYP2C19 and CYP2D6 genes are highly polymorphic (Table 13–1). The CYP2D6 gene, which has more than 90 alleles, is associated with both ultraextensive and poor metabolism. The CYP2C19 and CYP2C9 genes are both associated with polymorphisms resulting in poor metabolizers.^{10,59}

The clinical implications of polymorphisms are vast. A prodrug may not be bioactivated because the patient is a poor metabolizer. Conversely, a drug may not reach a therapeutic concentration because the patient is an ultraextensive metabolizer.²⁸

Polymorphisms exist for enzymes other than CYP enzymes. A classic one is the inheritance of rapid or slow “acetylator” phenotypes. Acetylation is important for the biotransformation of amines ($R-NH_2$) or hydrazines (NH_2-NH_2). Slow acetylators are at increased risk of toxicity associated with the slower biotransformation of certain nitrogen-containing xenobiotics such as isoniazid, procainamide, hydralazine, and sulfonamides.⁷⁸

Polymorphic genes that code for enzymes in important metabolic pathways affect the toxicity of a xenobiotic by altering the response to, or the disposition of, the xenobiotic. An example occurs in glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD is a critical enzyme in the hexose monophosphate shunt, a metabolic pathway located in the red blood cell (RBC) that produces NADPH, which is required to maintain RBC glutathione in a reduced state. In turn, reduced glutathione prevents hemolysis during oxidative stress.¹² In patients deficient in G6PD, oxidative stress produced by electrophilic xenobiotics results in hemolysis.

Induction of CYP Enzymes

Biotransformation by induced CYP enzymes results in either increased activity of prodrugs or enhanced elimination of drugs. Stopping an inducing agent may result in the opposite effects. Either way, maintaining therapeutic concentrations of affected drugs is difficult, resulting in either toxicity or subtherapeutic concentrations. Interestingly, not all CYP enzymes are inducible. The inducible enzymes include CYP2A, CYP2B, CYP2C, CYP2E, and CYP3A.⁵⁰

While varied mechanisms of induction exist, the most common and significant is nuclear receptor (NR)-mediated increase in gene transcription.⁵⁰ NRs are the largest group of transcription factors (proteins) that switch genes on or off.⁸⁷ They regulate reproduction, growth, and biotransformation enzymes, including CYP enzymes.⁸⁴ NRs exist mostly within the cytoplasm of cells. The CYP families 2 and 3 both have gene activation triggered through the NR pregnane X receptor (PXR) and the constitutive androstane receptor (CAR). The CYP 1A subfamily uses the aryl hydrocarbon receptor (AhR) as its NR. Ligands, molecules that bind to and affect the reactivity of a central molecule, are typically small and lipophilic, enabling them to enter cells. Many xenobiotics are ligands. Ligands bind the NRs, resulting in structural changes that enable the NR-ligand complexes to be translocated into the cell nucleus. Within the nucleus, NR-ligand complexes bind to proteins such as the retinoid X receptor (RXR), shared by the PXR and the CAR, or the AhR nuclear translocator (Arnt), or by the AhR. This new complex then interacts with specific response elements of DNA, initiating the transcription of a segment of DNA, and resulting in the phenotypic expression of the respective CYP enzyme.

The ligand-binding domain of the PXR is very hydrophobic and flexible, enabling this pocket to bind many substrates of varied sizes and reflecting why the PXR can be activated by a broad group of ligands.^{65,84} For example, xenobiotic ligands that bind the NR PXR that targets the CYP3A4 gene include rifampin, omeprazole, carbamazepine, and troleandomycin. Phenobarbital, a classic inducing xenobiotic, is a ligand that binds the CAR.⁸⁷ The induction of CYP1A subfamily enzymes is through the interaction with the NR AhR. Exogenous AhR ligands are hydrophobic, cyclic, planar molecules. Classic AhR ligands include polycyclic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-p-dioxin and benzo[a]pyrene.⁶⁵

Induction requires time to occur because it involves de novo synthesis of new proteins. Similarly, withdrawal of the inducer results in a slow return to the original enzyme concentration.⁵⁰ Polyaromatic hydrocarbons (PAHs) result in CYP1A subfamily induction within 3 to 6 hours with a maximum effect within 24 hours.⁸⁰ The inducer rifampin does not affect verapamil trough concentrations maximally until one week; followed by a two-week return to baseline steady state after withdrawal of rifampin.⁵⁰ Xenobiotics with long half-lives require longer periods to reach steady-state concentrations that maximize induction. Phenobarbital and fluoxetine, which have long half-lives, may fully manifest induction only after weeks of exposure. Conversely, xenobiotics with short half-lives, such as rifampin or venlafaxine, can reach maximum induction within days.¹⁰

Inconsistency in CYP induction exists in all organs and among individuals.^{50,65} In an in vitro study of the effects of inducing xenobiotics on 60 livers, differences in enzyme induction ranged from 5-fold for CYP3A4 and CYP2C9 up to more than 50-fold for CYP2A6 and CYP2D6.⁵⁰ The inconsistency likely results from both polymorphisms and multiple environmental factors including diet, tobacco, and pollutants.⁵⁰ There is variation in the extent to which inducers can generate new CYP enzymes. Identical dosing regimens with rifampin have resulted in induction of in vivo hepatic CYP3A4 with up to 18-fold differences between subjects.⁵⁰ There is an inverse correlation of the degree of inducibility of an enzyme and the baseline enzyme concentration. Patients with a relatively low baseline concentration of a CYP enzyme will be more inducible than those with a high baseline concentration. Interestingly, the maximum concentrations of CYP enzymes seem to be quantitatively similar among individuals, suggesting a limit to which enzymes can be induced.⁵⁰

Although the focus of this section is on CYP enzymes, it appears that all phases of xenobiotic metabolism are regulated by NRs.⁸ Also, just as genetic polymorphisms exist for CYP enzymes, they exist for NRs including the AhR, the CAR, and the PXR. This results in varied sensitivities to the ligands that complex with the NRs, ultimately resulting in differences in CYP enzyme induction.^{50,87}

Inhibition of CYP Enzymes

CYP enzyme inhibition can result in increased bioavailability of a drug or decreased bioactivation of a prodrug.⁶⁶ Inhibition of CYP enzymes is the most common cause of harmful drug-drug interactions.⁶⁶ Inhibition of CYP enzymes by coadministered xenobiotics has resulted in the removal of many medications from the market in recent years, including

terfenadine, mibefradil, bromfenac, astemizole, cisapride, cerivastatin, and nefazodone.⁹² The appendix at the end of this chapter includes a comprehensive listing of cytochrome P450 substrates, inhibitors, and inducers.

Inhibition mechanisms include irreversible (mechanism-based inhibition) and the more common reversible processes. The most common type of reversible inhibition is competitive, where the substrate and inhibitor both bind the active site of the enzyme.^{66,92} Binding is weak and is formed and broken down easily, resulting in the enzyme becoming available again. It occurs rapidly, usually beginning within hours.¹⁰ Because the degree of inhibition varies with the concentration of the inhibitor, the time to reach the maximal effect correlates with the half-life of the xenobiotic in question.¹⁰ A competitive inhibitor can be overcome by increasing the substrate concentration. Each substrate of a CYP enzyme is an inhibitor of the metabolism of all the other substrates of the same enzyme, thereby increasing their concentrations and half-lives. Reversible, noncompetitive inhibition occurs when an inhibitor binds a location on an enzyme that is not the active site, resulting in a structural change that inhibits the active enzyme site. For example, noncompetitive inhibitors of CYP2C9 include nifedipine, tranylcypromine, and medroxyprogesterone.⁷⁷ Another reversible mechanism results from competition between one xenobiotic and a metabolite of a second xenobiotic at its CYP enzyme substrate binding site. For example, the metabolites of clarithromycin and erythromycin produced by CYP3A inhibit further CYP3A activity. The effect is reversible and usually increases with repeated dosing.⁷⁷ Some reversible inhibitors bind so tightly to the enzyme that they essentially function as irreversible inhibitors.⁶⁶

Irreversible inhibitors have reactive groups that covalently, and thus permanently, bind the enzyme. They display time-dependent inhibition because the amount of active enzyme at a given concentration of irreversible inhibitor will be different depending on how long the inhibitor is preincubated with the enzyme. Because the enzyme will never be reactivated, inhibition lasts until new enzyme is synthesized.⁶⁶ One measure of inhibitor potency is the inhibitory concentration, K_i , the concentration of the inhibitor that produces 50% inhibition of the enzyme. The more potent the inhibitor, the lower the value.⁸⁰ Values below 1 $\mu\text{mol/L}$ are regarded as potent.⁶² The azole antifungals are very potent, with K_i values of 0.02 $\mu\text{mol/L}$.⁸⁰

The impact of an inhibitor is also affected by the fraction of the substrate that is biotransformed by the inhibited, target enzyme. The inhibition of a CYP enzyme will have little impact if the enzyme only metabolizes a fraction of the affected drug.⁶² Conversely, drugs that are primarily metabolized by a single CYP enzyme are more susceptible to interactions.⁶⁶ Simvastatin is mainly biotransformed by CYP3A4. The potent and specific CYP3A inhibitor itraconazole prevents its metabolism, resulting in an increased risk of rhabdomyolysis.¹

Specific CYP Enzymes

CYP1A1 and 1A2. While 1A1 is located primarily in extrahepatic tissue, 1A2 is a hepatic enzyme and is involved in the metabolism of 10% to 15% of all pharmaceuticals.^{10,50} They both are very inducible by polycyclic aromatic hydrocarbons, including those in cigarette smoke and charred food. They bioactivate several procarcinogens including benzo[a]pyrene.⁴³ Xenobiotics activated by the CYP1 enzyme family in the GI tract are linked to colon cancer.⁵⁹

CYP2C9. The CYP2 enzyme family, with its 76 alleles, is one of the most polymorphic of the CYP enzymes (Table 13–1).^{24,88} The CYP2C9 enzyme is the most abundant enzyme of the CYP2C enzyme subfamily, which with CYP2C19, comprises approximately 10% to 20% of the CYP enzymes in the liver and is involved in 15% to 20% of all drug metabolism.^{24,88} This enzyme biotransforms S-warfarin, the more active isomer of warfarin. Warfarin is one of the most commonly reported causes of adverse drug events. There is an association between slow metabolism and an increased risk of bleeding in patients taking warfarin.^{13,76}

CYP2D6. This enzyme is of historical significance because the exploration of differences in pharmacokinetics among individuals taking the antihypertensive debrisoquine was an important part of the beginning of pharmacogenetics. This enzyme is highly polymorphic, with more than 90 allelic variants.⁶³ Twenty-five percent of pharmaceuticals, including 50% of the commonly used antipsychotics, are substrates for CYP2D6.^{38,59,63} Because CYP2D6 is the only drug-metabolizing CYP enzyme that is noninducible, the polymorphisms are the primary reason for the substantial interindividual variation in enzyme activity.⁶³

CYP2E1. This enzyme comprises 7% of the total CYP enzyme content in the human liver.⁵⁸ It metabolizes small organic compounds, including ethanol, carbon tetrachloride, and halogenated anesthetics.⁸⁰ It also biotransforms low-molecular-weight xenobiotics including benzene, acetone, and N-nitrosamines.⁸⁰ Some of its substrates are procarcinogens, which are bioactivated by CYP2E1. Besides CYP1A2, this is the only other CYP enzyme linked to cancer.⁵⁹ The assessment for a relationship between CYP2E1 and cancer is intense because many of its substrates are environmental xenobiotics. The induction of CYP2E1 is associated with increased liver injury by reactive metabolites of carbon tetrachloride and vinyl chloride (Chap. 23).³⁰ During the metabolism of substrates that include carbon tetrachloride, ethanol, acetaminophen (APAP), aniline, and N-nitrosomethylamine, CYP2E1 actively produces free radicals and other reactive metabolites

associated with adduct formation and lipid peroxidation (Chaps. 9 and 35).¹⁴ CYP2E1 is inhibited by acute elevations of ethanol, an effect illustrated by the acute administration of ethanol inhibiting the metabolism of APAP.³⁰ The chronic ingestion of ethanol hastens its own metabolism through CYP2E1 induction.

CYP3A4. CYP3A4 is the most abundant CYP in the human liver, comprising 40% to 55% of the mass of hepatic CYP enzymes.^{10,24} The CYP3A4 enzyme is the most common one found in the intestinal mucosa and is responsible for much first-pass drug metabolism.¹⁰ It is involved in the biotransformation of 50% to 60% of all pharmaceuticals.^{58,97} It has broad substrate specificity because it accommodates large lipophilic substrates and can adopt multiple conformations. It can even simultaneously fit two relatively large compounds (ketoconazole, erythromycin) in its active site.⁷⁵

Methadone, extensively metabolized by CYP3A4, is associated with many examples of adverse drug interactions.⁴¹ Torsade de pointes is reported in methadone patients who are also exposed to CYP3A4 inhibitors including ciprofloxacin,⁵⁷ itraconazole,⁶¹ and the antiretrovirals atazanavir and ritonavir.²³ Ketoconazole inhibits CYP3A4, causing a 15-fold to 72-fold increase in serum concentrations of terfenadine.⁵⁹ Bioflavonoids in grapefruit juice decrease metabolism of some substrates by 5-fold to 12-fold.^{10,59} The CYP3A4 enzyme does not exhibit significant genetic polymorphism; however, there are large interindividual variations in enzyme concentrations that can affect metabolic rates.⁹⁷

Phase II Biotransformation Reactions

Phase II biotransformation reactions are synthetic, catalyzing the conjugation of products of phase I reactions or xenobiotics with endogenous molecules that are generally hydrophilic. Conjugation usually terminates the pharmacologic activity of xenobiotics and greatly increases their water solubility and excreatability.^{52,83,95} Conjugation occurs most commonly with glucuronic acid, sulfates, and glutathione. Less common phase II reactions include conjugation with amino acids such as glycine, glutamic acid, and taurine as well as acetylation and methylation.

Glucuronidation is the most common phase II synthesis reaction.⁵² Glucuronyl transferase has relatively low substrate affinity but it has high capacity at higher substrate concentrations.⁸³ The glucuronic acid, donated by uridine diphosphate glucuronic acid, is conjugated with the nitrogen, sulfhydryl, hydroxyl, or carboxyl groups of substrates. Smaller conjugates usually undergo renal elimination, whereas larger ones undergo biliary elimination.⁴⁸

Sulfation complements glucuronidation because it is a high-affinity but low-capacity reaction that occurs primarily in the cytosol. For example, the affinity of sulfate for phenol is very high (the K_m is low), so that when low doses of phenol are administered, the predominant excretion product is the sulfate ester. Because the capacity of this reaction is readily saturated, glucuronidation becomes the main method of detoxification when high doses of phenol are administered.^{52,95} Sulfate conjugates are highly ionized and very water soluble. Of note, sulfation is reversible by the action of sulfatases within the liver. The resultant metabolites may be resulfated, and the cycle may repeat itself further.⁹⁵

Glutathione S-transferases are important because they catalyze the conjugation of the tripeptide glutathione (glycine-glutamate-cysteine, or GSH) with a diverse group of reactive, electrophilic metabolites of phase I CYP enzymes. The reactive compounds initiate an attack on the sulfur group of cysteine, resulting in conjugation with GSH that detoxifies the reactive metabolite. Of the three phase II reactions addressed, hepatic concentrations of glutathione by far account for the greatest amount of cofactors used. Although intracellular glutathione is difficult to deplete, when it does occur, severe hepatotoxicity often follows.⁹⁵ Some GSH conjugates are directly excreted. More commonly, the glycine and glutamate residues are cleaved and the remaining cysteine is acetylated to form a mercapturic acid conjugate that is readily excreted in the urine. A familiar example of this detoxification is the avid binding of N-acetyl-p-benzoquinoneimine (NAPQI), the toxic metabolite of APAP, by glutathione.^{4,9}

As with the CYP enzymes, many phase II enzymes are inducible. For example, UDP-glucuronosyltransferase, which performs glucuronidation, is inducible via the PXR, CAR, and AhR nuclear receptors after binding with rifampin, phenobarbital, and PAHs, respectively. Its activity varies 6-fold to 15-fold in liver microsomes.⁸⁷

Membrane Transporters

Although the focus on drug disposition has traditionally been on biotransformation, membrane transporter proteins greatly impact drug disposition.³⁵ Transporter proteins mediate the cellular uptake and efflux of endogenous compounds and xenobiotics.⁹⁸ Their baseline physiologic role is to transport sugars, lipids, amino acids, and hormones so as to regulate cellular solute and fluid balance. Biotransformation cannot occur unless xenobiotics are taken up into the cells via transport proteins. After xenobiotics have undergone phase I and II metabolism, the metabolites undergo transport protein mediated efflux from the cell, an action that has been called phase III metabolism.³⁹

The transport proteins that are most relevant to xenobiotic uptake and efflux are those mediating the efflux from the apical (luminal) membrane of enterocytes (P-glycoprotein), the uptake from the portal venous blood into the hepatocytes, the efflux from the hepatocytes via the canalicular membrane into the bile, the uptake into renal proximal tubular cells, and

the efflux from renal proximal tubular cells into urine.⁹⁸ Drug disposition is facilitated or prevented by the transport proteins.⁴⁴

Most transporters are in the adenosine triphosphate binding cassette (ABC) family of transmembrane proteins that use energy from ATP hydrolysis.^{11,35} This family includes the P-glycoprotein family. Some transporters move substrates both into and out of cells. Organs important for drug disposition have multiple transporters that have overlapping substrate capabilities, a redundancy that enhances protection. In the small intestine, P-glycoprotein is important because it can actively extrude xenobiotics back into the intestinal lumen.¹¹ The degree of phenotypic expression of P-glycoprotein affects the bioavailability of many xenobiotics, including paclitaxel, digoxin, and protease inhibitors. Hepatocyte efflux transporters move biotransformed xenobiotics into bile. Transporters in endothelial cells of the blood–brain barrier prevent CNS entry of substrate xenobiotics.^{11,35}

As with biotransformation enzymes and nuclear receptors, membrane transporters may also be inhibited or induced. Digoxin, a high-affinity substrate for P-glycoprotein, has increased bioavailability when administered with P-glycoprotein inhibitors such as clarithromycin or atorvastatin.³⁵ Loperamide is a substrate for P-glycoprotein that limits its intestinal absorption or CNS entry. Coadministration with quinidine, a P-glycoprotein inhibitor, results in increased opioid CNS effects of loperamide.³⁵ As with the biotransformation enzymes, polymorphisms exist for membrane transporters. However, the clinical significance of these is not clear.¹⁶

MECHANISMS OF CELLULAR INJURY

Ideally and commonly, potentially toxic metabolites produced by phase I reactions are detoxified during phase II reactions. However, detoxification does not always occur. This section reviews mechanisms of cellular injury related to xenobiotic biotransformation.

Synthesis of Toxins

Sometimes a xenobiotic is mistaken for an endogenous substrate by synthetic enzymes that biotransform it into an injurious compound. The incorporation of the rodenticide fluoroacetate into the tricarboxylic acid cycle is an example of this mechanism of toxic injury (Fig. 13–3).⁶⁹ Another example is illustrated by analogs of purine or pyrimidine bases that are phosphorylated and inserted into growing DNA or RNA chains, resulting in mutations and disruption of cell division. This mechanism is used therapeutically with 5-fluorouracil (5-FU), an antitumor, pyrimidine base analog. When phosphorylated to 5-fluoro-dUTP and incorporated into growing DNA chains, it causes structural instability of the cellular DNA and inhibits tumor growth.⁷³

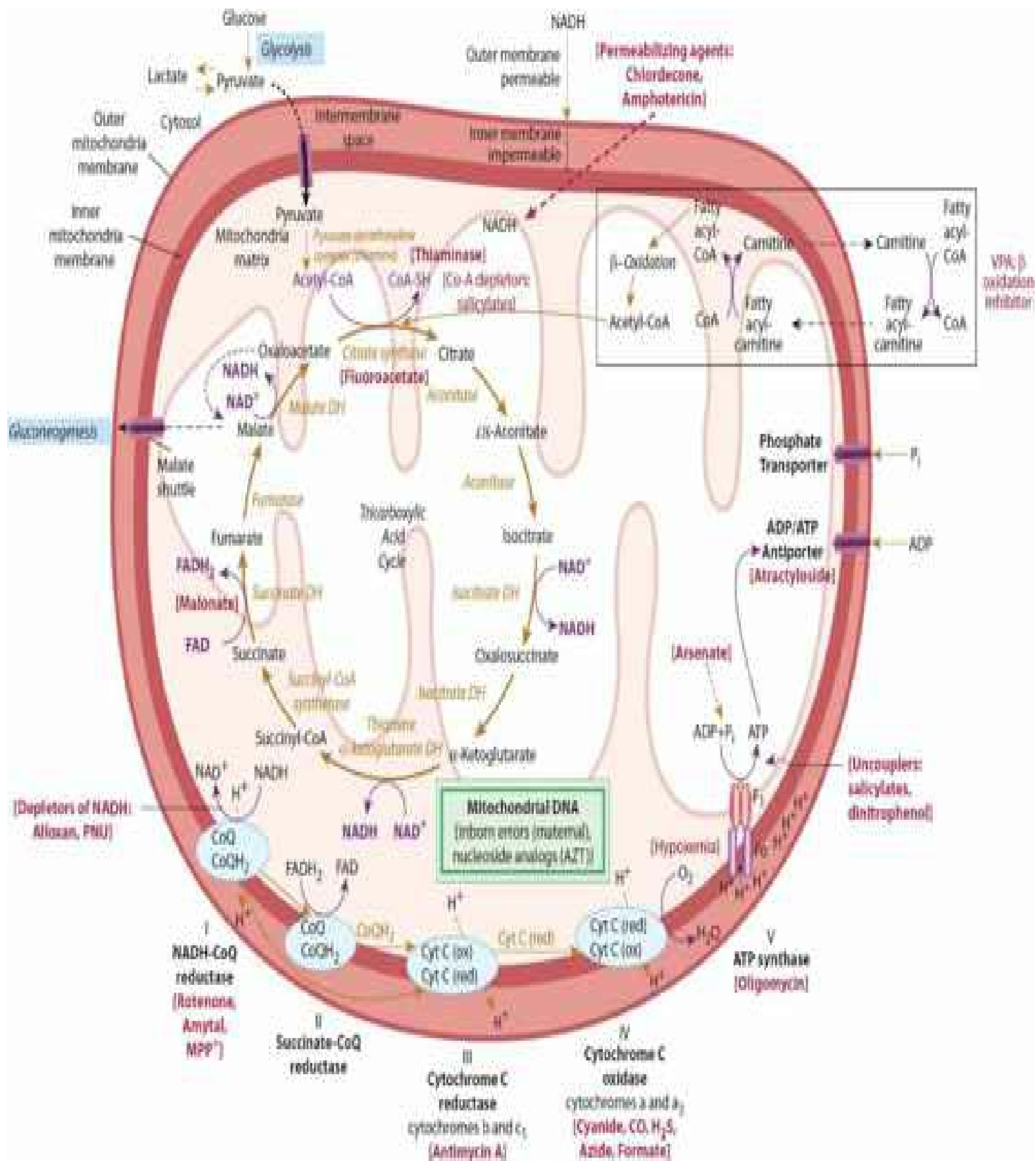


FIGURE 13–3. Pyruvate is converted to acetylcoenzyme A (acetyl-CoA), which enters the Krebs cycle as shown. Reducing equivalents, in the form of NADH and FADH, donate electrons to a chain of cytochromes beginning with NADH dehydrogenase. These reactions “couple” the energy released during electron transport to the production of ATP. Ultimately, electrons combine with oxygen to form water. The sites of action of xenobiotics that inhibit oxidative metabolism are shown. The sites where thiamine functions as a coenzyme are also illustrated. DH = dehydrogenase.

Injury by Metabolites of Biotransformation

Many toxic products result from metabolic activation (Table 13–2).⁴⁰ The CYP enzymes most associated with bioactivation are 1A1, 1B1, 2A6, and 2E1, whereas 2C9 and 2D6 yield little toxic activation.³²

TABLE 13–2. Examples of Xenobiotics Activated to Toxins by Human Cytochrome P450 Enzymes

<i>CYP Substrate</i>	<i>Toxicity</i>	<i>Enzyme</i>
1A1	Benzo[a]pyrene (PAH)	IARC Group 1
1A2	APAP	Hepatotoxicity
	Aflatoxin B (<i>Aspergillus</i> mycotoxin)	IARC Group 1
	2-Naphthylamine (azo dye production)	IARC Group 1
	NNK (nitrosamine in tobacco)	IARC Group 1
	N-Nitrosodiethylamine (gas and lubricant additive, copolymer softener)	IARC Group 2A
2B6	Chrysene (PAH)	IARC Group 2B
	Cyclophosphamide	IARC Group 1
2C 8,9	Phenytoin	IARC Group 2B
	Valproic acid	Hepatotoxicity
2D6	NNK (nitrosamine in tobacco)	IARC Group 1
2F1	APAP	Hepatotoxicity
	3-Methylindole (in perfumes, cigarettes for flavor)	Pneumotoxicity
	Valproic acid	Hepatotoxicity
2E1	APAP	Hepatotoxicity
	Acrylonitrile	IARC Group 2B
	Benzene	IARC Group 1
	Carbon tetrachloride	IARC Group 2B
	Chloroform	IARC Group 2B
	Ethylene dibromide (former gas additive and fumigant)	IARC Group 2A
	Ethyl carbamate (former antineoplastic)	IARC Group 2A
	Halothane	Hepatotoxicity
	Methylene Chloride	IARC Group 2B
	N-Nitrosodimethylamine (formerly in rocket fuel)	IARC Group 2A
	Styrene	IARC Group 2A
	Trichloroethylene	IARC Group 2A
	Vinyl chloride	IARC Group 1
3A4	APAP	Hepatotoxicity
	Aflatoxin B ₁ (<i>Aspergillus</i> mycotoxin)	IARC Group 1
	Chrysene (PAH)	IARC Group 2B
	Cyclophosphamide	IARC Group 1
	1-Nitropyrene (PAH)	IARC Group 2B
	Senecionine (pyrrolizidine alkaloid)	Hepatotoxicity
	Sterigmatocystin (<i>Aspergillus</i> mycotoxin)	IARC Group 2B

Group 1 = known carcinogen; Group 2A = probable carcinogen; Group 2B = possible carcinogen; IARC = International Agency for Research on Cancer of the World Health Organization; PAH = polycyclic aromatic hydrocarbon.

Highly reactive metabolites exert damage at the site where they are synthesized; reacting too quickly with local molecules to be transported elsewhere. This commonly occurs in the liver, the major site of biotransformation of xenobiotics^{31,79} (Chap. 23). However, metabolism in the lungs, skin, kidneys, GI tract, and nasal mucosa can also create toxic metabolites that cause local injury.^{9,46} Overdoses of APAP lead to excessive hepatic production of the highly reactive electrophile NAPQI, which initiates a damaging covalent bond with hepatocytes⁴ (Chap. 35). Acute renal tubular necrosis also occurs in patients with overdose of APAP, attributed to its biotransformation by prostaglandin H synthase within renal

tubular cells to a highly reactive semiquinoneimine.^{22,91}

Monoamine oxidases (MAOs) are mitochondrial enzymes present in many tissues. They oxidize many amines, including dopamine, epinephrine, and serotonin, and xenobiotics such as primaquine and haloperidol. The metabolic activity of MAOs was responsible for the outbreak of parkinsonism associated with the use of methylphenyltetrahydropyridine (MPTP), an unintended by-product of attempts to synthesize a “designer” analog of meperidine, methylphenylpropionoxypiperidine (MPPP). After crossing the blood–brain barrier, MPTP is biotransformed by MAO in glial cells to methylphenyldihydropyridine (MPDP⁺), which is converted to MPP⁺. The MPP⁺ is subsequently taken up by specific dopamine transport systems into dopaminergic neurons in the substantia nigra, resulting in inhibition of oxidative phosphorylation and subsequent neuronal death.²⁹

Free Radical Formation

Within an atom, it is energetically favorable for electrons to exist in pairs or as a part of a chemical bond. An element or compound with an unpaired electron, called a radical or free radical, is highly reactive and short lived. It rapidly seeks other species in order to obtain another electron. Radicals include the superoxide anion O₂^{•−}, which is produced by adding an electron to O₂, and the highly reactive hydroxyl radical HO•, which is produced by splitting the H₂O₂ molecule into two equal halves. The H₂O₂ molecule itself is reactive and is also associated with injury. The superoxide and hydroxyl radicals react with other molecules in order to stabilize themselves; however, by taking an electron in order to do so, they generate new free radical species, potentially initiating a chain reaction. The production of radicals is a normal occurrence for which the human body has defense mechanisms. However, some xenobiotics promote the formation of reactive oxidant species to the extent that antioxidant mechanisms are overwhelmed, a condition called oxidative stress. Oxidizing species are called such because, by reducing themselves by taking away electrons, they oxidize the species from which they took the electrons.⁶

Although oxidative stress may result in oxidative damage to nucleic acids and proteins, other classic targets are polyunsaturated fatty acids (PUFAs) in cellular membranes, resulting in lipid peroxidation (the oxidative destruction of lipids). This attack removes the particularly reactive hydrogen atom, with its lone electron, from a methylene carbon of a PUFA, leaving an unpaired electron and causing the formation of a lipid radical. This lipid radical attacks other PUFAs, initiating a chain reaction that destroys the cellular membrane. Membrane degradation products initiate inflammatory reactions in the cells, resulting in further damage.^{6,79}

Molecular oxygen (O₂) has a lone pair of electrons in its orbit. Because oxygen is a relatively weak univalent electron acceptor (and most organic molecules are weak univalent electron donors), oxygen cannot efficiently oxidize amino acids and nucleic acids. However, the unpaired electrons of O₂ readily interact with the unpaired electrons of transition metals and organic radicals. Metals frequently catalyze the creation of oxygen free radicals. Figure 13–4 reflects the typical steps in the formation of a hydroxyl radical. The damaging effects of the free radicals are decreased by reaction with antioxidants such as ascorbate, tocopherols, and glutathione.⁵² Deficiencies of antioxidants, especially glutathione, are associated with increased oxidative damage. Free radicals are also neutralized by several enzymes, including peroxidase, superoxide dismutase, and catalase.

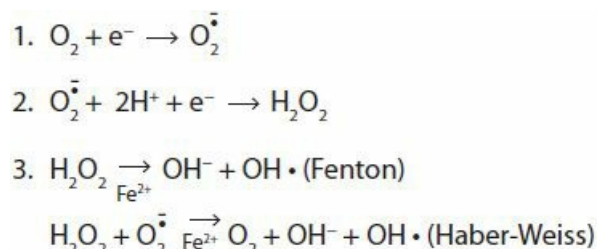


FIGURE 13–4. Hydroxyl radical formation. (1) First is the addition of an electron to O₂ to create the superoxide ion. (2) Then the very reactive superoxide combines with hydrogen and another electron to produce hydrogen peroxide. (3) Finally, in the presence of a metal ion catalyst such as iron, hydrogen peroxide undergoes various reactions to produce the hydroxyl radical. The dot in these formulas represents an unpaired electron, the hallmark of a free radical.^{37,52}

The ethanol-inducible CYP2E1 enzyme produces significant amounts of superoxide and peroxide free radicals, and, in the presence of iron, hydroxyl free radicals that readily initiate lipid peroxidation. This has been studied extensively in models of the metabolism of carbon tetrachloride, ethanol, and APAP.¹⁹ The formation of free radicals is implicated in the pulmonary injury caused by paraquat, the myocardial injury caused by doxorubicin, and the liver injury caused by carbon tetrachloride.^{55,70} Paraquat reacts with NADPH to form a pyridinyl free radical, which, in turn, reacts with oxygen to generate the superoxide anion radical. Doxorubicin is metabolized to a semiquinone free radical in the cardiac mitochondria, which, in the presence of oxygen, forms a superoxide anion radical that initiates myocardial lipid

peroxidation.⁵⁵ Carbon tetrachloride (CCl_4) is metabolized to the trichloromethyl radical ($\cdot\text{CCl}_3$) that binds covalently to cellular macromolecules. In the presence of oxygen, this is converted to the trichloromethylperoxyl radical ($\cdot\text{CCl}_3\text{O}_2$) that can initiate lipid peroxidation (Fig. 13–5).⁷¹ See Chap. 108 for a more extensive discussion.

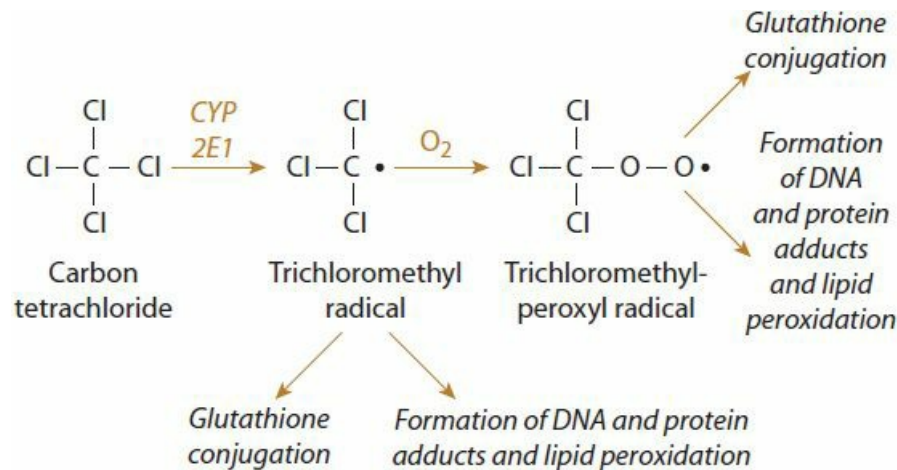


FIGURE 13–5. This is carbon tetrachloride metabolism by the hepatocyte. Under hypoxic conditions, the CCl_3 radical is the predominant species formed. At higher oxygen tensions, the CCl_3 radical is oxidized to the $\text{CCl}_3\text{OO}\cdot$ radical, which is more readily detoxified by glutathione. Both free radicals bind to hepatocytes and cause cellular injury.

CRITICAL BIOCHEMICAL PATHWAYS AND XENOBIOTICS THAT AFFECT THEM

Energy metabolism is the foundation of cellular function. It provides high-energy fuel, predominantly in the form of ATP, for all energy-dependent cellular processes such as synthesis, active transport, and maintenance of electrolyte balance and membrane integrity. Numerous pathways interconnect glycogen, fat, and protein reserves in many tissues that store and retrieve ATP and glucose. The brain and RBCs are entirely dependent on glucose for energy production, while other tissues can also use ketone bodies and fatty acids to synthesize ATP. Rapid cell death occurs if the production or use of ATP is inhibited, thus the goal of many metabolic processes is the production and mobilization of cellular energy.

Catabolic pathways, those that break down molecules into smaller units enabling the production of cellular energy, include glycolysis, the citric acid (tricarboxylic acid, or Krebs) cycle, and oxidative phosphorylation via the electron transport chain. Glycolysis produces small amounts of ATP through the anaerobic metabolism of glucose. Pyruvate, the end product of glycolysis, yields far more ATP when it is converted to acetylcoenzyme A (acetyl-CoA) and “processed” in the citric acid cycle (Fig. 13–3). Fat and protein yield their energy through their conversion to acetyl-CoA and other intermediates of the citric acid cycle. The citric acid cycle and oxidative phosphorylation, via the electron transport chain, result in most ATP synthesis. Oxidative phosphorylation disposes of electrons or “reducing equivalents” and converts their energy to ATP. A lack of oxygen stops the electron transport chain and ATP production. Oxidative metabolism is highly energy efficient, producing 36 moles of ATP for each mole of glucose metabolized, compared to the 2 moles of ATP produced by anaerobic glycolysis. The following sections review the basics of cellular energy metabolism and several important xenobiotics that affect these critical metabolic functions (Table 13–3).^{24,45}

TABLE 13–3. Inhibitors of Glucose Metabolism and ATP Synthesis

<i>Step/Location</i>	<i>Action</i>	<i>Examples</i>
Glycolysis	Inhibits NADH production	Iodoacetate (at GAPDH) NO ⁺ (at GAPDH)
	Bypasses ATP producing step	Arsenate, As ³⁺
Gluconeogenesis	Inhibits NADH production	4-(Dimethylamino)phenol <i>p</i> -benzoquinone Hypoglycin A
Fatty acid metabolism	Inhibits NADH production	Aflatoxin Amiodarone Hypoglycin Perhexiline Protease inhibitors Salicylates Tetracycline Valproic acid
Citric Acid Cycle	Inhibits NADH production	Arsenite, As ³⁺ <i>p</i> -Benzoquinone Fluoroacetate
Electron-transport chain at complex I	Inhibits electron transport	MPP ⁺ Paraquat Rotenone
Electron-transport chain at complex III	Inhibits electron transport	Antimycin-A Fusiculosin Cations: Zn ²⁺ , Hg ²⁺ , Cu ²⁺ , and Cd ²⁺ Substituted phenols (pentachlorophenol and dinitrophenol) (also uncouplers)

Electron-transport chain at complex IV	Inhibits electron transport	Azide Carbon monoxide Cyanide Formate Hydrogen sulfide Nitric oxide Phosphine Protamine
Electron-transport chain at ATP synthase	Inhibits ATP production	Arsenate, As^{3+} Mycotoxins (numerous, including oligomycin) Organic chlorines (DDT and chlordane) Organotin (cyhexatin) Paraquat
Mitochondria ADP/ATP antiporter	Disrupts the movement of ADP into and ATP out of the mitochondria at the ADP/ATP antiporter	Atractyloside DDT Free fatty acids
Mitochondria inner membrane	Uncouples oxidative phosphorylation by disrupting the proton gradient → stops proton flow at ATP synthase → stops ATP synthesis	Substituted phenols (pentachlorophenol and dinitrophenol) Lipophilic amines (amiodarone, perhexiline, buprenorphine) Benzonitrile Thiadiazole herbicides NSAIDs with ionizable groups (salicylates, diclofenac, indomethacin, piroxicam) Valinomycin Chlordane
Mitochondria inner membrane	Diverts electrons to alternate pathways (vs. to the electron-transport chain)	Doxorubicin MPP ⁺ Naphthoquinones (menadione) N-nitrosoamines Paraquat

GAPDH = glyceraldehyde 3-phosphate dehydrogenase; MPP⁺ = 1-methyl-4-phenylpyridinium.

Glycolysis

Glycolysis is the first biochemical pathway in the metabolism of glucose. Other sugars enter this pathway after conversion to glycolytic intermediates (Fig. 13–6). The glycolytic process converts one molecule of glucose to two of pyruvate plus two molecules of ATP plus two molecules of NADH. Pyruvate may follow many paths. Under anaerobic conditions, the two pyruvate molecules produced from one glucose molecule are reduced by lactate dehydrogenase to two lactate molecules in an NADH-requiring step that regenerates NAD^+ . Thus, anaerobic glycolysis yields two molecules of lactate plus two molecules of ATP. When NAD^+ and oxygen are available, pyruvate is transported from the cytosol into the mitochondria where it enters the citric acid cycle by being converted by pyruvate decarboxylase to acetyl-CoA (Fig. 13–3).^{24,45} In energy-rich conditions, pyruvate is used in fatty acid synthesis, whereas in energy-poor situations, it is used in gluconeogenesis.

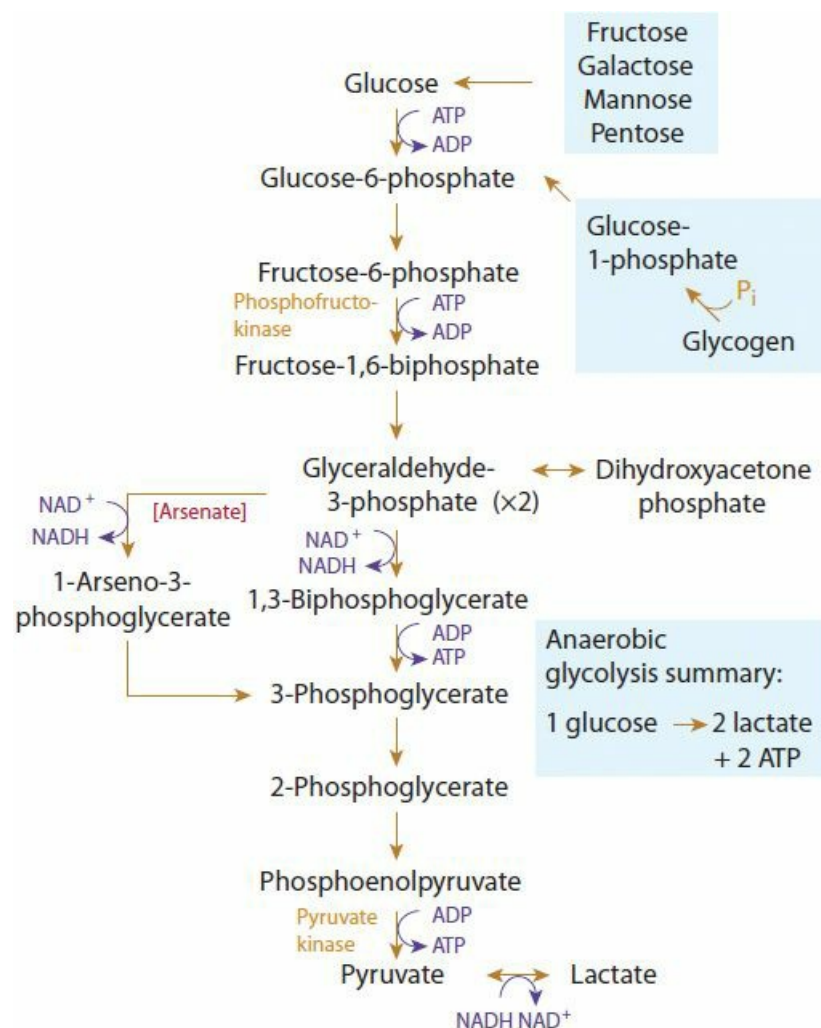


FIGURE 13–6. During glycolysis, the anaerobic metabolism of one mole of glucose to two moles of pyruvate results in the net production of two moles of ATP. Arsenate (As^{5+}) results in the creation of an unstable intermediary that bypasses a step that typically creates one of those moles of ATP. Pyruvate kinase and phosphofructokinase, the enzymes whose activities are regulated by glucagon via cyclic adenosine monophosphate–dependent phosphokinase, are shown.

Arsenate (As^{5+}) affects the glycolytic step where 3-phosphoglyceraldehydeshydrogenase (3-PGA) catalyzes the oxidation of glyceraldehyde-3-phosphate to 1,3-diphosphoglycerate, a reaction that preserves a high-energy phosphate bond used to synthesize ATP in the next step of glycolysis (Fig. 13–6).³⁶ Arsenate acts as an analog of phosphate at this step, resulting in an unstable arsenate intermediate that is rapidly hydrolyzed to 3-phosphoglycerate. While glycolysis continues, there is the loss of ATP synthesis because 1,3 biphosphoglycerate is not made.³⁶

Citric Acid Cycle

The citric acid cycle uses acetyl-CoA derived from glycolysis, fat, or protein to regenerate NADH from NAD^+ . The cycle is a major source of electrons (in the form of NADH) and is critical to the aerobic production of ATP (Fig. 13–3). Each acetyl-CoA molecule that is oxidized within the citric acid cycle ultimately forms one molecule each of CO_2 and guanosine triphosphate (GTP), and more importantly, three molecules of NADH and one molecule of reduced flavin adenine dinucleotide (FADH_2), which enter the electron transport chain, producing a total of 12 molecules of ATP. In addition, the citric acid cycle provides important intermediates for amino acid synthesis and for gluconeogenesis.⁴⁵

Various xenobiotics inhibit the citric acid cycle. The rodenticides, sodium fluoroacetate and fluoroacetamide, are combined with coenzyme A, CoASH, to create fluoroacetyl CoA (FACoA). The FACoA substitutes for acetyl CoA, entering the TCA cycle by condensation with oxaloacetate to form fluorocitrate. Fluorocitrate metabolism results in a metabolite that blocks aconitase within the cycle, resulting in citrate accumulation and the termination of oxidative metabolism (Fig. 13–3) (Chap. 115).

Thiamine is an important cofactor for two citric acid cycle enzymes: the conversion of pyruvate to acetyl-CoA by pyruvate decarboxylase and for the conversion of α -ketoglutarate to succinyl-CoA by α -ketoglutarate dehydrogenase (Fig. 13–3).²⁴ The life-threatening effects of thiamine deficiency are likely related to impairment of these enzyme functions (Antidotes in Depth: A24). Arsenite (As^{3+}) inhibits these thiamine-dependent enzymes within the citric acid cycle.⁶⁹

The Electron Transport Chain

The electron transport chain is the location where the “phosphorylation” of oxidative phosphorylation occurs. Oxidative phosphorylation is the creation of high-energy bonds by phosphorylation of ADP to ATP, “coupled” to the transfer of electrons from reduced coenzymes to molecular oxygen via the electron transport chain. The success of aerobic metabolism requires the disposal of electrons within NADH and FADH, generated by oxidative metabolism within glycolysis and the citric acid cycle. The electron transport chain consists of a series of cytochrome–enzyme complexes within the inner mitochondrial membrane (Fig. 13–3). Within these complexes, NADH is split into $\text{NAD}^+ + \text{H}^+ + \text{two electrons}$ at complex I at the beginning of the chain while FADH_2 is split into $\text{FADH} + \text{H}^+ + \text{two electrons}$ at complex II. These reactions have two results. First, the regenerated NAD^+ and FADH are recycled back to the citric acid cycle, enabling oxidative metabolism to continue. Second, these actions provide the energy required to pump protons (H^+) from the mitochondrial matrix into the intermembrane space. This action causes the matrix to become relatively alkaline compared to the now acidified intermembrane space and the creation of a proton gradient across the inner mitochondrial membrane. The final step in the electron flow of oxidative phosphorylation is the reduction of molecular oxygen to water by complex IV, cytochrome a-a_3 (Fig. 13–3).^{24,45} This hydrogen ion gradient provides the energy needed to create the high-energy bonds of ATP at complex V.

Mitochondria oxidize substrates, consume oxygen, and make ATP. Xenobiotics that interrupt oxidative phosphorylation impair ATP production either by inhibiting specific electron chain complexes or by acting as “uncouplers.” Both of these mechanisms result in rapid depletion of cellular energy stores, followed by failure of ATP-dependent active transport pumps, loss of essential electrolyte gradients, and increases in cell volume.²⁵

Inhibitors of specific cytochromes block electron transport and cause an accumulation of reduced intermediates proximal to the site of inhibition. This stops the regeneration of oxidized substrates for the citric acid cycle, particularly NAD^+ and FADH, further impairing oxidative metabolism. Cyanide, carbon monoxide, and hydrogen sulfide block the cytochrome a-a_3 –mediated reduction of O_2 to H_2O . The very dramatic clinical effects of these exposures illustrate the importance of aerobic metabolism (Chap. 126). Other xenobiotics are less commonly associated with inhibition of the electron transport chain (Table 13–3).^{85,89}

Severe metabolic acidosis is a clinical manifestation of xenobiotics that inhibit aerobic respiration. This metabolic acidosis is primarily caused by the accumulation of protons in the mitochondrial matrix that are not used in the production of ATP. While lactic acid accumulates, it is only a marker for metabolic acidosis associated with the impairment of oxidative metabolism.⁷⁴

Xenobiotics that uncouple oxidative phosphorylation, like inhibitors of the electron transport chain, reduce ATP synthesis. However, with uncouplers, protons continue to be pumped into the intermembrane space, electrons continue to flow down the chain to reduce oxygen, and substrate consumption continues. Uncouplers dissipate the proton gradient across the mitochondrial inner membrane by allowing the protons to cross back into the mitochondrial matrix. Since it is the proton gradient that drives the production of ATP at complex V, ATP production is reduced. Thus, oxygen consumption is “uncoupled” from ATP production. The redox energy created by electron transport that cannot be coupled to ATP synthesis is released as heat. Various xenobiotics uncouple ATP synthesis (Table 13–3). A classic one is dinitrophenol, used in the past as an herbicide and as a weight-loss product (Chap. 42). Xenobiotics that are capable of carrying hydrogen ions across membranes are generally lipophilic weak acids. These xenobiotics must have an acid-dissociable group to carry the proton and a bulky lipophilic group to cross a membrane.⁴⁷ Dinitrophenol is able to carry its proton from the cytosol into the more alkaline mitochondrial matrix where it dissociates, acidifying the matrix and destroying the proton gradient across the inner mitochondrial membrane. Interestingly, the phenolate anion of dinitrophenol is relatively lipophilic and can cross back out to the cytosol where it gains a new proton and starts the process over again. Long-chain fatty acids uncouple oxidative phosphorylation by a similar mechanism.^{47,89} Fatal exposures to dinitrophenol and to pentachlorophenol, a wood preservative, are associated with severe hyperthermia attributed to heat generation by uncoupled oxidative phosphorylation.⁶⁸ The hyperthermia and acidosis associated with severe salicylate poisoning are attributed to its uncoupling of oxidative phosphorylation.⁸¹

Hexose Monophosphate Shunt

The hexose monophosphate shunt provides the only source of cellular NADPH. NADPH is used in biosynthetic reactions, particularly fatty acid synthesis, and is an important source of reducing power for the maintenance of sulfhydryl groups that protect the cell from free radical injury.^{7,37} As noted earlier, G6PD is a key enzyme in the pathway (Fig. 13–7). Reduced glutathione, which is quantitatively the most important antioxidant in cells, depends on the availability of NADPH. RBCs are especially vulnerable to deficiency of NADPH, which results in hemolysis during oxidative stress.

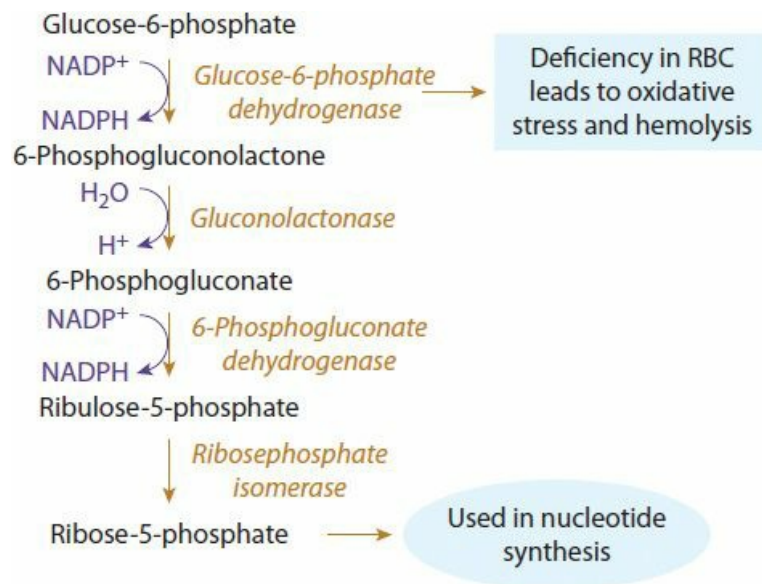


FIGURE 13–7. The oxidation reactions of the hexose monophosphate shunt are an important source of NADPH for reductive biosynthesis and for protection of cells against oxidative stress. Deficiency of glucose-6-phosphate dehydrogenase, the first enzyme in the pathway, may result in red blood cell (RBC) hemolysis during oxidative stress.

Another manifestation of oxidative stress in RBCs is the oxidation of the iron in hemoglobin from Fe^{2+} to Fe^{3+} , producing methemoglobin that occurs both spontaneously and as a response to xenobiotics such as nitrites and aminophenols. Because most reduction of methemoglobin is done by NADH-dependent methemoglobin reductase, which is not deficient in persons who lack G6PD, such persons do not develop methemoglobinemia under normal circumstances. However, when oxidative stress is severe and methemoglobinemia develops, people who have G6PD deficiency have limited ability to use the alternative NADPH-dependent methemoglobin reductase ([Chap. 127](#)).⁸⁶

Gluconeogenesis

Gluconeogenesis facilitates the conversion of amino acids and intermediates of the citric acid cycle to glucose. It occurs primarily in the liver but also in the kidney. It is an important source of glucose during fasting and enables maintenance of glycogen stores. Most of the steps in the synthesis of glucose from pyruvate are simply the reverse of glycolysis, with three irreversible exceptions: (1) the conversion of glucose-6-phosphate to glucose; (2) the conversion of fructose-1,6-diphosphate to fructose-6-phosphate; and (3) the synthesis of phosphoenolpyruvate from pyruvate. The synthesis of phosphoenolpyruvate from pyruvate is especially complex. Pyruvate is first converted to oxaloacetate within the mitochondria; then to malate, which is transported out of the mitochondria and converted in the cytosol back to oxaloacetate; and then to phosphoenolpyruvate ([Fig. 13–8](#)). Certain amino acids—notably alanine, glutamate, and aspartate—are readily converted to citric acid cycle intermediates and can be used in the synthesis of glucose through this cycle.⁴⁵ Glycerol, produced by the breakdown of triglycerides in adipose tissue, is another substrate for gluconeogenesis.

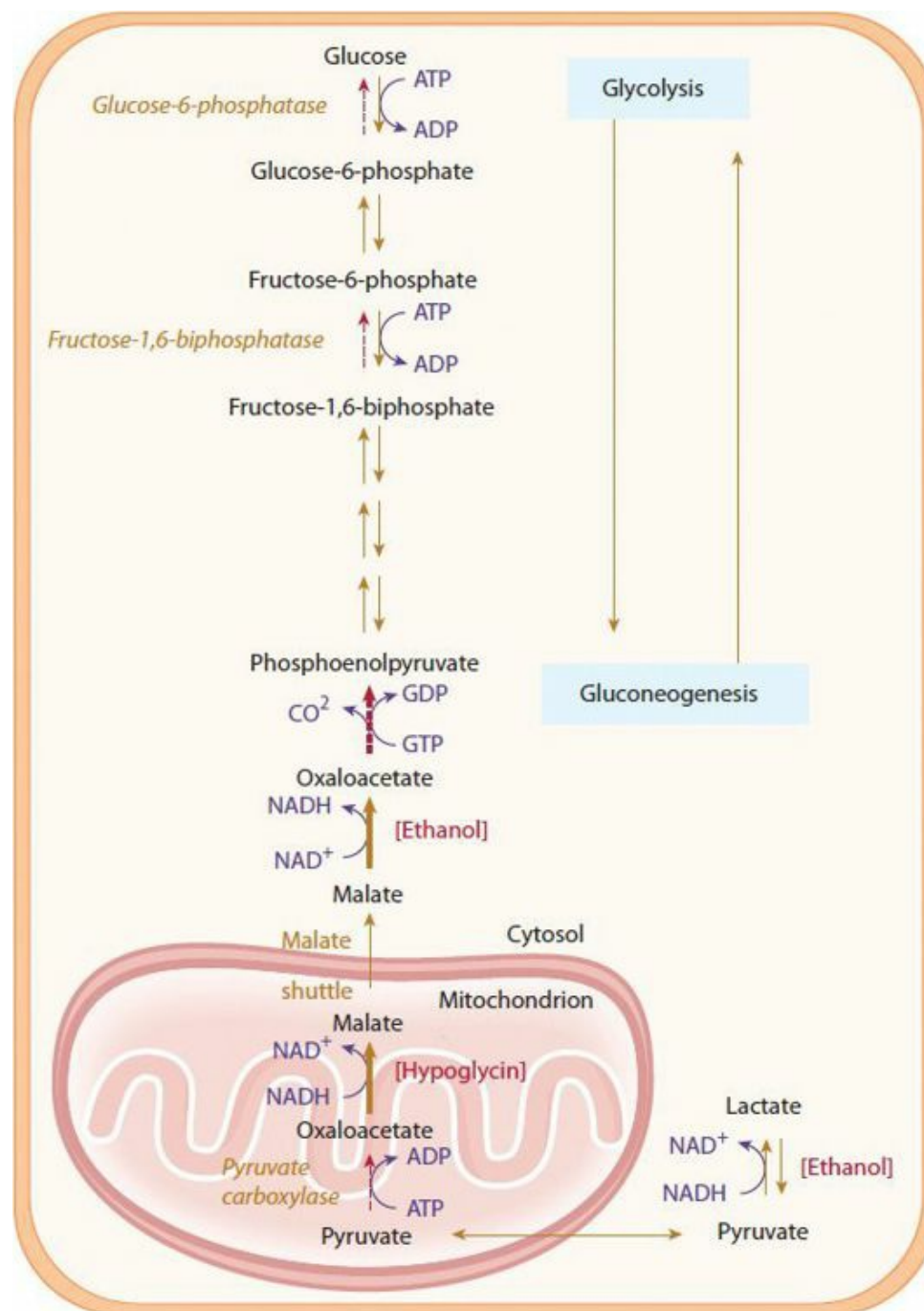


FIGURE 13–8. Gluconeogenesis reverses the steps of glycolysis, with the exception of the bypass of the three irreversible steps shown. The step from pyruvate to phosphoenolpyruvate involves both cytosolic and mitochondrial reactions that use ATP. Hypoglycin A inhibits the intramitochondrial conversion of oxaloacetate to malate by depleting NADH through interference with β -oxidation of fatty acids. Ethanol decreases cytosolic supplies of NAD^+ .

The regulation of gluconeogenesis is opposite to that of glycolysis, stimulated by glucagon and catecholamines but inhibited by insulin. Gluconeogenesis requires the cytosolic NAD^+ and mitochondrial NADH. It is impaired by processes that increase the cytosol-reducing potential as measured by the cytosol NADH/NAD^+ ratio (see discussion below).

A number of xenobiotics impair gluconeogenesis, resulting in hypoglycemia when glycogen stores are depleted (Table 13–3). Hypoglycin A, an unusual amino acid found in unripe ackee fruit that is the cause of Jamaican vomiting sickness, produces profound hypoglycemia.⁸¹ Its metabolite methylenecyclopropylacetic acid (MCPA) indirectly inhibits gluconeogenesis by blocking the oxidation of long-chain fatty acids, an important source of NADH in mitochondria. It also inhibits the metabolism of several glycogenic amino acids, including leucine, isoleucine, and tryptophan, and blocks their entrance into the citric acid cycle. MCPA may also prevent the transport of malate out of the mitochondria.^{72,81,82} Hypoglycemia also occurs in fasting patients with elevated ethanol concentrations.^{3,27,46} This is likely a result of the impairment of gluconeogenesis by the increased cytosolic $\text{NADH}:\text{NAD}^+$ ratio associated with the metabolism of ethanol. This inhibits the two cytosolic steps that require NAD^+ —the conversions of lactate to pyruvate and of malate to oxaloacetate.^{2,46}

Fatty Acid Metabolism

Fatty acid metabolism occurs primarily in hepatocytes. Fatty acids mobilized in adipose tissue enter hepatocytes by passive diffusion. Fatty acid synthesis is stimulated by insulin and inhibited by glucagon and epinephrine. Acetyl-CoA is the primary building block of free fatty acids (FFAs). In energy-replete cells, fatty acids are combined with glycerol phosphate to form triacylglycerol (triglycerides), the first step in the synthesis of fat for storage. Hepatic triglycerides are bound to lipoprotein to form very-low-density lipoprotein and then transported and stored in adipocytes. When hepatocytes are energy depleted, triglycerides are broken down to FFAs and glycerol. This process is suppressed by insulin but supported by glucagon or epinephrine. FFAs undergo β -oxidation in the mitochondria, a process that breaks the FFA into acetyl-CoA molecules that can then enter the citric acid cycle. FFAs require activation before transport into the mitochondria. This is accomplished by acylcoenzyme A (acyl-CoA) synthetase, which adds a CoA group to the FFA in an energy-dependent synthetic reaction. These are transported into the mitochondria by a process that utilizes cyclical binding to carnitine, a “carnitine shuttle” (Fig. 13–3). Once inside the mitochondria, FFAs are converted to acetyl-CoA by β -oxidation, involving the sequential removal of two-carbon fragments, each time acting at the second carbon (the β carbon) position of the fatty acid. Each two-carbon molecule removed from the FFA produces one NADH and one FADH_2 , which are oxidized in the electron transport chain, and one mole of acetyl-CoA, which enters the citric acid cycle. This process produces 1.3 times more ATP per molecule of carbon metabolized than does the oxidative metabolism of glucose or other carbohydrates.⁴⁵

Many xenobiotics interrupt fatty acid metabolism at various steps, resulting in accumulation of triglycerides in the liver (Table 13–3; Fig. 13–9). The mechanisms of disruption of fatty acid metabolism are poorly defined.¹⁵ Some xenobiotics, including ethanol, hypoglycin, and nucleoside analogs, inhibit β -oxidation, at least indirectly, through effects on NADH concentrations. Protease inhibitors are associated with a syndrome of peripheral fat wasting, central adiposity, hyperlipidemia, and insulin resistance.

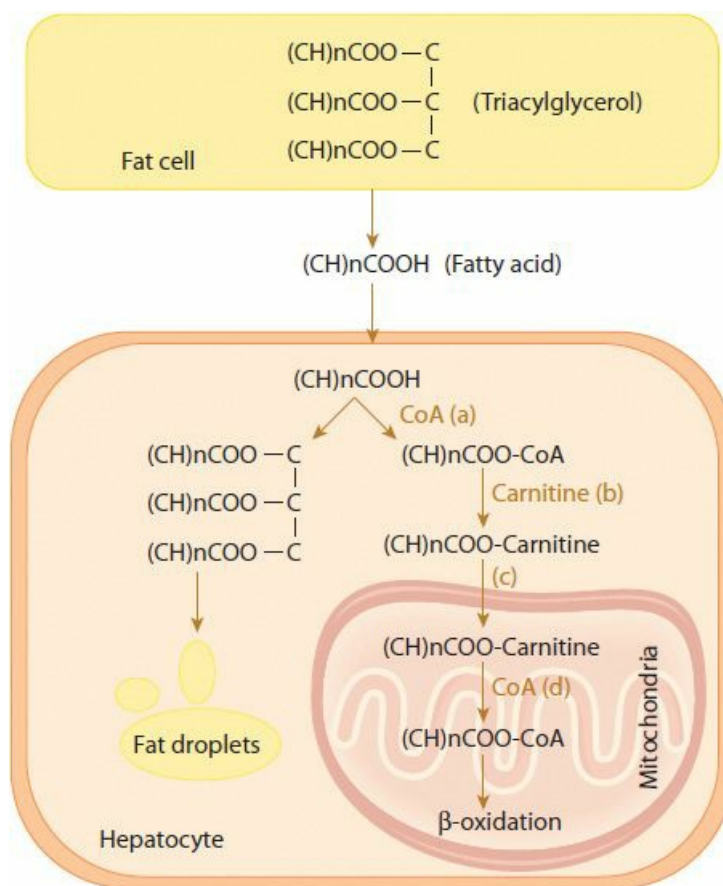


FIGURE 13–9. Steatosis, an accumulation of fat, results when xenobiotics interfere with the oxidation of fatty acids. Other processes that increase intracellular accumulation of fat include impaired lipoprotein synthesis, impaired lipoprotein release, increased mobilization of free fatty acids, increased uptake of circulating lipids, and increased production of triglycerides. β -Oxidation occurs in the mitochondria. The carnitine shuttle is used to transport long-chain fatty acids from the cellular cytosol across the mitochondrial membrane. The enzymes involved are (a) acyl-CoA synthetase, (b) carnitine palmitoyltransferase I, (c) carnitine acylcarnitine translocase, and (d) carnitine palmitoyltransferase II. Acyl-CoA is the intramitochondrial substrate for β -oxidation. Potential mechanisms of inhibition of β -oxidation include induction of carnitine deficiency, inhibition of the transferase or translocase, and increased NADH:NAD⁺ ratio via increased use of NAD⁺ or by inhibition of NADH use. The specific site of action is not defined for many toxins that cause steatosis.

The condition of alcoholic ketoacidosis is related in part to inhibition of gluconeogenesis in the alcoholic patient and in part to an exuberant response to nutritional needs by the fatty acid machinery. Vomiting in the alcoholic patient leads to

decreased intake of carbohydrate, which stimulates a starvation response with increases in serum glucagon, cortisol, growth hormone, and epinephrine concentrations, and decreases in serum insulin. When the need for carbohydrate is not met by gluconeogenesis, lipolysis, which is normally inhibited by insulin, is intensified and fatty acid mobilization progresses. Glucagon stimulates mitochondrial carnitine acyltransferase, and β -oxidation of fatty acids is increased. The increased mitochondrial NADH:NAD⁺ ratio favors the production of β -hydroxybutyrate over acetoacetate, its oxidized form. The administration of fluids, dextrose, and thiamine to the alcoholic patient leads to correction of this process.⁵³

SUMMARY

- Biotransformation is a complex process, involving numerous enzyme systems, that usually detoxifies xenobiotics, however, “metabolic activation” may occur.
- Phase I reactions add functional groups to lipophilic xenobiotics to enhance their reactivity, preparing them for further detoxification by synthetic phase II reactions that enhance hydrophilicity and renal elimination.
- The phase I cytochrome P450 (CYP) enzymes biotransform most xenobiotics; CYP3A4 is the most abundant one, metabolizing 50% to 60% of all pharmaceuticals.
- CYP enzyme activity is quite variable due to genetic polymorphisms, genetic changes that exist in at least 1% of the human population. Enzyme activity also varies because of induction and inhibition.
- The most common method of induction is a nuclear receptor-mediated increase in gene transcription. Inhibition of CYP enzymes is the most common cause of harmful drug–drug interactions, the most common type being competitive, where the substrate and inhibitor both bind the active site of the enzyme.
- Drug disposition is also effected by membrane transporter (MT) proteins that mediate the cellular uptake and efflux of xenobiotics.
- P-glycoprotein is an MT protein that mediates the efflux of xenobiotics from the apical (luminal) membrane of intestinal enterocytes.

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APPENDIX

Cytochrome P450 Substrates, Inhibitors, and Inducers¹

	SUBSTRATES		INHIBITORS		INDUCERS
1A2	Analgesics Acetaminophen Naproxen Antidepressants Amitriptyline Clomipramine Duloxetine ¹ Fluvoxamine Imipramine Mirtazapine Antipsychotics Clozapine Haloperidol Olanzapine	Cardiovascular Metoprolol Propranolol Verapamil Hormones Estradiol Flutamide Other Medications Caffeine Cyclobenzaprine Ondansetron Theophylline ¹ Tizanidine ¹ Warfarin-R Zolmitriptan	Antibiotics (Fluoroquinolones) Ciprofloxacin ¹ Norfloxacin Antibiotics (Macrolides) Clarithromycin Erythromycin Troleandomycin Antidepressants Duloxetine Fluvoxamine ¹	Cardiovascular Amiodarone Metoprolol Verapamil Others Acyclovir Cimetidine Famotidine Grapefruit juice	Antiepileptics Carbamazepine Phenytoin Proton Pump Inhibitors Lansoprazole ¹ Omeprazole ¹ Others Nafcillin Polycyclic hydrocarbons (char-grilled meat, cigarette smoke) Rifampicin Rifampin Ritonavir ¹
3A4	Antibiotics Clarithromycin Dapsone Erythromycin Rifabutin Telithromycin Antidepressants (Minor for most) Amitriptyline Bupropion ¹ Citalopram Clomipramine Escitalopram Imipramine Mirtazapine Nefazodone Sertraline Trazodone Antidysrhythmics Amiodarone Disopyramide Quinidine ¹ Antifungals Itraconazole Ketoconazole Voriconazole Antihistamines Chlorpheniramine Desloratadine Loratadine	Immune Modulators Cyclosporine ¹ Sirolimus ¹ Tacrolimus ¹ Tamoxifen Opioids Alfentanil ¹ Buprenorphine Codeine Dextromethorphan Fentanyl ¹ Meperidine Methadone Morphine Oxycodone Sufentanil Tramadol Protease Inhibitors Indinavir Nelfinavir Ritonavir Saquinavir ¹ Proton Pump Inhibitors (Minor for most) Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole HMG CoA Reductase Inhibitors Atorvastatin Lovastatin ¹ Simvastatin ¹	Antidepressants Fluoxetine Fluvoxamine Nefazodone ¹ Nortriptyline Sertraline Antibiotics (Macrolides) Clarithromycin ¹ Erythromycin Telithromycin ¹ Antibiotics (Other) Chloramphenicol Gprofloxacin Isoniazid Norfloxacin Antifungals (Azoles) Fluconazole Itraconazole ¹ Ketoconazole ¹ Posaconazole ¹ Voriconazole ¹	Calcium Blockers Diltiazem Verapamil Protease Inhibitors Amprenavir Atazanavir ¹ Fosamprenavir Indinavir ¹ Nelfinavir ¹ Ritonavir ¹ Saquinavir ¹ Hepatitis C Medications Boceprevir ¹ Telaprevir ¹ Others Amiodarone Cimetidine Cocaine Cyclosporine Ergotamines Felbamate Grapefruit juice	Antibiotics Rifabutin Rifampicin Rifampin ¹ Rifapentine Anti-HIV Medications Amprenavir Efavirenz Nelfinavir Nevirapine Ritonavir ¹ Antiepileptics Carbamazepine ¹ Felbamate Oxcarbazepine Phenytoin ¹ Topiramate Steroids Desamethasone Methylprednisolone Prednisolone Others St. John's wort ¹

	Antipsychotics (Minor for most) Aripiprazole Clozapine Haloperidol Quetiapine Risperidone Thioridazine Ziprasidone Benzodiazepines Alprazolam Clonazepam Diazepam Midazolam [†] Triazolam [†] Calcium Blockers Amlodipine Diltiazem Felodipine [†] Nicardipine Nifedipine Nimodipine Nisoldipine Verapamil	Steroids and Hormones Desamethasone Estradiol Fluticasone [†] Hydrocortisone Methylprednisolone Prednisone Progesterone Hepatitis C Medications Boceprevir Telaprevir Others Carbamazepine Osipride [†] Cyclobenzaprine Diclofenac Ergotamines [†] Losartan Ondansetron Pioglitazone Propranolol Salmeterol Sildenafil [†] Vardenafil [†] Voriconazole Warfarin-R Zaleplon Zolpidem			
2C9	Angiotensin II Receptor Blockers Ibuprofen Losartan Insulin Secretagogues Chlorpropamide Glimepiride Glipizide Glyburide Tolbutamide NSAIDs Celecoxib Diclofenac Flurbiprofen Ibuprofen Indomethacin Meloxicam Naproxen Piroxicam	Others Amitriptyline Cyclophosphamide Fluoxetine Fluvastatin Phenobarbital Phenytoin [†] Pioglitazone Rosuvastatin Sertraline Tamoxifen Voriconazole Warfarin-S	Antibiotics (Macrolides) Clarithromycin Erythromycin Troleandomycin Antibiotics (Other) Isoniazid Metronidazole Sulfamethoxazole Antidepressants Fluoxetine Fluvoxamine Paroxetine Sertraline	Antifungals (Azoles) Fluconazole [†] Itraconazole Ketoconazole Voriconazole Others Amiodarone Cimetidine Grapefruit juice Ritonavir [†] Valproic acid	Antiepileptics Carbamazepine Phenobarbital Phenytoin Others Nefinavir Rifampicin Rilampin [†] Rilapentine Ritonavir [†] St. John's Wort
2C19	Antidepressants Amitriptyline Citalopram Clomipramine Desipramine Doxepin Escitalopram Fluoxetine Imipramine Anticonvulsants Diazepam Phenobarbital Phenytoin	Proton Pump Inhibitors (Major for most) Esomeprazole Lansoprazole Omeprazole [†] Pantoprazole Rabeprazole Others Atomoxetine Carisoprodol Clopidothel Cyclophosphamide Indomethacin Methadone Nefinavir Olanzapine Progesterone Propranolol Voriconazole Warfarin-R	Antibiotics (Macrolides) Clarithromycin Erythromycin Troleandomycin Antidepressants (SSRIs) Citalopram Fluoxetine Fluvoxamine [†] Paroxetine Sertraline Antifungals (Azoles) Fluconazole [†] Ketoconazole Voriconazole	Anticonvulsants Felbamate Oxcarbazepine Topiramate Others Chloramphenicol Cimetidine Grapefruit juice Indomethacin Isoniazid Ritonavir [†] Ticlopidine [†] Proton Pump Inhibitors Lansoprazole Omeprazole [†] Pantoprazole Rabeprazole	Antiepileptics Carbamazepine Phenobarbital Phenytoin Others Prednisone Rifampicin Rilampin [†] Rilapentine Ritonavir [†] St. John's Wort

2D6	Antidepressants (SSRIs) Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline Antidepressants (Other) (Major for most) Amitriptyline Clomipramine Desipramine ¹ Doxepin Duloxetine Escitalopram Imipramine Maprotiline Mirtazapine Nortriptyline Venlafaxine Antidysrhythmics Flecainide Mexiletine Quinidine Antipsychotics (Major for most) Aripiprazole Chlorpromazine Fluphenazine Haloperidol Perphenazine Promethazine Risperidone Thioridazine ¹	Antihistamines Chlorpheniramine Desloratadine Diphenhydramine Loratadine β-Adrenergic Antagonists Carvedilol Metoprolol Pindolol Propranolol Timolol Opioids Codeine Dextromethorphan Hydrocodone Oxycodone Others Amphetamine Atomoxetine Cyclobenzaprine Debrisoquine Metoclopramide Ondansetron Tamoxifen Tramadol	Antidepressants Bupropion ¹ Citalopram Duloxetine Escitalopram Fluoxetine ¹ Paroxetine ¹ Sertraline Antihistamines Chlorpheniramine Cimetidine Diphenhydramine Hydroxyzine Ranitidine Antipsychotics Chlorpromazine Haloperidol Perphenazine Promethazine Thioridazine	Others Amiodarone Celecoxib Chloramphenicol Chloroquine Cocaine Doxorubicin Methadone Quinidine ¹ Ritonavir ¹ Ticlopidine	Dexamethasone Rifampicin Rifampin ¹ Ritonavir ¹ Tramadol
2E1	Others Acetaminophen Chlorzoxazone Ethanol Isoniazid Theophylline	Inhaled Anesthetics Enflurane Isoflurane Halothane Methoxyflurane	Disulfiram	Others Ethanol Isoniazid St. John's wort	

¹This table list is not complete and may reflect some variation in author opinions as to whether a xenobiotic is a substrate, inhibitor, or inducer. ²Substrate is sensitive; area under the concentration vs. time curve (AUC) values have been shown to increase 5-fold or more when coadministered with a known CYP1A inhibitor. ³Substrate has a narrow therapeutic range and safety concerns occur when coadministered with an inhibitor. ⁴A strong inhibitor (at least a 5-fold increase in AUC or greater than 80% decrease in clearance). ⁵A strong inducer (at least a 4-fold increase in enzyme activity). ⁶Ritonavir has paradoxical dose and time-dependent inhibitory and induction effects.

NSAID = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor.

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14 NEUROTRANSMITTERS AND NEUROMODULATORS

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This chapter reviews the normal physiology of neurotransmission, the molecular action and biochemistry of several major neurotransmitters and their receptors, and the toxicologic mechanisms by which numerous xenobiotics act at the molecular level. Acetylcholine, norepinephrine, epinephrine, dopamine, serotonin, γ -aminobutyric acid (GABA), γ -hydroxybutyrate (GHB), glycine, glutamate, and adenosine are neurotransmitters and neuromodulators of toxicologic interest discussed herein.

When examining molecular actions of xenobiotics on neurotransmitter systems, it quickly becomes apparent that substances rarely possess single pharmacologic actions. As examples, doxepin, in part, antagonizes voltage-gated sodium channels, histaminic H_1 and H_2 receptors, α -adrenergic receptors, muscarinic acetylcholine receptors, dopamine D_2 receptors, and GABA_A receptors; prevents potassium efflux; and inhibits norepinephrine, serotonin, and adenosine uptake. Similarly, carbamazepine blocks voltage-gated sodium channels; inhibits uptake of norepinephrine, adenosine, and serotonin; antagonizes adenosine and muscarinic receptors; activates GABA_B receptors; and binds to benzodiazepine-binding sites on mitochondria. For obvious reasons, then, this chapter cannot include every action of every xenobiotic on the nervous system. Nor is it meant to be a complete discussion of toxic syndromes produced by various xenobiotics, as these are discussed in specific chapters. Rather, this chapter provides a general and basic understanding of mechanisms of action of various xenobiotics affecting neurotransmitter function and receptors, especially in the central nervous system. With this focus, the clinical effects produced are more easily understood and predicted, and specific treatments can be rationally undertaken. Given the complexity of the nervous system and the numerous actions of a given xenobiotic, it is not always clear which neurotransmitter system is producing an observed effect. Therefore, specific xenobiotics may be found in several sections. An attempt is made to note the major mechanism of action of a xenobiotic, although other actions are noted when possible.

NEURON PHYSIOLOGY AND NEUROTRANSMISSION

Membrane Potentials, Ion Channels, and Nerve Conduction

Membrane-bound sodium-potassium adenosine triphosphatase (ATPase) moves three sodium ions (Na^+) from inside the cell to the interstitial space while pumping two potassium ions (K^+) into the cell. Because the cell membrane is not freely permeable to large, negatively charged intracellular molecules, such as proteins, an equilibrium results in which the inside of the neuron is negative with respect to the outside. This typical neuronal resting membrane potential is -65 mV.

Sodium, calcium (Ca^{2+}), K^+ , and chloride (Cl^-) ions move into and out of neurons through ion channels. When moving through ion channels, which are long polypeptides comprising several subunits that span the plasma membrane multiple times, ions always move passively down electrochemical gradients. Many different ion channels are structurally comparable, sharing similar amino acid sequences.¹⁹ Channels for a specific ion can also vary in structure, depending on the specific subunits that have combined to form the channel. Because of structural similarity of different channels, it is not surprising that many xenobiotics are able to bind to more than one type of ion channel.

More than 40 different ion channels have been described in various nerve terminals,¹²⁸ and it is estimated that a human being contains hundreds of different varieties of ion channels for Na^+ , Cl^- , Ca^{2+} , and K^+ . Most ion channels fall into two general classes: voltage-gated (voltage-dependent) ion channels and ligand-gated ion channels.¹²⁸ Voltage-gated channels open or close in response to changes in membrane potential. Ligand-gated channels open or close when a ligand (eg, neurotransmitter) binds to and changes the conformation of the channel.

A commonly accepted model describes voltage-gated Na^+ channels and some other voltage-gated ion channels in three possible states. Using Na^+ channels as an example, the Na^+ channel is closed at rest and impermeable to Na^+ , preventing Na^+ from moving into the cell. When the channel undergoes activation, the channel opens, allowing Na^+ to move

intracellularly, down its electrochemical gradient. The channel then undergoes a third conformational change by becoming inactivated, preventing further influx of Na^+ . The term recovery describes the conversion of inactive channels back to the resting state, a process that requires repolarization of the cell membrane.

Depolarization of a neuron usually results from an initial inward flux of cations (Na^+ or Ca^{2+}), or prevention of K^+ efflux. The fall in membrane potential (movement toward 0 mV) results in further activation of these voltage-dependent Na^+ channels, allowing yet a greater influx of cations. When the membrane potential falls to threshold, Na^+ channels are activated en masse, and there is a large influx of Na^+ .

Depolarization of a segment of the neurolemma causes the adjacent neuronal membrane to reach threshold, resulting in the propagation of an action potential down the neuron. Sodium channel activation is quickly followed by inactivation, ending depolarization. Over the short-term, repolarization of the neuron subsequently occurs mainly from efflux of K^+ and some influx of Cl^- .

Neurotransmitter Release

Neurotransmitters are chemicals that are released from nerve endings into the synapse, where they produce effects by binding to receptors on postsynaptic or presynaptic cell membranes. The receptors may be on other neurons or effector organs such as smooth muscle. Concentrations of neurotransmitters in cytoplasm are usually low because of rapid enzymatic degradation and diffusion out of the nerve ending. To provide a source of neurotransmitters that is protected from degradation and that can rapidly be released, neurotransmitters are concentrated and stored within vesicles in the nerve terminal. As a wave of depolarization from Na^+ influx reaches the nerve ending, the membrane depolarization causes voltage-gated Ca^{2+} channels to open, allowing Ca^{2+} to move rapidly into the cell. This influx of Ca^{2+} triggers exocytosis of vesicle contents into the synapse via the *snare complex*. The voltage-gated Ca^{2+} channels responsible for inward Ca^{2+} currents that trigger neurotransmitter release are members of the Ca_v2 subfamily (N, P/Q, and R subtypes).^{134,164}

Ziconotide, a derivative of a conotoxin that is used for analgesia, blocks N-type Ca^{2+} channels on nociceptive neurons in the dorsal root to prevent neurotransmitter release. Cardiovascular calcium channel blockers used in clinical practice do not block these subtypes of voltage-dependent Ca^{2+} channels, but block the L-subtype. However, L-subtype Ca^{2+} channels reside elsewhere on neurons, thus explaining the ability of traditional Ca^{2+} channel blockers to affect some neurologic functions.

Vesicle Transport of Neurotransmitters

The pH inside neurotransmitter vesicles is about 5.5, which is lower than that in the cytoplasm. A vacuolar ATPase in the vesicular membrane is responsible for movement of protons into the vesicular lumen at the expense of ATP hydrolysis. Vesicular uptake pumps (transporters) that move neurotransmitters or their precursors from the cytoplasm into the vesicle lumen, in turn, are powered by the electrochemical H^+ gradient. That is, the movement of an H^+ out of the vesicle into the cytoplasm is coupled to the movement of a neurotransmitter from the cytoplasm into the vesicle.

Various vesicular transporters for neurotransmitters have been sequenced to date. VGAT transports GABA and glycine. VMAT2 transports all three monoamines, dopamine, norepinephrine, and serotonin (VMAT1 transports monoamines into non-neuronal vesicles). VACHT is responsible for acetylcholine (ACh) transport, and 3 VGluTs (VGluT1-3) move glutamate into vesicles.

Neurotransmitters are confined within the vesicle, to a great extent, by ion trapping, as they are more ionized and less able to diffuse back out of the vesicle at the lower pH. Anything that causes a decrease in the pH gradient across the vesicle membrane results in the movement of neurotransmitters into the cytoplasm.¹⁹⁷ For example, amphetamines move into vesicles, where they buffer protons, causing the movement of monoamine neurotransmitters out of vesicles, and raising cytoplasmic concentrations of neurotransmitters, and ultimately raising the synaptic monoamine concentration.^{197,198}

Neurotransmitter Reuptake

Although acetylcholine is inactivated in the synapse by enzymatic degradation, other neurotransmitters have their synaptic effects terminated by active uptake into neurons or glial cells. These plasma membrane neurotransmitter transporters are distinct from those transporters responsible for movement of neurotransmitters into vesicles. Cell membrane transporters for different neurotransmitters are Na^+ -dependent transport proteins, during which the uptake of neurotransmitters is accompanied by the movement of Na^+ across the synaptic membrane.² These uptake transporters are commonly known as either uptake or reuptake pumps; the term “reuptake” will be used in this chapter for purposes of consistency.

Neurotransmitter reuptake transporters are subdivided into two main families.² One family (SLC6) includes structurally similar uptake pumps for GABA, glycine, norepinephrine, dopamine, and serotonin. They generally comprise 600 to 700 amino acids and form loops spanning the plasma membrane 12 times. Four GABA reuptake transporters (GAT-1 through

GAT-4) transport GABA into neurons and glial cells. DAT, SERT, and NET are responsible for reuptake of dopamine, serotonin, and norepinephrine, respectively. GLYT-1 and GLYT-2 are responsible for glycine uptake into neurons or astrocytes.

The second family (SLC1) comprises five glutamate reuptake transporters (excitatory amino acid transporters {EAATs}), which appear to traverse the plasma membrane 10 times and move glutamate from the synapse into glial cells and neurons.

Several properties make transporter proteins of particular toxicologic significance. First, they are capable of moving neurotransmitters in either direction; when cytoplasmic neurotransmitter concentrations are significantly elevated, neurotransmitters can be transported back into the synapse. Second, these transporters are not always completely specific. For instance, the uptake transporter for norepinephrine can move dopamine and other bioactive amines into the neuron. Third, a xenobiotic that acts at the level of the membrane transporter may affect functions of several different neurotransmitters, depending on its specificity for a particular transporter. As an example, fluoxetine is fairly specific at inhibiting reuptake of serotonin, whereas cocaine inhibits the reuptake of serotonin, norepinephrine, and dopamine.

Neurotransmitter Receptors

Channel Receptors. The first general class of neurotransmitter receptors comprises ligand-gated ion channels (LGICs; channel receptors; ionotropic receptors), in which the receptor for the neurotransmitter is part of an ion channel. These channels comprise multiple subunits that combine in various combinations to create channels that vary in response to a given neurotransmitter or other agonist/antagonist. LGICs for neurotransmitters discussed in this chapter are divided into two main groups, based on structure of subunits and assemblies. Most neurotransmitter LGICs are pentameric and display four transmembrane helices. LGICs for glutamate, however, are tetrameric and comprise three transmembrane helices.¹²⁰

By binding to its LGIC receptor, the neurotransmitter allosterically changes the configuration of the ion channel so that ions traverse the channel in greater quantities per unit time. As an example, the acetylcholine nicotinic receptor at the neuromuscular junction is a ligand-gated Na⁺ channel. When acetylcholine binds to the nicotinic receptor, the channel’s configuration changes, allowing Na⁺ to move into the cell and trigger an action potential. The action potential then propagates down muscle via voltage-gated Na⁺ channels. Table 14–1 lists other examples of channel receptors.

TABLE 14–1. Types of Neurotransmitter and Neuromodulator Receptors	
<i>Ion Channel</i>	<i>G Protein–Coupled Receptor</i>
ACh nicotinic	ACh muscarinic
GABA _A	GABA _B
Glycine (inhibitory)	Dopamine
Glutamate AMPA	Norepinephrine
Glutamate NMDA	5-HT _{1,2,4–7}
Glutamate kainate	Adenosine
5-HT ₃	Glutamate metabotropic

ACh = acetylcholine; AMPA = amino-3-hydroxy-5-methyl-4-isoxazole propionate; GABA = γ-aminobutyric acid; 5-HT = 5-hydroxytryptamine (serotonin); NMDA = N-methyl-D-aspartate.

G Protein–Coupled Receptors. The second general class of neurotransmitter receptors are linked to G proteins, which are part of a superfamily of proteins with guanosine triphosphatase (GTPase) activity responsible for signal transduction across plasma membranes.¹⁸⁷ G proteins comprise three polypeptide subunits: α, β, and γ chains. These chains span the plasma membrane several times, and they associate with a separately transcribed neurotransmitter receptor that spans the cell membrane seven times, with an external binding site for neurotransmitters. Some receptors (eg, GABA_B receptor) coupled to G proteins are obligatory heterodimers comprising two separate proteins, both of which must be present for activity.

Both the α subunit and the β-γ subunits of a G protein may account for activity resulting from a neurotransmitter binding to its receptor. The α chain normally binds guanosine diphosphate (GDP) in the cytoplasm and is inactive. When a neurotransmitter binds to its receptor on the outside of the cell membrane, GDP dissociates from the α chain and guanosine triphosphate (GTP) binds in its place, activating the α subunit. The activated α subunit then dissociates from receptor and from the β and γ chains. Both the activated α subunit and β-γ subunits modulate effectors in the plasma membrane.¹⁸⁷ The effector influenced by α or β-γ subunits may be an enzyme that the subunits stimulate or inhibit (eg, adenylate cyclase) or an ion channel that is opened or closed directly or through other chemical reactions (eg, channel phosphorylation).³² Intrinsic

GTPase activity in the α chain eventually converts the GTP to GDP, inactivating the α subunit and allowing it to reassociate with the β - γ chains and the neurotransmitter receptor, terminating the consequences of neurotransmitter binding.¹⁸⁷

G proteins are mainly categorized by the type of α chain they contain. The three main families of G proteins coupled to neurotransmitter receptors are G_s (containing the α_s subunit), $G_{i/o}$ (containing α_i or α_o), and G_q (or $G_{q/11}$ containing α_q). G_s stimulates membrane-bound adenylate cyclase; activation of a neurotransmitter receptor coupled to G_s causes a rise in intracellular 3',5'-cyclic adenosine monophosphate (cAMP) concentration. Neurotransmitter receptors activating G_i may inhibit adenylate cyclase or modulate K^+ and Ca^{2+} channels. Receptors coupled to G_q act through membrane-bound phospholipase C to increase intracellular calcium concentrations. See Table 14–1 for a list of the neurotransmitter receptors coupled to G proteins. A given neurotransmitter can activate different classes of receptors (eg, ion-channel and G protein) or different types of receptors in the same class. For example, $GABA_A$ receptors are Cl^- channels, whereas $GABA_B$ receptors are coupled to G proteins. Dopamine D_1 -like receptors (D_1 and D_5) are linked to G_s , whereas D_2 -like receptors (D_2 , D_3 , and D_4) are linked to G_i or G_o .

Importantly, a single G protein-coupled receptor may activate more than one type of G protein in the same cell, depending on various circumstances, including duration of receptor activation. Evidence continues to accumulate indicating that G protein-coupled receptors for the same or different neurotransmitters can form both heterodimers and oligomers, resulting in yet more variation in response to neurotransmitter binding. Examples may include combinations of various dopamine receptors, combinations of dopamine and 5-HT receptors, and combinations of dopamine and glutamate receptors.^{135,137,172}

Receptor downregulation occurs at various levels. For example, prolonged receptor activation results in receptor phosphorylation by G protein kinases (GPKs), causing receptor binding to a member of the arrestin family of proteins. This, in turn, prevents further activation of the G protein by the receptor, and eventually triggers receptor endocytosis.^{3,104,183}

Neuronal Excitation and Inhibition

Excitatory neurotransmitters usually act postsynaptically by causing Na^+ or Ca^{2+} influx, or by preventing K^+ efflux, triggering depolarization and an action potential (Fig. 14–1). These effects may be mediated by channel or G protein-coupled receptors.

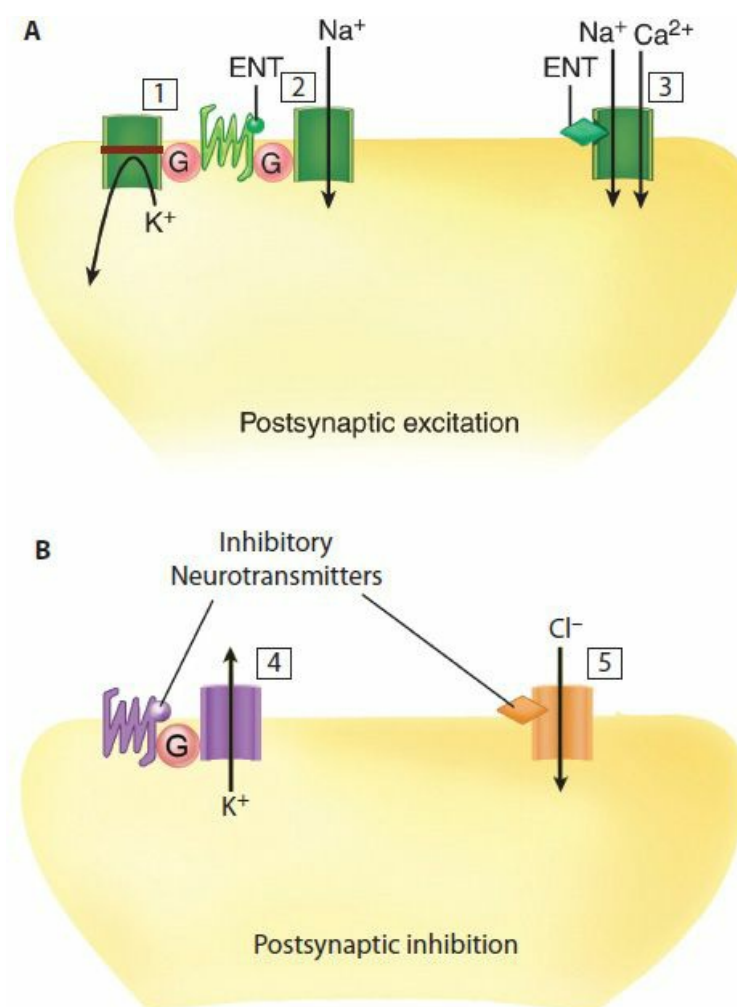


FIGURE 14–1. Common mechanisms of postsynaptic excitation and inhibition. (A) An excitatory neurotransmitter (ENT)

binds to receptors linked to G proteins to prevent K^+ efflux [1] or to allow Na^+ influx [2], producing membrane depolarization. An ENT may bind to and activate a cation channel [3] to allow Na^+ and/or Ca^{2+} influx with resultant membrane depolarization. **(B)** An inhibitory neurotransmitter hyperpolarizes the membrane (makes membrane potential more negative) by binding to receptors linked to G proteins to enhance K^+ efflux [4], or to Cl^- channels to allow Cl^- influx [5]. Some Cl^- channels are regulated by G proteins as well. G = G protein.

Postsynaptic inhibition can be mediated by channel receptors or by receptors coupled to G proteins (Fig. 14–1). Inhibition is usually accomplished by neuronal influx of Cl^- or efflux of K^+ to hyperpolarize the neuron and move membrane potential farther away from threshold, making it more difficult for a given stimulus to depolarize the membrane to threshold voltage.

Presynaptic inhibition, the prevention of neurotransmitter release, is usually mediated by receptors coupled to G proteins. When a neurotransmitter released from a neuron binds to a receptor on that same neuron to limit further neurotransmitter release, the receptor is termed an autoreceptor.^{176,139} Autoreceptors reside on dendrites, cell bodies, axons, and presynaptic terminals. Autoreceptors on dendrites and cell bodies (somatodendritic autoreceptors) usually inhibit further neurotransmitter release by increasing K^+ efflux, thereby hyperpolarizing the neuron away from threshold (Fig. 14–2). However, activation of autoreceptors found on presynaptic terminals (terminal autoreceptors) usually limits increases in intracellular Ca^{2+} concentration by limiting Ca^{2+} influx or preventing Ca^{2+} release from intracellular stores, impairing exocytosis of neurotransmitter vesicles (Fig. 14–2). Types of neurotransmitter receptors that serve as autoreceptors also usually reside postsynaptically, where they may mediate different physiologic effects.

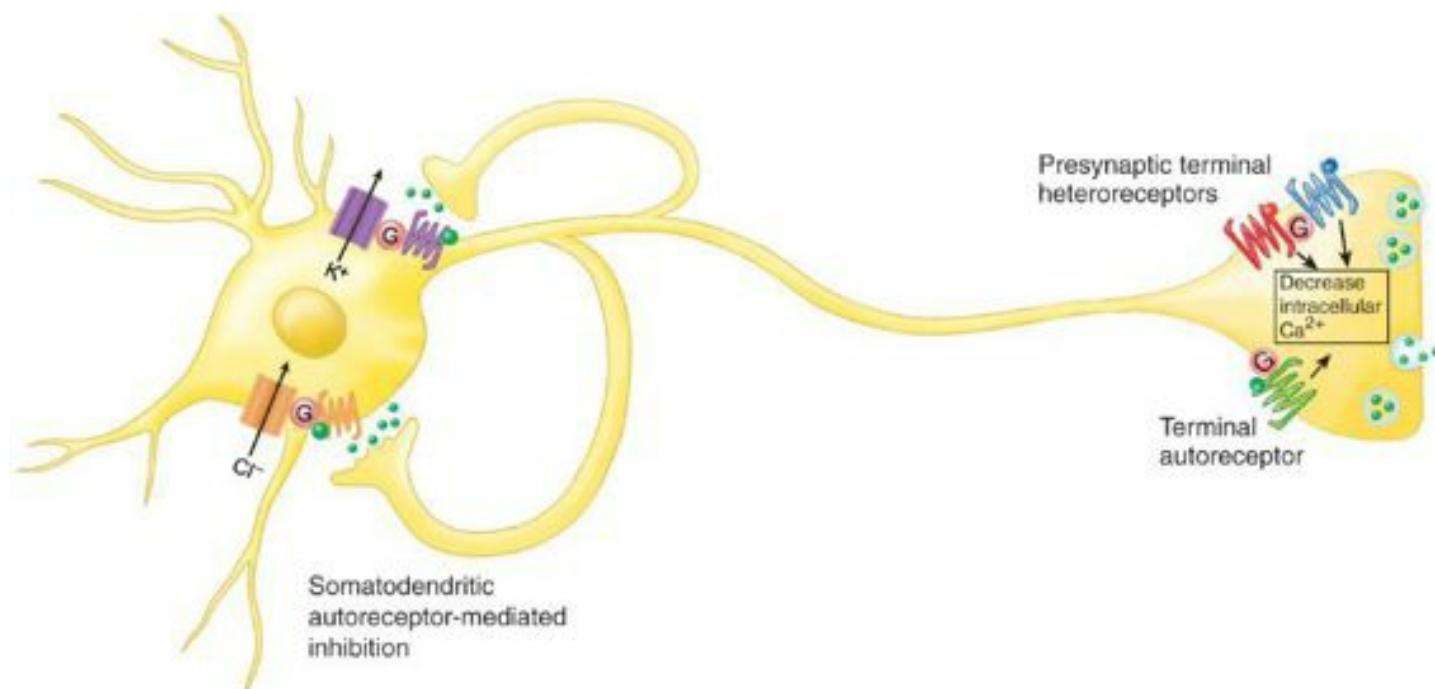


FIGURE 14–2. Common mechanisms of presynaptic inhibition (the inhibition of neurotransmitter {NT} release). A neuron releases NT (green dots), which returns to activate receptors on the cell body or dendrites (somatodendritic autoreceptors), or on the axonal terminal (terminal autoreceptors). Such activation limits further release of NT by completing a negative feedback loop. At somatodendritic autoreceptors, NT binding produces activation of G proteins, which promote either K^+ efflux or Cl^- influx; both processes hyperpolarize the neuron away from threshold. At terminal autoreceptors, NT binding activates G proteins, which, through various mechanisms, lower intracellular Ca^{2+} concentrations to prevent exocytosis of NT vesicles, despite depolarization. Presynaptic inhibitory receptors for other types of NTs (heteroreceptors) are also shown. Excitatory axonal terminal autoreceptors and heteroreceptors that serve to enhance neurotransmitter release are not illustrated. G = G protein.

Inhibition of neurotransmitter release from nerve terminals is not limited to actions by autoreceptors. Presynaptic terminal inhibitory receptors for various neurotransmitters may be found on a single neuron (heteroreceptors). For example, stimulation of presynaptic α_2 receptors found on postganglionic parasympathetic nerve terminals prevents acetylcholine release.

Finally, stimulation of receptors on presynaptic nerve endings may enhance, rather than inhibit, neurotransmitter release. Such receptors also are usually coupled to G proteins. For example, stimulation of β_2 receptors on adrenergic nerve terminals enhances norepinephrine release.

ACETYLCHOLINE

Acetylcholine (ACh) is a neurotransmitter of the central and peripheral nervous system. Centrally, it is found in both brain and spinal cord; cholinergic fibers project diffusely to the cerebral cortex. Peripherally, ACh serves as a neurotransmitter in autonomic and somatic motor fibers (Fig. 14–3).

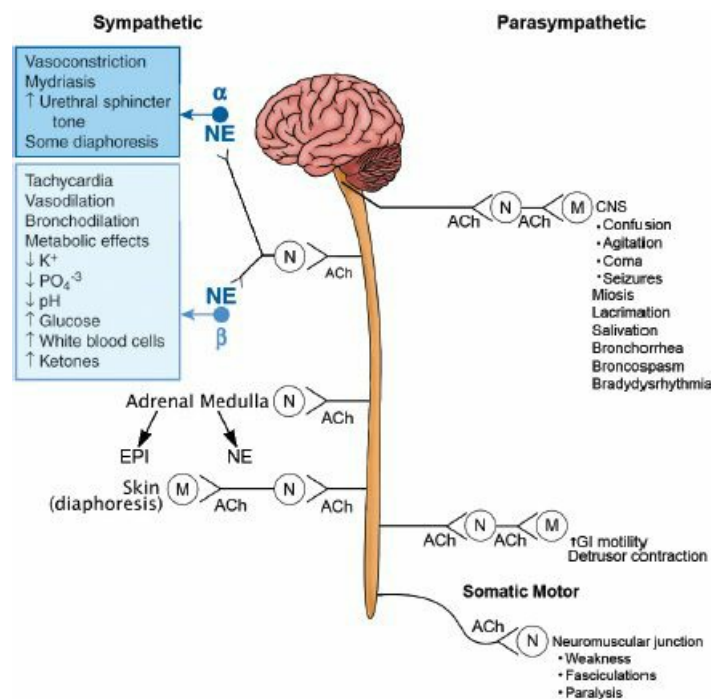


FIGURE 14–3. Diagram of the cholinergic nervous system, including adrenergic involvement in the autonomic nervous system. ACh binds to various nicotinic receptors (N) in CNS, in sympathetic and parasympathetic ganglia, and the adrenal glands. All nicotinic receptors shown are neuronal nicotinic receptors (nnAChRs) except for those at skeletal muscle, which are neuromuscular junction nicotinic receptors (NMJ nAChRs). ACh also binds to various subtypes of muscarinic (M) receptors in the CNS and on effector organs innervated by postsynaptic parasympathetic neurons and to most sweat glands. NE and/or EPI released in response to ACh stimulation of nnAChRs activates α- and β-adrenergic receptors. ACh = acetylcholine; CNS = central nervous system; EPI = epinephrine; NE = norepinephrine.

Synthesis, Release, and Inactivation

Acetylcholine is synthesized from acetyl coenzyme A and choline by the enzyme choline acetyltransferase. Acetylcholine moves into synaptic vesicles via the vesicular membrane transporter, VACHT, where it is stored before release into the synapse by Ca²⁺-dependent exocytosis. ACh undergoes enzymatic degradation in the synapse to choline and acetic acid by acetylcholinesterase. A Na⁺-dependent transporter in the neuronal membrane (ChT) then pumps choline back into the cytoplasm to be used again as a substrate for ACh synthesis (Fig. 14–4). Pseudocholinesterase (also known as plasma cholinesterase or butyryl cholinesterase) is made in the liver and plays no role in the degradation of synaptic ACh. However, it does metabolize some xenobiotics, including cocaine and succinylcholine.

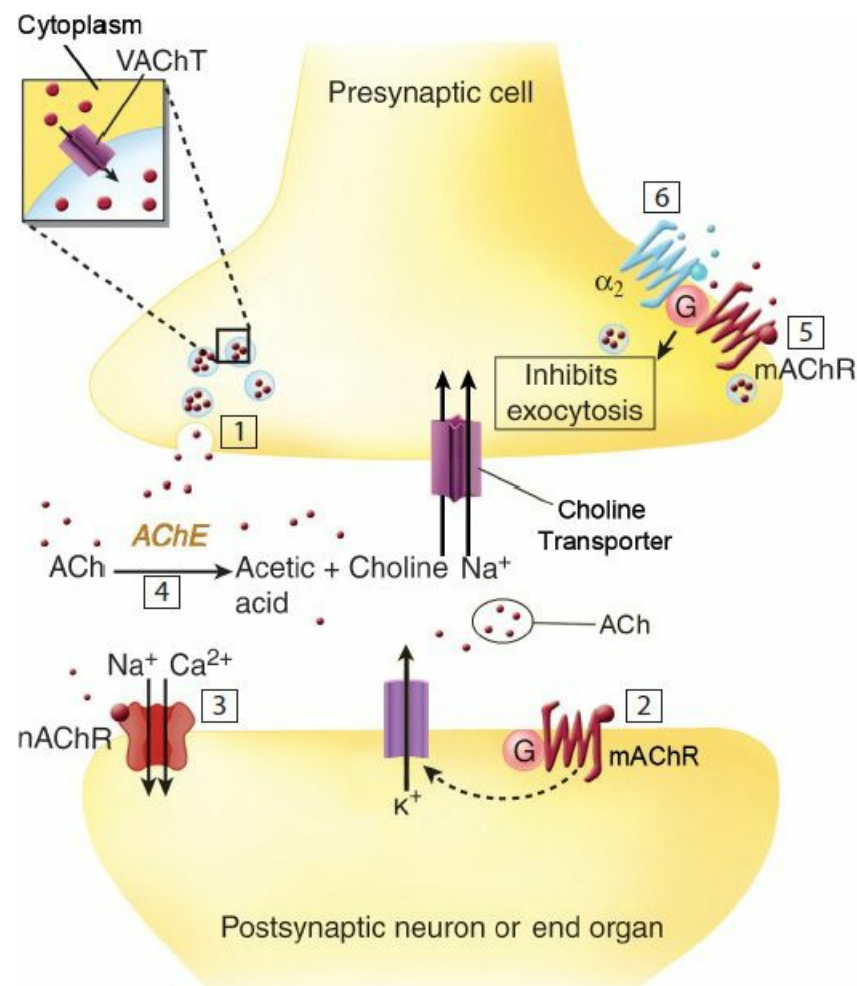


FIGURE 14–4. Cholinergic nerve ending. Activation of postsynaptic muscarinic receptors (mAChR) hyperpolarizes the postsynaptic membrane through G protein-mediated enhancement of K⁺ efflux. Several subtypes of muscarinic receptors coupled to various G proteins exist—a muscarinic receptor coupled to a G protein that opens K⁺ channels is shown only as an example [2]. Postsynaptic nicotinic receptor (nAChR) activation causes Na⁺ influx and membrane depolarization [3]. Ca²⁺ influx appears to be the main cation involved with some neuronal nicotinic receptors. Presynaptic muscarinic and α₂-adrenergic receptor activation prevents ACh release through lowering of intracellular Ca²⁺ concentrations. The xenobiotics listed in Table 14–2 may act to enhance or prevent release of ACh [1]; activate or antagonize postsynaptic muscarinic (M) receptors [2]; activate or antagonize nicotinic (N) receptors [3]; inhibit acetylcholinesterase [4]; prevent ACh release by stimulating presynaptic muscarinic autoreceptors [5] or α₂-adrenergic heteroreceptors [6]; or enhance ACh release by antagonizing presynaptic autoreceptors [5] or by antagonizing presynaptic α₂-adrenergic heteroreceptors [6] (on parasympathetic postganglionic terminals). ACh = acetylcholine; AChE = acetylcholinesterase; G = G protein; VACHT = vesicular transporter for ACh. Norepinephrine is shown as light blue dots.

TABLE 14–2. Examples of Xenobiotics Affecting Cholinergic Neurotransmission

Cholinomimetics	Cholinolytics
Cause ACh release	Direct nicotinic antagonists
α_2 -Adrenergic receptor antagonists ^a	α -Bungarotoxin ^c
Aminopyridines	Nondepolarizing neuromuscular blockers
Black widow spider venom	Trimethaphan
Carbachol	Indirect neuronal nicotinic antagonists
Guanidine	Physostigmine
Anticholinesterases	Tacrine
Donepezil	Galantamine
Edrophonium	Direct muscarinic antagonists
<i>N</i> -methylcarbamate insecticides	Antihistamines
Organic phosphorus insecticides	Atropine
Physostigmine	Benztropine
Rivastigmine	Clozapine
Direct nicotinic agonists	Cyclic antidepressants
Carbachol	Cyclobenzaprine
Coniine	Disopyramide
Cytisine	Orphenadrine
Nicotine	Phenothiazines
Succinylcholine ^b	Procainamide
Varenicline	Scopolamine
Indirect neuronal nicotinic agonists	Trihexyphenidyl
Chlorpromazine	Inhibit ACh release
Ethanol	α_1 -Adrenergic receptor agonists ^d
Ketamine	Botulinum toxins
Local anesthetics	Crotalinae venoms
Phencyclidine	Elapidae β -neurotoxins
Volatile anesthetics	Hypermagnesemia
Direct muscarinic agonists	
Arecoline	
Bethanechol	
Carbachol	
Cevimeline	
Methacholine	
Muscarine	
Pilocarpine	

^aAntagonism of α_2 -adrenoceptors enhances ACh release from parasympathetic nerve endings. ^bDepolarizing neuromuscular blockers. ^c α -Bungarotoxin exemplifies many elapid α -neurotoxins that produce paralysis and death from respiratory failure. ^dStimulation of presynaptic α_1 -adrenergic receptors on parasympathetic nerve endings prevents ACh release.

ACh = acetylcholine.

Acetylcholine Receptors

Nicotinic Receptors. After release from cholinergic nerve endings, ACh activates two main types of receptors: nicotinic and muscarinic.¹⁰⁵ Nicotinic receptors (nAChRs) reside in the CNS (mainly in spinal cord), on postganglionic autonomic neurons (both sympathetic and parasympathetic), in the adrenal medulla, and at skeletal neuromuscular junctions, where they mediate muscle contraction (Fig. 14-3).

Nicotinic receptors at neuromuscular junctions (NMJ nAChRs) are part of a Na^+ channel made from five protein subunits. Stimulation of these receptors by ACh results mainly in Na^+ influx, depolarization of the endplate, and triggering of an action potential that is propagated down the muscle by voltage-gated Na^+ channels.

Nicotinic receptors on central or peripheral neurons or in the adrenal gland are termed neuronal nAChRs. Neuronal nAChRs are also ion channels, although in some cases Ca^{2+} influx through the receptor may be more important than Na^+ influx. Neuronal nAChRs also comprise five subunits.

Muscarinic Receptors. Muscarinic receptors reside in the CNS (mainly in the brain), on end organs innervated by

postganglionic parasympathetic nerve endings, and at most postganglionic sympathetically innervated sweat glands (Fig. 14–3). Five subtypes of muscarinic receptors, M_{1-5} , are recognized and linked to several G proteins. For example, in the heart, ACh released from the vagus nerve binds to M_2 receptors linked to G_i . G_i opens K^+ channels, allowing efflux of K^+ down its concentration gradient, which makes the inside of the cell more negative and more difficult to depolarize, slowing the heart rate. Different subtypes of muscarinic receptors also act as autoreceptors in various locations, M_1 being the most common.

Xenobiotics

Table 14–2 provides examples of xenobiotics that affect cholinergic neurotransmission.

Modulators of Acetylcholine Release. Figure 14–4 illustrates sites of actions of numerous xenobiotics that influence the cholinergic nervous system. Botulinum toxins, some neurotoxins from pit vipers, and elapid β -neurotoxins prevent release of ACh from peripheral nerve endings.⁷² This results in ptosis, other cranial nerve findings, weakness, and respiratory failure. Hypermagnesemia also inhibits ACh release, probably by inhibiting Ca^{2+} influx into the nerve endings.¹⁰⁵

Guanidine, aminopyridines, and black widow spider venom enhance the release of ACh from nerve endings. Aminopyridines, in part, block voltage-gated K^+ channels to prevent K^+ efflux; the resultant action potential widening (delayed repolarization) causes prolongation of Ca^{2+} channel activation, enhancing influx of Ca^{2+} , which promotes neurotransmitter release. Aminopyridines are used therapeutically in Lambert–Eaton syndrome, myasthenia gravis, multiple sclerosis, and experimentally in calcium channel blocker overdose.

Black widow spider venom causes ACh release by opening neuronal Ca^{2+} channels with resultant muscle cramping and diaphoresis.⁸

Nicotinic Receptor Agonists and Antagonists. Xenobiotics that bind to and activate nicotinic receptors may stimulate postganglionic sympathetic and parasympathetic neurons, skeletal muscle end-plates, the adrenal medulla, and neurons within the CNS (Fig. 14–3). Prolonged depolarization at the receptor eventually causes diminution of responses to receptor occupancy.¹⁵³ For example, poisoning by nicotine, both a neuronal and NMJ nAChR agonist, may produce hypertension, tachycardia, vomiting, diarrhea, muscle fasciculations, and convulsions, followed by hypotension, bradydysrhythmias, paralysis, and coma. Succinylcholine is a neuromuscular blocker that initially stimulates and then blocks muscular activity through prolonged depolarization of NMJ nAChRs.

Xenobiotics that block NMJ nAChRs without stimulation at skeletal neuromuscular junctions produce weakness and paralysis. Examples include tubocurarine and atracurium. α -Neurotoxins from elapids (eg, α -bungarotoxin) directly antagonize NMJ nAChRs, producing ptosis, weakness, and respiratory failure from paralysis.²¹⁴

Peripheral neuronal nAChR blockade produces autonomic ganglionic blockade. Trimethaphan was used as a pharmacologic ganglionic blocker; however, it is not entirely specific for neuronal nAChRs. Occasionally, trimethaphan caused weakness and paralysis from NMJ nAChR blockade.

The function of neuronal nAChRs can be modulated by a variety of xenobiotics that do not bind to the ACh binding site, but bind instead to a number of distinct allosteric sites. For example, aside from their ability to inhibit acetylcholinesterase, physostigmine, tacrine, and galantamine bind to a noncompetitive allosteric activator site on neuronal nAChRs to enhance channel opening and ion conductance. Furthermore, a diverse range of xenobiotics, including chlorpromazine, phencyclidine, ketamine, local anesthetics, and ethanol bind to a noncompetitive negative allosteric site(s) on nAChRs to inhibit inward ion fluxes without directly affecting ACh binding. Steroids can desensitize neuronal nAChRs by binding to yet an additional allosteric site.¹⁵⁵

Muscarinic Receptor Agonists and Antagonists. Peripheral muscarinic agonists produce bradycardia, miosis, salivation, lacrimation, vomiting, diarrhea, bronchospasm, bronchorrhea, and micturition. Central muscarinic agonists produce sedation, extrapyramidal dystonias, rigidity, coma, and convulsions. The anticholinergic toxic syndrome results from blockade of muscarinic receptors and is more appropriately referred to as an antimuscarinic toxic syndrome.¹⁷⁹ CNS muscarinic blockade produces confusion, agitation, myoclonus, tremor, picking movements, abnormal speech, hallucinations, and coma. Peripheral antimuscarinic effects include mydriasis, anhidrosis, tachycardia, and urinary retention. Muscarinic antagonists number in the hundreds (Table 14–2 for common examples).

Acetylcholinesterase Inhibition. Xenobiotics inhibiting acetylcholinesterase (ie, anticholinesterase) raise ACh concentrations at both nicotinic and muscarinic receptors, producing a variety of CNS, sympathetic, parasympathetic, and skeletal muscle signs and symptoms.³⁴ Anticholinesterases include organic phosphorus compounds and N-methylcarbamates. Organic phosphorus compounds are usually encountered as insecticides, although topical medicinal organic phosphorus compounds are used for the treatment of glaucoma and lice. N-methylcarbamates are found as insecticides and pharmaceuticals. Medicinal N-methylcarbamates include physostigmine, pyridostigmine, rivastigmine, and neostigmine. Edrophonium, galantamine, tacrine, donepezil, and metrifonate are non-carbamate, reversible anticholinesterases.

α_2 -Adrenergic Receptor Agonists and Antagonists. Agonists and antagonists of α_2 -adrenergic receptors are discussed in detail below. Briefly, stimulation of presynaptic α_2 -adrenergic receptors on postganglionic parasympathetic nerve endings decreases ACh release. Conversely, presynaptic α_2 antagonism increases ACh release (Fig. 14–4).

NOREPINEPHRINE AND EPINEPHRINE

Norepinephrine (NE), epinephrine (EPI), dopamine (DA), and serotonin (5-hydroxytryptamine {5-HT}) are similar in many respects. Neurotransmitter synthesis, vesicle transport and storage, uptake, and degradation share many enzymes and structurally similar transport proteins. Cocaine, reserpine, amphetamines, and monoamine oxidase inhibitors (MAOIs) affect all four types of neurons. In addition, these xenobiotics produce several different effects in the same system. For example, in the noradrenergic neuron, amphetamines work mainly by causing the release of cytoplasmic NE, but they also inhibit NE reuptake, and their metabolites inhibit monoamine oxidase. Actions of xenobiotics that affect all bioactive amine neurotransmitters are described in the most detail for noradrenergic neurons. For the sake of brevity, similar mechanisms of action are simply noted in discussions of dopaminergic and serotonergic neurotransmission.

Norepinephrine is released from postganglionic sympathetic terminals (Fig. 14–3). The adrenal gland, acting as a modified sympathetic ganglion, releases EPI and lesser amounts of NE in response to stimulation of neuronal nAChRs. Epinephrine-containing neurons also reside in the brainstem.

The locus ceruleus is the main noradrenergic nucleus and resides in the floor of the fourth ventricle on each side of the pons. Axons radiate from this nucleus out to all layers of the cerebral cortex, to the cerebellum, and to other structures. Norepinephrine demonstrates both excitatory and inhibitory actions in the CNS. Norepinephrine released from locus ceruleus projections in the hippocampus increases cortical neuron activity through β -adrenergic receptor activation and G protein-mediated inhibition of K^+ efflux. Norepinephrine released in outer cortical areas produces inhibitory effects mediated by α_2 -adrenergic receptor agonism. Consistent with this, NE demonstrates anticonvulsant actions in animals. The anticonvulsant action of carbamazepine may be partly a result of inhibition of NE uptake.⁵⁴ Despite antagonistic actions on different cortical neurons, electrical stimulation of the locus ceruleus produces widespread cortical activation and excitation. This overall effect probably explains a great deal of the hyperattentiveness and lack of fatigue that accompanies use of xenobiotics that mimic or increase noradrenergic activity in the brain. Neuronal firing in the locus ceruleus increases during waking and dramatically falls during sleep.

Synthesis, Release, and Reuptake

Figure 14–5 is a representation of a noradrenergic neuron. Tyrosine hydroxylase is the rate-limiting enzyme in NE synthesis and is sensitive to negative feedback by NE. This enzyme requires Fe^{2+} as a cofactor and exists as a homotetramer that is upregulated by chronic exposure to caffeine and nicotine. Under normal dietary conditions tyrosine hydroxylase is completely saturated by tyrosine, and increasing dietary tyrosine does not appreciably increase dopa synthesis. Dopa undergoes decarboxylation by L-amino acid decarboxylase (dopa decarboxylase) to DA. Dopa decarboxylase is not specific for dopa. For example, it also catalyzes the formation of serotonin from 5-HT.

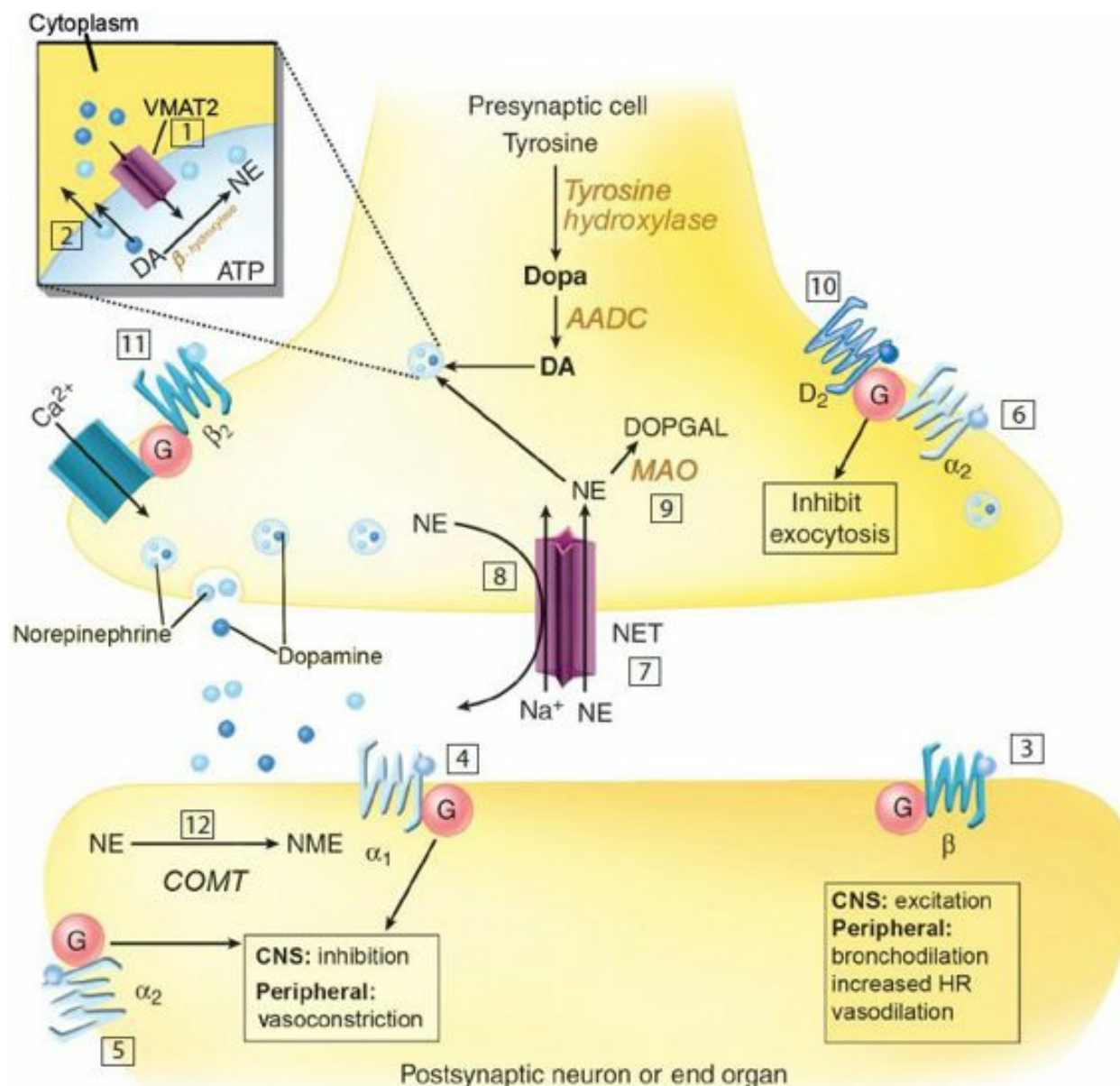


FIGURE 14–5. Noradrenergic nerve ending. The postsynaptic membrane may represent an end organ or another neuron in the CNS. Brief examples of effects resulting from postsynaptic receptor activation are shown. Xenobiotics in [Tables 14–4 and 14–5](#) produce effects by inhibiting transport of dopamine (DA) or norepinephrine (NE) into vesicles through VMAT2 [1]; causing movement of NE and DA from vesicles into the cytoplasm [2]; activating or antagonizing postsynaptic α - and β -adrenergic receptors [3–5]; modulating NE release by activating or antagonizing presynaptic α_2 -autoreceptors [6], dopamine₂ (D_2) heteroreceptors [10], or β_2 -autoreceptors [11]; blocking reuptake of NE (NET inhibition) [7]; causing reverse transport of NE from the cytoplasm into the synapse via NET by raising cytoplasmic NE concentrations [8]; inhibiting monoamine oxidase (MAO) to prevent NE degradation [9]; or inhibiting COMT to prevent NE degradation [12]. AADC = aromatic L-amino acid decarboxylase; β -hydroxylase = dopamine- β -hydroxylase; COMT = catechol-O-methyltransferase; CNS = central nervous system; DOPGAL = 3,4-dihydroxyphenylglycoaldehyde; G = G protein; NET = membrane NE reuptake transporter; NME = normetanephrine; VMAT2 = vesicle uptake transporter for NE.

About one-half of cytoplasmic DA is actively pumped into vesicles by VMAT2. The remaining DA is quickly deaminated.

In the vesicle, DA is converted to NE by dopamine- β -hydroxylase. Vesicles isolated from peripheral nerve endings contain DA, NE, dopamine- β -hydroxylase, and ATP, and all of these substances are released into the synapse during Ca^{2+} -dependent exocytosis triggered by neuronal firing. In neurons containing EPI as a neurotransmitter, NE is released from vesicles into the cytoplasm, where it is converted to EPI by phenylethanolamine-N-methyl-transferase. Epinephrine is then transported back into vesicles before synaptic release.¹⁰⁵

Norepinephrine is removed from the synapse, mainly by reuptake into the presynaptic neuron by the NE transporter (NET). Although this transporter has great affinity for NE, it also transports other amines, including DA, tyramine, MAOIs, and amphetamines. Once pumped back into the cytoplasm, NE can either be transported back into vesicles for further storage and release, or can be quickly degraded by monoamine oxidase (MAO), an enzyme expressed on the outer mitochondrial membrane.

MAO is present in all human tissues except red blood cells. It exists as two isozymes, MAO-A and MAO-B,¹²⁷ each

with partially overlapping substrate affinities (Table 14–3). Neuronal MAO, bound to the outer mitochondrial membrane, oxidatively deaminates cytoplasmic amines, including neurotransmitters, to attenuate elevated cytoplasmic concentrations of bioactive amines. Hepatic and intestinal MAO prevents large quantities of dietary bioactive amines from entering the circulation and producing systemic effects.

TABLE 14–3. Characteristics of Monoamine Oxidase (MAO) Isozymes

	<i>MAO Isozymes</i>	
	<i>MAO-A</i>	<i>MAO-B</i>
Location		
Brain	+	+++
Intestines	+++	+
Liver	++	++
Platelets	+	++++
Placenta	++++	+
Substrates		
Norepinephrine	++++	+
Epinephrine	++	++
Dopamine	++	++
Serotonin	++++	+
Tyramine	++	++

Catechol-O-methyltransferase (COMT) is an intracellular enzyme widely distributed throughout the body, including the central nervous system, which is responsible for metabolism of DA, L-dopa, NE, and EPI. In extraneuronal tissue, COMT metabolizes catecholamines, including those that have entered the systemic circulation.

Adrenergic Receptors

The two main types of adrenergic receptors are α -adrenergic receptors and β -adrenergic receptors. All adrenergic receptors are coupled to G proteins.

β -Adrenergic Receptors. β -Adrenergic receptors are divided into three major subtypes (β_1 , β_2 , and β_3), depending on their affinity for various agonists and antagonists.¹⁸¹ β_1 -adrenergic receptors and β_2 -adrenergic receptors are linked to G_s , and their stimulation raises cAMP concentration and/or activates protein kinase A which, in turn, produces several effects, including regulation of ion channels. At least some β_3 -adrenergic receptors may be coupled to $G_{i/o}$ proteins. Up-regulation of β_3 receptors responsible for a negative inotropic effect in diseased myocardium may protect against adverse effects of chronic excessive catecholamine stimulation. β_3 receptor activation by nebivolol may also be responsible for nitric oxide production in some vascular beds.⁶³

The β -adrenergic receptors are polymorphic, with genetic variation in humans.^{26,86} Polymorphism influences response to medications, regulation of receptors, and clinical course of disease.^{26,87,109} In general, peripheral β_1 -adrenergic receptors are found mainly in the heart and in the juxtaglomerular apparatus. β_2 -adrenergic receptors also reside in the heart as well as other organs where their activation mediates additional adrenergic effects such as bronchodilation and vasodilation.⁸⁷ Presynaptic β_2 -adrenergic receptor activation causes release of NE from nerve endings (positive feedback). β_3 -adrenergic receptors reside mainly in fat, but they also reside in skeletal muscle, gallbladder, and colon where they regulate metabolic processes. β_3 -adrenergic receptors' polymorphism may contribute to clinical expressions of non-insulin-dependent diabetes and obesity.^{26,196,216}

α -Adrenergic Receptors. α -Adrenergic receptors are linked to G proteins that inhibit adenylate cyclase to lower cAMP concentrations, affect ion channels, increase intracellular Ca^{2+} through inositol triphosphate and diacylglycerol production, or produce other actions. These receptors are divided into two main types, α_1 and α_2 , and at least six subtypes— α_{1A} , α_{1B} ,

α_{1D} , α_{2A} , α_{2B} , and α_{2C} .^{47,80,181} Most α_1 -adrenergic receptors are coupled to G_q , whereas most α_2 -adrenergic receptors are coupled to $G_{i/o}$.

In peripheral tissue, α_1 -adrenergic receptors reside on the postsynaptic membrane in continuity with the synaptic cleft. Stimulation of these receptors on blood vessels commonly results in vasoconstriction.

α_2 -Adrenergic receptors reside on both sides of the synapse. Presynaptic α_2 -adrenergic receptor activation mediates negative feedback, limiting further release of NE (Fig. 14–5). Postganglionic parasympathetic neurons also contain presynaptic α_2 -adrenergic receptors that, when stimulated, prevent release of ACh (Fig. 14–4).

Postsynaptic α_2 -adrenergic receptors on vasculature also can mediate vasoconstriction. Initially, it was suggested that postsynaptic α_2 -adrenergic receptors resided mainly outside of the synapse and mediated vasoconstrictive responses to circulating α -adrenergic agonists such as NE, whereas postsynaptic α_1 -adrenergic receptors responded to NE released from nerve endings. However, it has been demonstrated that in at least some tissues (eg, saphenous vein), NE released following nerve stimulation produces vasoconstriction through action at α_2 -adrenergic receptors, making the previous differentiation not as distinct.^{47,95} Because both α_1 -adrenergic receptors and α_2 -adrenergic receptors on non-cerebral vasculature mediate vasoconstriction, a patient with hypertension from high concentrations of circulating catecholamines (eg, pheochromocytoma or clonidine withdrawal) or from extravasation of NE from an intravenous line commonly requires both α_1 -adrenergic receptor and peripheral α_2 -adrenergic receptor blockade to vasodilate adequately (eg, phentolamine).

Stimulation of postsynaptic α_2 -adrenergic receptors in the brainstem inhibits sympathetic output and produces sedation. α_{2A} -Adrenergic heteroreceptor activation on non-noradrenergic cells is important in explaining sedation, antinociception, hypothermia, effects on cognition, and centrally mediated bradycardia and hypotension in response to administration of α_2 agonists (Fig. 14–6).⁶⁷ Dexmedetomidine, an imidazole and potent α_{2A} -adrenergic receptor agonist, is used for sedation in intensive care patients, although hypotension and bradycardia occur as expected side effects.¹⁸

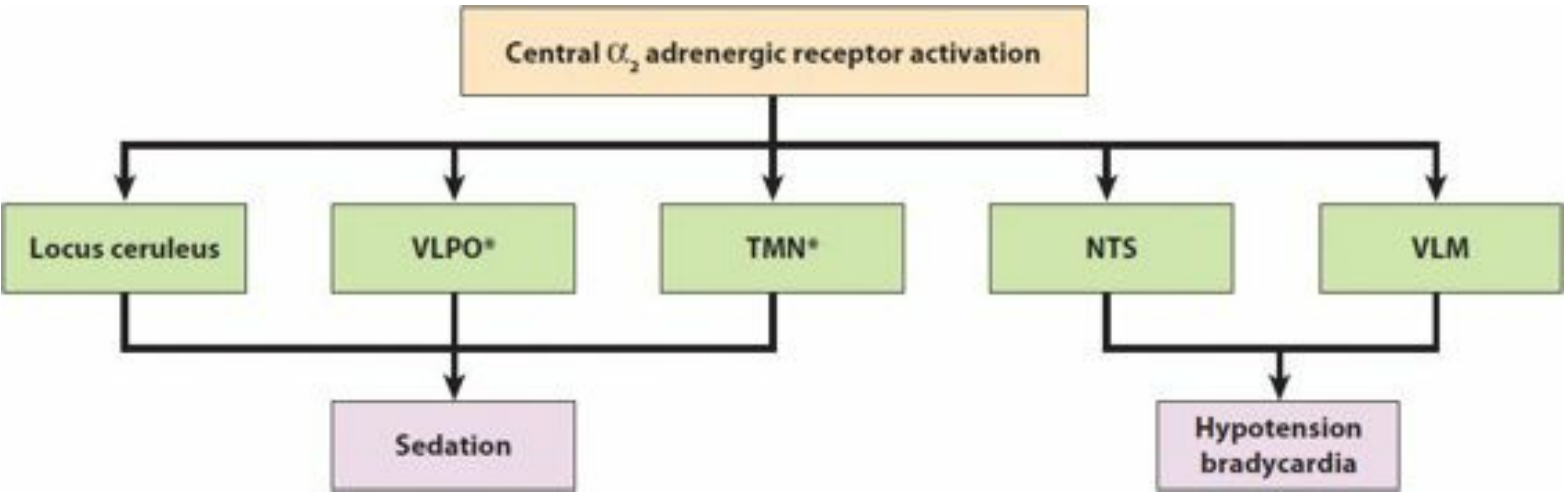


FIGURE 14–6. Central action of agents that activate α_2 -adrenergic receptors. Activation of α_2 -adrenergic receptors on noradrenergic neurons in the locus ceruleus produces sedation. Activation of receptors in the nucleus tractus solitarius (NTS) and ventrolateral medulla (VLM) contributes to hypotension and bradycardia. *In animal models, α_2 -receptor activation of GABAergic neurons in the ventrolateral preoptic nucleus (VLPO) and of histaminergic neurons in the tuberomamillary nucleus (TMN) also contributes to sedation, and may do so in humans.

Xenobiotics

Xenobiotics producing pharmacologic effects that result in or mimic increased activity of the adrenergic nervous system are sympathomimetics (Table 14–4). Those with the opposite effect are sympatholytics (Table 14–5).

TABLE 14–4. Examples of Sympathomimetics

Direct acting

α -Adrenergic receptor agonists

Epinephrine

Ergot alkaloids

Methoxamine

Midodrine

Norepinephrine

Phenylephrine

β -Adrenergic receptor agonists

Albuterol

Dobutamine

Epinephrine

Isoproterenol

Metaproterenol

Norepinephrine

Terbutaline

Indirect acting

Amphetamine

Cocaine

Fenfluramine

MAOIs

Methylphenidate

Pemoline

Phenmetrazine

Propylhexedrine

Tyramine

Mixed acting

Dopamine

Ephedrine

Mephentermine

Metaraminol

Phenylpropanolamine

Pseudoephedrine

Selective α_2 -adrenergic receptor antagonists

Yohimbine

MAOIs

Amphetamine metabolites
Clorgyline
Isocarboxazid
Linezolid
Methylene blue
Moclobemide
Pargyline
Phenelzine
Rasagiline
Selegiline
Tranylcypromine
Inhibit norepinephrine reuptake
Amphetamine
Atomoxetine
Benztropine
Bupropion
Carbamazepine
Cocaine
Cyclic antidepressants
Diphenhydramine
Duloxetine
Orphenadrine
Pemoline
Reboxetine
Tramadol
Trihexyphenidyl
Venlafaxine

MAOI = monoamine oxidase inhibitor.

TABLE 14–5. Examples of Sympatholytics

α -Adrenergic receptor antagonists (non-selective or α_1)

Clozapine

Cyclic antidepressants

Doxazosin

Ergot alkaloids

Olanzapine

Phenothiazines

Phenoxybenzamine

Phentolamine

Prazosin

Risperidone

Terazosin

Tolazoline

Trazodone

Inhibit dopamine- β -hydroxylase

Diethyldithiocarbamate

Disulfiram

MAOIs

β -Adrenergic receptor antagonists

Atenolol

Esmolol

Labetalol

Nadolol

Pindolol^a

Practolol^a

Propranolol

Sotalol

α_2 -Adrenergic receptor agonists^b

α -Methyldopa^c

Apraclonidine

Brimonidine

Clonidine

Dexmedetomidine

Guanfacine

Moxonidine

Naphazoline

Oxymetazoline

Rilmenidine

Tetrahydrozoline

Tizanidine

Xylometazoline

Inhibitors of vesicle reuptake

Reserpine

Tetrabenazine

^aPartial β -adrenergic receptor agonist. ^bXenobiotics in these categories vary in their relative selectivity for α_2 -adrenoceptors or imidazoline-binding sites. ^cMetabolized to α -methylnorepinephrine, which activates α_2 -adrenoceptors.

MAOI = monoamine oxidase inhibitor.

Sympathomimetics. Direct-acting agents. Xenobiotics whose sympathomimetic actions result from direct binding to α -adrenergic receptors or β -adrenergic receptors are called direct-acting sympathomimetics. Most do not cross the blood–brain barrier in significant quantities.

Indirect-acting agents. Xenobiotics that produce sympathomimetic effects by causing the release of cytoplasmic NE from the nerve ending in the absence of vesicle exocytosis are called indirect-acting sympathomimetics. Amphetamine is the prototype of indirect-acting sympathomimetics and is used for the discussion of what is known about their mechanisms of action.²⁹ In general, mechanisms of indirect release of NE by amphetamines, cocaine, phencyclidine, MAOIs, and mixed-acting xenobiotics noted in Table 14–4 are similar in that their actions depend on their ability to produce elevated cytoplasmic NE concentrations.

Amphetamine and structurally similar indirect-acting sympathomimetics move into the neuron mainly by the membrane transporter that transports NE into the neuron. Lipophilic indirect-acting sympathomimetics may also move into the neuron by diffusion. From the cytoplasm, amphetamines are transported into neurotransmitter vesicles, where they buffer protons to raise intravesicular pH. As noted earlier, much of the vesicle's ability to concentrate NE (and other neurotransmitters) is a result of ion trapping of NE at the lower pH. The rise in intravesicular pH produced by amphetamines causes NE to leave the vesicle and move into the cytoplasm.^{197,198} This movement may be caused by diffusion or reverse transport of NE by VMAT2. In the cytoplasm, amphetamines also compete with NE and DA for transport into vesicles, which further contributes to elevated cytoplasmic NE concentrations. In the case of amphetamine, the rise in cytoplasmic concentrations of NE may be further enhanced by the ability of amphetamine metabolites to inhibit MAO, which impairs NE degradation.

Every time the Na^+ -dependent uptake transporter, NET, moves a bioactive amine (eg, tyramine) into the neuron where it is released, a binding site for NE on NET conceptually transiently faces inward and becomes available for reverse transport of NE out of the neuron. The normally low concentration of cytoplasmic NE prevents significant reverse transport. In the face of elevated cytoplasmic NE concentrations produced by indirect-acting sympathomimetics, NET moves NE out of the neuron and back into the synapse, where the neurotransmitter stimulates adrenergic receptors (indirect action). This process is sometimes referred to as facilitated exchange diffusion, or displacement, of NE from the nerve ending. Evidence supporting reverse transport produced by amphetamines is that inhibitors of the transporter (eg, tricyclic antidepressants) prevent amphetamine-induced NE release.

While all indirect-acting sympathomimetics cause reverse NE transport by increasing cytoplasmic NE concentrations, those that move into the neuron by the membrane transporter (eg, amphetamines, MAOIs, DA, tyramine) further enhance reverse transport because their uptake may cause more NE-binding sites on NET to face inward per unit time.

Although cocaine inhibits NET, it also causes some NE release. In fact, cocaine similarly lessens pH gradients across vesicle membranes to raise cytoplasmic concentrations of NE.¹⁹⁸ That cocaine produces less NE release than amphetamines is partly explained by cocaine-induced inhibition of the membrane transporter and possibly by the fact that cocaine does not move into the neuron by active uptake (ie, does not increase the number of NE-binding sites facing inward), but diffuses into the neuron. In fact, most of cocaine's severe sympathomimetic effects may result from its action on the brain rather than peripheral nerve endings.²⁰⁵

Phencyclidine (PCP) is a hallucinogen that possesses multiple pharmacologic actions. Like toxicity from many

hallucinogens, PCP toxicity is accompanied by increased adrenergic activity, which results, in part, from PCP-induced decreases in pH gradients across the vesicle membrane¹⁹⁸ and indirect release of NE. Like cocaine, PCP moves into the neuron by diffusion rather than uptake through the membrane transporter, at least partly explaining less PCP-induced NE release than typically occurs in amphetamine poisoning.

In addition to causing ACh release, black widow spider venom causes vesicle exocytosis of NE, producing hypertension and diaphoresis over the palms, soles, upper lip, and nose. All of the aforementioned indirectly acting sympathomimetics, except black widow spider venom, enter the CNS.

Mixed-acting agents. Mixed-acting sympathomimetics act directly and indirectly. For example, ephedrine indirectly causes NE release and directly activates adrenergic receptors. Intravenously administered DA indirectly causes NE release, explaining most of its vasoconstricting activity, but also directly stimulates dopaminergic and β -adrenergic receptors. Direct α -agonism occurs at high doses. Except for DA, these xenobiotics cross the blood–brain barrier to produce central effects.

Reuptake inhibitors. Inhibitors of NE reuptake raise concentrations of NE in the synapse to produce excessive stimulation of adrenergic receptors.

There are two main means by which inhibitors of bioactive amine inhibit reuptake: competitive and noncompetitive. Noncompetitive inhibitors, such as cyclic antidepressants, carbamazepine, venlafaxine, methylphenidate, and cocaine, bind at or near the carrier site on NET to prevent NET from moving NE and similar xenobiotics into or out of the neuron. Various xenobiotics used for their antimuscarinic effects also block NET noncompetitively. These include benztropine, diphenhydramine, trihexyphenidyl, and orphenadrine.¹³⁹ Atomoxetine also inhibits NET.

The second mechanism, competitive inhibition of NET, characterizes most indirect-acting sympathomimetics, including amphetamines and structurally similar xenobiotics (eg, mixed-acting agents, MAOIs). These xenobiotics prevent NE reuptake by competing with synaptic NE for binding to the carrier site on NET, a mechanism by which they can move into the neuron. In fact, an additional adrenergic action of amphetamines, mixed-acting agents, MAOIs, and tyramine is to raise synaptic NE concentrations by competing for uptake, thereby compounding their indirect or direct actions.

MAOIs. MAOIs are transported by NET into the neuron, where they act through several mechanisms (Table 14–4).^{1,127} Inhibition of MAO, their main pharmacologic effect, results in increased cytoplasmic concentrations of NE and some indirect release of neurotransmitter into the synapse. As a minor effect they also may displace NE from vesicles by raising pH in a manner similar to amphetamines. These actions explain the initial sympathomimetic findings following MAOI overdose and may also account for occasional and unpredictable adrenergic crises that occur despite dietary compliance.

Nonspecific MAOIs inhibit both isoenzymes of MAO, preventing intestinal and hepatic degradation of bioactive amines. A person taking such an MAOI who then is exposed to indirect-acting sympathomimetics (eg, tyramine in cheese, ephedrine, DA, amphetamines) has a much larger cytoplasmic concentration of NE to transport into the synapse and may, therefore, develop central and peripheral sympathomimetic findings. MAOIs specific for the MAO-B isozyme are less likely to predispose to food or drug interactions by maintaining significant hepatic and intestinal MAO activity. Furthermore, reversible MAO-A specific inhibitors are also less likely to provoke this reaction because their reversibility allows competition of exogenous amines with the inhibitor, resulting in its displacement from the enzyme and normal metabolism of the bioactive amines.²¹⁹ Isozyme specificity may be lost as the dose of the MAOI is increased. In fact, selegiline, currently marketed as a selective MAO-B inhibitor, partially inhibits MAO-A activity at therapeutic doses. Rasagiline is a newer MAO-B inhibitor that has 100-fold greater affinity for MAO-B than MAO-A, but still loses specificity at supratherapeutic doses.^{69,79} MAOI isozyme specificity may also be of low importance when indirect-acting agents are administered parenterally (eg, intravenous DA or amphetamines). Linezolid is an antibiotic that displays nonspecific MAO inhibition,¹⁴⁶ while methylene blue mainly inhibits MAO-A.¹⁷⁷

Occasionally, patients suffering from refractory depression respond to a combination of MAOIs and tricyclic antidepressants. This combination therapy is usually unaccompanied by excessive adrenergic activity because the inhibition of the membrane uptake transporter by the tricyclic antidepressant attenuates excessive reverse transport of elevated cytoplasmic NE concentrations produced by MAOIs.

COMT inhibitors. Inhibitors of COMT are administered in the treatment of Parkinson disease to prevent the catabolism of concomitantly administered L-dopa. Entacapone only acts peripherally, whereas tolcapone also crosses the blood–brain barrier where it can also prevent DA degradation as well.

α_2 -Adrenergic receptor antagonists. Yohimbine produces selective competitive antagonism of α_2 -adrenergic receptors to produce a mixed clinical picture. Peripheral postsynaptic α_2 blockade produces vasodilation. Blockade of presynaptic α_2 -adrenergic receptors on cholinergic nerve endings (Fig. 14–4) enhances ACh release, occasionally producing bronchospasm¹⁰² and contributing to diaphoresis. Similar presynaptic actions on peripheral noradrenergic nerves enhance catecholamine release (Fig. 14–5). Antagonism of central α_2 -adrenergic receptors in the locus ceruleus results in CNS stimulation, whereas blockade of postsynaptic α_2 -adrenergic receptors in the nucleus tractus solitarius may enhance sympathetic output (Fig. 14–6). The final result includes hypertension, tachycardia, anxiety, fear, agitation, mania,

mydriasis, diaphoresis, and bronchospasm.¹¹¹

Sympatholytics. Direct antagonists. Direct α -adrenergic receptor and β -adrenergic receptor antagonists are noted in Table 14–5. After overdose, β -adrenergic receptor selectivity may be less significant. Some β -adrenergic receptor antagonists also are partial agonists.

Xenobiotics that prevent norepinephrine release. Xenobiotics that block the vesicle uptake transporter prevent the movement of NE into vesicles and deplete the nerve ending of this neurotransmitter, preventing NE release after depolarization. Reserpine and ketanserin inhibit both VMAT1 and VMAT2, whereas tetrabenazine only inhibits VMAT2. Like guanethidine, reserpine causes transient NE release with the initial dose or early in overdose. β -Adrenergic receptor antagonists block presynaptic β_2 -adrenergic receptors to limit catecholamine release from nerve endings, although most of the antihypertensive action of β -adrenergic antagonists at therapeutic doses results from inhibition of renin release in the kidney.

α_2 -Adrenergic receptor agonists. Numerous imidazoline derivatives (eg, clonidine) and structurally similar xenobiotics used as centrally acting antihypertensives or long-acting topical vasoconstrictors act by activating α_2 -adrenergic receptors. These xenobiotics also display various affinities for what are termed imidazoline-binding sites, apart from α_2 -adrenergic receptors. Although imidazoline-binding sites have been proposed and subdivided into I₁, I₂, and I₃,⁵¹ and endogenous ligands for these binding sites have been discovered (eg, agmatine, imidazole-acetic acid ribotide, harmaline, other β -carbolines),^{16,73,167} it must be recognized that the molecular structures of imidazoline-binding sites have not been determined, nor have signaling pathways been characterized. As a result, major professional societies such as The International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification have not adopted the term imidazoline receptor.¹⁰⁸ The role of imidazoline-binding sites in mediating responses to xenobiotics remains controversial and ill defined.

The ventromedial (depressor) and the rostral-ventrolateral (pressor) areas of the ventrolateral medulla (VLM) are responsible for the central regulation of cardiovascular tone and blood pressure. They receive afferent fibers from the carotid and aortic baroreceptors, which form the tractus solitarius via the nucleus tractus solitarius (NTS).⁹⁴

Ingestions of xenobiotics that activate α_2 -adrenergic receptors (Table 14–5) produce a mixed clinical picture. Peripheral postsynaptic α_2 -adrenergic receptor stimulation produces vasoconstriction, pallor, and hypertension, often with reflex bradycardia (Fig. 14–5). Peripheral presynaptic α_2 -adrenergic receptor stimulation prevents NE release (Fig. 14–5), reducing sympathetic activation. Central α_2 -adrenergic receptor stimulation in the locus ceruleus accounts for CNS and respiratory depression (Fig. 14–6). Recently acquired knowledge about α_2 -adrenergic receptor subtypes and their effects on non-adrenergic neurons makes analysis of their hypotensive and sedative effects complex. Recent animal evidence supports that sedation is not entirely mediated by α_2 -adrenergic receptor activation on noradrenergic neurons in the locus ceruleus.⁶⁷ Stimulation of postsynaptic α_{2A} -adrenergic receptors in the NTS in the VLM is thought to inhibit sympathetic output and enhance parasympathetic tone, explaining hypotension with bradycardia (Fig. 14–6).⁹⁴

Dopamine- β -hydroxylase inhibition. Inhibition of dopamine- β -hydroxylase, a copper-containing enzyme (Fig. 14–5), prevents the conversion of DA to NE, resulting in less NE release and less α - and β -adrenergic receptor stimulation. Disulfiram and diethyldithiocarbamate, copper chelators, produce such inhibition.⁵³ Because NE release mediates most of the ability of DA to cause vasoconstriction, NE is the vasopressor of choice in a hypotensive patient taking disulfiram. MAOIs and α -methyl dopa also inhibit dopamine- β -hydroxylase, although this is not their main mechanism of action.¹²⁷

Dopamine is relatively contraindicated in hypotensive patients who have overdosed on MAOIs. First, DA acts indirectly, and its administration might produce excessive adrenergic activity and exaggerated rises in blood pressure. Second, even if an adrenergic storm does not occur, most of the α -mediated vasoconstriction of dopamine is secondary to NE release. In the presence of MAOIs, NE synthesis may be impaired from concomitant dopamine- β -hydroxylase inhibition, and DA may not reliably raise blood pressure if cytoplasmic and vesicular stores have been depleted. In the presence of impaired NE release or α -adrenergic receptor blockade by any cause, unopposed dopamine-induced vasodilation from action on peripheral DA and β -adrenergic receptors may paradoxically lower blood pressure further. Norepinephrine and EPI can be used to support blood pressure relatively safely in patients taking MAOIs because they have little or no indirect action and are metabolized by COMT when given intravenously.

DOPAMINE

Because DA is the direct precursor of NE, noradrenergic vesicles contain DA. The release of NE from peripheral sympathetic nerves, therefore, always results in release of some DA (Fig. 14–5), as does the release of NE and EPI from the adrenal gland, explaining most of DA in blood. In peripheral tissues, activation of DA receptors causes vasodilation of renal, mesenteric, and coronary vascular beds. Dopamine can also stimulate β -adrenergic receptors and, at high doses, can directly stimulate α -adrenergic receptors. When DA is administered intravenously, most vasoconstriction is caused by

dopamine-induced NE release.

Dopamine accounts for about one-half of all catecholamines in the brain and is present in greater quantities than NE or 5-HT. By contrast to the diffuse projections of noradrenergic neurons, dopaminergic neurons and receptors are highly organized and concentrated in several areas, especially in the basal ganglia and limbic system.^{100,178}

Excessive dopaminergic activity in the striatum and/or other areas from any cause (eg, increased release, impaired uptake, increased receptor sensitivity) can produce acute choreoathetosis⁹⁶ and acute Gilles de la Tourette syndrome, with tics, spitting, and cursing. Excessive dopaminergic activity in the limbic system and frontal cortex, and perhaps in other areas, produces paranoia and psychosis. Dopaminergic activity in the nucleus accumbens and is thought responsible for much of the drug craving and addictive behavior in patients abusing sympathomimetics, opioids, alcohol, and nicotine. Diminished dopaminergic tone (eg, impaired release, receptor blockade) in the striatum produces various extrapyramidal disorders such as acute dystonias and parkinsonism.^{166,192,208}

Synthesis, Release, and Reuptake

The steps of DA synthesis and vesicle storage are the same as those for NE, except that DA is not converted to NE after transport into vesicles (Fig. 14–7). Dopamine is removed from the synapse via reuptake by DAT, the membrane-bound DA transporter. DAT and NET exhibit 66% homology in their amino acid sequences. Like NET, DAT is not completely specific for DA and transports amphetamines and other structurally similar sympathomimetics. Cytoplasmic DA has a fate similar to NE. It is pumped back into vesicles by VMAT2 (brain) and VMAT1 (neuroendocrine tissue, adrenal glands) or degraded by MAO and COMT.

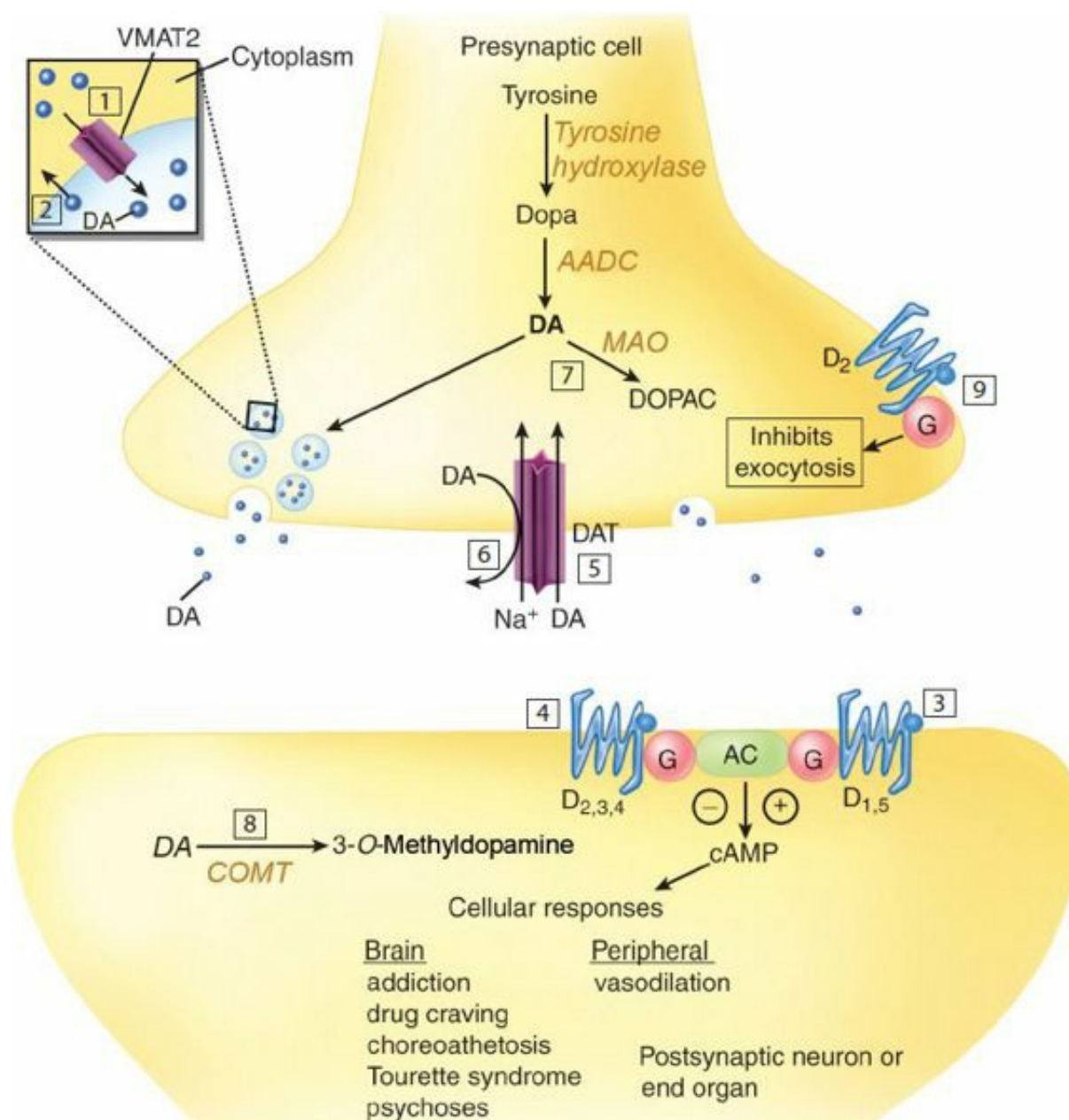


FIGURE 14–7. A dopaminergic nerve ending and postsynaptic membrane. Dopamine (DA) released from nerve endings binds to various postsynaptic DA receptors (D) on neurons or peripheral end organs. Stimulation of presynaptic D₂ receptors [9] lessens DA release. Xenobiotics in Table 14–6 may act to inhibit vesicle uptake [1]; cause DA to leave the

vesicle and move into the cytoplasm [2]; activate or antagonize DA receptors [3, 4, 9]; inhibit DAT to prevent DA reuptake [5]; cause reverse transport of cytoplasmic DA (via DAT) into the synapse by raising cytoplasmic DA concentrations [6]; prevent DA degradation by inhibiting monoamine oxidase (MAO) [7]; or prevent DA degradation by inhibiting catechol-O-methyltransferase (COMT) [8]. (Both DA and dopa are substrates for COMT.) Inhibition or stimulation of adenylate cyclase by DA receptors is shown for illustration, though other G-protein-mediated effects can result. AADC = L-aromatic amino acid decarboxylase; DAT = membrane DA reuptake transporter; DOPAC = 3,4-dihydroxyphenylacetic acid; VMAT2 = vesicle membrane uptake transporter.

DOPAMINE RECEPTORS

All DA receptors are coupled to G proteins and are divided into two main groups. Dopamine D₁-like receptors (D₁ and D₅) are expressed as various subtypes and are linked to G_s to stimulate adenylate cyclase and to raise cAMP concentrations.¹⁸¹ D₁ receptors are found in the nuclei of the basal ganglia and the cerebral cortex, and D₅ receptors are concentrated in the hippocampus and hypothalamus. Dopamine is five to 10 times more potent at D₅ receptors than it is at D₁ receptors.

D₂-like receptors (D₂, D₃, D₄) are linked to G_{i/o} to produce several actions, including inhibition of adenylate cyclase and the lowering of cAMP concentrations. Again, numerous subtypes of receptors exist (eg, D_{2s}, D_{2L}). D₂ receptors are concentrated in the basal ganglia and limbic system. Some D₂ receptors also reside on presynaptic membranes, where their activation limits neurotransmitter release, including the peripheral release of NE (Figs. 14–5 and 14–7). D₃ receptors are concentrated in the hypothalamic and limbic nuclei, whereas D₄ receptors are concentrated in the frontal cortex and limbic nuclei (rather than basal ganglia nuclei). Most agonists bind to the D₃ receptors with higher affinity than to D₂ receptors, whereas most antagonists bind preferentially to D₂ receptors.^{100,178} Most agonists and antagonists express a lower affinity for D₄ receptors than they express for D₂ receptors; a notable exception is clozapine.

Xenobiotics

Table 14–6 provides examples of xenobiotics that affect dopaminergic neurotransmission.

TABLE 14–6. Examples of Xenobiotics Affecting Dopaminergic Neurotransmission

Dopamine agonism

Direct stimulation of dopamine receptors

Apomorphine

Bromocriptine

Cabergoline

l-Dopab

Fenoldopam

Lisuride

Pramipexole

Ropinirole

Inhibit dopamine metabolism

MAOIs

COMTIs

Indirect acting

Amantadine

Amphetamine

Benztropine

Diphenhydramine

MAOIs

Methylphenidate

Pemoline

Trihexyphenidyl

Inhibit dopamine reuptake

Amantadine

Amphetamine

Benztropine

Bupropion

Cocaine

Diphenhydramine

Methylphenidate

Orphenadrine

Trihexyphenidyl

Increase dopamine receptor sensitivity

Amphetamine

Antipsychotics

Metoclopramide

Phenytoin

Dopamine antagonism

Block dopamine receptors

Amoxapine

Aripiprazole

Buspirone

Butyrophenones

Clozapine

Cyclic antidepressants

Domperidone

Loxapine

Metoclopramide

Olanzapine

Phenothiazines

Pimozide

Quetiapine

Risperidone

Thioxanthenes

Ziprasidone

Destroy dopaminergic neurons

MPTP/MPP⁺

Prevent vesicle dopamine uptake

Reserpine

Tetrabenazine

^aAssociated with fibrotic valvulopathy due to 5-HT_{2B} agonism. ^bMetabolized to dopamine, which acts as an agonist.

COMTI = catechol-o-methyltransferase inhibitor; MAOI = monoamine oxidase inhibitor; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP⁺ = 1-methyl-4-phenylpyridinium.

Dopamine Agonism. Indirect-acting and mixed-acting xenobiotics. Most indirect-acting and mixed-acting sympathomimetics cause DA release. The mechanism of action is similar to that causing NE release. These xenobiotics diffuse into the neuron or undergo uptake by DAT before being transported into vesicles by VMAT2 where they buffer protons and displace DA into the cytoplasm for reverse transport by DAT into the synapse. Benztropine, diphenhydramine, trihexyphenidyl, and orphenadrine also cause DA release, perhaps contributing to their abuse potential, which is noted below.¹³⁹ Excessive dopaminergic activity following therapeutic doses or overdoses of decongestants (eg, pseudoephedrine), amphetamines, methylphenidate, and pemoline can produce acute choreoathetosis and Gills de la Tourette syndrome.^{25,116} Ingestion of excessive doses of L-dopa (which is converted to DA) may present with similar symptoms.

Direct agonists. Bromocriptine is an ergot derivative that directly activates DA receptors (mainly D₂-like). Toxic effects include those described above for indirect-acting agents. Apomorphine directly activates D₂ receptors. Such action at the chemoreceptor trigger zone (CTZ) produces vomiting, whereas agonism in the basal ganglia explains the use of apomorphine in the treatment of Parkinson disease. Fenoldopam is a D₁ receptor agonist that is used as a vasodilator in the treatment of hypertensive emergencies.

D₁-like and D₂-like receptor activation is the predominant mediator of locomotor effects from DA agonists. Activation of either D₁-like or D₂-like receptors produces antiparkinsonian effects.^{76,178} Cabergoline, ropinirole, and pramipexole are D₂-like receptor agonists used to treat Parkinson disease.^{11,51,71}

Reuptake inhibition. Xenobiotics inhibiting DAT prevent DA reuptake and include cocaine, amphetamines, methylphenidate, and probably amantadine. Increased dopaminergic activity from cocaine toxicity may produce choreoathetosis and Gills de la Tourette syndrome. In general, antidepressants are not strong DA reuptake blockers. However, bupropion appears to be more active in this regard.¹⁷³

As noted earlier, much of the craving and addiction produced by sympathomimetics probably results from excessive dopaminergic activity in the mesolimbic system.¹⁹² Interestingly, the anticholinergics benztropine, diphenhydramine, trihexyphenidyl, and orphenadrine are also DA reuptake inhibitors, possibly explaining their abuse potential.^{139,188} In fact, benztropine is one of the most potent DA reuptake inhibitors known. Amantadine, an antiparkinsonian drug that causes DA release and some inhibition of DA reuptake (as well as being anticholinergic), is also abused.

Increased receptor sensitivity. Several xenobiotics are thought to increase sensitivity of DA receptors, resulting in choreoathetosis, even with therapeutic doses (eg, phenytoin). Evidence exists that increased DA receptor sensitivity may be

responsible for movement disorders resulting from amphetamines.²⁸ Tardive dyskinesia (discussed below) may also result from increased DA receptor sensitivity and occurs following chronic administration of D₂ receptor antagonists.

MAO inhibition. MAOIs inhibit the breakdown of cytoplasmic DA. Some of the food and drug interactions with MAOIs result from excessive release of DA from nerve endings.

COMT inhibition. COMT inhibitors (eg, entacapone, tolcapone) are given with levodopa to patients with Parkinson disease to prevent peripheral degradation of levodopa to 3-O-methyldopa. This allows more levodopa to traverse the blood–brain barrier and to be converted to DA by neuronal dopa decarboxylase. Tolcapone also inhibits COMT in the brain.⁸⁹ Other substrates of COMT include dopa, DA, NE, EPI, and their hydroxylated metabolites. COMT inhibitors might potentiate the effects of these drugs when administered intravenously.⁸⁹

Dopamine Antagonism. **Direct receptor blockade.** Blockade of DA receptors is the specific aim of many therapeutics. The antipsychotic actions of butyrophenones, phenothiazines, and other antipsychotics mainly correlate with their ability to block D₂-like receptors. Many phenothiazines block both D₁-like and D₂-like receptors, whereas haloperidol mainly blocks D₂-like receptors. Unfortunately, antipsychotics and metoclopramide also block DA receptors in the striatum, producing various extrapyramidal symptoms, including acute parkinsonism and dystonias.

Atypical antipsychotics produce fewer extrapyramidal effects and are thought to carry less risk of producing tardive dyskinesia.¹⁷⁰ The relative affinity of an antipsychotic for 5-HT_{2A} receptors over D₂ receptors has predictive value for atypicals with a lower risk of extrapyramidal symptoms.¹⁶⁰ These include clozapine, olanzapine, quetiapine, risperidone, and ziprasidone.

The ratio of muscarinic (M₁) blockade to D₂-receptor blockade is also important in limiting extrapyramidal symptoms. Antipsychotics exhibiting strong antimuscarinic effects (eg, olanzapine, clozapine, thioridazine) are also less likely to induce extrapyramidal symptoms.¹⁷⁰

Buspirone, an anxiolytic, antagonizes D₂ receptors, which explains occasional extrapyramidal reactions. Various cyclic antidepressants, especially amoxapine, block D₂ receptors to some extent.

The chronic use of dopamine receptor antagonists causes upregulation of DA receptors. The continued use of or, especially, withdrawal of DA receptor antagonists (antipsychotics, metoclopramide, and occasionally antidepressants) can result in excessive dopaminergic activity and tardive dyskinesia, characterized by choreiform movements typical of excessive dopaminergic influence in the striatum.

The blockade of DA receptors by numerous xenobiotics, including butyrophenones, phenothiazines, and metoclopramide, can produce a poorly understood disorder called neuroleptic malignant syndrome. Neuroleptic malignant syndrome may also rarely follow acute withdrawal of DA agonists (eg, stopping L-dopa, bromocriptine, or tolcapone). Neuroleptic malignant syndrome is characterized, in part, by mental status changes, autonomic instability, rigidity, and hyperthermia.

Indirect Antagonism. Reserpine and tetrabenazine inhibit VMAT to prevent transport of DA into storage vesicles and deplete nerve endings of DA. In fact, reserpine was used as an antipsychotic before the introduction of phenothiazines. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a meperidine analog, undergoes activation by MAO, including that in glial cells, to a metabolite, 1-methyl-4-phenylpyridinium (MPP⁺), that undergoes uptake by and causes death of dopaminergic neurons. Both MAOIs and inhibitors of DA transporters prevent MPTP-induced destruction of dopaminergic neurons.

SEROTONIN

Serotonin (5-HT, 5-OH-tryptamine) is an indole alkylamine found throughout nature (animals, plants, venoms) and has the most complex receptor family of all known neurotransmitters. In the CNS, several hundred thousand serotonergic neurons lie in or in juxtaposition to numerous midline nuclei in the brainstem (raphe nuclei), from which they project to virtually all areas of the brain and spinal cord. Serotonin is involved with mood, emotion, learning, memory, personality, affect, appetite, aggression, motor function, temperature regulation, sexual activity, pain perception, sleep induction, and other basic functions. Serotonin is not essential for any of these processes, but modulates their quality and extent. A number of psychiatric disorders, including depression, anxiety, obsessive-compulsive disorder, dementia, schizophrenia, and eating disorders, are linked to altered serotonin function. Consequently, modification of serotonergic neurotransmission is an integral part of the treatment plan for most of these conditions.¹⁶⁵

The serotonergic system is extremely diverse, with 14 types of receptors that act to stimulate or inhibit neurons, including those of other neurotransmitter systems. Serotonin is also the precursor for the pineal hormone, melatonin. Despite the important role 5-HT plays in the CNS, less than 5% of the body's 5-HT is found within the CNS, with the great majority of 5-HT being located within enterochromaffin cells of the intestine and a small amount of serotonin sequestered by platelets.¹⁵

Peripherally, 5-HT is released by enterochromaffin cells in response to intestinal stimulation, which contributes to peristalsis and fluid secretion. Platelets take up 5-HT while passing through the enteric circulation. Serotonin is released from activated platelets to interact with other platelet membranes (promote aggregation) and with vascular smooth muscle.¹⁵

Experimentally, 5-HT exhibits diverse effects on the cardiovascular and peripheral nervous systems, although the importance of these actions remains uncertain in the normal physiologic state. Serotonin-induced vasoconstriction or vasodilation found in experimental studies involves multiple types of 5-HT receptors and, in turn, is influenced by multiple other factors. 5-HT_{1B} receptor agonists (eg, sumatriptan) produce coronary artery vasoconstriction in some patients as an adverse event.^{147,210}

Centrally, it is particularly difficult to ascribe a specific symptom or physical finding to serotonergic neurons because of the diversity of their physiologic actions. However, 5-HT definitely plays an important role in the action of many hallucinogenic or illusionogenic drugs, which act as partial agonists at cortical 5-HT₂ receptors. Proserotonergics are used to treat depression, whereas 5-HT receptor (5-HT₂) antagonists have greater importance in the management of schizophrenia.⁶⁴

Generally, in areas where they overlap, 5-HT acts in opposition to DA. For example, 5-HT serves to increase prolactin, adrenocorticotrophic hormone (ACTH), and growth hormone secretion, whereas DA decreases prolactin secretion. As another example, activation of basal ganglial 5-HT_{2A} receptors inhibits DA release.⁶⁴ However, well-known exceptions exist, such as cortical 5-HT₃ receptors³¹ and 5-HT_{1A} receptors that are capable of promoting DA release under certain circumstances.¹⁴⁴

Synthesis, Release, and Reuptake

Serotonin does not cross the blood–brain barrier. It is synthesized from the amino acid Ltryptophan, which passes through the blood–brain barrier using a neutral amino acid transporter. **Figure 14–8** illustrates 5-HT synthesis. Tryptophan-5-hydroxylase is the rate-limiting enzyme of 5-HT synthesis. Increases in tryptophan are predictably accompanied by increased 5-HT production. L-Amino acid decarboxylase (dopa decarboxylase) converts 5-hydroxytryptophan to 5-HT. Cytoplasmic 5-HT is transported into vesicles by VMAT2, where it is concentrated by ion trapping before release by Ca²⁺-dependent exocytosis. In contrast to vesicles containing DA or NE, 5-HT vesicles contain almost no ATP. After release into the synapse, a transporter (SERT) in the neuronal membrane moves 5-HT back into the neuron, where it reenters vesicles or is degraded by MAO.¹⁶⁵

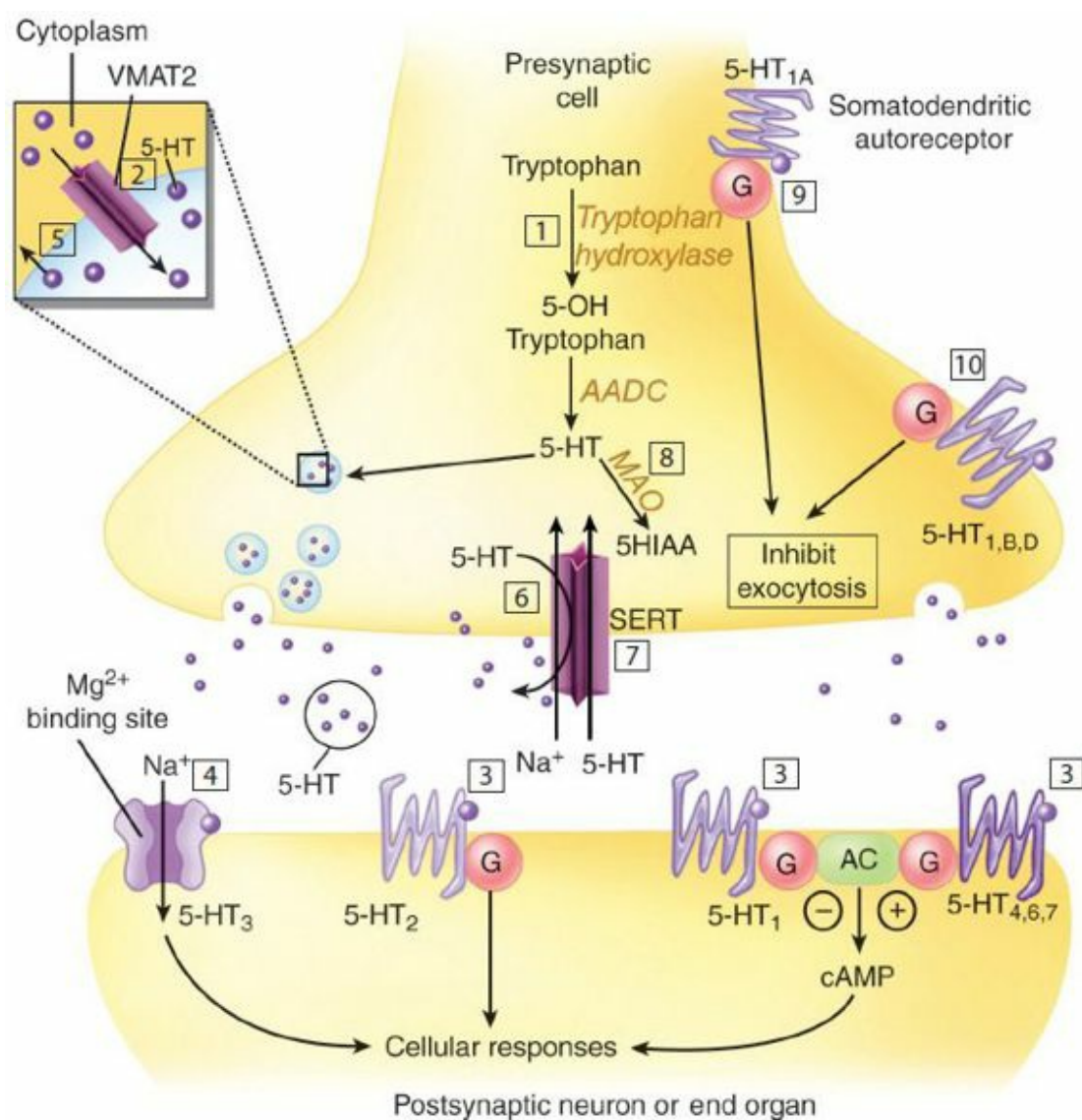


FIGURE 14–8. A serotonergic nerve ending and postsynaptic membrane. Tryptophan hydroxylase [1] converts tryptophan to 5-hydroxytryptophan (5-OH-tryptophan). Aromatic L-amino acid decarboxylase (AADC) then metabolizes 5-OH-tryptophan to serotonin (5-HT). Serotonin is concentrated within vesicles through uptake by VMAT2 before exocytosis [2]. After uptake into the neuron by SERT [7], 5-HT is transported back into vesicles or undergoes degradation by monoamine oxidase (MAO) to an intermediate compound, which is converted to 5-hydroxyindoleacetic acid (5-HIAA) [8]. 5-HT_{1,2,4,6,7} receptors [3,9,10] are coupled to G proteins, while 5-HT₃ receptors [4] are ligand-gated cation channels that may conduct Na⁺ and/or Ca²⁺ (only Na⁺ is illustrated). 5-HT₃ cation channels also appear to be blocked by Mg²⁺ until the cell is depolarized, allowing Mg²⁺ to dissociate—a mechanism similar to that found at NMDA glutamate receptors. In addition to residing on postsynaptic membranes, 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors serve as presynaptic autoreceptors that, when stimulated, decrease further release of 5-HT [9,10]. Presynaptic 5-HT_{1A} receptors mainly serve as somatodendritic autoreceptors, whereas presynaptic 5-HT_{1B} and 5-HT_{1D} receptors serve as terminal autoreceptors. Xenobiotics in Table 14–7 act to enhance 5-HT synthesis [1]; inhibit VMAT2 to prevent vesicle uptake of 5-HT [2]; raise cytoplasmic concentrations of 5-HT, resulting in reverse transport of 5-HT into the synapse by SERT [6]; by displacing 5-HT from vesicles [5] or inhibiting MAO [8]; activate or antagonize 5-HT receptors [3,4,9,10]; or by inhibiting 5-HT reuptake [7]. G = G protein; SERT = membrane 5-HT uptake transporter; VMAT2 = vesicle membrane uptake transporter.

Serotonin is preferentially metabolized by the MAO-A isozyme. Paradoxically, the serotonergic nerve terminal is almost devoid of MAO-A, but contains abundant amounts of MAO-B. It has been hypothesized that the large amounts of MAO-B metabolize other xenobiotics that might inappropriately promote 5-HT release (eg, dopamine). However, the small amount of MAO-A found in serotonergic neurons provides adequate degradation of 5-HT.¹⁴²

Serotonin Receptors

There are seven major functioning receptor types (5-HT₁–5-HT₇) and numerous subtypes.

5-HT₁ Receptors. Receptors in the 5-HT₁ class are coupled to G proteins and commonly increase K⁺ efflux and decrease cAMP concentrations. Members of the 5-HT₁ receptor class express greatest affinity for 5-HT and are thus

biologically active under normal physiologic conditions. 5-HT_{1A} receptors reside predominantly on raphe nuclei, where they act as somatodendritic autoreceptors.^{101,132,151} Hippocampal 5-HT_{1A} receptors reside postsynaptically, where they also inhibit through similar mechanisms.¹⁰¹

Central 5-HT_{1D} and 5-HT_{1B} receptors primarily act as inhibitory terminal autoreceptors and heteroreceptors. They are found less commonly on postsynaptic membranes.¹⁶⁵ Originally 5-HT_{1B} receptors were not believed to exist in humans. However, most of the actions described in older literature regarding 5-HT_{1D} receptors can now be attributed to 5-HT_{1B} receptors. Cranial blood vessels (eg, meninges) possess 5-HT_{1D} and 5-HT_{1B} receptors, whose activation produces vasoconstriction and decreased inflammation.^{147,165}

5-HT_{1E} and 5-HT_{1F} receptors are more recently discovered members of the 5-HT₁ receptor class. Their functional activity is yet to be determined.

5-HT₂ Receptors. The three subtypes of 5-HT₂ receptors are coupled to G proteins, thus serving to decrease K⁺ efflux and/or increase intracellular Ca²⁺ concentration by raising concentrations of inositol triphosphate and diacylglycerol.¹⁶⁵ The three subtypes of 5-HT₂ receptors are so similar in characterization that investigational probes have great difficulty in distinguishing the subtypes. 5-HT_{2A} receptors are most concentrated in the cerebral cortex, where they serve as excitatory postsynaptic receptors. Their activation increases glutamate release from pyramidal cells, but also can lead to release of GABA.¹³⁰ 5-HT_{2A} receptors also reside on platelets, where their activation produces platelet aggregation. 5-HT_{2C} receptors (previously 5-HT_{1C}) reside on the choroid plexus, where they regulate cerebrospinal fluid production. Activation of 5-HT_{2B} receptors in the GI tract promotes stomach contraction.¹⁶⁵ At least some xenobiotics that activate 5-HT_{2B} receptors on cardiac valves cause a valvulopathy identical to that of carcinoid syndrome, though both sides of the heart can be involved following 5-HT_{2B} agonists, whereas carcinoid syndrome usually affects the right sided valves.²⁴

5-HT₃ Receptors. 5-HT₃ receptors are isopentameric ligand-gated cation channels that are structurally similar to ACh nicotinic receptors, GABA_A Cl⁻ channels, glycine, and NMDA glutamate receptors.³¹ They are localized to both presynaptic and postsynaptic membranes. Upon activation, postsynaptic receptors stimulate the neuron by opening the channel to cause depolarization through Na⁺ and/or Ca²⁺ influx. In addition, these channels are normally blocked by Mg²⁺ in a voltage-dependent manner similar to glutamatergic NMDA receptors (see Glutamate later). Centrally, 5-HT₃ receptors are expressed diffusely, but are especially concentrated in the CTZ, where their activation induces emesis.¹⁶⁵ In the cerebral cortex, their activation leads to increased release of DA and decreased release of ACh.³¹ Cortical 5-HT₃ receptors are frequently identified on GABA interneurons where they increase inhibitory, GABAergic tone. In contrast to cerebral actions, activation of peripheral 5-HT₃ receptors on cholinergic nerves in the gut enhances ACh release to increase gastrointestinal motility.¹⁴⁰

5-HT₄ Receptors. 5-HT₄ receptors are coupled to G proteins (G_s). Their activation leads to increased cAMP concentrations. 5-HT₄ receptors are scattered diffusely throughout the brain, and their exact role remains undefined, although they are known to increase the release of ACh.¹⁴⁰ Peripheral 5-HT₄ receptors reside in the heart, intestines, and adrenal gland where their activation produces tachycardia, aldosterone and cortisol release, and contraction of gut and bladder smooth muscle. Whether these actions are important under normal physiologic conditions is not clear, but peripheral 5-HT₄ receptors promote the release of ACh and increase gut motility.¹⁴⁰

5-HT₅ Receptors. 5-HT₅ receptors exist in two subtypes: 5-HT_{5a} and 5-HT_{5b}. Humans only have the 5-HT_{5a} subtype, which is coupled to G_{i/o}.¹⁶⁵ This receptor may act as a somatodendritic autoreceptor but the functionality of this role is unknown, in contrast to the predominant importance of 5-HT_{1a} autoreceptors.

5-HT₆ and 5-HT₇ Receptors. 5-HT₆ and 5-HT₇ receptors are positively coupled to cAMP formation through G proteins.¹⁶⁵ Their distribution is poorly defined. However, many antidepressants and antipsychotics antagonize these receptors. They are currently a source of great interest because of the possibility of avoiding DA blockade to achieve antipsychotic activity. The 5-HT₇ receptor may be particularly important in regulating circadian rhythms.¹⁰⁶

Xenobiotics

Table 14–7 provides examples of xenobiotics that affect serotonergic neurotransmission.

TABLE 14–7. Examples of Xenobiotics Affecting Serotonergic Neurotransmission

Serotonin Agonism

Enhance 5-HT synthesis

l-Tryptophan

5-Hydroxytryptophan

Direct 5-HT agonists

Buspirone

Cisapride

Ergots and indoles

Hallucinogenic substituted amphetamines

mCPP

Lisuride

Mescaline

Metoclopramide

Triptans

Vilazodone

Increase 5-HT release

Amphetamine

Cocaine

Dexfenfluramine

Dextromethorphan

l-Dopa

Fenfluramine

MDMA

Mirtazapine

Reserpine (initial)

Increase 5-HT tone by unknown mechanism

Lithium

Inhibit 5-HT breakdown

MAOIs

Inhibit 5-HT reuptake

Amoxapine

Amphetamines

Atomoxetine

Carbamazepine

Citalopram

Clomipramine

Cocaine

Cyclic antidepressants

Dextromethorphan

Duloxetine

Escitalopram

Fluoxetine

Fluvoxamine

Lamotrigine

Meperidine

Nefazodone

Sertraline

Tramadol

Trazodone

Venlafaxine Vilazodone

Serotonin Antagonism

Direct 5-HT antagonists

Agomelatine

Aripiprazole

Clozapine

Cyclic antidepressants

Cyproheptadine

Ergots and indoles (eg, LSD)

Haloperidol

Ketanserin

Mescaline

Methysergide

Metoclopramide

Mirtazapine

Nefazodone

Olanzapine
Ondansetron
Paliperidone
Phenothiazines
Phentolamine
Propranolol
Quetiapine
Risperidone
Trazodone
Ziprasidone
Enhance 5-HT uptake
Tianeptine
Inhibit vesicle uptake
Reserpine
Ketanserin
Tetrabenazine

^aClomipramine is the most potent 5-HT uptake inhibitor of the tricyclic antidepressants.

5-HT, serotonin; LSD = lysergic acid diethylamide; MAOI = monoamine oxidase inhibitor; mCPP = m-chlorophenylpiperazine (metabolite of trazodone and nefazodone); MDMA = methylenedioxymethamphetamine.

Serotonin Agonists. The body rapidly metabolizes orally administered 5-HT via intestinal and hepatic MAO. However, L-tryptophan is an amino acid precursor to 5-HT that is readily absorbed by the intestinal tract. This method of augmenting CNS 5-HT production was previously used as an unproved sleep aid until it was associated with the eosinophilia myalgia syndrome in 1990. 5-Hydroxytryptophan (5-HTP) is the immediate precursor to 5-HT. 5-HTP is commonly available without a prescription. The anxiolytics, buspirone, gepirone, and ipsapirone act as partial agonists at somatodendritic and postsynaptic 5-HT_{1A} receptors. Sumatriptan, an antimigraine medication, mainly activates 5-HT_{1D} and 5-HT_{1B} receptors.¹⁴⁷ The action of sumatriptan may result from vasoconstriction of meningeal and other cranial, extracerebral vasculature; no impairment of cerebral blood flow follows its use. Other members of the triptan class include rizatriptan, zolmitriptan, and naratriptan. Vilazodone is an antidepressant with both partial 5-HT_{1A} receptor agonism and SERT inhibition.⁴⁴

Metoclopramide and tegaserod are prokinetic drugs that activate 5-HT₄ receptors to increase gut motility.¹⁴⁰ Because 5-HT₄ receptors are also found in the heart and urinary bladder detrusor muscle, 5-HT₄ agonists occasionally produce urinary incontinence and tachycardia.

Numerous indoles and phenylalkylamines, including ergot alkaloids, lysergic acid diethylamide (LSD), psilocybin, and mescaline, exhibit both agonistic and antagonistic properties at multiple 5-HT receptors. Their hallucinogenic/illusionogenic action is best explained by partial agonism at 5-HT_{2A} receptors.⁶⁴ Some substituted amphetamines (eg, methylenedioxymethamphetamine, XTC) directly stimulate 5-HT receptors.¹⁹⁸

Cocaine and indirect-acting sympathomimetics, especially amphetamines, cause 5-HT release as previously described.¹⁹⁸ Centrally, DA undergoes uptake into serotonergic neurons to displace 5-HT from the neuron. Ingestion of L-dopa or other xenobiotics that increase synaptic DA concentrations can cause 5-HT release.¹³²

Inhibitors of 5-HT reuptake include amphetamines, cocaine, various antidepressants, meperidine, tramadol, and dextromethorphan. Several antidepressants specifically inhibit 5-HT reuptake. Examples of selective 5-HT reuptake inhibitors (SSRIs) include fluoxetine, sertraline, paroxetine, and citalopram. The use of SSRIs sometimes produces

extrapyramidal side effects for reasons that remain unclear because of the numerous actions of 5-HT in the basal ganglia.⁷⁴ Two anticonvulsants, carbamazepine and lamotrigine, appear to inhibit 5-HT reuptake.¹⁹¹ Again, reserpine and tetrabenazine prevent 5-HT uptake into vesicles.

MAO-A accounts for most 5-HT degradation, and nonspecific MAOIs and MAO-A inhibitors (clorgyline, moclobemide) raise 5-HT concentrations and, through indirect action, probably cause 5-HT release. Some medications (eg, methylene blue, procarbazine, linezolid) have the undesired side effect of causing MAO inhibition, which occasionally produces serotonin toxicity when combined with other serotonergic drugs.

Serotonin Antagonists. Trazodone and nefazodone act mainly as antagonists at 5-HT₂ receptors, but are also weak reuptake inhibitors. Both undergo metabolism to m-chlorophenylpiperazine (mCPP), which activates most 5-HT receptors, but is especially active at 5-HT_{2C} receptors. Agomelatine is a novel antidepressant that antagonizes 5-HT_{2C} receptors and stimulates melatonin MT₁ and MT₂ receptors.⁵⁰ Ketanserin and ritanserin specifically antagonize 5-HT_{2C} receptors, while methysergide and cyproheptadine antagonize 5-HT₁ and 5-HT₂ receptors.¹⁴²

Mirtazapine exhibits complex actions, including antagonism of 5-HT_{2A}, 5-HT_{2C}, and 5-HT₃ receptors.⁶⁶ It also indirectly increases 5-HT_{1A} activity and enhances release of NE through antagonism of α_2 -adrenergic receptors. Mirtazapine demonstrates potent antagonism of histaminic and muscarinic receptors.⁶⁶

Most antipsychotics and tricyclic antidepressants antagonize 5-HT_{2A} and, to a lesser extent, 5-HT_{2C} receptors. In fact, investigators are interested in developing antipsychotics similar to risperidone that possess potent antagonistic properties at 5-HT₂ receptors, without accompanying potent DA receptor antagonism, in order to limit extrapyramidal side effects. These investigations have resulted in the introduction of olanzapine, sertindole, ziprasidone, zotepine, quetiapine, and amisulpride.¹³⁰

Ondansetron, granisetron, tropisetron, dolasetron, and alosetron antagonize 5-HT₃ receptors.¹⁴⁰ Their antiemetic action is thought to be explained by several mechanisms. Central antagonism at the CTZ lessens vomiting. Peripheral 5-HT₃ receptor antagonism in the gut prevents ACh release, decreasing gut motility. Finally, antagonism of vagal 5-HT₃ receptors decreases afferent stimulatory signals to the vomiting center in the brainstem. Metoclopramide antagonizes 5-HT₃ and D₂ receptors. Ondansetron and some experimental 5-HT₃ antagonists are being studied in the treatment of schizophrenia because of their ability to prevent DA release.

Tianeptine is an antidepressant with several pharmacologic effects, including enhancement of 5-HT reuptake, thus lowering synaptic 5-HT concentrations.¹⁶³

Serotonin Toxicity. Serotonin toxicity (formerly called serotonin syndrome) represents an iatrogenic and largely idiosyncratic condition that is most commonly caused by the combination of two or more proserotonergic xenobiotics, although it can happen following single 5-HT agonists in overdose or at therapeutic dosages.¹³⁶ Animal models indicate that serotonin toxicity can be prevented by the blockade of 5-HT_{1A} receptors and 5-HT_{2A} receptors.^{81,142,144} Serotonin toxicity is characterized by alterations in mentation and cognition, autonomic nervous system dysfunction, and neuromuscular abnormalities. Symptoms may include confusion, agitation, convulsions, coma, tachycardia, diaphoresis, hyperthermia, hypertension, shivering, myoclonus, tremor, hyperreflexia, and muscle rigidity (especially of legs).¹³⁶ Serotonin toxicity is often confused with neuroleptic malignant syndrome in its more severe presentation due to their similar manifestations. Serotonin toxicity usually responds to supportive care alone but may improve with 5-HT_{1A} and 5-HT_{2A} receptor antagonists such as cyproheptadine.^{22,136} Serotonin toxicity can be caused by xenobiotics, increasing CNS 5-HT neurotransmission (Table 14–7). In addition, xenobiotics that act to increase CNS DA concentrations, such as levodopa and bromocriptine, have potential to precipitate serotonin syndrome by indirectly causing 5-HT release (Chap. 75).

γ -Aminobutyric Acid

GABA is one of two main inhibitory neurotransmitters of the central nervous system (glycine is discussed later). Xenobiotics that enhance GABA activity are generally used as anticonvulsants, sedative-hypnotics, anxiolytics, and general anesthetics. Xenobiotics that antagonize GABA activity typically produce CNS excitation and convulsions. GABA is synthesized from glutamate, the brain's main excitatory neurotransmitter.

In general, GABA inhibition predominates in the brain. In the spinal cord, through monosynaptic and polysynaptic reflex pathways, GABA mediates a number of physiologically minor peripheral effects outside the CNS (eg, vasodilation, bladder relaxation). Spinal cord GABA is important in attenuating skeletal muscle reflex arcs.¹²²

Synthesis, Release, and Reuptake

Figure 14–9 illustrates GABA synthesis. Glutamate is converted to GABA via glutamic acid decarboxylase (GAD), which

requires pyridoxal phosphate (PLP) as a cofactor. Pyridoxal phosphate is synthesized from pyridoxine (vitamin B₆) by the enzyme pyridoxine kinase (PK).¹³³ VGAT, a vesicle-bound transporter, transports GABA into vesicles from where it is released through Ca²⁺-dependent exocytosis into the synapse.¹²² Reuptake of GABA from the synapse back into the presynaptic neurons is mediated by the Na⁺-dependent transporter, GAT-1, whereas uptake into glial cells and possibly postsynaptic neurons is mediated by GAT-2, GAT-3, and GAT-4. Evidence also suggests that GABA is released into the synapse from cytoplasm by reverse transport under some conditions. In glial cells, cytoplasmic GABA can undergo degradation by GABA-transaminase (GABA-T) to succinic semialdehyde (SSA), part of which then undergoes oxidation to succinate. GABA-T also requires PLP as a cofactor.¹⁵⁰ The transamination of GABA to SSA by GABA-T results in the conversion of α -ketoglutarate to glutamate, which then moves back into neurons to be used for resynthesis of GABA.

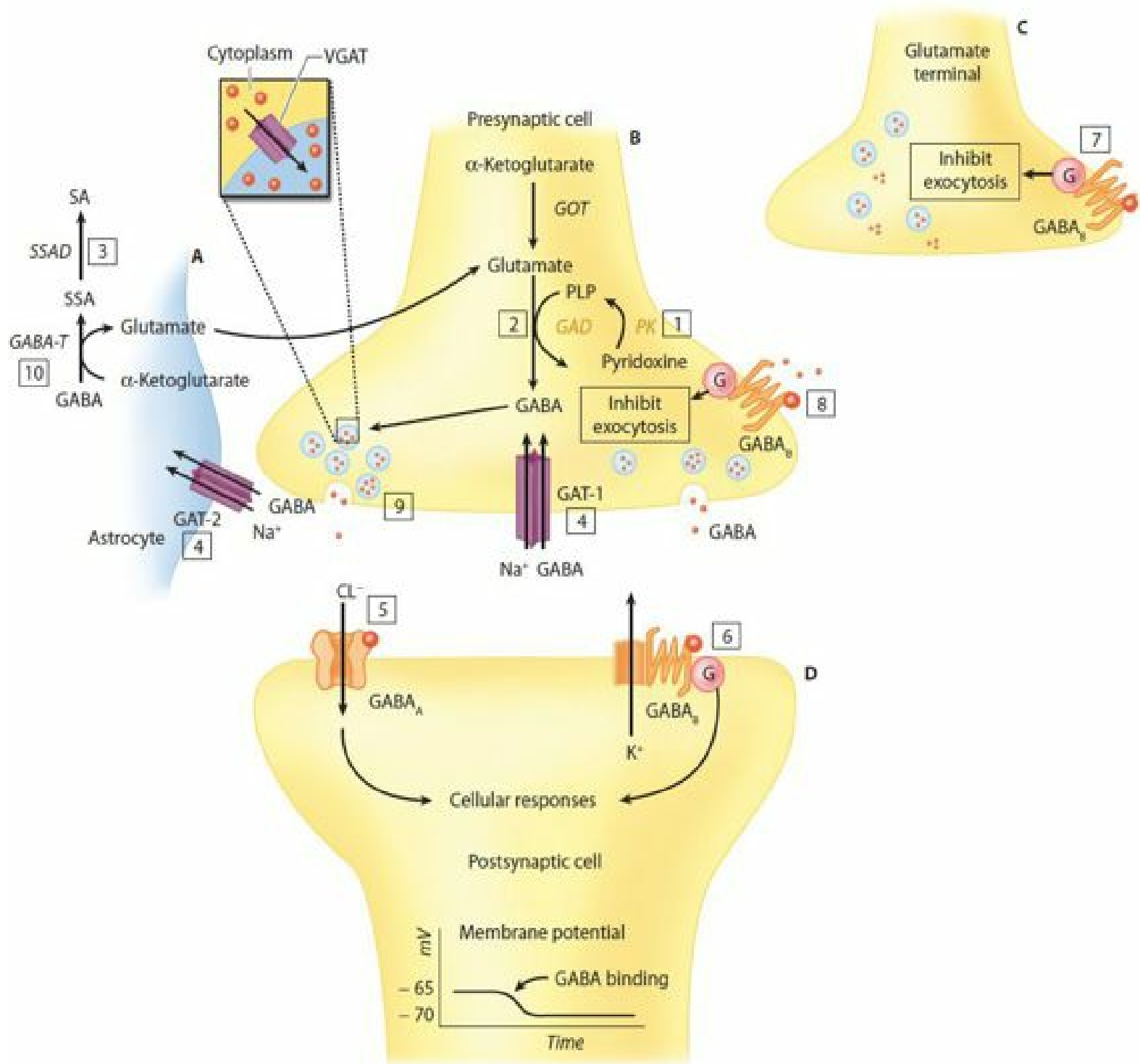


FIGURE 14–9. GABAergic neurotransmission. γ -aminobutyric acid (GABA) released from a presynaptic neuron (B) binds to postsynaptic GABA_A or GABA_B receptors to hyperpolarize and inhibit neuron D [5,6] or to presynaptic GABA_B heteroreceptors on neuron C [7] to inhibit neurotransmitter release by blocking Ca²⁺ influx (an excitatory glutamatergic neuron is shown as an example). Stimulation of GABA_B autoreceptors on neuron B [8] also reduces further release of GABA. Synaptic GABA undergoes reuptake into the presynaptic neuron by GAT-1, and uptake into glial cells and possibly postsynaptic neurons by GAT-2, GAT-3, and GAT-4 (GAT-2 is shown mediating uptake into glial cell A as an example.) Acute falls in pyridoxal phosphate (PLP) lead to impaired glutamic acid decarboxylase (GAD) activity and low GABA

concentrations. Although GABA-transaminase (GABA-T) also requires PLP, acute falls in PLP do not affect this enzyme as dramatically because of tight PLP binding to the GABA-T complex. Xenobiotics in Table 14–9 act to impair PLP formation by inhibiting pyridoxine kinase (PK) [1]; to increase GABA concentrations by either stimulating GAD [2] or inhibiting SSAD [3]; to inhibit GABA reuptake [4]; to stimulate or block GABA receptors [5–8]; to cause GABA release [9]; or to inhibit GABA-T [10]. Glutamic-oxaloacetic transaminase (GOT), GABA-T, and SSAD are mitochondrial enzymes. G = G protein; GAT = membrane GABA reuptake transporter; SA = succinic acid; SSA = succinic semialdehyde; SSAD = SSA dehydrogenase; VGAT = vesicle membrane GABA uptake transporter.

GABA Receptors

There are two main types of GABA receptors (Table 14–8). GABA_A receptors are Cl[−] channels that mediate inhibition by allowing Cl[−] to move into and hyperpolarize the neuron. Most GABA_A receptors are located postsynaptically and mediate fast or phasic inhibition. About 5% to 10% of GABA_A receptors are located outside the synapse and are responsible for slower tonic current that is present at resting membrane potential.^{73,115,141,175} Situated at various sites in relation to the GABA recognition site on the Cl[−] channel are sites for exogenous and endogenous modulators where numerous excitatory and depressant xenobiotics bind, and through which GABA_A receptor responsiveness is regulated under normal physiologic conditions (Fig. 14–10). The common denominator for modulation at the GABA_A complex is an increase or decrease in inward Cl[−] current.

TABLE 14–8. GABA Receptors and Their Characteristics		
	GABA _A	GABA _B
Receptor	Cl [−] Channel	G Protein-Coupled
Bicuculline antagonism	Yes	No
Baclofen agonism	No	Yes
Benzodiazepine agonism	Yes	No
Barbiturate agonism	Yes	No
Picrotoxin antagonism	Yes	No

GABA_A receptors exist as pentamers, composed of various subunits, and throughout the CNS there are regional variations in expressions of multiple subunit genes for GABA_A complexes. To date 19 subunits have been identified (α_1 to α_6 , β_1 - β_3 , γ_1 - γ_3 , δ , ϵ , θ , π , ρ_1 - ρ_3). GABA_A receptors are composed most commonly of two α subunits, two β subunits, and either a γ or δ subunit. Multiple isoforms of subunits exist, but within a single receptor, the isoforms of individual subunits appear to be identical. While the large numbers of isoforms and different combinations of subunits could theoretically produce more than 2000 different GABA_A Cl[−] channels, only a few dozen combinations exist naturally.^{42,141} The most common is $\alpha_1\beta_2\gamma_2$.^{11,186} Previously, GABA_C receptors were classified as a separate type of GABA receptor, but are now classified as GABA_A receptors comprising homo-oligomers and hetero-oligomers formed by ρ subunits (ρ_1 to ρ_3).

The second type of GABA receptor, GABA_B, is a G protein–coupled receptor found presynaptically, postsynaptically, and on extrasynaptic membranes. GABA_B receptors are heterodimers formed by two subunits, GABA_{B1} and GABA_{B2}. The GABA_{B1} subunit binds to GABA or other ligands such as baclofen, and the GABA_{B2} subunit couples the receptor with the effector G_{i/o} protein.¹³ GABA_B receptors are distributed both in the CNS and peripheral nervous system and mediate both presynaptic and postsynaptic inhibition.²¹ Presynaptic inhibition results from preventing Ca²⁺ influx so as to impair exocytosis of neurotransmitter vesicles, including those containing excitatory glutamate. Through presynaptic actions, GABA_B receptors serve not only as heteroreceptors for glutamatergic and other nerve terminals, but also as autoreceptors, where their activation in response to synaptic GABA provides feedback inhibition of further neurotransmitter release (Fig. 14–9). Postsynaptic inhibition is mediated by increasing K⁺ efflux through K⁺ channels, resulting in hyperpolarization of the membrane away from threshold. In addition to their effects on ion channels, GABA_B receptors, via the G_{i/o} protein, inhibit adenylate cyclase and, thus, the cAMP-protein kinase A pathway, which is necessary for the phosphorylation and upregulation of NMDA receptors.¹³

Xenobiotics

Table 14–9 provides examples of xenobiotics that affect GABAergic neurotransmission.

TABLE 14–9. Examples of Xenobiotics Affecting GABAergic Neurotransmission

<i>GABA Agonism</i>	<i>GABA Antagonism</i>
Stimulate GAD	Direct GABA _A antagonists
Valproate	Bicuculline
Direct GABA _A agonists	Cephalosporins
Muscimol	Ciprofloxacin
Progabide ^a	Imipenem
Indirect GABA _A agonists	Nalidixic acid
Barbiturates	Norfloxacin
Benzodiazepines	Ofloxacin
Chloral hydrate	Penicillins
Clomethiazole	Indirect GABA _A antagonists
Ethanol	Aztreonam
Etomidate	Clozapine
Felbamate	Cyclic antidepressants
Ivermectin	Flumazenil
Meprobamate	Lindane
Methaqualone	MAOIs
Propofol	Maprotiline
Steroids	Organic chlorine insecticides
Topiramate	Penicillins
Trichloroethanol	Pentylenetetrazol
Volatile anesthetics	Picrotoxin
Zaleplon	Inhibit GAD
Zolpidem	Cyanide
Zopiclone	Domoic acid
Direct GABA _B agonists	Hydrazines
Badofen	Isoniazid
GHB	4-Methoxypyridoxine ^d
Inhibit GABA-T	Direct GABA _B antagonists
Vigabatrin	Phaclofen ^b
Inhibit GABA reuptake	Saclofen ^b
Tiagabine	Inhibit PK
Valproate	Hydrazines ^c
	Isoniazid ^c

^aDirectly activates GABA_A and GABA_B receptors as well as being metabolized to GABA. ^bThought not to cross the blood–brain barrier in meaningful amounts. ^cMajor site of action is PK inhibition, though some direct GAD inhibition occurs. ^dFound in *Ginkgo biloba*.

GABA = γ -aminobutyric acid; GABA-T = GABA transaminase; GAD = glutamic acid decarboxylase; GHB = γ -hydroxybutyric acid; PK = pyridoxine kinase; MAOI = monoamine oxidase inhibitor.

Modulation of GABA Production and Degradation. Isoniazid (INH) and other hydrazines (eg, monomethylhydrazine from mushrooms) lower CNS GABA concentrations by several mechanisms. Most important, they compete with pyridoxine for binding to PK, impairing PLP production.¹³³ Pyridoxal phosphate binding to the GAD complex is easily reversible.¹⁵⁰ The acute decrease in PLP concentration is rapidly accompanied by impaired GABA synthesis and a decrease in GABA concentration. Lack of normal GABA inhibition produces seizures typical of hydrazine toxicity. Although PLP is also required for GABA degradation by GABA-T, acute decreases in PLP do not affect this enzyme nearly as much, because PLP is more tightly bound to the GABA-T complex and remains associated with the enzyme.¹⁵⁰ To a lesser extent, isoniazid binds to the GAD-PLP complex to prevent GABA formation.

Large ingestions of *Ginkgo biloba* seeds have resulted in recurrent seizures that may result from decreased GABA

concentrations. Ginkgo seeds contain 4-methoxypyridoxine, which acts as a competitive antagonist of pyridoxal phosphate, thereby inhibiting glutamate decarboxylase and impairing GABA synthesis.^{91,138}

Cyanide inhibits numerous enzymes besides cytochrome oxidase. Domoic acid (see Glutamate later) may also inhibit GAD.⁴³

In vitro studies demonstrate the ability of valproate to increase brain GABA concentrations, either by inhibition of succinic semialdehyde dehydrogenase or by activation of GAD.⁸⁸ Gabapentin may increase the rate of GABA synthesis in the brain by stimulating GAD, although the main mechanism of action of gabapentin is to bind to calcium channels.²⁰² Vigabatrin, an anticonvulsant, acts by irreversibly inhibiting GABA-T.¹⁹⁴

GABA_A Agonism. Figure 14–10 schematically illustrates the GABA_A receptor complex. In general, GABA_A agonists cause CNS depression, ranging from mild sedation and nystagmus to ataxia, stupor, and coma. Many indirect agonists that bind to the GABA_A complex have no activity in the absence of GABA. With some exceptions, their pharmacologic actions require the binding of GABA to its receptor and do not result from a direct effect on Cl[−] conductance exclusive of GABA binding. Many of these xenobiotics demonstrate additional actions that are not mediated through the GABA_A complex.

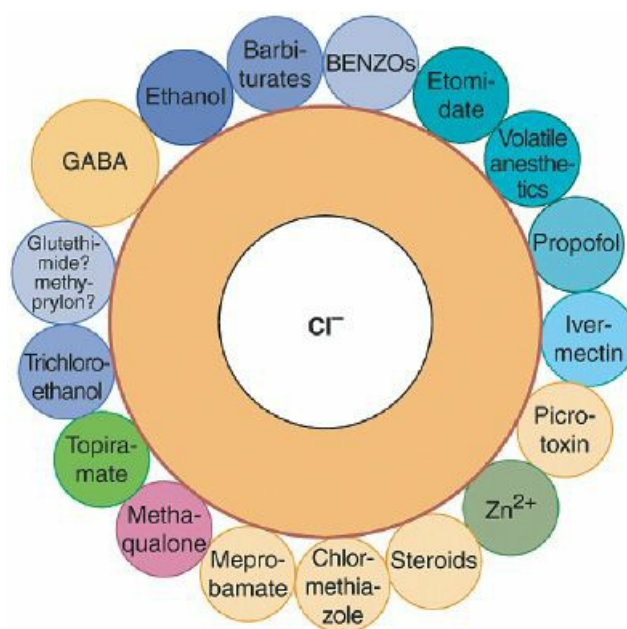


FIGURE 14–10. Representation of the GABA_A Cl[−] channel receptor complex. Benzodiazepines (BENZOs), barbiturates, picrotoxin, steroids, and GABA (γ-aminobutyric acid) clearly bind to different sites on the channel. Although separate circles represent different agents capable of binding to and of modulating Cl[−] influx through the GABA_A receptor complex, it is not always apparent where these xenobiotics bind on the channel. Chloral hydrate undergoes metabolism to trichloroethanol, which interacts with the GABA_A receptor complex. Zolpidem, zopiclone, and zaleplon are nonbenzodiazepines that bind to the benzodiazepine site. Given the structural similarity of glutethimide and methypylon to barbiturates, it is speculated that their action may be mediated at GABA_A receptors.

Direct GABA agonists. The main direct GABA agonist of toxicologic interest is muscimol, found in some poisonous mushrooms. Muscimol binds at the GABA binding site on the GABA_A complex to mimic the action of GABA.¹⁵² Ibotenic acid, a direct glutamate agonist found in the same mushrooms, is decarboxylated to muscimol just as glutamate is decarboxylated to GABA.

Indirect GABA agonists. Benzodiazepines bind to GABA_A complexes to increase the affinity of GABA for its receptor and to increase the frequency of Cl[−] channel opening in response to GABA binding.¹⁸⁵ The benzodiazepine binding site on the GABA_A receptor is located in a pocket between an α subunit and a γ₂ subunit.²¹¹ Benzodiazepines also inhibit adenosine uptake apart from GABA_A activity (see Adenosine later). The historical terms “benzodiazepine receptor” and “omega receptor” (for benzodiazepines) are being abandoned, and benzodiazepine-binding sites on subtypes of GABA_A receptors are categorized as high, intermediate, or low affinity benzodiazepine-binding sites, based on zolpidem binding.¹⁷⁴

It follows that various isoforms of GABA_A Cl[−] channels differ in their affinity for different benzodiazepines. GABA_A receptors containing γ₂ subunits are more sensitive to benzodiazepines than are GABA_A receptors containing γ₁ and γ₃ subunits. Sensitivity and response to benzodiazepine binding is also highly dependent on the specific α subunit composition of the GABA_A receptor. GABA_A receptors containing an α₄ or α₆ subunit are completely insensitive to and will not bind benzodiazepines, whereas GABA_A receptors containing α₁, α₂, α₃, or α₅ subunits are sensitive to benzodiazepine binding.

This has important implications in that the development of tolerance to ethanol confers cross-tolerance to benzodiazepines through a change in α subunits. In addition, specific subunits may mediate different effects of benzodiazepines. For example, sedating and amnestic effects are mediated through binding to α_1 subunits while anxiolytic effects appear to be mediated by binding to α_2 subunits.⁵⁷

Zolpidem, zaleplon, and zopiclone are non-benzodiazepines that act as agonists at the benzodiazepine binding site on the GABA_A receptor. They exhibit a high selectivity for the α_1 subunit and low selectivity for α_2 , α_3 , and α_5 subunits.^{189,211} This selective binding to α_1 subunits is thought to account for their relatively selective sedative properties at therapeutic doses, and lack of anxiolysis, as compared to benzodiazepines.

Barbiturates bind to the GABA_A complex to produce several effects.^{98,185} All barbiturates enhance the action of GABA by producing more Cl⁻ influx for a given amount of GABA binding by increasing the duration of Cl⁻ channel opening. Whereas phenobarbital does not change the affinity of GABA or benzodiazepines for their binding sites, depressant barbiturates, such as pentobarbital, do increase GABA and benzodiazepine binding site affinities for their ligands, further enhancing inward Cl⁻ currents. At high concentrations, at least some barbiturates directly open Cl⁻ channels to cause Cl⁻ influx.⁹⁸ Phenobarbital can directly open the Cl⁻ channel at antiepileptic concentrations. In addition, barbiturates possess other actions that depress all excitable membranes, including cardiac and smooth muscle.

The intravenous anesthetics propofol and etomidate enhance inward GABA_A Cl⁻ currents, and at high concentrations they directly open chloride channels in the absence of GABA.¹⁰ The respiratory depressant and immobilizing effects of etomidate and propofol are mediated by β_3 subunits, while the sedative effects are mediated through agonism at β_2 subunits.^{190,221} Volatile general anesthetics also directly activate GABA_A Cl⁻ channels.

Some of ethanol's action is mediated through binding to the GABA_A complex. The degree to which ethanol enhances the effect of GABA on Cl⁻ influx depends on the GABA_A receptor subunit composition. For example, receptors with an α_4 or α_6 subunit and a δ subunit respond to very low concentrations of ethanol.^{199,213}

Methaqualone produces at least part of its pharmacologic effect through indirect GABA_A activity. Little is known of the mechanisms of action of glutethimide and methyprylon. Their structural similarities to barbiturates suggest that they have activity at the GABA_A receptor. Trichloroethanol, a metabolite of chloral hydrate, and clomethiazole interact at the GABA_A complex in a manner similar to barbiturates, although it is not clear whether they are binding to an identical site on the Cl⁻ channel.²¹⁶ Ivermectin, an anthelmintic, activates GABA_A Cl⁻ channels by increasing GABA binding. Meprobamate displays barbituratelike action at the GABA_A receptor and, at high concentrations, is able to cause Cl⁻ influx in the absence of GABA.¹⁶⁹ High concentrations of felbamate also cause inward Cl⁻ currents in the presence of GABA, although this seems unimportant at therapeutic doses.¹⁶⁹ Part of the anticonvulsant action of topiramate may result from enhanced Cl⁻ influx through binding to GABA_A receptors.¹⁸⁰

Inhibition of GABA reuptake. Valproate and the anticonvulsants guvacine and tiagabine work, in part, by inhibiting GABA reuptake. Although valproate is structurally similar to GABA, its inhibition of the GABA transporter does not appear to be competitive.¹⁴⁸

GABA_A Antagonism. Direct GABA_A antagonists. Xenobiotics that act by any mechanism to decrease GABA_A activity can cause CNS excitation and convulsions by decreasing inhibitory inward Cl⁻ currents. Direct antagonists bind to the same site as GABA to prevent GABA binding, the prototype being the convulsant bicuculline. Various antibiotics interact with the GABA_A receptor to antagonize the action of GABA. In a dose-dependent manner, both imipenem and cephalosporins appear to directly antagonize GABA binding and can produce seizures at high doses or at therapeutic doses in susceptible individuals.²¹² Evidence suggests that penicillin may also directly antagonize GABA binding. Electrophysiologic and radioligand-binding studies indicate that norfloxacin, ciprofloxacin, ofloxacin, and enoxacin interact with the GABA binding site to prevent GABA binding.²¹² Theophylline and at least some NSAIDs markedly enhance GABA antagonism by some fluoroquinolones in vitro.²¹² Virol A, from *Cicuta virosa*, appears to directly antagonize binding of GABA to its receptor on the GABA_A complex.²⁰⁶

Indirect GABA_A antagonists. Penicillin is well known for producing convulsions at high doses (eg, >20 million units of penicillin per day with renal insufficiency), and both penicillin and aztreonam, a monobactam, appear to block the Cl⁻ channel to prevent GABA-mediated inward Cl⁻ currents.²¹²

Picrotoxin, from *Anamirta cocculus* (fish berries), and the experimental convulsant, pentylenetetrazol, bind to the picrotoxin site of the GABA_A receptor complex to inhibit the action of GABA. Excessive doses produce CNS excitation and convulsions. Some organochlorine insecticides (eg, lindane) also inhibit the action of GABA by binding to what appears to be the picrotoxin site and cause convulsions.¹¹⁷ Both α -thujone, the active component in wormwood oil, and

cicutoxin from the water hemlock noncompetitively antagonize GABA_A activity.^{78,207}

Flumazenil competitively antagonizes benzodiazepines, zolpidem, zaleplon, and zopiclone at their binding sites to reverse their pharmacologic effects.^{20,186} Paradoxically, large doses of flumazenil exhibit anticonvulsant activity in animals. This is explained, at least in part, by the ability of flumazenil to inhibit adenosine reuptake.^{159,195}

Cyclic antidepressants, including amoxapine and maprotiline, and at least two MAOIs (isocarboxazid and tranylcypromine) inhibit GABA-mediated Cl⁻ influx at GABA_A receptors.^{121,193} Their potency at inhibiting Cl⁻ influx correlates with the frequency of seizures that occur in patients taking therapeutic doses of these medications. Impaired GABA_A activity may contribute to or be primarily responsible for seizures that occur in patients who overdose on these xenobiotics. Their exact binding on the GABA_A receptor complex remains unknown, although some evidence suggests at least indirect activity at the picrotoxin-binding site.

Some subtypes of GABA_A receptors are susceptible to inhibition by zinc ions.¹⁸⁵ What role this plays in normal physiology or toxicology is not established.

GABA_A withdrawal. Acute withdrawal from all GABA_A direct and indirect agonists appears almost identical except for time course; the common denominator is impaired Cl⁻ influx. Withdrawal of all GABA_A agonists can cause tremor, hypertension, tachycardia, respiratory alkalosis, diaphoresis, agitation, hallucinations, and convulsions. When GABA_A receptors are chronically exposed to an agonist, changes in gene expression of receptor subunits occur, which lessens Cl⁻ influx in response to GABA or drug binding, producing tolerance. Importantly, withdrawal of the agonist produces yet further changes in subunit expression. For example, benzodiazepine-insensitive α_4 -subunit expression is increased following discontinuation of many GABA agonists, including benzodiazepines, zolpidem, zopiclone, zaleplon, neurosteroids, and ethanol. Expression of other subunits, including α_1 , γ_2 , β_2 , and β_1 also change in response to exposure and/or withdrawal of GABA_A agonists.⁵⁷ Alterations in GABA_A receptor subunit composition following chronic exposure to and withdrawal of an agonist can, therefore, affect the ability to successfully treat withdrawal symptoms. While any GABA_A receptor agonist may be used to treat withdrawal from another, some agents work better than others in different clinical settings. For example, patients experiencing severe alcohol withdrawal may have an increased proportion of GABA_A receptors containing benzodiazepine-insensitive α_4 subunits, and contain fewer GABA_A receptors with benzodiazepine-sensitive α_1 subunits.²⁷ Even extremely high doses of benzodiazepines in these patients may not effectively control severe alcohol withdrawal. A better treatment option in such a setting would be GABA_A agonists such as propofol or phenobarbital that either act on a different site on the GABA_A receptor or directly open the Cl⁻ channel.^{10,27} Phenytoin and carbamazepine do not stop GABA_A withdrawal seizures because their pharmacologic effects are independent of GABA_A agonism.

GABA_B agonists. The main GABA_B receptor agonist of toxicologic significance is baclofen, which is used for treatment of spasticity and some types of neuropathic pain. Coma, hypothermia, hypotension, bradydysrhythmias, and seizures characterize its toxicity. The convulsions that occur in patients with baclofen overdose are proposed to result from disinhibition (inhibition of inhibitory neurons). Carbamazepine's activation of GABA_B receptors has been demonstrated, although this is not thought to explain most of its anticonvulsant action. Some of the actions of γ -hydroxybutyrate following pharmacologic doses may be mediated through activation of GABA_B receptors.

GABA_B withdrawal. Baclofen withdrawal is similar clinically to GABA_A withdrawal. Hallucinations, agitation, tremor, increased sympathetic activity, and convulsions are the main characteristics of baclofen withdrawal. Withdrawal from chronic intrathecal baclofen administration may also be accompanied by large swings in autonomic tone (hypotension, hypertension, tachycardia, bradycardia) and transient cardiomyopathy and shock. Reinstitution of oral baclofen therapy following oral withdrawal, or intrathecal baclofen following intrathecal withdrawal is the treatment of choice when possible.¹²²

γ -HYDROXYBUTYRATE

γ -Hydroxybutyrate (GHB; γ -hydroxybutyric acid) exists endogenously, but toxicologic interest stems from its use in supraphysiologic doses as a drug of abuse and as a treatment for narcolepsy.^{17,55,107} GHB is rapidly absorbed and freely crosses the blood-brain barrier. Toxicity resulting from ingestion of GHB is explained by GHB receptor and GABA_B receptor activation, and comprises agitation, tremor, rapid onset of coma, vomiting, bradycardia, hypotension, hypotonia, and apnea that usually resolve within several hours. Although seizures are noted in experimental animals, it is debated whether GHB causes true convulsive activity in human beings. Human experiments with "therapeutic" doses of GHB have not found EEG changes consistent with seizure activity.¹⁰⁷ Interestingly, patients with the rare inborn error of metabolism, succinic semialdehyde dehydrogenase (SSAD) deficiency, have elevated GHB concentrations and tend to experience

seizures.⁶⁵ Valproate elevates endogenous GHB concentrations by inhibiting SSAD.

Controversy exists as to whether GHB should be considered a neurotransmitter or simply a neuromodulator because it is unclear whether GHB is concentrated within vesicles for synaptic release. There is evidence demonstrating a sodium-dependent reuptake transporter for GHB.

GHB receptors are heterogeneously distributed throughout the brain, with highest concentrations in the hippocampus, cortex, limbic areas, and thalamus, as well as in regions innervated by dopaminergic terminals and dopaminergic nuclei. GHB receptors exist on neurons, mainly at the synaptic level, but are absent from glial or peripheral cells. At least two general GHB receptors have been described thus far, based on binding affinity for GHB and other ligands.

Several proposed pathways for endogenous GHB formation exist (Fig. 14–11).¹⁷ Evidence exists for GHB's metabolism back to GABA, although this appears minimal at physiologic GHB concentrations.⁵⁵ However, effects resulting from pharmacologic doses of GHB may result, in part, from secondary GABA formation.

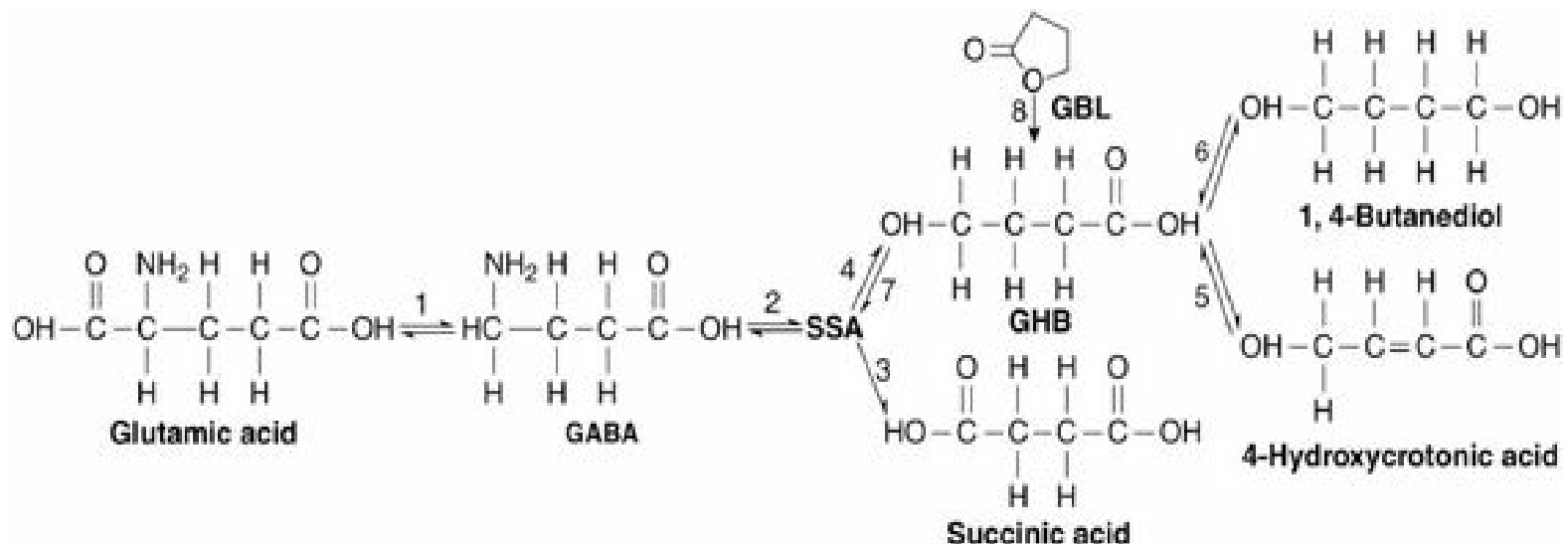


FIGURE 14–11. Potential pathways of γ -hydroxybutyrate (GHB) synthesis and degradation. GABA = γ -aminobutyric acid; GBL = γ -butyrolactone; SSA = succinic semialdehyde; [1] = glutamic acid decarboxylase; [2] = GABA-transaminase; [3] = succinic semialdehyde dehydrogenase; [4] = specific succinic semialdehyde reductase and/or nicotinamide adenine dinucleotide phosphate (NADPH)-dependent aldehyde reductase 2; [5] = mitochondrial β oxidation; [6] = alcohol dehydrogenase and aldehyde dehydrogenase; [7] = GHB dehydrogenase; [8] = γ -lactonase.

Although normal endogenous GHB concentrations are probably not high enough to activate GABA_B receptors, such receptor activation may occur with exogenous administration of GHB. Furthermore, there appears to be functional interplay between GHB and GABA_B receptors.¹⁷

Specific interactions between GHB and DA are complex and not fully delineated. Treatment with GHB appears to inhibit DA release, probably via stimulation of GABA_B receptors.²¹⁷ GHB also affects the firing rates of dopaminergic neurons, DA synthesis, and levels of DA and its major metabolites. GHB is thought to affect sleep cycles, temperature regulation, cerebral glucose metabolism and blood flow, memory, and emotional control, and it may be neuroprotective.

Although GHB can suppress alcohol withdrawal, it is also addictive, and both tolerance and a withdrawal syndrome are described. Withdrawal is characterized, in part, by insomnia, cramps, paranoia, hallucinations, tremor, and anxiety.

GLYCINE

Glycine acts as an inhibitory neurotransmitter in the spinal cord and lower brainstem. In the CNS, serine is converted to glycine by serine hydroxymethyltransferase (SHMT). Some sources of serine include degradation of proteins and phospholipids through dietary intake and formation from 3-phosphoglycerate in a three-step biosynthetic pathway.

Release and Reuptake

Glycine is transported into storage vesicles by VGAT (also known as VIAAT) and undergoes Ca^{2+} -dependent exocytosis upon neuronal depolarization (Fig. 14–12). Glycine is removed from the synapse through reuptake by a Na^{+} -dependent transporter into presynaptic neurons and into glial cells. Two glycine membrane transporters have been cloned and share homology with GABA uptake transporters. GLYT-1 is found both in astrocytes and neurons, whereas GLYT-2 is localized on axons and terminal boutons of neurons that contain vesicular glycine. Although both transporters are associated with glycinergic neurons in the brainstem and spinal cord, GLYT-1 is also found in the forebrain in regions devoid of

glycinergic neurotransmission. At the latter location, GLYT-1 may regulate extracellular glycine that is available for NMDA receptor activation, and GLYT-1 inhibitors could then enhance NMDA responses (Table 14–11). Glycine transporters can also function in reverse, moving glycine out of the cell.⁵

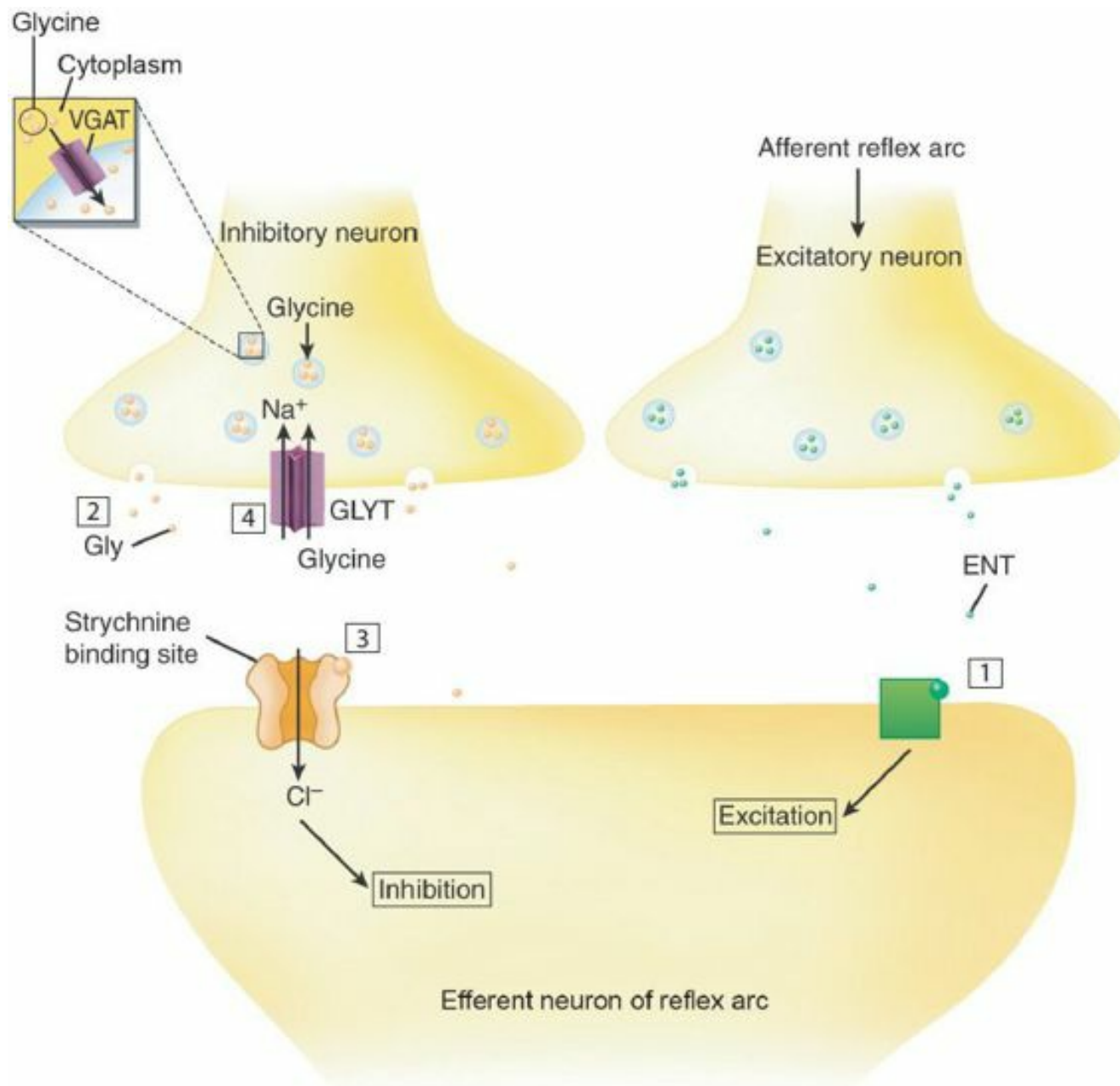


FIGURE 14–12. Inhibitory glycinergic neurotransmission. Glycine is concentrated within vesicles by uptake via VGAT, the vesicle membrane transporter. Signals from the afferent limb of a reflex arc (top right) cause the release of an excitatory neurotransmitter (ENT) that crosses the synapse to bind to a neuron in the efferent limb of the reflex arc [1]. To prevent excessive neuronal firing and motor activity, glycine (Gly) released from a glycinergic inhibitory neuron [2] binds to glycine Cl^- channel receptors [3] and causes inhibition by hyperpolarization through Cl^- influx. Synaptic glycine is transported back into the neuron by at least two subtypes of membrane glycine transporters, GLYT-1 and GLYT-2 [4]. Strychnine binds to the glycinergic Cl^- channel to decrease the binding of glycine, which prevents Cl^- influx. Although strychnine is shown to bind to a separate site from glycine, there is evidence that these sites may overlap. GLYT = glycine reuptake transporter.

Glycine Receptors

The glycine receptor is a Cl^- channel that shares significant amino acid homology with the GABA_A Cl^- channel. It is well established that both GABA and glycine are excitatory in the embryonic central nervous system prior to becoming the main inhibitory neurotransmitters of the mature CNS.^{46,103,162} Glycine receptors are pentameric proteins made up of α and β subunits. Three isoforms of the α subunit (two of which exist after the neonatal period) and one isoform of the β subunit are described.¹³¹ An anchoring protein, gephyrin, binds to the β subunit and allows for clustering of glycine receptors at postsynaptic membranes. Like GABA receptors, glycine receptors may also be found outside the synapse, where their

function is an area of current research.^{103,215} Glycine receptor activation causes an inward Cl^- current that hyperpolarizes the membrane. Glycine binding is also important for functioning of the NMDA receptor as discussed later.

Xenobiotics

Table 14–10 provides examples of xenobiotics that affect inhibitory glycine Cl^- channels. The amino acids β -alanine, taurine, and serine can activate glycinergic Cl^- channels. Both ethanol and propofol potentiate glycine-mediated inward Cl^- currents, just as they do at GABA_A Cl^- channels.^{125,131} Volatile halogenated anesthetics, ivermectin, δ -9-tetrahydrocannabinol, and chlormethiazole also potentiate glycinergic transmission.²¹⁵ Clozapine inhibits glycine reuptake.⁸²

TABLE 14–10. Examples of Xenobiotics Affecting Inhibitory Glycine Chloride Channels

<i>Glycine Agonists</i>	<i>Glycine Antagonists</i>
β -Alanine	Glycine reuptake inhibitor
Ethanol	Atropine
Halogenated anesthetics (volatile)	Clozapine
Ivermectin	Ginkgolide B
Propofol	Picrotoxin
Serine	Strychnine

Strychnine is the main xenobiotic affecting glycinergic transmission. Strychnine binds to the α subunit of the glycine receptor to prevent the action of glycine on Cl^- influx,⁴ at least in part by decreasing the binding of glycine to its receptors. This physiologic antagonism of glycine produces increased muscle tone, rigidity, opisthotonus, trismus, rhabdomyolysis, and death from respiratory failure. Given the similarity in Cl^- channels, it is not surprising that strychnine binds to the GABA_A complex in vitro. However, the affinity of strychnine for this complex is less than that for glycine receptors, and most of its toxicologic action is a result of physiologic antagonism of glycine-induced inhibition.

Picrotoxin binds to the glycine receptor to impair Cl^- influx.¹¹⁸ Evidence exists for a direct antagonistic effect of picrotoxin at the glycine binding site(s), in contrast to GABA_A Cl^- channels, where it acts at a site separate from where GABA binds. Ginkgolide B appears to inhibit the glycine receptor by directly blocking the Cl^- channel.²¹⁵ Tetanus toxin produces rigidity and trismus by preventing glycine release from neuronal terminals in the spinal cord and brainstem.

GLUTAMATE

Glutamate is the main excitatory neurotransmitter in the CNS and the immediate precursor to the main inhibitory neurotransmitter, GABA. Balance between glutamate neuronal stimulation and GABA neuronal inhibition is essential to maintain normal CNS function.^{82,90} Glutamate is essential for memory, learning, perception, locomotion, and neuropsychiatric well-being.^{14,36,46} A number of psychiatric and neurologic disorders are associated with altered glutamatergic function, including schizophrenia, depression, anxiety, posttraumatic stress disorder, addiction and withdrawal, autism, epilepsy, Alzheimer disease, and amyotrophic lateral sclerosis (ALS).^{36,46,62,82,119} Although glutamate receptor stimulation is essential for normal brain activity, excessive endogenous or exogenous stimulation plays a significant role in mediating neuronal damage in acute, progressive, and chronic psychiatric and neurologic diseases, including damage from trauma, ischemia, hypoglycemia, and status epilepticus.^{14,126} A rise in synaptic glutamate concentrations after neurological insult that induces further damage and apoptosis is termed glutamate-related excitotoxicity.^{46,119} Conversely, glutamate antagonists demonstrate neuroprotective properties and anticonvulsant activity in animal models of CNS injury. Unfortunately, clinical trials with currently available glutamate antagonists for treatment of patients with ischemic stroke and traumatic brain injury have proved disappointing.⁴⁶

Synthesis, Release, and Reuptake

Glutamate does not cross the blood–brain barrier and must be synthesized from products of glucose metabolism or other precursors within the CNS. Glutamate primarily is synthesized from glutamine by the enzyme glutaminase located within the mitochondrial compartment.⁵⁸ Glutamate is stored within vesicles and then released into the synapse by Ca^{2+} -dependent exocytosis. Synaptic glutamate that is taken up by glial cells undergoes conversion back to glutamine by the enzyme glutamine synthase. Glial cells then release glutamine, which is taken up by neurons before conversion back to glutamate and subsequent transport into vesicles (Fig. 14–13). Reverse transport of glutamate from the cytoplasm into the synapse by

the membrane transporter may occur under some circumstances.⁹ There are five different cell surface excitatory amino acid transporters (EAAT) that differ in their predominant CNS locations.

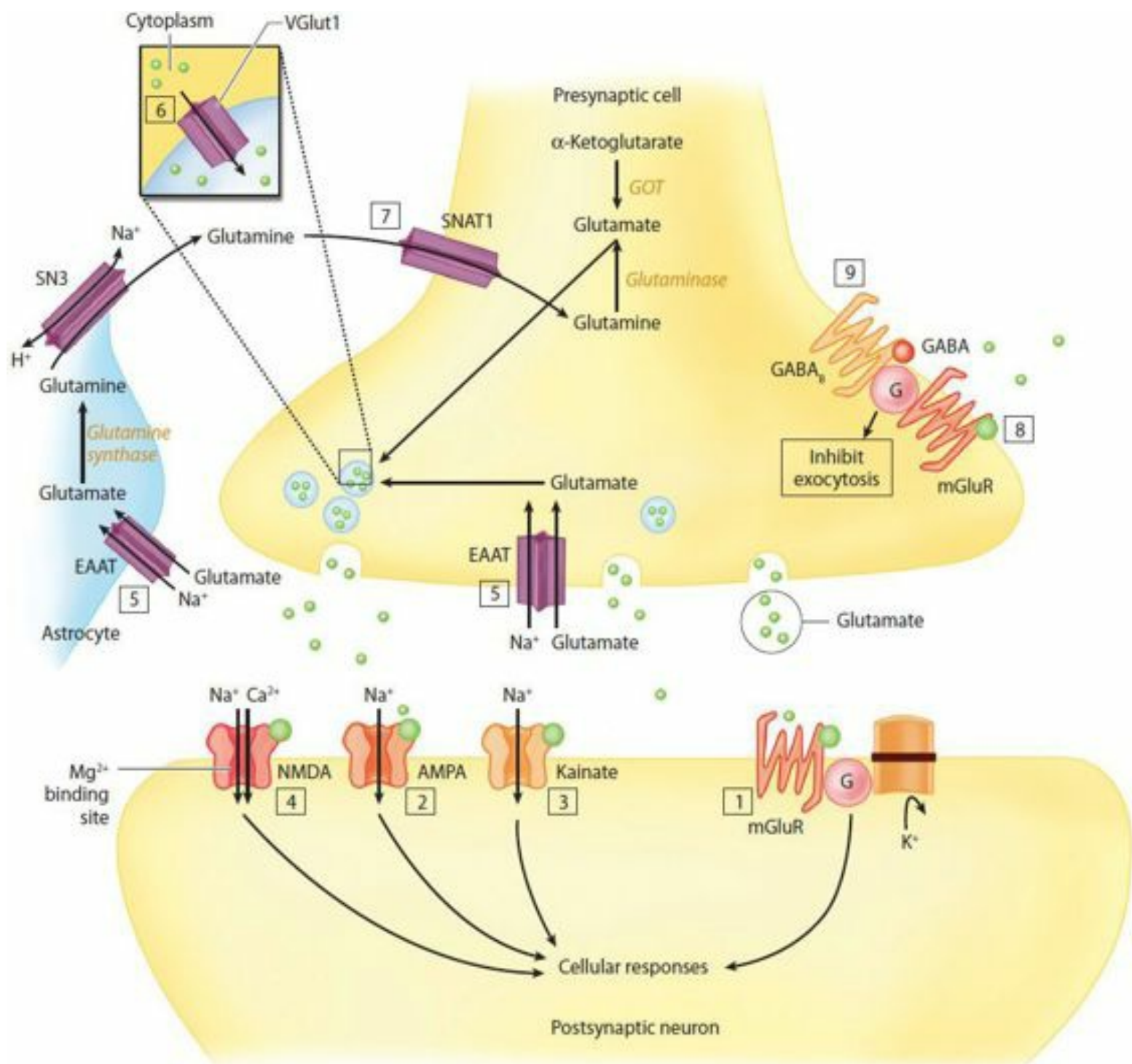


FIGURE 14–13. Glutamatergic neurotransmission. Glutamic oxaloacetic transaminase (GOT) converts α -ketoglutarate to glutamate in mitochondria. Glutamate also forms from glutamine via mitochondrial glutaminase. Glutamate is transported into vesicles [6] by VGLUT1 (or possibly other subtypes) for exocytotic release into the synapse. Synaptic glutamate activates four main types of receptors. AMPA [2], kainate [3], and NMDA [4] receptors are cation channels. Membrane depolarization in response to their activation causes neuronal excitation through cation influx. Metabotropic receptors (mGluR) [1,8] are coupled to G proteins and are expressed on pre- and postsynaptic membranes. In addition, some mGluRs reside outside of the synapse. Postsynaptic mGluR excitation in this example [1] results from preventing K⁺ efflux, but other mechanisms of excitation exist. Presynaptic mGluRs act to inhibit [8] glutamate (and other neurotransmitter) release through modulating intracellular Ca²⁺ concentrations, as do presynaptic GABA_B receptors in response to GABA binding [9].

Figure 14–14 provides a more detailed illustration of the NMDA receptor. Excessive influx of Ca²⁺ through NMDA receptors (and through some AMPA and kainate receptors) causes neuronal damage and cell death. A Mg²⁺ ion normally blocks the NMDA receptor channel to prevent Ca²⁺ influx despite glutamate binding. However, depolarization of the neuronal membrane by cation influx resulting from activation of any of the other receptor types causes Mg²⁺ to dissociate from the NMDA receptor and to allow potentially damaging inward Ca²⁺ currents in response to glutamate binding.

Glutamate undergoes reuptake by neurons and glial cells by various subtypes of EAAT, the membrane bound glutamate transporter [5]. In glial cells, glutamate is converted to glutamine by glutamine synthase, and glutamine is transported out of glial cells by the system N amino acid transporter (SN3). Glutamine then moves back into neurons through another amino acid transporter (SNAT1) [7] where it undergoes conversion back to glutamate. Various xenobiotics in [Table 14–11](#) affect glutamatergic neurotransmission, in part, by stimulating or blocking the various glutamate receptors [1–4,8] or by preventing glutamate reuptake [5]. G = G protein.

Glutamate Receptors

Once glutamate undergoes release into the synaptic cleft, it can bind to one of three ionotropic receptors or eight metabotropic receptors. The three ionotropic glutamate receptors are cation channels and named according to their affinity for specific agonists: kainate, AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionate), and NMDA (N-methyl-D-aspartate). All comprise four subunits and are responsible for fast excitatory glutamatergic activity.^{35,46,56,90,93,129,161} The eight metabotropic receptors are linked to G proteins and produce actions that are slower, more diverse, and longer-lasting than those of ionotropic receptors.^{56,93} Presynaptic terminal glutamate receptors modulate the release of various neurotransmitters, including glutamate, while postsynaptic glutamate receptors are usually excitatory, although some inhibitory actions are demonstrated. ([Fig. 14–13](#)).^{129,161} A single neuron may express numerous types of glutamate receptors. Every type of glutamate receptor has been identified on both presynaptic and postsynaptic membranes, but many are not active under normal physiologic conditions. This complexity offers protection against the devastating effects of uncontrolled excitatory neurotransmission.

Ionotropic Glutamate Receptors. Ionotropic cationic glutamate receptors share structural similarity, especially kainate and AMPA receptors. These receptors are homomeric or heteromeric tetramers with a central ion channel pore. The inward current carried through most ionotropic glutamate receptors results from Na^+ and/or Ca^{2+} influx.^{90,129,203}

AMPA receptors are hetero- and homotetramers comprising GluA1–4 subunits that are the most common ionotropic glutamate receptors found in the brain and are responsible for most glutamatergic excitation, mainly through Na^+ influx under normal conditions.^{30,90,145,203} Post-transcriptional modification or RNA editing of AMPA receptor subunits alters ion permeability and function. In adults, nearly all GluA2 subunits are edited, resulting in maintenance of Na^+ permeability, but loss of Ca^{2+} permeability. In contrast, some unedited GluA2 subunits demonstrate Ca^{2+} and Zn^{2+} permeability.^{46,90,129,145,158} These AMPA receptors permeable to Ca^{2+} are more prevalent in many neurological diseases where they may contribute to excitotoxicity.^{90,129}

Kainate receptors are named for their affinity for kainate, found in red algae. These receptors comprise GluK1-5 subunits joined in homomeric and heteromeric tetramers.^{85,90,171} Activation allows Na^+ influx, and lesser K^+ efflux, resulting in neuronal depolarization. RNA editing of GluK1 and GluK2 subunits abolishes Ca^{2+} permeability while maintaining Na^+ conductance, but some subunits remain unedited and permeable to Ca^{2+} .^{30,158} Recent studies indicate that some kainate receptors may also signal through G-proteins in a yet-to-be understood mechanism.³⁷

NMDA receptors are heteromeric tetramers of subunits that may include GluN1, GluN2A-2D, and GluN3A-3B (7 isoforms), but most commonly comprise two GluN1 and two GluN2 subunits.^{14,46,90,92,203} NMDA receptors reside near AMPA receptors, forming a functional synaptic unit at virtually all central synapses.²⁰³ NMDA receptor activation allows for Ca^{2+} and Na^+ influx (and some K^+ efflux), resulting in neuronal depolarization and excitation ([Fig. 14–14](#)). The NMDA ion channel is normally blocked by Mg^{2+} in a voltage-dependent manner, preventing Ca^{2+} influx despite glutamate binding ([Fig. 14–14](#)).^{82,92} For Ca^{2+} to flow through the channels, three conditions must be met: (1) the neuronal membrane must be depolarized by at least 20 to 30 mV through some other mechanism (eg, activation of another type of glutamate receptor) so that Mg^{2+} will leave the channel, (2) two molecules of glutamate must bind to the receptor, and (3) two molecules of glycine must bind to their binding sites on the receptor.^{46,56,92,119} The amino acid D-serine may substitute for glycine.^{14,90} Thus, the NMDA receptor is both a ligand-gated and voltage-gated ion channel ([Fig. 14–14](#)). Direct Ca^{2+} influx through both NMDA and Ca^{2+} -selective AMPA channel receptors contributes to excitotoxicity. Excessive stimulation of NMDA and AMPA receptors by glutamate released during times of ischemia, trauma, hypoglycemia, or convulsions triggers damaging rises in intracellular Ca^{2+} concentrations, activation of numerous enzymes, and free radical formation, all of which incite cell death.¹²⁶ Antagonists of NMDA Ca^{2+} channels demonstrate anticonvulsant and neuroprotective activity. Zinc is packaged into synaptic vesicles in axons and is co-released with glutamate into the synaptic cleft during neuronal activity where it acts as an endogenous modulator of NMDA receptors.²⁰³

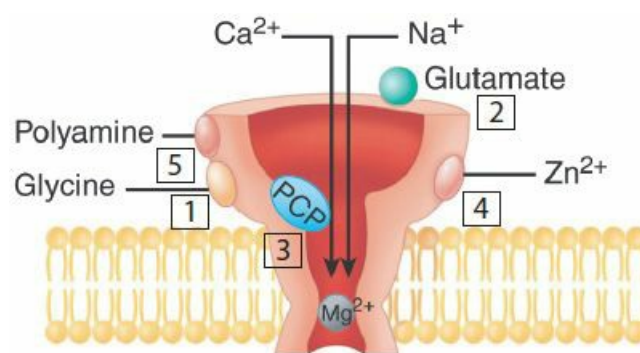


FIGURE 14–14. Representation of the NMDA glutamate receptor. The NMDA receptor is a voltage-gated and ligand-gated Ca^{2+} channel. Glutamate binds to its receptor on the channel [2] to open the Ca^{2+} channel and to allow Ca^{2+} and Na^{+} influx and lesser amounts of K^{+} efflux. Mg^{2+} normally blocks the Ca^{2+} channel, preventing cation influx in response to glutamate binding. Mg^{2+} leaves the channel when the membrane is depolarized by 20–30 mV. Glycine must also bind to its site on the NMDA receptor complex for successful glutamate agonism. Polyamines bind on the extracellular surface of the receptor [5]. Zn^{2+} binds [4] to inhibit Ca^{2+} influx. The phencyclidine (PCP) binding site [3] lies within the channel. Xenobiotics in Table 14–11 may antagonize glycine binding [1]; block the Ca^{2+} channel by binding to the PCP binding site [3]; bind to the polyamine binding site [5]; or directly stimulate the glutamate-binding site [2].

Metabotropic Glutamate Receptors. Metabotropic glutamate receptors (mGlu) are linked to various G proteins on post- and presynaptic membranes (Fig. 14–13). Eight different receptors (mGlu1–8) have been isolated. In contrast to ionotropic glutamate receptors, mGlu may excite or inhibit at postsynaptic membranes, and appear mainly to inhibit at presynaptic locations, regulating synaptic transmission and neuronal excitability.

Metabotropic glutamate receptors are commonly subdivided into three main groups based on their sequence homology, intracellular signaling mechanisms and response to specific experimental agonists.^{182,200} As a general rule, group I receptors (mGlu1 [a,b,c,d] and mGlu5 [a,b]) reside postsynaptically; activation produces excitation through blockade of K^{+} efflux or by activating phospholipase C, producing rises in intracellular Ca^{2+} , resulting in cell depolarization.^{36,56,182,200} The mGlu5 receptors are physically coupled to NMDA receptors by scaffolding proteins and are functionally coupled to NMDA receptors by protein kinase C.^{36,56,182} In animal experiments, agonists of group I receptors produce convulsions, while antagonists display anticonvulsant action.^{56,114,119,182} Group II (mGlu2, mGlu3) and Group III (mGlu4, mGlu6, mGlu7, mGlu8) metabotropic receptors most commonly serve as presynaptic autoreceptors and heteroreceptors and, when activated, inhibit adenylate cyclase activity.^{36,56,161,172,200} This, in turn, prevents Ca^{2+} influx and inhibits release of neurotransmitters, including glutamate, GABA, DA, and adenosine. Group II presynaptic autoreceptors may play an important role in decreasing further glutamate release during pathologic conditions, when extracellular concentrations of glutamate exceed normal physiologic levels. They are positioned outside the synaptic active zone and, therefore, only become activated when glutamate spills out of the synapse.¹⁶¹ The mGlu7 receptor is positioned within the active zone of the synapse, but has a low affinity for glutamate, allowing for a continuous but mild inhibitory effect on glutamate release.^{161,200} Agonists of Groups II and III metabotropic receptors produce anticonvulsant effects in animals.¹²⁴

The glutamate binding pocket is so well conserved among the mGlu receptors that it has been difficult to find subtype selective agonists or competitive antagonists. Therefore, drug development is now focused on negative and positive allosteric modulators (NAMs and PAMs).¹⁷² Allosteric modulators bind mGlu receptors at a site distinct from the glutamate binding site and alter the functioning of the receptor in the presence of glutamate. The NAMs block activation of G proteins by the mGlu receptor, while PAMs facilitate the action of direct receptor agonists. Allosteric modulators are being developed to treat hyperlocomotion, psychosis, and schizophrenia.^{36,56,172}

Xenobiotics

Table 14–11 provides examples of xenobiotics that affect glutamatergic neurotransmission.

TABLE 14–11. Examples of Xenobiotics Affecting Glutamatergic Neurotransmission

Glutamate agonism

Direct glutamate receptor agonists

BMAA

Domoic acid

Homoquinolinic acid
Ibotenic acid
ODAP (formerly BOAA)
Quisqualate
Willardine
AMPA receptor modulators
Aniracetam
BMAA
Cyclothiazide
Dysiherbaine
Minocycline
ODAP (formerly BOAA)
Kainate receptor modulators
Concanavalin A
Domoic acid
Dysiherbaine
Neodysiherbaine A
NMDA receptor modulators
Nitric oxide
Glycine NMDA receptor agonists
Alanine
d-Cycloserine
Kynurenic acid
Milacemide
Serine
Glutamate reuptake inhibitor
Clozapine
Nitropropionic acid
Glutamate antagonism
Prevent glutamate release
Diazoxide
Felbamate

Lamotrigine
Nimodipine
Riluzole
Sulfasalazine
Increase glutamate reuptake
Ceftriaxone
Lithium
Riluzole
AMPA receptor antagonists
Quinoxalinediones
Talampanel
Topiramate
NMDA receptor antagonists
Amantadine
Buprenorphine
Conatoxins
Dextrophan
Dimebon
Dizocilpine (MK801)
Ethanola
Ketamine
Memantine
Meperidine
Methadone
Methoxetamine
Neramexane
Orphenadrine
Pentamidine
Phencyclidine
Promethazine
Remacemide
Selfotel

Tramadol

NMDA glycine antagonists

Felbamate

Kynurenic acid

Meprobamate

Xenon

Kainate receptor antagonists

Quinoxalinediones

Topiramate

Metabotropic negative allosteric modulator

Fenobam

Polyamine antagonists

Aptiganel

Arecaine

Argiotoxin

Diethylenetriamine

Eliprodil

Ifenprodil

^aEthanol is a noncompetitive antagonists at some NMDA receptors.

BMAA = α -amino- β -methylaminopropionic acid; ODAP = L- β -N-oxalyl- α , β -diaminopropionic acid; BOAA = β -N-oxalylamino-L-alanine; NMDA = N-methyl-D-aspartate.

Glutamate Agonism. Domoic acid produces amnesic shellfish poisoning, partly characterized by confusion, agitation, convulsions, memory disturbance, neuronal damage, and death.⁷⁵ The structural similarity between domoic acid and glutamate is thought to explain excessive activation of AMPA and kainate receptors with secondary NMDA receptor activation and resultant neuronal damage.⁷⁷ Domoic acid toxicity in birds is thought to have explained their attack on the city of Capitola, CA in 1961, and may have partly inspired Hitchcock's creation of the movie, *The Birds*.³⁹

Investigators hypothesize that other naturally occurring glutamate receptor agonists produce additional neurologic diseases. The neurogenic form of lathyrism results from using chickling peas (*Lathyrus sativus*) as a food staple. Neurolathyrism was common in German concentration and prisoner of war camps during World War II and still occurs in some parts of the world. Chickling peas contain L- β -N-oxalyl- α , β -diaminopropionic acid (ODAP), previously known as β -N-oxalylamino-L-alanine (BOAA), an agonist of AMPA receptors.^{99,209} Influx of Ca^{2+} likely contributes to motor neuron cell death in neurolathyrism.²⁰⁹

Endemic ALS–Parkinson disease in Guam has been hypothesized to be from chronic toxicity from β -methylamino-L-alanine (BMAA), which is formed by cyanobacteria symbiotically residing within the roots of Cycads (*Cycas micronesica*). BMAA and its carbamate are structurally similar to glutamate,²³ and experiments demonstrate that prolonged exposure to BMAA produces Ca^{2+} influx into substantia nigra pars compacta dopaminergic neurons and excitotoxic effects through activation of metabotropic glutamate receptors (mGlu1), and to a lesser extent, AMPA receptors.⁴⁰ Consumption of raw Cycas seeds, of flour made from Cycas, or of animals that have eaten Cycas, results in an accumulation of protein-bound BMAA within brain tissues of humans that can be demonstrated at autopsy. However, autopsies of patients throughout the world with ALS, Alzheimer disease, and Parkinson disease, in absence of Cycas exposure, also demonstrate elevated brain BMAA concentrations, and cyanobacteria that produce BMAA are ubiquitous, making interpretation of

BMAA's role in producing ALS–Parkinson disease difficult.

Ibotenic acid, from poisonous mushrooms, activates NMDA and some metabotropic glutamate receptors. It undergoes decarboxylation to muscimol, a direct agonist of GABA_A receptors. Glufosinate is a tripeptide and glutamate analogue isolated from *Streptomyces* and utilized in herbicides. Glufosinate produces excitotoxicity in humans, manifesting as drowsiness, amnesia, confusion, coma, seizures or death, through activation of NMDA receptors.¹²³

There is in vitro evidence that ketamine causes glutamate release from neuronal terminals. Ketamine and methoxetamine may directly activate AMPA glutamate receptors, and this effect may explain their potential antidepressant action.^{38,110,119,129}

Because noncompetitive NMDA receptor antagonism reproduces many signs and symptoms of schizophrenia and autism, investigators are directing efforts at increasing activity at NMDA channels in an effort to treat these diseases,^{184,220} and potentiating activity at the glycine-binding site may enhance NMDA receptor function. After crossing the blood–brain barrier, milacemide undergoes conversion to glycine, which is required for NMDA receptor activation.¹⁸⁴ D-Cycloserine also crosses the blood–brain barrier to stimulate glycine receptors on NMDA calcium channels.⁹² Sarcosine (N-methylglycine) is a glycine transporter-1 inhibitor, raising synaptic glycine concentrations near NMDA receptors.⁸³

N-acetylcysteine (NAC) modulates glutamate through the astrocytic antiporter cysteine/glutamate, resulting in stimulation of metabotropic glutamate receptors and activation of NMDA receptors. Also, NAC likely potentiates AMPA receptors. Some have suggested NAC as a treatment for Parkinson disease and for depressive symptoms of bipolar disease.¹¹⁰

Aniracetam inhibits deactivation of AMPA receptors and has been advocated as a nootropic agent for patients with dementia.^{90,97} Minocycline and cyclothiazide attenuate receptor desensitization and demonstrate neuroprotective effects.^{84,90,129}

Glutamate Antagonism. Prevention of glutamate release. Riluzole is used to treat ALS and is being considered for neuroprotection in Parkinson disease and for treatment of depression. Overall, riluzole increases glutamine/glutamate ratios. It indirectly prevents release of glutamate by inhibiting voltage-dependent Na⁺ channels and facilitates uptake of glutamate from the synapse by stimulating EAAT activity.^{46,119,129} Riluzole also enhances AMPA trafficking, enhances membrane insertion of AMPA receptors, and promotes neurogenesis through stimulation of growth factors.^{46,92,119} Lamotrigine diminishes glutamate release through blockade of voltage-gated Na⁺ channels and increases AMPA receptor activity.¹¹⁹ Felbamate antagonizes NMDA receptors and prevents glutamate release.⁴⁶ Gabapentin and pregabalin inhibit presynaptic Ca²⁺ channels to lessen glutamate release.

AMPA receptor antagonists. Talampanel, a noncompetitive antagonist, has been investigated in the treatment of ALS and has anticonvulsant properties.¹²⁹ Some wasp and spider venoms contain AMPA receptor antagonists.¹²⁹

NMDA receptor antagonists. Phencyclidine, ketamine, and metho-xetamine act as noncompetitive antagonists by binding within the ion channel (PCP binding site) to block Ca²⁺ influx following glutamate binding (Fig. 14–14).^{82,92}

Dextromethorphan and its first-pass metabolite, dextrorphan, exhibit anticonvulsant activity and psychoactive effects in animals. Most of the actions of dextromethorphan are due to its metabolite, dextrorphan, which antagonizes the actions of glutamate at NMDA receptors by binding to the PCP binding site. Both compounds directly block N- and L-subtype voltage-dependent Ca²⁺ channels.^{92,168}

Tramadol displays multiple mechanisms of action as an analgesic, including a weak affinity for opioid receptors, inhibition of monoamine reuptake, and inhibition of NMDA glutamatergic activity at clinically relevant concentrations by an unknown mechanism.⁷⁰ Methadone, meperidine, and buprenorphine are opioid analgesics that antagonize NMDA receptors at therapeutic doses, and this mechanism of action may contribute to their analgesic effect.⁴⁵

Dizocilpine (MK-801) antagonizes NMDA receptors by binding to the PCP binding site in the NMDA Ca²⁺ channel, producing adverse effects, similar to phencyclidine.⁴⁹ Amantadine, memantine, and orphenadrine act as low-affinity antagonists at the PCP site, but are not associated with psychotomimetic adverse effects from such action.⁹² Memantine is a low-affinity NMDA receptor antagonist, which is approved for the treatment of Alzheimer disease, but has also recently been utilized for the treatment of other neurological and psychiatric disorders.^{14,46,119,201,203} Ifenprodil is a GluN2B-subunit-selective antagonist of NMDA receptors that has been advocated for neuroprotection in stroke patients.¹⁴⁹ Pentamidine antagonizes glutamate binding at NMDA channels.⁴⁹

Ethanol noncompetitively antagonizes NMDA receptors, resulting in upregulation of this glutamatergic system.²⁰³ Alcohol-tolerant individuals show marked reductions to subjective intoxicating effects of ketamine.¹¹⁹ In some animal models of ethanol withdrawal seizures, NMDA receptor antagonists demonstrate better anticonvulsant action than GABA_A agonists.

Glycine antagonism. Felbamate's anticonvulsant activity may result, in part, from antagonism of glycine at NMDA

receptors.^{157,218} Kynurenic acid, a metabolite of L-tryptophan, prevents NMDA activation through glycine antagonism. Meprobamate also antagonizes NMDA glutamate receptors by a yet-to-be-determined mechanism.¹⁵⁷ However, given the structural similarity to felbamate, meprobamate may antagonize the action of glycine.

Polyamine Antagonism. Ifenprodil and eliprodil antagonize the action of glutamate at NMDA channels by preventing polyamine binding.⁶⁸

ADENOSINE

Adenosine is an important modulator of brain activity and body physiology. Adenosine receptors are vastly distributed throughout the body, which emphasizes the pivotal role that adenosine plays in neurotransmission and metabolic activity.

The overall action of adenosine is to lessen oxygen requirements and to increase oxygen and substrate delivery.⁵⁹

Adenosine can be found in small concentrations in most extracellular fluids as a consequence of ATP metabolism. This is in contrast to classical neurotransmitters, which are secreted in discrete quanta upon stimulation of presynaptic neurons. In the brain, adenosine primarily limits glutamate and ACh release, thereby preventing excessive postsynaptic neuronal stimulation.^{113,204} Adenosine also counterbalances the effects of DA stimulation in the basal ganglia.^{113,204}

Synthesis, Release, and Reuptake

Adenosine is derived from the breakdown of ATP, which is commonly co-released with other neurotransmitters (eg, NE, ACh, glutamate) into the synapse before subsequent degradation by ectonucleotidases (Fig. 14–15). During times of adequate oxygen delivery and oxidative phosphorylation, intracellular ATP concentrations are many times greater than those of adenosine, with normal intracellular adenosine concentrations ranging from 50 to 300 nM.⁶⁰ Intracellular adenosine concentrations increase rapidly during ischemia, hypoxia, or elevated metabolic activity (eg, seizures).^{59,113} A bidirectional equilibrative nucleoside transporter (ENT) typically moves adenosine from the synapse back into the neuron under normal conditions, but can reverse adenosine transport when intracellular adenosine concentrations become elevated (Fig. 14–15).¹¹³ The normal overall cellular preference is to convert adenosine back to ATP via adenosine kinase, but some adenosine also undergoes conversion to inosine by adenosine deaminase.¹¹³ Synaptic adenosine then activates adenosine receptors on neuronal and non-neuronal tissue (eg, vasculature). The actions of adenosine are terminated by reuptake into glial cells and neurons (Fig. 14–15).^{113,204} Exogenously administered adenosine used in the treatment of supraventricular tachycardia does not cross the blood–brain barrier and, therefore, is not centrally active. The half-life of adenosine in the blood is less than 10 seconds.

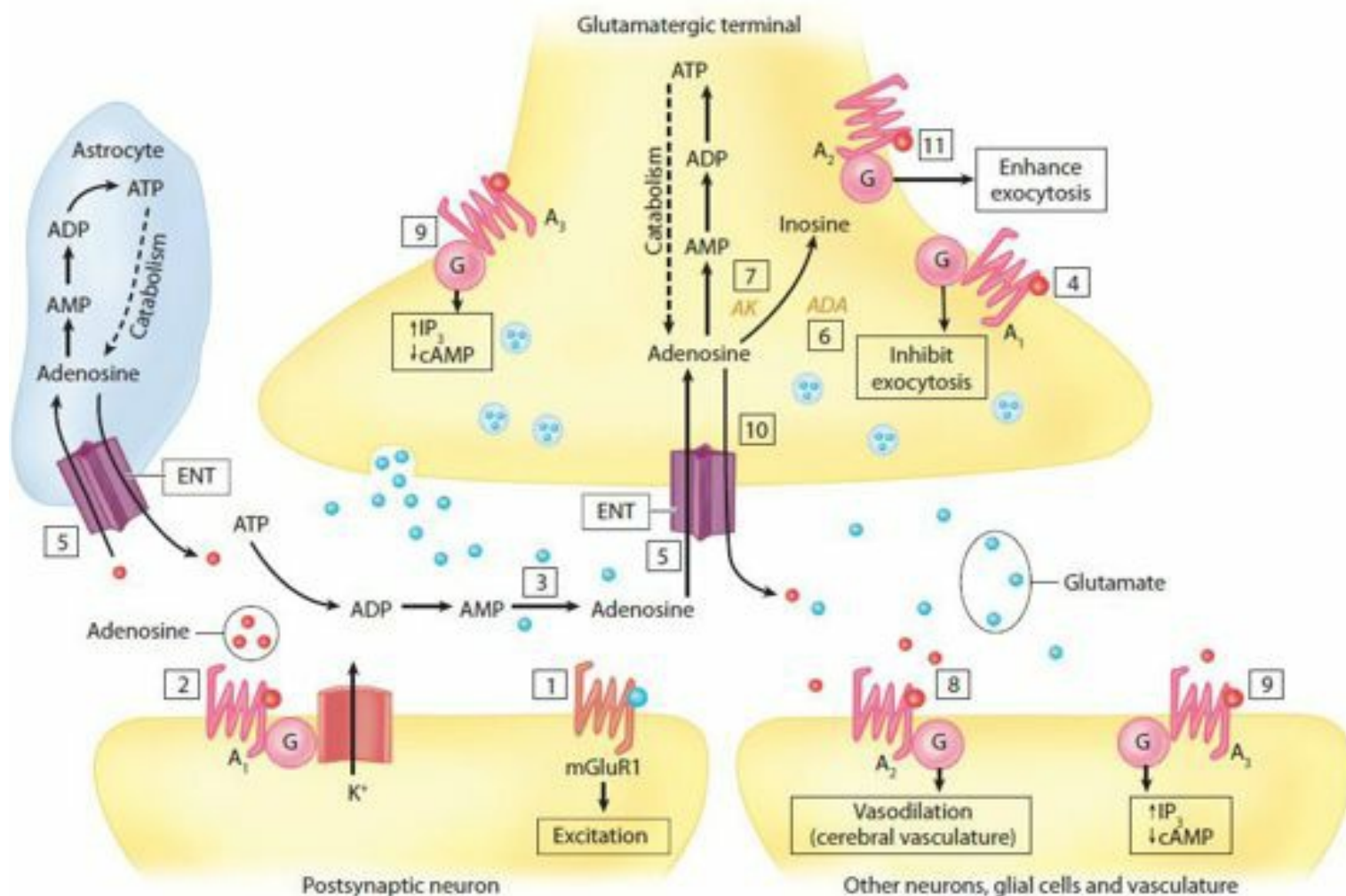


FIGURE 14–15. Adenosine's role in regulating excitatory neurotransmission, using glutamate as an example. In this example, glutamate excites a postsynaptic neuron by activating metabotropic glutamate receptors (mGluR1) [1]. ATP enters the synapse when glutamate is released. Adenosine formed from metabolism of ATP within the synapse [3] binds to postsynaptic A_1 receptors [2], which open K^+ channels to inhibit the neuron through hyperpolarization. Adenosine also activates presynaptic A_1 receptors [4] to lower intracellular Ca^{2+} concentrations, thereby impairing further glutamate release. Activation of presynaptic A_2 receptors has the opposite effect, enhancing glutamate exocytosis [11]. After uptake by ENT [5], adenosine is acted upon either by adenosine kinase (AK) [7] to form AMP, or by adenosine deaminase (ADA) [6] to form inosine. Adenosine also binds to neuronal postsynaptic A_2 receptors (especially in the striatum) and to vascular A_2 receptors to cause vasodilation [8]. A_3 receptors [9] are not activated by normal concentrations of adenosine. During times of excessive catabolism (eg, seizures, hypoglycemia, stroke) when intracellular adenosine concentrations rise markedly, adenosine moves into the synapse through reverse transport via ENT [5]. Resultant stimulation of A_1 and A_2 receptors results in inhibitory actions to decrease oxygen requirements and to increase substrate delivery through vasodilation as described above. However, the resultant stimulation of A_3 receptors [9] may contribute to neuronal damage and death. Xenobiotics in Table 14–12 act to inhibit adenosine uptake [5]; to inhibit ADA [6]; to inhibit AK [7]; to increase adenosine release; and to antagonize A_1 [2,4] and A_2 [8,11] receptors. ADP = adenosine diphosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; ENT = equilibrative nucleoside transporter; G = G protein; IP₃ = inositol triphosphate.

Adenosine Receptors

The purine P_1 receptor family comprises four adenosine receptor subtypes linked to G proteins: A_1 , A_{2A} , A_{2B} , and A_3 .⁶⁰ Postsynaptic A_1 stimulation results in K^+ channel opening and K^+ efflux, with subsequent hyperpolarization of the neuron (Fig. 14–15). Evidence suggests that G protein-mediated Cl^- influx may explain postsynaptic hyperpolarization by A_1 activation in some cases. Presynaptic A_1 stimulation modifies voltage-dependent Ca^{2+} channels, lessening Ca^{2+} influx during depolarization, which limits exocytosis of neurotransmitter. Therefore, activation of A_1 receptors prevents release of neurotransmitters presynaptically and inhibits their responses postsynaptically.¹¹³

In the central and autonomic nervous systems, A_1 receptors reside on presynaptic and postsynaptic membranes, where

they serve as inhibitory modulators for numerous neurotransmitter systems; they are particularly prevalent in association with glutamatergic neurons in the CNS.¹¹³ The A₁ receptor is prevalent throughout the central nervous system, with high concentrations in the cerebral cortex, hippocampus, cerebellum, thalamus, brain stem, and spinal cord. Agonism of A₁ receptors by adenosine produces sedation, neuroprotection, anxiolysis, temperature reduction, anticonvulsant activity, and spinal analgesia.^{60,204}

Peripheral A₁ receptor activation produces bronchoconstriction, decreased glomerular filtration, decreased heart rate, slowed atrioventricular conduction, and decreased atrial myocardial contractility.⁶⁰

In the CNS, A_{2A} receptors demonstrate limited distribution. They are concentrated on cerebral vasculature and produce vasodilation when stimulated.⁶⁰ Additionally, A_{2A} receptors are especially prevalent on neurons in the striatum, where they inhibit the activity of D₂ receptors.²⁰⁴ Antagonism of A_{2A} receptors in the striatum increases dopamine-mediated motor activity without the dyskinesia that commonly occurs with DA agonists.^{113,204} Some A_{2A} receptors are found presynaptically as heterodimers with A₁ receptors. They act to diminish the inhibition of presynaptic A₁ receptors when adenosine concentrations increase.¹¹³ Under normal conditions the presynaptic A_{2A} receptors are relatively inactive.

A_{2B} receptors are expressed diffusely throughout the brain, and are most commonly identified on glial cells. A_{2B} receptors demonstrate low affinity for adenosine, and little is known of their physiologic role.²⁰⁴ A_{2A} and A_{2B} receptors are coupled to G_s. The rise in cAMP concentration resulting from A_{2A} activation on cerebral vasculature and elsewhere explains vasodilation.^{60,204} For example, peripheral A₂ receptor activation also results in coronary artery vasodilation.⁶⁰

A₃ receptors express low affinity for adenosine. In the CNS, A₃ receptors are expressed primarily in the hippocampus and thalamus. A₃ receptors act through G proteins to decrease adenylate cyclase activity and increase phospholipase C activity.¹¹³ The low concentrations of adenosine found during normal metabolism minimally activate A₃ receptors to produce inhibitory effects. During times of excessive ATP degradation (eg, hypoxia, seizures), adenosine accumulates at and activates A₃ receptors to produce complex responses that appear to enhance ischemic cellular injury and death, at least in part through disinhibition of presynaptic metabotropic glutamate receptor responses. Thus, A₃ receptor antagonists are being examined for neuroprotective actions.⁵⁹

Adenosine and Seizure Termination

In humans and in animal models of status epilepticus, including those from xenobiotics, there are two alternating phases of electrical activity noted on electroencephalography. Periods of high-frequency spike activity (ictal) are accompanied by marked increases in cerebral oxygen consumption and metabolic requirements and alternate with interictal periods of isolated spike waves during which metabolic demands are less. The high-frequency phase lasts only a few minutes before suddenly terminating, sometimes with a few seconds of electrocerebral silence. A gradual increase in electrical activity during the interictal phase eventually leads to a recurrence of high-frequency spike activity.⁷

These periodic, spontaneous self-terminations of high-frequency electrical activity initially occur before neurons exhaust oxygen and energy supplies and result from adenosine released from depolarizing neurons and glial cells.^{7,48} Adenosine acts on presynaptic receptors to prevent further release of excitatory neurotransmitters and acts on postsynaptic receptors to inhibit their actions.^{48,204}

Any xenobiotic that directly or indirectly enhances adenosine’s action at A₁ receptors in the brain will usually exhibit anticonvulsant activity. Conversely, A₁ receptor antagonists lower the seizure threshold and make seizure termination more difficult and less likely to respond to anticonvulsants. Xenobiotics that antagonize A_{2A} receptors produce cerebral vasoconstriction and may limit oxygen delivery during times of increased demand.⁷

Xenobiotics

Table 14–12 provides examples of xenobiotics that affect adenosine receptors.

TABLE 14–12. Examples of Xenobiotics Affecting Adenosine Receptors	
Adenosine agonism	
Direct nonselective agonists	
Adenosine	

ADAC (adenosine amine congener)

Inosine

Direct selective A₁ agonists

Tecadenoson

Direct selective A₂ agonists

Regadenoson

Inhibit reuptake

Acadesine

Acetate

Benzodiazepines

Calcium channel blockers

Carbamazepine

Cyclic antidepressants

Dipyridamole

Ethanol

Indomethacin

Papaverine

Inhibit adenosine deaminase

Acadesine

Dipyridamole

Pentostatin

Inhibit adenosine kinase

Acadesine

Increase adenosine release

Opioids

Inhibit xanthine oxidase

Allopurinol

Increase A₁ receptor activity

Isoflurane

Sevoflurane

Adenosine antagonism

A₁ blockade

Caffeine

Carbamazepine

Theophylline

A₂ blockade

Caffeine

Theophylline

^aEthanol's inhibition of adenosine uptake may, at least in part, be explained by metabolism to acetate.

Direct Adenosine Agonists. ADAC (adenosine amine congener) is a direct A₁ receptor agonist used in the treatment of Huntington disease.⁹ Regadenoson is a selective A_{2A} agonist clinically used as a diagnostic agent for pharmacological stress testing.⁶⁰ Tecadenoson is a selective A₁ receptor agonist that is used for treatment of supraventricular tachycardia.^{52,60}

Indirect Adenosine Agonists. Papaverine and dipyridamole inhibit adenosine reuptake.^{60,61} Like other adenosine agonists, papaverine and dipyridamole demonstrate anticonvulsant activity when injected into the CNS. Such actions are not achievable with safe systemic doses. Sevoflurane and isoflurane are two commonly used general anesthetic gases with adenosine agonist activities.⁶⁰

In addition to their actions at GABA_A receptors, benzodiazepines inhibit adenosine reuptake.¹¹² This may explain observations that methylxanthines, potent adenosine receptor antagonists, have reversed benzodiazepine-induced sedation in humans. The potencies of benzodiazepines as inhibitors of adenosine uptake show good correlation with clinical anxiolytic and anticonflict potencies, suggesting that such inhibition contributes to their action. The anticonvulsant effect of large doses of flumazenil also results, at least in part, from inhibition of adenosine uptake. Carbamazepine inhibits adenosine reuptake, although this is not thought to account for most anticonvulsive action.

Adenosine may mediate many of the acute and chronic motor effects of ethanol on the brain. Ethanol, possibly through its metabolite, acetate, prevents adenosine reuptake, raising synaptic adenosine concentrations.⁶ Excessive stimulation of several adenosine receptors in the cerebellum may explain much of the motor impairment from low ethanol concentrations. In fact, animals made tolerant to ethanol develop cross-tolerance to adenosine agonists. In mice, adenosine receptor agonists increase ethanol-induced incoordination, while adenosine antagonists decrease this intoxicating response.⁶

There are numerous inhibitors of adenosine reuptake, including propentofylline, nimodipine, cyclic antidepressants, and other calcium channel blockers.^{154,156} A₁ receptors located at the spinal cord are important modulators of pain transmission. Cyclic antidepressant-induced inhibition of adenosine uptake may explain some of their effectiveness in treating neuropathic pain.⁶¹ The analgesic effectiveness of opioids can be partially attributed to their ability to increase the release of adenosine within the spinal cord.^{12,61}

Dipyridamole inhibits adenosine deaminase, raising adenosine concentrations. During times of elevated adenosine concentrations that occur with cardiac or cerebral ischemia, adenosine further enhances adenosine's beneficial actions by three mechanisms: inhibition of adenosine kinase, inhibition of adenosine deaminase, and inhibition of adenosine reuptake.¹⁴³

Adenosine Antagonists. The main adenosine antagonists of toxicologic concern are methylxanthines. Theophylline and caffeine are selective P₁ antagonists, blocking both A₁ and A₂ receptors.^{7,12} The response to methylxanthines by A₃ receptors varies widely, depending on the species. Human A₃ receptors demonstrate very low affinity for methylxanthines.⁶⁰

Peripherally, methylxanthines produce excessive release of catecholamines from peripheral nerve endings (and probably the adrenal gland) by blocking presynaptic A₁ receptors. In turn, catecholamine-mediated responses are exaggerated by blockade of inhibitory postsynaptic A₁ receptors on end organs.⁶⁰

Centrally, enhanced release and actions of excitatory neurotransmitters (eg, glutamate) explain methylxanthine-induced convulsions that are frequently refractory to anticonvulsants. The reasons why theophylline convulsions carry such a high mortality stem from lack of A₁-mediated self-termination (continual high-frequency spike activity and large metabolic demands), compounded by vasoconstriction caused by blockade of A₂ receptors.

Like phenytoin, the major anticonvulsant effect of carbamazepine results from Na⁺ channel blockade. Unlike phenytoin, carbamazepine antagonizes A₁ receptors.^{33,41} This may explain the higher frequency of seizures after carbamazepine

overdose than after phenytoin overdose. The absence of A₂ blockade by carbamazepine theoretically allows for increases in cerebral blood flow to meet metabolic demands of the seizing brain.

SUMMARY

- Neurotransmitter systems share common physiologic features, including neurotransmitter reuptake, vesicle membrane pumps, ion trapping of neurotransmitters within vesicles, calcium-dependent exocytosis, and receptors coupled to either G proteins or to ion channels.
- It is not surprising, then, that a single xenobiotic frequently produces effects on several different neurotransmitter systems. As the number of new xenobiotics encountered by man continues to grow, an understanding of their molecular actions in the nervous system helps to anticipate and better understand various pharmacologic and adverse effects resulting from therapeutic or toxic doses.

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15 WITHDRAWAL PRINCIPLES

Richard J. Hamilton

In the central nervous system (CNS), excitatory neurons fire regularly, and inhibitory neurons inhibit the transmission of these impulses. Whenever action is required, the inhibitory tone diminishes, permitting the excitatory nerve impulses to travel to their end organs. Thus, all action in human neurophysiology can be considered to result from disinhibition.

Tonic inhibition (sustained, as opposed to phasic or transient inhibition) triggered by the constant presence of a xenobiotic produces an adaptive change in the affected neuron such that the constant presence of that xenobiotic is required to prevent dysfunction. A withdrawal syndrome occurs when the constant presence of this xenobiotic is removed or reduced and the adaptive changes persist. Withdrawal is a dysfunctional condition in which tonic inhibitory neurotransmission is significantly reduced, essentially producing excitation (Fig. 15–1). Every withdrawal syndrome has two characteristics: (1) a preexisting physiologic adaptation to a xenobiotic, the continuous presence of which prevents withdrawal, and (2) decreasing concentrations of that xenobiotic. In contrast, simple tolerance to a xenobiotic is characterized as a physiologic adaptation that shifts the dose–response curve to the right; that is, greater amounts of a xenobiotic are required to achieve a given effect. Physiologic dependence, generally simply called dependence, occurs when the absence of the xenobiotic leads to the development of a specific withdrawal syndrome. Dependence needs to be distinguished from addiction, which is compulsive drug-seeking behavior. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), uses the term substance use to combine the DSM-IV disorders of substance abuse and substance dependence.³

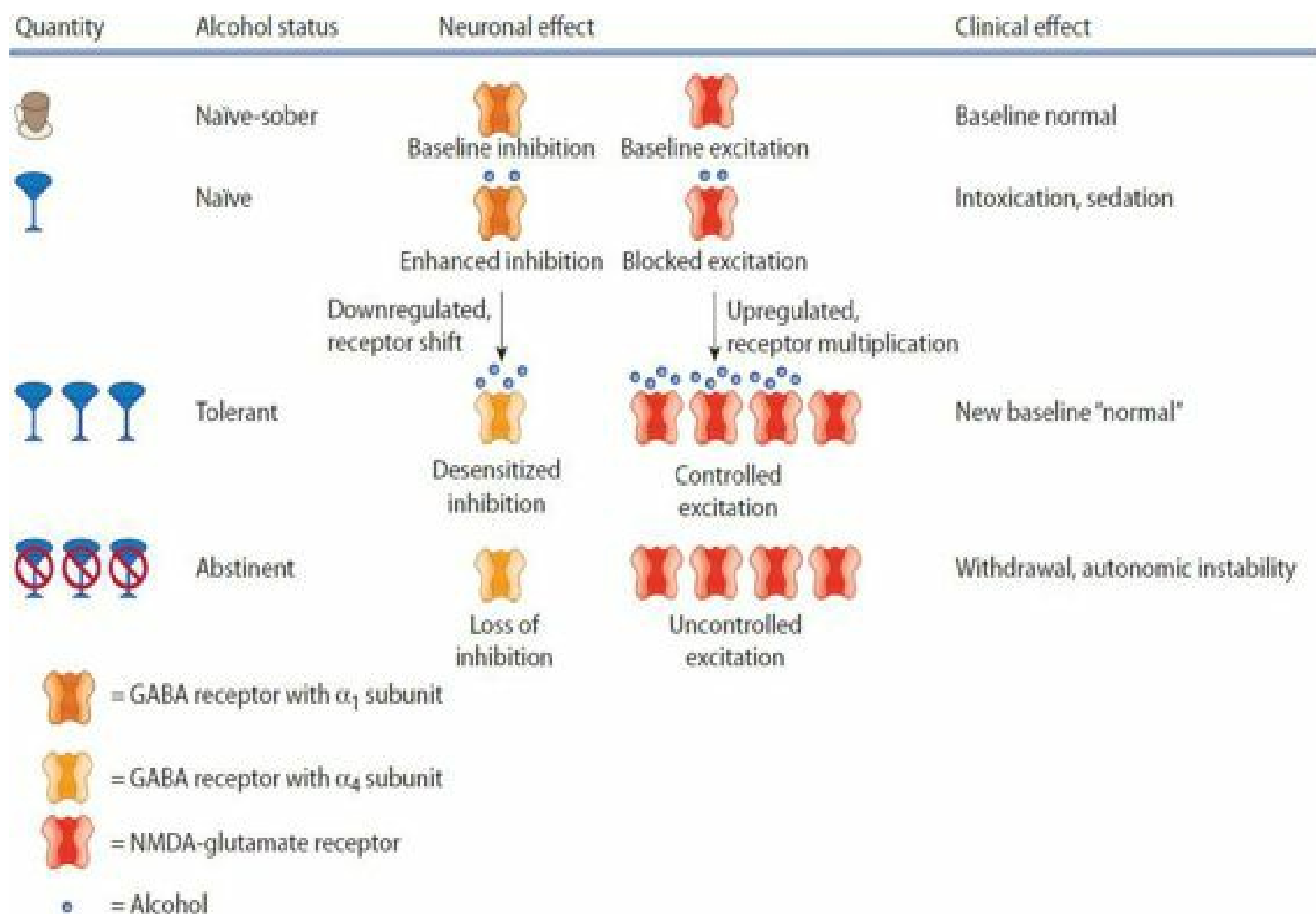


FIGURE 15–1. Alcohol intoxication, tolerance, and withdrawal. Alcohol consumption in an alcohol-naïve person

produces intoxication and sedation by simultaneous agonism at the γ -aminobutyric acid (GABA) receptor–chloride channel complex and antagonism at the N-methyl-D-aspartate (NMDA)-glutamate receptor. Continuous alcohol consumption leads to the development of tolerance through changes in both the GABA receptor–chloride channel complex (a subunit shift from α_1 to α_4 , resulting in reduced sensitivity to the sedating effects of alcohol) and the NMDA subtype of glutamate receptor (upregulation in number, resulting in enhanced wakefulness). There is conceptually a concentration at which the tolerant patient may appear clinically normal despite having an elevated blood alcohol concentration. Tolerant patients who are abstinent lose the tonic effects of alcohol on these receptors, resulting in withdrawal.

Withdrawal is manifested by either of the following: (1) a characteristic withdrawal syndrome for the substance, or (2) the same (or a closely related) substance is taken to relieve withdrawal symptoms. Note that either criterion fulfills this definition. Logically, all syndromes have the first criterion, so it is the presence of the second criterion that is critical to understanding physiology and therapy.

For the purposes of defining a unifying pathophysiologic pattern of withdrawal syndromes, this chapter considers syndromes in which both features are present. An analysis from this perspective distinguishes xenobiotics that affect the inhibitory neuronal pathways from those that affect the excitatory neuronal pathways, such as cocaine. According to this definition, cocaine does not produce a withdrawal syndrome but rather a postintoxication syndrome that often results in lethargy, hypersomnolence, movement disorders, and irritability. Although referred to as withdrawal, this syndrome does not meet the definition for a withdrawal syndrome because the same (or a closely related) substance is not taken to relieve or avoid withdrawal symptoms. This postintoxication syndrome, the so-called “crack crash” or “washed-out syndrome,” is caused by prolonged use of cocaine, and patients ultimately return to their premorbid function without intervention. This distinction is important for toxicologists, because (1) withdrawal syndromes that demonstrate both features of the DSM-IV-TR criteria are treated with reinstatement and gradual withdrawal of a xenobiotic that has an effect on the receptor and (2) withdrawal syndromes that do not demonstrate the second feature require only supportive care and resolve spontaneously. The term “drug discontinuation syndromes” has been used in particular with serotonin reuptake inhibitors to describe the symptoms that result when a drug used therapeutically is discontinued but this is in fact a withdrawal syndrome. Addiction and dependence are terms often used in the context of the psychosocial aspects of xenobiotic use and are meant to convey the continued use of a xenobiotic despite adverse consequences.

Finally, withdrawal syndromes are best described and treated according to the class of receptors primarily affected because this concept also organizes the approach to patient care. For each receptor and its agonists, research has identified genomic and nongenomic effects that produce neuroadaptation and withdrawal syndromes. Six mechanisms appear to be involved: (1) genomic mechanisms via mRNA, (2) second-messenger effects via protein kinases, cyclic adenosine monophosphate (cAMP),^{17,19} or calcium ions, (3) receptor endocytosis, (4) expression of various receptor subtypes depending on location within the synapse (synaptic localization), (5) intracellular signaling via effects on other receptors, and (6) neurosteroid modulation. Some or all of these mechanisms are demonstrated in each of the known withdrawal syndromes.^{23,24} These mechanisms develop in a surprisingly rapid fashion and modify the receptor and its function in such complex ways as to depend on the continued presence of the xenobiotic to prevent dysfunction.^{21,28,37,43,44}

GABA_A RECEPTORS (BARBITURATES, BENZODIAZEPINES, ETHANOL, VOLATILE SOLVENTS)

GABA_A receptors are part of a superfamily of ligand-gated ion channels, including nicotinic acetylcholine receptors and glycine receptors, which exist as pentamers arranged around a central ion channel. When activated, they hyperpolarize the postsynaptic neuron by facilitating an inward chloride current (without a G protein messenger), decreasing the likelihood of the neuron firing an action potential. γ -aminobutyric acid type A (GABA_A) receptors have separate binding sites for GABA, barbiturates, benzodiazepines, loreclezole, and picrotoxin (Chap. 14).³¹ Barbiturates and benzodiazepines bind to separate receptor sites and enhance the affinity for GABA_A at its receptor site.

The GABA receptor is a pentamer comprised of two α subunits, two β subunits, and one additional subunit, most commonly γ , which is a key element in the benzodiazepine binding site. Each receptor has two GABA binding sites that are located in a homologous position to the benzodiazepine site between the α and β subunits. Although the mechanism is unclear, benzodiazepines have no direct functional effect without the presence of GABA. Conversely, certain barbiturates (perhaps all, in a dose-dependent manner) and propofol can directly increase the duration of channel opening, thereby producing a net increase in current flow without GABA binding. This process has therapeutic implications and accounts for why high-dose barbiturates are nearly universally successful in stopping status epilepticus and treating severe withdrawal.

This prototypical pentameric GABA_A receptor assembly is derived from permutations and combinations of two, three, four, or even five different subunits. The subtypes of GABA receptors can even vary on the same cell. In fact, GABA receptors are heterogeneous receptors with different subunits and distinct regional distribution. Although the preponderance of subtypes $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, and $\alpha_3\beta_3\gamma_2$ accounts for 75% of GABA receptors, there are at least 16 others of import.⁴⁴ The

recognition of additional subunits of GABA_A receptors has permitted the development of targeted pharmaceuticals, such as zolpidem.⁵

Previously, ethanol was thought to have GABA receptor activity, although a clearly identified binding site was not evident. Traditional explanations for this effect included (1) enhanced membrane fluidity and allosteric potentiation (so-called cross-coupling) of the five proteins that construct the GABA_A receptor, (2) interaction with a portion of the receptor, and/or (3) enhanced GABA release. Research with chimeric reconstruction of GABA_A and N-methyl-D-aspartate (NMDA) channels demonstrates highly specific binding sites for high doses of ethanol that enhance GABA_A and inhibit NMDA receptor-mediated glutamate neurotransmission. However, research has not clarified whether ethanol at low doses is a direct agonist of GABA_A receptors or a potentiator of GABA_A receptor binding.³²

Ethanol exhibits six mechanisms of adaptation to chronic exposure and is the prototypical xenobiotic for studying neuroadaptation and withdrawal.^{11,23,27} These six mechanisms appear to apply to benzodiazepines as well.^{1,32} The mechanisms are (1) altered GABA_A receptor gene expression via alterations in mRNA and peptide concentrations of GABA_A receptor subunits in numerous regions of the brain (genomic mechanisms), (2) posttranslational modification through phosphorylation of receptor subunits with protein kinase C (second-messenger effects), (3) subcellular localization by an increased internalization of GABA_A receptor α_1 -subunit receptors (receptor endocytosis), (4) modification of receptor subtypes with differing affinities for agonists to the synaptic or nonsynaptic sites (synaptic localization), (5) regulation via intracellular signaling by the NMDA, acetylcholine, serotonin, and β -adrenergic receptors, and (6) neurosteroidal modulation of GABA receptor sensitivity and expression.^{9,17,25} Furthermore, changes in GABA_A subunit composition and function are evident within one hour of administration of a single dose of ethanol.²⁶

Intracellular signaling via the NMDA subtype of the glutamate receptor appears to explain the “kindling” hypothesis, in which successive withdrawal events become progressively more severe.^{7,27} The activity of excitatory neurotransmission increases the more it fires, a phenomenon known as long-term potentiation, and is the result of increased activity of mRNA and receptor protein expression, a genomic effect of intracellular signaling.⁴¹ As NMDA receptors increase in number and function (upregulation) and GABA_A receptor activity diminishes, withdrawal becomes more severe.^{16,27,40} The dizocilpine (MK-801) binding site of the NMDA receptor appears to be the major contributor, and this effect is recognized in neurons that express both NMDA and GABA_A receptors.² When alcohol or any xenobiotic with GABA agonist activity is withdrawn, inhibitory control of excitatory neurotransmission, such as that mediated by the now upregulated NMDA receptors, is lost.²⁸ This loss results in the clinical syndrome of withdrawal: CNS excitation (tremor, hallucinations, seizures), and autonomic stimulation (tachycardia, hypertension, hyperthermia, diaphoresis) (Chap. 81).³⁷

Volatile solvents, such as gasoline, diethyl ether, and toluene, are widely abused xenobiotics whose effects also appear to be mediated by the GABA receptor (Chap. 84).^{35,39} These solvents can produce CNS inhibition and anesthesia at escalating doses via the GABA_A receptor in a fashion similar to that of ethanol.^{6,18,46}

GABA_B RECEPTORS (GHB AND BACLOFEN)

GABA_B agonists such as γ -hydroxybutyric (GHB) acid, GHB precursors and analogs, and baclofen have similar clinical characteristics with regard to adaptation and withdrawal.⁴⁷ The GABA_B receptor is a heterodimer of the GABA_{B1} and GABA_{B2} receptors. Unlike GABA_A, the GABA_B receptor couples to various effector systems through a signal-transducing G protein.^{10,47} GABA_B receptors mediate presynaptic inhibition (by preventing Ca²⁺ influx) and postsynaptic inhibition (by increasing K⁺ efflux). The postsynaptic receptors appear to have an inhibitory effect similar to that of the GABA_A receptors, though the mechanism differs. The presynaptic receptors provide feedback inhibition of GABA release.

GHB is a naturally occurring inhibitory neurotransmitter with its own distinct receptor (Chap. 83).⁴ Physiologic concentrations of GHB activate at least two subtypes of a distinct GHB receptor (antagonist-sensitive and antagonist-insensitive). However, at supraphysiologic concentrations, such as those that occur after overdose and abuse, GHB binds directly to the GABA_B receptor and is metabolized to GABA (which then activates the GABA_B receptor). The GHB withdrawal syndrome clinically resembles the withdrawal syndrome from ethanol and benzodiazepines and can be severe. In most cases, distinctive clinical features of GHB withdrawal are the relatively mild and brief autonomic instability and the persistence of psychotic symptoms.⁴²

Baclofen is also a GABA_B agonist. The presynaptic and postsynaptic inhibitory properties of baclofen allow it, paradoxically, to cause seizures associated with both acute overdose (because of decreased release of presynaptic GABA via autoreceptor stimulation) and withdrawal. Withdrawal is probably a result of the loss of the chronic inhibitory effect of baclofen on postsynaptic GABA_B receptors. Discontinuation of baclofen produces hyperactivity of neuronal Ca²⁺ channels

(N, P/Q type),¹² leading to seizures, hypertension, hallucinations, psychosis, and coma. However, these manifestations may not differ clinically from the withdrawal symptoms of GABA_A agonists.

Typically, the development of a baclofen withdrawal occurs 24 to 48 hours after discontinuation or a reduction in the dose of baclofen. Case reports highlight the development of seizures, hallucinations, psychosis, dyskinesias, and visual disturbances. Additionally the intrathecal baclofen pump has become an effective replacement for oral dosing, but severe withdrawal can occur when the pump malfunctions or becomes disconnected. Reinstatement of the prior baclofen-dosing schedule appears to resolve these symptoms within 24 to 48 hours. Benzodiazepines and GABA_A agonists (not phenytoin) are the appropriate treatment for seizures induced by baclofen withdrawal.³⁸

OPIOID RECEPTORS (OPIOIDS)

Similar to the behavior of ethanol and GABA_A receptors, opioid binding to the opioid receptors results in a series of genomic and nongenomic neuroadaptations, especially via second-messenger effects. When opioids bind to opioid receptors they alleviate pain by inhibiting neurons, while activating G_s proteins and stimulating K⁺ efflux currents. The opioid receptors are also linked to the G_{i/o} proteins. They act through adenylyl cyclase and inactivate inward Na⁺ current, thus suppressing the intrinsic excitability of a neuron (Chap. 38).

Chronic use of all xenobiotics with opioid-receptor affinity results in a decreased efficacy of the receptor to open potassium channels by genomic mechanisms and second-messenger effects. Following chronic opioid use, the expression of adenylyl cyclase increases through activation of the transcription factor known as cAMP response element-binding protein (CREB) (Fig. 15–2).^{15,29} This situation results in upregulation of cAMP-mediated responses such as the inward Na⁺ channels responsible for intrinsic excitability. The net effect is that only higher concentrations of opioids result in analgesia and other opioid effects. In the dependent patient, when opioid concentrations drop, inward Na⁺ flux occurs unchecked, and the patient experiences the opioid withdrawal syndrome. The clinical findings associated with this syndrome are largely a result of uninhibited activity at the locus ceruleus.^{21,29}

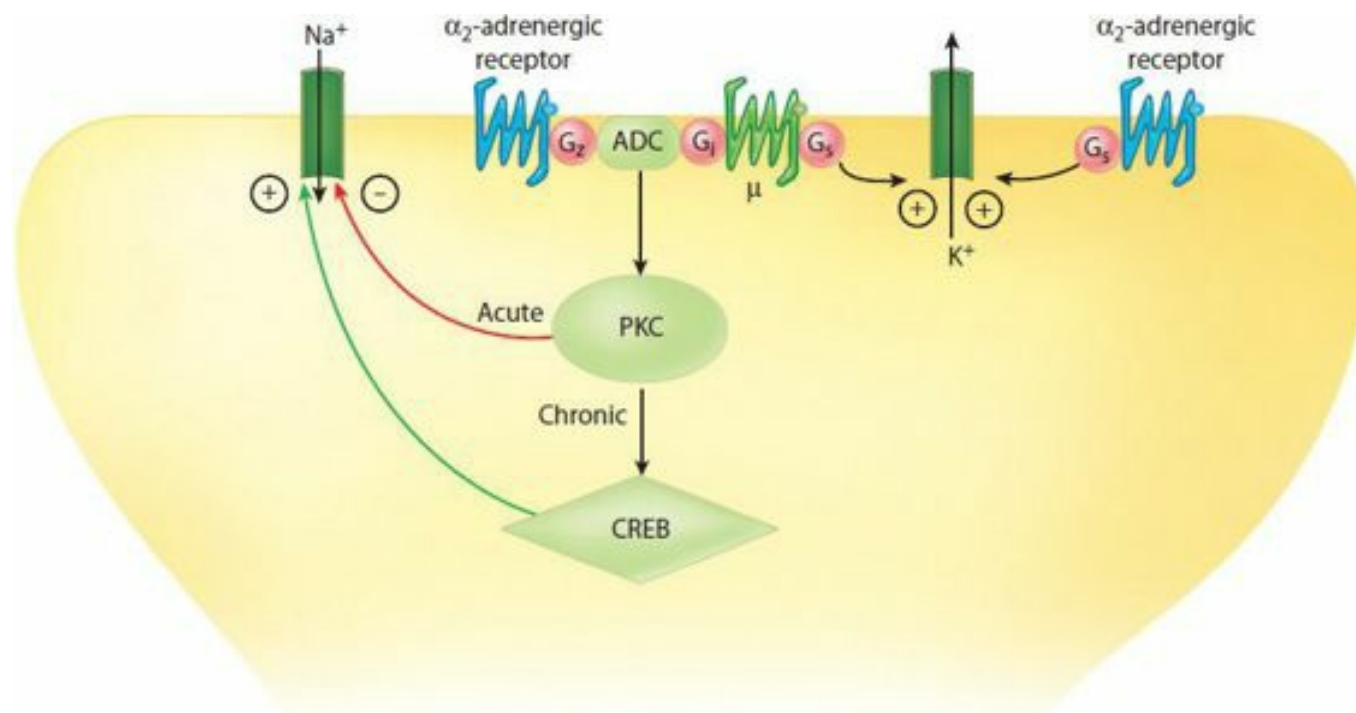


FIGURE 15–2. Immediate and long-term effects of opioids. The immediate effects of both opioids and α₂-adrenergic agonists are to increase inhibition through enhanced potassium efflux and inhibited sodium influx. Long-term effects alter gene expression to enhance sodium influx and restore homeostasis. CREB = cAMP response element-binding protein; ADC = adenylyl cyclase; PKC = protein kinase C. (μ) = α₂-adrenergic receptor.

Furthermore, opioid receptors and central α₂-adrenergic receptors both exert an analogous effect on the potassium channel in the locus ceruleus. Clonidine binds to the central α₂-adrenergic receptor and stimulates potassium efflux, as do opioids, and produces similar clinical findings, which explains why clonidine has efficacy in treating certain aspects of the opioid withdrawal syndrome (cross tolerance). In addition, the antagonistic effect of naloxone at the opioid receptor seems

to partially reverse the effect of clonidine on this shared potassium efflux channel.

Rapid and ultrarapid opioid detoxification are forms of intentional iatrogenic withdrawal that use opioid antagonists to accelerate a return to premorbid receptor physiology. In theory, although not necessarily in practice, inducing opioid withdrawal under general anesthesia with high-dose opioid antagonists permits the transition from drug dependency to naltrexone maintenance without enduring an intense withdrawal syndrome (Chap. 38).^{13,14, 20}

α_2 -ADRENERGIC RECEPTORS (CLONIDINE)

In a manner related to their role in treating opioid withdrawal, prolonged exposure to clonidine and related medications are associated with a withdrawal syndrome. α_2 -Adrenergic receptors are located in the central and peripheral nervous systems. Clonidine is a central and peripheral α_2 -adrenergic agonist. Stimulation of central presynaptic α_2 -adrenergic receptors inhibits sympathomimetic output and results in bradycardia and hypotension. Within 24 hours after the discontinuation of chronic clonidine use, norepinephrine concentrations rise as a result of enhanced efferent sympathetic activity. This increase results in hypertension, tachycardia, anxiety, diaphoresis, and hallucinations.

Dexmedetomidine is a medication that is gaining use as a sedative in the intensive care unit. Like clonidine it is a central and peripheral presynaptic α_2 -adrenergic agonist, but dexmedetomidine has greater specificity for the α_2 receptor and hence stronger sedative properties. It cannot be given in bolus doses because it causes hypertension and tachycardia by stimulating peripheral α_2 receptors on vascular smooth muscle (much like the initial phase of a clonidine overdose).²²

Dexmedetomidine has been used as an adjunct to treat alcohol, benzodiazepine, and opioid withdrawal and is reported to cause less respiratory depression than benzodiazepines but more bradycardia.³⁴ Importantly, dexmedetomidine has a withdrawal syndrome exactly like that of clonidine, including hypertension, tachycardia, and agitation. In fact, clonidine has been used to treat this withdrawal successfully.^{36,45}

ADENOSINE (A) RECEPTORS (CAFFEINE)

The release of most neurotransmitters is accompanied by the passive release of adenosine as a byproduct of adenosine triphosphate (ATP) breakdown. The released adenosine binds to postsynaptic A_1 receptors where it typically has inhibitory effects on the postsynaptic neuron. It also binds to presynaptic A_1 autoreceptors to limit further release of neurotransmitters. A_2 receptors are found on the cerebral vasculature and peripheral vasculature where stimulation promotes vasodilation. Caffeine and other methylxanthines, such as theophylline, antagonize the inhibitory effect of adenosine, primarily on postsynaptic A_1 receptors. As a result, acute use results in increases in heart rate, ventilation, gastrointestinal motility, gastric acid secretion, and motor activity. Chronic caffeine use results in tolerance and the above symptoms diminish. Caffeine use upregulates A_1 receptors by a variety of mechanisms, including increases in receptor number, increases in receptor affinity, enhancement of receptor coupling to the G protein, and increases in G protein-stimulated adenylyl cyclase. An animal study demonstrates that the adenosine receptor has a threefold increase in affinity for adenosine at the height of withdrawal symptoms. This model suggests that long-term caffeine administration results in an increase in receptor affinity for adenosine, thus restoring a state of physiologic balance (normal motor inhibitory tone). When caffeine is withdrawn, the enhanced receptor affinity results in a strong adenosine effect and clinical symptoms of withdrawal: headache (cerebral vasodilation), fatigue, and hypersomnia (motor inhibition).

ACETYLCHOLINE RECEPTORS (NICOTINE)

A nicotinic receptor is a type of acetylcholine receptor located in the autonomic ganglia, adrenal medulla, CNS, spinal cord, neuromuscular junction, and carotid and aortic bodies. Nicotinic receptors are fast-response cation channels that are not coupled to G proteins, distinguishing them from muscarinic receptors, which are coupled to G proteins. Nicotinic acetylcholine receptors have both excitatory and inhibitory effects. As in other withdrawal syndromes, changes brought on by chronic use of nicotinic agonists, such as nicotine in cigarettes, appear to be related to selective upregulation of cAMP.^{8,43}

SEROTONIN REUPTAKE INHIBITORS DISCONTINUATION SYNDROME

As mentioned above, drug discontinuation syndrome is a term used to describe the withdrawal syndrome associated with the therapeutic use of serotonin reuptake inhibitors. It meets the definition of withdrawal syndromes in that symptoms begin when xenobiotic concentrations drop, and the syndrome abates when the xenobiotic is reinstated.³⁰ Headache, nausea, fatigue, dizziness, and dysphoria are commonly described symptoms. The condition appears to be uncomfortable but not life threatening, rapidly resolves with reinstatement of a xenobiotic of the same class, and slowly resolves when the

medication is discontinued after a more gradual taper (Chap. 75).³³

SUMMARY

- Withdrawal occurs when a xenobiotic that has produced adaptive changes in a neuron is removed.
- The treatment of a withdrawal syndrome generally involves readministration of the xenobiotic from which the patient is withdrawing.
- In some situations, crosstolerant xenobiotics can be administered. Examples include the use of benzodiazepines and barbiturates to treat ethanol withdrawal or clonidine for opioid withdrawal.

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SECTION II

PATHOPHYSIOLOGIC BASIS: ORGAN SYSTEMS

16 ELECTROPHYSIOLOGIC AND ELECTROCARDIOGRAPHIC PRINCIPLES

Cathleen Clancy

ELECTROPHYSIOLOGIC PRINCIPLES

The clinical tool most commonly used to assess cardiac function is the surface electrocardiogram (ECG). The ECG records the sum of the electrical changes occurring within the myocardium. The electrophysiologic basis of cardiac function and the ECG are complex and are subject to alteration by numerous xenobiotics. Ion currents flowing through various ion channels are responsible for cardiac function. Electrophysiologic studies have identified the functional types of membrane receptors and ion channels. Molecular genetic studies have identified the gene coding for the key cardiac ion channels and have elucidated the structural and physiologic relationships that lead to the toxic effects of many xenobiotics. These channels are critical for maintenance of the intracellular ion concentrations necessary for action potential development, impulse conduction throughout the heart, and myocyte contraction. This chapter will first review the individual ion channels and their currents, and then summarize their contribution and effects on the ECG.

ION CHANNELS OF THE MYOCARDIAL CELL MEMBRANE

Sodium Channels

The voltage-sensitive sodium channels are responsible for the initiation of depolarization of the myocardial membrane. All currently identified voltage-sensitive channels, including the sodium and calcium channels, have structures similar to the potassium channel assembly. The sodium channel gene encodes a single protein that contains four functional domains (D I to D IV). Each of these domains has the six membrane-spanning regions characteristic of the voltage-gated potassium channel and is structurally similar to an α subunit of the potassium channel (Fig. 16–1A). The single, large α subunit of the sodium channel assembles with regulatory β subunits to form the functional unit of the sodium channel. The best characterized of the sodium channels, the SCN5A gene-encoded α channel, is inactivated by xenobiotic interactions between the D III and the D IV domains to physically block the inner mouth of the sodium channel pore.³² Six specific receptor sites are identified on the α subunit with different xenobiotics binding at specific sites: tetrodotoxin, saxitoxin, conotoxin (site 1); veratridine, batrachotoxin, grayanotoxin (site 2); α scorpion toxins, sea anemone toxins (site 3); β -scorpion toxins (site 4); brevetoxins, ciguatoxins (site 5); delta conotoxins (site 6); and local anesthetic and related antidysrhythmic and antiepileptic binding at another receptor site.¹⁵

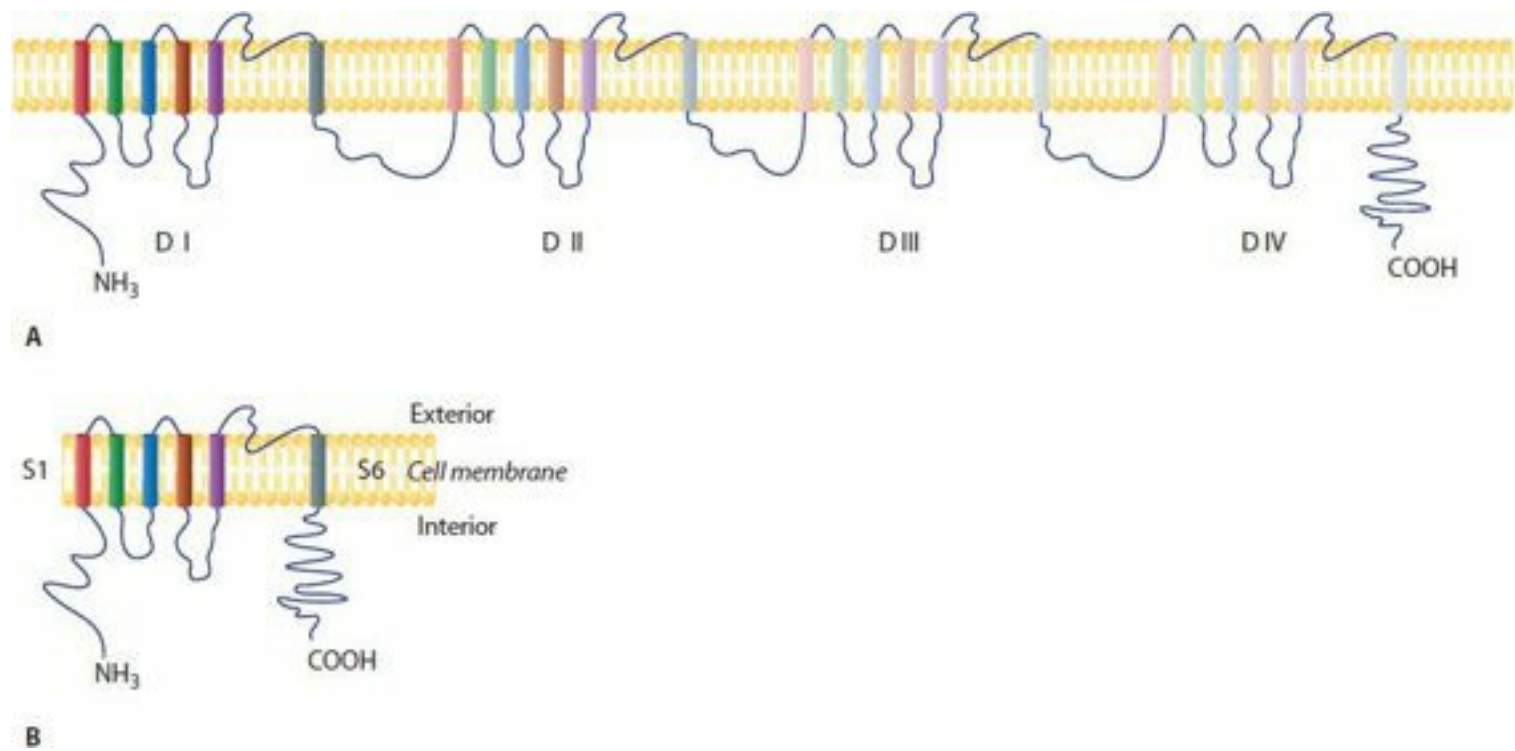


FIGURE 16–1. Structure of the sodium and potassium channels. (A) The structure of the α subunit of the sodium channel. The protein molecule has 4 functional domains (D I–D IV) each analogous to one of the potassium channel α subunits. One of these molecules assembles with β subunits to form the membrane sodium channel. (B) The structure of the α subunit of the voltage gated potassium channel. The protein molecule has six membrane spanning regions (S1–S6); the voltage sensitive region is S4 and the actual ion channel is located between S5 and S6. Four of these α subunits assemble with four β subunits to form the potassium channel complex.

Potassium Channels

Ion channels that change their conductance of current with changes in the transmembrane voltage potential are called rectifying channels. The voltage sensitive potassium channels are categorized based upon their speed of activation and their voltage response. They include the “delayed rectifier” potassium currents, particularly the I_{K_r} (rapidly activating) and the I_{K_s} (slowly activating) channels.⁴⁶

The various voltage gated potassium channels share an underlying structural similarity. The α subunit is a protein molecule with six membrane-spanning α -helical domains, termed S1 to S6 (Fig. 16–1B). The pore domain is located between the S5 and S6 regions of the α subunit, and the S4 region is the voltage sensor region.^{32,55} Four of the α subunits encoded by the KvLQT1 gene assemble with β units encoded by the minK gene (originally thought to be the minimal potassium channel subunit) to form the I_{K_s} potassium channel.³² Human ether a-go-go related gene (HERG) encodes the α subunit that assembles with β subunit proteins encoded by the minK related protein 1 (MiRPI) gene to form the I_{K_r} potassium channel. The C-terminus region of the α subunit encoded by HERG has a cyclic nucleotide binding domain and an N-terminus region similar to domains involved in signal transduction in cells.³²

Many xenobiotics interact with the HERG-encoded subunit of the potassium channel to reduce the current through the I_{K_r} channel and prolong the action potential duration. The HERG α subunit of the channel is particularly susceptible to xenobiotic-induced interactions due to two important differences from the other channels. First, the S6 domain of the HERG channel has aromatic domains on the inner cavity pore that can bind to aromatic xenobiotics. Additionally, the inner cavity and entrance of the HERG channel is larger than the other voltage-gated potassium channels.³² This larger pore can accommodate larger xenobiotics that are then trapped within the pore when the channel closes.^{32,54,55,60}

Calcium Channels

Calcium channel conductivity across the myocardial cell membrane is critical for maintaining the appropriate duration of cell membrane depolarization and for initiation of cellular contraction. The best characterized of the calcium channels are the slow (L-type), the fast (T-type), and the ryanodine receptor calcium channel. They are more prominently involved in cardiac contractility and discussed in Chap. 17.

ION CHANNELS AND MYOCARDIAL CELL ACTION POTENTIAL

An understanding of the basic electrophysiology of the myocardial cell is essential to understand the toxicity of xenobiotics and to plan appropriate therapy. **Figure 16–2A** shows the typical action potential of myocardial cell depolarization, the electrolyte fluxes responsible for the action potential, and the resulting ECG complex. The action potentials of the contractile and the conductive cells are depicted.

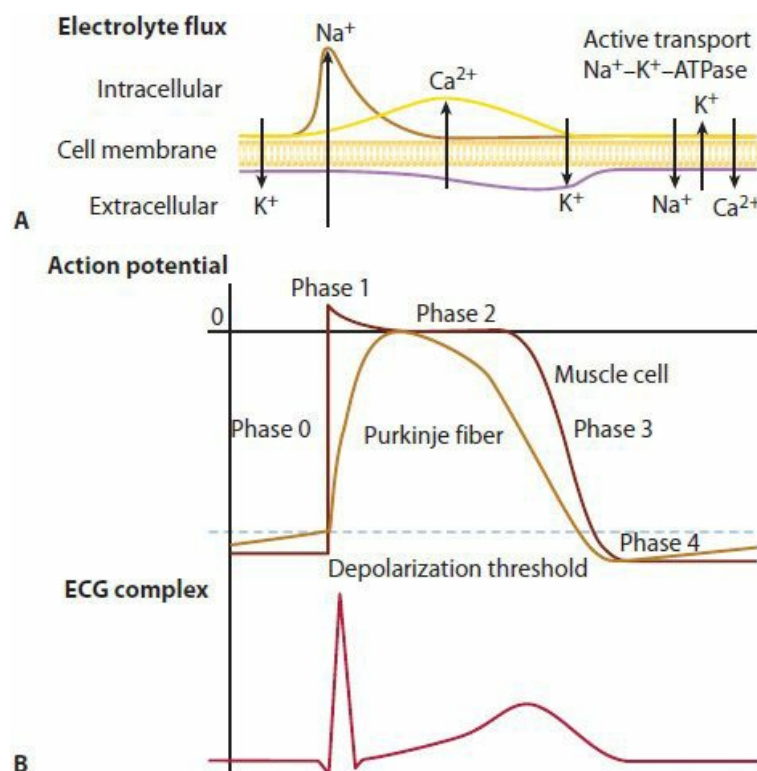


FIGURE 16–2. Relationship of electrolyte movement across the cell membrane (**A**) to the action potential and the surface ECG recording (**B**) over a single cardiac cycle.

The action potential is divided into five phases: (1) phase 0, depolarization, (2) phase 1, overshoot, (3) phase 2, plateau, (4) phase 3, repolarization, and (5) phase 4, resting. Phase 0 begins when the cell is excited either by a stimulus from an adjoining cell or by spontaneous depolarization of a pacemaker cell. The stimulus causes selective voltage-gated fast sodium channels (I_{Na^+}) to open, resulting in rapid depolarization of the membrane. At the end of phase 0, the voltage-sensitive sodium channels close and a transient outward potassium current (I_{To}) occurs, resulting in a partial repolarization of the membrane—this constitutes phase 1.

During phase 2 (plateau phase), the inward depolarizing calcium currents are largely balanced by the outward repolarizing potassium currents. Voltage-sensitive calcium channels that open allow Ca^{2+} movement down the 5000–10,000 fold concentration gradient into the cell. These channels are categorized based on their conductance (fast or slow) and their sensitivity to voltage changes.^{16,51} The calcium currents (mostly the “long-lasting” current) gradually decrease as the channels inactivate. Simultaneously, the outward potassium “delayed rectifier” currents, particularly the I_{Ks} (slowly activating) current increases, terminating the plateau phase of the action potential and initiating cellular repolarization (phase 3). Other, smaller, outward potassium currents (not shown in **Fig. 16–2A**) play a lesser role in the duration of the action potential and development of phase 3, including I_{Kur} (ultra-rapid), I_{Kr} (rapidly activating), I_{Kp} (plateau), $I_{\text{K-Ach}}$ (acetylcholine-dependent), and $I_{\text{K-ATP}}$ (adenosine triphosphate-dependent) currents.

In phase 3, the rapid repolarization phase, the cell membrane repolarizes as a result of the slow delayed rectifier, I_{Ks} and to a lesser extent the other K^+ currents, the $\text{Na}^+-\text{Ca}^{2+}$ exchanger current, and the sodium/potassium pump.

Phase 4 is the resting state for much of the myocardium, except the pacemaker cells, and it corresponds to diastole in the cardiac cycle. During phases 3 and 4, active transport of Na^+ , K^+ , and Ca^{2+} against their electrochemical gradients returns the myocyte to its baseline resting state. The transmembrane electrochemical gradient is maintained during the resting state by a $\text{Ca}^{2+}-\text{Na}^+$ exchange mechanism and by ATP-dependent pumps in the membrane that together move Ca^{2+} out of the cells.⁵¹

In the pacemaker cells (**Fig. 16–2B**), during phase 4 of the action potential, gradual electrical depolarization of the membrane occurs due to potassium currents (called the I_{Kf} for “funny” or the I_{Kh} for “hyperpolarization-activated” current).^{5,19} The membrane potential gradually increases in these pacemaker cells until the threshold potential is reached, the fast inward sodium channels open, and the I_{Na} current initiates the next phase 0. This electrical impulse is then propagated via the His-Purkinje conducting system of the heart.

In addition to its role in myocardial contractility, Ca^{2+} influx is also important in pacemaker function. Although spontaneous pacemaker cell depolarization has traditionally been ascribed to inward cation current through “pacemaker channels”^{1,19} recent research suggests that it may actually be driven by rhythmic release of calcium from the sarcoplasmic reticulum.^{39,40} Regardless, Ca^{2+} fluxes play an important role in the spontaneous depolarization (phase 4) of the action potential in the sinoatrial (SA) node.⁴¹ The rate of pacemaker cell depolarization is enhanced by β -adrenergic stimulation through phosphorylation of proteins on the sarcoplasmic reticulum and by a phosphorylation-independent action of cAMP at the pacemaker channels.^{1,39} Depolarization of cells in the SA node spreads to surrounding atrial cells where it triggers the opening of fast sodium channels and impulse propagation. Calcium flux also allows normal propagation of electrical impulses via the specialized myocardial conduction tissues in the atrioventricular (AV) node.

During phases 0 to 2, the cell cannot be depolarized again with another stimulus; the cell is absolutely refractory. During the latter half of phase 3, as the calcium channels recover from their inactivated to their resting state, an electrical stimulus of sufficient magnitude may cause another depolarization; the cell is said to be relatively refractory. During phase 4, the cell is no longer refractory and any appropriate stimulus that reaches the threshold level may cause depolarization.

ELECTROCARDIOGRAPHY

The ECG measures the sum of all electrical activity in the heart. It is used extensively in medicine and its interpretation is widely understood by physicians of nearly all disciplines. It is an invaluable diagnostic tool for patients with cardiovascular complaints. However, it is also a valuable source of information in poisoned patients and has the potential to enhance and direct their care. Although it seems obvious that an ECG would be required following exposure to a medication used for cardiovascular indications, many medications with no overt cardiovascular effects at therapeutic doses are cardiotoxic in overdose. Furthermore, in patients with unknown exposures, the ECG can suggest specific xenobiotics or demonstrate electrolyte abnormalities, long before blood is drawn. For example, oropharyngeal or dermal burns in a patient whose ECG has evidence of hyperkalemia or hypocalcemia suggests exposure to hydrofluoric acid⁶⁴ (Chap. 107). Alternatively, a patient manifesting signs of the opioid toxidrome with runs of torsade de pointes might have taken methadone (Chap. 38).²⁴ QT prolongation may be a clue to the etiology of an overdose with an atypical antipsychotic such as quetiapine (Chap. 70). The ECG can also be used to predict complications of poisoning, such as seizures following a cyclic antidepressant overdose (Chap. 71). Therefore, an ECG should be examined early in the initial evaluation of most poisoned patients.

History of the ECG

In the 1900s, Willem Einthoven graphically displayed the electrical activity of the heart and named the different waves—P, QRS, and T. He called this tracing an “elektrokardiogramme,” and was awarded a Nobel Prize in 1924 for his efforts. The acronym EKG, still employed by some authors, was derived from Einthoven’s spelling. The acronym ECG, which is consistent with our current spelling of electrocardiogram, is used throughout this text.

Since this initial description, both the normal electrophysiology of the heart and the pharmacologic effects of various xenobiotics on the ECG have been described. Despite the large number, diversity, and complexity of the various cardiac toxins, there are only a limited number of electrocardiographic manifestations.

Basic Electrophysiology of an ECG

Simplistically, a positive or upward deflection on the oscilloscope is generated when an electrical force moves toward an electrical sensor or electrode, and a downward deflection occurs if the force moves away. An ECG represents the sum of movement of all electrical forces in the heart in relation to the surface electrode, and the height above baseline represents the magnitude of the force (Fig. 16–3). Only during depolarization or repolarization does the ECG tracing leave the isoelectric baseline, because it is only during these periods that measurable net currents are flowing in the heart. During the other periods, mechanical effects are occurring in the myocardium, but large amounts of current are not flowing.

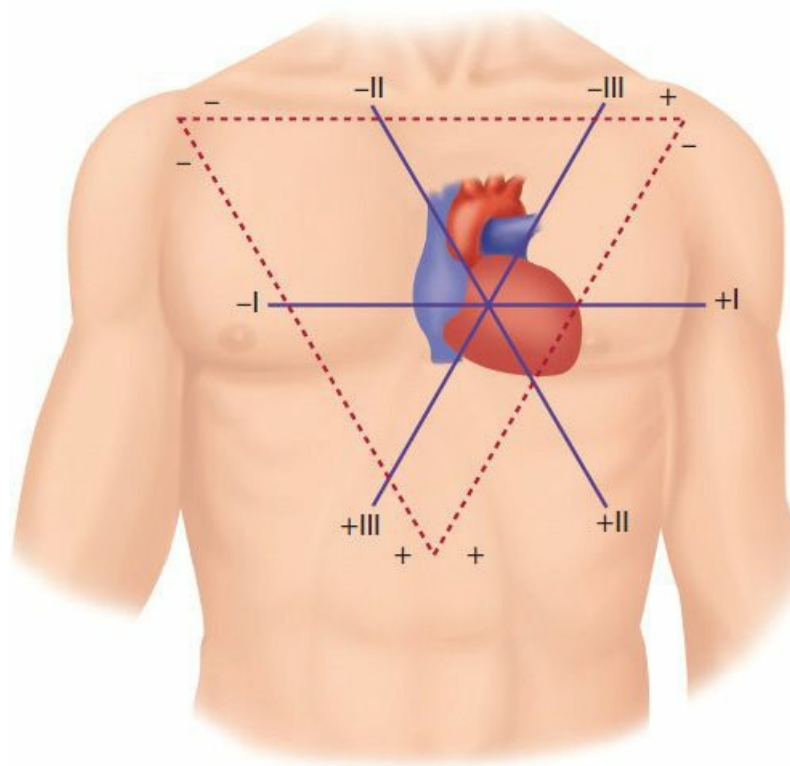


FIGURE 16–3. The hexaxial reference system derived from the Einthoven equilateral triangle defining the electrical potential vectors of electrocardiography. The relationships of the original three limb leads are illustrated. The equiangular (60°) Einthoven triangle formed by leads I, II, and III is shown (dotted lines) with positive and negative poles of each of the leads indicated. Leads I, II, and III are also presented as a triaxial reference system that intersects in the center of the ventricles.

Leads

Although the reading from a single ECG lead provides an immense amount of information, to visualize the heart in a nearly three-dimensional perspective, multiple leads must be assessed simultaneously. Given the cylindrical nature of both the heart and thorax, at any given moment some of these leads will record positive voltage and others negative. The lead placement that was described and refined in the early 1900s by Einthoven forms the basis for the bipolar or limb leads, described as I, II, and III (Fig. 16–3). The Einthoven triangle is an equilateral triangle formed by the sum of these leads. Unipolar limb leads and precordial leads were subsequently added to the standard ECG. Unipolar leads were created when the limb leads were connected to a common point where the sum of the potentials from leads I, II, and III was zero. The currently used unipolar augmented (a) leads (aV_R , aV_L , and aV_F) are based on these unipolar leads (Fig. 16–4). The voltage potential of these unipolar, “augmented leads” is small, thus it is amplified by incorporating the voltage change of the other two augmented leads. Together, leads I, II, III, aV_R , aV_F , and aV_L form the hexaxial reference system that is used to calculate the electrical axis of the heart in the frontal plane. The precordial leads, called V_1 through V_6 , are also unipolar measurements of the change in electric potential measured from a central point to the sixth anterior and left lateral chest positions (Fig. 16–5). If V_2 is placed over the right ventricle, part of the initial positive ventricular deflection (QRS complex) reflects right ventricular activation, with electrical forces moving toward the electrode. The majority of the subsequent terminal negative deflection reflects activation of other muscle tissue (septum, left ventricular wall) when the electrical forces are moving away from the electrode. Recordings from each of these 12 leads (I, II, III, aV_R , aV_L , aV_F , V_1 – V_6) evaluate the heart from two different planes in 12 different positions, yielding a three-dimensional electrical “picture” of the heart, with respect to time and voltage.

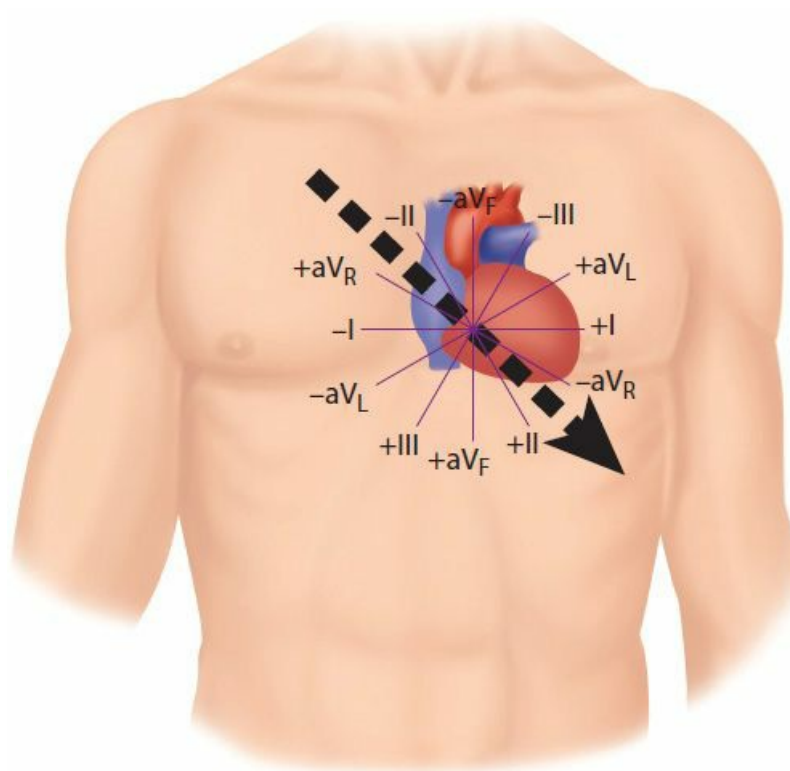


FIGURE 16–4. The hexaxial reference system derived from the Einthoven equilateral triangle defining the electrical potential vectors of electrocardiography showing the relationship between cardiac anatomy and electrocardiographic leads.

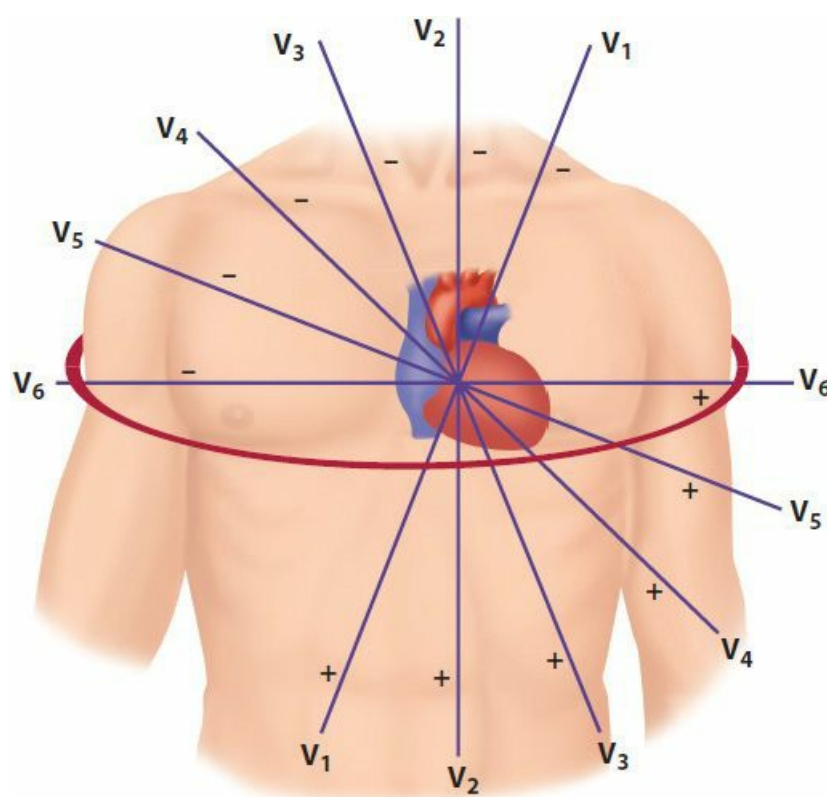


FIGURE 16–5. Visualized as a cross-section, each of the chest leads is oriented through the atrioventricular (AV) node and exits through the patient's back, which is negative.

A continuous cardiac monitor often relies on recordings from one of two bipolar leads: a modified left chest lead (MCL₁) or a lead II. The recording from an MCL₁, in which the positive electrode is in the V₁ position, is similar in appearance to a V₁ recording on a 12-lead ECG. This lead visualizes ventricular activity well; however, lead II shows atrial activity (ie, the P wave) much more clearly. Right ventricular precordial leads (V₁, V₃₋₆R) are sensitive and specific for determining the presence of right ventricular infarctions, although specific applications to poisoning have not been reported.

Various Intervals and Waves

The ECG tracing has specific nomenclature to define the characteristic patterns. Waves refer to positive or negative deflections from baseline, such as the P, T, or U wave. A segment is defined as the distance between two waves, such as the ST segment, and an interval measures the duration of a wave plus a segment, such as QT or PR interval. Complexes are a group of waves without intervals or segments between them (QRS). Electrophysiologically, the P wave and PR interval on the ECG tracing represent the depolarization of the atria. The QRS complex represents the depolarization of the ventricles. The plateau is depicted by the ST segment and repolarization is visualized as the T wave and the QT interval (QT). The U wave, when present, generally represents an afterdepolarization (Fig. 16–6).

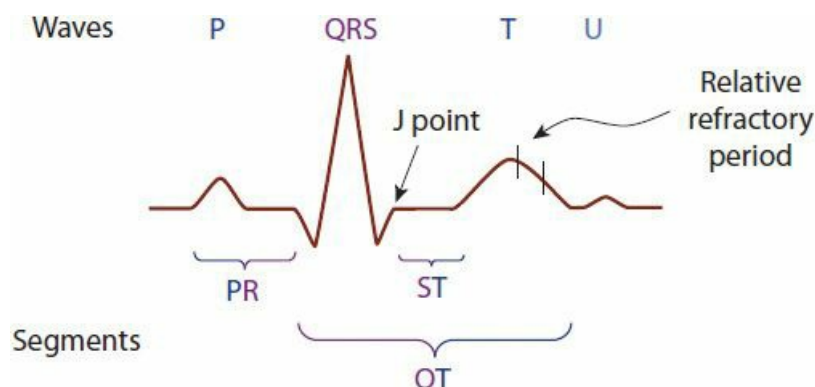


FIGURE 16–6. The normal ECG. The U wave is the small, positive deflection following the T wave. P wave, atrial depolarization; QRS, ventricular depolarization; ST segment, T wave, QT interval, and U wave, ventricular repolarization.

The P Wave

The P wave is the initial deflection on the ECG that occurs with the initiation of each new cardiac cycle.

Electrophysiology. The early, middle, and late portions of the P wave are represented sequentially by the electrical potential initiated by the sinus node. The impulse is propagated directly through the right atrial muscle, producing contraction. The impulse is also propagated by specialized conduction tissue across the interatrial septum, to produce contraction of the left atrium. Additionally, internodal pathways rapidly conduct the impulse to the AV node. The electrical excitation of the sinus node differs from that of the ventricular myocardium in that current is mediated primarily by Ca^{2+} influx via slow T-type calcium channels, and I_{Kf} potassium currents (f for “funny”) or I_{Kh} (h for “hyperpolarization-activated”), not by Na^+ entering through fast sodium channels. Furthermore, the vagus nerve exerts a profound suppressive influence on the nodal tissues.

Abnormal P Wave. Clinically, abnormalities of the P wave occur with xenobiotics that depress automaticity of the sinus node, causing sinus arrest and nodal or ventricular escape rhythms (β -adrenergic antagonists, calcium channel blockers). The P wave is absent in rhythms with sinus arrest, such as occurs with xenobiotics that produce vagal tone such as cardioactive steroids and cholinergics. A notched P wave suggests delayed conduction across the atrial septum and is characteristic of quinidine poisoning or atrial enlargement (Fig. 16–7). P waves decrease in amplitude as hyperkalemia becomes more severe until they become indistinguishable from the baseline (Chap. 19).



FIGURE 16–7. A notched P wave (arrow) suggests delayed conduction across the atrial septum and is characteristic of quinidine poisoning.

PR Interval

The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex (normal is 120 to 200 msec).

Electrophysiology. Despite rapid conduction by specialized conduction tissue from the SA to the AV node, the AV node delays transmission of the impulse into the ventricles, ostensibly to allow for complete atrial emptying. Thus, the PR interval represents the interval between the onset of atrial depolarization and the onset of ventricular depolarization.

Children usually have more rapid conduction and a shorter PR interval, and older adults generally have a longer PR interval. The segment between the end of the P wave and the beginning of the QRS complex (the PQ segment) reflects atrial contraction and is usually isoelectric. Atrial repolarization coincides with the Q wave, but its ECG findings, or atrial T waves, are obscured by the QRS complex.

Abnormal PR Interval. Xenobiotics that decrease interatrial or AV nodal conduction cause marked lengthening of the PR segment until such conduction completely ceases. At this point, the P wave no longer relates to the QRS complex; this is AV dissociation, or complete heart block. Some xenobiotics suppress AV nodal conduction by blocking calcium channels in nodal cells, as does magnesium, β -adrenergic receptor antagonists, or cholinergics through enhanced vagal tone. Although the therapeutic concentrations of digoxin, as well as early cardioactive steroid poisoning, cause PR prolongation through vagal tone, direct electrophysiologic effects account for the bradycardia of poisoning ([Chap. 65](#) and Antidotes in Depth: A19).

QRS Complex

The QRS complex is the second and typically largest deflection on the ECG. The normal QRS duration in adults varies between 60 and 120 msec. The normal QRS complex axis in the frontal plane lies between -30° and 90° , although most individuals will have an axis between 30° and 75° . This axis will vary with the weight and age of the patient. Alterations in myocardial function may also alter the electrical axis of the heart.

Electrophysiology. The QRS complex reflects the electrical forces generated by ventricular depolarization mediated primarily by Na^+ influx into the myocardial cells. Although under normal conditions both ventricles depolarize nearly simultaneously, the greater mass of the left ventricle causes it to contribute the majority of the electrical forces. The QRS complex is primarily positive in leads I and aV_L on the surface ECG recording because under normal conditions the depolarization vector is directed at 60° and is thus moving toward these leads.

The simultaneous and rapid depolarization of the ventricles results in a very short period of electrical activity recorded on the electrocardiogram. Of course, mechanical systole lasts well past the end of the QRS complex and is maintained by continued depolarization during the plateau phase of the action potential. The return to, and maintenance of, the baseline, or isoelectric potential, simply represents that the entire heart is depolarized and there is no significant net flow of current during this period.

The axis of the terminal 40 msec (0.04 seconds) of the QRS complex represents the late stages of ventricular depolarization and generally follows the direction of the overall axis. This axis is determined by examining the last box (0.04 seconds or 40 msec) of the QRS complex.

Abnormal QRS Complex. In the presence of a bundle-branch block, the two ventricles depolarize sequentially rather than concurrently. Although, conceptually, conduction through either the left or right bundle may be affected, many xenobiotics preferentially affect the right bundle ([Fig. 16–8](#)). The specific reasons for this effect are unclear, but it may be related to differing refractory periods of the tissues. This effect typically results in the left ventricle depolarizing slightly more rapidly than the right. The consequence on the ECG is both a widening of the QRS complex and the appearance of the right ventricular electrical forces that was previously obscured by those of the left ventricle. These changes are typically the result of the effects of a xenobiotic that blocks fast sodium channels. Implicated xenobiotics include cyclic antidepressants,^{10,12} quinidine and other type IA and IC antidysrhythmics²⁰ phenothiazines, amantadine,⁵⁷ diphenhydramine,⁵⁸ carbamazepine,³³ and cocaine.² In the setting of cyclic antidepressant (CA) poisoning, an increased QRS duration has both prognostic and therapeutic value ([Chap. 71](#)).^{7,12,28} In one prospective analysis of ECGs in CA poisoned patients, the maximal limb lead QRS duration was prognostic of seizures (0% if < 100 msec; 30% if greater) and ventricular dysrhythmias (0% if < 160 msec; 50% if greater).¹²

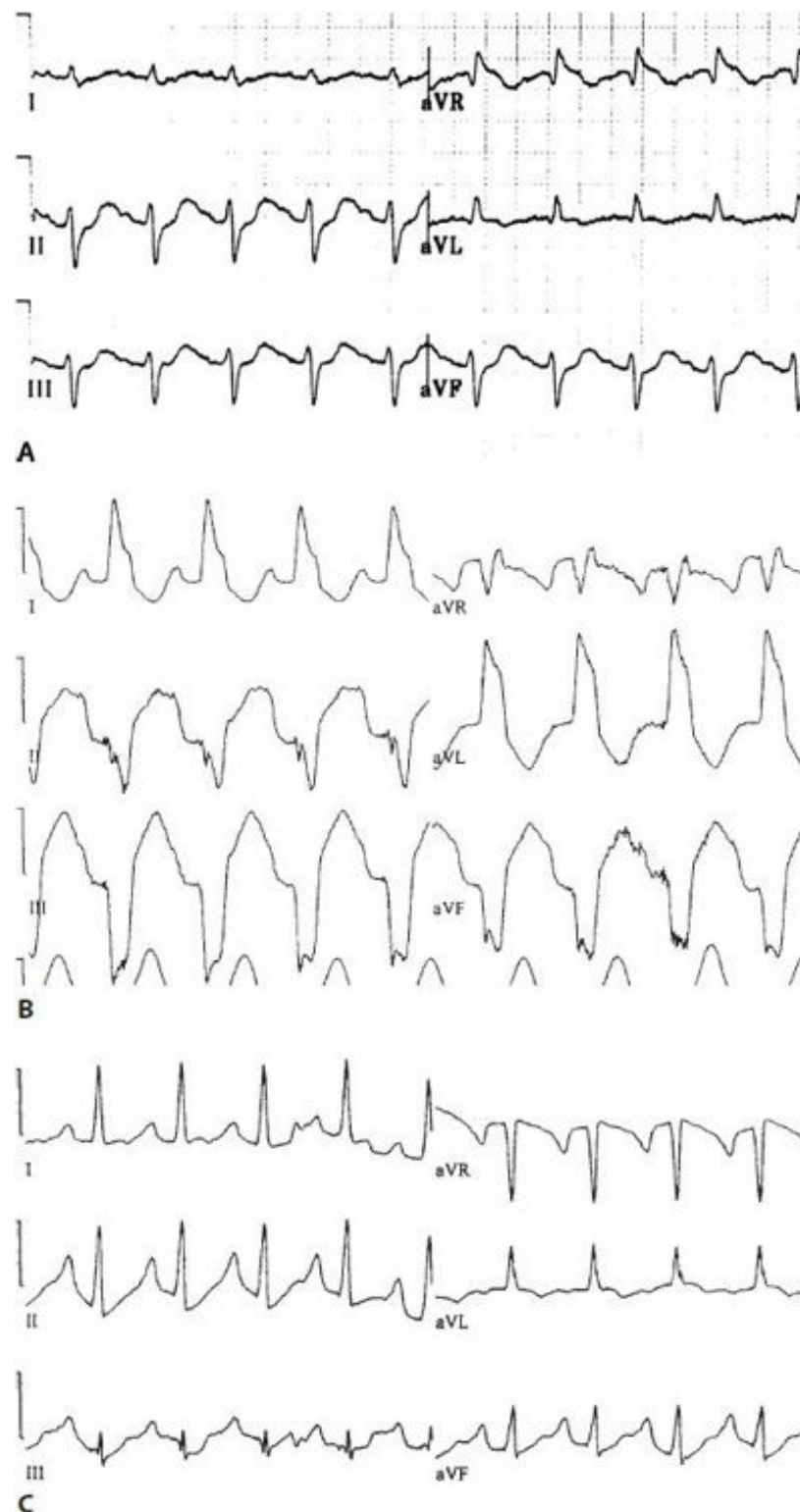


FIGURE 16–8. A 35 year-old woman was found unresponsive in a hallway with an empty bottle of doxepin. Note the progression from (A) a wide QRS interval (108 msec, axis +10), to (B) at >35 min: an RBBB with an axis of -50 and a rightward shift of the terminal 40 msec of the QRS axis, and (C) in the next hour, marked improvement occurred after infusion of hypertonic sodium bicarbonate.

The terminal 40-msec axis of the QRS complex also contains information regarding the likelihood, but not the extent, of poisoning by sodium channel blockers. In a patient poisoned by a sodium channel blocker, the terminal portion of the QRS has a rightward deviation greater than 120° . The common abnormalities include an R wave (positive deflection) in lead aV_R and an S wave (negative deflection) in leads I and aV_L .^{11,36} The combination of a rightward axis shift in the terminal 40 msec of the QRS complex (Fig. 16–9) with a prolonged QT and a sinus tachycardia is highly specific and sensitive for CA poisoning.⁴⁷ Another study suggests that although ECG changes, like a prolonged QRS duration, are better at predicting severe outcomes than the CA concentration, neither is very accurate.⁷ One retrospective study suggests that an absolute height of the terminal portion of aV_R that is greater than 3 mm, predicted seizures or dysrhythmias in CA-poisoned patients.³⁵ However, in infants younger than 6 months, a rightward deviation of the terminal 40-msec QRS axis is physiologic and not predictive of cyclic antidepressant toxicity.¹⁰

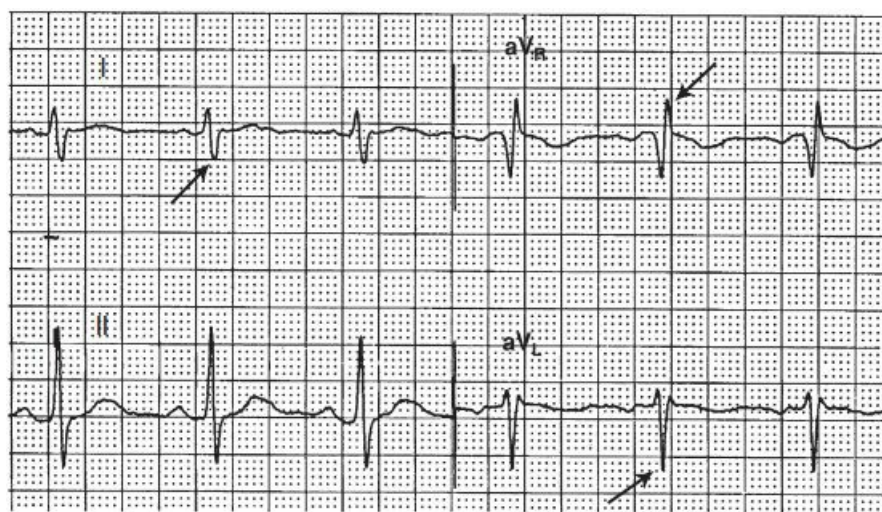


FIGURE 16–9. ECG of a patient with a tricyclic antidepressant overdose. The arrows highlight prominent S wave in leads I and aV_L and R wave in aV_R demonstrate the terminal 40-msec rightward axis shift.

An apparent increase in QRS complex duration and morphology, which is an elevation or distortion of the J point called a J wave or an Osborn wave (Fig. 30–3) is a common finding in patients with hypothermia.^{49,63} Hypermagnesemia is also associated with lengthening of the QRS complex duration and a slight narrowing of the QRS complex may occur with hypomagnesemia. Significant hyperkalemia may also cause widening and distortion of the QRS complex.

ST Segment

The ST segment is defined as the distance between the end of the QRS complex and the beginning of the T wave.

Electrophysiology. The ST segment reflects the period of time between depolarization and the start of repolarization, or the plateau phase of the action potential. During this period, no major currents flow within the myocardium, which explains why under normal circumstances the ST segment is isoelectric. Although both the degree of displacement from the baseline and the length of this segment are important, the ST segment duration is usually measured by its effects on the QT duration (see “The QT Interval”).

Abnormal ST Segment. Displacement of the ST segment from its baseline typically characterizes myocardial ischemia or infarction (Fig. 16–10). The subsequent appearance of a Q wave is diagnostic of myocardial infarction. The ECG patterns of these entities reflect the different underlying electrophysiologic states of the heart. Ischemic regions are highly unstable and produce currents of injury because of inadequate repolarization, which is related to lack of energy substrate to power the Na⁺-K⁺-ATPase. Myocardial infarction represents the loss of electrical activity from the necrotic, inactive ventricular tissue, allowing the contralateral ventricular forces to be predominant on the ECG. Patients who are poisoned by xenobiotics that cause vasoconstriction, such as cocaine (Chap. 78), other α -adrenergic agonists, or the ergot alkaloids, are particularly prone to develop focal myocardial ischemia and infarction. The specific ECG manifestations help to identify the region of injury and may, to some extent, be correlated with an arterial flow pattern: inferior (leads II, III, aV_F; right coronary artery); anterior (leads I, aV_L; left anterior descending artery); or lateral (leads aV_L, V_{5–6}; circumflex branch). However, any poisoning that results in profound hypotension or hypoxia may also result in ECG changes of ischemia and injury. In these patients, the injury may be more global, involving more than one arterial distribution. Diffuse myocardial damage may not be identifiable on the ECG because of global, symmetric electrical abnormalities. Under these circumstances, the diagnosis is established by other noninvasive testing, such as by echocardiogram or by finding elevated concentrations of serum markers for myocardial injury such as troponin.

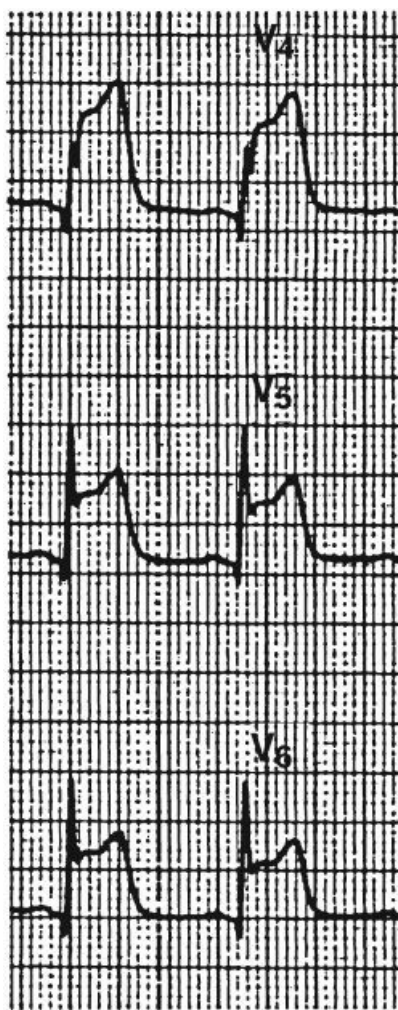


FIGURE 16–10. Leads V₄ to V₆ suggestive of a lateral STEMI are shown from the ECG of a 27 year-old man with substernal chest pain after using crack cocaine.

Many young, healthy patients have ST segment abnormalities that mimic those of myocardial infarction. The most common normal variant is termed “early repolarization” or “J-point elevation,” and is identified as diffusely elevated, upwardly concave ST segments, located in the precordial leads and typically with corresponding T waves of large amplitude (Fig 16–11).¹³ The J point is located at the beginning of the ST segment just after the QRS complex. Because this ECG variant is common in patients with cocaine-associated chest pain (Chap. 78),²⁷ its recognition is critical to instituting appropriate therapy.

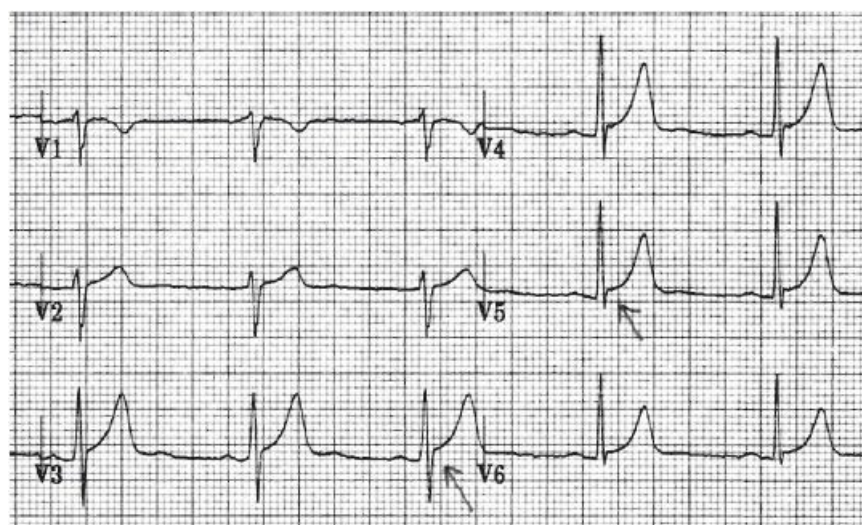


FIGURE 16–11. Healthy 34 year-old man whose ECG demonstrates diffusely elevated, upwardly concave ST segments in leads V3 to V5, and T waves of large amplitude suggestive of an “early repolarization” abnormality.

The Brugada electrocardiographic pattern (Fig 16–12) is characterized by terminal positivity of the QRS complex and ST-segment elevation in the right precordial leads. The Brugada pattern is found in some patients with mutations of the gene that codes for the α subunit of the sodium channel. These patients are at risk for sudden death, and a similar ECG pattern

often occurs in patients who are poisoned by sodium-channel–blocking xenobiotics, including CAs, cocaine,²⁶ classes IA (procainamide) class IC (flecainide, encainide) antidysrhythmics.³⁷ In CA-poisoned patients, this pattern is associated with an increased risk of hypotension, but not sudden death or dysrhythmias.⁹ This pattern is also associated with lithium toxicity.

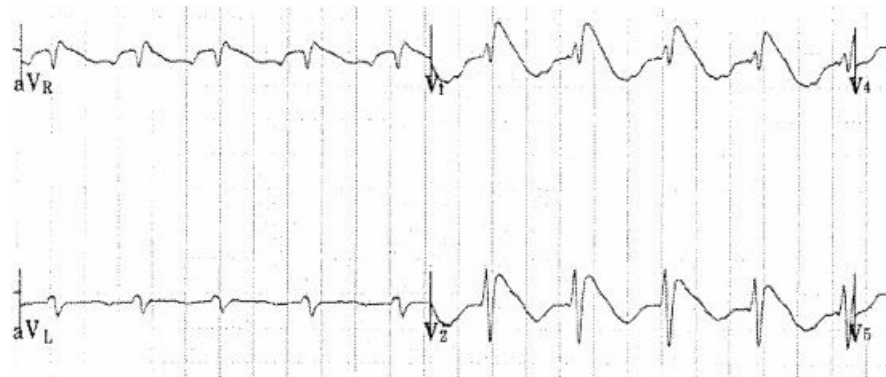


FIGURE 16–12. The Brugada pattern is characterized by terminal positivity of the QRS complex and ST-segment elevation in the right precordial leads and is a similar ECG pattern to that noted in patients poisoned by sodium channel blocking agents such as cyclic antidepressants.⁴ (Used with permission of Vikhyat Bebarta, MD.)

Sagging ST segments, inverted T waves, and normal or shortened QT intervals are characteristic effects of cardioactive steroids, such as digoxin. These repolarization abnormalities are sometimes identified by their similar appearance to “Salvador Dali’s mustache” (Fig. 16–13). As a group, these findings, along with PR prolongation, are commonly described as the “digitalis effect.” They are found in patients with therapeutic drug concentrations and in patients with cardioactive steroid poisoning. As the serum concentration or, more precisely, the tissue concentration increases, clinical and electrocardiographic manifestations of toxicity will appear, which include profound bradycardia or ventricular dysrhythmias.

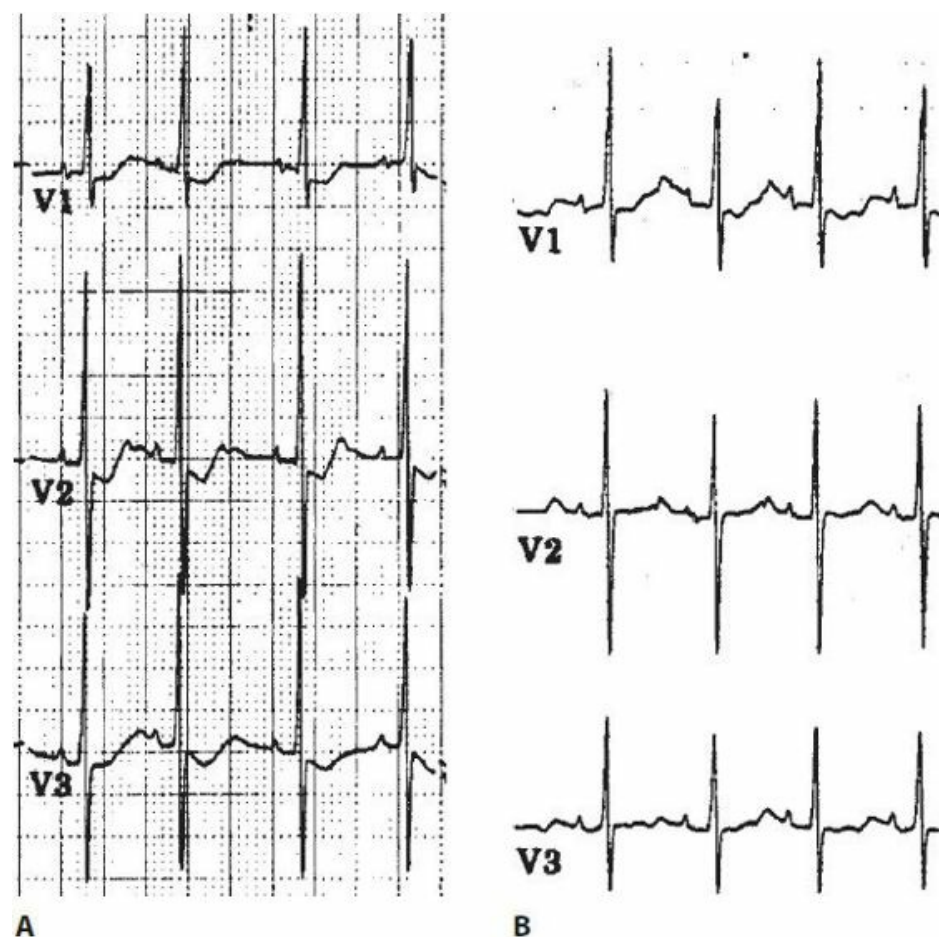


FIGURE 16–13. Two day-old boy erroneously given 50 µg/kg of digoxin, presented with heart rate 60 beats/min, given digibind. (A) ECG from hospital day 2, before digoxin-specific Fab, and shows “digitalis effect” of the ST segment in leads V1 to V3 (digoxin concentration 4 ng/mL). (B) This finding resolves after the child was switched to amiodarone; notice the QT prolongation.

Changes in the ST segment duration are frequently caused by abnormalities in the serum Ca^{2+} concentration. Hypercalcemia causes shortening of the ST segment through enhanced Ca^{2+} influx during the plateau phase of the cardiac cycle speeding the onset of repolarization. For practical purposes this effect is more commonly identified by reduction of the QT duration (Fig. 16–14). In patients with hypercalcemia, the morphology and duration of the QRS complex and T and P waves remain unchanged. Xenobiotic-induced hypercalcemia may result from exposure to antacids (ie, milk alkali syndrome), diuretics (eg, hydrochlorothiazide), cholecalciferol (vitamin D), vitamin A, and other retinoids. Hypocalcemia causes prolongation of the ST segment and QT interval.

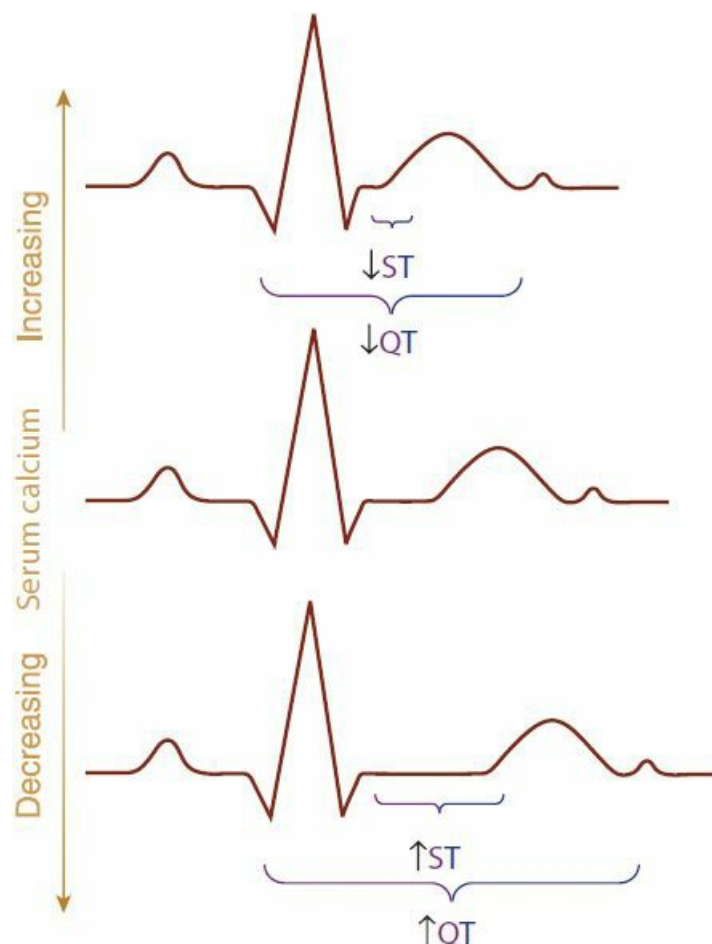


FIGURE 16–14. Electrocardiographic findings associated with changes in serum calcium concentration.

T Wave

The T wave is the third deflection that occurs on the ECG.

Electrophysiology. The T wave represents ventricular repolarization, during which time current is again flowing, although at a cellular level in the opposite direction from that during depolarization. Cardiac repolarization on the larger level generally follows the same pattern as depolarization and thus the deflection is usually in the same direction as the QRS complex. During repolarization, the intracellular potential of the cardiac myocyte becomes more negative as a result of a net loss of positive charge because of the increasing outward flow of potassium ions. As repolarization progresses, the voltage-dependent ion channels “reset” themselves as the intracellular potential falls past their set points. Thus, the initial part of the T wave represents the absolute refractory period of the heart, because at this time there are an insufficient number of reset voltage-dependent calcium channels to allow an impulse to cause a contraction. The latter part of the T wave represents the relative refractory period of the heart, during which time a sufficient number of these calcium channels are available to open with an aberrant depolarization and initiate a contraction.

Abnormal T Wave. Isolated peaked T waves are usually evidence of early hyperkalemia.⁴² Hyperkalemia initially causes tall, tented T waves with normal QRS and QT interval, and a normal P wave (Fig. 16–15). As the serum potassium concentration rises to 6.5 to 8 mEq/L, the P wave diminishes in amplitude and the PR and QRS intervals prolong. Progressive widening of the QRS complex causes it to merge with the ST segment and T wave, forming a “sine wave.” ECG manifestations of hyperkalemia may occur following chronic exposure to numerous xenobiotics, including potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or potassium supplements (Chap. 19). Fluoride, arsine, and cardioactive steroid poisoning produces acute hyperkalemia, but the latter rarely produces hyperkalemic ECG changes. Peaked T waves also occur following myocardial ischemia and may also be confused with early repolarization effects (see ST Segment). Consequently, the ability to properly identify electrolyte abnormalities by electrocardiography is often limited.

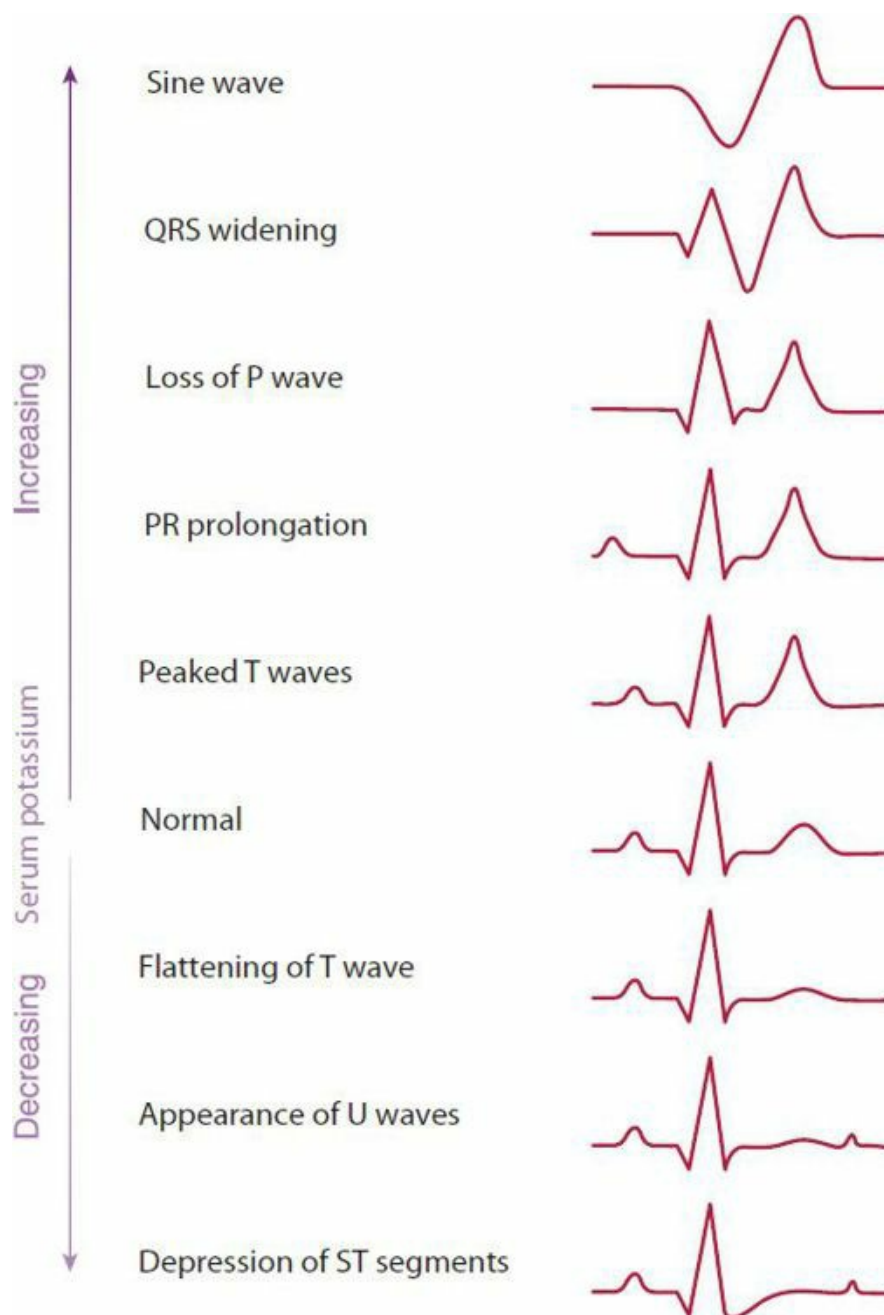


FIGURE 16–15. Electrocardiographic manifestations associated with changes in serum potassium concentration.

Hypokalemia typically reduces the amplitude of the T wave and, ultimately, causes the appearance of prominent U waves (Fig. 16–15). Its effects on the ECG are manifestations of altered myocardial repolarization. Lithium similarly affects myocardial ion fluxes and causes reversible changes on the ECG that may mimic mild hypokalemia, although documentation of low cellular potassium concentrations is lacking. Patients chronically poisoned with lithium have more T-wave abnormalities (typically flattening) than do those who are poisoned acutely, but these abnormalities are rarely of clinical significance.⁶¹

QT Interval

The QT is measured from the beginning of the QRS complex to the end of the T wave. The QT interval normally varies because of biologic diurnal effects and autonomic tone, technical issues with the environment or with processing and acquiring the ECG, and observer variability.^{3,43,44} The bipolar limb lead with the largest T wave should therefore be used for this measurement.

The QT interval is normally prolonged at slower heart rates and shortens as the heart rate increases. This is especially important since many of the xenobiotics that affect the QT interval also affect the heart rate. As the normal QT varies also with the heart rate, numerous formulas and tables are available to obtain the corrected QT, known as the QTc.²⁵ Using the QTc allows the determination of the appropriateness of the QT independent of the heart rate.

With a rate of 50 to 90 beats/min, the commonly used Bazett formula ($QTc \text{ (msec)} = QT \text{ (msec)} / \sqrt{RR \text{ interval (sec)}}$) is adequate for determining a rate corrected QT interval (QTc). If the RR interval is calculated as 60/beats/min, 99% of men have a QTc < 450 msec and 99% of women have a QTc < 460 msec.⁴⁵ A QTc interval > 500 msec weakly correlates with an increased risk of developing ventricular dysrhythmias. However, at higher heart rates, a normal patient will have an

inaccurately calculated “prolonged” QTc interval using the Bazett formula. Studies suggest that medications such as bupropion prolong the QT interval when the “increase” in the QTc may be only a result of the increased heart rate.²⁹ A variety of formulas and corrections are proposed to attempt to identify normal QT intervals on ECGs at higher heart rates,^{6,18,38} including the Fridericia formula ($QTc = QT / \sqrt[3]{RR \text{ interval (sec)}}$) and the Framingham linear regression analysis ($QT_{LC} = QT + 0.154 (1 - RR)$).⁵⁶ Which correction formula is optimal remains unknown, and the FDA requests that “presentation of data with a Fridericia correction is likely to be appropriate in most situations, but other methods could be more appropriate” when performing a “thorough QT study” for any drug with proarrhythmic potential.²³ A recent QT nomogram that plots QT interval duration versus heart rate may better predict the risk for lethal dysrhythmia.¹⁷

With slow heart rates, a prominent U wave can obscure the terminal portion of the T wave and with fast heart rates the subsequent P wave can obscure the terminal portion of the T wave. In these patients the QTc should be estimated by following the downslope of the T wave. The QTc is often measured to approximate repolarization, although this is not fully appropriate because alterations in depolarization may affect it.

QT interval measurements from the computerized ECG algorithms are less accurate than careful manual determinations of the interval.³¹ In August 2000, a panel of experts convened to address these issues and suggested that the QT interval should be measured manually in one of the limb leads that best shows the end T wave; the QT interval should be measured and averaged over 3 to 5 beats; and large U waves should be included in the QT interval measurement if they merge into the T wave and obscure the end of the T wave.⁴ However, a subsequent study of 334 health care professionals found that only 60% of the physicians were able to correctly measure a sample QT interval on the survey, although nearly all indicated correctly that the measurement should be from the beginning of the QRS to the end of the T wave.³⁴

Electrophysiology. The QT represents the entire duration of ventricular systole and thus is comprised of several electrophysiologic periods. Prolongation of the QT interval generally corresponds to an increase in the duration of phase 2 or 3 of the action potential. Although as noted above, depolarization abnormalities can affect the QT. These are uncommon, and the plateau phase and repolarization are primarily reflected by the QT. Variations in the speed of the paper,²¹ T-wave morphology, irregular baseline, and the presence of U waves may make this determination difficult.⁴

Abnormal QT Interval. A prolonged QT reflects an increase in the time period that the heart is “vulnerable” to the initiation of ventricular dysrhythmias (Table 16–1, Fig. 16–16). This occurs because although some myocardial fibers are refractory during this time period, others are not (ie, relative refractory period). Early afterdepolarizations (EADs) may occur in patients with lengthened repolarization time (Table 16–2). An EAD occurs when a myocardial cell spontaneously depolarizes before its repolarization is complete (Fig. 16–17). If this depolarization is of sufficient magnitude, it may capture and initiate a premature ventricular contraction, which itself may initiate ventricular tachycardia, ventricular fibrillation, or torsade de pointes. There are two types of EADs based on whether they occur during phase 2 (type 1) or phase 3 (type 2) of the cardiac action potential. The ionic basis of EADs is unclear, but may be via the L-type calcium channel; EADs are suppressed by magnesium.⁸

TABLE 16–1. Xenobiotic Causes of Long QT^a

Antidysrhythmics

Classes IA, IC, and III antidysrhythmics

Antifungals: itraconazole, ketoconazole

Antihistamines: diphenhydramine

Antihypertensives: angiotensin converting enzyme inhibitors

Antimicrobials: amantadine, chloroquine, halofantrine, fluoroquinolones, macrolides, pentamidine, trimethoprim-sulfamethoxazole

Antiretrovirals: ritonavir-boosted saquinavir

Electrolyte disturbances

Hypocalcemia: fluoride oxalate (eg, ethylene glycol)

Hypokalemia: soluble barium

Other: arsenic trioxide, cocaine, foscarnet, methadone, organic phosphorus insecticides, tacrolimus

Psychotropics: atypical antipsychotics, citalopram, cyclic antidepressants, droperidol, haloperidol, pimozide, phenothiazines, quetiapine, venlafaxine, ziprasidone

^aAdditional information can be found at www.crediblemeds.org, hosted by the Arizona CERT.



FIGURE 16–16. 33 year-old woman who ingested excessive methadone along with ethanol 3 hours before admission. Her ECG shows a sinus bradycardia and QT prolongation.

TABLE 16–2. Electrophysiologic Basis for Delayed Afterdepolarization and Early Afterdepolarization

	<i>Phase of Action Potential Affected by Depolarization</i>	<i>Clinical Effect</i>	<i>Mechanism</i>
Delayed after-depolarization	Phase 4	Cardioactive steroid–induced dysrhythmias	↑ Intracellular Ca^{2+} → Activation of a nonselective cation channel or Na^{+} - Ca^{2+} exchanger → Transient inward current carried mostly by Na^{+} ions
Early after-depolarization	Phase 2 Phase 3	↑ Repolarization time Long QT syndrome (hereditary and acquired) Drug-induced torsade de pointes, ventricular tachycardia	Multifactorial (K^{+} , Na^{+} - K^{+} , Ca^{2+} , Na^{+} currents) Suppressed by magnesium

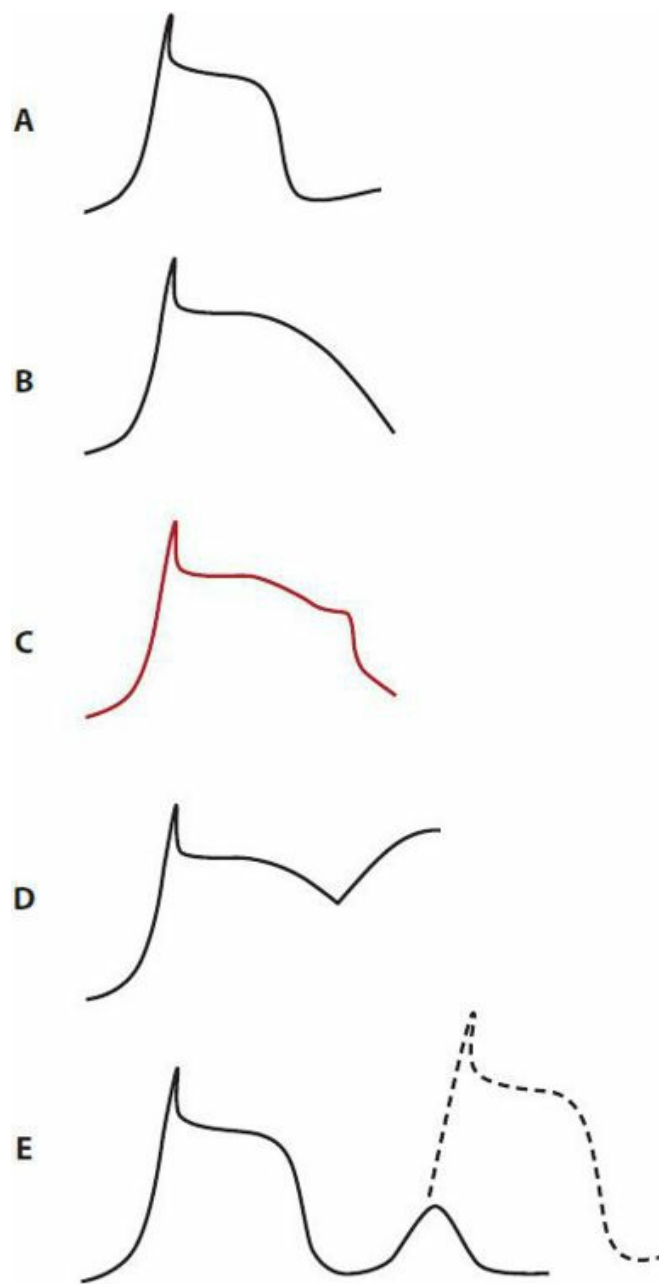


FIGURE 16–17. Afterdepolarization. (A) The normal action potential. (B) Prolonged duration action potential. (C) Prolonged duration action potential with an early after depolarization (EAD) occurring during the downslope of phase 3 of the action potential. (D) Early afterdepolarization that reaches the depolarization threshold and initiates another depolarization, or a triggered beat. (E) Delayed afterdepolarization, which occurs after repolarization is complete.

Xenobiotics that cause sodium channel blockade ([Chaps. 67 and 71](#)) prolong the QT duration by slowing cellular depolarization during phase 0. Thus, the QT duration increases because of a prolongation of the QRS complex duration, and the ST segment duration remains near normal. Xenobiotics that cause potassium channel blockade similarly prolong the QT, but through prolongation of the plateau and repolarization phases. This specifically prolongs the ST segment duration. Although at a cellular level these xenobiotics are antidysrhythmic, the multicellular effects may be prodysrhythmic. The highly selective serotonin reuptake inhibitor citalopram causes QT prolongation due to the sodium and calcium channel blocking effects of its metabolite didesmethyl-citalopram. In a recent large retrospective cohort study, users of both typical antipsychotics (thioridazine and haloperidol) and atypical antipsychotics (clozapine, quetiapine, olanzapine, risperidone) had a risk of sudden cardiac death that was twice that of non-users of antipsychotics. Xenobiotic-induced QT prolongation and the subsequent risk of dysrhythmias is the postulated etiology.⁵² Hypocalcemia may produce a prolonged QT interval, and is caused by a number of xenobiotics, including fluoride, calcitonin, ethylene glycol, phosphates, and mithramycin ([Table 19–9](#)). Hypokalemia alone does not usually prolong the QT. Arsenic poisoning may cause prolongation of the QT and result in torsade de pointes. The mechanism is unknown, although increases in cardiac Ca^{2+} currents and reduction in surface expression of the cardiac potassium channel HERG are postulated.²²

QT Dispersion. The QT interval may vary in duration from lead to lead, reflecting a dispersion or variability in regional myocardial repolarization. Both QT and QTc dispersion can be calculated. The normal QT and QTc interval dispersions are 30 to 50 msec and 40 to 60 msec, respectively. The conduction characteristics vary regionally throughout the heart. For example, the subendocardial cells have a longer action potential duration than do epicardial cells; this is called dispersion of repolarization and is normal. This is important to allow the heart to contract and relax in an

appropriate manner even though the impulse takes time to travel through the full thickness of the myocardial wall, from endocardium to epicardium. The subpopulations of the various ion channels (primarily potassium channels in the setting of repolarization) differ in character and density and account for this variation.⁴⁶ Ischemia and xenobiotics preferentially affect certain layers of the myocardium and alter, generally increasing, the regional heterogeneity of repolarization. M cells, located in the mid myocardium, are very sensitive to the effects of xenobiotics and may increase the repolarization heterogeneity.³⁰ This is reflected on the ECG as an increase in QT dispersion and a prolongation of the vulnerable period. This prolonged vulnerable phase is associated with occurrences of ventricular dysrhythmias. A measured QT dispersion greater than 80 msec after myocardial infarction was associated with VT with a sensitivity rate of 73% and a specificity rate of 86%.⁵⁰ This heterogeneity is also correlated with both the efficacy and prodysrhythmic potential of therapy.⁵⁹ However, the overall assessment of QT dispersion (from a standard 12-lead ECG) has not gained popularity as a useful clinical tool.

U Wave

The U wave is a small deflection that occurs after the T wave and usually with a similar orientation. Distinguishing a U wave from a notched T wave is difficult. The apices of a notched T wave are usually < 150 msec apart, and the peaks of a TU complex are > 150 msec apart.

Electrophysiology. U waves occur when there is fluctuation in the membrane potential following myocardial repolarization. Prominent U waves are generally representative of an underlying electrophysiologic abnormality, although they may be physiologic. Physiologic U waves may be caused by repolarization of the Purkinje fibers, or they may correspond to late repolarization of myocardial cells in the mid-myocardium, and are implicated in the initiation of cardiac dysrhythmias.⁴

Abnormal U Wave. Abnormal U waves are typically caused by spontaneous afterdepolarization of membrane potential that occurs in situations where repolarization is prolonged (Fig. 16–17). An EAD occurs in situations where the prolonged repolarization period allows calcium channels (which are both time and voltage dependent) to close and spontaneously reopen because they may close at a membrane potential that is above their threshold potential for opening. M cells in the mid-myocardium are particularly sensitive to xenobiotics causing prolonged repolarization and EADs. In this situation, the opening of the calcium channels produces a slight membrane depolarization that is identified as a U wave. A delayed afterdepolarization (DAD) is noted during phase 4 of the action potential. It occurs when the myocyte is overloaded with Ca^{2+} , as in the setting of cardioactive steroid toxicity. The excess intracellular Ca^{2+} can trigger the ryanodine receptors on the myocyte sarcoplasmic reticulum to release Ca^{2+} , causing slight depolarization that is erroneously recognized as a U wave. If the afterdepolarization is of sufficient magnitude to reach threshold, the cell may depolarize and initiate a premature ventricular contraction. Transient U-wave inversion can also be caused by myocardial ischemia or left ventricular overload as occurs in systemic hypertension.

Abnormal QU Interval. The QU interval is the distance between the end of the Q wave and the end of the U wave. Differentiation between the QU and the QT intervals is difficult if the T and U waves are superimposed. When hypomagnesemia coexists with hypokalemia, as is usually the case, QU prolongation and torsade de pointes may occur.⁶²

CARDIAC DYSRHYTHMIAS AND CONDUCTION ABNORMALITIES

Xenobiotics may produce adverse effects on the electrical activity of the heart, often by acting directly on the myocardial cells. Because metabolic abnormalities (especially acidemia, hypotension, hypoxia, and electrolyte abnormalities) can further exacerbate the toxicity, or can actually be the sole cause of the cardiovascular abnormalities, correction of metabolic abnormalities must be a high priority in the treatment of patients with cardiovascular manifestations of poisoning. The terminal phase of any serious poisoning may include nonspecific hemodynamic abnormalities and cardiac dysrhythmias. However, many xenobiotics directly or primarily affect cardiac rhythm or conduction, often through effects on the cardiac ion channels.

The distinction between xenobiotics that cause a rapid rate and those that cause a slow rate on the ECG is somewhat artificial, because many can do both. For example, patients poisoned by CAs almost always develop sinus tachycardia, but most who die will have a wide complex bradycardia immediately prior to death. In either case, abnormalities in the pattern or rate on the ECG can provide the clinician with immediate information about a patient's cardiovascular status. ECG disturbances in many poisoned patients may be categorized in more than one manner (abnormal pattern, fast rate, slow rate). In any case, when ECG abnormalities are detected, appropriate interpretation, evaluation, and therapy must be rapidly performed.

Xenobiotics that directly cause dysrhythmias or cardiac conduction abnormalities usually affect the myocardial cell membrane. Other xenobiotics that modify ion channels may alter the transmembrane potentials within myocytes and may result in the spontaneous generation of an abnormal rhythm.

Mechanisms of Dysrhythmia Initiation and Propagation

Dysrhythmias can be related to one or more of three mechanisms: abnormal spontaneous depolarization (enhanced automaticity), afterdepolarization (triggered automaticity), and reentry.⁴⁶ In normal myocardium, spontaneous, phase 4 depolarization occurs most rapidly in the sinus node, the normal pacemaker for the heart. Speeding or slowing the rate of phase 4 depolarization of the pacemaker cell results in sinus tachycardia or sinus bradycardia, respectively. However, xenobiotics can also speed the depolarization of other myocardial cells that have pacemaker potential allowing them to overtake the sinus node as the primary pacemaker. This mechanism, called increased automaticity, accounts for many of the dysrhythmias that occur with cardioactive steroid and β -adrenergic agonist poisoning.

Afterdepolarizations, mentioned above, typically occur during phase 3 or 4 of the action potential, and may reach the threshold potential, causing the fast sodium channels to open and initiate an action potential. EADs account for the “trigger beats” that initiate episodes of VT, commonly torsade de pointes (TdP), when the action potential is prolonged, as discussed below. DADs are typically associated with cardioactive steroid toxicity⁴⁶ and excessive sympathetic stimulation.

Most afterdepolarizations do not propagate rapidly throughout the myocardium and do not generate ectopic beats. However, because the normal dispersion of repolarization is increased by certain xenobiotics, ectopic beats (eg, atrial premature contraction or ventricular premature contraction) may propagate abnormally within the myocardium. Ectopy is the ECG manifestation of myocardial depolarization initiated from a site other than the sinus node. Ectopy may be lifesaving under circumstances in which the atrial rhythm cannot be conducted to the ventricles (ie, “escape rhythm”), as during high-degree AV blockade induced by cardioactive steroids (Chap. 65). Alternatively, ectopy may lead to dramatic alterations in the physiologic function of the heart or deteriorate into lethal ventricular dysrhythmias.

Occasionally, because of the altered regional repolarization (ie, increased dispersion of repolarization), an impulse may reach a branch point with a partial block (ie, relatively refractory) to conduction in one of the branches (Fig. 16–18). The impulse is carried through only one of the branches and then spreads through the myocardial cells. After a short delay, the impulse reaches the distal end of the previously blocked pathway. By this time, the region is no longer refractory and conducts the impulse in a retrograde fashion. The impulse may continue in a continuous loop circuit, depolarizing the heart with each passage; this process is called reentry. Reentrant mechanisms appear to be responsible for the majority of the malignant tachydysrhythmias attributable to poisoning.

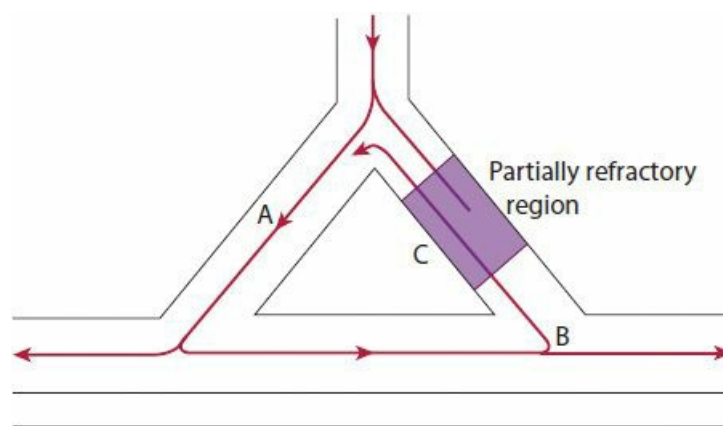


FIGURE 16–18. Mechanism of reentrant dysrhythmias. An impulse traveling down a conduction pathway reaches a branch point with one branch refractory (C). The impulse is conducted down branch A and spreads through the myocardium eventually to reach B, the distal end of the originally refractory branch. However, branch C is no longer refractory, and the impulse is conducted retrograde up through branch C, again to be conducted down branch A. The myocardium is depolarized during each loop around the circuit as the impulse spreads from the distal end of branch A to the rest of the heart.

Tachydysrhythmias

Both supraventricular and ventricular tachydysrhythmias can occur in poisoned patients (Table 16–3). Sinus tachycardia is the most common rhythm disturbance that occurs in poisoned patients. Parasympatholytic xenobiotics, such as atropine, raise the heart rate to its innate rate by eliminating the inhibitory tonic vagal influence. However, more rapid rates require direct myocardial stimulatory effects, generally mediated by β -adrenergic agonism. For example, catecholamine excess, as occurs in patients with cocaine use, psychomotor agitation, or fever, may cause sinus tachycardia with rates faster than 150 beats/min. Ventricular dysrhythmias frequently accompany hypotension, hypoxia, acidemia, electrolyte abnormalities, and other metabolic derangements that may be present in poisoned patients or may be a direct effect of the xenobiotic.

TABLE 16–3. Xenobiotics Causing Ventricular and Supraventricular Tachydysrhythmias

Amantadine

Antidysrhythmics: classes IA, IC, and III ([Table 16–2](#))

Anticholinergics

Antihistamines

Antipsychotics

Botanicals (Diverse) ([Chap. 121](#))

Carbamazepine

Cardioactive steroids

Chloroquine and quinine

Cyclic antidepressants

Cyclobenzaprine

Hydrocarbons and solvents

Halogenated hydrocarbons

Inhalational anesthetics

Jellyfish venom

Metal salts

Arsenic

Lithium

Magnesium

Potassium

Pentamidine

Phenothiazines

Phosphodiesterase inhibitors (eg, methylxanthines)

Propoxyphene

Sedative-hypnotics

Chloral hydrate

Ethanol (“holiday heart”)

Sympathomimetics (eg, cocaine)

Thyroid hormone

The intrinsic pacemaker cells of the heart undergo spontaneous depolarization and reach threshold at a predictable rate. Under normal circumstances the sinus node is the most rapidly firing pacemaker cell of the heart; and as a result it controls the heart rate. Other potential pacemakers exist in the heart, but their rate of spontaneous depolarization is considerably slower than that of the sinus node. Thus, they are reset during depolarization of the myocardium and they never spontaneously reach threshold. Xenobiotics, such as sympathomimetics, which speed the rate of rise of phase 4, or diastolic depolarization, speed the rate of firing of the pacemaker cells. As long as the sinus node is preferentially affected, it

maintains the pacemaker activity of the heart. If the firing rate of another intrinsic pacemaker exceeds that of the sinus node, ectopic rhythms may develop.

Certain xenobiotics are highly associated with ventricular tachydysrhythmias following poisoning. Those that increase the adrenergic tone on the heart, either directly, or indirectly, may cause ventricular dysrhythmias. Whether a result of excessive circulating catecholamines observed with cocaine and sympathomimetics, myocardial sensitization secondary to halogenated hydrocarbons or thyroid hormone, or increased second messenger activity secondary to methylxanthines, the extreme inotropic and chronotropic effects cause dysrhythmias. Altered repolarization, increased intracellular Ca^{2+} concentrations, or myocardial ischemia can cause dysrhythmias. Additionally, xenobiotics that produce focal myocardial ischemia, such as cocaine, ephedrine, or ergots can lead to malignant ventricular dysrhythmias. Finally, an uncommon cause of xenobiotic-induced ventricular dysrhythmias is persistent activation of sodium channels, such as following aconitine poisoning. Although not all wide QRS complex tachydysrhythmias are ventricular in origin, making this assumption is generally considered to be prudent. For example, in a patient poisoned with cyclic antidepressants or cocaine, the differentiation of aberrantly conducted sinus tachycardia (common) from ventricular tachycardia (rare) is important, but difficult. Although guidelines for determining the origin of a wide complex tachydysrhythmia exist,¹⁴ they are imperfect, difficult to apply, and unstudied in poisoned patients.

Bidirectional ventricular tachycardia is associated with severe cardioactive steroid toxicity and results from alterations of intraventricular conduction, junctional tachycardia with aberrant intraventricular conduction, or, on rare occasions, alternating ventricular pacemakers (Fig. 16–19). Aconitine, usually obtained from traditional Chinese or other alternative therapies that contain plants of the *Aconitum* spp (such as *Aconitum napellus* (monkshood), may cause bidirectional ventricular tachycardia (Chaps. 45 and 121).

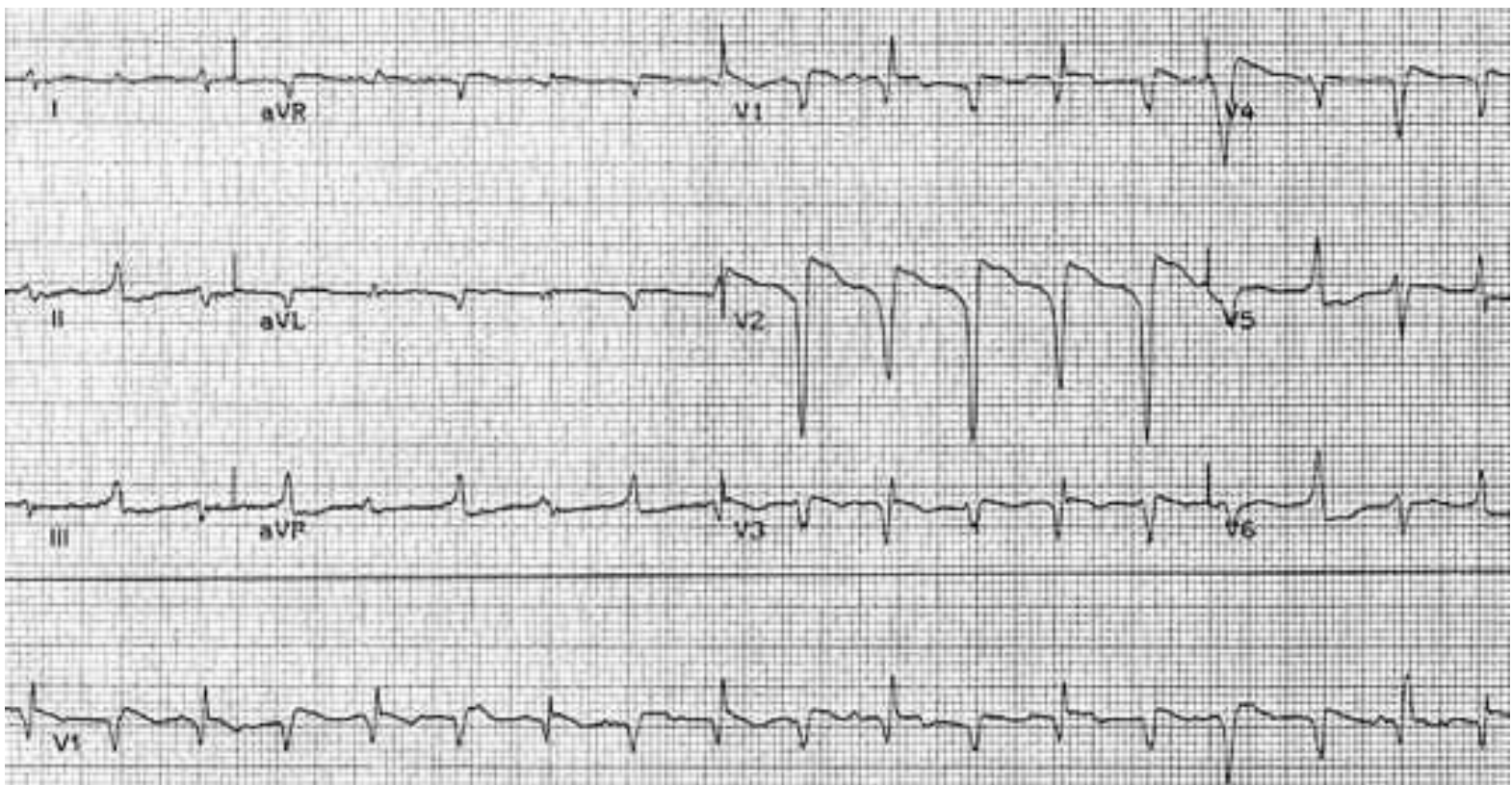


FIGURE 16–19. Digoxin-induced bidirectional ventricular tachycardia. The ECG demonstrates the alternating QRS axis characteristic of bidirectional ventricular tachycardia and is nearly pathognomonic for cardioactive steroid poisoning. The 89 year-old patient's serum digoxin concentration was 4.0 ng/mL. (Used with permission of Ruben Olmedo, MD, Mount Sinai School of Medicine.)

Tachydysrhythmia Associated with a Prolonged QT Interval: Torsade de Pointes

Xenobiotics that alter myocardial repolarization and prolong the QT interval predispose to the development of afterdepolarization-induced contractions during the relative refractory period (R on T phenomena), which may initiate ventricular tachycardia. If TdP is noted this is undoubtedly the mechanism, and the QT interval should be carefully assessed and appropriate treatment initiated (Fig. 16–20).



FIGURE 16–20. Torsade de pointes in a patient who ingested an unknown amount of thioridazine.

Ventricular tachycardia, including TdP, is usually a reentrant-type rhythm. The presence of a prolonged QT interval on the ECG may indicate the possible existence of conditions within the myocardium that favor occurrence of reentry dysrhythmias, as discussed above. The long action potential duration resulting from prolongation in the duration of phase 2 or 3 increases the occurrence of EADs. These, in combination with an increased dispersion of repolarization, increase the risk for reentrant dysrhythmias, particularly TdP.

Many xenobiotics may also interact with cardiac membrane ion channels and increase the risk of TdP. Most of these xenobiotics interact with the HERG-encoded subunit of the potassium channel to reduce the current through the I_{K_r} channel and prolong the action potential duration. The HERG subunit of the channel is particularly susceptible to xenobiotic interactions because of the larger inner cavity with aromatic binding domains.^{53,54,60} Acquired QT interval prolongation and TdP from xenobiotics occur most often with class IA and IC antidysrhythmics, the cyclic antidepressants, and the antipsychotics. Although class Ic antidysrhythmics (such as encainide and flecainide) cause greater QT prolongation, class IA agents (such as quinidine and procainamide) are responsible for more reported cases. This is probably a result of the relatively infrequent use of the class Ic antidysrhythmics, due paradoxically, to concerns about the higher risk of prodysrhythmic effects. Class IB agents, such as lidocaine, have no significant effect on potassium channels and the QT interval, and do not cause TdP. Acquired QT interval prolongation and TdP also commonly result from metabolic and electrolyte abnormalities, particularly hypocalcemia, hypomagnesemia, and hypokalemia (Chaps. 19 and 64).

Bradydysrhythmias

Bradycardia, heart block, and asystole are the terminal events following fatal ingestions of many xenobiotics, but some xenobiotics tend to cause sinus bradycardia (Table 17–2) and conduction abnormalities (Table 16–4) early in the course of toxicity. Sinus bradycardia with an otherwise normal electrocardiogram is characteristic of xenobiotics that reduce central nervous system outflow (Chap. 17). Xenobiotics that cause CNS sedation, such as the sedative-hypnotics, most opioids, and α_2 -adrenergic receptor agonist (“centrally acting”) antihypertensive drugs, will usually decrease sympathetic outflow to the heart and produce a heart rate in the range of 40 to 60 beats/min. Differentiating among these xenobiotics is not possible based on ECG criteria alone. Xenobiotics that directly affect ion flux across myocardial cell membranes cause abnormalities in AV nodal conduction. Calcium channel blockers, β -adrenergic antagonists, and cardioactive steroids (Chaps. 61, 62, and 65) are the leading causes of sinus bradycardia and conduction disturbances. Indirect metabolic effects may also be contributory, such as severe hyperkalemia (which may accompany any acidosis), which results in a wide complex, sinusoidal bradycardic rhythm.

TABLE 16–4. Xenobiotics Causing Conduction Abnormalities and/or Heart Block

α_1 and α_2 -adrenergic agonists
β_1 and β_2 -adrenergic antagonists
Amantadine
Anesthetics (local)
Antidepressants
Antidysrhythmics (classes I and III)
Antihistamines
Antimicrobials

Chloroquine and quinine

Macrolides

Quinolones

Antipsychotics

Atypical antipsychotics (quetiapine, olanzapine, risperidone)

Droperidol

Haloperidol

Phenothiazines

Calcium channel blockers

Carbamazepine

Cardioactive steroids

Cholinergics

Cocaine

Cyclic antidepressants

Cyclobenzaprine

Electrolytes

Potassium

Magnesium

Metal salts

Arsenic

Methadone

Pentamidine

Propoxyphene

Xenobiotics that have direct depressant effects on the cardiac pacemaker are most likely to produce bradycardia. The ECG manifestations of calcium channel blocker and β -adrenergic antagonist overdoses are difficult to distinguish. In general, both decrease dromotropy (conduction), although the specific pharmacologic actions of the drugs differ even within the class. For example, most members of the dihydropyridine subclass of calcium channel blockers do not have any antidromotropic effect, whereas verapamil and diltiazem routinely produce PR prolongation. Similarly, while most β -adrenergic antagonists produce sinus bradycardia and first-degree heart block, certain members of this group, such as propranolol, may prolong the QRS complex through their sodium channel blocking abilities ([Chap. 62](#)). Others, such as sotalol, which has properties of the class III antidysrhythmics, blocks myocardial potassium channels and prolongs the QT interval duration. Bradycardia associated with cardioactive steroids is typically accompanied by electrocardiographic signs of “digitalis effect,” including PR prolongation and ST segment depression ([Chap. 65](#)).

CONDUCTION ABNORMALITIES AND AV NODAL BLOCK

The cardiac toxicity of some xenobiotics results from their effects on the propagation of the electrical impulse through the conduction system of the heart. The ECG abnormalities produced may be a result of effects on the AV node, producing first-, second-, or third-degree (complete) heart block, or on the His-Purkinje system, producing intraventricular conduction delays such as bundle-branch blocks. The effects of xenobiotics on myocardial conduction are often mediated through

interactions with the sodium or potassium membrane channels. For example, xenobiotics that affect the fast inward I_{Na} currents (such as the type I antidysrhythmics and cyclic antidepressants) prolong the action potential duration, slow ventricular myocyte depolarization, and slow intraventricular conduction. This produces widening of the QRS complex and prolongation of the QT interval on the ECG. [Table 16–4](#) lists some of the xenobiotics that cause conduction abnormalities. Many of the antidysrhythmics derive their clinical benefit from their ability to alter sodium and potassium channel function and slow conduction through the myocardium. Xenobiotics that depress phase 0 (the inward I_{Na} currents) produce slowing of conduction and widening of the QRS complex. Xenobiotics that prolong depolarization and repolarization (phase 2 or 3 of the action potential) produce prolongation of the QT interval on the ECG. The classes of the antidysrhythmics, their effects on the ion channels and on the action potential, and the resulting ECG abnormalities, are shown in [Table 16–5](#) and discussed in detail in [Chaps. 16](#) and [64](#).

TABLE 16–5. Classes of Antidysrhythmics

Class	Pharmacologic Blockade			Prolongation of ECG Intervals			Examples
	Sodium Channels	Potassium Channels	Calcium Channels	PR	QRS	QT	
Sodium channel blockers							
IA	+++ / ++++	++	0	±	↑	↑	Disopyramide Procainamide Quinidine
IB	+ / ++	±	0	±	±	±	Lidocaine Phenytoin Mexiletine Tocainide
IC	+++	+++ / ++++	0	↑	↑	↑↑	Encainide Flecainide Propafenone Moricizine
β-Adrenergic antagonists							
II	0	0	+(indirect)	↑	±	±	Atenolol Esmolol Metoprolol Propranolol Timolol
Potassium channel blockers							
III	+	++	0	↑	±	↑	Amiodarone Dofetilide Dronedarone Sotalol Ibutilide*
Calcium channel blockers							
IV	0	0	+++	↑	±	±	Verapamil Diltiazem

+ = Mild blockade; ++ = moderate blockade; +++ = marked blockade; ↑ = increases; ± = no significant effect

*Ibutilide activates a slow inward sodium channel rather than blocking outward potassium currents, but it is classified as class III because of its increased action potential duration and atrial and ventricular refractoriness, which are typical of class III antidysrhythmics.

PEDIATRIC ECG

Normal Pediatric ECG

The normal pediatric ECG differs in many ways from the normal adult ECG. The resting heart rate of infants and children is substantially faster than that of adults and, in general, conduction is faster. In a term infant, the right ventricle is substantially larger than the left, and the ECG demonstrates prominent R waves in the right precordium and deep S waves in the left lateral precordium.⁴⁸ This may be misinterpreted as cyclic antidepressant toxicity.¹⁰ An adult ratio of left to right ventricular size is usually reached by the age of 6 months. In infants, Q waves commonly exist in the inferior and lateral precordial leads, but are abnormal in leads I and aV_L. The T waves are the most notable difference between pediatric and adult ECGs. The T waves in the right precordial leads in children are deeply inverted until 7 years and sometimes older, in which case it is called a persistent juvenile T-wave pattern.

Abnormal Pediatric ECG

Although congenital heart disease is the most common cause of ECG abnormalities in children, electrolyte disorders and xenobiotics may also cause changes in electrophysiology that are reflected on the ECG. Abnormalities that are useful markers on the adult ECG may not always be as useful in children. For example, in older children, a retrospective chart review of 37 children diagnosed with tricyclic antidepressant overdose and 35 controls (<11 years) found interpatient variability, unrelated to age, so great that a rightward deviation of the terminal 40-msec QRS axis could not distinguish between poisoned and healthy children.¹⁰

SUMMARY

- Electrocardiography is one of the few widely available diagnostic procedures that reveals immediate, useful clinical information.
- A thorough mechanistic understanding of the etiologies of the various waves and intervals may help provide an early clue to the etiology of a patient's toxicity.
- QRS prolongation is characteristic of sodium channel blockade.
- QT prolongation is characteristic of potassium channel blockade.

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17 CARDIOLOGIC PRINCIPLES II: HEMODYNAMICS

Robert A. Hessler

Adequate tissue perfusion depends on maintenance of volume status, vascular resistance, cardiac contractility, and cardiac rhythm. All of these components of the hemodynamic system are vulnerable to the effects of xenobiotics. Cardiovascular toxicity may therefore be manifested by the development of hemodynamic instability, heart failure, cardiac conduction abnormalities, or dysrhythmias. The presence of a specific pattern of cardiovascular anomalies (toxicologic syndrome or “toxidrome”) may suggest a particular class or type of xenobiotic.

In addition, an alteration in hemodynamic functioning may be the indirect result of metabolic abnormalities. Poisoning with a xenobiotic may lead to development of acid base disturbances, hypoxia, or electrolyte abnormalities with secondary hemodynamic changes. In these patients, supportive care with ventilation, oxygenation, and fluid and electrolyte repletion may improve the cardiovascular status. For example, salicylates may cause hypotension and cardiovascular collapse. These hemodynamic effects are primarily due to the systemic acidosis and electrolyte disturbances ([Chap. 39](#)).

PHYSIOLOGY OF THE HEMODYNAMIC SYSTEM

Maintaining cardiac contractility, heart rate and rhythm, and vascular resistance requires complex modulation of the cardiac and vascular systems. Xenobiotics can cause hemodynamic abnormalities as a result of direct effects on the myocardial cells, on the cardiac conduction system, or on the arteriolar smooth muscle cells. These effects are frequently mediated by interactions with cellular ion channels or cell membrane neurohormonal receptors. These complex cellular systems provide multiple sites for xenobiotics to demonstrate their toxicologic effects. Xenobiotics and xenobiotic metabolites can interact with the cellular receptors, intracellular signal mechanisms, or with the effector enzymes and intracellular organelles.

Toxic effects of xenobiotics can obviously be due to direct poisoning from excessive amounts of a xenobiotic that follow an overdose. Additionally, slower accumulation of the xenobiotic or active metabolites (due to alterations in metabolism) can also lead to adverse effects. However, the toxic effects of a xenobiotic may be due largely to the properties and characteristics of the host subject. Underlying medical conditions, presence of other xenobiotics, electrolyte abnormalities, concurrent acid-base, and hydration status can all contribute to the potential adverse hemodynamic effects of a xenobiotic. Even with a usually non-harmful concentration of a xenobiotic, hemodynamic toxicity may occur due entirely to underlying genetic differences in the cellular receptors or the intracellular signal transducers in the particular patient.

This complex interaction between the xenobiotic and patient’s physiology and genetic diversity is exemplified by the cardiac disorder, Brugada syndrome. This congenital cardiac channelopathy ([Chaps. 16 and 64](#)) predisposes to sudden cardiac death due to polymorphic ventricular tachycardia or ventricular fibrillation. Brugada syndrome is characterized by an atypical right bundle branch pattern with a characteristic cove-shaped ST segment elevation in leads V1 to V3 of the electrocardiogram (ECG) in the absence or structural heart disease, ischemia, or electrolyte disturbances).^{9,86} This typical type 1 Brugada ECG pattern is shown in [Fig. 16–12](#). However, this distinctive ECG pattern may be concealed²⁶ and only unmasked by sleep, fever, bradycardia, or by xenobiotics such as vagotonic medications or class I antidysrhythmics (sodium channel blocking agents).^{3,58} The reason for this variable and dynamic response to xenobiotics is the heterogeneous genetic basis of the disorder. Mutations in 10 different genes have been linked to the Brugada syndrome; more than 300 different mutations have been identified in the SCN5A gene alone (which encodes the α subunit of the cardiac sodium channel). Brugada syndrome is also associated with mutations in other cardiac ion channels and with mutations of the glycerol-3-phosphate 1-like (GDP1L) gene, which interacts with the cardiac sodium channel subunits at the cell membrane.⁴ The complexity of the potential xenobiotic interactions and variable potential for toxicity has led to the establishment of a Web page (www.brugadadrugs.org) established by the Netherlands Heart Foundation and the University of Amsterdam to provide up-to-date classification of xenobiotics into those to avoid, those to preferably avoid, and those to potential use for treatment.^{58,59}

Autonomic Nervous System and Hemodynamics

In addition to the voltage-dependent ion channels, the cell membrane contains channels that open in response to receptor

binding of neurotransmitters or neurohormones.⁶⁰⁻⁶² The hemodynamic effects of many xenobiotics are mediated by interactions with membrane receptors and by changes in the autonomic nervous system. The autonomic nervous system is functionally divided into the sympathetic (ie, adrenergic) and parasympathetic (ie, cholinergic) systems. The two systems, which share certain common features, function semi-independently of each other. Through complex feedback, the two systems provide the balance needed for existence under changing external conditions.

The sympathetic nervous system is primarily responsible for the maintenance of arteriolar tone and cardiac function. Norepinephrine is the primary postganglionic neurotransmitter of the sympathetic nervous system. On release into the synapse, norepinephrine binds to the postsynaptic adrenergic receptors to elicit an effect by the postsynaptic cell.

ADRENERGIC RECEPTORS

Cellular Physiology of Adrenergic Receptors

The effects of adrenergic xenobiotics on the cell are primarily mediated through a secondary messenger system of cyclic adenosine monophosphate (cAMP). The intracellular cAMP concentration is regulated by the membrane interaction of three components: the adrenergic receptor, a “G-protein” complex, and adenyl cyclase, the enzyme that synthesizes cAMP in the cell.^{10,22,78,79} These receptors are described in detail in Chap. 14.

The G protein serves as a “signal transducer” between the receptor molecule in the cell membrane and the effector enzyme, adenyl cyclase, in the cytosol. The G proteins consist of three subunits: α , β , and γ .^{14,52,53} The α subunit of the G protein complex binds to the adrenergic receptor in the cell membrane and to the adenyl cyclase enzyme. The G protein complex exists in several isomeric forms, depending on their interactions with the adenyl cyclase enzyme. These forms, G_s , G_i , and G_q have different functions in the regulation of cellular activity. The G_s protein complexes contain α_s subunits that stimulate adenyl cyclase when “activated” by adrenergic receptor interaction. These G_s complexes are primarily responsible for the stimulatory activity of β -adrenergic agonist agents. β_1 - and β_2 -adrenergic receptors interact primarily with β_s subunits in stimulatory G_s protein complexes. The α_i subunits of G_s proteins inhibit the activity of adenyl cyclase. Some β_2 -adrenergic receptors and the α_2 -adrenergic receptors interact with inhibitory G_i proteins to decrease the activity of adenyl cyclase. A third form, G_q , interacts with the α_1 -adrenergic receptors, but does not interact directly with adenyl cyclase. Instead, the G_q interacts with phospholipase C to mediate the cell response to α_1 -adrenergic stimulation.

The G protein complex is composed of the cellular receptor and the three subunits, α , β , and γ , which are involved in the cellular response to catecholamines. In the absence of a catecholamine at the receptor site, the receptor protein is bound to the β and β - γ -dimer of the G protein, and guanosine diphosphate (GDP) is bound to the α subunit. Catecholamine binding to the receptor causes a conformational change in the α subunit; GDP dissociates and guanosine triphosphate (GTP) binds to the α subunit. The α subunit (with GTP bound) then dissociates from the receptor and from the β - γ -dimer. This “activated” α subunit can now interact with adenyl cyclase or other effector enzymes. Interaction of the α_s subunit with adenyl cyclase increases the activity of the enzyme resulting in a rapid increase in the intracellular cAMP (Fig. 17-1).^{10,14,41,52,69}

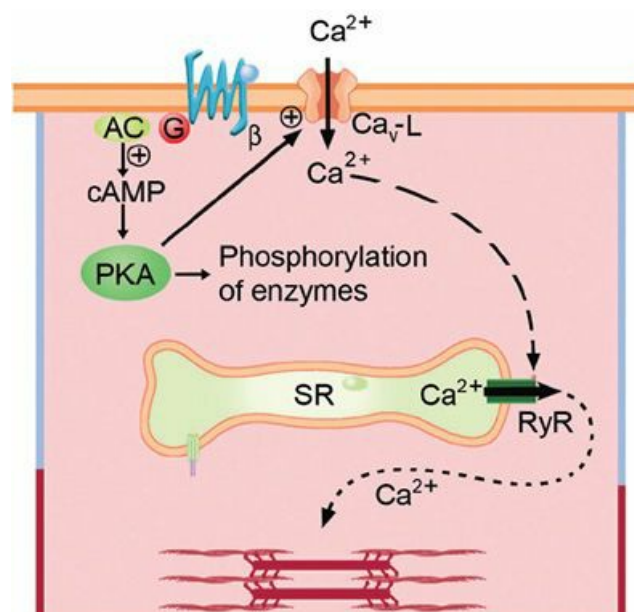


FIGURE 17-1. Binding of the β -adrenergic agonist to the β receptor of a myocardial cell causes the G_s protein to activate AC to produce cAMP. The cAMP interacts with and activates PKA. Subsequent phosphorylation by PKA changes the activity of multiple other various cellular proteins, including phospholamban, calcium channels, and troponin, all of which

increase the activity of the myocardial cell. Refer to the text for more details. AC = adenylyl cyclase; cAMP = cyclic adenosine monophosphate; Ca_v-L = L-type voltage-dependent calcium channel; PKA = protein kinase A; RyR = ryanodine receptor; SR = sarcoplasmic reticulum.

cAMP acts as a secondary messenger in the cell. cAMP interacts with protein kinase A (PKA) and other cAMP-dependent protein kinases to increase their protein phosphorylating activity.⁴⁰ In the absence of cAMP, PKA is a tetramer of two regulatory and two catalytic subunits. cAMP binds to the regulatory subunits to release the active enzymatic units from the tetramer (Fig. 17-1). The activated protein kinases then transfer phosphate groups from ATP to serine (as well as to threonine and tyrosine amino acid groups) on enzymes that are involved in intracellular regulation and activities. Phosphorylation may increase or decrease the activity of specific enzymes, and specific protein kinases are highly selective in the proteins that they phosphorylate.^{75,76}

PKA phosphorylates a variety of cellular proteins involved in Ca²⁺ regulation, including the voltage-sensitive calcium channel, phospholamban, and troponin;^{27,28,74} these are all involved in the regulation and control of cellular muscle fiber contraction. Phosphorylation of the L-type calcium channel increases the entry of calcium ions into the cell during membrane depolarization.⁵⁷ Phosphorylation of phospholamban decreases its ability to inhibit the calcium ATPase pump on the sarcoplasmic reticulum (SR). This decreased inhibition of the calcium ATPase pump increases the efficiency of Ca²⁺ storage in the SR. This enhances both the cellular contractility as the Ca²⁺ is released into the cell cytosol and the relaxation of muscle fibers as the Ca²⁺ is pumped back into the SR.⁵⁷

Physiologic Effects of Adrenergic Receptor Subclasses. The existence of two types of adrenergic receptors, α and β , was first proposed in 1948 to explain both the excitatory and the inhibitory effects of catecholamines on different smooth muscle tissue.¹ The α receptor was subsequently subdivided into α_1 and α_2 when norepinephrine and other α -adrenergic agonists were found to inhibit the release of additional norepinephrine from neurons into the synapse. The α_1 -adrenergic receptors are located on postsynaptic cells outside the central nervous system, primarily on blood vessels, and mediate arteriole constriction. The “autoregulatory” α_2 -adrenergic receptors are primarily located on the presynaptic neuronal membrane and, when stimulated, decrease release of additional norepinephrine into the synapse. Additionally, some α_2 -adrenergic receptors are also found on the postsynaptic membrane in the central nervous system. Activation of these postsynaptic α_2 -receptors in the cardiovascular control center in the medulla and elsewhere in the central nervous system decreases sympathetic outflow from the brain. Thus, α_2 -adrenergic agonists generally decrease peripheral vascular resistance, decrease heart rate, and decrease blood pressure. The α_1 - and α_2 -adrenergic receptors also interact with circulating catecholamines and other sympathomimetics. The effects of sympathomimetics vary in the different organ systems due to differences in the adrenergic receptors and in the cellular responses to the receptor interactions.

The β -adrenergic receptors are subclassified into three subtypes: β_1 , β_2 , and β_3 (Table 17-1). The most prevalent β -adrenergic subtype in the heart is β_1 (80%), although β_2 (20%) and β_3 (few) receptors are also present.^{8,17,21,61} Stimulation of the β_1 -adrenergic receptors increases heart rate, contractility, conduction velocity, and automaticity. The β_2 -adrenergic receptors primarily cause relaxation of smooth muscle with resulting bronchodilation and arteriolar dilation. The β_3 receptors are located primarily on adipocytes where they play a role in lipolysis and thermogenesis.¹¹

TABLE 17-1. Types and Function of the β -Adrenergic Receptor

Type	Location	Function
β_1	Heart	Increase rate Increase inotropy Increase sinoatrial and atrioventricular node conduction
	Kidney	Increase renin
	Eye	Increase aqueous humor
	Adipose tissue	increase lipolysis
β_2	Heart	Increase rate (?) Increase inotropy
	Liver	Increase glycogenolysis Increase gluconeogenesis
	Skeletal muscle	Increase glycogenolysis
	Smooth muscle (bronchi, arterioles, gastrointestinal tract, uterus)	Relaxation
β_3	Adipose tissue	Increase lipolysis and thermogenesis
	Bladder	Increases relaxation
	Heart	Decrease inotropy (?)

The β_1 -, β_2 -, and α_2 -adrenergic receptors all interact with G_s proteins and stimulate the adenylyl cyclase enzyme. Differences in the resultant clinical effects are primarily related to the location and number of the different receptors in different tissues and to differences in the specificity of the tissue protein kinases activated by cAMP. Stimulation of the β_1 -adrenergic receptor results in increased heart rate and increased contractility. β_2 -Adrenergic receptor stimulation causes relaxation, as opposed to contraction, of smooth muscle. Because both β -adrenergic receptor subtypes interact with stimulatory G_s proteins, their clinical effects would appear to be paradoxical. However, there are two primary reasons for their different effects when G_s complexes are stimulated by β_1 - or β_2 -adrenergic agonists. First, PKA is not a single enzyme, but a group of related isoenzymes variably expressed in different tissues.^{7,30,56} The actions and the substrates of the varied protein kinase isoenzymes differs between β_1 - and β_2 -adrenergic responsive tissues. Second, whereas β_1 -adrenergic stimulation results in cAMP-mediated effects throughout the cytoplasm, β_2 -adrenergic stimulation is compartmentalized within the cell. The effect of β_2 -adrenergic stimulation of G_s type receptors is primarily localized phosphorylation of the L-type calcium channels, increasing their activity.^{13,35,87,88} Additionally, some β_2 -adrenergic receptors are also coupled to G_i -type receptors that inhibit adenylyl cyclase and prevent the diffuse cytoplasmic increases in cAMP.^{71,72,88} Also, β_2 -adrenergic receptor stimulation does not result in phosphorylation of phospholamban³⁸ or troponins.¹³

The α_2 -adrenergic receptor interacts with a G_i protein that has an inhibitory interaction with adenylyl cyclase. Binding of α_2 -adrenergic agonists to the receptor inhibits (not stimulates) adenylyl cyclase and decreases intracellular cAMP.

The α_1 -adrenergic receptors also are associated with G proteins. However, rather than being associated with G_s proteins and adenylyl cyclase, the α_1 -adrenergic receptors are associated with G_q proteins that are linked to phospholipase C.⁷⁷ Agonist binding to the receptor activates the hydrolysis of phosphatidyl inositol 4,5-bisphosphate (PIP₂) to 1,2-diacylglycerol (DAG) and inositol triphosphate (IP₃).²⁵ The IP₃ acts as an intracellular messenger, binds to receptors on the SR, and initiates the release of calcium ion.⁵ DAG activates protein kinase C, which phosphorylates slow calcium channels and other intracellular proteins, and increases the influx of calcium ion into the cell (Fig. 17-2).^{63,70,91}

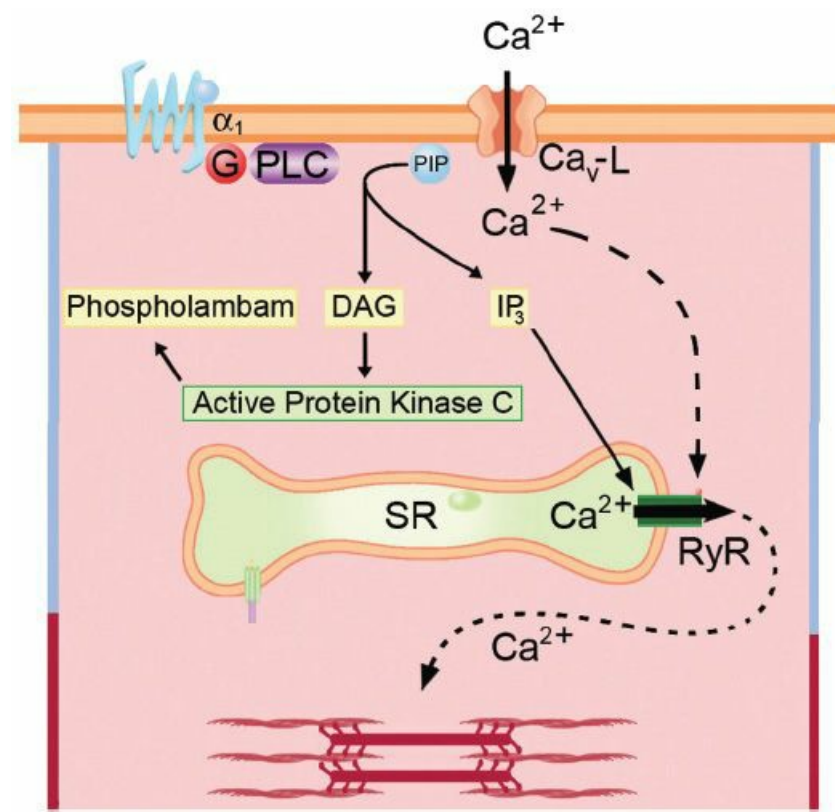


FIGURE 17–2. Binding of the α -adrenergic agonist to the α_1 adrenergic receptor causes the Gq protein to activate PLC. PLC catalyzes the hydrolysis of PIP to produce DAG and IP_3 . IP_3 interacts with the RyR on the sarcoplasmic reticulum to enhance release of calcium from this cellular store. The calcium and DAG activate protein kinase C, which phosphorylates and changes the activity of various cellular proteins including phospholamban. Refer to the text for more details. $\text{Ca}_V\text{-L}$ = L-type voltage-dependent calcium channel; DAG = 1,2-diacylglycerol; IP_3 = inositol triphosphate PIP = 4,5-bisphosphate; PLC = phospholipase C; RyR = ryanodine receptor.

Many xenobiotics interact with G-protein membrane receptors and alter the intracellular cAMP or Ca^{2+} concentration. β -Adrenergic antagonist overdose results in decreased stimulation of adenylyl cyclase by G_s proteins, decreased production of cAMP, decreased activation of the cAMP-dependent kinases, and decreased Ca^{2+} release (Chap. 62). Similarly, by different mechanisms, calcium channel blocker overdose results in decreased cytoplasmic calcium concentration (Chap. 61).

Glucagon receptors, which are similar to the β -adrenergic receptors, are coupled to G_s proteins and stimulate adenylyl cyclase activity.^{2,23,38,84,89} The ability of glucagon to increase cAMP is further enhanced by its inhibitory activity on phosphodiesterase (preventing cAMP breakdown).^{18,48} Phosphodiesterase inhibitors, such as amrinone, milrinone, and enoximone, exert at least some of their inotropic activity by preventing the degradation of cAMP and enhancing calcium cycling.^{42,81,85} In a canine model of propranolol poisoning, amrinone significantly increased inotropy, stroke volume, and cardiac output.⁴²

Intracellular Calcium, Calcium Channels, and Myocyte Contractility

The contraction and relaxation cycle of the myocyte is controlled by the flux of Ca^{2+} into and out of the SR into the cytoplasm of the cell.^{15,39,66} Only a small proportion of the Ca^{2+} involved in myofibril contraction actually enters the cell through the exterior cell membrane during the action potential and membrane depolarization. The majority of the calcium is actually released from the SR of the cell invaginations of the myocyte membrane known as T-tubules place L-type calcium channels in close approximation to calcium release channels (ryanodine receptors {RyR}) on the sarcoplasmic reticulum. The local increase in Ca^{2+} concentration that follows the opening of a single L-type calcium channel triggers the opening of the associated RyR channels resulting in a large release of Ca^{2+} from the SR.¹² Myocytes contain tens of thousands of couplons, clusters of L-type calcium channels and RyR channels. The Ca^{2+} released from one couplon is not sufficient to trigger firing of neighboring couplons. Therefore, myocyte contraction requires synchronized release of Ca^{2+} from numerous couplons throughout the myocyte. The cell membrane depolarization synchronizes opening of L-type channels and subsequent Ca^{2+} release from the sarcoplasmic reticulum.^{16,57} This phenomenon of calcium-induced calcium release results in a rapid increase in the intracellular Ca^{2+} concentration and initiates a rapid myosin and actin interaction.¹⁵

At the conclusion of cellular contraction, SR-associated Ca^{2+} -adenosine triphosphatase (ATPase) pumps return the

cytosolic Ca^{2+} -ATPase into the SR. This SR associated Ca^{2+} -ATPase pump is regulated by phospholamban, a cellular protein. When phospholamban is bound to the Ca^{2+} -ATPase pump, the activity of the pump is decreased and less Ca^{2+} -ATPase is stored in the SR. Phosphorylation of phospholamban decreases its affinity for binding to the Ca^{2+} -ATPase pump. Dissociation of the phosphorylated phospholamban increases the activity of the Ca^{2+} -ATPase pump. β -Adrenergic stimulation increases protein kinase activity and leads to phosphorylation of phospholamban, dissociation of the phosphorylated phospholamban from the pump, and an increase in the total SR Ca^{2+} stores.^{19,20} The increased activity of the SR associated Ca^{2+} -ATPase pump enhances the contractility and increases the rate of relaxation of the myocytes.

Cellular contraction occurs when myosin filaments interact with the actin-tropomyosin helix. A complex of troponins T, I, and C binds to the actin helix near the myosin binding site and act as regulators of the interaction. Troponin T binds the regulatory complex to the actin helix, troponin I prevents myosin from accessing its binding site on the actin helix, and troponin C acts as a Ca^{2+} trigger to initiate contraction. When the intracellular Ca^{2+} concentration increases, 4 molecules of Ca^{2+} bind to troponin C and a conformational shift occurs in the troponin complex. Troponin I shifts away and the myosin-binding site is exposed. Myosin then binds to the exposed site and myofibril contraction occurs (Fig. 17-3).^{31,32,67,68}

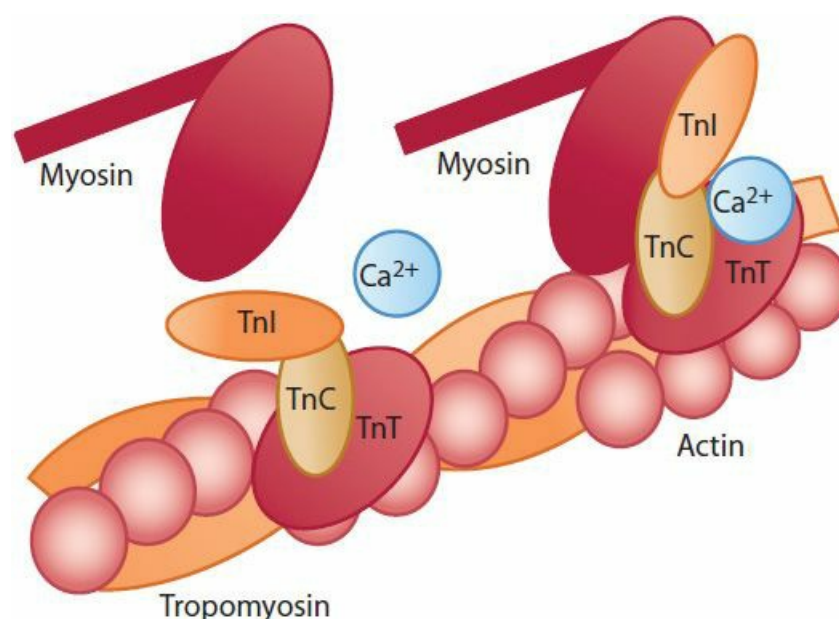


FIGURE 17-3. Troponin regulation of actin and myosin interaction. On the left, TnI blocks the binding site for myosin on the tropomyosin-actin helix. On the right, calcium binding to TnC causes a conformational shift in the troponin molecules, and myosin binds to the actin helix and initiates myofibril contraction. TnC = troponin C; TnI = troponin I; TnT = troponin T.

Calcium transport through the cellular membrane ion channels is critical for normal cardiac muscle function and contractility and for maintenance of vascular smooth muscle tone. The physiologic response to calcium channel blockers and to xenobiotics that interact with the α - or β -adrenergic receptors is mediated through changes in the intracellular Ca^{2+} . Calcium channel blockers in current clinical use primarily block the L-type calcium channel, although their specificity differs for the calcium channels on the vascular smooth muscle cells versus on the myocardial cells. This results in variable effects of the different calcium channel blockers on the vascular tone and peripheral vascular resistance, and on the contractility and electrical activity of the myocardial cells. Additionally, certain calcium channel blockers interact with the neuronal calcium channels, such as the P/Q type, and are used to treat neurologic disorders such as migraine headache.

Patients poisoned by calcium channel blockers have less Ca^{2+} entry into the cell during cardiac membrane depolarization. Administration of exogenous Ca^{2+} increases the concentration gradient across the cell membrane, enhances flow through available Ca^{2+} channels, and restores the triggered response of the RyR-2 channels to release Ca^{2+} from the sarcoplasmic reticulum (Antidotes in Depth: A29). Because β -adrenergic antagonists have negative effects on Ca^{2+} handling by the SR, similar effects occur in the myocyte affected by β -adrenergic antagonists.

In the vascular smooth muscle, the cytosolic Ca^{2+} concentration maintains the basal contraction of the vascular muscle. Any decrease of Ca^{2+} influx results in relaxation and arterial vasodilation.⁵⁵ Any influx of calcium binds calmodulin, and the resulting complex stimulates myosin light-chain kinase activity.⁴⁷ The myosin light-chain kinase phosphorylates myosin. The phosphorylated myosin has increased activity for binding to actin, which causes contraction (Fig. 61-1).^{6,32}

CARDIOVASCULAR EFFECTS OF XENOBIOTICS

Xenobiotics may produce adverse effects on the cardiovascular system by acting on the myocardial cells or the autonomic nervous system to directly affect the heart rate, blood pressure, or cardiac contractility. Because metabolic abnormalities (especially acidemia, hypotension, hypoxia, and electrolyte abnormalities) can further exacerbate toxicity, or can be the sole cause of the cardiovascular abnormalities, correction of metabolic abnormalities must be a high priority in the treatment of patients with cardiovascular manifestations of poisoning. The terminal phase of any serious poisoning may include nonspecific hemodynamic abnormalities and cardiac dysrhythmias.

Heart Rate Abnormalities

Xenobiotics that directly cause dysrhythmias or cardiac conduction abnormalities usually affect the myocardial cell membrane. These abnormal rhythms, cardiac conduction abnormalities, and heart blocks are discussed in [Chap. 16](#).

Bradycardia. Sinus bradycardia is probably the most common xenobiotic-induced bradycardia. Xenobiotics ([Table 17–2](#)) produce bradycardia through different mechanisms. The xenobiotic may affect the central or peripheral nervous system or may affect rhythm generation or conduction in the heart. Most xenobiotics that cause central nervous system sedation, such as the sedative-hypnotics, opioids, and α_2 -adrenergic receptor agonist (“centrally acting”) antihypertensives, will usually decrease sympathetic outflow to the heart and produce sinus bradycardia in the range of 40 to 60 beats/min. Digoxin, certain cholinergics, and α_1 agonists may produce bradycardia and heart block through the enhancement of vagal tone. Sodium channel activators, such as aconitine, cause bradycardia due to intracellular Na^+ overload with a resultant alteration in Ca^{2+} handling. The most profound bradycardia results from overdoses of xenobiotics that have direct depressant effects on the cardiac pacemakers.⁷³ The inability to propagate an impulse within the cardiac conducting system may produce bradycardia or even asystole. Examples of xenobiotics that can produce pacemaker or conduction effects include calcium channel blockers and β -adrenergic antagonists.

TABLE 17–2. Xenobiotics Causing Bradycardia

α_1 -Adrenergic agonists (reflex bradycardia)
Phenylephrine
Phenylpropanolamine
α_2 -Adrenergic agonists (centrally acting)
Clonidine
Methyldopa
β -Adrenergic antagonists
Antidysrhythmics
Amiodarone
Sotalol
Calcium channel blockers
Cardioactive steroids
Cholinergics
Carbamates or organic phosphorus compounds
Edrophonium
Neostigmine

Physostigmine
Opioids
Sedative hypnotics
Sodium channel openers
Aconitine
Andromedotoxin
Ciguatoxin
Veratridine

Bradycardia, heart block, and asystole frequently are terminal events in patients with massive overdose of many noncardiotoxic xenobiotics. These dysrhythmias may occur as a result of direct effects on the myocardium or of indirect metabolic effects. For example, severe hyperkalemia or metabolic acidosis results in a wide complex, sinusoidal bradycardic rhythm.

Tachycardia. Sinus tachycardia is the most common rhythm disturbance that occurs in poisoned patients. Parasympatholytic drugs, such as atropine, raise the heart rate by elimination of the inhibitory vagal influence. However, more rapid rates result from direct myocardial stimulatory effects, generally mediated by β -adrenergic agonism. For example, catecholamine excess (eg, cocaine, psychomotor agitation, methylxanthines, sedative-hypnotic withdrawal) may cause sinus tachycardia with rates faster than 150 beats/min. Tachycardia may also be an indirect effect in response to hypotension, hypoxia, acidemia, fever electrolyte abnormalities, and other metabolic derangements that may be present in poisoned patients ([Table 17-3](#)).

TABLE 17-3. Xenobiotics Causing Sinus Tachycardia and Tachydysrhythmias

Amantadine
Antidysrhythmics
Anticholinergics
Antihistamines
Botanicals and plants ([Chaps. 45](#) and [121](#))
Carbamazepine
Cardioactive steroids
Chloroquine and quinine
Cyclic antidepressants
Cyclobenzaprine
Flumazenil
Hydrocarbons and solvents
Halogenated hydrocarbons
Inhalational anesthetics
Jellyfish venom
Metal salts

Arsenic

Iron

Lithium

Magnesium

Potassium

Pentamidine

Phenothiazines

Phosphodiesterase inhibitors

Amrinone

Methylxanthines

Propoxyphene

Sedative-hypnotics

Chloral hydrate

Ethanol

Sympathomimetics

Amphetamines

Catecholamines

Cocaine

Thyroid hormone preparations

Decreased Cardiac Contractility and Congestive Heart Failure

Xenobiotics can reduce cardiac contractility with a resulting decrease in cardiac ejection fraction and cardiac output, a decrease in blood pressure, and development of congestive heart failure (CHF). Cardiogenic pulmonary edema generally occurs as a result of the direct effects of the xenobiotic on the contractility, or inotropy, of the heart, or through increases in the preload or afterload. Acute cardiogenic pulmonary edema, resulting from impaired left heart filling (which may be due to decreased cardiac output), occurs in patients poisoned by a nondihydropyridine calcium channel blocker or β -adrenergic receptor antagonist. Other xenobiotics that can exert direct depressant effects on cardiac contractility include antihistamines, phenothiazines, antidysrhythmics, and local anesthetics. Many of these xenobiotics reduce contractility through sodium channel blockade, which, by slowing intraventricular conduction, reduces the ability of the heart to contract efficiently. Pulmonary edema may also result from the fluid overload accompanying ingestion of large quantities of sodium-containing xenobiotics (eg, sodium penicillin), the renal effects of medications such as nonsteroidal antiinflammatory drugs, or as a late consequence of xenobiotics that cause kidney failure ([Chap. 28](#)).

Xenobiotics can cause cardiomyopathy through chronic toxic effects directly on the myocardium or indirectly through effects on blood pressure or cardiac vasculature ([Table 17–4](#)). In most cases, the exact mechanism of the toxicity is not known. However, free radical generation, nitric oxide formation, acetaldehyde production, myocardial ischemia, mechanical overload, nutritional deficiency, and persistent tachycardia are each implicated in the cellular toxicity of the various xenobiotics and development of cardiomyopathy.

TABLE 17–4. Xenobiotics Commonly Associated with Cardiomyopathy

Anthracyclines (dactinomycin, daunorubicin, idarubicin, doxorubicin)

Antimony

Cobalt

Cocaine

Ethanol

Emetine from syrup of ipecac

HMG Co-A reductase inhibitors

Blood Pressure Abnormalities

Blood pressure is dependent upon cardiac and vascular function. The blood pressure is directly related to the heart rate (HR), the stroke volume (SV), and the systemic vascular resistance (SVR): $\text{Blood pressure} = \text{HR} \times \text{SV} \times \text{SVR}$. The systolic component of the blood pressure measurement is a reflection of the inotropic state of the myocardium, whereas the diastolic component reflects the vascular tone. It is important to consider both components of the blood pressure. Blood pressure may be expressed also as the mean arterial pressure (MAP) during a single cardiac cycle. Since at normal heart rates the duration of diastole is approximately twice that of systole, the MAP is calculated as $(\{2 \times \text{diastolic}\} + \{\text{systolic}\})/3$. Xenobiotics may affect either component, and compensatory mechanisms within the cardiovascular system may produce recognizable patterns of blood pressure alterations.

Many xenobiotics affect blood pressure by modulation of normal neurotransmission at the postganglionic sympathetic neurons. Through these interactions they may cause, for example, vasoconstriction with an α -adrenergic agonist or increased inotropy with a β_1 -adrenergic agonist. Because of the functional similarity of most sympathomimetics, physical examination alone seldom identifies the specific causative xenobiotic in any tachycardic patient. However, often a clinical constellation of signs and symptoms can be identified that is associated with this general class. For example, patients who ingest sympathomimetic amines such as cocaine or amphetamines typically have central nervous system stimulation, hypertension, and tachycardia ([Chap. 3](#)).

Hypertension Caused by Xenobiotics. Hypertension may be the result of an increase in either inotropy or vascular resistance or both. For example, stimulation of the α_1 -adrenergic receptor causes hypertension through vasoconstriction, and stimulation of the β_1 -adrenergic receptor causes hypertension through enhanced myocardial contractility ([Table 17–5](#)).

TABLE 17–5. Xenobiotics that Commonly Cause Hypertension

<i>Hypertensive Effects Mediated by α-Adrenergic Receptor Interaction</i>	<i>Hypertensive Effects Not Mediated by α-Adrenergic Receptor Interaction</i>
Direct α -adrenergic receptor agonists	β -Adrenergic receptor agonists ^b
Clonidine ^a	Nonselective
Epinephrine	Isoproterenol
Ergotamines	Cholinergics ^a
Methoxamine	Corticosteroids
Norepinephrine	Nicotine ^a
Phenylephrine	Thromboxane A ₂
Tetrahydrozoline	Vasopressin
Indirect-acting agonists	
Amphetamines	
Cocaine	
Dexfenfluramine	
Monoamine oxidase inhibitors	
Phencyclidine	
Yohimbine	
Direct- and indirect-acting agonists	
Dopamine	
Ephedrine	
Metaraminol	
Naphazoline	
Oxymetazoline	
Phenylpropanolamine	
Pseudoephedrine	

^aThese may cause transient hypertension followed by hypotension. ^bThese may cause hypotension.

The hemodynamic results of a xenobiotic overdose depend on the specific xenobiotic ingested and the relative action on the various types of receptors. This suggests that, among β -adrenergic agonists, only those with a predominant β_1 -adrenergic effect cause hypertension. Nonselective β -adrenergic agonists (those that agonize at both β_1 and β_2) produce β_1 -mediated systolic hypertension (through inotropic effects) with β_2 -mediated vascular vasodilation and diastolic hypotension. This may result in a widened pulse pressure, which is the numerical difference between the systolic and diastolic pressures. Exposure to selective β_2 -adrenergic agonists (eg, albuterol) may also result in tachycardia and enhanced inotropy with a widened pulse pressure in a manner analogous to nonselective β agonists. The resulting blood pressure depends on the relative physiologic balance between inotropy and vasodilation.

Xenobiotics that interact only with the α_1 -adrenergic receptor (such as phenylephrine) cause vasoconstriction and hypertension. Baroreceptors detect the increased blood pressure and signal the parasympathetic nervous system neurons of the vagus nerve to fire and slow the heart rate. In the absence of β -adrenergic stimulation, a “reflex” bradycardia results. Norepinephrine is an α_1 -adrenergic agonist with additional β -adrenergic activity. Profound hypertension is the primary hemodynamic toxic effect due to the activity of norepinephrine as both a positive inotrope (β_1) and a vasoconstrictor (α_1). Reflex bradycardia does not occur as a result of stimulation of the cardiac β_1 -adrenergic receptors.

Hypotension Caused by Xenobiotics. Typically, hypotension in adults is arbitrarily defined as a systolic blood pressure of less than 90 mm Hg or a MAP of less than 70 mm Hg. However, this is not an adequate clinical parameter. Young children and adults with a small body habitus may have a normal systolic pressure less than 90 mm Hg ([Chap. 3](#)). Patients with hypothermia have decreased metabolic demands, and a lower blood pressure may be considered “normal” for these patients. Most importantly, patients with long-standing hypertension may have inadequate tissue perfusion even with a MAP of more than 70 mm Hg. The cerebral arterioles normally constrict or dilate to maintain a relatively constant cerebrovascular blood flow despite changes in the peripheral blood pressure. Chronically hypertensive patients lose this autoregulatory response as a consequence of atherosclerotic disease, arteriolar hypertrophy, or arteriolar smooth muscle constriction. These narrowed arterioles may require a higher peripheral blood pressure to properly perfuse the brain.

Clinically, hypotension is defined as blood pressure that is inadequate to perfuse tissues. The clinical assessment of tissue perfusion is based on the vital signs, skin color, capillary refill, mental status, urine output and concentration, and acid–base balance (eg, serum lactate concentration). However, if a xenobiotic directly affects one or more of these

parameters, the clinical assessment of volume and hemodynamic status may be difficult. Measurement of central venous pressure is beneficial in the early treatment of the sepsis syndrome, and most likely would be beneficial in the treatment of other causes of hypotension, including those occurring in poisoned patients. Ultrasound of the inferior vena cava (IVC) has been shown to be useful for assessing volume status and estimating central venous pressure (CVP).^{34,51,83,90} Invasive measurement of cardiac filling pressure, cardiac output, systemic vascular resistance, and arterial pressures may be necessary in critically ill patients with severe poisoning.^{64,65}

Poor tissue perfusion may result from hypovolemia, decreased peripheral vascular resistance, myocardial depression, or a dysrhythmia that reduces cardiac output. A single xenobiotic may exert several effects on the hemodynamic system, such as diltiazem, a calcium channel blocker that causes negative inotropy and vasodilation. Appropriate treatment of the hypotension requires an understanding of the pathophysiologic consequences of the xenobiotic and the resultant hemodynamic derangement (Table 17–6).

TABLE 17–6. Heart Rate and ECG Abnormalities of Xenobiotics Causing Hypotension

<i>Characteristic ECG Abnormalities</i>			
<i>Heart Rate</i>	<i>Sinus Rhythm</i>	<i>Heart Block or Prolonged Intervals</i>	<i>Dysrhythmia</i>
Bradycardia	α_2 -Adrenergic agonists Opioids Sedative-hypnotics	β -Adrenergic antagonists Calcium channel blockers Cholinergics Cardioactive steroids Magnesium (severe) Methadone Propafenone Sotalol	Cardioactive steroids Plant toxins Aconitine Andromedotoxin Veratridine Propafenone Propoxyphene Sotalol
Tachycardia	Amphetamines Angiotensin-convert- ing enzyme inhibitors Anticholinergics Arterial vasodilators Bupropion Cocaine Disulfiram Diuretics Iron Yohimbine	Anticholinergics Antidysrhythmics Antihistamines Arsenic Bupropion Cocaine Cyclic antidepressants Phenothiazines Quinine/chloroquine	Anticholinergics Antidysrhythmics Antihistamines Arsenic Chloral hydrate Cocaine Cyclic antidepressants Methylxanthines Noncyclic antidepressants Phenothiazines Sympathomimetics

Hypotension in a poisoned patient may also be due to intravascular volume depletion. Intravascular volume may decrease due to gastrointestinal, urinary, or insensible losses; or fluid may redistribute from the intravascular space into the intracellular, interstitial, pleural, or peritoneal spaces. Xenobiotics can cause significant intravascular volume depletion through all of these mechanisms.

Hypotension may also be caused by xenobiotics that affect venous tone. These xenobiotics increase venous capacitance, decrease the central venous pressure, and result in relative hypovolemia. The effects may be mediated via central effects on the sympathetic nervous system or direct effects on the peripheral vasculature. Sedative hypnotics and central α_2 -adrenergic agonists (eg, clonidine) decrease the central sympathetic outflow and may result in hypotension. Other xenobiotics directly block peripheral α_1 -adrenergic receptors or stimulate β_2 -adrenergic receptors on the blood vessels to produce vascular smooth muscle relaxation, venodilation, and hypotension. A large number of xenobiotics are reported to cause hypotension; however, the hypotension often is not a direct action of the xenobiotic. Rather, the cause of hypotension is coexisting hypoxia, acidemia, anaphylaxis, volume depletion, or dysrhythmias.

Identification of the specific xenobiotic causing hypotension requires the integration of a detailed history, complete physical examination, and laboratory studies. Often the identification of the specific xenobiotic responsible for hypotension is based on other physical findings associated with the xenobiotic or recognition of a specific toxic syndrome.

ASSESSMENT OF VOLUME STATUS IN THE POISONED PATIENT

Assessment of volume status may be particularly difficult in the poisoned patient because of functional alterations in the patient’s autonomic nervous system and the pharmacologic effects of the xenobiotic. For example, the usual signs of salt and water depletion, such as dry mucous membranes, dry skin, low blood pressure, tachycardia, narrowed pulse pressure, clouded sensorium, and decreased urine output, can be mimicked by a number of xenobiotics, including tricyclic antidepressants. Additionally, hypovolemic patients may present with diaphoresis, flushed skin, hypertension, bradycardia, or increased urine output following exposure to a cholinergic xenobiotic such as an organic phosphorus compound. In most cases, clinical assessment of CVPs and neck vein distension or the hemodynamic response to a fluid bolus can assist in the determination of the patient’s volume status. A central venous or pulmonary artery pressure catheter may be required in some critically ill patients.

Additional information about the patient’s volume status can potentially be obtained with ultrasound measurements of the IVC. Ultrasound can noninvasively measure the IVC size and variation with respiration correlates with volume status.^{34,90} Studies demonstrate that a decrease of more than 50% in the IVC diameter from expiration to inspiration correlates with a CVP of less than 8 mm Hg.⁵¹ However, other studies find that this index varies significantly by the chosen location for the ultrasound measurements.⁸³ Furthermore, there is a poor correlation between the ultrasound CVP determination and actual measured CVP.⁵⁴ Other ultrasound venous measurements have also been tested including the internal jugular vein³³ and compression ultrasound of a forearm vein, IVC collapsibility, and internal jugular vein collapsibility with only moderate correlation with the actual CVP.⁸² While ultrasound may not be absolutely predictive of the volume status, the information can be useful as an adjunct to clinical assessment of hydration status and end organ perfusion.

Additional information about the adequacy of the patient’s volume status may be obtained by orthostatic vital sign testing (Table 17–7).²¹ Normally, the cardiovascular system responds to sitting or standing with vasoconstriction and a slight increase in heart rate. Even with a 30% or greater volume loss, the supine blood pressure may remain normal in young, previously healthy patients. However, patients with hypovolemia are unable to maintain adequate intravascular pressure when upright and have either an exaggerated reflex increase in heart rate or a drop in blood pressure (ie, orthostasis).

TABLE 17–7. Orthostatic Vital Signs (“Tilt” Testing)

1. After the patient is supine for 2 min, determine the blood pressure and pulse rate.
2. Stand the patient for at least 1 min and determine the blood pressure and pulse rate again, and observe for any orthostatic symptoms such as dizziness or lightheadedness. If it is impossible for the patient to stand, have the patient sit up with feet dangling for at least 2 min before determining vital signs.

The test is positive if any one of the following is true:

Systolic blood pressure decreases > 20 mm Hg

Diastolic blood pressure decreases > 10 mm Hg

Pulse increases > 10 beats/min

Development of clinical symptoms of hypovolemia (dizziness, syncope, lightheadedness)

Significance of a positive test: corresponds roughly to 10 to 15 mL/kg volume loss

A variety of xenobiotics can produce orthostatic blood pressure changes (Table 17–8).^{24,44} Volume depletion is the most common cause of xenobiotic-induced orthostatic vital sign changes. However, xenobiotics may produce orthostatic vital sign changes even with a normal volume status. For instance, α_1 -adrenergic antagonists or direct-acting vasodilators may prevent an adequate vasoconstrictor response or β -adrenergic antagonists may block the normal slight heart rate increase, and result in positive orthostatic vital sign testing. In these cases, cardiac output and blood pressure decrease when the patient is upright.

TABLE 17–8. Xenobiotics Causing Orthostatic Hypotension

Antianginals

β -Adrenergic antagonists

Calcium channel blockers

Nitrates

Antidepressants

Cyclic antidepressants

Monoamine oxidase inhibitors

Antihypertensives

Angiotensin-converting enzyme inhibitors

Angiotensin receptor antagonists

Central α_2 -adrenergic agonists

Clonidine

Guanabenz

Guanfacine

Methyldopa

Antiparkinsons

Bromocriptine

L-Dopa

Pergolide mesylate

Antipsychotics

Butyrophenones

Phenothiazines

Atypical

Central nervous system depressants

Ethanol

Opioids

Sedative-hypnotics

Diuretics

Loop diuretics

Thiazides

Ganglionic blockers

Trimethaphan

Miscellaneous

Reserpine

Peripheral α -adrenergic

antagonists

Phenoxybenzamine

Vasodilators

Hydralazine

Prazosin

While various assessments can be useful for predicting the volume status, the most accurate immediate assessment is probably the demonstration of increased cardiac output after a fluid challenge. The passive leg-raising test may be used as a bedside test to evaluate the adequacy of fluid resuscitation. The test is performed by having the patient sit upright in a semi-recumbent position at about 45 degrees. The head is then lowered to the recumbent position and the legs are raised to about 45 degrees. This transiently increases the circulatory volume by around 130 to 300 mL, and it may result in changes in the arterial pressure and heart rate.^{29,50} Several studies have shown that this simple maneuver is a good predictor of hemodynamic response to a fluid bolus especially in intensive care patients.^{36,37,43,45,46,49,80}

Definitive care of the poisoned patient with hemodynamic compromise or a dysrhythmia begins with recognition that a xenobiotic may be present. Infectious, cardiovascular disease, and other metabolic disorders must always be considered; however, the toxic effects of xenobiotics must be included in the differential diagnosis. A variety of clinical clues, when present, should heighten the clinician's suspicion that a xenobiotic effect may be responsible for the hemodynamic or dysrhythmic problem (Table 17–9).

TABLE 17–9. Clues That an Unanticipated Xenobiotic Might Be Causing Hemodynamic Compromise or Dysrhythmia

History

Concomitant seizure

Gastrointestinal disturbances (colicky pain, nausea, vomiting, diarrhea)

Prior ingestion of medications (consider possibility that the container is mislabeled or misidentified)

Depression (even if patient denies ingestion)

Suspected myocardial ischemia in patient < 35 years old

Past Medical History

Treatment with any cardiac medications (especially antidysrhythmics or digoxin)

History of psychiatric illness, asthma, or hypertension

History of drug use or abuse

Physical examination and vital signs

Heart rate

Sinus tachycardia with rate >130 beats/min

Sinus tachycardia without apparent identified cause

Sinus bradycardia

Respiratory rate

Any unexplained depression or elevation in rate

Temperature

Hyperthermia especially if $> 106^{\circ}\text{F}$ ($> 41.1^{\circ}\text{C}$)

Hypothermia if $< 86^{\circ}\text{F}$ ($< 30^{\circ}\text{C}$)

Dissociation between typically paired changes, for example:

Hypotension and bradycardia (tachycardia expected)

Fever and dry skin (diaphoresis expected)

Hypertension and tachycardia (reflex bradycardia anticipated)

Depressed mental status and tachypnea (decreased respirations common)

Relatively rapid changes in vital signs

Initial hypertension becomes hypotension

Increasing sinus tachycardia or hypertension

General

Alteration in consciousness, such as depressed mental status, confusion, or agitation

Findings usually not associated with cardiovascular diseases

Ataxia, bullae, dry mucous membranes, lacrimation, miosis or mydriasis, nystagmus, unusual odor, flushed skin, salivation, tinnitus, tremor, visual disturbances

Findings consistent with a toxic syndrome

Especially findings consistent with anticholinergics, sympathomimetics, or sedative hypnotics

Laboratory Tests

Any unexpected or unexplained laboratory result, especially:

Metabolic acidosis

Respiratory alkalosis

Hypokalemia or hyperkalemia

SUMMARY

- Xenobiotics can interact with the heart or blood vessels to produce hypotension or hypertension, congestive heart failure, dysrhythmias (including bradycardias and tachycardias), or cardiac conduction delays.
- These toxic effects often occur through interactions with specific receptors or with the ion channels in the cell membrane.
- Disruption of the normal cellular regulation of metabolic processes or of the cellular ionic status leads to the cardiovascular and hemodynamic compromise.
- The occurrence of these abnormalities, individually or in combination, might suggest a particular xenobiotic or class of xenobiotics as the etiologic (toxic syndrome) and might dictate initial treatment. However, often significant abnormalities in vital signs must be corrected before the xenobiotic is identified.
- By understanding both the pharmacology of the xenobiotic and the physiology of the heart and vasculature, appropriately tailored treatment can be delivered.

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18 DERMATOLOGIC PRINCIPLES

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INTRODUCTION

Dermatology is a specialty in which visual inspection may allow for rapid diagnosis. Some authors suggest a brief examination before a lengthy history because some of the classic skin diseases with obvious morphologies allow a “doorway diagnosis” to be established. The tools the physician needs are readily available and include a magnifying glass, glass slide (for diascopy), flashlight, alcohol pad to remove scale or makeup, scalpel, and at times a Wood’s lamp. Universal precautions should always be used.

The ability to describe lesions accurately is an important skill, as is the ability to recognize specific patterns. These abilities aid clinicians in their approach to the patient with a cutaneous eruption both in developing a differential diagnosis and while communicating with other physicians. The classic dermatologic lesions are defined in [Table 18–1](#).

TABLE 18–1. Dermatologic Diagnostic Descriptions of Lesions of the Skin

<i>Primary Cutaneous Lesions</i>	<i>Secondary Cutaneous Lesions</i>
Comedone: open and closed dilated pores (blackheads and whiteheads, respectively)	Erosion: a loss of the epidermis up to the full thickness of the epidermis but not through the basement membrane
Macule: a circumscribed flat variation of color that may be brown, blue, yellow, red, or hyper- or hypopigmented, <1 cm	Ulcer: a loss of full-thickness epidermis and papillary dermis, reticular dermis, or subcutis
Patch: a circumscribed flat variation of color that may be brown, blue, yellow, red, or hyper- or hypopigmented, >1 cm	Lichenification: thickening of the epidermis and accentuation of natural skin lines
Papule: a circumscribed elevation of <1 cm in diameter	Atrophy: thinning of the epidermis
Plaque: a circumscribed elevation of >1 cm in diameter	Scale: flaking caused by accumulation of stratum corneum (hyperkeratosis) or delayed desquamation
Nodule: a circumscribed elevation often >2 cm in diameter, involves the dermis and at times subcutis	Scar: a thickened, often discolored surface
Pustule: a circumscribed collection of purulent fluid that varies in size	
Tumor: an elevation of >0.5 cm in diameter	
Vesicle: a circumscribed collection of clear fluid <1 cm in diameter	
Bulla: a circumscribed collection of clear fluid >1 cm in diameter	
Wheal: a firm edematous plaque resulting from infiltration of the dermis with fluid	

The skin shields the internal organs from harmful xenobiotics in the environment and maintains internal organ integrity. The adult skin covers an average surface area of 2 m². Despite its outwardly simple structure and function, the skin is extraordinarily complex. The skin can be affected by xenobiotic exposures that occur through many routes. Dermal exposures themselves are important because they account for approximately 1% of the fatalities reported to the American Association of Poison Control Centers (AAPCC) ([Chap. 136](#)). The clinician must obtain essential information as to the dose, timing, route, and location of exposure. Knowledge of the physical and chemical properties of the xenobiotic can be

used to make relevant predictions of adverse cutaneous reaction and whether the response will be local or systemic. The location of xenobiotic injury determines the histologic morphology, the severity of the reaction pattern, and the overall clinical findings. It should be noted, however, that different xenobiotics may produce clinically similar skin changes and conversely that an individual xenobiotic may produce diverse cutaneous lesions.

SKIN ANATOMY AND PHYSIOLOGY

The skin has three main components that interconnect anatomically and interact functionally: the epidermis, the dermis, and the subcutis or hypodermis (Fig. 18–1). Some experts further categorize the components of the skin into three reactive units: The superficial reactive unit, which is composed of the epidermis, the dermal–epidermal junction (DEJ), and the superficial or papillary dermis with its vascular system; the dermal reactive unit, which is composed of the reticular layer of the dermis and the dermal microvascular plexus; and the subcutaneous reactive unit, which consists of fat lobules and septae.³⁶ The primary physiologic roles of the epidermis, the outermost layer of the skin, are to serve as a barrier, maintain fluid balance, and prevent infection. The degree of barrier function of the epidermis varies with the thickness of the epidermis, which ranges from 1.5 mm on the palms and soles to 0.1 mm on the eyelids. The epidermis is composed of four layers: the horny layer (stratum corneum); granular layer (stratum granulosum); spinous layer (stratum spinosum); and basal layer (stratum germinativum), which overlies the basement membrane zone (BMZ) (Fig. 18–1). The keratinocyte, or squamous cell, which is an ectodermal derivative, comprises the majority of cells in the epidermis.

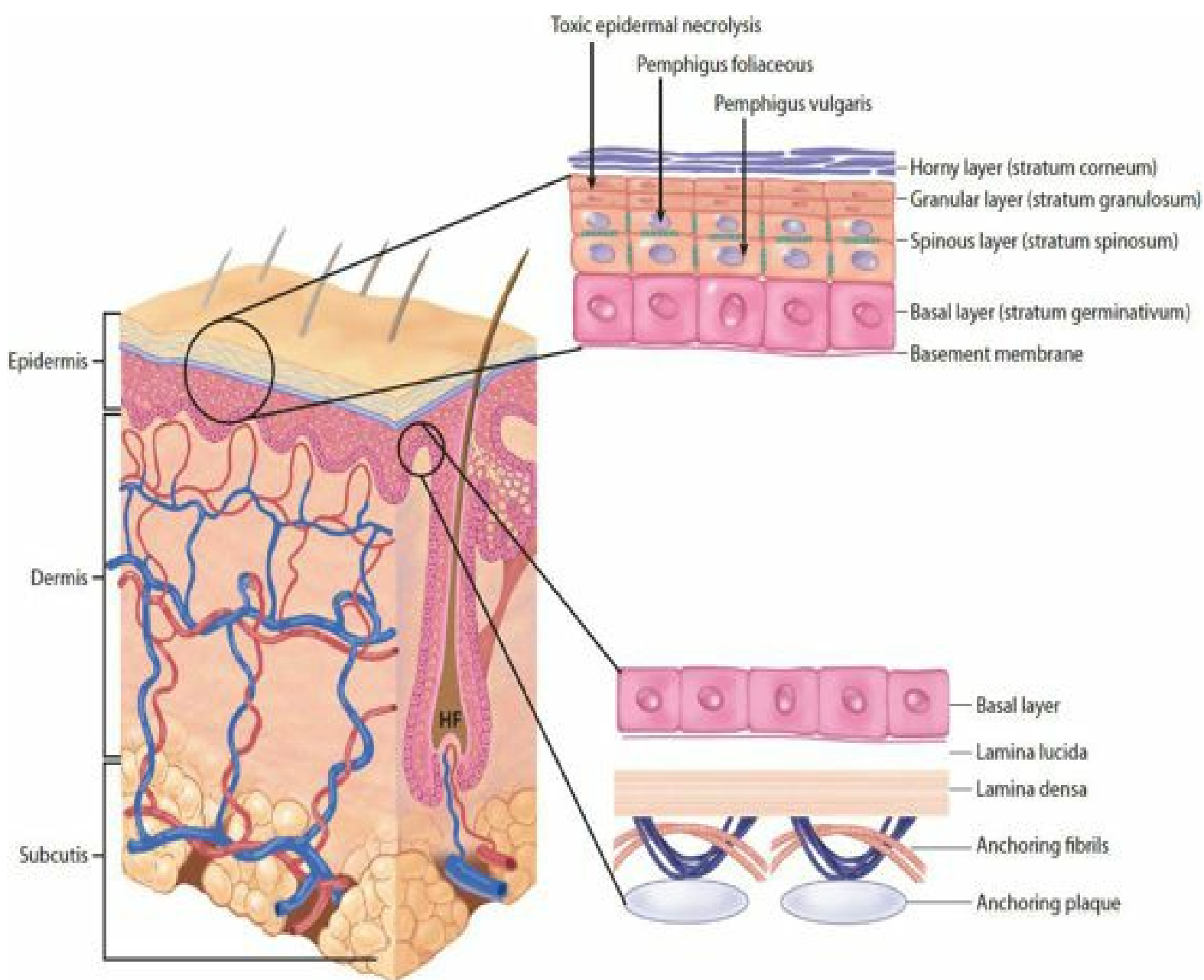


FIGURE 18–1. Skin histology and pathology. Intraepidermal cleavage sites in various xenobiotic-induced blistering diseases. Whereas in pemphigus foliaceus, the cleavage is below or within the granular layer; in pemphigus vulgaris, it is suprabasilar. This accounts for the differing types of blisters found in the two diseases. HF = hair follicle.

The stratum corneum, a semipermeable surface composed of differentiated keratinocytes, is predominantly responsible

for the physical barrier function of the skin. Disruption or abnormal formation of the stratum corneum leads to inadequate function of this barrier, whether by disorders of proliferation or desquamation. For example, accelerated cornification leads to retained nuclei in the stratum corneum (parakeratosis), causing gaps in the stratum corneum as in psoriasis, which impedes barrier function.³⁶ Alternately, in some forms of ichthyosis, there may be decreased desquamation, leading to epidermal retention, which influences the barrier function of the stratum corneum.⁴ Barrier function is also partly maintained by the upper spinous and granular layers. In this layer, there are Odland bodies, also known as membrane-coating granules, lamellar granules, and keratinosomes. The contents of these organelles provide a barrier to water loss while mediating stratum corneum cell cohesion.¹⁸ The stratum corneum is covered by a surface film composed of sebum emulsified with sweat and breakdown products of keratinocytes.³² This surface film functions as an external barrier as protection from the entry of bacteria, viruses, and fungi. The role of the surface film, however, is limited with regard to percutaneous absorption. The major barrier molecules to percutaneous absorption in the skin are lipids called ceramides.³² Diseases characterized by dry skin, such as atopic dermatitis and psoriasis, are in part caused by decreased concentrations of ceramide in the stratum corneum, which allows increased xenobiotic penetration because of barrier degradation.³² Similarly, hydrocarbon solvents, such as gasoline or methanol, and detergents commonly produce a “defatting dermatitis” by keratolysis or the dissolution of these surface lipids.

The cells of the basal layer control the renewal of the epidermis. The basal layer contains stem cells and transient amplifying cells, which are the proliferative cells resulting in new epidermal formation that occurs approximately every 28 days.³⁶ As the basal cells migrate toward the skin surface, they flatten, lose their nuclei, develop keratohyalin granules, and eventually develop into keratinocytes of the stratum corneum. The basal layer of the epidermis is just above the BMZ and is populated by melanocytes and Langerhans cells in addition to basal keratinocytes. Melanocytes contain melanin, which is the major chromophore in the skin that is responsible for absorbing ultraviolet (UV) and other light energies. Melanocytes are primarily responsible for producing skin pigmentation. Langerhans cells are bone marrow–derived dendritic cells with a primary role in immunosurveillance. These cells function in the recognition, uptake, processing, and presentation of antigens to previously sensitized T lymphocytes. In addition, Langerhans cells may carry antigens via dermal lymphatics to regional lymph nodes.

The BMZ consists of three layers—the lamina lucida, the lamina densa, and the sublamina densa—and separates the epidermis from the dermis (Fig. 18–1). It provides a site of attachment for basal keratinocytes and permits epidermal–dermal interaction. The BMZ is also of clinical significance because it is the target of genetic defects and autoimmune attack leading to a variety of inherited and acquired cutaneous diseases.

The DEJ provides resistance against trauma, gives support to the overlying structures, organizes the cytoskeleton in the basal cells, and serves as a semipermeable barrier. The dermis below the DEJ contains the adnexal structures, blood vessels, and nerves. It is arranged into two major regions, the upper papillary dermis and the deeper reticular dermis. The dermis provides structural integrity and contains many important appendageal structures. The structural support is provided by both collagen and elastin fibers embedded in glycosaminoglycans, such as chondroitin A and hyaluronic acid. Whereas collagen accounts for 70% of the dry weight of the skin, elastic fibers comprise only 1% to 2% of the skin’s dry weight. Several important cells, including fibroblasts, macrophages, and mast cells, are residents of the dermis, each with its own unique function. Traversing the dermis are venules, capillaries, arterioles, nerves, and glandular structures.

The arteriovenous framework of the skin is derived from a deep plexus of perforating vessels within the skeletal muscle and subcutaneous fat. From this deep plexus, smaller arterioles transverse upward to the junction of the reticular and papillary dermis, where they form the superficial plexus. Capillary venules form superficial vascular loops that ascend into and descend from the dermal papillae (Fig. 18–1). The communicating blood vessels provide channels through which xenobiotics exposed on the skin surface can be transported internally. This circulatory network provides nutrition for the tissue and is involved in temperature and blood pressure regulation, wound repair, and numerous immunologic events.¹² Parallel to the vasculature are cutaneous nerves, which serve the dual function of receiving sensory input and carrying sympathetically mediated autonomic stimuli that induce piloerection and sweating.²¹

The apocrine glands consist of secretory coils and intradermal ducts ending in the follicular canal. The secretory coil is located in the subcutis and consists of a large lumen surrounded by columnar to cuboidal cells with eosinophilic cytoplasm.²¹ Apocrine glands, which are concentrated in select areas of the body such as the axilla, produce secretions that are rendered odoriferous by cutaneous bacterial flora.

The eccrine glands, in contrast, produce an isotonic to hypotonic secretion that is modified by the ducts and emerges on the skin surface as sweat. The eccrine unit consists of a secretory gland as well as intradermal and intraepidermal ducts. The coiled secretory gland is located in the area of the deep dermis and subcutis. Xenobiotics can be concentrated in the sweat and increase the intensity of the local skin reactions. Certain antineoplastics, such as cytarabine and bleomycin, directly damage the eccrine sweat glands, resulting in anhidrosis.

Sebaceous glands also reside in the dermis. They produce an oily, lipid-rich secretion that functions as an emollient for the hair and skin, and can be a reservoir of noxious environmental xenobiotics. Pilosebaceous follicles, which are present all over the body, consist of a hair shaft, hair follicle, sebaceous gland, sensory end organ, and erector pili. Certain

halogenated aromatic chemicals, such as polychlorinated biphenyls (PCBs), dioxin, and 2,4-dichlorophenoxyacetic acid, are excreted in the sebum and cause hyperkeratosis of the follicular canal. This produces a syndrome, chloracne, that appears clinically similar to severe acne vulgaris but predominates in the malar, retroauricular, and mandibular regions of the head and neck and typically develops after several weeks of exposure (Fig. 18–2). Similar syndromes result from exposure to brominated and iodinated compounds and are known as bromoderma and ioderma, respectively.⁶⁶



FIGURE 18–2. Chloracne caused by dioxin poisoning. Comedones and papulopustular lesions, nodules, and cysts have led to a gross deformity of the nose. (Used with permission of Dr. Alexandra Geusau.)

The subcutis serves to insulate, cushion, and allow for mobility of the overlying skin structures. Adipocytes represent the majority of cells found in this layer. Leptin, an adipose-derived hormone responsible for long-term feedback of appetite and satiety signaling, is synthesized and regulates fat mass (adiposity) in this layer.

The hair follicle is divided into three portions, the hair bulb, infundibulum, and isthmus.⁵⁵ The deepest portion of the hair follicle contains the bulb with matrix cells. The matrix cells are highly mitotically active and often are the target of cytotoxic xenobiotics. The rate of growth and the type of hair are unique for different body sites. Hair growth proceeds through three distinct phases: the active prolonged growth phase (anagen phase) during which matrix cell mitotic activity is high; a short involutional phase (catagen phase); and a resting phase (telogen phase). The length of anagen phase determines the final length of the hair and varies depending on site of the body. For example, hair on the scalp has the longest anagen phase ranging from 2 to 8 years with hair growth at a rate of 0.37 to 0.44 mm/d.³⁶ Understanding the phases of hair growth is important because hair growth can be used to identify clues regarding the timing and mechanism of action of a xenobiotic.

The nail plate, which is often considered analogous to the hair, is also a continuously growing structure. Fingernails grow at average of 0.1 mm/d, and toenails grow at about one-third that rate. The mitotically active cells of the nail matrix that produce the nail plate are subject to both traumatic and xenobiotic injury, which in turn affect the appearance and growth of the nail plate. Because nail growth is consistent, location of an abnormality in the plate, such as Mees lines (transverse white lines), can predict the timing of exposure.

TOPICAL TOXICITY

Transdermal Xenobiotic Absorption

Although there is no active uptake mechanism for xenobiotics by the skin, many undergo percutaneous absorption by passive diffusion. Lipid solubility, concentration gradient, molecular weight, and certain specific skin characteristics are important determinants of dermal absorption.^{22,23,48,52} Absorption is determined to a great extent by the lipid solubility of the specific xenobiotic.^{15,37} The pharmacokinetic profile of transdermally administered xenobiotics is markedly different than by the enteral or other parenteral routes.¹⁷ As with any route of administration, adverse effects and toxicity caused by excessive absorption after patch application may occur after therapeutic use and misuse. For example, adverse effects and toxicity are reported with nicotine, fentanyl, nonsteroidal antiinflammatory drugs (NSAIDs), and lidocaine transdermal delivery devices. Other xenobiotics, topically applied without a specific delivery device, including podophyllin, camphor, phenol, organic phosphorus compounds, ethanol, organochlorines, nitrates, and hexachlorophene, may be associated with systemic toxicity and mortality (Special Considerations: SC1).

Direct Dermal Toxicity

Exposure to any one of a myriad of industrial and environmental xenobiotics can result in dermal “burns.” Although the majority of these xenobiotics injure the skin through chemical reactivity rather than thermal damage, the clinical appearances of the two are often identical. Injurious xenobiotics may act as oxidizing or reducing agents, corrosives, protoplasmic poisons, desiccants, or vesicants. Often an injury may initially appear to be mild or superficial with minimal erythema, blanching, or discoloration of the skin. Over the subsequent 24 to 36 hours, there may be progression to extensive necrosis of the skin and subcutaneous tissue.

Both inorganic and organic acids are capable of penetrating and damaging the epidermis via protein denaturation and cytotoxicity; however, organic acids tend to be less irritating. The damaged tissue coagulates and forms a thick eschar that limits the spread of the xenobiotic. The histopathologic finding after acid injury is termed coagulative necrosis.¹⁰ Inorganic acids that are frequently used in industry include hydrochloric and sulfuric acids, but the weakly acidic hydrofluoric (HF) acid that is used for the etching of glass, metal, and stone leads to the severe injury. HF acid, because of its limited dissociation constant, is able to penetrate intact skin with subsequent penetration into deeper tissues. The fluoride ion is an extremely cytotoxic agent, causing severe tissue damage, including bone destruction, by interfering with a variety of cellular enzyme systems. Severe pain is caused by the capacity of fluoride ions to bind tissue calcium, thus affecting nerve conduction.⁵⁸ In the dermis, the proton (H^+) and fluoride ions (F^-) may ionize and cause both acid-induced tissue necrosis and fluoride-induced toxicity (Chap. 107).⁵

Alkali exposures characteristically produce a liquefactive necrosis, which allows continued penetration of the corrosive xenobiotic. Consequently, cutaneous and subcutaneous injury after alkali exposure is typically more severe than after an acid exposure, with the exception of HF acid. With alkali burns, there are generally no vesicles but rather necrotic skin caused by the disruption of barrier lipids and denaturation of proteins with subsequent fatty acid saponification. Common strong alkalis include sodium, ammonium, and potassium hydroxide; sodium and potassium carbonate; and calcium oxide. These are used primarily in the manufacture of bleaches, dyes, vitamins, pulp, paper, plastics, drain openers, and soaps and detergents. Alkali burns from wet cement result from the liberation of calcium hydroxide, which has an initial pH of 10 to 12 that rises to 12 to 14 as the cement sets.³⁵

Thermal damage can also be the result of a xenobiotic exposure. For example, the exothermic reaction generated by the wetting of elemental phosphorus or sodium may result in a thermal burn. In these circumstances, the products of reactivity, phosphoric acid, and sodium hydroxide, respectively, may produce secondary chemical injury. Alternatively, skin exposure to a rapidly expanding gas, such as nitrous oxide from a whipped cream cartridge or compressed liquefied nitrogen, or to frozen substances, such as dry ice (CO_2), can produce a freezing injury, or frostbite.

Hydrocarbon-based solvents are typically liquids that are capable of dissolving non-water-soluble solutes.¹⁰ Although the most prominent effect is a dermatitis caused by loss of ceramides from the stratum corneum of the epidermis, prolonged exposure can result in deeper dermal irritation and pressure and hydrocarbon skin exposure.

PRINCIPLES OF DERMAL DECONTAMINATION

On contact with xenobiotics, the skin should be thoroughly cleansed to prevent direct effects and systemic absorption. In general, water in copious amounts is the decontaminant of choice for skin irrigation. Soap should be used when adherent xenobiotics are involved. After exposures to airborne xenobiotics, the mouth, nasal cavities, eyes, and ear canals should be irrigated with appropriate solutions such as water or a 0.9% NaCl solution. For nonambulatory patients, the decontamination process may be conducted using special collection stretchers if available.⁹

There are a few situations in which water should not be used for skin decontamination. These situations include contamination with the reactive metallic forms of the alkali metals, sodium, potassium, lithium, cesium, and rubidium, which react with water to form strong bases. The dusts of pure magnesium, sulfur, strontium, titanium, uranium, yttrium, zinc, and zirconium will ignite or explode on contact with water. After exposure to these metals, any residual metal should be removed mechanically with forceps, gauze, or towels and stored in mineral oil. Phenol, a colorless xenobiotic used in the manufacturing of plastics, paints, rubber, adhesives, and soap, has a tendency to thicken and become difficult to remove after exposure to water. Suggestions for phenol decontamination include alternating washing with water and polyethylene glycol (PEG 400) or 70% isopropanol for 1 minute each for a total of 15 minutes.³⁸ Calcium oxide (quicklime) thickens and forms $Ca(OH)_2$ after exposure to water, which releases heat and causes cutaneous ulcerations, suggesting that mechanical removal as above is advised.

DERMATOLOGIC SIGNS OF SYSTEMIC DISEASES

Cyanosis

Normal cutaneous and mucosal pigmentation is caused by several factors, one of which is the visualization of the capillary

beds through the translucent epidermis and dermis. Cyanosis manifests as a blue or violaceous appearance of the skin, mucous membranes, and nailbeds. It occurs when excessive concentrations of reduced hemoglobin (>5 g/dL) are present, as in hypoxia or polycythemia, or when oxidation of the iron moiety of heme to the ferric state (Fe^{3+}) forms methemoglobin, which is deeply pigmented (Chap. 127). The presence of the more deeply colored hemoglobin moiety within the dermal plexus results in cyanosis that is most pronounced on areas of thin skin such as the mucous membranes or underneath fingernails. Also, in the differential diagnosis for a patient with discoloration of the skin is pseudochromhidrosis, also termed extrinsic apocrine chromhidrosis. This results from staining of the sweat by chromogenic bacteria, including *Corynebacterium*, *Malassezia furfur*, and *Bacillus* species; the latter two species have been known to cause blue discoloration of the skin. Several cases of blue pseudochromhidrosis caused by topiramate use are reported in the literature; the diagnosis can be made by the ability of the clinician to wipe off the discoloration with a damp cotton swab.¹¹

Xanthoderma

Xanthoderma is a yellow to yellow-orange macular discoloration of the skin.²⁵ Xanthoderma can be caused by xenobiotics such as carotenoids, which deposit in the stratum corneum, and cause carotenoderma. Carotenoids are lipid soluble and consist of α -carotene, β -carotene, β -cryptoxanthin, lycopene, lutein, and zeaxanthin and serve as precursors of vitamin A (retinol). The carotenoids are excreted via sweat, sebum, urine, and gastrointestinal (GI) secretions. Jaundice is typically a sign of hepatocellular failure or hemolysis and is caused by hyperbilirubinemia, either conjugated or unconjugated, a condition in which the yellow bilirubin deposits in the subcutaneous fat, leading to a common cause of xanthoderma. Jaundice caused by hyperbilirubinemia from liver failure may be accompanied by other cutaneous stigmata, including spider angiomas, telangiectasias, palmar erythema, and dilated superficial abdominal veins (caput medusa). True hyperbilirubinemia is differentiated from hypercarotenemia by the presence of scleral icterus in patients with the former, which is absent in patients with the latter. In addition, the cutaneous discoloration seen in hypercarotenemia can be removed by wiping the skin with an alcohol swab. Lycopopenia, an entity similar to carotenemia, is caused by the excessive consumption of tomatoes. Additionally, topical exposure to dinitrophenol or picric acid or stains from cigarette use produces localized yellow discoloration of the skin.

Pruritus

Pruritus is the poorly localized, unpleasant sensation that elicits a desire to scratch. The biologic purpose of pruritus is to provoke scratching in order to remove a pruritogen, a response likely to have originated when most pruritogens were parasites. Pruritus is a common manifestation of urticarial reactions, but it may also be of nonimmunologic origin. Pruritus is the most common dermatologic symptom and can arise from a primary dermatologic condition or may be a symptom of an underlying systemic disease in an estimated 10% to 50% of patients.²⁸ Patients with hepatocellular disease frequently have pruritus, which is mediated by the release of bile acids. In addition, in patients with chronic liver disease and obstructive jaundice, pruritus can be caused by central mechanisms, as suggested by elevated central nervous system (CNS) endogenous opioid concentrations. Pruritus can also be caused by topical exposure to the urticating hairs of *Tarantula* spiders, spines of the stinging nettle plant (*Urtica* species), or via stimulation of substance P by certain xenobiotics such as capsaicin.²⁴ Virtually any xenobiotic can cause a cutaneous reaction that can be associated with pruritus whether by inducing hepatotoxicity, cholestasis, phototoxicity, or histamine release (ie, neurologically mediated). Xenobiotics commonly implicated in neurally mediated itch include tramadol, codeine, cocaine, morphine, butorphanol, and methamphetamine.²⁸

Flushing

Vasodilation of the dermal arterioles leads to flushing, or transient reddening of the skin commonly of the face, neck, and chest. Flushing can occur after autonomically mediated vasodilation, as occurs with stress, anger, or exposure to heat, or it can be chemically induced by vasoactive xenobiotics. Xenobiotics that cause histamine release through a type I hypersensitivity reaction are the most frequent cause of xenobiotic-induced flush. Histamine and saurine poisoning can result from the consumption of scombrototoxic fish and can produce flushing. Flushing after the consumption of ethanol is common in patients of Asian and Inuit descent and is similar to the reaction after ethanol consumption in patients exposed to disulfiram or similar xenobiotics (Chap. 79). The increased production of and inability to efficiently metabolize acetaldehyde, the initial metabolite of ethanol, results in the characteristic syndrome of vomiting, headache, and flushing. Niacin causes flushing through an arachidonic acid-mediated pathway that is generally prevented by aspirin.^{7,62} Vancomycin, if too rapidly infused, causes a transient bright red flushing mediated by histamine and at times can be accompanied by hypotension. This reaction typically occurs during and immediately after the infusion, and is termed “red man syndrome.” Idiopathic flushing can be managed with nonselective β -adrenergic antagonists (nadolol, propranolol) or clonidine, and anxiolytics may have benefit if emotional distress or anxiety is evident. Other nontoxicologic causes of flushing, including carcinoid syndrome, pheochromocytoma, mastocytosis, anaphylaxis, medullary carcinoma of the thyroid, pancreatic cancer, menopausal flushing, and renal carcinoma, must be considered as etiologies in a flushed patient.²⁷

Sweating

Xenobiotic-induced diaphoresis may be part of a physiologic response to heat generation or may be pharmacologically mediated after parasympathetic or sympathomimetic xenobiotic use. Because the postsynaptic receptor on the eccrine glands is muscarinic, most muscarinic agonists stimulate sweat production. Sweating occurs after exposure to cholinesterase inhibitors, such as organic phosphorus compounds, but it may also occur with direct-acting muscarinic agonists such as pilocarpine. Alternatively, antimuscarinics, such as belladonna alkaloids and antihistamines, reduce sweating and produce dry skin. Certain xenobiotics, including the anticholinergics glycopyrrolate, propantheline bromide, and botulinum toxin, have proven useful for the treatment of hyperhidrosis. Botulinum toxin A derived from *Clostridium botulinum* temporarily chemodenervates eccrine sweat glands at the neuromuscular junction via inhibition of presynaptic acetylcholine release and is approved by the Food and Drug Administration for the treatment of primary focal axillary hyperhidrosis.²

XENOBIOTIC-INDUCED DYSPIGMENTATION

Cutaneous pigmentary changes can result from the deposition of xenobiotics that can be ingested and carried to the skin by the blood or may permeate the skin from topical applications. Many heavy metals are associated with dyspigmentation. Argyria, a slate-colored discoloration of the skin resulting from the systemic deposition of silver particles in the skin after excessive ingestion, can be localized or widespread. The discoloration tends to be most prominent in areas exposed to sunlight, probably secondary to the fact that silver stimulates melanocyte proliferation. Histologically, fine black granules are found in the BMZ of the sweat glands, blood vessel walls, and DEJ and along the erector pili muscles ([Chap. 101](#)). Gold, which was historically used parenterally in the treatment of rheumatoid arthritis, caused a blue or slate-gray pigmentation often periorbitally known as chrysiasis. The pigmentation is also accentuated in sun-exposed areas, but unlike argyria, sun-protected areas do not histologically demonstrate gold. Also, melanin is not increased in the areas of hyperpigmentation. The hyperpigmentation is probably secondary to the gold itself, but the cause of its distribution pattern remains unknown. Histologically, the gold is found within lysosomes of dermal macrophages and distributed in a perivascular and perieccrine pattern in the dermis. Bismuth produces a characteristic oral finding of the metallic deposition in the gums and tongue known as bismuth lines as well as a blue-gray discoloration of the face, neck, and dorsal hands. Chronic arsenic exposure may be the result of pesticides or contaminated well water, which can cause cutaneous hyperpigmentation with a bronze hue with areas of scattered hypopigmentation that develop from 1 and 20 years after exposure. Lead also deposits in the gums, causing the characteristic “lead lines,” which are the result of subepithelial deposition of lead granules. Intramuscular injection of iron can cause staining of the skin, resulting in pigmentation similar to that seen in tattoos, and iron storage disorders, known as hemochromatosis, can result in a bronze appearance of the skin.²⁰

Medications are also often implicated in dyspigmentation. The tetracycline class antibiotic minocycline is a highly lipid-soluble, yellow crystalline xenobiotic that turns black with oxidation. Minocycline-induced discoloration of the skin can be accompanied by darkening of the nails, sclerae, oral mucosa, thyroid, bones, and teeth. Hyperpigmentation from minocycline is divided into three types depending on the color, anatomic distribution, and whether iron- or melanin-containing granules are found within the skin. Other medications commonly associated with hyperpigmentation include amiodarone, zidovudine, bleomycin and other chemotherapeutics, antimalarials, and psychotropics (chlorpromazine, thioridazine, imipramine, desipramine, amitriptyline).²⁹ Although not true dyspigmentation, as noted earlier, topiramate has been linked to blue pseudoachromhidrosis.¹¹

XENOBIOTIC-INDUCED CUTANEOUS REACTIONS (DRUG REACTIONS)

The skin is one of the most common targets for adverse drug reactions.³ Drug eruptions occur in approximately 2% to 5% of inpatients and in more than 1% of outpatients. Several cutaneous reaction patterns account for the majority of clinical presentations occurring in patients with xenobiotic-induced dermatotoxicity ([Table 18–2](#)). The following drug reactions will be discussed in detail: urticarial drug reactions, erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), fixed drug eruption, and drug-induced hypersensitivity syndrome.

TABLE 18–2. Xenobiotics Commonly Associated with Various Cutaneous Reaction Patterns

Acneiform

ACTH

Amoxapine

Androgens

Azathioprine

Bromides

Corticosteroids

Danazol

Dantrolene

Halogenated hydrocarbons

Iodides

Isoniazid

Lithium

Oral contraceptives

Phenytoin

Alopecia

Anticoagulants

Antineoplastics

Hormones

NSAIDs

Phenytoin

Radiation

Retinoids

Selenium

Thallium

Allergic Contact Dermatitis

Bacitracin

Balsam of Peru

Benzocaine

Carba mix

Catechol

Cobalt

Diazolidinyl urea

Ethylenediamine dihydrochloride

Formaldehyde

Fragrance mix
Imidazolidinyl urea
Lanolin
Methylchloroisothiazolinone or methylisothiazolinone
Neomycin sulfate
Nickel
p-Tert-butylphenol formaldehyde resin
p-Phenylenediamine
Quaternium-15
Rosin (colophony)
Sesquiterpene lactones
Thimerosal
Urushiol

Erythema Multiforme

Antimicrobials
Allopurinol
Barbiturates
Carbamazepine
Cimetidine
Codeine
Gold
Glutethimide
Ethinyl estradiol
Furosemide
Ketoconazole
Methaqualone
NSAIDs
Nitrogen mustard
Phenolphthalein
Phenothiazines
Phenytoin
Sulfonamides

Thiazides

Erythroderma

Allopurinol

Anticonvulsants

Boric acid

Calcium channel blockers

Cimetidine

Dapsone

Gold

Lithium

Penicillins

Quinidine

Sulfonamides

Vancomycin

Fixed Drug Eruption

Acetaminophen

Allopurinol

Barbiturates

Captopril

Carbamazepine

Chloral hydrate

Chlordiazepoxide

Chlorpromazine

Erythromycin

D-Penicillamine

Fiorinal

Gold

Griseofulvin

Lithium

Phenolphthalein

Methaqualone

Metronidazole

Minocycline

Naproxen

NSAIDs

Oral contraceptives

Salicylates

Hair Loss

Telogen Effluvium

β-Adrenergic antagonists (eg, propranolol)

Anticoagulants (especially heparin)

Anticonvulsants (eg, phenytoin, valproic acid, carbamazepine)

Antithyroid (propylthiouracil, methimazole)

Heavy metals

Interferon-α-2b

Oral contraceptives (discontinuation)

Retinoids (acitretin, isotretinoin) and vitamin A excess

Anagen Effluvium

Alkylating agents: cyclophosphamide, ifosfamide, mechlorethamine

Anthracyclines: daunorubicin, doxorubicin, idarubicin

Arsenic

Bismuth

Chemotherapeutics (taxanes: paclitaxel, docetaxel, topoisomerase-inhibitors: topotecan, irinotecan, etoposide, vincristine, vinblastine, busulfan, actinomycin D, gemcitabine)

Gold

Thallium

Maculopapular or Exanthematous Drug Eruption

Antimicrobials

Anticonvulsants

Antihypertensive agents

Photosensitivity Reactions

Amiodarone

Benoxaprofen

Chlorpromazine

Ciprofloxacin

Dacarbazine

5-Fluorouracil

Furosemide

Griseofulvin

Hydrochlorothiazide

Hematoporphyrin (Porphyria)

Levofloxacin

NSAIDS

Oxybenzone

Piroxicam

Psoralen

Sulfanilamide

Tetracyclines

Tolbutamide

Vinblastine

Phototoxic Dermatitis

Celery

Dispense blue 35

Eosin

Fig

Fragrance materials

Lime

Parsnip

Tar

Toxic Epidermal Necrolysis

Allopurinol

L-Asparaginase

Amoxapine

Mithramycin

Nitrofurantoin

NSAIDs

Penicillin

Phenytoin

Prazosin

Pyrimethamine-sulfadoxine

Streptomycin

Sulfonamides

Sulfasalazine

Trimethoprim-sulfamethoxazole

Vasculitis

Allopurinol

Bortezomib

Cephalosporins (commonly Cefaclor)

Cimetidine

G-CSF

Gold

Hydralazine

Levamisole

Methotrexate

Minocycline

NSAIDs

Oral contraceptives

Penicillamine

Penicillin

Phenytoin

Propylthiouracil

Quinolones

Serum (antithymocyte globulin)

Sulfonamides

Vesiculobullous

Amoxapine

Barbiturates

Captopril

Carbon monoxide

Chemotherapeutics

Dipyridamole

Furosemide

Griseofulvin

Penicillamine

Penicillin

Rifampin

Sulfonamides

Xanthoderma

Generalized

Carotenoderma

Canthaxanthin (tanning pills)

Dipyridamole (yellow compound)

Hepatic jaundice (acetaminophen, isoniazid)

Hemolytic jaundice

Quinacrine

Localized

Dihydroxyacetone (spray tanning)

Picric acid

Methylenedianiline

Phenol, topical

Nail Changes: Beau Lines and Mees Lines (Leukonychia)

Arsenic

Cyclophosphamide

Doxorubicin

Hydroxyurea

Paclitaxel

Thallium

ACTH = adrenocorticotrophic hormone; G-CSF = granulocyte colony-stimulating factor; NSAID = nonsteroidal antiinflammatory drug.

Urticarial Drug Reactions

Urticarial drug reactions are characterized by transient, pruritic, edematous, pink papules, or wheals that arise in the dermis, which blanch on palpation and are frequently associated with central clearing. At times the urticarial lesions can be targetoid and mimic EM. Approximately 40% of patients with urticaria experience angioedema and anaphylactoid reactions

as well.¹ The reaction pattern is representative of a type I, or IgE-dependent, immune reaction and commonly occurs as part of clinical anaphylaxis or anaphylactoid (non-IgE-mediated) reactions. Widespread urticaria may occur after systemic absorption of an allergen or after a minimal localized exposure in patients highly sensitized to the allergen. After limited exposure, a localized form of urticaria may occur. Regardless of the specific clinical presentation, the reaction occurs as a result of immunologic recognition of a putative antigen by IgE antibodies, thus triggering the immediate degranulation of mast cells, which are distributed along the dermal blood vessels and nerves. The release of histamine, complements C3a and C5a, and other vasoactive mediators results in extravasation of fluid from dermal capillaries as their endothelial cells contract. This produces the characteristic urticarial lesions described earlier. Activation of the nearby sensory neurons produces pruritus. Nonimmunologically mediated mast cell degranulation producing an identical urticarial syndrome may also occur after exposure to any xenobiotic.¹⁴

Erythema Multiforme

Historically, it was believed that EM existed on a spectrum with SJS and TEN given overlapping clinical features and morphology; however, these entities have been reclassified on the basis that most cases of EM are believed to be triggered by viral infection (herpes simplex virus most commonly) and most cases of SJS/TEN are triggered by xenobiotics.⁴⁹ EM is an acute self-limited disease characterized by target-shaped, erythematous macules and patches on the palms and soles, as well as the trunk and extremities (Fig. 18–3). The Nikolsky sign, defined as sloughing of the epidermis when direct pressure is exerted on the skin, is absent. Mucosal involvement is absent or mild in EM minor and severe in EM major. Although less common than viral-induced EM, xenobiotics such as sulfonamides, phenytoin, antihistamines, many antibiotics, rosewood, and urushiol can elicit EM. Differentiating EM from SJS/TEN, which can also present with targetoid lesions, can be difficult, especially in the case of bullous EM, and biopsy may be required.



FIGURE 18–3. Erythema multiforme: typical targetoid macules on the palm. (Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick’s Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012. Fig. 39–3.)

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Toxic epidermal necrolysis and SJS (Fig. 18–4) are considered to be related disorders that belong to a spectrum of increasingly severe skin eruptions.⁴³ SJS is defined by less than 10% body surface area epidermal detachment, SJS–TEN overlap is defined by 10% to 30% involvement, and TEN is defined by more than 30% epidermal sloughing. Although on a spectrum, SJS has a mortality rate of 5%, far lower than the approximately 25% to 50% mortality rate for TEN.^{47,50} TEN is a rare, life-threatening dermatologic emergency whose incidence is estimated at 0.4 to 1.2 cases per 1 million persons, and xenobiotics are causally implicated in 80% to 95% of the cases. More than 220 xenobiotics are implicated in causing TEN. The largest study examining medication triggers of TEN divided these medications into long-term (used for months to years) and short-term ones. Short-term xenobiotics most commonly implicated in the development of TEN included

trimethoprim–sulfamethoxazole and other sulfonamide antibiotics followed by cephalosporins, quinolones, and aminopenicillins.⁵¹ With chronic medication use, the increased risk largely occurred during the first 2 months of treatment and was greatest for carbamazepine, phenobarbital, phenytoin, valproic acid, oxicam NSAIDs, allopurinol, and corticosteroids.

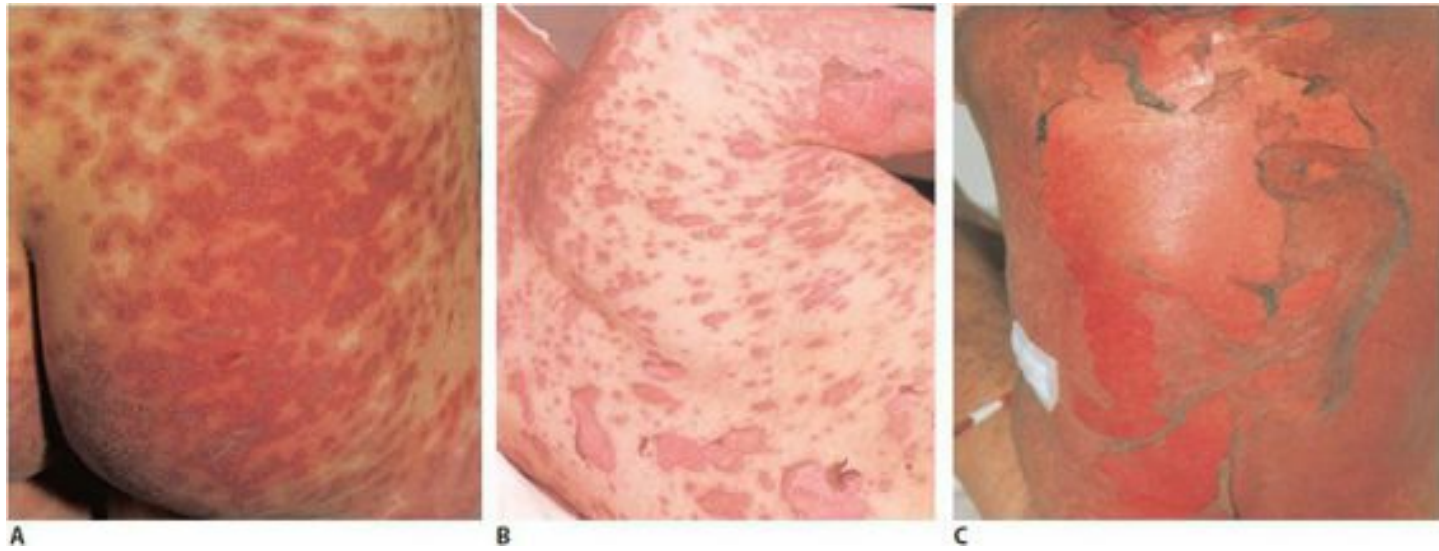


FIGURE 18–4. Toxic epidermal necrolysis. (A) Early eruption. Erythematous dusky red macules (flat atypical target lesions) that progressively coalesce and show epidermal detachment. (B) Advanced eruption. Blisters and epidermal detachment have led to large, confluent erosions. (C) Full-blown epidermal necrolysis characterized by large erosive areas reminiscent of scalding. (Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick’s Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012.)

Classically, the eruption of TEN is painful and occurs within 1 to 3 weeks of the exposure to the implicated xenobiotic(s). The eruption is preceded by malaise, headache, abrupt onset of fever, myalgia, arthralgia, nausea, vomiting, diarrhea, chest pain, or cough. About 1 to 3 days later, signs begin in the mucous membranes, including the eyes, mouth, nose, and genitals in 90% of cases.⁴⁷ Next a macular erythema develops that subsequently becomes raised and morbilliform on the face, neck, and central trunk, which then progresses to involve the extremities. Individual lesions may appear targetoid because of their dusky centers and progress to bullae in the next 3 to 5 days involving the entire thickness of the epidermis. The nails may be involved becoming necrotic and can slough off. A Nikolsky sign may occur, and although suggestive, is not pathognomonic of TEN because it occurs in a variety of other dermatoses, including pemphigus vulgaris. If the diagnosis is suspected, a punch biopsy should be performed for immediate frozen section and the suspected triggering xenobiotic discontinued immediately. The histopathology typically shows partial or full-thickness epidermal necrosis, with subepidermal bullae with a sparse infiltrate and vacuolization with numerous dyskeratotic keratinocytes along the DEJ adjacent to the necrotic epidermis.

The incidence of TEN is higher in patients with advanced HIV disease.^{43,59} There is general agreement that the keratinocyte cell death in TEN is the result of apoptosis, which is suggested based on electronic microscopic studies with DNA fragmentation analysis.⁴³ Cytotoxic T lymphocytes are the main effector cells, and experimental evidence points to involvement of the Fas-ligand (FasL) and perforin–granzyme pathways. There are several theories as to the pathogenesis of SJS/TEN. These include that a xenobiotic might induce upregulation of FasL by keratinocytes constitutively expressing Fas, leading to a death receptor–mediated apoptotic pathway; the xenobiotic might interact with major histocompatibility class I–expressing cells, and then drug-specific CD8⁺ cytotoxic T lymphocytes accumulate within epidermal blisters, releasing perforin and granzyme B that kill keratinocytes; or that the xenobiotic may also trigger the activation of CD8⁺ T lymphocytes and natural killer (NK) cells, to secrete granulysin, with keratinocyte death not requiring cell contact.⁴² Serum FasL concentrations are elevated up to 4 days before mucosal involvement in patients with SJS/TEN and may become useful clinically because an early predictor of these severe dermatologic diseases.⁴¹ Serum granulysin, a proinflammatory cytolytic enzyme released by CD8⁺ T lymphocytes found in the blisters of TEN, has been investigated as a potential early predictive marker of SJS/TEN.¹⁹ A rapid immunochromatographic test that detects elevated serum granulysin (>10 ng/mL) in 15 minutes has shown promise in a small study in which its sensitivity was noted to be 80% and specificity 95.8% for differentiating SJS/TEN from ordinary exanthematous drug eruptions.¹⁹ However, this test is not yet commercially available.

Because immediate removal of the inciting xenobiotic is critical to survival, patients with TEN related to a xenobiotic with a long half-life have a poorer prognosis and should be transferred to a burn or other specialized center for sterile wound care. Risk factors for mortality, such as age, extent of epidermal detachment, and base deficit, have been proposed.

In a recent study, only serum bicarbonate concentration less than 20 mEq/L was found to portend hospital death in patients with TEN.⁶⁴ Porcine xenografts or human skin allografts, including amniotic membrane transplantation, are used and are widely accepted therapies.⁴⁶ Although corticosteroids are not generally recommended, there is emerging support for the use of intravenous immunoglobulin (IVIG), cyclophosphamide, and cyclosporine.⁴⁶ A large meta-analysis of 17 studies revealed a trend toward improved mortality with high-dose IVIG in adults and good prognosis in children; however, the authors concluded that there was no significant evidence to support a clinical benefit, so this treatment remains controversial.²⁶ Patients with TEN may develop metabolic abnormalities, sepsis, multiorgan failure, pulmonary emboli, and GI hemorrhages. The major microbes leading to sepsis are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. In a patient with SJS/TEN with ophthalmic involvement early ophthalmologic consultation is necessary because blindness is a potential complication.

Mimickers of TEN include SJS, staphylococcal scalded skin syndrome, severe exanthematous drug eruptions, EM major, linear IgA dermatosis, paraneoplastic pemphigus, acute graft-versus-host disease, drug-induced pemphigoid, pemphigus vulgaris, and acute generalized exanthematous pustulosis; however, discussion of some of these entities is beyond the scope of this chapter (Table 18–3).

Bullous Reactions (Blistering Reactions)

In addition to SJS and TEN, other bullous cutaneous reactions include drug-induced pseudoporphyria, fixed drug eruption, acute generalized exanthematous pustulosis, phototoxic drug eruptions, and drug-induced autoimmune blistering diseases. Xenobiotic-related cutaneous blistering reactions may be clinically indistinguishable from autoimmune blistering diseases such as pemphigus vulgaris or bullous pemphigoid (Fig. 18–5). Certain topically applied xenobiotics such as the vesicant cantharidin derived from “blister beetles” in the Coleoptera order and Meloidae family are used in the treatment of molluscum and viral warts. In high concentrations, xenobiotics can lead to necrosis of both skin and mucous membranes. Other systemic xenobiotics cause a similar reaction pattern mediated by the production of antibody directed against the cells at the DEJ (Table 18–3).

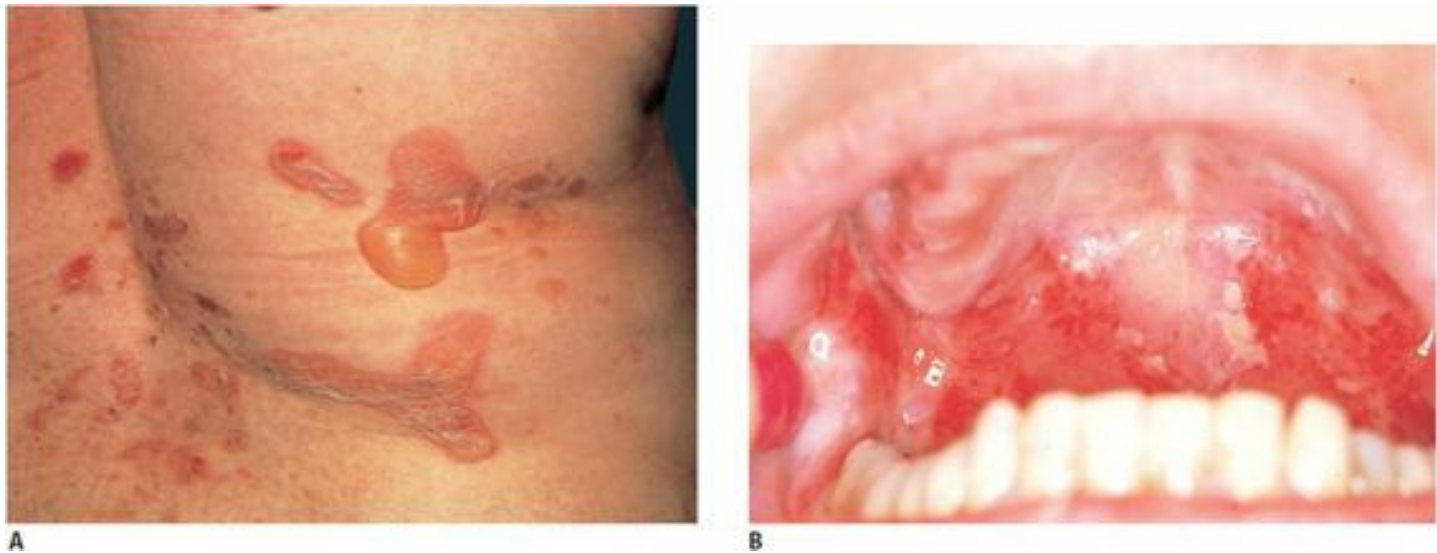


FIGURE 18–5. Pemphigus vulgaris. (A) Flaccid blisters. (B) Oral erosions. (Part A used with permission of Lawrence Lieblisch, MD. Part B reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: Fitzpatrick’s Dermatology in General Medicine. 8th ed. New York: McGraw-Hill; 2012.)

TABLE 18–3. Differential Diagnosis of Xenobiotic-Induced Blistering (Vesiculobullous) Disorders

<i>Disease</i>	<i>Fever</i>	<i>Mucositis</i>	<i>Morphology</i>	<i>Onset</i>	<i>Miscellaneous</i>
Xenobiotic-induced pemphigoid	No	Rare	Tense bullae (sometimes hemorrhagic)	Acute	Diuretics a common cause, especially furosemide, spironolactone; often pruritic
Staphylococcal scalded skin syndrome	Yes	Absent	Erythema, skin tenderness, periorificial crusting	Acute	Affects children younger than 5 years, adults on dialysis, and those on immunosuppressive therapy
Xenobiotic-induced pemphigus	No	Usually absent	Erosions, crusts, patchy erythema (resembles pemphigus foliaceus)	Gradual	Commonly caused by penicillamine and other "thiol" drugs; often resolves after inciting agent is discontinued
Xenobiotic-triggered pemphigus	No	Present	Mucosal erosions, flaccid bullae	Gradual	Caused by "nonthiol" drugs; more likely to persist after discontinuation of drug; may require long-term immunosuppressive therapy
Paraneoplastic pemphigus	No	Present (usually severe)	Polymorphous skin lesions, flaccid bullae	Gradual	Resistant to treatment; associated with malignancy, especially lymphoma
Acute graft-versus-host disease	Yes	Present	Morbilloform rash, bullae and erosions	Acute	Closely resembles toxic epidermal necrolysis
Acute generalized exanthematous pustulosis	Yes	Rare	Superficial pustules	Acute	Self-limiting on discontinuation of drug
Xenobiotic-induced linear IgA bullous dermatosis	No	Rare	Tense, subepidermal bullae	Acute	Vancomycin is most commonly implicated

A number of medications, many of which contain a “thiol group” such as penicillamine and captopril, can induce either pemphigus resembling pemphigus foliaceus, a superficial blistering disorder in which the blister is at the level of the stratum granulosum, or pemphigus vulgaris, in which blistering occurs above the basal layer of the epidermis (Fig. 18–1). Other xenobiotics, such as furosemide, penicillin, and sulfasalazine, produce tense bullae that resemble bullous pemphigoid. Direct immunofluorescence studies might show epidermal intracellular immunoglobulin deposits at the DEJ. Treatment options include stopping the offending xenobiotic and at times treating with immunosuppressants used to treat bullous pemphigoid and pemphigus vulgaris. The reaction may persist for up to 6 months after the offending xenobiotic is withdrawn.

Fixed Drug Eruption. Fixed drug eruption is another bullous drug eruption that is characterized by well-circumscribed erythematous to dusky violaceous patches that may have central bullae or erosions and develops 1 to 2 weeks after first exposure to the drug. This reaction pattern is so named because reexposure to the xenobiotic causes lesions in the same area but typically within 24 hours of exposures (Fig. 18–6). Typical locations include the acral extremities, genitals, and intertriginous sites, and this process may be confused with TEN if widely confluent as in “generalized fixed drug eruption.” This reaction pattern is generally not life threatening and heals with residual postinflammatory hyperpigmentation. Bullous fixed-drug reactions result from exposure to diverse xenobiotics such as angiotensin-converting enzyme inhibitors and a multitude of antibiotics. As mentioned earlier, EM can have a bullous variant that can also be confused with SJS/TEN.



FIGURE 18–6. Fixed drug eruption caused by tetracycline. A well-defined plaque on the knee merging with three satellite lesions. The large plaque exhibits epidermal wrinkling, a sign of incipient blister formation. This was the second such episode after ingestion of a tetracycline. No other lesions were present. (Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012.)

Coma Bullae. “Coma bullae” are tense bullae on normal appearing skin that occur within 48 to 72 hours in comatose patients with sedative–hypnotic overdoses, particularly phenobarbital, or carbon monoxide poisoning. They may also be seen in patients in coma from infectious, neurologic, or metabolic causes. Although these blisters are thought to result predominantly from pressure-induced epidermal necrosis, they occasionally occur in non–pressure-dependent areas, suggesting a systemic mechanism. Histologically, an intraepidermal or subepidermal blister may be observed. There is accompanying eccrine duct and gland necrosis.

Drug-Induced Hypersensitivity Syndrome

The drug hypersensitivity syndrome, also called drug reaction with eosinophilia and systemic symptoms (DRESS), can be severe and potentially life threatening. The skin may be involved with systemic immunologic diseases such that an alteration in the metabolism of certain xenobiotics leads to a hypersensitivity syndrome. The hypersensitivity syndrome is characterized by the triad of fever, skin eruption, and internal organ involvement.³¹ The frequency has been estimated between one in 1000 to one in 10,000 with anticonvulsants or sulfonamide antibiotic exposures and usually begins within 2 to 6 weeks after the initial exposure. For anticonvulsants, the inability to detoxify arene oxide metabolites has been suggested to be a key factor; after a patient has a documented drug-induced hypersensitivity syndrome to one anticonvulsant, it is important to note that cross-reactivity between phenytoin, carbamazepine, and phenobarbital is well documented, both in vivo and in vitro.⁴⁵ In the case of sulfonamides, acetylator phenotype and lymphocyte susceptibility to the metabolite hydroxylamine are risk factors for developing drug hypersensitivity syndrome. Further support for the role of genetic predisposition comes from data in Northern European populations in which the presence of the HLA-A*3101 allele significantly increases the risk of developing carbamazepine-induced hypersensitivity syndrome.³³ Fever and a cutaneous eruption are the most common symptoms. Accompanying malaise, pharyngitis, and cervical lymphadenopathy may also be present. Atypical lymphocytes and eosinophilia occur initially. The exanthem is initially generalized and morbilliform, and conjunctivitis and angioedema may occur (Fig. 18–7). Later the eruption becomes edematous and facial edema, which is often present, is a hallmark of this syndrome. Half of patients with drug-induced hypersensitivity syndrome will have hepatitis, interstitial nephritis, vasculitis, CNS manifestations (including encephalitis, aseptic meningitis), interstitial pneumonitis, acute respiratory distress syndrome, and autoimmune hypothyroidism. Hepatic involvement can be fulminant and is the most common cause of death associated with this syndrome. Colitis with bloody diarrhea and abdominal pain may occur. In addition to the aromatic anticonvulsants (phenobarbital, carbamazepine, and phenytoin), lamotrigine, allopurinol, sulfonamide antibiotics, dapsone, and the protease inhibitor abacavir have been implicated. Early withdrawal of the offending xenobiotic is crucial, and treatment is generally supportive.^{40,63} If cardiac or pulmonary involvement is present, systemic corticosteroids are often recommended; however, their benefit on outcome has not been demonstrated, and relapse may occur during tapering, necessitating long-term courses of therapy.



FIGURE 18–7. A patient with a hypersensitivity syndrome associated with phenytoin. He has a symmetric, bright red, exanthematous eruption, confluent in some sites. The patient had associated lymphadenopathy. (Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012.)

Erythroderma

Erythroderma, also known as exfoliative dermatitis, is defined as a generalized redness and scaling of the skin. However, it does not represent one disease entity; rather, it is a severe clinical presentation of a variety of skin diseases, including psoriasis, atopic dermatitis, drug reactions, or cutaneous T-cell lymphoma (CTCL). At times the underlying etiology of erythroderma is never discovered, and this is termed “idiopathic erythroderma.” The importance of this presentation is its association with systemic complications such as hypothermia; peripheral edema; and loss of fluid, electrolytes, and albumin with subsequent tachycardia and cardiac failure. Many xenobiotics can lead to erythroderma ([Table 18–2](#)). When ingested, boric acid can cause systemic toxicity in addition to a bright red eruption (“lobster skin”) usually followed within 1 to 3 days by a generalized exfoliation.⁵³

Vasculitis

Xenobiotic-induced vasculitis ([Fig. 18–8](#)) comprises 10% to 15% of secondary cutaneous vasculitis. It generally occurs from 7 to 21 days after initial exposure to the xenobiotic or 3 days after rechallenge and is considered to be a secondary cause of cutaneous small vessel vasculitis (typically involving dermal postcapillary venules). Many xenobiotics are implicated as triggers of cutaneous vasculitis ([Table 18–2](#)).⁵⁷ Cutaneous vasculitis is characterized by purpuric, nonblanching macules that usually become raised and palpable. The purpura tends to occur predominantly on gravity-dependent areas, including the lower extremities, particularly the feet, ankles, and buttocks. Sometimes the reaction pattern can have edematous purpuric wheals (urticarial vasculitis), hemorrhagic bullae, or ulcerations. The underlying histopathology shows a leukocytoclastic vasculitis, which is characterized by fibrin deposition in the vessel walls. There is a perivascular infiltrate with intact and fragmented neutrophils that appear as black dots, known as “nuclear dust,” and extravasated red blood cells. This reaction pattern may be limited to the skin or may be more serious and involve other organ systems, particularly the kidneys, joints, liver, lungs, and brain. The purpura results from the deposition of circulating immune complexes, which form as a result of a hypersensitivity to a xenobiotic. Treatment consists of withdrawing the putative xenobiotic and systemic corticosteroid therapy if systemic involvement is present. A syndrome of vasculitis, neutropenia, and retiform purpura has been reported as a result of levamisole-adulterated cocaine.¹³ The earlobe is a common site of purpuric lesions from levamisole, and it is estimated that up to 70% of the cocaine and less than 3% of the heroin supply in the United States contained levamisole.^{6,60,61}



FIGURE 18–8. Leukocytoclastic vasculitis in a patient with mixed cryoglobulinemia manifested as palpable purpura and acrocyanosis. The patient had tuberculosis, positive antinuclear antibody, and hepatitis. (Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012.)

Purpura. Purpura is the multifocal extravasation of blood into the skin or mucous membranes ([Fig. 18–9](#)). Ecchymoses are therefore considered to be purpuric lesions. Cytotoxic medications that either diffusely suppress the bone marrow or specifically depress platelet counts below 30,000/mm³ predispose to purpuric macules. Xenobiotics that interfere with platelet aggregation, such as aspirin, clopidogrel, ticlopidine, and valproic acid, may cause purpura, as may thrombolytics. Anticoagulants, such as heparin and warfarin, may also result in purpura ([Chaps. 22](#) and [60](#)).

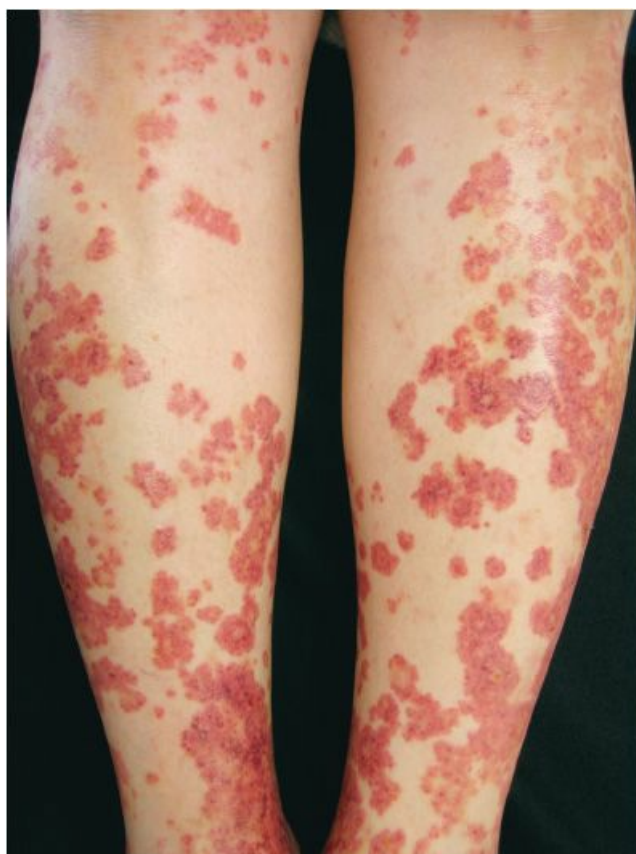


FIGURE 18–9. Purpura. Nonblanching red erythematous papules and plaques (palpable purpura) on the legs representing leukocytoclastic vasculitis. (Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012.)

Anticoagulant-Induced Skin Necrosis. Skin necrosis from warfarin, low-molecular-weight heparin, or unfractionated heparin usually begins 3 to 5 days after the initiation of treatment, which corresponds with the expected early decline of protein C function with warfarin ([Fig. 18–10](#)). The estimated risk is one in 10,000 persons. It is four times higher in women, especially if they are obese, with peaks in the sixth to seventh decades of life. The necrosis is secondary to thrombus formation in vessels of the dermis and subcutaneous fat. Heparin-induced cutaneous necrosis results from antibodies that bind to complexes of heparin and platelet factor 4 and induce platelet aggregation and consumption. There

may be bullae, ecchymosis, ulcers, and massive subcutaneous necrosis, usually in areas of abundant subcutaneous fat, such as the breasts, buttocks, abdomen, thighs, and calves. It may be associated with protein C or S deficiency, anticardiolipin antibody syndrome, and factor V Leiden mutations.⁴⁴ Treatment involves discontinuing the medication; administration of vitamin K; and, if warfarin induced, switching to heparin. Treatment may include fresh-frozen plasma and protein C. Skin grafting may be necessary if full-thickness necrosis occurs.



FIGURE 18–10. Skin necrosis in a patient after 4 days of warfarin therapy. (Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012.)

Contact Dermatitis

When a xenobiotic comes in contact with the skin, it can result in either an allergic contact dermatitis (20% of cases) or more commonly an irritant contact dermatitis (80% of cases). Contact dermatitis is characterized by inflammation of the skin with spongiosis (intercellular edema) of the epidermis that results from the interaction of a xenobiotic with the skin. Well-demarcated erythematous vesicular or scaly patches or plaques may be noted on areas in direct contact with the xenobiotic while the remaining areas are spared. Bullae may be present.

Allergic contact dermatitis fits into the classic delayed hypersensitivity, or type IV, immunologic reaction. The development of this reaction requires prior sensitization to an allergen, which, in most cases, acts as a hapten by binding with an endogenous molecule that is then presented to an appropriate immunologic T cell. Upon reexposure, the hapten diffuses to the Langerhans cell, is chemically altered, and bound to an HLA-DR, and the complex is expressed on the Langerhans cell surface. This complex interacts with primed T cells either in the skin or lymph nodes, causing the Langerhans cells to make interleukin-1 and the activated T cells to make interleukin-2 and interferon. This subsequently activates the keratinocytes to produce cytokines and eicosanoids that activate mast cells and macrophages, leading to an inflammatory response (Fig. 18–11).³⁰

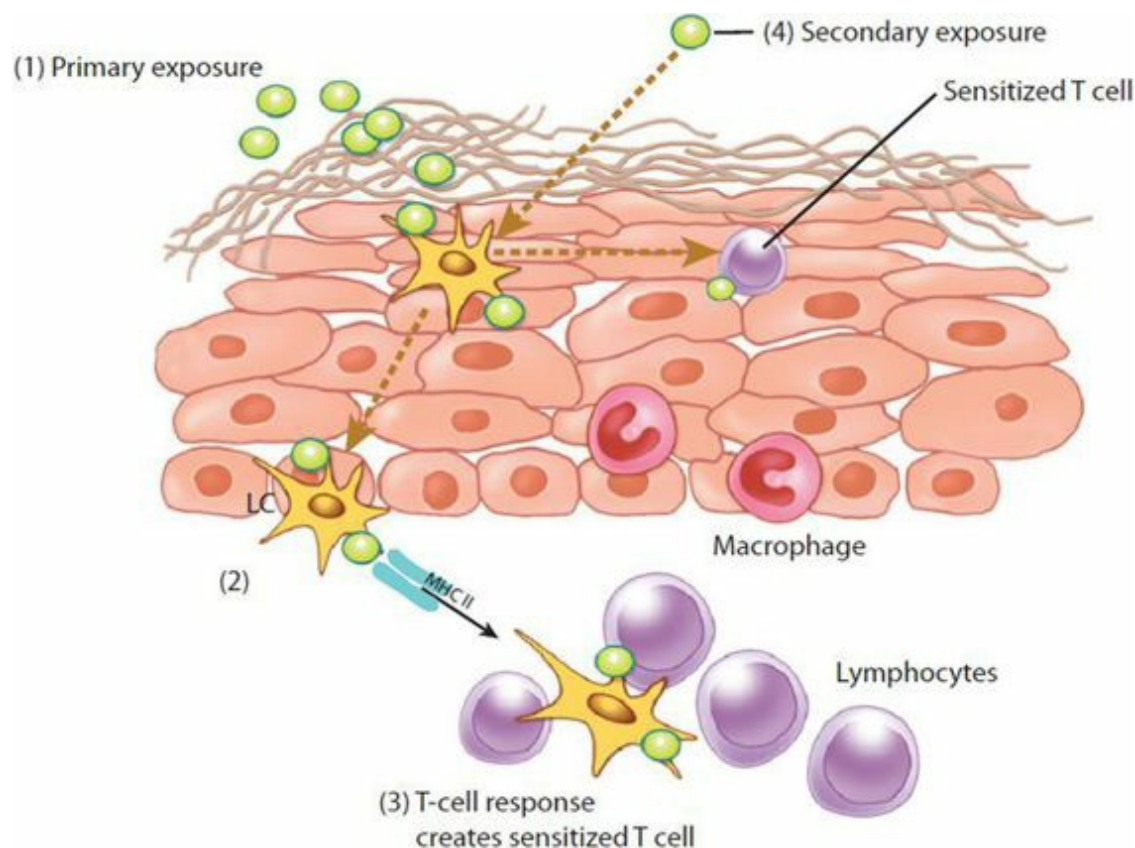


FIGURE 18–11. Contact dermatitis. (1) Causative xenobiotic, typically a hapten of less than 500 Da diffuses through the stratum corneum and binds to receptor on Langerhans cell (LC). (2) The antigen is processed with major histocompatibility complex II (MHC II) receptor site, presented to T-helper lymphocytes, and carried through the lymphatics to regional lymph nodes. (3) There it undergoes the sensitization phase by producing memory, effector, and suppressor T lymphocytes. (4) On reexposure to the same or to a cross-reactive antigen, the LC represents the antigen to T lymphocytes (----->), which are now sensitized. This initiates an inflammatory process that appears as indurated, scaly patches.

Many allergens are associated with contact dermatitis; a complete list is beyond the scope of this chapter. However, some common xenobiotics are listed in [Table 18–2](#). Among the most common plant-derived sensitizers are urushiol (*Toxicodendron* species), sesquiterpene lactone (ragweed), and tuliposide A (tulip bulbs). Metals, particularly nickel, are commonly implicated in contact dermatitis and should be considered in patients with erythematous, vesicular or scaly patches or plaques around the umbilicus from nickel buttons on pants, and on the ear lobes from earrings. Several industrial chemicals, such as the thiurams (rubber) and urea formaldehyde resins (plastics), account for the majority of occupational contact dermatitis. Medications, particularly topical medications such as neomycin, commonly cause contact dermatitis. An important allergen that is becoming more frequent is paraphenylenediamine (PPD), a black dye in permanent and semipermanent hair coloring, leather, fur, textiles, industrial rubber products, and black henna tattoos. According to the North American Contact Dermatitis Group, the frequency of sensitization to PPD has been found to be 5.0%.⁶⁵ Management strategies commonly used are outlined in [Table 18–4](#). A thorough history in addition to patch testing (the gold standard) will often identify the culprit.

TABLE 18–4. Overview of Treatment of Acute Contact Dermatitis

Identification of contactant and future avoidance
Drying agents, such as topical aluminum sulfate or calcium acetate: if weeping
Emollients: lichenified lesions
Corticosteroids, topical, rarely systemic: for severe reactions
Calcineurin inhibitors (tacrolimus or pimecrolimus)
Cyclosporine (oral)
Phototherapy, ultraviolet A or B

Irritant dermatitis, although clinically indistinguishable from direct damage to the skin and does not require prior antigen sensitization. Still, the inflammatory response to the initial mild insult is the cause of the majority of the damage. Irritant xenobiotics include acids, bases, solvents, and detergents, many of which, in their concentrated form or after prolonged exposure, can cause direct cellular injury. The specific site of damage varies with the chemical nature of the xenobiotic. Many xenobiotics can affect the lipid membrane of the keratinocyte, but others can diffuse through the membrane, injuring the lysosomes, mitochondria, or nuclear components. When the cell membrane is injured, phospholipases are activated and affect the release of arachidonic acid and the synthesis of eicosanoids. The second-

messenger system is then activated, leading to the expression of genes and the synthesis of various cell surface molecules and cytokines. Interleukin-1 is secreted, which can activate T cells directly and indirectly by stimulation of granulocyte-macrophage colony-stimulating factor production. Treatment is similar to allergic contact dermatitis.

Photosensitivity Reactions

Photosensitivity may be caused by topical or systemic xenobiotics. Nonionizing radiation, particularly to ultraviolet A (UVA) (320–400 nm) and less often to ultraviolet B (UVB) (280–320 nm), are the wavelengths that commonly cause photosensitivity. There are generally two types of xenobiotic-related photosensitivities, phototoxic and photoallergic.³⁹ Phototoxic reactions occur within 24 hours of the first exposure, usually within hours, and are dose related. These reactions result from direct tissue injury caused by UV-induced activation of a phototoxic xenobiotic. The clinical findings include erythema, edema, and vesicles in a light-exposed distribution and resemble a severe sunburn that can last for days to weeks with patients complaining of burning and stinging (Fig. 18–12). A subtype of phototoxic reaction includes phytophotodermatitis in which linear streaks of erythema occur after skin contact with furocoumarins from plants plus exposure to sunlight (Table 18–2). Photoallergic reactions occur less commonly, may occur after even small exposures, and resemble allergic contact dermatitis with lichenoid papules or an eczematous dermatitis on exposed areas and is often pruritic. These are type IV hypersensitivity reactions that develop in response to a xenobiotic that has been altered by absorption of nonionizing radiation, acting as a hapten and eliciting an immune response on first exposure. Only on recurrent exposure do the lesions develop. Studies indicate that benzophenone-3 (oxybenzone), often found in sunscreen, is the most common cause of photoallergic dermatitis.^{8,16} Other common photoallergens include xenobiotics such as promethazine, NSAIDs, fragrances, and antibacterial agents. Photoallergic reactions can be diagnosed by the use of photopatch tests. Both phototoxic and photoallergic reactions are managed with symptomatic treatment, including topical or, if needed, systemic corticosteroids. Identification and avoidance of the triggering xenobiotic are crucial in addition to avoidance of sun exposure and wearing a broad-spectrum sunscreen (SPF 30 or above) that blocks both UVA and UVB preferably without para-aminobenzoic acid (PABA). PABA is a sensitizing agent to many patients and is rarely included in current sunscreen products.



FIGURE 18–12. Phototoxicity associated with a heterocyclic antidepressant. Note the erythema and edema on sun-exposed areas and sparing of sun-protected chest and shaded upper lip and neck. (Photo contributed by Dr. Adrian Tanew. Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick's Dermatology in General Medicine*. 7th ed. New York: McGraw-Hill; 2008.)

Sclerodermalike Reactions

A number of environmental xenobiotics are associated with localized or diffuse sclerodermalike reactions. Sclerodermatous refers to a tightened, indurated surface change of the skin that typically occurs on the face, hands, forearms, and trunk and is three times more common in women. This may be accompanied by facial telangiectasias and Raynaud syndrome. Raynaud syndrome consists of skin color changes of white, blue, and red accompanied by intense pain

with exposure to cold and can cause acral ulcerations if left untreated. The fibrotic process usually does not remit with removal of the external stimulus, and specific autoantibodies are absent. The association of scleroderma-like reactions with polyvinyl chloride manufacture is likely related to exposure to vinyl chloride monomer. Similar reports of this syndrome are associated with exposure to trichloroethylene and perchloroethylene, which are structurally similar to vinyl chloride. Epoxy resins, silica, and organic solvents have been implicated as environmental causes. The xenobiotics bleomycin, carbidopa, pentazocine, and taxanes are causative.

In Spain, patients exposed to imported rapeseed oil mixed with an aniline denaturant developed widespread cutaneous sclerosis. This became known as the “toxic oil syndrome.” A similar syndrome, after ingestion of contaminated L-tryptophan as a dietary supplement used as a sleeping aid, resulted in the eosinophilia myalgia syndrome, which is characterized by myalgia, paralysis, edema, arthralgias, alopecia, urticaria, mucinous yellow papules, and erythematous plaques.⁵⁴

Hair Loss

Xenobiotics have the potential to cause distinctive patterns of hair loss (Table 18–2). Anagen effluvium, or hair loss during the anagen stage of the growth cycle, is caused by interruption of the rapidly dividing cells of the hair matrix, producing rapid hair loss within 2 to 4 weeks. Telogen effluvium, or toxicity during the resting stage of the cycle, typically produces hair loss 2 to 4 months later and occurs as a side effect of medication or in the setting of systemic disease or altered physiologic states (eg, postpartum). Anagen toxicity is commonly associated with xenobiotic exposures such as to doxorubicin, cyclophosphamide, vincristine, and thallium.⁵⁶ Many antineoplastics reduce the mitotic activity of the rapidly dividing hair matrix cells, leading to the formation of a thin, easily breakable shaft. Thallium, a toxin classically associated with hair loss, causes alopecia by two mechanisms. Thallium distributes intracellularly, similar to potassium, altering potassium-mediated processes and thereby disrupting protein synthesis. By binding sulfhydryl groups, thallium also inhibits the normal incorporation of cysteine into keratin. Thallium toxicity results in alopecia 1 to 4 weeks after exposure. Within 4 days of exposure, a hair mount observed using light microscopy will demonstrate tapered or bayonet anagen hair with a characteristic bandlike black pigmentation at the base. Seeing this anagen effect can reveal the timing of exposure (Chap. 102). Soluble barium salts, such as barium sulfide, are applied topically as a depilatory to produce localized hair loss. The mechanism of hair loss is undefined.

Nails

The nail consists of a horny layer the “nail plate” and four specialized epithelia: proximal nail fold, nail matrix, nailbed, and hyponychium. The nail matrix consists of keratinocytes, melanocytes, Langerhans cells, and Merkel cells.

Nail hyperpigmentation occurs for unclear reasons but may be caused by focal stimulation of melanocytes in the nail matrix leading to melanonychia. The pigment deposition can be longitudinal, diffuse, or perilar in orientation and typically develops several weeks after chemotherapy.⁵⁶ Black dark-skinned patients are more commonly affected because of a higher concentration of melanocytes. Cyclophosphamide, doxorubicin, hydroxyurea, zidovudine, and bleomycin are among the most common xenobiotics that cause melanonychia, and the pigmentation generally resolves with cessation of therapy. When approaching a patient with a single streak of longitudinal melanonychia, it is crucial to include nail melanoma in the differential diagnosis.

Nail findings may serve as important clues to xenobiotic exposures that have occurred in the recent past. Matrix keratinization, in a programmed and scheduled pattern, leads to the formation of the nail plate. Certain changes in nails, such as Mees and Beau lines, result from a temporary arrest of the proximal nail matrix proliferation. These lines can be used to predict the timing of a toxic exposure because of the reliability of rate of growth of the nails at approximately 0.1 mm/d. Mees lines, first described in 1919 in the setting of arsenic poisoning, can be used to approximate the date of the insult by the position of growth of the Mees line a patterned leukonychia (not indentation) causing transverse white lines.³⁴ Multiple Mees lines suggest multiple exposures over time. Arsenic, thallium, doxorubicin, vincristine, cyclophosphamide, methotrexate, and 5-fluorouracil are examples of xenobiotics that cause Mees lines, but Mees lines may be noted after any period of critical illness such as sepsis or trauma. Beau lines are transverse grooves or indentations more often in the central portion of the nail plate, most commonly caused by trauma (eg, manicures) or dermatologic disease affecting the proximal nailfold. Beau lines present on multiple digits, especially at the same level on each nail, indicate a systemic illness or xenobiotic exposure (Fig. 18–13).



FIGURE 18–13. Presence of proximal indented Beau line and distal band of leukonychia caused by cyclophosphamide seen 3 months after bone marrow transplantation. (Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012.)

SUMMARY

- The integument is constantly exposed to both topical and systemic xenobiotics, and these exposures may result in reactive dermatoses.
- Prompt examination of the skin, hair, and nails can provide invaluable clues about the route and nature of the offending xenobiotic.
- A careful history, clinical examination, and consultation with a dermatologist and biopsy when indicated can aid in identifying the etiology and nature of the reaction and lead to prompt treatment.

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SC1 SPECIAL CONSIDERATIONS

Transdermal Toxicology

Lewis S. Nelson

HISTORY AND CURRENT USE

Applying a xenobiotic to the skin to treat a systemic medical condition is not new. Ointments and other salves have been applied topically for thousands of years for the treatment of local and systemic diseases. During World War I, dynamite workers used nitroglycerin applied to their hatbands to prevent angina when they were away from work and no longer exposed to organic nitrates.³¹ Mustard seed plaster for chest congestion, releasing allyl isothiocyanate, and topical elemental mercurials for syphilis are other examples from the early 20th century.²⁴ Over the past 30 years, an increasing number of medications have been formulated in transdermal delivery systems or patches to allow for systemic delivery of a xenobiotic. The first commercially available patch delivered scopolamine for motion sickness (1979), which was followed by nitroglycerin for chronic angina (1981) and then fentanyl for chronic pain management (1990). In the United States, the nicotine patch remains the most widely used transdermal delivery system both because of the high need for smoking cessation and its nonprescription availability. Certain medicinal xenobiotics, such as testosterone, can be administered topically without a patch as a spray or gel.¹⁸ Furthermore, nonmedicinals can be absorbed transdermally, as occurs with nicotine after direct exposure to moist tobacco leaf in patient with “green tobacco sickness” or with organic phosphorus pesticides.³

The skin is the largest organ in the body, although it is not generally used as a route for intentional xenobiotic delivery. However, there are several benefits of transdermal delivery of systemic medication. This route provides a noninvasive means to discreetly administer medications. Patches result in steady serum concentrations that reduce side effects particularly for xenobiotics with short half-lives. The patches can be left in place for long periods of time, which improves compliance. Importantly, the avoidance of first-pass metabolism permits a means to effectively deliver poorly orally bioavailable xenobiotics. However, because all absorption through the skin is passive, there is a large degree of variability among both patients and xenobiotics.

This chapter does not cover xenobiotics applied to the skin to produce an effect locally. These xenobiotics can be available in patch formulation (eg, lidocaine and capsaicin) or as a directly applied preparation, such as a variety of antibiotics or acne creams. Locally acting formulations (eg, lidocaine) typically provides only trivial amounts of systemic xenobiotic;⁶ with tretinoin, despite devastating fetal complication when taken orally, these same effects do not occur when applied topically.¹⁶

TRANSDERMAL ADMINISTRATION PHARMACOLOGY

Passive Administration

The same hydrophobic property that allows the skin to prevent water loss hinders the ability to administer a water-soluble xenobiotic transdermally. To reach the systemic circulation, a xenobiotic applied to the stratum corneum (horny layer) (Fig. 18–1) must initially pass through about a dozen layers of keratinized epidermal cells and then into the dermis. This keratinaceous horny layer is highly impervious to water movement because of the presence of ceramides, fatty acids, and other lipids.⁵ This property both physiologically maintains the ability to lose excess water in dry environments and pathologically is lost in burn victims. For a xenobiotic to partition into the waxy stratum corneum, it must be sufficiently lipid soluble. However, this same xenobiotic must subsequently partition out of the stratum corneum into the aqueous underlying tissue, and this requires sufficient hydrophilicity.²² The ability to partition into these various phases (lipid and water) is described by the octanol:water partition coefficient. These vary widely among xenobiotics. For example, this coefficient and logP for fentanyl (717; 2.53) and nicotine (15; 1.18) suggests sufficient ability to cross the stratum corneum, but morphine (0.7, –0.15) cannot pass through this outer layer.

Fick’s first law can be used to describe xenobiotic permeation across the stratum corneum. In this model, steady-state flux (J) is related to the diffusion coefficient (D) of the xenobiotic based on the thickness of the stratum corneum (h), the partition coefficient (P) between the stratum corneum and the xenobiotic in its vehicle, and the xenobiotic concentration (C) that is applied, which is assumed to be constant. This equation demonstrates the influence of solubility and partition

coefficient of a xenobiotic on diffusion across the stratum corneum. Molecules showing intermediate partition coefficients (log P of 1–3) have adequate solubility within the lipid domains of the stratum corneum to permit diffusion through this domain still having sufficient hydrophilic nature to allow partitioning into the viable tissues of the epidermis.

Permeation enhancers improve absorption by solubilizing the xenobiotic or altering the characteristics of the stratum corneum, effectively increasing the lipid solubility of the xenobiotic.²⁷ Approaches include optimizing the solubility of the xenobiotic or enhancing the properties of the skin itself.⁵ Enhancers include solvents such as ethanol, fatty acids, fatty esters, and surfactants that serve as vehicles to improve the solubility of a xenobiotic in the lipids of the stratum corneum layer.⁵ An alternative means of enhancing lipophilicity is the addition of organic functional groups to create a prodrug that is cleaved after being absorbed.²⁵ This is similar to the significantly enhanced neurotoxicity when dimethylmercury is applied to the skin and compared with methylmercury.²⁰ Additionally, the use of nanoparticles enhances xenobiotic solubility and surface contact area.²⁸

Few xenobiotics have the correct molecular requirements to be able to be systemically delivered by the transdermal route. The upper limit of the molecular weight (MW) of an acceptable xenobiotics is 500 Da (fentanyl is 337 Da), and the xenobiotic must be sufficiently potent to exert its desired effect at concentrations that can reliably be obtained. Although only small quantities, typically less than 2 mg daily, are delivered, the largest nicotine patch delivers 21 mg daily.

As suggested by Fick's law, the ability to cross the dermis is related to the concentration gradient provided by the transdermal delivery apparatus. To allow sufficient delivery, a large amount of xenobiotic is contained in the apparatus to maintain the concentration gradient over time. For example, the 50-μg/h fentanyl patch (which delivers 1.2 mg daily) contains 8.4 mg (8400 μg) of fentanyl in the patch.^{12,31} This excess amount of drug minimizes the fluctuations in delivery over time as the concentration gradient naturally falls during movement of xenobiotic from the patch to the skin. Upon completion of the 3-day use of a fentanyl patch, the amount of fentanyl remaining in a patch ranged from 24% to 85%; at the end of use, 27% to 74% of the contents of a nicotine patch may remain.^{17,24,32} Furthermore, to prevent rapid movement into the skin and maintain a functional concentration gradient, a rate-controlling membrane is present that allows a measured amount of drug to pass per area of skin contact surface.

Applying xenobiotic to broken skin or tissue lacking a stratum corneum, such as the mucosa, results in a substantial increase in its absorption which may be more than five- and more than 30-fold, respectively, for fentanyl.^{11,18} However, because the pharmacokinetics of transmucosal delivery tend to be more predictable than by the transdermal route, certain formulations such as fentanyl citrate (Actiq or Fentora) or nicotine (Nicorette gum) may be administered transmucosally. However, the greater penetrability accounts for the toxicity associated with improper application to a mucosal surface.^{5,23} A small amount of xenobiotic can enter the body by way of the skin appendages, such as the sweat glands or hair follicles.^{5,22} Furthermore, application of salicylic acid for treatment of hyperkeratinization disorders can cause salicylate poisoning.^{1,27}

Properties of the skin that account for pharmacokinetic variability include hydration status and temperature. Absorption varies based on the site of application on the body and is based on both thickness of the stratum corneum and blood flow.^{2,25,26} Although the average skin thickness of the human body is 40 microns, it ranges between 20 and 80 microns because of many factors, including body location, race, age, and sex. As an example, in skin samples from eight individuals, there was more than a 50% difference in the permeability of fentanyl.¹⁵ Because the stratum corneum thickness may be most relevant to diffusion rates, those areas that have similar thickness, such as the chest, extremities, and abdomen, provide the most consistent delivery and are generally used as sites for transdermal device application.^{26,28} Intertriginous areas, where skin contacts other skin (axillae, groin, inframammary, and intergluteal), may allow greater absorption because of enhanced contact surface, temperature, and moisture.

Active Administration

The passive approach requires the optimization of formulation or xenobiotic carrying vehicle to increase skin permeability. However, passive methods do not greatly improve the permeation of xenobiotics with MWs greater than 500 Da. In contrast active methods, normally involving physical or mechanical methods of enhancing delivery are generally superior. The delivery of xenobiotics of differing lipophilicity and MW, including proteins, peptides, vaccines, and oligonucleotides, is improved by active energy-requiring techniques such as iontophoresis, electroporation, and ultrasonography.^{10,21} In general, these techniques are not yet in wide use (Tables SC1–1 and SC1–2).

TABLE SC1–1. Common Xenobiotics Available in Patch Formulations

Buprenorphine (BuTrans)

Clonidine (Catapres-TTS, generic)

Estradiol (Climara)

Estradiol/levonorgestrel (Climara Pro)

Norelgestromin/ethinyl estradiol (Ortho Evra)

Fentanyl (Duragesic, Novaplus Fentanyl, generic)

Granisetron (Sancuso)

Methylphenidate (Daytrana)

Nicotine (Habitrol, Nicoderm CQ, Nicotrol, generic)

Nitroglycerin (Nitro-Dur)

Oxybutynin (Oxytrol)

Rivastigmine (Exelon)

Rotigotine (Neupro)

Scopolamine (Transderm Scop)

Selegiline (Emsam)

Testosterone (Androderm) and (Intrinsa)

TABLE SC1–2. Description of Advanced Transdermal Drug Delivery Systems

Electroporation: uses high-voltage microsecond duration electrical pulses to create transient pores within the skin (for larger molecules such as peptides)

Iontophoresis: uses electrodes to pass a small current through a xenobiotic (pilocarpine for sweat testing for cystic fibrosis and for lidocaine)

Ultrasonography: uses low-frequency ultrasound to promote transcutaneous delivery, also called sonophoresis

Microneedle-based devices: approximately 10 to 100 microns in length, generally arranged in arrays on patch devices; each microneedle is coated in xenobiotic to be delivered, and the small size avoids the production of pain

Needleless injection: compressed air is used to force xenobiotics across the skin surface; may deliver local anesthetics before intravenous line placement

Patch Technology

In most current patches, the xenobiotic to be delivered is incorporated into the adhesive layer. There may be multiple layers of adhesive separated by membranes that serve to regulate the release. To allow a longer duration of drug delivery, a reservoir may be added. This compartment contains the xenobiotic in solution or suspension, and a rate-regulating membrane ensures that the release follows zero order kinetics to avoid fluctuations in concentration. Increasing the surface area of contact by enlarging the patch proportionally increases the amount of xenobiotic delivered. The membrane itself is not altered. Removal of the rate-regulating membrane, however, results in rapid absorption of toxic quantities of xenobiotic.⁷

The initial fentanyl patch (Duragesic) used a reservoir that contained a large quantity of xenobiotic. This reservoir could have been accessed inadvertently by a child chewing the patch or intentionally by a person seeking to abuse the liquid contents.¹⁹ Cutting the reservoir patch could disperse the fentanyl and result in either overdose or loss of analgesia. Patch construction defects also occurred that potentially allowed leakage.¹³ Alternatively, by incorporating the xenobiotic into a fabric mesh, the matrix patch eliminates the reservoir and reduces the risk for abuse. The matrix patch may be cut to change dosage delivered, based on surface contact area, without risking spillage of any liquid content. The clinical pharmacology of the matrix fentanyl patch is similar to that of the reservoir patch.⁸

Pharmacokinetics

The initial detection of a xenobiotic in the serum after transdermal application is not surprisingly delayed compared with other routes of administration. The delay depends on the properties of the xenobiotic, the skin, and the environment. Very lipophilic xenobiotics form a depot in the subcutaneous tissue as they slowly dissolve in the aqueous tissue for diffusion to allow vascular uptake. Highly hydrophilic xenobiotics slowly penetrate the lipid layers of the epidermis, which is why ionic (salt) forms of xenobiotics are administered by a subcutaneous or intramuscular route. For example, fentanyl will not be detected in the serum before 1 to 2 hours after placement of a patch, and the peak concentration may not occur for one day or longer. For this reason, the use of a fentanyl patch is not indicated for the treatment of acute pain, particularly postoperative pain.¹⁹ Because the natural history of acute pain is to rapidly improve over several days, during which time the fentanyl concentrations continue to rise, the risk of toxicity rises.²⁹ However, in patients with chronic pain, this pharmacokinetic profile may be beneficial as long as opioids are indicated and safe use is monitored. Furthermore, as noted, permeation enhancers may alter the xenobiotic or the skin sufficiently to alter the absorption kinetics.

The pharmacokinetic profiles of serial doses of patches is based on removal of the patch after the specified time period and application of a new patch to a different location.¹⁹ This is important to allow a new subcutaneous depot to form while the existing depot is absorbed rather than adding a bolus dose from the adhesive to the existing depot.

Washing the skin or removing the patch will not result in a rapid fall in serum concentrations or a reduction in clinical effect.¹² Rather, these will resolve over several hours because of the persistence of the dermal depot.¹⁹ For example, the effective half-life of fentanyl after removal of a fentanyl patch is approximately 18 hours.¹² Therefore, simple removal of the fentanyl patch will not be sufficient treatment of a patient experiencing respiratory depression, and respiratory support or naloxone should be used.

Adverse Effects

Because transdermal administration places the xenobiotic in close contact with the environment, there is substantial risk of variation in absorption because of changes in ambient conditions. For example, patches exposed to heat, from heating blankets or saunas, can release xenobiotic at a rate greater than expected under conventional ambient conditions.⁴ Exposed patches may be damaged, either during the manufacturing process or subsequently, which can alter their release profile, resulting in toxicity.¹³ Certain patches, such as those with a metal backing, can get exceedingly hot during exposure to magnetic resonance imaging studies and result in burns.

Despite these techniques to enhance xenobiotic delivery, transdermal systems require that large amounts of xenobiotic be present externally to maximize the transcutaneous gradient. Much of the xenobiotic typically remains in the patch when it is removed after its intended course of therapy,¹⁷ raising concerns for safe disposal, especially around children,³⁰ and abuse potential among others.¹⁴ This latter issue is of greatest concern with the fentanyl reservoir patch.¹⁹

Perhaps the most insidious adverse effect associated with patches is their complicated pharmacology. Because many prescribers are unfamiliar with the dosing and initiation of therapy with transdermal products, those xenobiotics with consequential adverse effects in overdose, such as fentanyl, are commonly linked to poor outcomes even with intended therapeutic use.^{9,19}

SUMMARY

- Few xenobiotics have the appropriate chemical properties, such as lipophilicity and potency, to permit transdermal absorption.
- Transdermal delivery of a xenobiotic has certain therapeutic advantages over other routes, such as bypassing first-pass hepatic metabolism and providing a discreet administration.
- The pharmacokinetics of transdermal xenobiotic delivery are unique compared with other routes. Absorption is typically slower but more prolonged, which is potentially beneficial in situations in which long-term, continuous dosing is required.

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19 FLUID, ELECTROLYTE, AND ACID–BASE PRINCIPLES

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A meaningful analysis of fluid, electrolyte, and acid–base abnormalities must be based on the clinical characteristics of each patient. Although a rigorous appraisal of laboratory parameters often yields the correct differential diagnosis, the history and physical examination provide an understanding of the extracellular fluid volume (ECFV) and pathophysiology. Thus, the evaluation always begins with an overall assessment of the patient's status.

INITIAL PATIENT ASSESSMENT

History

The history should be directed toward clinical questions associated with fluid and electrolyte abnormalities. Xenobiotic exposure commonly results in fluid losses through the respiratory system (hyperpnea and tachypnea), gastrointestinal (GI) tract (vomiting and diarrhea), skin (diaphoresis), and kidneys (polyuria). Patients with ECFV depletion may complain of dizziness, thirst, and weakness. Usually the patients can identify the source of fluid loss.

A history of exposure to nonprescription and prescription medications, alternative or complementary therapies, and other xenobiotics may suggest the most likely electrolyte or acid–base abnormality. In addition, premorbid conditions and the ambient temperature and humidity should always be considered.

Physical Examination

The vital signs are invariably affected by significant alterations in ECFV. Whereas hypotension and tachycardia may characterize life-threatening ECFV depletion, an initial finding may be an increase of the heart rate and a narrowing of the pulse pressure. Abnormalities may be recognized through an ongoing dynamic evaluation, realizing that the measurement of a single set of supine vital signs offers useful information only when markedly abnormal. Orthostatic pulse and blood pressure measurements provide a more meaningful determination of functional ECFV status ([Chaps. 3 and 17](#)).

The respiratory rate and pattern can give clues to the patient's metabolic status. Hyperventilation (manifested by tachypnea, hyperpnea, or both) may be caused by a primary respiratory stimulus (respiratory alkalosis) or may be a response to the presence of metabolic acidosis. Although hypoventilation (bradypnea or hypopnea or both) is present in patients with metabolic alkalosis, it is rarely clinically significant except in the presence of chronic lung disease. More commonly, hypoventilation is associated with a primary depression of consciousness and respiration as well as respiratory acidosis. Unless the clinical scenario (ie, nature of the overdose or poisoning, presence of renal or pulmonary disease, findings on physical examination or laboratory testing) is diagnostic, arterial or venous blood gas analysis is required to determine the acid–base disorder associated with a change in ventilation.

The skin should be evaluated for turgor, moisture, and the presence or absence of edema. The moisture of the mucous membranes can also provide valuable information. These are nonspecific parameters and may not correlate directly with the status of hydration. This dissociation is especially true with xenobiotic exposure because many xenobiotics alter skin and mucous membrane moisture without necessarily altering ECFV status. For example, antimuscarinics commonly result in dry mucous membranes and skin without producing ECFV depletion. Conversely, patients exposed to sympathomimetics (eg, cocaine) or cholinergics (eg, organic phosphorus compounds) may have moist skin and mucous membranes even in the presence of significant fluid losses. This dissociation of ECFV and cutaneous characteristics reinforces the need to assess patients meticulously.

The physical findings associated with electrolyte abnormalities are generally nonspecific. Hyponatremia, hypernatremia, hypercalcemia, and hypermagnesemia all may produce a depressed level of consciousness. Neuromuscular excitability such as tremor and hyperreflexia may occur with hypocalcemia, hypomagnesemia, hyponatremia, and hyperkalemia. Weakness may be caused by either hyperkalemia or hypokalemia. Also, multiple, concurrent electrolyte disorders can produce confusing clinical presentations, or patients may appear normal. Rarer diagnostic findings, such as Chvostek and Trousseau signs (primarily found in hypocalcemia), may be useful in assessing patients with potential xenobiotic exposures.

Rapid Diagnostic Tools

The electrocardiogram (ECG) is a useful tool for screening several common electrolyte abnormalities (Chap. 16). It is easy to perform, rapid, inexpensive, and routinely available. Unfortunately, because poor sensitivity (0.43) and moderate specificity (0.86) were demonstrated when ECGs were used to diagnose hyperkalemia, in actuality, the test is of limited diagnostic value.¹⁴⁰ However, the ECG is valuable for the evaluation of changes in serum potassium and calcium concentrations ($[K^+]$ and $[Ca^{2+}]$) in an individual patient.

In many patients, bedside assessment of urine specific gravity by dipstick analysis may provide valuable information about ECFV status. A high urine specific gravity (>1.015) signifies concentrated urine and is often associated with ECFV depletion. However, urine specific gravity may be similarly elevated in conditions of ECFV excess, such as congestive heart failure or third spacing. Furthermore, when renal impairment or diuretic use is the source of the volume loss, the specific gravity is usually approximately 1.010 (known as isosthenuria). Patients with lithium-induced diabetes insipidus (DI) excrete dilute urine (specific gravity <1.010) despite ongoing water losses, and patients with excess antidiuretic hormone (ADH) secretion (eg, methylenedioxymethamphetamine {MDMA}) excrete concentrated urine (specific gravity >1.015) in the presence of a normal to expanded ECFV.

The urine dipstick is particularly useful for rapidly determining the presence of ketones, which are often associated with common causes of metabolic acidosis (eg, diabetic ketoacidosis, salicylate poisoning, alcoholic ketoacidosis). The urine ferric chloride test rapidly detects exposure to salicylates with a high sensitivity and specificity although it is rarely used today (Chap. 39).

Laboratory Studies

A simultaneous determination of the venous serum electrolytes, blood urea nitrogen (BUN), glucose, and arterial or venous blood gases is adequate to determine the nature of the most common acid–base, fluid, and electrolyte abnormalities. More complex clinical problems may require determinations of urine and serum osmolalities, urine electrolytes, serum ketones, serum lactate, and other tests. A systematic approach to common problems is discussed in the following sections.

ACID–BASE ABNORMALITIES

Definitions

The lack of a clear understanding and precise use of the terminology of acid–base disorders often leads to confusion and error. The following definitions provide the appropriate frame of reference for the remainder of the chapter and this textbook.

Whereas the terms acidosis and alkalosis refer to processes that tend to change pH in a given direction, acidemia and alkalemia only refer to the actual pH. By definition, a patient is said to have:

- A metabolic acidosis if the arterial pH is less than 7.40 and serum bicarbonate concentration ($[HCO_3^-]$) is less than 24 mEq/L. Because acidemia stimulates ventilation (respiratory compensation), metabolic acidosis is usually accompanied by a PCO_2 less than 40 mm Hg.
- A metabolic alkalosis if the arterial pH is greater than 7.40 and serum $[HCO_3^-]$ is greater than 24 mEq/L. Because alkalemia inhibits ventilation (respiratory compensation), metabolic alkalosis is usually accompanied by a PCO_2 greater than 40 mm Hg.
- A respiratory acidosis if the arterial pH is less than 7.40 and partial pressure of carbon dioxide (PCO_2) is greater than 40 mm Hg. Because an elevated PCO_2 stimulates renal acid excretion and the generation of HCO_3^- (renal compensation), respiratory acidosis is usually accompanied by a serum $[HCO_3^-]$ greater than 24 mEq/L.
- A respiratory alkalosis if the arterial pH is greater than 7.40 and PCO_2 is less than 40 mm Hg. Because a decreased PCO_2 decreases renal net acid excretion and increases the excretion of HCO_3^- (renal compensation), respiratory alkalosis is usually accompanied by a serum $[HCO_3^-]$ less than 24 mEq/L.

It is important to note that under most circumstances, a venous pH permits an approximation of arterial pH (see Chap. 29 for a further discussion of the relationship between arterial and venous pH). Any combination of acidoses and alkaloses can be present in any one patient at any given time. The terms acidemia and alkalemia refer only to the resultant arterial pH of blood (acidemia referring to a pH <7.40 and alkalemia referring to a pH >7.40). These terms do not describe the processes that led to the alteration in pH. Thus, a patient with acidemia must have a primary metabolic or respiratory acidosis but may have an alkalosis present at the same time. Clues to the presence of more than one acid–base abnormality include the clinical presentation, an apparent excess or insufficient “compensation” for the primary acid–base abnormality, a delta (Δ) anion gap-to- $\Delta [HCO_3^-]$ ratio that significantly deviates from one, or an electrolyte abnormality that is uncharacteristic of the primary acid–base disorder.

Determining the Primary Acid–Base Abnormality

It is helpful to begin by determining whether the patient has an acidosis or an alkalosis. This is followed by an assessment of the pH, PCO_2 , and $[\text{HCO}_3^-]$. With these three parameters defined, the patient's primary acid–base disorder can be classified using the aforementioned definitions. Next it is important to determine whether the compensation of the primary acid–base disorder is appropriate. It is generally assumed that overcompensation cannot occur.⁹⁷ That is, if the primary process is metabolic acidosis, respiratory compensation tends to raise the pH toward normal but never to greater than 7.40. If the primary process is respiratory alkalosis, compensatory renal excretion of HCO_3^- tends to lower the pH toward normal but not to less than 7.40. The same is true for primary metabolic alkalosis and primary respiratory acidosis. As a rule, compensation for a primary acid–base disorder that is inadequate or excessive is indicative of the presence of a second primary acid–base disorder.

Based on patient data, the Winters equation (Equation 19–1)⁷ predicts the degree of the respiratory compensation (the decrease in PCO_2) in metabolic acidosis as follows:

$$\text{PCO}_2 = (1.5 \times [\text{HCO}_3^-]) + 8 \pm 2 \quad (\text{Eq. 19–1})$$

Thus, in a patient with an arterial $[\text{HCO}_3^-]$ of 12 mEq/L, the predicted PCO_2 may be calculated as

$$(1.5 \times 12) + 8 \pm 2$$

or

$$26 \pm 2 \text{ mm Hg.}$$

If the actual PCO_2 is substantially lower than is predicted by the Winters equation, it can be concluded that both a primary metabolic acidosis and a primary respiratory alkalosis are present. If the PCO_2 is substantially higher than the predicted value, then both a primary metabolic acidosis and a primary respiratory acidosis are present.

An alternative to the Winters equation is the observation by Narins and Emmett that in compensated metabolic acidosis, the arterial PCO_2 is usually the same as the last two digits of the arterial pH.⁹⁷ For example, a pH of 7.26 predicts a PCO_2 of 26 mm Hg.

Guidelines are also available to predict the compensation for metabolic alkalosis,⁵⁶ respiratory acidosis, and respiratory alkalosis.⁷⁴ Patients with a metabolic alkalosis compensate by hypoventilating, resulting in an increase of their PCO_2 above 40 mm Hg. However, the concomitant development of hypoxemia limits this compensation so that respiratory compensation in the presence of a metabolic alkalosis usually results in a PCO_2 of 55 mm Hg or less. It is difficult to be more accurate about the expected respiratory compensation for a metabolic alkalosis, although the compensation, as in the case of metabolic acidosis, is nearly complete within hours of onset.

By contrast, the degree of compensation in primary respiratory disorders depends on the length of time the disorder has been present. In a matter of minutes, primary respiratory acidosis results in an increase in the serum $[\text{HCO}_3^-]$ of 0.1 times the increase (Δ) in the PCO_2 . This increase is a result of the production and dissociation of H_2CO_3 . Over a period of days, respiratory acidosis causes the compensatory renal excretion of acid. This compensation increases the serum $[\text{HCO}_3^-]$ by 0.3 times the ΔPCO_2 . Primary respiratory alkalosis acutely decreases the serum $[\text{HCO}_3^-]$ by 0.2 times the ΔPCO_2 . If a respiratory alkalosis persists for several days, renal compensation, by the urinary excretion of HCO_3^- , decreases the serum $[\text{HCO}_3^-]$ by 0.4 times the ΔPCO_2 .

Calculating the Anion Gap

The concept of the anion gap is said to have arisen from the “Gamblegram” originally described in 1939;⁴⁴ however, its use was not popularized until the determination of serum electrolytes became routinely available. The law of electroneutrality states that the net positive and negative charges of all fluids must be equal. Thus, all of the negative charges present in the serum must equal all of the positive charges, and the sum of the positive charges minus the sum of the negative charges must equal zero. The problem that immediately arose (and produced an “anion gap”) was that all charged species in the serum were not routinely measured.

Normally present but not routinely measured cations include calcium and magnesium; normally present but not routinely measured anions include phosphate, sulfate, albumin, and organic anions (eg, lactate and pyruvate).³⁶ Whereas Na^+ and K^+ normally account for 95% of extracellular cations, Cl^- and HCO_3^- account for 85% of extracellular anions. Thus, because more cations than anions are among the electrolytes usually measured, subtracting the anions from the cations normally yields a positive number, known as the anion gap. The anion gap is therefore derived as shown in Equation 19–2:

$$\begin{aligned}
& [\text{Na}^+] + [\text{K}^+] + [\text{Unmeasured Cations (U}_c\text{)}] = [\text{Cl}^-] + [\text{HCO}_3^-] \\
& \quad + [\text{Unmeasured Anions (U}_a\text{)}] \\
& \text{Anion Gap} = [\text{U}_a] - [\text{U}_c]
\end{aligned}$$

or

$$\text{Anion Gap} = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]) \quad (\text{Eq. 19-2})$$

Because the serum $[\text{K}^+]$ varies over a limited range of perhaps 1–2 mEq/L above and below normal and therefore rarely significantly alters the anion gap, it is often deleted from the equation for simplicity. Most prefer this approach, yielding Equation 19–3:

$$\text{Anion Gap} = ([\text{Na}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]) \quad (\text{Eq. 19-3})$$

Using Equation 19–3, the normal anion gap was initially determined to be 12 ± 4 mEq/L.³⁶ However, because the normal serum $[\text{Cl}^-]$ is higher on modern laboratory instrumentation, the current range for a normal anion gap is 7 ± 4 mEq/L.¹³⁸

A variety of pathologic conditions may result in a rise or fall of the anion gap. High anion gaps result from increased presence of unmeasured anions or decreased presence of unmeasured cations (Table 19–1).^{36,80} Conversely, a low anion gap results from an increase in unmeasured cations or a decrease in unmeasured anions (Table 19–2).^{36,42,52,119}

TABLE 19–1. Xenobiotic and Other Causes of a High Anion Gap

<i>Increase in Unmeasured Anions</i>	<i>Decrease in Unmeasured Cations</i>
Metabolic acidosis (Table 19–3)	Simultaneous hypomagnesemia, hypocalcemia, or hypokalemia
Therapy with sodium salts of unmeasured anions	
Sodium citrate	
Sodium lactate	
Sodium acetate	
Therapy with certain antibiotics	
Carbenicillin	
Sodium penicillin	
Alkalosis	

TABLE 19–2. Xenobiotic and Other Causes of a Low Anion Gap

<i>Increase in Unmeasured Cations</i>	<i>Decrease in Unmeasured Anions</i>	<i>Overestimation of Chloride</i>
Hypercalcemia	Hypoalbuminemia	Bromism
Hypermagnesemia	Dilution	Iodism
Hyperkalemia		Nitrate excess
Lithium poisoning		
Multiple myeloma		

Anion Gap Reliability

Several authors have considered the usefulness of the anion gap determination.^{19,43,64} When 57 hospitalized patients were studied to determine the cause of elevated anion gaps in patients whose anion gap was greater than 30 mEq/L, the cause was always a metabolic acidosis with elevated lactate or ketoacidosis.⁴³ In patients with smaller elevations of the anion gap, the ability to define the cause of the elevation diminished; in only 14% of patients with anion gaps of 17 to 19 mEq/L could the cause be determined. Another study determined that although the anion gap is often used as a screening test for hyperlactatemia (as a sign of poor perfusion), only patients with the highest serum lactate concentrations had elevated anion gaps.⁶⁴ Finally, in a sample of 571 patients, those with greater elevations in anion gaps tended to have more severe illness. This logically correlated with higher admission rates, a greater percentage of admissions to intensive care units, and a higher mortality rate.¹⁹ Thus, although the absence of an increased anion gap does not exclude significant illness, a very elevated anion gap can generally be attributed to a specific cause (typically lactate or ketones) and usually indicates a relatively severe illness.

Metabolic Acidosis

After the diagnosis of metabolic acidosis is established by finding an arterial pH less than 7.40, $[\text{HCO}_3^-] < 24 \text{ mEq/L}$, and $\text{PCO}_2 < 40 \text{ mm Hg}$, the serum anion gap should be analyzed. Indeed, the popularity of the anion gap is primarily based on its usefulness in categorizing metabolic acidosis as being of the high anion gap or normal anion gap type. This determination should be made after correcting the anion gap for the effect of hypoalbuminemia, a common and important confounding factor in sick patients. The anion gap decreases approximately 3 mEq/L per 1-g/dL decrease in the serum [albumin].⁴¹ In general, the electrolyte abnormalities that frequently accompany metabolic acidosis usually have only small and insignificant effects on the anion gap.

It should be noted that although many clinicians rely on the mnemonics **MUDPILES** (M, methanol; U, uremia; D, diabetic ketoacidosis; P, paraldehyde; I, iron; L, lactic acidosis; E, ethylene glycol; and S, salicylates) or **KULT** (K, ketones; U, uremia; L, lactate; T, toxins), to help remember this differential diagnosis, these mnemonics include rarely used drugs (phenformin, paraldehyde) and omit important others (eg, metformin, cyanide).

A high anion gap metabolic acidosis results from the absorption or generation of an acid that dissociates into an anion other than Cl^- that is neither excreted nor metabolized. The retention of this “unmeasured” anion (eg, glycolate in ethylene glycol poisoning) increases the anion gap. A normal anion gap metabolic acidosis results from the absorption or generation of an acid that dissociates into H^+ and Cl^- . In this case, the “measured” Cl^- is retained as HCO_3^- is titrated and its concentration reduced during the acidosis, and no increased anion gap is produced. Normal anion gap acidosis, also referred to as hyperchloremic metabolic acidosis, may be caused by intestinal or renal bicarbonate losses as in diarrhea or renal tubular acidosis, respectively. Other causes of high and normal anion gap metabolic acidoses are described elsewhere^{1,2} and shown in [Tables 19–3 and 19–4](#).

TABLE 19–3. Xenobiotic and Other Causes of a High Anion Gap Metabolic Acidosis

Carbon monoxide
Cyanide
Ethylene glycol
Hydrogen sulfide
Isoniazid
Iron
Ketoacidoses (diabetic, alcoholic, and starvation)
Lactate
Metformin
Methanol
Paraldehyde
Phenformin
Propylene glycol
Salicylates
Sulfur (inorganic)
Theophylline
Toluene
Uremia (acute or chronic kidney failure)

TABLE 19–4. Xenobiotic Causes of a Normal Anion Gap Metabolic Acidosis

Acetazolamide

Acidifying agents

Ammonium chloride

Arginine hydrochloride

Hydrochloric acid

Lysine hydrochloride

Calcineurin inhibitors (eg, tacrolimus, sirolimus)

Cholestyramine

Cleistanthus collinus (Plant)

Mafenide acetate (Sulfamylon)

Toluene

Topiramate

Narrowing the Differential Diagnosis of a High Anion Gap Metabolic Acidosis

The ability to diagnose the etiology of a high anion gap metabolic acidosis is an essential skill in clinical medicine. The following discussion provides a rapid and cost-effective approach to the problem. As always, the clinical history and physical examination may provide essential clues to the diagnosis. For example, iron poisoning is virtually always associated with significant GI symptoms, the absence of which essentially excludes the diagnosis ([Chap. 46](#)). Furthermore, when iron overdose is suspected, an abdominal radiograph may show the presence of tablets. The acidosis associated with isoniazid (INH) toxicity results from seizures, the absence of which excludes INH as the cause of a metabolic acidosis ([Chap. 58](#)). Methanol poisoning may be associated with visual complaints or abnormal funduscopic examination findings ([Chap. 109](#)). Methyl salicylate has a characteristic wintergreen odor ([Chap. 26](#)). When these findings are absent, the laboratory analysis must be relied on, as follows:

1. Begin with the serum electrolytes, BUN, creatinine, and glucose. A rapid blood glucose reagent test should be performed to help confirm or exclude hyperglycemia. Although hyperglycemia should raise the possibility of diabetic ketoacidosis, the absence of an elevated serum glucose does not exclude the possibility of euglycemic diabetic ketoacidosis,⁶⁶ or alcoholic or starvation ketoacidosis, which are often associated with normal or even low serum glucose concentrations. An elevated BUN and creatinine are essential to diagnose acute or chronic kidney failure.
2. Proceed to the urinalysis. Do not wait for the laboratory results because all of these urinary studies are easily performed. In addition, if there is a suspicion of a high anion gap metabolic acidosis and only the arterial or venous blood gas analysis is completed, the evaluation may begin here while the electrolyte determination is pending. A urine dipstick for glucose and ketones helps with the diagnosis of diabetic ketoacidosis and other ketoacidoses. However, the absence of urinary ketones does not exclude a diagnosis of alcoholic ketoacidosis ([Chap. 80](#)), and ketones are often present in severe salicylism ([Chap. 39](#)) and biguanide-associated metabolic acidosis ([Chap. 53](#)). The urine of a patient who has ingested fluorescein-containing antifreeze (ethylene glycol) may fluoresce when exposed to a Wood lamp. Also, because ethylene glycol is metabolized to oxalate, calcium oxalate crystals may be present in the urine of a poisoned patient. Although the presence of a fluorescent urine and calcium oxalate crystals are useful findings, their absence does not exclude ethylene glycol poisoning ([Chap. 109](#)). When clinically available, a urine ferric chloride test should be performed. Although highly sensitive and specific for the presence of salicylates, this test is not specific for the diagnosis of salicylism because small amounts of salicylate will be detected in the urine even days after its last use ([Chap. 39](#)). Thus, a serum salicylate concentration must be obtained to quantify the findings of a positive urine ferric chloride test result. A negative urine ferric chloride test result essentially excludes a diagnosis of salicylism.
3. A blood lactate concentration can be helpful. In theory, if the lactate (measured in mEq/L) can entirely account for the fall in serum $[\text{HCO}_3^-]$, then the cause of the high anion gap can be attributed to lactic acidosis. However, it is important to remember that glycolate (a metabolite of ethylene glycol) can produce a false-positive elevation of the lactate concentration with many current laboratory techniques.^{91,139}

When the above analysis of a high anion gap metabolic acidosis is nondiagnostic, the diagnosis is usually toxic alcohol ingestion, starvation, alcoholic ketoacidosis (with minimal urine ketones), or a multifactorial process involving small amounts of lactate and other anions. One approach is to provide the patient with 1 to 2 hours of intravenous (IV) hydration, dextrose, and thiamine. If the acidosis improves, the etiology is either ketoacidosis or metabolic acidosis with hyperlactatemia. In the absence of improvement, a more detailed search for the toxic alcohols, involving measurement of either the osmol gap or actual methanol and ethylene glycol concentrations, should be initiated (discussed later).

The Δ Anion Gap-to- $\Delta[\text{HCO}_3^-]$ Ratio

Many patients have mixed acid–base disorders such as metabolic acidosis and respiratory alkalosis. Depending on the relative effects of the acid–base disorders, the patient may have significant acidemia or alkalemia, minor alterations in pH, or even a normal pH. Although the clinical presentation, degree of compensation for the primary acid–base disorder, or the presence of unexpected electrolyte abnormalities may suggest whether more than one primary acid–base disorder is present, comparing the Δ anion gap (ΔAG) with the $\Delta[\text{HCO}_3^-]$ gap may be useful.

In a patient with a simple high anion gap metabolic acidosis, each 1 mEq/L decrease in the serum $[\text{HCO}_3^-]$ should (at least initially) be associated with a 1 mEq/L rise in the anion gap.⁹⁷ This occurs because the unmeasured anion is paired with the acid that is titrating the HCO_3^- . Any deviation from this direct relationship may be an indication of a mixed acid–base disorder.^{53,97,102} Thus, the ratio of the change in the anion gap (ΔAG) to the deviation of the serum $[\text{HCO}_3^-]$ from normal (Equation 19–4) evolved:

$$\text{Anion Gap Ratio} = \Delta\text{AG}/\Delta[\text{HCO}_3^-] \quad (\text{Eq. 19–4})$$

A ratio close to one would suggest a pure high anion gap metabolic acidosis. When the ratio is greater than one, there is a relative increase in $[\text{HCO}_3^-]$ that can result only from a concomitant metabolic alkalosis or renal compensation such as renal generation of HCO_3^- for a respiratory acidosis. Alternatively, when the ratio is less than one, the additional presence of either hyperchloremic (normal anion gap) metabolic acidosis or compensated respiratory alkalosis is suggested. Although the usefulness of this relationship has been supported strongly by some authors,^{100,102} others suggest that it is often flawed and frequently misleading.^{30,115}

After reviewing the arguments, the statements of one author³⁰ appear to be correct in concluding that “the exact relationship between the ΔAG and $\Delta[\text{HCO}_3^-]$ in a high anion gap metabolic acidosis is not readily predictable and deviation of the $\Delta\text{AG}/\Delta[\text{HCO}_3^-]$ ratio from unity does not necessarily imply the diagnosis of a second acid–base disorder.” Regardless, very large deviations from a value of one usually are associated with the presence of a second primary acid–base disorder.

The Osmol Gap

The osmol gap, which is sometimes used to screen for toxic alcohol ingestion, is defined as the difference between the values for the measured serum osmolality and the calculated serum osmolarity. Osmolarity is a measure of the total number of particles in 1 liter of solution. Osmolality differs from osmolarity in that the number of particles is expressed per kilogram of solution. Thus, osmolarity and osmolality represent molar and molal concentrations of solutes, respectively. In clinical medicine, whereas osmolarity is usually calculated, osmolality is usually measured.

Calculating osmolarity requires a summing of the known particles in solution. Because molarity and milliequivalents are particle-based measurements, unlike weight or concentration, the known constituents of serum have to be converted to molar values. Assumptions are required based on the extent of dissociation of polar compounds (eg, NaCl), the water content of serum, and the contributions of various other solutes such as Ca^{2+} and Mg^{2+} . The nature and limitations of these assumptions are beyond the scope of this chapter. Readers are referred to several reviews for more details.^{59,101} Many equations have been used and evaluated for calculating serum osmolarity. One investigation that used 13 different methods to evaluate sera from 715 hospitalized patients³² concluded that Equation 19–5 provided the most accurate calculation:

$$1.86([\text{Na}^+] \text{ in mEq/L}) + ([\text{Glucose}] \text{ in mg/dL}/18) + ([\text{BUN}] \text{ in mg/dL}/2.8) \quad (\text{Eq. 19–5})$$

Obvious sources of potential error in this calculation include laboratory error in determining the measured parameters and the failure to account for a number of osmotically active particles.

The measurement of serum osmolality has the potential for error stemming from the use of different laboratory

techniques.³⁵ It is essential to assure that the freezing point depression technique or osmometry is used because when the boiling point elevation method is used, xenobiotics with low boiling points (ethanol, isopropanol, methanol) will not be detected.

Conceptual errors may also result. In methanol poisoning, the methanol molecule has osmotic activity that is measured but not calculated, and no increase in the anion gap is present until it is metabolized to formate. Although the metabolite also has osmotic activity, its activity is accounted for by Na^+ in the osmolarity calculation because it is largely dissociated, existing as Na^+ formate. Thus, shortly after a ethylene glycol ingestion, there will be an elevated osmol gap and a normal anion gap; later, the anion gap will increase, and the osmol gap will decrease. This effect is highlighted by several case reports.^{9,26}

Using Equation 19–5 to calculate osmolarity, it is often stated that the “normal” osmol gap is 10 ± 6 mOsm/L.³² However, when more than 300 adult samples were studied with a more commonly used equation (Eq. 19–6),

$$2([\text{Na}^+] \text{ in mEq/L}) + ([\text{Glucose}] \text{ in mg/dL}/18) + ([\text{BUN}] \text{ in mg/dL}/2.8) \quad (\text{Eq. 19-6})$$

normal values were -2 ± 6 mOsm/L.⁵⁹ Almost identical results are reported in children.⁸⁷

The largest limitation of the osmol gap calculation is due to the documented large standard deviation around a small “normal” number.^{32,59} An error of 1 mEq/L ($<1.0\%$) in the determination of the serum $[\text{Na}^+]$ may result in an error of 2 mOsm/L in the calculation of the osmol gap. Considering this variability, the molecular weights (MWs) and relatively modest serum concentrations of the xenobiotics in question (eg, ethylene glycol; MW, 62 Da; at a concentration of 50 mg/dL theoretically contributes only 8.1 mOsm/L) and the predicted fall in the osmol gap as metabolism occurs, small or even negative osmol gaps can never be used to exclude toxic alcohol ingestion.⁵⁹ This overall concept is illustrated by an actual patient with an osmol gap of 7.2 mOsm (well within the normal range) who ultimately required hemodialysis for severe poisoning.¹²⁷ An additional error may result when including ethanol in the determination of the osmol gap. When present, ethanol is osmotically active and should be included in the calculated osmolarity. In theory, because the MW of ethanol is 46 g/mol, dividing the serum ethanol concentration (in mg/dL) by 4.6 will yield the osmolar contribution in mmol/L. However, because the physical interaction of ethanol with water is complex, it may be more scientifically accurate to divide by lower numbers as the ethanol concentration increases.¹⁰⁶ However, because the osmol gap is a screening tool, we suggest continuing to use the 4.6 divisor in an attempt to reduce clinical false-negative test results.

Finally, although exceedingly large serum osmol gaps may be suggestive of toxic alcohol ingestions, common conditions such as alcoholic ketoacidosis, metabolic acidosis with elevated lactate, kidney failure, and shock are all associated with elevated osmol gaps.^{65,118,123} This may be surprising because lactate, acetoacetate, and β -hydroxybutyrate should not account for any increase in the osmol gap because they are charged (and accounted for in the osmolarity calculation). Apparently, these conditions are associated with the accumulation of small uncharged molecules in the serum.

Thus, although the negative and positive predictive values of the osmol gap are too poor to recommend this test to routinely screen for xenobiotic ingestion, the presence of very high osmol gaps (>50 – 70 mOsm/L) usually indicates a diagnosis of toxic alcohol ingestion (Chap. 109).

Differential Diagnosis of a Normal Anion Gap Metabolic Acidosis

Although the differential diagnosis of a normal anion gap metabolic acidosis is extensive (Table 19–4), most cases result from either urinary or GI HCO_3^- losses: renal tubular acidosis (RTA) or diarrhea, respectively. A number of xenobiotics also can cause this disorder, including toluene,²³ which also may cause a high anion gap metabolic acidosis. When the findings of the history and physical examination cannot be used to narrow the differential diagnosis, the use of a urinary anion gap is suggested.^{13,110}

The urinary anion gap can be calculated as shown in Equation 19–7:

$$([\text{Na}^+] + [\text{K}^+]) - [\text{Cl}^-] \quad (\text{Eq. 19-7})$$

The size of this gap is inversely related to the urinary ammonium (NH_4^+) excretion.⁵¹ As NH_4^+ elimination increases, the urinary anion gap narrows and may become negative because NH_4^+ serves as an unmeasured urinary cation and is accompanied predominantly by Cl^- .

The normal anion gap metabolic acidosis associated with diarrhea results from HCO_3^- loss. During this process, the kidney’s ability to eliminate NH_4^+ is undisturbed; in fact, it increases as a normal response to the acidemia. Thus, with GI HCO_3^- losses the urinary anion gap should decrease and may become negative. By contrast, a patient with RTA has lost the

ability to either reabsorb HCO_3^- (type 2 RTA) or increase NH_4^+ excretion in response to metabolic acidosis (types 1 and 4 RTA) and the urinary anion gap should become more positive. Indeed, when the urinary anion gap was calculated in patients with diarrhea or RTA, it was found that patients with diarrhea had a mean negative gap (-20 ± 5.7 mEq/L) compared with a positive gap (23 ± 4.1 mEq/L) in those with RTA.⁵¹ Therefore, when evaluating the patient with a normal anion gap metabolic acidosis, the determination of a urinary anion gap may help to determine the source of the disorder.

Adverse Effects of Metabolic Acidosis

The acuity of onset and severity of metabolic acidosis determine the consequences of this disorder. Acute metabolic acidosis is usually characterized by obvious hyperventilation (caused by respiratory compensation). At arterial pH values less than 7.20, cardiac and central nervous system abnormalities may become evident. These may include decreases in blood pressure and cardiac output, cardiac dysrhythmias, and progressive obtundation.^{1,2} Chronic metabolic acidosis may not manifest clinical symptoms. The symptoms of anorexia and fatigue may be the only manifestations of chronic acidosis, and compensatory hyperventilation may be undetectable. Because the consequences of even severe metabolic acidosis are not specific, the presence of metabolic acidosis is most often suggested by the history and physical examination.

Management Principles in Patients with Metabolic Acidosis

The treatment of metabolic acidosis depends on its severity and cause. Most cases of severe poisoning, with a serum $[\text{HCO}_3^-]$ concentration less than 8 mEq/L and an arterial pH value less than 7.20 should probably be treated with HCO_3^- to increase the pH to greater than 7.20, as described in detail elsewhere.^{1,2} As an example, to raise the serum $[\text{HCO}_3^-]$ by 4 mEq/L in a 70-kg person with an estimated HCO_3^- distribution space of 50% of body weight, approximately 140 mEq must be administered. When ECFV overload (caused by heart failure, kidney failure, or the sodium bicarbonate therapy itself) cannot be prevented or managed by administering loop diuretics, hemofiltration or hemodialysis may be necessary.

In patients with arterial pH values greater than 7.20, the cause of the acidosis should guide therapy. Metabolic acidosis primarily caused by the overproduction of acid, as in the case of ketoacidosis and toxic alcohol poisoning, requires very large quantities of HCO_3^- and may not respond well to sodium bicarbonate therapy. Treatment in these patients should be directed at the cause of acidosis (eg, insulin and IV fluids in diabetic ketoacidosis; fomepizole in methanol, ethylene glycol and DEG poisonings {Antidotes in Depth: A30} fluids, glucose, and thiamine in alcoholic ketoacidosis; fluid resuscitation, antibiotics, and vasopressors in sepsis-induced hyperlactatemia). Patients with metabolic acidosis primarily caused by underexcretion of acid (eg, acute or chronic kidney failure, RTA) should be treated with a low-protein diet (if feasible) and oral sodium bicarbonate or substances that generate HCO_3^- during metabolism. Such patients can usually be managed with an oral sodium citrate solution such as Shohl solution, which yields 1 mEq base/mL. The goal of therapy is to increase the serum $[\text{HCO}_3^-]$ to 20 to 22 mEq/L and the pH to 7.30.

METABOLIC ALKALOSIS

Adverse Effects of Metabolic Alkalosis

Life-threatening metabolic alkalosis is rare but can result in tetany (from decreased ionized $[\text{Ca}^{2+}]$); weakness (from decreased serum $[\text{K}^+]$); or altered mental status leading to coma, seizures, and cardiac dysrhythmias. In addition, metabolic alkalosis shifts the oxyhemoglobin dissociation curve to the left, impairing tissue oxygenation (Chap. 29). The expected compensation for a metabolic alkalosis is hypoventilation and increased PCO_2 . As discussed before, respiratory compensation is irregular and inadequate at best, invoking the teleologic argument that hypoxia is more undesirable than alkalemia.⁹⁷ Several authors, however, have reported that severe hypoventilation and respiratory failure can occur in response to metabolic alkalosis, suggesting an actual, although uncommon, risk.¹⁰³

Approach to the Patient with Metabolic Alkalosis

Metabolic alkalosis results from GI or urinary loss of acid, administration of exogenous base, or renal HCO_3^- retention (ie, impaired renal HCO_3^- excretion). Table 19–5 lists the causes of metabolic alkalosis. Compared with metabolic acidosis, metabolic alkalosis is less common and less frequently a consequence of xenobiotic exposure.

TABLE 19–5. Xenobiotic and Other Causes of Metabolic Alkalosis

<i>Gastrointestinal Acid Loss</i>	<i>Urinary Acid Loss</i>	<i>Base Administration</i>	<i>Renal Bicarbonate Retention</i>
Nasogastric suction (protracted)	Common	Acetate (dialysis or hyperlimentation)	Hypercapnia (chronic)
Vomiting	Diuretics	Bicarbonate	Hypochloremia
	Glucocorticoids	Carbonate (antacids)	Hypokalemia
	Rare	Citrate	Volume contraction
	Hypercalcemia	(posttransfusion)	
	Licorice (containing glycyrrhizic acid)	Milk alkali syndrome	
	Magnesium deficiency		

The etiologies of metabolic alkalosis can be characterized from a therapeutic standpoint as chloride responsive or chloride resistant. Chloride-responsive etiologies such as diuretic use, vomiting, nasogastric suction, and Cl^- diarrhea are usually associated with a urinary $[\text{Cl}^-] < 10 \text{ mEq/L}$.⁵⁶ Patients with these disorders respond rapidly to infusion of 0.9% NaCl solution when concomitant therapy addresses the underlying problem.^{1,2} Chloride-resistant disorders exemplified by hyperaldosteronism and severe K^+ depletion are characterized by urinary $[\text{Cl}^-] > 10 \text{ mEq/L}$ and tend to be resistant to 0.9% NaCl solution therapy.^{46,56} Patients with these disorders often require K^+ repletion or drugs that reduce mineralocorticoid effects, such as spironolactone, before correction can occur.⁴⁶ When 0.9% NaCl solution repletion is ineffective or emergent correction of the alkalosis is required, some authors have suggested infusions of lysine or arginine HCl or dilute HCl.^{1,2} However, this technique is rarely necessary.

XENOBIOTIC-INDUCED AND OTHER ALTERATIONS OF WATER BALANCE

Significant fluid abnormalities commonly occur in the setting of xenobiotic exposure. GI losses in the form of vomiting, diarrhea, GI hemorrhage, and third spacing such as from GI burns result from a variety of xenobiotic toxicities and their management with emetics and cathartics. Renal fluid losses result from the ability of many xenobiotics to increase the glomerular filtration rate (inotropes), impair Na^+ reabsorption (diuretics), or enhance urine volume in response to an obligate solute load (salicylates). Fluid losses also may occur through the skin as a result of sweating (sympathomimetics, cholinergics, and uncouplers of oxidative phosphorylation) or the lung as a result of increased minute ventilation (salicylates and sympathomimetics) or bronchorrhea (cholinergics). To the extent that these lost fluids contain Na^+ , various signs, symptoms, and laboratory evidence of ECFV depletion may be present.

The diagnosis and treatment of abnormal serum electrolyte concentrations are usually addressed after repletion of the ECFV deficit with isotonic, Na^+ -containing fluids (eg, blood products, 0.9% NaCl solution, lactated Ringer solution). Other fluid balance issues are discussed in Chaps. 17 and 28 and in chapters relating to individual xenobiotics. This section focuses on body water balance (abnormalities of which manifest as hypernatremia and hyponatremia) and specifically on the toxicologically relevant syndromes of DI and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Sodium concentration in the extracellular space is intrinsically related to and directly reflects total body water balance. This occurs because the sodium cation is largely restricted to the extracellular space, and its serum concentration is primarily, if indirectly, controlled by factors that control water balance. Thus, both the serum $[\text{Na}^+]$ and plasma osmolality vary inversely with changes in the quantity of body water.

Plasma osmolality is maintained through a complex interaction between dietary water intake; the hypothalamus, pituitary gland, and kidney; and the effects of hormones such as arginine vasopressin (ADH) and adrenal mineralocorticoids.^{15,18,99,135} Briefly, changes in osmolality are caused by changes in water intake and insensible (dermal, respiratory, and stool) and sensible (urinary, sweat) water losses. Urinary water losses are controlled by ADH. Increases in the osmolality of the extracellular fluid (ECF) stimulate anterior hypothalamic osmoreceptors, thereby stimulating thirst and ADH synthesis and release by the posterior pituitary gland. ADH release reaches its maximum concentration at a plasma osmolality of about 295 mOsm/kg. ADH is transported to the kidney via the bloodstream, where it stimulates the synthesis of cyclic adenosine monophosphate (cAMP). cAMP increases the water permeability of the distal convoluted tubule and collecting duct by overstimulating the insertion of aquaporin channels in the apical membrane, increasing water reabsorption and urine concentration, and minimizing urinary water losses. Conversely, as plasma osmolality falls, thirst and ADH release are diminished. This results in decreased renal cAMP generation, decreased water permeability of the distal convoluted tubule and collecting duct, and excretion of a relatively dilute urine that ultimately corrects the body water excess. Marked alterations in water intake combined with perturbations of these various processes often lead to

hypernatremia or hyponatremia.

Hypernatremia

Table 19–6 summarizes the xenobiotics that cause hypernatremia. Hypernatremia may be caused by the parenteral administration of sodium-containing drugs or rapid and excessive oral Na⁺ intake.³ Oral NaCl and oral sodium citrate were once used as emetics and antiemetics, respectively. As might be expected, they produced severe hypernatremia.¹⁸ One case of fatal hypernatremia resulted from gargling with a supersaturated NaCl solution.⁹⁰ Similarly, massive ingestion of sodium hypochlorite bleach was associated with hypernatremia.¹¹³

TABLE 19–6. Xenobiotic Causes of Hypernatremia

<i>Sodium Gain</i>	<i>Water Loss</i>	<i>Water Loss Due to Diabetes Insipidus</i>
Antacids sodium bicarbonate	Cholestyramine	α-Adrenergic antagonists
Sodium salts (acetate, bicarbonate, chloride, citrate, hypochlorite)	Diuretics	Amphotericin
Seawater	Lactulose	Antivirals: abacavir, adefovir, cidofovir, tenofovir
	Mannitol	Colchicine
	Povidone-iodine	Demeclocycline
	Sorbitol	Ethanol
	Urea	Foscarnet
		Glufosinate
		Ifosfamide
		Lithium
		Lobenzarit disodium
		Methoxyflurane
		Mesalazine
		Minocycline
		Opioid antagonists
		Propoxyphene
		Rifampin
		Streptozotocin
		V ₂ -receptor antagonists: conivaptan, tolvaptan
		Valproic acid

More commonly, hypernatremia results from relatively electrolyte-free (hypotonic) water losses due to xenobiotics or conditions that cause urinary, GI, and dermal fluid losses.³ Indeed, all fluid losses from the body, except hemorrhage and those from fistulas, are hypotonic (and have the potential to cause hypernatremia). The lack of adequate fluid replacement is a key element in the development of hypernatremia because even the large fluid losses caused by DI or cholera-induced diarrhea will not cause hypernatremia if they are adequately replaced. Thus, in patients with hypernatremia caused by fluid losses, the reason why the losses were not replaced by the patient should always be sought.

Xenobiotics that produce significant diarrhea, such as lactulose, can cause hypernatremia through unreplaced stool water losses. A similar pathogenesis accounts for the hypernatremia caused by the polyethylene-containing solution used for bowel preparation for colonoscopy.¹² Of particular concern is the use of cathartics in the management of poisonings, especially when fluid losses are not anticipated. For example, multiple doses of sorbitol can produce severe hypernatremic dehydration and death in both children and adults.^{21,38,48,136}

Significant water loss also can occur through the skin. Although diffuse diaphoresis resulting from cocaine or organic phosphorus insecticide toxicity has the potential to produce hypernatremia, this rarely, if ever, occurs. However, application of a remedy containing hyperosmolar povidone–iodine to the skin of burned patients may produce significant water losses and hypernatremia.¹²⁰

Diagnosis and Treatment. The symptoms of significant hypernatremia consist largely of altered mental status ranging from confusion to coma and neuromuscular weakness that occasionally results in respiratory paralysis. If hypernatremia is associated with Na⁺ losses and marked ECFV depletion, cardiovascular symptoms, tachycardia, and orthostatic

hypotension may be present. Treatment consists of first replacing the Na^+ deficit (with isotonic fluids such as 0.9% NaCl solution), if present, and then replacing the water deficit. The water deficit may be estimated by assuming that the fractional increase in serum $[\text{Na}^+]$ is equal to the fractional decrease in total body water. Thus, a serum $[\text{Na}^+]$ that has increased by 10% (from 144 mEq/L–158 mEq/L) indicates that the water deficit is 10% (3.6 L in a 60-kg person with 36 L of body water).

When the hypernatremia develops over several hours, for example, as occurs after ingestion or administration of a sodium salt, rapid correction is indicated. However, when hypernatremia develops over several days or when the duration is unknown, slow correction of hypernatremia (over several days) is recommended.³ The adaptation of brain cells to the water deficit (including the gain of intracellular solute including K^+ , Na^+ , inositol, glutamate, taurine, and creatine) makes cerebral edema a frequent complication of rapid water replacement. Although some sources suggest that 0.9% NaCl solution is an appropriate replacement fluid regardless of the magnitude of the water deficit, more recent emphasis has been on the use of hypotonic fluids to correct hypernatremia in the absence of a significant sodium deficit.³

Diabetes Insipidus

The greatest water losses and therefore the potentially most severe cases of hypernatremia occur during DI, which is always characterized by greater or lesser degrees of hypotonic polyuria. DI may be neurogenic, resulting from failure to sense a rising osmolality or from a failure to release ADH, or nephrogenic, resulting from failure of the kidney to respond appropriately to ADH. Although there are many nontoxicologic causes of DI (eg, trauma, tumor, sarcoidosis, vascular, and congenital), xenobiotic-induced DI is also common and may be mediated through either central or peripheral mechanisms.

Ethanol, opioid antagonists, and α -adrenergic agonists all suppress ADH release.^{94,95} Lithium,^{79,122} demeclocycline,¹²¹ methoxyflurane,⁸³ propoxyphene, foscarnet,⁹⁸ mesalazine,⁸¹ streptozotocin, amphotericin,⁶¹ glufosinate,¹³⁰ lobenzarit,¹¹⁴ rifampin,¹⁰⁷ and colchicine¹³⁵ are associated with nephrogenic DI (Table 19–6). In addition, nephrogenic DI may be caused by severe hypokalemia from diuretic use and hypercalcemia from vitamin D poisoning.¹³⁵ Of all of these xenobiotics, lithium has been the most extensively evaluated. Although polyuria is a common finding with lithium therapy (occurring in 20%–70% of patients on maintenance therapy), the exact incidence of DI and hypernatremia is unknown. Estimates range from 10% to 20% to as high as 80%.

Diagnosis. Patients with DI complain of polyuria and polydipsia. Urine volumes typically exceed 30 mL/kg/d¹³⁵ and may be as high as 9 L/d with nephrogenic DI⁷⁹ and 12 to 14 L/d with neurogenic (central) DI.⁹⁵ Nocturia, fatigue, and decreased work performance are often noted.¹³⁵ Neurogenic DI resulting from hypothalamic or pituitary damage is typically associated with other signs of neuroendocrine dysfunction.⁹⁵

After polyuria is confirmed (eg, in adults, by measuring a urine output >200 mL over one hour), the urine osmolality or specific gravity should be measured. The diagnosis of DI is established by the occurrence of dilute urine (urine osmolality <300 mOsm/kg, urine specific gravity <1.010) in the presence of increased serum $[\text{Na}^+]$ and a serum osmolality greater than 295 mOsm/kg.¹³⁵ After this determination, a trial of desmopressin, an arginine vasopressin analog, helps to differentiate between neurogenic and nephrogenic DI. If the etiology of the DI is neurogenic, the patient will promptly respond to desmopressin with a decrease in urine output and increase in urine osmolality. In nephrogenic DI, desmopressin will have no significant effect.

Treatment. The initial approach to a hypernatremic patient with DI involves the repletion of the water deficit (as described earlier) and the restoration of electrolyte depletion, if necessary. If a reversible cause for the DI can be established, it should be corrected. Specifically, xenobiotics implicated as the cause of DI should be discontinued or their dose reduced. Patients with neurogenic DI should be maintained on either vasopressin or desmopressin. The latter is preferred because of the lack of vasopressor effects and ease of administration. In the past, patients were occasionally treated with oral medications known to produce SIADH (see later). Patients with nephrogenic DI can be treated with thiazide diuretics,³³ prostaglandin inhibitors,^{29,77} or amiloride, all of which reduce the urine flow rate.¹⁴

Hyponatremia

Hyponatremia may be associated with a high, normal, or low serum osmolality. Patients with myeloma or severe hyperlipidemia may exhibit artifactual hyponatremia whenever the measurement technique requires dilution of the serum sample rather than direct measurement by a sodium electrode. These patients have a normal serum osmolality and no symptoms related to their artifactual hyponatremia, and they require no therapy.

Hyperglycemic patients develop hyponatremia because the increase in plasma osmolality caused by hyperglycemia results in a water shift from the intracellular to the extracellular space. The reduction in serum $[\text{Na}^+]$, which may cause symptoms, is approximately 1.6 mEq/L for every 100 mg/dL increase in serum glucose concentration above normal. The contribution of hyperglycemia to the hyponatremia should be calculated to determine if other causes of hyponatremia should also be sought. All other causes of hyponatremia are associated with a low plasma osmolality. In fact, in the absence of

myeloma, hyperlipidemia, and hyperglycemia, the serum osmolality need not be measured in hyponatremic patients and may be assumed to be low.

Hyponatremia associated with a low plasma osmolality usually results from water intake in excess of the renal capacity to excrete it. When renal water excretion is normal, very large intake is required to cause hyponatremia. Usually such large quantities of water are ingested over a short period of time by people with psychiatric or neurologic disorders such as psychogenic polydipsia.^{50,111} Xenobiotic-induced water excess comparable to psychogenic polydipsia is quite uncommon. An example occurs during urologic procedures, such as transurethral resection of the prostate (TURP), in which large volumes of irrigation solution are required. Because the wounds are electrically cauterized, these fluids cannot contain conductive electrolytes such as sodium. Sorbitol, dextrose, and mannitol were tried as irrigation solutions in an attempt to maintain a normal osmolality, but their optical characteristics were undesirable during the surgery. Thus, irrigation during TURP is performed with glycine-containing solutions. If a large volume of 1.5% glycine (osmolality, 220 mOsm/kg) is absorbed through the prostatic venous plexus, a rapid reduction in serum $[Na^+]$ may result and will persist until the glycine is metabolized.^{58,89} Symptoms in these patients are probably a result of several factors: hyponatremia, the glycine itself, and NH_3 , a glycine metabolite. A similar complication has also been described during hysteroscopy.¹⁰⁴

Rarely, hyponatremia results from the loss of a body fluid with a $[Na^+]$ greater than the ECF $[Na^+]$ (of 154 mEq/L). This may occur in patients with adrenal insufficiency through hypertonic urinary losses (although increased ADH secretion as a consequence of ECF sodium depletion is probably a more important mechanism; see later discussion). In burn patients, Na^+ may be lost directly from the ECF. When treated with topical applications of silver nitrate cream, hyponatremia may develop from the diffusion of sodium through permeable skin into the hypotonic dressing.²⁴ Ingestion of licorice that contains glycyrrhizic acid produces a syndrome of hyponatremia, hypokalemia, and hypertension that resembles mineralocorticoid excess. Although the exact mechanism of hyponatremia is debated, one report suggested that a glycyrrhizic acid–induced reduction in 11- β -hydroxysteroid dehydrogenase activity could account for the findings.³⁷ Lithium, which is usually associated with DI and hypernatremia, has been reported to cause renal sodium wasting and hyponatremia that seems to be unrelated to ADH effects.⁸⁸

Most cases of hyponatremia are caused by water intake in excess of a reduced renal excretory capacity. This reduction in urinary water excretion may be physiologic (as during ECF sodium depletion) or pathologic (in association with kidney, heart, or liver failure).⁴ Because these conditions are accompanied by alterations in renal sodium handling, signs and symptoms of ECFV depletion, such as postural hypotension, or ECFV excess, such as edema, usually accompany the hyponatremia. Other patients cannot excrete water normally because malignancy or various brain or pulmonary diseases cause ADH secretion.⁴ In some cases, the tumors are associated with paraneoplastic disease and directly secrete ADH. Xenobiotics, such as diuretics, may cause ECFV depletion, but most directly stimulate ADH secretion or augment the renal effects of ADH. Drugs such as the thiazide diuretics cause hyponatremia by several mechanisms, including interference with maximal urinary dilution, and by ADH-induced water retention in response to decreased ECFV.^{4,40} Patients with excess secretion or action of ADH who have near-normal ECFV have SIADH. Table 19–7 summarizes these and other causes of hyponatremia.

TABLE 19–7. Xenobiotic and Other Causes of Hyponatremia

Angiotensin-converting enzyme inhibitors
Arginine
Diuretics
Glycine (transurethral prostatectomy syndrome)
Licorice (containing glycyrrhizic acid)
Lithium
Nonsteroidal antiinflammatory drugs
Primary polydipsia
SIADH
Silver nitrate
Amiloride

Amiodarone
Amitriptyline (and other cyclic antidepressants)
Antipsychotics
Atomoxetine
Biguanides (metformin and phenformin)
Bortezomib
Carbamazepine (and oxcarbamazepine)
Cisplatin (and other platinum chemotherapeutics)
Clofibrate
Cyclophosphamide
Desmopressin (DDAVP)
Diazoxide
Duloxetine
Hallucinogenic amphetamines, MDMA (methylenedioxymethamphetamine),
methylenedioxymethamphetamine,
methylenedioxymethamphetamine
ethcathinone
Nicotine
Opioids
Oxytocin
Selective serotonin reuptake inhibitors
Sibutramine
Sulfonylureas
Tramadol
Tranylcypromine
Valproate
Vasopressin
Vincristine and vinblastine

SIADH

SIADH is characterized by hyponatremia and plasma hypotonicity in the absence of abnormalities of ECFV, adrenal, thyroid, or kidney. Early reviews claimed that SIADH was a disorder of volume overload based largely on evidence of weight gain.⁹⁴ The consistent absence of edema, however, and the fact that the decrease in serum $[\text{Na}^+]$ cannot be accounted for by the fluid gain (weight gain) suggest that water retention is only part of the mechanism.⁷³ Urinary Na^+ loss and Na^+ redistribution from the extracellular to the intracellular space is apparently important as well.

There are many nontoxicologic etiologies of SIADH, most of which result from pulmonary or intracranial pathology. These causes include infections, malignancies, and surgery.^{4,73,95} Table 19–7 summarizes xenobiotics known to produce

SIADH. The antidiabetics, including drugs from both the sulfonylurea (eg, chlorpropamide) and biguanide (eg, metformin) classes, produce hyponatremia more commonly than other drugs.⁹³ Their actions are multifactorial and can include both the potentiation of endogenous ADH and the stimulation of ADH release.⁹³ Many psychiatric medications, including the selective serotonin reuptake inhibitors, cyclic antidepressants, and antipsychotics, are implicated in causing SIADH.^{71,78,126,133} The effects of these drugs may be mediated by the complex interactions between the dopaminergic and noradrenergic systems that control ADH release.¹²⁶ Additional evidence supports a role of serotonin in drug-induced SIADH. Serotonin (specifically 5-HT₂ or 5-HT_{1C} agonism) directly stimulates ADH release¹⁰ and water intake.⁶³ An important role of serotonin is supported by the occurrence of SIADH with MDMA use.⁶²

Diagnosis. The clinical presentation of patients with hyponatremia depends on the cause, the absolute serum [Na⁺], and the rate of decline in serum [Na⁺]. Patients with associated ECFV excess or depletion present with evidence of altered ECFV, as well as signs and symptoms of the disease that caused the abnormality in ECFV, such as adrenal insufficiency or heart failure.⁴ Rarely do these patients exhibit symptoms of hyponatremia and hyposmolality of body fluids per se. This may be because of the moderate degree of hyponatremia (>130 mEq/L) or the moderate rate of decline in [Na⁺] or because the loss of Na⁺ and water limits the development of cerebral edema.⁷⁶ It is important to note that patients with hyponatremia and a low plasma osmolality (excluding those with primary polydipsia) all have a urinary osmolality that is relatively high regardless of whether they have excess, diminished, or normal ECFV. Consequently, these disorders can only be differentiated by the history, physical examination, and other laboratory test results.

Patients with SIADH, if symptomatic, usually present with signs and symptoms of hyponatremia. As noted earlier, the clinical manifestations of hyponatremia are dependent on both the absolute serum [Na⁺] and its rate of decline.^{76,95} Whereas chronic, slow depression of the [Na⁺] is usually well tolerated, rapid decreases may be associated with symptoms and sometimes catastrophic events. Symptoms include headache, nausea, vomiting, restlessness, disorientation, depression, apathy, irritability, lethargy, weakness, and muscle cramps. In more severe cases, respiratory depression, coma, and seizures may develop.

The diagnosis of SIADH is based on establishing the presence of hyponatremia, a low serum osmolality, and impaired urinary dilution in the absence of edema, hypotension, hypovolemia, and kidney, adrenal, or thyroid dysfunction.⁷³ As discussed earlier, the presence of any of these clinical findings suggests that another cause of hyponatremia may be present. A serum uric acid concentration may be helpful in differentiating SIADH from other causes of hyponatremia. In the presence of hyponatremia and impaired urinary dilution, patients with SIADH have hypouricemia, but patients exhibiting ECFV excess or depletion characteristically have hyperuricemia.²⁷

Treatment. Treatment of patients with demonstrable ECFV excess or depletion should be directed at the abnormal ECFV and its cause rather than the hyponatremia. In almost all cases, the hyponatremia will improve with correction of the ECFV.^{4,76} In a similar way, correction of the serum glucose in hyperglycemic patients and the removal of glycine by hemodialysis in patients with the TURP syndrome will correct the serum [Na⁺]. The rate of correction of the serum [Na⁺] in these patients is generally not of concern.

In patients with SIADH, treatment begins with fluid restriction. Because the goal of this therapy is to establish a negative fluid balance, careful attention to intake and output is required. If an offending xenobiotic can be identified, it should be discontinued. Although most cases resolve in 1 to 2 weeks,^{73,95} SIADH caused by chronic cerebral or pulmonary conditions or by malignancy often persists. If this occurs, therapy with demeclocycline, lithium, or tolvaptan may be helpful because severe fluid restriction is often intolerable. Tolvaptan, an oral ADH antagonist with specificity for the V₂ receptor, is currently the recommended treatment for chronically hyponatremic patients in whom fluid restriction is unsuccessful because it is easier to titrate with fewer potential side effects than demeclocycline and lithium. In all asymptomatic or mildly symptomatic patients (usually patients with chronic hyponatremia of more than 2 days' duration), correction should proceed slowly and certainly at a rate less than 0.5 mEq/L/h during the first 48 hours. This is because if the correction of hyponatremia is faster than the reuptake of the solutes (K⁺, Na⁺, inositol, glutamate, taurine, and creatine) extruded from brain cells during the development of hyponatremia, brain shrinkage will occur with breaching of the blood–brain barrier. This effect may cause osmotic demyelination syndrome (ODS). ODS, which is associated with central pontine and extrapontine myelinolysis, may have a delayed onset of 2 to 6 days and causes irreversible brain damage and death in 50% and 15% of patients, respectively.^{4,11,128} Risk factors for ODS, in addition to too rapid correction of chronic hyponatremia, include serum [Na⁺] below 115 mEq/L and patients who are elderly, hypokalemic, alcoholic, or malnourished. In asymptomatic patients, as described earlier, water restriction is recommended and usually sufficient, but occasionally tolvaptan may be appropriate. When hyponatremia is associated with life-threatening clinical presentations, including respiratory depression, altered mental status, seizures, or coma, careful infusion of hypertonic 3% saline ([Na⁺] = 513 mEq/L) (eg, 1–2 mL/kg/h), with or without furosemide, is indicated.^{4,73} Alternatively, conivaptan (an ADH V₁ and V₂ receptor antagonist) may be administered intravenously as an initial bolus of 20 mg followed by a continuous infusion of 40 mg/d for no more than 4 days.^{55,57} In these symptomatic patients, the goal is to increase the serum [Na⁺] 1 mEq/L/h (5–6

mEq/L over 6 hours) or until the symptoms abate.^{4,76} After this initial correction and amelioration of symptoms, the serum [Na⁺] should be increased at a rate less than 0.5 mEq/L/h, preferably by water restriction alone. Formulas are available to help calculate the rate of correction of hyponatremia.⁴ Equation 19–8 may be helpful.

When 1 L of fluid is infused:

$$\text{Change in serum [Na}^+ \text{]} = \frac{\text{infusate [Na}^+ \text{]} - \text{serum [Na}^+ \text{]}}{\text{Total body water} + 1 \text{ L}} \quad (\text{Eq. 19-8})$$

where the infusate [Na⁺] in mEq/L equals:

3% Sodium chloride	513
0.9% Sodium chloride	154
Lactated Ringer solution	130
0.45% Sodium chloride	77
0.33% Sodium chloride	56

XENOBIOTIC-INDUCED ELECTROLYTE ABNORMALITIES

Potassium

Xenobiotic-induced alterations in serum [K⁺] are potentially more serious than alterations in other electrolyte concentrations because of the critical role of potassium in a variety of homeostatic processes. Potassium balance is complex.^{20,105,117} The total-body potassium content of an average adult is about 54 mEq/kg, of which only 2% is located in the intravascular space. The large intracellular store of potassium is maintained by a variety of systems, the most important of which is membrane Na⁺-K⁺-adenosine triphosphatase (ATPase). The relationship between total body stores and serum [K⁺] is not linear, and small changes in the total body potassium may result in dramatic alterations in serum concentrations, and, more important, in the ratio of extracellular to intracellular [K⁺].

People eating a western diet ingest 50 to 150 mEq/d of potassium, approximately 90% of which is subsequently eliminated in the urine. The body has two major defenses against a potassium load: acutely, potassium is transferred into cells; chronically, potassium is excreted in the urine by decreased proximal tubular reabsorption and increased distal tubular secretion (to a maximum of 600–700 mEq/d).²⁰ After a meal, K⁺ transfers into intracellular space through insulin and catecholamine-mediated uptake of potassium in liver and muscle cells.¹¹² Renal potassium excretion is primarily modulated by the renin–angiotensin–aldosterone system. In addition, the GI absorption of potassium decreases as the serum [K⁺] increases.

Hypokalemia results from decreased oral intake, GI losses caused by repeated vomiting or diarrhea, urinary losses through increased K⁺ secretion or decreased reabsorption, and processes that shift potassium into the intracellular compartment.^{18,20,137} Table 19–8 summarizes the xenobiotics commonly associated with hypokalemia.

TABLE 19–8. Xenobiotic Causes of Altered Serum Potassium

<i>Hypokalemia</i>	<i>Hyperkalemia</i>
β-Adrenergic agonists	α-Adrenergic agonists (phenylephrine)
Aminoglycosides	β-Adrenergic antagonists
Amphotericin	Amiloride
Barium (soluble salts)	Angiotensin-converting enzyme inhibitors
Bicarbonate	Angiotensin receptor blockers
Caffeine	Arginine hydrochloride
Carbonic anhydrase inhibitors	Cardioactive steroids
Cathartics	Fluoride
Chloroquine	Heparin
Cisplatin	Nonsteroidal antiinflammatory drugs
Dextrose	Penicillin (potassium)
Hydroxychloroquine	Potassium salts
Infliximab	Spironolactone
Insulin	Succinylcholine
Licorice (containing glycyrrhizic acid)	Triamterene
Loop diuretics	Trimethoprim
Metabolic alkalosis	
Osmotic diuretics	
Quinine	
Salicylates	
Sodium penicillin and its analogs	
Sodium polystyrene sulfate	
Sulfonylureas	
Sympathomimetics	
Tenofovir	
Theophylline	
Thiazide diuretics	
Toluene	

The neuromuscular manifestations of hypokalemia are reviewed elsewhere.⁷² Patients with hypokalemia are often asymptomatic when the decrease in serum $[K^+]$ is mild (serum concentrations of 3.0–3.5 mEq/L). Occasionally, hypokalemia interferes with renal concentrating mechanisms, and polyuria is noted. More significant potassium deficits (serum concentrations of 2.0–3.0 mEq/L) cause generalized malaise and weakness. As the $[K^+]$ falls to less than 2 mEq/L, weakness becomes prominent, and areflexic paralysis and respiratory failure may occur, often necessitating intubation and mechanical ventilation.⁷² Rhabdomyolysis is also likely. These neuromuscular manifestations are so prominent that they may be erroneously attributed to a neuromuscular syndrome such as Guillain-Barré. Other clinical findings associated with hypokalemia include GI hypoperistalsis (ileus); manifestations of cardioactive steroid toxicity; worsening hyperglycemia in patients with diabetes; and the symptoms and signs of the metabolic abnormalities that often accompany hypokalemia such as hyponatremia, metabolic acidosis, or alkalosis.¹³⁷

Electrocardiographic changes also are common, even with mild potassium depletion, although the absence of ECG changes should never be used to exclude significant hypokalemia. Common ECG findings of hypokalemia include depression of the ST segment, decreased T-wave amplitude, and increased U-wave amplitude ([Chap. 16](#)). These findings may herald life-threatening rhythm disturbances.¹³⁷

Treatment of hypokalemia involves discontinuing or removing the offending xenobiotic and correcting the potassium deficit. Potassium supplementation may be given orally or intravenously. The choice of potassium salt should be based on the associated acid–base abnormality, if present. Thus, potassium chloride should be administered when metabolic alkalosis is present, and another salt of potassium (eg, potassium citrate or potassium bicarbonate) should be administered when metabolic acidosis is present.¹³⁷ Potassium phosphate should be considered part of the K^+ supplement when hypophosphatemia is present, as occurs in diabetic ketoacidosis, or when hyperchloremia is present. Hypomagnesemia, which may cause or accompany hypokalemia (eg, in diuretic-induced hypokalemia), must be corrected because this abnormality may prevent successful potassium replacement.

The debate over the maximum safe infusion rate for IV potassium is summarized elsewhere.^{75,137} Based on experience with more than 1300 infusions, one group concluded that under intensive care monitoring, IV administrations of 20 mEq/h (by central or peripheral vein) were well tolerated. They also found that each 20 mEq of potassium administered resulted in an average increase in serum $[K^+]$ of 0.25 mEq/L. Others have used significantly larger doses (up to 100 mEq/h) in life-threatening circumstances.²⁸

Hyperkalemia results from decreased urinary elimination (renal insufficiency, potassium-sparing diuretics, hypoaldosteronism), increased intake (either orally or intravenously), or redistribution from tissue stores.^{18,20} The last mechanism is of major toxicologic importance. Overdoses of both cardioactive steroids (Chap. 65) and β -adrenergic antagonists (Chap. 62) cause hyperkalemia by promoting net potassium release from intracellular reservoirs. Presumably because of other protective mechanisms, overdose with a β -adrenergic antagonist produces only a moderate rise in serum $[K^+]$ (usually to 5.0–5.5 mEq/L). By contrast, a similar rise in serum $[K^+]$ as a consequence of blockade of the Na^+-K^+ -ATPase pump during acute cardioactive steroid toxicity may be lethal (Chap. 65). This suggests that hyperkalemia per se is not the cause of the lethality of cardioactive steroid toxicity. Thus, the focus of therapy should involve efforts to neutralize or eliminate the cardioactive steroid rather than reduce the serum $[K^+]$.¹⁶ Table 19–8 lists xenobiotics that cause hyperkalemia.

After oral overdoses of potassium salts, patients usually complain of nausea and vomiting. Ileus, intestinal irritation, bleeding, and perforation may complicate the clinical course.^{116,117} In the absence of potassium ingestion, GI symptoms of hyperkalemia are usually very mild. Neuromuscular manifestations include weakness with an ascending flaccid paralysis and respiratory compromise, with intact sensation and cognition.^{72,85,105} The similarity of these signs and symptoms to those associated with hypokalemia is striking, suggesting that hyperkalemia may be diagnosed with certainty only by laboratory measurement.

The cardiac manifestations of hyperkalemia are distinct, prominent, and life threatening. ECG patterns progress through characteristic changes.¹¹⁶ Although the progression of ECG changes is very reproducible, there is great individual variation with respect to the serum $[K^+]$ at which these ECG findings occur. Initially, the only ECG finding may be the presence of tall, peaked T waves. As the serum $[K^+]$ concentration increases, the QRS complex tends to blend into the T waves, the P-wave amplitude decreases, and the PR interval becomes prolonged. Next, the P wave is lost, and ST-segment depression occurs. Finally, the distinction between the S and T waves becomes blurred, and the ECG takes on a sine wave configuration (Chap. 16). Hemodynamic instability and cardiac arrest can result. As the patient's serum $[K^+]$ falls with therapy, these ECG changes resolve in a reverse fashion.

The treatment of severe hyperkalemia focuses on methods to (1) reverse the ECG effects, (2) transfer K^+ to the intracellular space, and (3) enhance K^+ elimination. Pharmacologic interventions, extensively discussed elsewhere,¹¹⁷ are summarized here. Calcium salt (eg, 10–20 mEq administered intravenously) (Antidote in Depth: A29) works almost immediately to protect the myocardium against the effects of hyperkalemia, although it does not reduce the serum $[K^+]$. However, a potentially life-threatening interaction occurs when the patient with cardioactive steroid toxicity is given calcium salts (Chap. 65); thus, this therapeutic modality is relatively contraindicated in such circumstances.

The administration of insulin (and dextrose to prevent hypoglycemia unless hyperglycemia is present), sodium bicarbonate, or inhalation of a β -adrenergic agonist all stimulate potassium entry into cells.⁸ They reduce the serum $[K^+]$ over approximately 30 minutes, but potassium begins to reenter the extracellular space over the next several hours. Cationic exchange resins, such as Na^+ polystyrene sulfonate, take longer to reduce the serum $[K^+]$ as they enhance GI potassium loss. Hemodialysis or peritoneal dialysis may be useful, especially when significant renal impairment is present.

Calcium

Calcium is the most abundant mineral in the body, and 98% to 99% is located in bone. Approximately half of the remaining 1% to 2% of calcium in the body is bound to plasma proteins (mostly albumin), and most of the rest is complexed to various anions, with free, ionized calcium representing a very small fraction of extraosseous stores. The serum $[Ca^{2+}]$ is maintained through interactions between dietary intake and renal elimination, modulated by vitamin D activity, parathyroid hormone, and calcitonin. More extensive discussions of calcium physiology are found elsewhere.^{6,96}

Xenobiotic-induced hypercalcemia is uncommon and usually caused by an increased dietary calcium as a result of milk or antacid usage, calcium supplements, or a decrease in its renal excretion such as occurs with thiazide use.^{6,18} Cholecalciferol, available as a rodenticide, can increase the serum $[Ca^{2+}]$ by increasing its release from bone, increasing GI absorption, and decreasing renal elimination. Vitamin D toxicity from excessive vitamin or milk intake also can cause hypercalcemia.⁶⁸ Table 19–9 lists other causes of hypercalcemia.

Symptoms of hypercalcemia consist of lethargy, muscle weakness, nausea, vomiting, and constipation. Life-threatening manifestations include complications from altered mental status such as aspiration pneumonia and cardiac dysrhythmias (Chap. 16). Treatment of clinically significant hypercalcemia focuses on removing the offending xenobiotic when possible,

decreasing GI absorption by administering a binding agent, increasing distribution into bone with a bisphosphonate (onset, 1–2 days), and enhancing renal excretion through forced diuresis with IV 0.9% NaCl solution and furosemide (onset, 4–6 hours).^{6,129} Hemodialysis may be required when significant renal impairment is present.

Xenobiotics more commonly cause hypocalcemia than hypercalcemia. Minor, usually clinically insignificant decreases in serum $[Ca^{2+}]$ can occur in association with anticonvulsant and aminoglycoside therapy.¹⁸ Severe, life-threatening hypocalcemia can occur, however, from ethylene glycol poisoning (Chap. 109) or as a manifestation of fluoride toxicity from either fluoride salts or hydrofluoric acid (Chap. 107).^{34,131} Calcium complex formation with fluoride or oxalate ions is responsible for the rapid development of hypocalcemia in these settings. Similar effects occur with excess phosphate¹³⁴ or citrate^{84,132} intake. This mechanism (calcium complex formation) decreases the ionized $[Ca^{2+}]$ but may or may not reduce the measured total serum $[Ca^{2+}]$. Other xenobiotics that produce hypocalcemia decrease absorption, enhance renal loss, or stimulate calcium entry into cells (Table 19–9).

TABLE 19–9. Xenobiotic Causes of Altered Serum Calcium

<i>Hypocalcemia</i>	<i>Hypercalcemia</i>
Aminoglycosides	All-trans-retinoic acid (ATRA)
Bicarbonate	Aluminum
Bisphosphonates	Androgens
Calcitonin	Antacids (calcium containing)
Citrate	Antacids (magnesium containing)
Edetate disodium	Cholecalciferol and other vitamin D analogs
Ethanol	Lithium
Ethylene glycol	Milk–alkali syndrome
Fluoride	Tamoxifen
Foscarnet	Thiazide diuretics
Furosemide (and other loop diuretics)	Vitamin A
Mithramycin	
Neomycin	
Phenobarbital	
Phenytoin	
Phosphate	
Theophylline	
Valproate	

Symptoms of hypocalcemia consist largely of neuromuscular findings, including paresthesias, cramps, carpopedal spasm, tetany, and seizures. Although ECG abnormalities are common (Chap. 16), life-threatening dysrhythmias are rare. Treatment strategies focus on calcium replacement. When hypomagnesemia or hyperphosphatemia is present, these abnormalities should be corrected or calcium replacement may fail.

Magnesium

Magnesium is the fourth most abundant cation in the body (after Ca^{2+} , Na^{+} , and K^{+}), with a normal total body store of about 2000 mEq in a 70-kg person.¹⁰⁸ Approximately 50% of magnesium is stored in bone, with most of the remainder distributed in the soft tissues. Because only approximately 1% to 2% of magnesium is located in the ECF, serum concentrations correlate poorly with total body stores.¹⁰⁹ Magnesium homeostasis is maintained through dietary intake and renal and GI excretion modulated by hormonal effects.⁵ Clinically significant hypermagnesemia is uncommon in the absence of kidney failure except when massive parenteral infusions of magnesium salts overwhelm renal excretory mechanisms. This has been reported with inadvertent IV infusion,^{17,22,60,92} urologic procedures involving irrigation with magnesium salts,^{39,69} and ingestion of large quantities of magnesium-containing antacids⁸⁶ and cathartics.^{45,49} Of concern is iatrogenic overdose from the use of magnesium-containing cathartics used in poison management.^{47,70,124} In a series of poisoned patients, a single dose of a magnesium-containing cathartic failed to produce any demonstrable rise in serum $[Mg^{2+}]$.¹²⁵ However, patients who received three doses of magnesium sulfate over 8 hours had a significant increase in their serum $[Mg^{2+}]$.¹²⁵ Thus, the potential for iatrogenic toxicity exists, mandating cautious use of magnesium-containing cathartics, especially in patients with renal insufficiency. Table 19–10 lists xenobiotic causes of hypermagnesemia.

TABLE 19–10. Xenobiotic Causes of Altered Serum Magnesium

<i>Hypomagnesemia</i>	<i>Hypermagnesemia</i>
Aminoglycosides	Antacids (magnesium containing)
Amphotericin	Cathartics (magnesium containing)
Cetuximab	Lithium
Cisplatin	Magnesium salts
Citrate	
Cyclosporine	
DDT	
EGFR antibodies (panitumumab and cetuximab)	
Ethanol	
Fluoride	
Foscarnet	
Insulin	
Laxatives	
Loop diuretics	
Methylxanthines	
Osmotic diuretics	
Phosphates	
Proton pump inhibitors	
Strychnine	
Tacrolimus	
Thiazide diuretics	

The symptoms of hypermagnesemia correlate with serum concentrations but depend somewhat on the rate of increase and host factors. At serum $[Mg^{2+}]$ of about 3 to 10 mEq/L, patients feel weak, nauseated, flushed, and thirsty. Bradycardia, a widened QRS complex on ECG, hypotension, and decreased deep tendon reflexes may be noted. As concentration increases, hypoventilation, muscle paralysis, and ventricular dysrhythmias occur. Serum $[Mg^{2+}]$ greater than 10 mEq/L, especially those concentrations greater than 15 mEq/L, often cause death.

Hypermagnesemia should be considered a life-threatening disorder. When significant neuromuscular or ECG manifestations are noted, administration of 5 to 20 mEq of Ca^{2+} intravenously will reverse some of the toxicity.^{6,54} Further therapy should focus on enhancing renal excretion by administering fluids and loop diuretics such as furosemide.⁵⁴ In the presence of renal failure or inadequate renal excretion, hemodialysis will rapidly correct hypermagnesemia.

Xenobiotic-induced hypomagnesemia is common but rarely life threatening. Renal losses (caused by diuretics), GI losses (caused by ethanol), intracellular shifts caused by insulin⁸² or β -adrenergic agonists, and complex formation (by fluoride or phosphate) are common.^{5,6} Table 19–10 lists these and other xenobiotic causes of hypomagnesemia. Of note, many causes of hypomagnesemia also cause hypokalemia and hypocalcemia.⁵ Therefore, when hypomagnesemia is suspected or discovered, the presence of other electrolyte abnormalities should be sought.

The symptoms of hypomagnesemia are lethargy, weakness, fatigue, neuromuscular excitation (tremor and hyperreflexia), nausea, and vomiting.^{25,31} Dysrhythmias may occur, especially in patients treated with cardioactive steroids. Signs and symptoms consistent with hypocalcemia and hypokalemia also may be present.

Treatment involves removing the offending xenobiotic (if it can be identified) and restoring magnesium balance. Although either oral or parenteral supplementation is usually acceptable for mild hypomagnesemia, parenteral therapy is required when significant clinical manifestations are present. When oral therapy is indicated, a normal diet or magnesium oxide, magnesium chloride, or magnesium lactate in divided doses (magnesium 20–100 mEq/d) will often correct the hypomagnesemia.^{5,6} When hypomagnesemia is severe or symptomatic, and kidney function is normal, 16 mEq (2 g) of magnesium sulfate can be given intravenously over several minutes to a maximum of 1 mEq/kg of magnesium in a 24-hour period.^{6,25,67} During any continuous magnesium infusion, frequent serum $[Mg^{2+}]$ determinations should be obtained and the presence of reflexes documented. If hyporeflexia occurs, the magnesium infusion should be discontinued.

SUMMARY

- The management of poisoned or overdosed patients must include an evaluation of their fluid, electrolyte, and acid–base status.
- Developing a stepwise approach to the evaluation of patients with a high anion gap metabolic acidosis is essential.
- The osmol gap can help confirm a suspicion of toxic alcohol poisoning but cannot exclude the diagnosis
- Disorders of sodium (water) are common manifestations of xenobiotic exposure. Since fluid and electrolyte abnormalities may result from both poisoning and the therapy of poisoned patients, reassessment and monitoring are essential to ensure a good clinical outcome.

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20 GASTROINTESTINAL PRINCIPLES

Matthew D. Zuckerman and Richard J. Church

Humans are in constant contact with a variety of xenobiotics. In addition to its critical role in absorbing nutrients, the gastrointestinal (GI) tract forms the initial functional barrier between ingested material and the body. An understanding of the GI tract's structure, physiology, and innervation is critical to the toxicologic concepts of absorption, motility, and toxic insult. This chapter discusses the normal role of the GI tract and its relationship to toxicology. Anatomic, pathologic, and microbiologic principles are discussed, including the role of the GI tract in the metabolism of xenobiotics. Examples of GI pathologies and their clinical manifestations are discussed, with examples when appropriate.

STRUCTURE AND INNERVATION OF THE GASTROINTESTINAL TRACT

The luminal GI tract can be divided into five distinct structures: oral cavity and hypopharynx, esophagus, stomach, small intestine, and colon ([Fig. 20–1](#)). These environments differ in luminal pH, specific epithelial cell receptors, and endogenous flora. The transitional areas between these distinct organs have specialized epithelia and muscular sphincters with specific functions and vulnerabilities. Knowledge of the anatomy of these transition zones is particularly important for the localization and management of foreign bodies. The functions of the pancreas and liver are closely integrated with those of the luminal organs. The pancreas is discussed here; the liver and its metabolic functions are discussed in Chaps. 13 and 23.

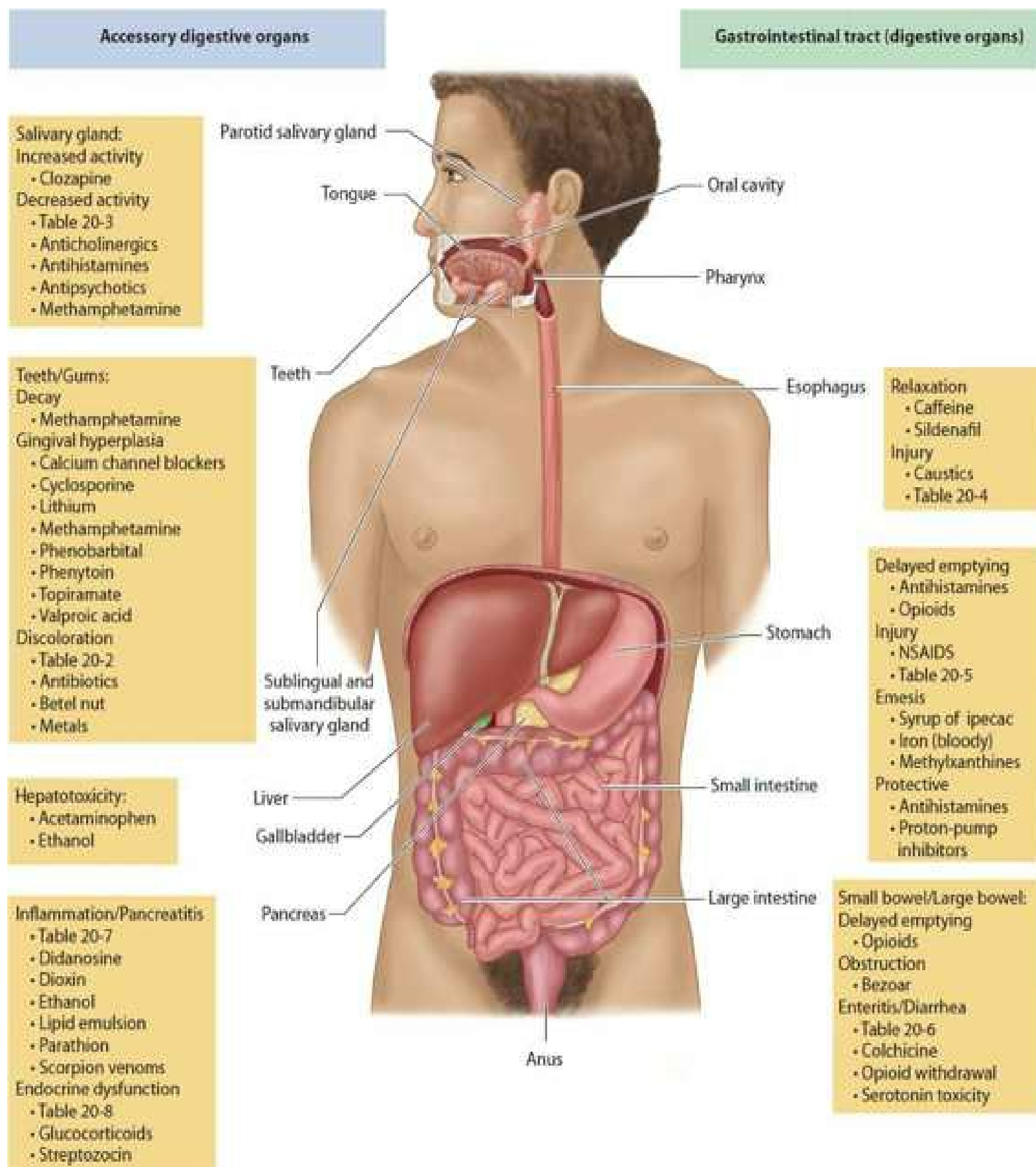


FIGURE 20–1. Anatomy of the gastrointestinal system. (Modified with permission from Mescher AL: Junqueira’s Basic Histology. 13th ed. New York: McGraw-Hill; 2013.)

The visceral structures of the GI tract are composed of several layers, including the epithelium, lamina propria, submucosa, muscle layers, and serosa (the last of which is only present in intraperitoneal organs). As the transition is made throughout the GI tract, differences in luminal pH, epithelial cell receptors, muscularity, and endogenous flora are encountered, affecting the absorption and metabolism of individual xenobiotics.

The epithelium, the innermost layer of the GI tract, is the most specialized cell type in the intestine and is composed of epithelial, endocrine, and receptor cells. Epithelial cells have polarity, with the basal surface facing the lamina propria and the apical surface facing the lumen. They are further specialized for specific functions of secretion or absorption. Additionally, the epithelial cells form part of the mucosal immune defense, where they are able to detect the presence of

microbial pathogens and downregulate the immune system in the presence of nonpathogenic or probiotic microbes. The major barrier to penetration of xenobiotics and microbes is the GI epithelium, a single-cell-thick membrane. The cell membrane is a semipermeable lipid bilayer that contains aqueous pores through which certain materials can pass, depending on their size or molecular structure. The membrane is not continuous because it consists of individual epithelial cells; however, these cells are joined to each other by structures known as tight junctions. The tight junctions have a gap of about 8 Å, which allows passage only of water, ions, and low-molecular-weight substances.

The muscle layer found beneath the lamina propria is made up of the muscularis mucosa, the circular muscles, and the longitudinal muscles. Contraction of the muscularis mucosa causes a change in the surface area of the gut lumen that alters secretion or absorption of nutrients. Whereas depolarization of circular muscle leads to contraction of a ring of smooth muscle and a decrease in the diameter of that segment of the GI tract, depolarization of longitudinal muscle leads to contraction in the longitudinal direction and a decrease in the length of that segment. The function of the muscle layers is integrated with the enteric nervous system to provide for a coordinated movement of luminal contents through the GI tract so as to maximize absorption and minimize bacterial growth. This integration facilitates the flow of chyme (undigested food) via a coordinated sequence of muscular contractions and relaxations, leading to segmentation of luminal contents, peristaltic movements, and unidirectional flow through the intestine.

The GI tract is innervated by the autonomic nervous system via both extrinsic and intrinsic pathways (Fig. 20–2). The extrinsic innervation permits communication among the brain, spinal cord, and chemoreceptors and mechanoreceptors located in the gut. Parasympathetic stimulation in the extrinsic pathway tends to be excitatory (“rest and digest”) and is carried via the vagus, splanchnic, and pelvic nerves to the myenteric and submucosal plexuses. In contrast, increased sympathetic tone (“fight or flight”) inhibits digestive and peristaltic activity via fibers that originate in the thoracolumbar cord and terminate in the myenteric and submucosal plexuses. The intrinsic innervation of the GI tract, or enteric nervous system, constitutes a reflex arc that modulates both peristalsis (via the myenteric plexus) and secretion (via the submucosal plexus) in response to parasympathetic and sympathetic tone.

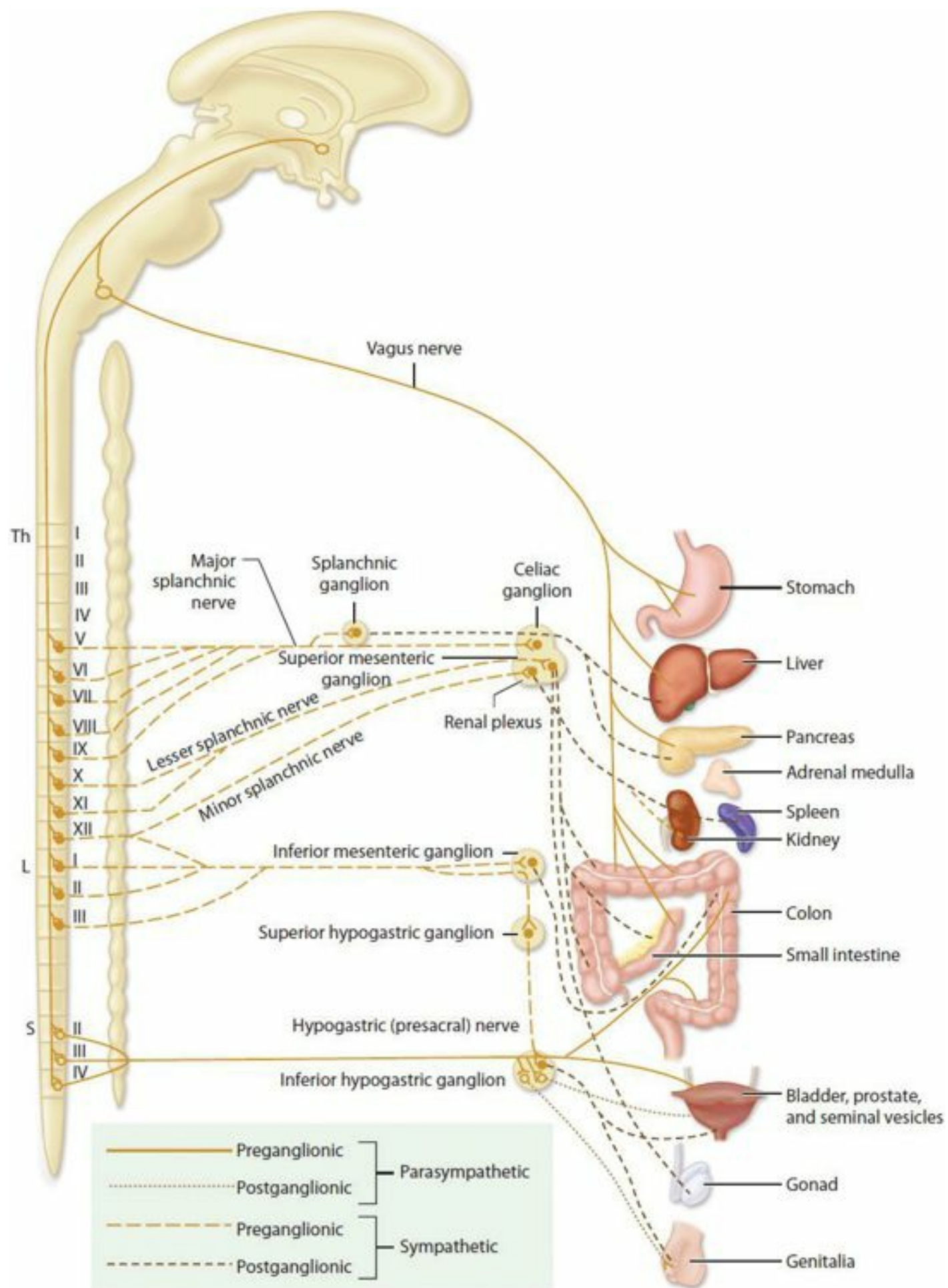


FIGURE 20–2. Innervation of the gastrointestinal system. (Adapted with permission from McAninch JW, Lue TF, Smith DR: Smith and Tanagho's General Urology. 18th ed. New York: McGraw-Hill Professional; 2013.)

THE IMMUNE SYSTEM AND MICROBIOLOGY OF THE GASTROINTESTINAL TRACT

An elaborate mucosal immune system has evolved to protect the GI tract from pathogens.⁴⁵ Mucosal immunity can be divided into an afferent limb, which recognizes a pathogen and induces the proliferation and differentiation of immunocompetent cells, and an efferent limb, which coordinates and affects the immune response. The afferent system includes the lymphoid follicles and specialized M-cells found therein that promote transit of antigens to antigen-presenting cells.³⁰ After being sensitized, immune cells undergo a complicated process of clonal expansion and differentiation, which occurs in mucosal and mesenteric lymphoid follicles, as well as in extraintestinal sites. Immunocompetent cells then return to the intestine and other mucous membranes and are scattered diffusely within the epithelial and lamina propria compartments.

The normal endogenous flora in the GI tract includes more than 400 species of bacteria along with a small number of fungi and viruses; the intestinal mucosa is normally colonized by large numbers of nonpathogenic anaerobic strains of *Bacteroides* spp, *Eubacterium* spp, *Clostridium* spp as well as aerobic strains of *Escherichia coli*, *Proteus* spp, *Enterobacter* spp, *Serratia* spp, *Lactobacillus* spp, and *Klebsiella* spp.¹⁸ The concentration of luminal bacteria varies by site, from lowest in the proximal small intestine to highest in the large intestine. En masse, these bacteria are more metabolically active than the liver. Endogenous bacteria occupy unique niches related to host physiology, environmental pressures, and microbial interactions, which result in long-term stability. The flora may be altered by various insults (particularly antibiotics) but usually returns to baseline after the insult is removed. Indeed, the cumulative total of microbial species in the enteric system (or enterotype) is remarkably consistent across countries and continents.²

The endogenous flora has multiple metabolic functions. A primary function in the colon is the salvage of malabsorbed carbohydrates by fermentation and production of short-chain fatty acids, a preferred substrate for colonic epithelial cells. This increased metabolic efficiency is best demonstrated when mice grown in germ-free conditions require a higher caloric intake to maintain weight.³⁷ This has led to some conjecture about the link between human flora and obesity, although this has yet to be born out.

Bacterial metabolism can significantly affect the disposition of enteral compounds. For example, the bacterial metabolism of digoxin contributes to its steady-state concentrations, and antibiotic treatment may reduce or eradicate the intestinal flora, predisposing to digoxin toxicity.⁹ Bacterial contribution to vitamin K metabolism is also demonstrated, necessitating dose adjustments of warfarin during and after antibiotic therapy. The metabolic activity of intraluminal bacteria is exploited in some treatment strategies. For example, sulfasalazine, used in the treatment of ulcerative colitis, is created through the linkage of 5-aminosalicylic acid to sulfapyridine. The azo bonds of the nonabsorbable sulfasalazine are broken by bacterial azoreductases, permitting the absorption of active metabolites in the colon at the site of inflammation.³³

The normal flora of the gut consists of probiotics—live, nonpathogenic bacteria and fungi that can also be used as prophylactic or therapeutic xenobiotics. These bacteria compete for and displace pathogenic bacteria, directly modulate intestinal immune function, and exert a trophic effect on the GI tract. They are used to decrease traveler's diarrhea, suppress antibiotic-induced diarrhea, and reduce inflammation in ileal pouches after colectomy in patients with ulcerative colitis.^{17,19,20}

REGULATORY SUBSTANCES OF THE GASTROINTESTINAL TRACT

There are three groups of regulatory peptide hormones that act on target cells within the GI tract. These are released from endocrine cells in the GI mucosa into the portal circulation and enter the systemic circulation to affect target cells. Gastrin, cholecystokinin (CCK), secretin, and glucose-dependent insulintropic polypeptide (GIP; formerly gastric inhibitory peptide) are considered the primary GI hormones. Somatostatin and histamine make up the paracrines, hormones that are released from endocrine cells and diffuse over short distances to act on target cells located in the GI tract. Vasoactive intestinal peptide (VIP), gastrin-releasing peptide (GRP), and enkephalins compose the last group known as neurocrines; substances that are synthesized in neurons of the GI tract, move by axonal transport down the axon, and are then released by action potentials in the nerves. The effects of these regulators are summarized in [Table 20–1](#).²⁶

TABLE 20–1. Regulatory Substances of the GI Tract

Substance	Site of Secretion or Release	Stimulus for Secretion/Release	Actions
Endocrines			
Gastrin	G cells of gastric antrum	Small peptides and amino acids Stomach distention Vagal stimulation (via GRP) Inhibited by H^+ in stomach (negative feedback)	\uparrow Gastric H^+ secretion \uparrow Growth of gastric mucosa
Cholecystokinin	I cells of duodenum and jejunum	Small peptides and amino acids Fatty acids and monoglycerides	\uparrow Contraction of gallbladder and relaxation of sphincter of Oddi \uparrow Pancreatic enzyme and HCO_3^- secretion \uparrow Growth of exocrine pancreas and gallbladder \downarrow Gastric emptying (allows more time for digestion and absorption)
Secretin	S cells of duodenum	H^+ in duodenal lumen Fatty acids in duodenal lumen	\downarrow Small intestinal H^+ \uparrow Pancreatic HCO_3^- secretion \uparrow Biliary HCO_3^- secretion \downarrow Gastric H^+ secretion \uparrow Growth of exocrine pancreas
GIP	K cells of small intestine	Fatty acids, amino acids, oral glucose	\uparrow Insulin release \downarrow H^+ secretion by gastric parietal cells
Motilin	Epithelial cells of duodenum	Periodic (not responsive to food)	\uparrow Propulsion of smooth muscle
Ghrelin	P/D1 cells of stomach	Fasting	\uparrow Gastric emptying Stimulates feeding
Paracrines			
Somatostatin	D cells throughout GI tract	H^+ in GI tract lumen Inhibited by vagal stimulation	\downarrow Release of all GI hormones \downarrow Gastric H^+ secretion \downarrow Pancreatic secretions \downarrow Splanchnic blood flow
Histamine	Mast cells of gastric mucosa	Vagal stimulation gastrin	\uparrow Gastric H^+ secretion
Nitric oxide	Enteric nerves	Cellular inflammation	\uparrow Epithelial secretion Vasodilation Smooth muscle relaxation
Neurocrines			
VP	GI tract neurons	H^+ in duodenal lumen	Smooth muscle relaxation \uparrow Pancreatic HCO_3^- secretion \uparrow Fluid and electrolyte secretion from intestinal epithelium and bile duct cholangiocytes \downarrow Gastric H^+ secretion
Gastrin-releasing peptide	Vagus nerves that innervate G cells	Vagal stimulation	\uparrow Gastrin release from G cells
Enkephalins (met-enkephalin, leu-enkephalin)	GI tract mucosa and smooth muscle neurons		\uparrow Contraction of GI smooth muscle \downarrow Intestinal secretion of fluid and electrolytes

GIP = glucose-dependent insulinotropic polypeptide (formerly gastric inhibitory peptide); GRP = gastrin-releasing peptide; VP = vasoactive intestinal peptide.

Xenobiotic effects on GI regulation can lead to intended or unintended consequences. Somatostatins reduce splanchnic blood flow and portal blood pressure, leading to their use as therapeutics for bleeding esophageal varices. Erythromycin agonizes motilin receptors, leading to increased GI propulsion, cramping, and diarrhea.

ANATOMIC AND PHYSIOLOGIC PRINCIPLES

Oropharynx and Hypopharynx

The main functions of the mouth and oropharynx are chewing, lubrication of food with saliva, and swallowing. Saliva initiates digestion of starch by α -amylase (ptyalin), triglyceride digestion by lingual lipase, lubrication of ingested food by mucus, and protection of the mouth and esophagus by dilution and buffering of ingested foods.

Saliva production is unique in that it is increased by both parasympathetic and sympathetic activity. Parasympathetic stimulation, via cranial nerves VII and IX, acts on muscarinic cholinergic receptors on acinar and ductal cells, increasing saliva production via vasodilation and increasing transport processes. Parasympathetic pathways are stimulated by food in the mouth, smells, conditioned reflexes, and nausea and are inhibited by sleep, dehydration, and fear. Sympathetic stimulation originates from preganglionic nerves in the thoracic segments T1 to T3. When β -adrenergic receptors are triggered by norepinephrine, production of saliva increases but at a rate less than that of parasympathetic stimulation.¹¹ It is theorized that the hypersalivation, or sialorrhea, associated with clozapine use may be related to agonism of parasympathetic muscarinic receptors or antagonism of adrenergic α receptors (resulting in unopposed β -adrenergic receptor-mediated vasodilation).⁵ Conversely, dysfunction of saliva production, via the anticholinergic side effects of other antipsychotics, can lead to dry mouth, or xerostomia.

Esophagus

The esophagus is a distensible muscular tube that extends from the epiglottis to the gastroesophageal junction. The lumen of the esophagus narrows at several points along its course, first at the cricopharyngeus muscle, then midway down alongside the aortic arch, and then distally where it crosses the diaphragm. The upper esophageal sphincter (UES) and lower esophageal sphincter (LES) are physiologic high-pressure regions that remain closed except during swallowing. Although the LES is a functional segment without anatomic features, the UES is marked by the presence of striated muscle.

The wall of the esophagus reflects the general structural organization of the GI tract noted previously, consisting of mucosa, submucosa, muscularis propria, and adventitia. The mucosal layer has three components. The nonkeratinizing stratified squamous epithelial layer faces the lumen; provides protection for underlying tissue; and houses several specialized cell types such as melanocytes, endocrine cells, dendritic cells, and lymphocytes. The lamina propria is the nonepithelialized portion of the mucosa, and the muscularis mucosa, a layer of longitudinally oriented smooth muscle bundles, is the third component.

The submucosa consists of loose connective tissue, and submucosal glands secrete a mucin-containing fluid via squamous epithelium-lined ducts, which facilitates lubrication of the esophageal lumen. The muscularis propria consists of an inner circular and outer longitudinal coat of smooth muscle; this layer also contains striated muscle fibers in the proximal esophagus that are responsible for voluntary swallowing.

The esophagus has no serosal lining. Only small segments of the intra-abdominal esophagus are covered by adventitia, a sheathlike structure that also surrounds the adjacent great vessels, tracheobronchial tree, and other structures of the mediastinum.

The esophagus provides a conduit for food and fluids from the pharynx to the stomach, and the sphincters generally prevent reflux of gastric contents into the esophagus. Normal transit of food involves coordinated motor activity, including a wave of peristaltic contraction, relaxation of the LES (facilitated by nitric oxide and VIP), and subsequent closure of the LES (facilitated by several hormones and neurotransmitters such as gastrin, acetylcholine, serotonin, and motilin). Xenobiotics can alter muscle tone in various segments of the esophagus, altering function. Caffeine is associated with relaxation of the LES and decreased peristalsis, increasing incidence of acid reflux.²⁹ Additionally, sildenafil, via its effect on nitric oxide, relaxes esophageal smooth muscle, decreasing the pathologically elevated esophageal tone common to patients with achalasia.⁷ Because of the rapid transit time of swallowed substances through this portion of the GI tract, digestion does not take place, and passive diffusion of substances from the food into the bloodstream is prevented.^{11,46}

Stomach

The stomach is a saccular organ covered entirely by peritoneum that has a capacity greater than 3 L. The stomach is divided into five anatomic regions: the cardia, fundus, corpus or body, antrum, and pyloric sphincter. The gastric wall consists of mucosa, submucosa, muscularis propria, and serosa. The interior surface of the stomach is marked by coarse rugae, or longitudinal folds. The mucosa is made up of a superficial epithelial cell compartment and a deep glandular compartment. The glandular compartment consists of gastric glands, which vary between regions of the stomach. The mucus glands of the

cardia, fundus, and body secrete mucus and pepsinogen. Oxyntic, or acid-forming, glands found in the fundus and body contain parietal, chief, and endocrine cells. The parietal cells contain vesicles that house hydrochloric acid–secreting proton pumps and secrete intrinsic factor, a substance necessary for the ileal absorption of vitamin B₁₂. Chief cells secrete the proteolytic proenzyme pepsinogen, which is cleaved to its active form, pepsin, upon exposure to the low luminal gastric pH of 3 to 4. Pepsin is subsequently inactivated in the duodenum when the pH increases to 6.0. The endocrine, or enterochromaffinlike (ECL), cells found in the mucosa of the body of the stomach produce histamine, which increases acid production and decreases gastric pH by stimulating H₂ receptors on the parietal cells. Somatostatin and endothelin, both modulators of acid production, are also produced in ECL cells (Fig. 49–4).

Hydrochloric acid is secreted when cephalic, gastric, and intestinal signals converge on the gastric parietal cells to activate proton pumps and release hydrochloric acid in an adenosine triphosphate–dependent process. During the cephalic phase, or the preparatory phase of the brain for eating and digestion, acetylcholine is released from vagal afferents in response to sight, smell, taste, and chewing. Acetylcholine stimulates the parietal cells via muscarinic receptors, resulting in an increase in cytosolic calcium and activation of the proton pump. G cells, located in the antrum of the stomach, produce and release gastrin in response to luminal amino acids and peptides. Gastrin activates receptors within parietal cells, leading to a similar increase in cytosolic calcium. Additionally, gastrin and vagal afferents induce the release of histamine from ECL cells, which stimulates parietal cell H₂ receptors. Lastly, the intestinal phase is initiated when food containing digested protein enters the proximal small intestine and involves gastrin as well as a number of other polypeptides in the secretion of hydrochloric acid from the stomach⁴⁶ (Fig. 20–3).

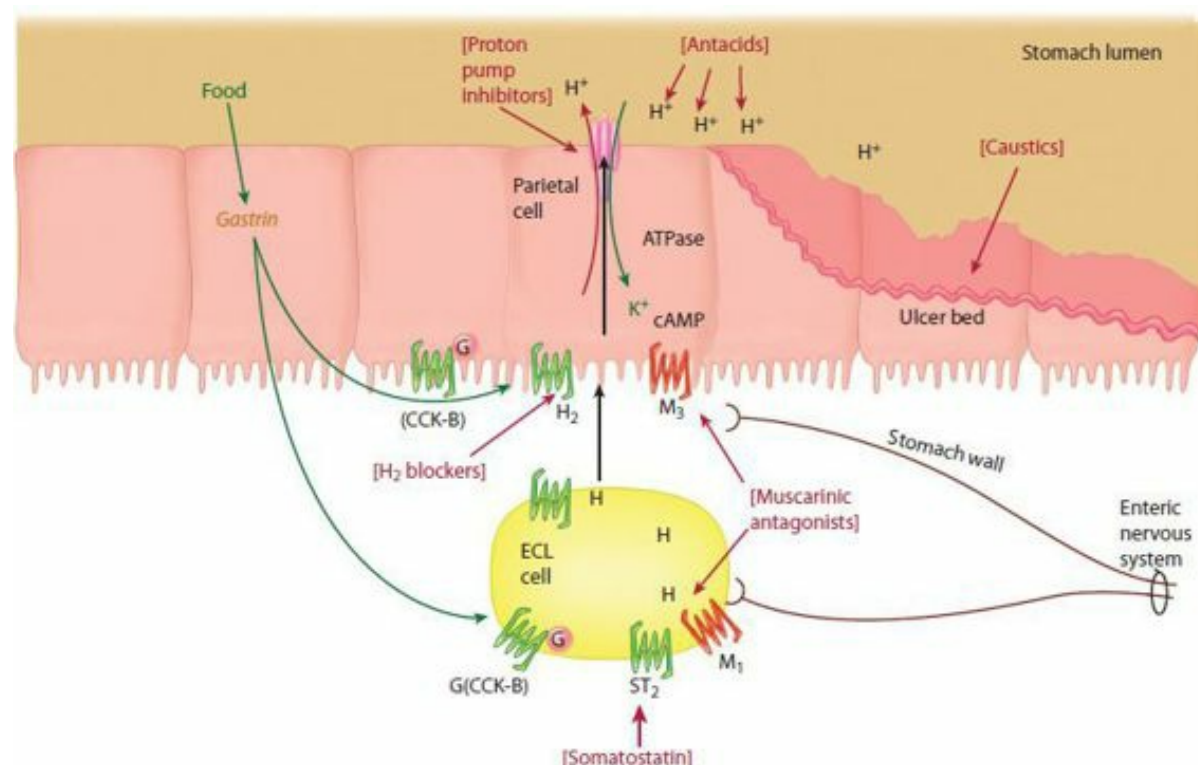


FIGURE 20–3. Effects of various xenobiotics on the gastrointestinal tract. CCK-B = cholecystokinin receptor B; ECL cell = enterochromaffinlike cell; H = histamine; H₂ = histamine-2 (H₂) receptor; M₁, M₃ = muscarinic receptors; ST2 = somatostatin-2 receptor.

The gastric mucosa is protected from gastric acidic secretions by several mechanisms, including a thin layer of surface mucus and channels that allow acid- and pepsin-containing fluids to exit glands without contact with the surface epithelium. Additionally, the surface epithelium secretes bicarbonate, raising the pH at the cell surface. Prostaglandins produced in the mucosal cells stimulate production of bicarbonate and mucus, and inhibit parietal cell production of acid; prostaglandin inhibition by nonsteroidal antiinflammatory drugs (NSAIDs) plays an important role in the pathogenesis of peptic ulcer disease.⁴⁶

In the stomach, ingested products are ground to particle sizes of less than 0.2 mm, which are then further processed and digested in preparation for absorption of nutrients in the small intestine. Many xenobiotics are weak acids that are no longer ionized in the acidic environment of the stomach, facilitating absorption through the lipid bilayer at the level of the stomach. Other factors that affect xenobiotic absorption include particle size, transit time, and type of drug delivery system. Different drug formulations, such as time release, enteric coating, slowly dissolving matrices, dissolution control via osmotic pumps, ion exchange resins, and pH-sensitive mechanisms, can affect bioavailability and the site of maximal release within the GI tract.

The time required for gastric emptying is determined by the complex interplay of innervation, muscle action, underlying

illness, and xenobiotic exposure. Digestion and absorption are time-dependent processes, and optimal absorption requires adjustment of the luminal environment through secretion of ions and water, to accommodate meals that vary considerably in nutrient composition, water content, and density. Osmoreceptors and chemoreceptors in the GI tract fine tune the digestive and absorptive processes by regulating transit and secretion using a variety of neurocrine, paracrine, and endocrine mechanisms. Interference with this integrated response may lead to stasis and bacterial overgrowth or rapid transit with decreased absorption and development of diarrhea. A large number of mediators affect motility, including common neurotransmitters, such as acetylcholine and norepinephrine; hormones; cytokines; inflammatory compounds; and others. In general, whereas parasympathetic impulses promote motility, sympathetic stimulation inhibits motility. Other transmitters, such as serotonin, promote transit, but dopamine and enkephalins can slow motility. Some xenobiotics, such as opioids and diphenhydramine, delay gastric emptying, but other xenobiotics, such as metoclopramide, may enhance gastric emptying. Our understanding of the complex neuroendocrine gastric axis continues to evolve in attempts to explain new phenomenon, such as the cannabinoid hyperemesis syndrome, which may be caused by cannabinoid receptors in the brain or gut.⁴¹

Small and Large Intestines

In an average adult, the small intestine is approximately 6 m in length and begins retroperitoneally as the duodenum, becoming intraperitoneal at the jejunum and ileum. The boundary between the small intestine and large intestine is the ileocecal valve, and the large intestine typically measures 1.5 m in an adult. The large intestine (or colon) is further divided into cecal, ascending, transverse, descending, and sigmoid segments. The sigmoid colon is continuous with the rectum and terminates at the anus. Whereas anterograde and retrograde peristalsis occurs in the small intestine, anterograde peristalsis predominates in the large intestine. This movement allows for mixing of food, maximizes contact with the mucosa, and is mediated by both the extrinsic and intrinsic nervous systems. The remarkable absorptive capacity of the small intestine is made possible by innumerable villi of the intestinal wall, which extend into the lumen and increase absorptive area. The epithelial border of the small intestine also contains mucin-secreting goblet cells, endocrine cells, and specialized absorptive cells; functionally, these cells create an ideal environment for nutrient absorption. The mucosa of the large intestine is devoid of villi. The large intestine functions primarily to absorb electrolytes and water, secrete potassium, salvage any remaining nutrients, and store and release waste. Intestinal epithelial cells also metabolize xenobiotics, a function typically attributed to the liver (see below).

Regeneration of injured or senescent intestinal epithelial cells begins in the crypts, with differentiation occurring as these cells migrate toward the intestinal lumen. This process occurs rapidly, with turnover of the small intestinal epithelium occurring every 4 to 6 days and large intestinal epithelium turnover occurring every 3 to 8 days. This rapid regeneration leaves the intestinal epithelium vulnerable to processes that interfere with cell replication (eg, radiation, chemotherapy). Sloughing of GI epithelium, typically manifested by hemorrhagic enteritis, is a valuable marker for xenobiotic insults that lead to mitotic arrest.

Anatomic and functional changes after bariatric surgery and bowel resection have important effects on drug bioavailability and toxicity. The common Roux-en-Y gastric bypass surgery, which diverts gastric contents into distal small bowel, may increase bioavailability by bypassing intestinal CYP3A or decrease bioavailability by bypassing the proximal jejunum as an area of drug absorption.¹⁶ Alterations in stomach and bowel pH after surgery may affect absorption of ionized drugs. Disruption of the enterohepatic recirculation may enhance elimination of drugs such as digoxin.⁴⁸ Many xenobiotics, such as ethanol, oral morphine, and caffeine, achieve maximum serum concentrations faster because of rapid transit. However, studies evaluating serum concentrations of known CYP substrates (caffeine [CYP1A2], tolbutamide [CYP2C9], omeprazole [CYP2C19], and midazolam [CYP3A]) in patients with gastric bypass surgery have not found any clinically significant changes in drug metabolism.⁴³ Because specific data are limited, current recommendations for dosing in postoperative patients are based on extrapolating from a xenobiotic site of absorption and kinetics and a particular patient's functional GI anatomy.

Pancreas

The pancreas is a retroperitoneal organ that serves both exocrine and endocrine functions. The exocrine portion of the gland produces digestive enzymes and occupies more than 80% to 85% of the mass of the pancreas. The exocrine pancreas is composed of acinar cells, specialized epithelial cells housing zymogen granules that release digestive enzymes and proenzymes into the duodenum. Columnar epithelial cells produce mucin and ductal cuboidal epithelial cells secrete a bicarbonate-rich fluid that neutralizes gastric acids. The pancreas secretes 2 to 2.5 L/day of this mixed solution. Typically, the digestive enzymes are released as proenzymes, such as trypsinogen, chymotrypsinogen, and procarboxypeptidase, which are activated upon contact with the higher pH of the duodenum; this process usually helps to prevent autodigestion of the pancreas itself. Enzymes on the brush border of the duodenum, including enteropeptidase, cleave proenzymes to their active forms. Only pancreatic amylase and lipase are secreted in their active forms.

Secretion of pancreatic enzymes is regulated by multiple factors, the most important of which are cholecystokinin and secretin, both produced in the duodenum. Cholecystokinin is released from the duodenum in response to fatty acids and the products of protein catabolism such as peptides and amino acids. Cholecystokinin stimulates acinar cells to release

digestive enzymes and proenzymes. Secretin is released by the duodenum in the presence of lowered pH caused by gastric acids and luminal fatty acids. Secretin triggers ductal cells to secrete bicarbonate and water. Acetylcholine also plays a role in the regulation of pancreatic exocrine function by stimulating digestive enzyme secretion from the acinus and potentiating the effects of secretin. Vagal reflexes increase acetylcholinergic tone in the setting of decreased pH, protein breakdown products, and fatty acids in the duodenal lumen.

The endocrine portion of the pancreas is composed of approximately one million clusters of cells known as the islets of Langerhans that secrete insulin, glucagon, and somatostatin. Other products of the endocrine pancreas include serotonin and VIP. Injury to the endocrine pancreas can result in impaired glucose homeostasis. In one study, more than one third of patients with an episode of alcoholic pancreatitis subsequently developed impaired glucose tolerance.³⁶

XENOBIOTIC METABOLISM

Although the liver is usually identified as the site of xenobiotic metabolism, similar functions occur in the luminal GI tract (including hydroxylation, sulfation, acetylation, and glucuronidation). Biotransformation is a property both of luminal bacteria and enterocytes. Metabolism by the intestine affects the amount of orally administered xenobiotic that actually enters the body and therefore contributes to the first-pass effect, or presystemic disposition.

One of the most well-described families of export proteins, P-glycoprotein (PGP), is found in the mucosa of the small and large intestines, hepatocytes, adrenal cortex, renal tubules, and capillary cells lining the blood–brain barrier.⁴⁹ The PGPs are susceptible to induction and inhibition in a manner similar to hepatic cytochrome oxidase enzymes. Many of the substrates of CYP3A have inhibitory effects on PGPs. Inhibitors of PGPs may raise serum concentrations of a xenobiotic, although inducers of PGPs may prevent therapeutic drug concentrations from ever reaching the target cell. The PGP system is important in drug interactions and drug resistance (Chap. 9).

Pathologic Conditions of the Gastrointestinal Tract

Oral Pathology. Discoloration of the teeth is reported with a number of medications, most notably tetracyclines (Table 20–2). Gingival hyperplasia, overgrowth of the gums around the teeth, is an uncommon adverse effect from chronic use of several xenobiotics. Some medications implicated in causing gingival hyperplasia include calcium channel blockers, cyclosporine, lithium, phenobarbital, phenytoin, topiramate, and valproic acid.¹ Xerostomia, or pathologic dryness of the mouth, is an uncomfortable effect of many xenobiotics that can lead to increased dental decay. The list of xenobiotics that can cause xerostomia is extensive, but the most commonly implicated classes of xenobiotics causing xerostomia are listed in Table 20–3. Chronic methamphetamine use is linked to characteristic oral pathology known as “meth mouth.” This condition, which is common in both inhalational and intravenous users, is characterized by extensive and severe tooth decay and is linked to poor hygiene, bruxism, and xerostomia associated with methamphetamine use.¹²

TABLE 20–2. Xenobiotics Causing Discoloration of the Teeth and Gums¹

Betel	Red
Cadmium	Yellow
Chlorhexidine oral rinse	Brown
Ciprofloxacin	Green
Doxycycline	Yellow
Fluoride	White flecking
Lead	Blue line
Quinine	Blue-gray or blue-black
Silver	Brown-grey to blue-grey
Tetracycline	Yellow to brown-grey

TABLE 20–3. Xenobiotics That Commonly Cause Xerostomia¹

- α₁-Adrenergic receptor antagonists
- α₂-Adrenergic receptor agonists

Anticholinergics
Antidepressants (cyclic antidepressants, maprotiline)
Antihistamines
Antipsychotics (phenothiazines)
Methamphetamine
Protease inhibitors

Esophagitis and Dysphagia. Xenobiotic-induced esophageal injury includes esophagitis (including pill esophagitis), ulceration, perforation, and stricture. The most common presenting complaint is a foreign body sensation in the throat.²³ Xenobiotics commonly implicated in esophagitis and esophageal ulcerations are listed in [Table 20–4](#). Patients with preexisting esophageal motility disorders are at higher risk of esophageal pathology. Additionally, xenobiotics with a gelatin matrix, rapid dissolvability, and large size predispose to esophageal injury. Although most symptoms resolve with withdrawal of the offending xenobiotics, patients with persistent or severe odynophagia should be evaluated with endoscopy to identify pathology and prevent perforation caused by retained pills.¹³

TABLE 20–4. Xenobiotics Implicated in Esophagitis and Esophageal Ulcerations

Antipsychotics
Bisphosphonates
Chemotherapeutics
Nonsteroidal antiinflammatory drugs
Potassium chloride
Quinine
Salicylates
Tetracycline

Webs, Strictures, and Esophageal Malignancy. Caustic injury is one of the most common causes of esophageal strictures and malignancies. Some authors have also postulated the role of pill esophagitis in the evolution of esophageal strictures.⁶ As many as 4% of patients with esophageal cancer report a history of caustic injury, and patients with a history of caustic ingestion may have more than a 1000-fold higher risk of developing an esophageal malignancy than the general population.²⁴ Other xenobiotics known to cause esophageal strictures include aluminum phosphide and ionizing radiation.⁴²

Gastritis and Peptic Ulcer Disease. Gastritis, or inflammation of the gastric mucosa, and peptic ulcer disease (PUD) are commonly related to xenobiotic exposure ([Table 20–5](#)). Symptoms of gastritis and PUD include epigastric pain, nausea, and vomiting but may also include hematemesis and melena.³² The primary distinction between gastritis and PUD is appearance at endoscopy: whereas gastritis is characterized by diffuse inflammation of the gastric mucosa, an ulcer is a discrete lesion of the mucosa. NSAIDs remain an important part of the pathogenesis of gastritis and PUD by interfering with prostaglandin synthesis and subsequently impairing the integrity of the gastric mucosal barrier to acid. Cyclooxygenase-2 (COX-2) selective inhibitors promised to decrease the incidence of gastric pathology caused by chronic NSAID use; however, unexpected cardiovascular side effects have limited their utility. New xenobiotics are focusing on inhibition of other inflammatory mediators that may have been previously overlooked, and co-administration of protective xenobiotics. 5-Lipoxygenase (5-LOX) inhibitors may reduce production of proinflammatory leukotrienes, and when co-administered with COX inhibitors, decrease gastric toxicity. Other reformulated NSAIDs are designed to release molecules of NO and H₂S, which help maintain gastric mucosal integrity. These next generation of drugs may preserve systemic antiinflammatory effects while enhancing the gastric safety profile.¹⁰

TABLE 20–5. Xenobiotics Commonly Implicated in Gastritis and Peptic Ulcer Disease

Corticosteroids
Ethanol
Isopropyl alcohol

Nicotine

Nonsteroidal antiinflammatory drugs

Radiation (ionizing)

Salicylates

Chronic treatment of peptic ulcer disease with antacids, H₂ blockers, or proton pump inhibitors can lead to hypochlorhydria or achlorhydria, the reduction or absence of gastric acid, respectively. By increasing the pH of the stomach, these conditions increase risk of bacterial overgrowth, atrophic gastritis, osteoporosis, hip fracture (via impaired calcium absorption), Salmonella and Vibrio cholerae infection, and gastric carcinoma.⁴⁷

Enteritis and Diarrhea. The symptoms of GI distress are nonspecifically associated with xenobiotic exposure. However, certain xenobiotics that increase peristalsis or impair fluid absorption can result in significant diarrhea. Opioid withdrawal, colchicine overdose, and serotonin toxicity are important toxidromes that may feature diarrhea as a prominent symptom. The rapid turnover of the GI mucosa makes it uniquely susceptible to xenobiotics that cause cell death and mitotic arrest. Hemorrhagic enteritis, manifested by hematochezia, can be a characteristic finding of certain exposures (Table 20–6).

TABLE 20–6. Xenobiotic-Induced Enteritis

<i>Mechanism</i>	<i>Xenobiotic</i>
Mechanical irritation	Aloe Bacterial food poisoning Laxatives Mushrooms (GI irritant class)
Cholinergic stimulation	Carbamates Neostigmine, physostigmine , pyridostigmine Mushrooms (muscarine containing) Nicotine Organic phosphorous compounds
Inhibitors of mucosal regeneration (hemorrhagic enteritis)	Arsenic Chemotherapeutics Colchicine Iron Mercuric salts Monochloroacetic acid Podophyllin Pokeweed (<i>Phytolacca americana</i>) Radiation (ionizing)
Mitochondrial poison	Thallium

Bezoars. The term bezoar refers to a concretion formed anywhere in the alimentary system and may be a complication of overdose. The risk of bezoar formation is increased in cases of massive pill ingestion and varies according to tablet size, adhesiveness, and liquid viscosity.⁴⁰ Comorbid illnesses or toxicities that delay gastric emptying and bowel transit time may increase the risk of bezoar formation. Effects from bezoars can range from mechanical obstruction to severe local irritation (and stricture formation) to continuous delayed absorption of xenobiotics and resulting toxicity. Suspicion for bezoar formation is raised in patients after ingestion who develop signs of obstruction (vomiting, abdominal pain, constipation) and in patients with delayed or prolonged toxicity (eg, rising serum iron concentrations 8 hours after ingestion) after overdose.⁴⁰ Depending on the nature of the bezoar, they may be diagnosed using plain radiography; however, in some instances, computed tomography (CT) with oral contrast can increase sensitivity. Recent studies have had limited success with ultrasonography as a diagnostic adjuvant, although this requires further study. Ultimately, a high suspicion of bezoar with negative radiographic evaluation findings may prompt direct visualization with endoscopy and colonoscopy or exploratory surgery. Bezoars frequently require surgical intervention, and several cases report dramatic recovery after removal.

Pancreatitis. Pancreatitis is an acute inflammatory process that results in autolysis of the pancreas from digestive enzymes. Cases range from mild to severe, with an overall mortality rate of 5%.¹⁶ The most common causes of pancreatitis are alcohol abuse and gallbladder disease; however, nonalcoholic xenobiotic-induced pancreatitis accounts for 0.1% to 2% of cases of acute pancreatitis.³ Populations at higher risk of drug-induced pancreatitis include children, women, elderly adults, and patients with HIV and inflammatory bowel disease.³ Acute pancreatitis is defined as having two of the following three criteria: (1) abdominal pain characteristic of acute pancreatitis, (2) serum amylase or lipase greater than three times the upper limit of normal (although amylase is less specific and may be unnecessary), and (3) characteristic findings of acute pancreatitis on CT scan.⁴ The diagnosis of xenobiotic-induced pancreatitis can be impossible to confirm because no diagnostic test or pattern of injury distinguishes xenobiotic-induced pancreatitis from other etiologies. However, the symptoms and laboratory abnormalities associated with xenobiotic-induced pancreatitis tend to resolve shortly after withdrawal of the offending xenobiotic; again, this can be challenging to differentiate from the natural course of mild to moderate disease. It is unclear whether rechallenge with an offending xenobiotic will cause pancreatitis again; however, any xenobiotic suspected of causing pancreatitis should be withheld unless the benefits outweigh this risk. The management of xenobiotic-induced pancreatitis does not differ from other causes and hinges on volume resuscitation, bowel rest, and careful monitoring.

Numerous xenobiotics are associated with pancreatitis, each with varying levels of quality and quantity of evidence; representative xenobiotics are listed in Table 20–7.^{3,21} The pathogenic mechanism varies among xenobiotics. The nucleoside reverse transcriptase inhibitor didanosine and dioxin may promote pancreatitis as a result of mitochondrial injury.^{31,35,38} Cholinergic xenobiotics, such as parathion and certain scorpion venoms, may result in pancreatitis caused by overstimulation.^{25,34} Vasospasm and ischemia are also purported as a mechanism, as in cases of pancreatitis secondary to ergot alkaloids.¹⁴

TABLE 20–7. Xenobiotics Commonly Associated with Pancreatitis^{3,21}

- Alcohols: ethanol and methanol
- Analgesics: acetaminophen, NSAIDs, codeine
- Antibiotics: isoniazid, metronidazole, sulfonamides, tetracycline
- Anticonvulsants: valproic acid, carbamazepine
- Cardiovascular: ACE inhibitors and ARBs, methyldopa
- Dioxin
- Diuretics: loop diuretics
- HIV medications: didanosine, nelfinavir
- HMG-CoA reductase inhibitors
- Hormones: corticosteroids, estrogens
- Hypoglycemics: sitagliptin
- Immunosuppressants: azathioprine, corticosteroids, mesalamine
- Pesticides: organic phosphorous compounds
- Venoms: *Buthus quiquestriatus*, *Tityus discrepans*

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; NSAID = nonsteroidal antiinflammatory drug.

The endocrine functions of the pancreas are also susceptible to injury from pancreatitis or toxic insult. Typically, this results from injury to pancreatic β cells leading to impaired glucose homeostasis, similar to diabetes. Streptozotocin is notable for its toxicity to pancreatic β cells and ability to induce diabetes in animal models. In one study of patients after episodes of alcoholic pancreatitis, more than one third developed impaired glucose tolerance.³⁶ There are rare xenobiotics that can cause damage to α cells in animal models; however, they do not consistently cause hypoglycemia (Table 20–8).

TABLE 20–8. Xenobiotics Associated with Endocrine Pancreatic Dysfunction

<i>α Cells</i>	
Cobalt salts	Decamethylene diguanidine
<i>β Cells</i>	
Alloxan	Glucocorticoids
Androgens	Growth hormone
Cyclizine	Pentamidine
Cyproheptadine	Somatostatin
Diazoxide	Streptozocin
Epinephrine	Sulfonamides
Glucagon	Vacor

Constipation. Decreased stooling (fewer than three bowel movements a week) associated with abdominal pain is a major source of morbidity for patients taking opioids and other drugs that slow gastric emptying and decrease gut motility. It is estimated that opioid-induced bowel dysfunction affects up to 40% of patients on long-term opioids.⁸ In its most extreme form, severe constipation is associated with bowel obstruction and perforation. Novel therapeutics for this include locally acting opioid receptor antagonists (eg, prolonged-release naloxone and methylnaltrexone) that may alleviate GI effects without decreasing analgesic effects.¹⁵

Foreign Bodies

The esophagus is the most common site of impaction from symptomatic foreign bodies. They tend to be found just proximal to a pathologic esophageal narrowing or in one of three anatomic places: at the cervical esophagus near the cricopharyngeus muscle, at the level of the aortic notch, or just above the gastroesophageal junction. The likelihood that a foreign object will lodge in the esophagus is related to its size and shape. The major complications of foreign bodies in the esophagus include pain, bleeding, obstruction, or perforation, which may lead to subsequent mediastinitis or fistula. The general rule is that conservative means can be used for up to 12 hours after ingestion of the esophageal foreign body. If serial radiographs demonstrate no movement after 12 hours, endoscopic retrieval or surgery should be considered because the risk of perforation increases after that time; some authors extend this observation period to 24 hours.²² Ingestion of button batteries proves an important exception to this rule. Esophageal button batteries can cause significant mucosal injury in 2 to 4 hours, with perforation in as little as 6 hours.²⁸ Proposed mechanisms for the rapid development of esophageal injury include alkaline burn, local current, and pressure necrosis.²⁸ Most recently, almost all button battery ingestions associated with serious or fatal outcomes were 20-mm lithium batteries, dangerous for their large size and higher voltage.^{27,28,39} Of note, lithium batteries do not contain an alkali solution, lending support to the concept that electrical current results in morbidity rather than leakage of caustic battery contents. All suspected esophageal button batteries should therefore undergo immediate endoscopic removal within 2 hours; success rates with this modality are reported as excellent. Button batteries that are in the stomach or beyond may be left to pass spontaneously in asymptomatic patients.

Foreign bodies are also commonly found in the stomach. Many small foreign bodies pass through the stomach and the remainder of the GI tract without difficulty. Objects greater than 5 cm in length or 2 cm in diameter may be unable to traverse the duodenum and may require endoscopic or surgical removal. Foreign bodies beyond the duodenum may not require any intervention except observation; however, some objects may become lodged at the ileocecal valve. Serial examinations and radiographs can be appropriate for asymptomatic patients; however, increasing abdominal pain or tenderness may mandate further imaging and surgical consultation. Recent increase in pediatric ingestion of strong, small magnets may be one exception to these recommendations. Multiple magnets may attract across bowel walls, preventing transit and leading to intestinal perforation. Ingestion of a single magnet may not increase morbidity and may be managed as above, but the ingestion of multiple magnets should be managed aggressively with surgical consultation for removal.⁴⁴ Body packers represent an unusual exception to these rules. Patients who are discovered to be internally concealing large quantities of illicit drugs may require whole-bowel irrigation to facilitate transit of colonic packets and even emergency laparotomy for obstruction or suspected packet rupture in cases of cocaine or methamphetamine smuggling³⁹ (Special Considerations: SC5).

SUMMARY

- The GI tract is vulnerable to a wide variety of pathogenic organisms.

- The GI tract modulates absorption and metabolism of xenobiotics.
- Endogenous flora contribute greatly to the function and pathology of the GI tract with both host and microbial components acting as one organ system.
- The GI tract involves a complex interplay of regulatory hormones.
- As function follows structure, effects of various xenobiotics are often related to the specific parts of the GI tract that are affected.

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21 GENITOURINARY PRINCIPLES

Jason Chu

The genitourinary system encompasses two major organ systems, the reproductive and the urinary systems. Successful reproduction requires interaction between two sexually mature individuals. Xenobiotic exposures to either individual can have an adverse impact on fertility, which is the successful production of children, and fecundity, which is an individual’s or a couple’s capacity to produce children. The role of occupational and environmental exposures in the development of infertility is difficult to define.^{14,41,95,99} Well-designed and conclusive epidemiologic studies are lacking because of the following factors: laboratory tests used to evaluate fertility are relatively unreliable, clinical endpoints are unclear, xenobiotic exposure is difficult to monitor, and indicators of biologic effects are imprecise. Although the negative impact of xenobiotics on fertility is often ignored, infertility evaluations are incomplete without a thorough xenobiotic and occupational history. Differences in the toxicity of xenobiotics in individuals may be sex or age related (or both). Xenobiotic-related, primary infertility may be the result of effects on the hypothalamic–pituitary–gonadal axis or a direct toxic effect on the gonads.⁸² Fertility is also affected by exposures that cause abnormal sexual performance. [Table 21–1](#) lists xenobiotics associated with infertility.

TABLE 21–1. Xenobiotics Associated with Infertility

<i>Men</i>	
<i>Xenobiotic</i>	<i>Effects</i>
Anabolic steroids	↓ LH, oligospermia
Androgens	↓ Testosterone production
Benzene	Chromosomal aberrations in sperm
Chemotherapeutics	Gonadal toxicity
Chlorambucil	Oligospermia
Combination chemotherapy (CVP, MOPP, MVPP)	Oligospermia
Cyclophosphamide	Oligospermia
Methotrexate	Oligospermia
Carbon disulfide	↓ FSH, ↓ LH, ↓ spermatogenesis
Chlordecone	Asthenospermia, oligospermia
Gimetidine	Oligospermia
DBCP	Azospermia, oligospermia
Diethylstilbestrol	Testicular hypoplasia
Ethanol	↓ Testosterone production, Leydig cell damage, asthenospermia, oligospermia, teratospermia
Ethylene oxide	Asthenospermia (in monkeys), oligospermia
Glycol ethers	Azoospermia, oligospermia, testicular atrophy
2-Ethoxyethanol	
2-Methoxyethanol	
Opioids	↓ LH, ↓ testosterone
Lead	↓ Spermatogenesis, asthenospermia, teratospermia
Nitrofurantoin	↓ Spermatogenesis
PCBs	↓ Sperm motility
Radiation (ionizing)	↓ Spermatogenesis
Sulfasalazine	↓ Spermatogenesis
Tobacco	↓ Testosterone
<i>Women</i>	
<i>Xenobiotic</i>	<i>Effects</i>
Chemotherapeutics	Gonadal toxicity
Cyclophosphamide	Ovarian failure
Busulphan	Amenorrhea
Combination chemotherapy (MOPP, MVPP)	Amenorrhea
Diethylstilbestrol	Spontaneous abortions
Ethylene oxide	Spontaneous abortions
Lead	Spontaneous abortions, still births
Oral contraceptives	Affect hypothalamic–pituitary axis, end-organ resistance to hormones, amenorrhea
Thyroid hormone	↓ Ovulation

CVP = cyclophosphamide, vincristine, and prednisone; DBCP = dibromochloropropane; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MOPP = Mustargen, Oncovin, procarbazine, and prednisone; MVP = mustine, vinblastine, procarbazine, and prednisolone; PCB = polychlorinated biphenyl.

Aphrodisiacs are used to heighten sexual desire and to counteract sexual dysfunction. Humans have long sought the

perfect aphrodisiac. However, of those tried, their effectiveness is variable, and toxic consequences occur commonly. Particularly popular are the various treatments for male sexual dysfunction, or erectile dysfunction.

Although many people search for a cure for impotence or infertility, others explore xenobiotics that can be used as abortifacients. Routes of administration used include oral, parenteral, and intravaginal, with an end result of pregnancy termination. However, many of these xenobiotics produce systemic toxic effects on the mother and a nonaborted fetus.

This chapter examines these issues, as well as the impact of xenobiotics on the urinary system, specifically, urinary retention and incontinence, and abnormalities detected in urine specimens. Renal ([Chap. 28](#)), reproductive ([Chap. 31](#)), and carcinogenic principles are discussed elsewhere in this text.

MALE FERTILITY

Male fertility is dependent on a normal reproductive system and normal sexual function. The male reproductive system is composed of the central nervous system (CNS) endocrine organs and the male gonads. The hypothalamus and the anterior pituitary gland form the CNS portion of the male reproductive system. Both organs begin low-level hormone secretion as early as in utero gestation. At puberty, the hypothalamus begins pulsatile secretion of gonadotropin-releasing hormone (GnRH). This stimulates the anterior pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in a similarly pulsatile fashion. The hormones exert their effects on the male target organs, inducing spermatogenesis and secondary body sexual characteristics.

Disruption of normal function of any part of the system affects fertility. A number of xenobiotics can adversely affect the male reproductive system and sexual function as shown in [Fig. 21-1](#).

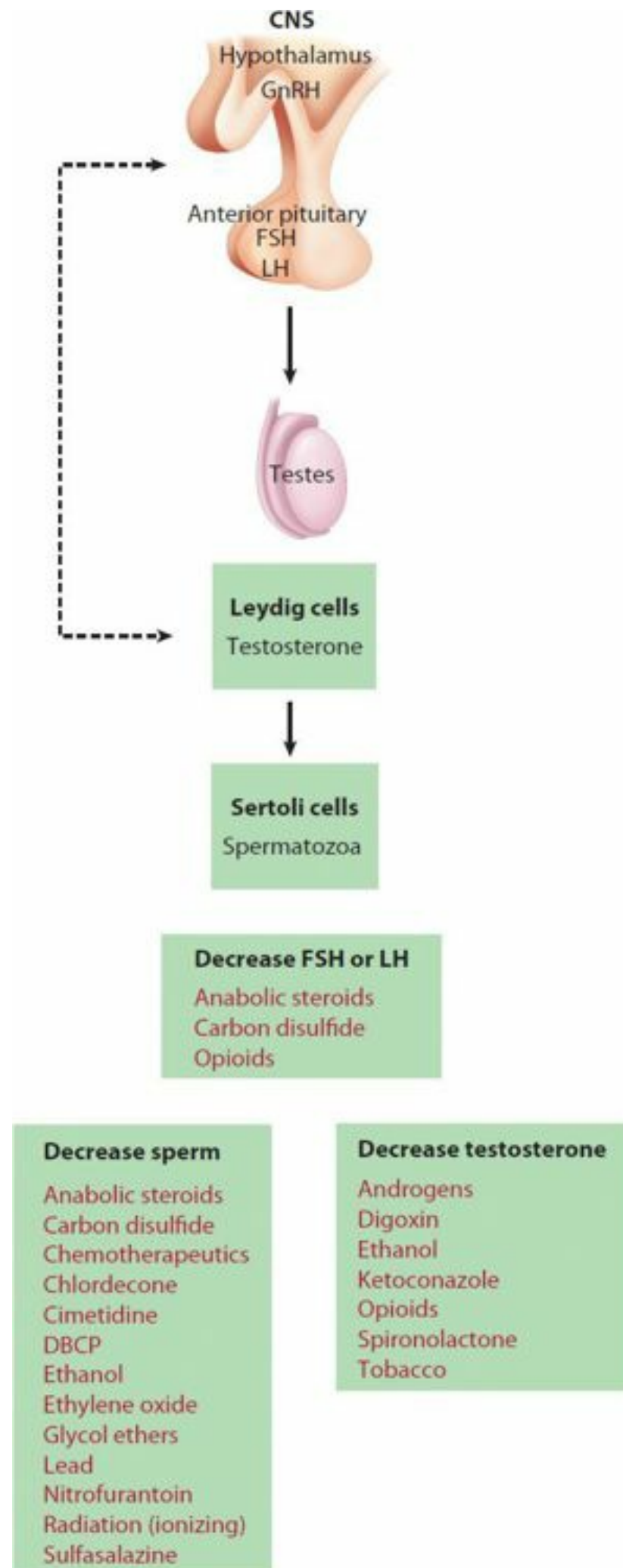


FIGURE 21–1. Schematic of the male reproductive axis and sites of xenobiotic effects. CNS = central nervous system; DBCP = dibromochloropropane; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

Spermatogenesis

Central to the male reproductive system is the process of spermatogenesis, which occurs in the testes. The bulk of the testes consist of seminiferous tubules with germinal spermatogonia and Sertoli cells. The remainder of the gonadal tissue is interstitium with blood vessels, lymphatics, supporting cells, and Leydig cells. Spermatogenesis begins with the maturation and differentiation of the germinal spermatogonia. The process is controlled by the secretion of GnRH from the hypothalamus, which stimulates the pituitary to release FSH and LH. FSH stimulates the development of Sertoli cells in the testes, which are responsible for the maturation of spermatids to spermatozoa. LH promotes production of testosterone by Leydig cells. Testosterone concentrations must be maintained to assure the formation of spermatids.²⁴ Both FSH and testosterone are required for initiation of spermatogenesis, but testosterone alone is sufficient to maintain the process.

Testicular Xenobiotics. Xenobiotics can affect any part of the male reproductive tract, but invariably, the end result is decreased sperm production defined as oligospermia, or absent sperm production, azoospermia. In contrast to oogenesis in women, spermatogenesis is an ongoing process throughout life that can be inhibited by decreases in FSH or LH or by Sertoli cell toxicity. Spermatogenic capacity is evaluated by semen analysis, including sperm count, motility, sperm morphology, and penetrating ability. Normal sperm count is greater than 40 million sperm/mL semen, and a count less than 20 million/mL is indicative of infertility.²⁴ Decreased motility (asthenospermia) less than 40% of normal or abnormal morphology (teratospermia) of greater than 40% of the total number of sperm also indicates infertility.^{24,108}

Physiology of Erection. The penis is composed of two corpus cavernosa and a central corpus spongiosum. The internal pudendal arteries supply blood to the penis via four branches. Blood outflow is via multiple emissary veins draining into the dorsal vein of the penis and plexus of Santorini. Within the penis, the corpora cavernosa share vascular supply and drainage because of extensive arteriolar, arteriovenous, and sinusoidal anastomoses.¹²⁸ When penile blood flow is greater than 20 to 50 mL/min, erection occurs. Maintenance of tumescence occurs with flow rates of 12 mL/min. The tunica albuginea limits the absolute size of erection.

In the flaccid state, sympathetic efferent nerves maintain arteriole constriction primarily through norepinephrine-induced α -adrenergic agonism. Whereas α -adrenergic receptor agonism in the erectile tissues decreases cyclic adenosine monophosphate (cAMP) to produce flaccidity, α -adrenergic antagonism can result in pathologic erection (priapism) as a consequence of parasympathetic dominance.¹²⁸ Other vasoconstrictors, such as endothelin, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), and thromboxane A_2 , play a role in maintaining corpus cavernosal smooth muscle tone in contraction, which results in a flaccid state.⁹⁰

Normal penile erection is a result of both neural and vascular effects. Psychogenic neural stimulation arising from the cerebral cortex inhibits norepinephrine release from thoracolumbar sympathetic pathways, stimulates nitric oxide (NO) and acetylcholine release from sacral parasympathetic tracts, and stimulates acetylcholine release from somatic pathways.⁹⁰ Reflex stimulation can also occur from the sacral spinal cord. The afferent limb of the reflex arc is supplied by the pudendal nerves and the efferent limb by the nervi erigentes (pelvic splanchnic nerves).

The central impulses stimulate various neurotransmitters to be released by peripheral nerves in the penis. Nonadrenergic–noncholinergic nerves and endothelial cells produce NO, which is the principal neurotransmitter mediating erection. NO activates guanylate cyclase conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Increasing concentrations of cGMP act as a second messenger, mediating arteriolar and trabecular smooth muscle relaxation to enable increased cavernosal blood flow and penile erection.⁹⁰ Both cGMP and cAMP pathways mediate smooth muscle relaxation. Cholinergic nerves release acetylcholine, which stimulates endothelial cells via M_3 receptors to produce NO and prostaglandin E_2 (PGE_2). PGE_2 and nerves containing vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) increase cellular cAMP to potentiate smooth muscle relaxation.

Penile corpus cavernosal smooth muscle relaxation allows increased blood flow into the corpus cavernosal sinusoids. Expansion of the sinusoids compresses the venous outflow and enables penile erection (Fig. 21–2).

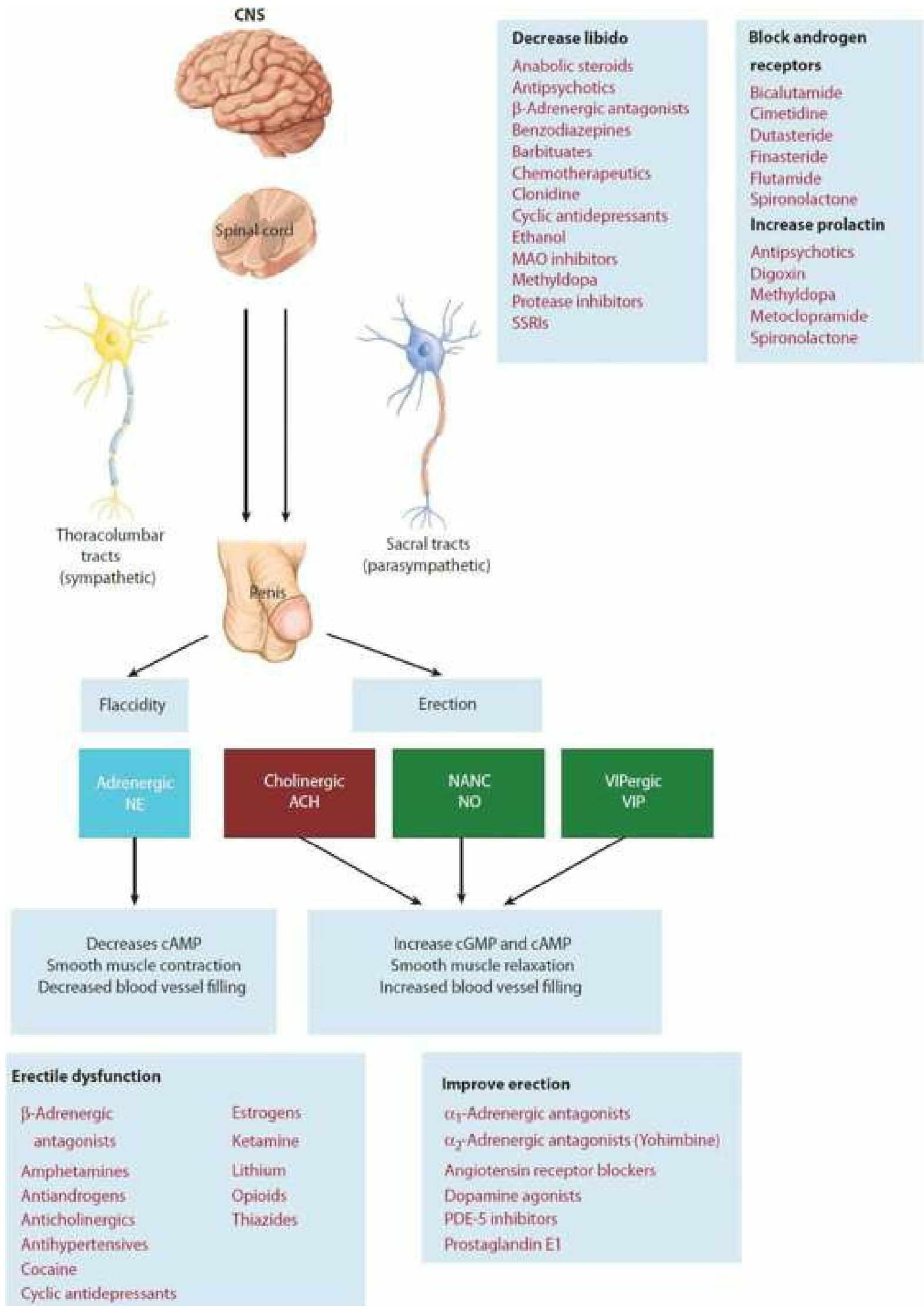


FIGURE 21–2. Schematic of the erection and xenobiotics that cause sexual dysfunction. ACH = acetylcholine; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; MAOI = monoamine oxidase inhibitor; NANC = nonadrenergic-noncholinergic; NE = norepinephrine; NO = nitric oxide; PDE = phosphodiesterase; VIP = vasoactive intestinal peptide; SSRI = selective serotonin reuptake inhibitor.

Sexual Dysfunction

Male sexual dysfunction can result from decreased libido (sexual desire), impotence, diminished ejaculation, and erectile dysfunction. Dopamine, norepinephrine, oxytocin, and adrenocorticotrophic hormone (ACTH) are central neurotransmitters and hormones that facilitate sexual function. Serotonin, prolactin, endogenous opioids, and GABA (γ-aminobutyric acid) inhibit sexual function centrally.³ Libido can be decreased by xenobiotics that block central dopaminergic or adrenergic pathways or by xenobiotics that increase serotonin or prolactin concentrations. Conversely, xenobiotics that increase dopamine can improve sexual function. Sexual dysfunction can also be caused by xenobiotics that decrease testosterone production and by xenobiotics that produce dysphoria. Xenobiotics that affect spinal reflexes can cause diminished ejaculation and erectile dysfunction.¹²⁶

Approximately 30 million men in the United States have erectile dysfunction, with an increased prevalence in older men.⁶ Erectile dysfunction is defined as the inability to achieve or maintain an erection for a sufficiently long period of time to permit satisfactory sexual intercourse⁶ and is divided into the following classifications: psychogenic, vasculogenic, neurologic, endocrinologic, and xenobiotic induced. Xenobiotic-induced erectile dysfunction is associated with the following categories of xenobiotics: antidepressants, antipsychotics, centrally and peripherally acting antihypertensives, CNS depressants, anticholinergics, exogenous hormones, antibiotics, and antineoplastics.^{76,107,126} Treatment of this disorder is varied and includes vacuum-constriction devices, penile prostheses, vascular surgery, and medications that can be administered via the intracavernosal, transdermal, and oral routes.

Antihypertensives. Erectile dysfunction is reported as an adverse effect with all antihypertensives and may be caused, in part, by a decrease in hypogastric artery pressure, which impairs blood flow to the pelvis.¹²⁶ Methyldopa and clonidine both are centrally acting α₂-adrenergic agonists that inhibit sympathetic outflow from the brain. Sexual dysfunction is reported in 26% of patients receiving methyldopa and in 24% of patients receiving clonidine.^{18,93} Erectile dysfunction associated with thiazide diuretics may be related to decreased vascular resistance, diverting blood from the penis.²⁵ Spironolactone acts as an antiandrogen by inhibiting the binding of dihydrotestosterone to its receptors. Impotence related to use of β-adrenergic antagonists is well documented^{5,59,122} and may be caused by unopposed α-adrenergic-mediated vasoconstriction resulting in reduced penile blood flow.

Ethanol. Ethanol is directly toxic to Leydig cells. Chronic ethanol abuse causes decreased libido and erectile dysfunction and is associated with testicular atrophy. In people with alcoholism, liver disease contributes to sexual dysfunction resulting from decreased testosterone and increased estrogen production or decreased breakdown. People with alcoholism can have autonomic neuropathies affecting penile nerves and subsequent erection. Heavy drinkers have more erectile dysfunction than episodic drinkers.¹²⁵

Antidepressants and Antipsychotics. Individuals who take antipsychotics therapeutically have varying degrees of sexual dysfunction related to their underlying disease and their medications. All psychoactive medications are associated with sexual dysfunction to some degree. Monoamine oxidase inhibitors (MAOIs), cyclic antidepressants (CAs), antipsychotics, and selective serotonin reuptake inhibitors (SSRIs) are associated with decreased libido and erectile dysfunction in men.³⁵ Thioridazine is associated with significantly lower LH and testosterone concentrations in men in comparison with other antipsychotics.²⁴ Antidepressants such as bupropion, nefazodone, mirtazapine, and duloxetine have lower incidences of sexual dysfunction in comparison with other antidepressants.¹⁰⁹ Table 21–2 lists xenobiotics associated with sexual dysfunction.

TABLE 21–2. Xenobiotics Associated with Sexual Dysfunction (Particularly Diminished Libido and Impotence)

- α₁-Adrenergic antagonists
- α₂-Adrenergic agonists
- β-Adrenergic antagonists^a
- Amphetamines
- Anabolic steroids

Antiandrogens^a
Anticholinergics^a
Anticonvulsants
Antiestrogens
Benzodiazepines
Calcium channel blockers
Chemotherapeutics
Cimetidine
Clonidine
Cocaine
Cyclic antidepressants
Digoxin
Diuretics
Ethanol
Gonadotropin-releasing hormone agonists^a
Ketoconazole
Lead
Lithium
Methotrexate
Methyldopa
Monamine oxidase inhibitors^a
Opioids
Oral contraceptives
Phenothiazines
Selective serotonin reuptake inhibitors
Spironolactone
Thiazides

^aAssociated with erectile dysfunction.

Xenobiotics Used in the Treatment of Erectile Dysfunction

Intracavernosal Agents. The three most commonly used intracavernosal agents used for erectile dysfunction are papaverine, PGE₁, and phentolamine. Papaverine is a benzylisoquinoline alkaloid derived from the poppy plant *Papaver somniferum*. It exerts its effects through nonselective inhibition of phosphodiesterase (PDE), leading to increased cAMP and cGMP concentrations and subsequent cavernosal vasodilation. Papaverine was used for the treatment of cardiac and cerebral ischemia but had limited efficacy. Presently, it is used as intracavernosal therapy for erectile dysfunction alone or

in conjunction with phentolamine. Systemic adverse effects include dizziness, nausea, vomiting, hepatotoxicity, metabolic acidosis with elevated lactate concentration with oral administration, and cardiac dysrhythmias with intravenous use. Intracavernosal administration is associated with penile fibrosis, which is usually a dose-related phenomenon, although fibrosis can also occur with limited use.³⁷ More concerning is the development of priapism with papaverine use.

Prostaglandin E₁ (Alprostadil) is a nonspecific agonist of PG receptors resulting in increased concentrations of intracavernosal cAMP, cavernosal smooth muscle relaxation, and penile erection. It is effective via intracavernosal administration as monotherapy. Other preparations include an intraurethral preparation, which is less effective, and a topical gel formulation.⁵⁶ Penile fibrosis can occur, but the incidence is lower compared with papaverine. Other adverse effects include penile pain, secondary to its effects as a nonspecific PG receptor agonist, and priapism.

Phentolamine is a competitive α -adrenergic antagonist at both α_1 and α_2 receptors. It effects erection by inhibiting the normal resting adrenergic tone in cavernosal smooth muscle, thus allowing increased arterial blood flow and erection. Intracavernosal use can cause hypotension, reflex tachycardia, nasal congestion, and gastrointestinal (GI) upset. Penile fibrosis and priapism are also reported.

Oral Agents. Since the development of the PDE-5 inhibitors, oral therapy has replaced intracavernosal injections as the mainstay for treatment of erectile dysfunction. Sildenafil was the first drug developed followed by vardenafil and tadalafil. These medications share a mechanism of action but differ in their pharmacokinetics. PDE-5 inhibitors increase NO-induced cGMP concentrations by preventing PDE breakdown of cGMP, enhancing NO-induced vasodilation to promote penile vascular relaxation and erection.²³

After oral administration, sildenafil is rapidly absorbed with a bioavailability of 40% and a median peak serum concentration of 60 minutes. Its mean volume of distribution is 105 L, and its elimination half-life is 3 to 5 hours. Metabolism is primarily by the CYP3A4 pathway with some minor metabolic activity via the CYP2C9 pathway. Serum concentrations of sildenafil are increased in patients older than 65 years as well as those with hepatic dysfunction or severe kidney disease (creatinine clearance <30 mL/min) and when used with CYP3A4 inhibitors (macrolide antibiotics, cimetidine, antifungal agents, protease inhibitors).³¹

Vardenafil has more selective inhibition of PDE-5 and less inhibition of PDE-6 compared with sildenafil. After oral administration, it has a 14% bioavailability, a volume of distribution of 208 L, a median peak serum concentration of 60 minutes and an elimination half-life of 4 to 5 hours. The CYP3A4 pathway is the primary hepatic metabolic pathway with minor contributions from CYP3A5 and CYP2C9 isoenzymes.^{17,20} The primary metabolite, M1, has PDE-5 inhibitory activity but is four times less potent than vardenafil.²⁰ As with sildenafil, vardenafil concentrations are increased in patients older than 65 years, and those with hepatic dysfunction or severe kidney disease (creatinine clearance <30 mL/min) and when used with CYP3A4 inhibitors (macrolide antibiotics, cimetidine, antifungal agents, protease inhibitors).⁶⁴

Tadalafil has a median peak serum concentration of 2 hours and a mean elimination half-life of 17.5 hours. It is predominantly metabolized by CYP3A4 isoenzymes. Unlike sildenafil and vardenafil, serum concentrations are not affected by age, hepatic dysfunction, kidney disease, or CYP3A4 inhibitors. However, the Food and Drug Administration (FDA) has issued recommendations to decrease the dosage of all PDE-5 inhibitors if used in conjunction with atazanavir.⁷

The most common adverse effects of the PDE-5 inhibitors are headache, flushing, dyspepsia, and rhinitis, which are related to PDE-5 inhibitory effects on extracavernosal tissue.⁵⁵ Blurred vision, increased light perception, and transient blue-green tinged vision are also reported and are related to the weak PDE-6 inhibition of sildenafil in the retina.⁵⁵ Vardenafil and tadalafil are associated with infrequent abnormal vision, including blurred and abnormal color vision.⁵⁷

More serious adverse effects of PDE-5 inhibitors include myocardial infarction, when used alone or with nitrates; subaortic obstruction; stroke; transient ischemic attack; priapism; and hearing loss.^{12,44,63,84,110,114} PDE-5 inhibitors are associated with adverse bleeding events, including epistaxis, variceal bleeding, intracranial hemorrhages, and aortic dissection. The FDA updated the labeling of the PDE-5 inhibitors warning of possible vision loss after reported cases of nonarteritic ischemic optic neuropathy (NAION) associated with PDE-5 inhibitor use.^{9,21,44}

When taken alone, the vasodilatory effects of PDE-5 inhibitors cause a modest decrease in systemic blood pressure. However, because of their mechanism of action via cGMP inhibition and vascular vasodilation, PDE-5 inhibitors can have synergistic interactions with the vasodilatory effects of nitrates, resulting in profound hypotension.^{23,65} A study of healthy male volunteers taking sildenafil demonstrated significantly less tolerance to a nitroglycerin infusion in comparison with placebo.¹²³ Because of this interaction, patients with acute myocardial ischemic syndromes using PDE-5 inhibitors should avoid taking organic nitrates as well.³¹ α_1 -Adrenergic antagonists are also contraindicated with concomitant PDE-5 inhibitor use because of increased hypotensive effects.⁶⁵ Hypotension occurred in patients using vardenafil in combination with terazosin and tamsulosin⁶⁵ and in patients using tadalafil with doxazosin.⁶⁶ However, patients using tadalafil with tamsulosin did not develop hypotension.⁶⁶

Yohimbine, an indole alkylamine alkaloid from the West African yohimbe tree (*Corynanthe yohimbe*), is an α_2 -

adrenergic antagonist with cholinergic activity used to treat erectile dysfunction and postural hypotension associated with anticholinergic drugs.⁷³ It is structurally similar to reserpine. Other names for yohimbine include Aphrodyne, corynine, hydroaergotocin, quebrachine, and the street name “yo-yo.”⁷⁴ Its use in the treatment of impotence is based on the theory that erection is linked to cholinergic stimulation and α_2 antagonism, resulting in an increase inflow and decrease outflow of blood to the penis. Although the agent Aphrodex, which contained 5 mg of yohimbine, 5 mg methyltestosterone, and 5 mg strychnine, improved performance in men with erectile failure,⁷⁷ its distribution was halted in 1973 because of safety concerns.¹⁰⁵

Yohimbine can be obtained by prescription, but extracts are also available in “health food” products marketed as “vitalizing agents for men and women.”³⁹ Yohimbine can also be extracted from the Rauwolfia root.⁴⁹ The “therapeutic” dose is 2 to 6 mg three times daily. The drug is rapidly absorbed, with peak serum concentrations occurring in 45 to 60 minutes. The half-life is 36 minutes, and clearance is by hepatic metabolism without renal excretion.⁹⁶ Maximum pharmacologic effects occur 1 to 2 hours after ingestion, and effects persist for 3 to 4 hours.⁷⁴

Because the erectile process involves various neurotransmitters, a single xenobiotic would be expected to only have a partial effect. In a double-blind study of 100 men with erectile failure treated with 18 mg/d of yohimbine, 42.6% of the treatment group and 27.6% of the placebo group reported some improvement in erectile function, which was not statistically significant.⁸⁹ Another study that compared a higher dose of yohimbine and placebo in 82 elderly men showed a statistically significant improvement with treatment.¹¹⁶

Adverse effects can occur with relatively low doses of yohimbine. Tachycardia, hypertension, mydriasis, diaphoresis, lacrimation, salivation, nausea, vomiting, and flushing can occur after intravenous administration.⁶⁰ Ten milligrams of yohimbine can elicit manic symptoms in patients with bipolar disorder,¹⁰² and 15 mg/d is associated with bronchospasm⁶⁸ and a lupuslike syndrome.¹⁰⁶ A 16 year-old woman who ingested 250 mg of yohimbine powder, purchased for its purported aphrodisiac activity, developed an acute dissociative reaction with weakness, paresthesias, headache, nausea, palpitations, and chest pain. She also developed tachycardia, tachypnea, diaphoresis, tremors, and a rash. Her symptoms resolved after 36 hours without treatment.⁷⁴ Another report describes a 62 year-old man who ingested 200 mg of yohimbine and developed tachycardia, hypertension, and a brief period of anxiety that resolved without treatment.⁴⁹ Symptomatic patients who ingest yohimbine should receive activated charcoal and should be observed until asymptomatic. Clonidine has been recommended for treatment of yohimbine’s central and peripheral effects.⁷⁴ β -Adrenergic antagonists may attenuate some of the peripheral toxicity but may also result in unopposed α_1 -adrenergic activity and worsening of hypertension and should be avoided. Benzodiazepine administration may be sufficient for the treatment of agitation and sympathomimetic effects related to yohimbine.

Sublingual apomorphine effects erection through activation of central dopaminergic pathways, most likely D₂ receptors in the paraventricular nucleus of the hypothalamus.⁵⁸ It reaches maximum serum concentrations within 40 to 60 minutes after sublingual administration and is metabolized hepatically with a half-life of 2 to 3 hours.¹¹ Common adverse effects are nausea, vomiting, headache, dizziness, and syncope. Unlike the PDE-5 inhibitors, apomorphine is not associated with hypotension when used with antihypertensive, such as nitrates.

Priapism. Priapism is defined as prolonged involuntary erection unassociated with sexual stimulation. Subtypes of priapism are ischemic (characterized by low cavernosal blood flow), nonischemic (characterized by increased arterial flow), and stuttering (recurrent ischemic priapism).⁸⁷ It most commonly occurs during the third and fourth decades of life and is caused by inflow of blood to the penis in excess of outflow. The corpora cavernosa become firm and the corpus spongiosum flaccid. Intracavernosal pressures can exceed arterial systolic pressure, resulting in cell death. Priapism can occur from an imbalance in neural stimuli or interference with venous outflow or as a result of xenobiotic-induced inhibition of penile detumescence. α -Adrenergic antagonists prevent constriction of blood vessels supplying erectile tissue, resulting in priapism.¹²⁸ One in 10,000 patients taking trazodone develops priapism, which is thought to be related to its α -adrenergic antagonist effects.¹⁰⁵ Priapism can result from the injection of papaverine for the treatment of impotence.⁸⁷ Other xenobiotics associated with xenobiotic-induced priapism include prazosin, labetalol, guanethidine, hydralazine, phenothiazines, androgens, anticoagulants, ethanol, marijuana, and cantharidin^{62,128} (Table 21–3).

TABLE 21–3. Xenobiotics Associated with Priapism

- Alprostadil
- Androgens
- Anticoagulants
- Dalteparin

Heparin

Warfarin

Antidepressants

Bupropion

Phenelzine

SSRIs

Trazodone

Antihypertensives

α -Adrenergic antagonists

Guanethidine

Hydralazine

Labetalol

Phentolamine

Antipsychotics

Aripiprazole

Butyrophenones

Clozapine

Olanzapine

Quetiapine

Risperidone

Ziprasidone

Cantharidin

Carukia barnesi (Irukandji syndrome)

Cocaine

Diazepam

Heparin

Hydroxyzine

Intravenous fat emulsions (in total parenteral nutrition)

Lithium

Methylphenidate

Oxcarbazepine

Papaverine

Phentolamine

Phosphodiesterase-5 inhibitors

Prednisone

Propofol

Spider envenomation

Latrodectus mactans (black widow)

Phoneutria nigriventer

(Brazilian wandering spider)

Yohimbine

SSRI = selective serotonin reuptake inhibitor.

The goal in the treatment of priapism is detumescence with retention of potency. Initial therapy includes sedation with benzodiazepines, analgesia with opioids, ice packs, treatment of underlying systemic diseases such as sickle cell disease, and early urologic consultation. Aspiration with or without 9% NaCl solution irrigation of the corpora cavernosa may be effective. If priapism occurs secondary to α_1 -adrenergic antagonism, an α_1 -adrenergic agonist (100–500 $\mu\text{g/mL}$ phenylephrine solution) can be instilled into the corpora cavernosa at a dosage of 0.5 to 1 mL every 3 to 5 minutes up to 1 hour.⁸⁷ Oral terbutaline (5–10 mg) was effective for PGE₁-induced prolonged erections.^{75,103} For ischemic priapism symptoms greater than 4 hours, the American Urological Association guidelines do not recommend oral sympathomimetics.⁸⁷ Intracavernosal methylene blue has been used successfully as an alternative to intracavernosal sympathomimetics.⁸⁰ If the above measures fail, an operative venous shunt placement may be required.^{117,128}

FEMALE FERTILITY

The female reproductive system consists of the female gonadal organs and the respective hormonal system (Fig. 21–3). Fertility encompasses the reproductive system, the process of oocyte fertilization, and gestation. Female infertility may result from changes in hormone concentrations, direct toxicity to the ovum, interference with the transport of the ovum, or inhibition of implantation of the ovum in the uterus. Women usually notice reproductive abnormalities more quickly than men because menses may be affected, although infertility may occur while normal menses persists. Evaluation of female fertility is more difficult because of the complexity of the systems involved and the inaccessibility of the female germ cell, but it is feasible and involves investigations of the anatomy and hormonal concentrations. The following is a discussion of oogenesis, xenobiotics that disrupt oogenesis, and xenobiotics that affect early embryo gestation.

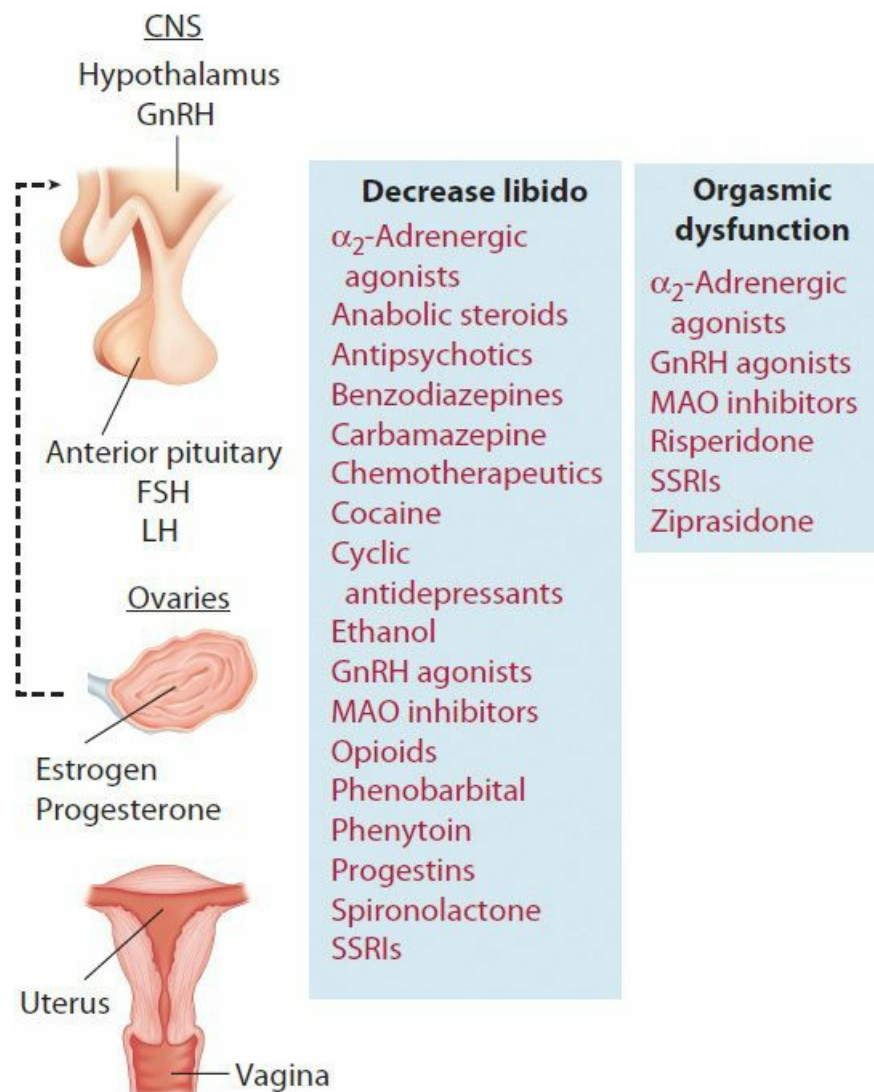


FIGURE 21–3. Schematic of female reproductive axis and sites of xenobiotic action. CNS = central nervous system; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor.

Oogenesis

In contrast to men, women have a limited number of reproductive cells (ovarian follicles). Follicles are most numerous while a fetus is in utero, with the number decreasing to approximately 2 million at birth. By the time a woman reaches puberty, the majority of follicles have degenerated, leaving 300,000 to 400,000 ova, of which approximately 400 will eventually produce mature ova during a woman's reproductive years. In contrast, men produce millions of spermatozoa each day. The process of oogenesis requires secretion of GnRH from the hypothalamus, resulting in production of LH and FSH from the pituitary, which are required for ovarian follicle maturation.²⁴ FSH induces early maturation by stimulating granulosa and thecal cell proliferation and estrogen production. LH is required for ovulation and for the formation of the corpus luteum. The corpus luteum continues estrogen production and produces progesterone, which stimulates the uterus to develop an endometrium receptive to any fertilized ovum. Successful ovulation requires not only hormone secretion but also appropriate cyclic secretion.

Female Sexual Dysfunction

The National Health and Social Life Survey found that 43% of women in the United States (in comparison with 31% of men) reported having sexual dysfunction.⁶⁹ In 1999, a consensus panel of the American Foundation for Urologic Disease modified the four categories of female sexual dysfunction in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision to include the following: (1) sexual desire disorders, which include hypoactive sexual desire disorder and sexual aversion disorder; (2) sexual arousal disorder; (3) orgasmic disorder; and (4) sexual pain disorders, which include dyspareunia, vaginismus, and noncoital sexual pain disorder.^{2,15} The organic etiologies of female sexual dysfunction parallel those of male sexual and erectile dysfunction: vascular, neurologic, muscular, psychogenic, endocrinologic, and xenobiotic-induced causes.¹⁹ The medications implicated in female sexual dysfunction are similar to those mentioned earlier that decrease male fertility with antihypertensives; antidepressants, especially SSRIs; and antipsychotics as the most frequent causes.⁴⁵

Treatments for xenobiotic-induced female sexual dysfunction include decreasing medication dosages, switching to alternate medications with less adverse effects on sexual function such as bupropion and nefazodone, temporary cessation of the medication (drug holiday), or adding another medication to stimulate sexual function. Bupropion alone was as effective as fluoxetine for the treatment of depression but with less sexual dysfunction,³⁶ and when used in conjunction with SSRIs, bupropion improved sexual function compared with SSRIs alone.^{30,34} Sildenafil was successful for treating spinal cord–induced¹¹³ and antidepressant-induced sexual dysfunction,⁹⁴ but larger trials had mixed results with sildenafil for sexual arousal disorder.^{16,27} Sublingual apomorphine improved sexual function in women with hypoactive sexual disorder.²⁶

The majority of medical therapy for female sexual dysfunction is centered on hormonal manipulation, both estrogen and androgen supplementation. Estrogen replacement therapy is available in oral, dermal, vaginal ring, and topical cream formulations alone or in combination with progesterone.¹²¹ Estrogen therapy is associated with a higher incidence of coronary disease, breast cancer, stroke, and venous thromboembolism. Androgen therapy includes testosterone, which is available in oral, dermal, and topical preparations, and dehydroepiandrosterone.⁸ Adverse effects are weight gain, increased cholesterol concentrations, and androgenization.

Abortifacients. An abortifacient is defined as a xenobiotic that affects early embryonic gestation to induce abortion. Xenobiotics may act by flushing the zygote from the fallopian tube, blocking the uterine horn inhibiting implantation, inducing fetal resorption, or producing oxytocinlike activity that results in uterine irritation and contraction. Abortifacients may also indirectly affect pregnancy by altering hormonal concentrations through placental inhibition of human chorionic gonadotropin or progesterone production or through interference with progesterone receptors.

The toxic effects of abortifacients are varied. Many produce GI symptoms such as abdominal pain, nausea, and vomiting. Abdominal pain may be related to the oxytocic uterine effects associated with misoprostol and mifepristone, cytotoxic effects on the GI mucosa associated with methotrexate, leading to stomatitis and ulcers or hepatotoxicity associated with pennyroyal oil.³² Mifepristone inhibits implantation or has abortive effects that can cause severe vaginal bleeding. Other toxic effects are not necessarily related to their abortive mechanisms but due to the specific xenobiotic. Plant-derived abortifacients such as *Aristolochia* can cause nephrotoxicity, dong quai can cause photosensitivity, blue cohosh can cause seizure, and quinine can cause cardiac dysrhythmias.⁹² Congenital abnormalities of the scalp and skull defects, cranial nerve palsies, and limb defects such as talipes equinovarus are also reported with misoprostol use that did not terminate pregnancy³² (Table 21–4).

TABLE 21–4. Xenobiotics Used as Abortifacients

Source	Common Name	Xenobiotic	Mechanism/Toxicity
Inhibit Implantation			
<i>Abrus precatorius</i>	Leparchy pea	Abrin	Cytotoxic to albumin
<i>Acanthospermum hispidum</i>	Bristly starbur	<i>Acanthospermum hispidum</i>	Preimplantation effects
<i>Aristolochia</i> spp	Birthwort	Aristolochic acid	Nephrotoxicity
<i>Momordica charantia</i>	Bitter melon	α -Momocharin	Similar to trichosanthin
<i>Cajanus cajan</i> "Hormonal therapy"	Pigeon pea —	Cajanus cajan Levonorgestrel, Yuzpe regimen, estradiol–levonorgestrel	Preimplantation effects Nausea, vomiting, abdominal pain, vaginal bleeding
<i>Lagenaria breviflora</i>	Wild colocynth	<i>Lagenaria breviflora</i>	Preimplantation effects
<i>Juniperus sabina</i>	Savin	Oil of savin	Hepatotoxicity in mice
<i>Ricinus communis</i>	Caster	Ricin	Cytotoxic to albumin
<i>Ruta graveolens</i>	Rue	Chalepurn	Hepatotoxicity, nephrotoxicity, photodermatitis
"Selective progesterone receptor modulator"	—	Mifepristone, ulipristal	Nausea, vomiting, abdominal pain, vaginal bleeding
Abortive			
<i>Ranunculus</i> spp	Buttercup	Devil's claw	Similar to pennyroyal oil
<i>Angelica sinensis</i>	Dong quai	Furanocoumarin, phytoestrogen	Anticoagulant effects, gynecomastia, photodermatitis
<i>Daphne genkwa</i>	Lilac daphne	Yuanhuacine	
Lyso disinfectant	—		Death after intrauterine administration
<i>Mentha pulegium</i>	Pennyroyal	Pulegone	Hepatotoxicity
Methotrexate	—		Cytotoxic effects
Mifepristone	—		Nausea, vomiting, abdominal pain, vaginal bleeding
<i>Momordica charantia</i>	Bitter melon	α -Momocharin	Similar to trichosanthin
<i>Moringa oleifera</i>	Horseradish tree	<i>Moringa oleifera</i>	100% abortifacient in rats
<i>Podophyllum peltatum</i>	Mayapple	Podophyllin	Podophyllin toxicity
<i>Trichosanthes kirilowii</i>	Snake gourd	Trichosanthin (compound Q)	Inhibits protein synthesis, ↓ HCG, ↓ progesterone
Cytotoxic			
<i>Aristolochia</i> spp	Birthwort	Aristolochic acid	Nephrotoxicity
<i>Caulophyllum thalictroides</i>	Blue cohosh	Methylcytosine	Nicotinic activity
<i>Cimicifuga racemosa</i>	Black cohosh	unknown	Nausea, vomiting, headache, rare hepatotoxicity
<i>Cinchona</i> spp	Quinine bark	Quinine	Cinchonism
<i>Ergot</i>	Ergot	Ergotamines	Vasospasm
<i>Lagenaria breviflora</i> Robert	Wild colocynth	<i>Lagenaria breviflora</i> Robert	Antiimplantation, oxytocic
Misoprostol		Prostaglandin E ₂ analogue	Marketed as Cytotec for gastric ulcers and Arthrotec

HCG = human chorionic gonadotropin

In a US poison center study, five of 43 pregnant women who intentionally overdosed used known abortifacients, including quinine, misoprostol, methylergonovine, and oral contraceptives. Four of these patients developed vaginal bleeding and cramping, but no short-term (1–3 days) fetal demise was reported.¹⁰¹ The use of abortifacients is more common in underdeveloped countries and in people without access to safer methods for termination or prevention of pregnancy.

Toxicity of Aphrodisiacs

Aphrodisiacs heighten sexual desire, pleasure, or performance and include xenobiotics from the plant, animal, and mineral kingdoms.³⁸ The search for an effective aphrodisiac has continued for thousands of years. Ancient fertility cults used

Datura, belladonna, and henbane as aphrodisiacs. Yohimbine has been used by African cultures to enhance sexual prowess, and mandrake was used in medieval Europe. A small sampling of other xenobiotics recommended as aphrodisiacs include oysters, live beetles, vitamin E, ginseng, saffron, horny goat weed, and tongkat ali. Because there are few measurable objective parameters, research in this area is lacking. Most published studies evaluating aphrodisiacs have been conducted in animals, and little information is available in humans. Toxicity can result from the aphrodisiac or adulterants¹³ (Table 21–5).

TABLE 21–5. Xenobiotics Used as Aphrodisiacs

<i>Xenobiotic</i>	<i>Toxicity</i>
<i>Oral</i>	
Cantharidin	Vesicant actions—GI mucositis and hemorrhage, hematuria
Cathinone (hagigat)	Hypertension, tachycardia
Dapsone	Methemoglobinemia, hemolysis
Ginseng	Ginseng abuse syndrome, vaginal bleeding
Lead	Anemia, abdominal pain
<i>Mandragora officinarum</i> (mandrake)	Anticholinergic
<i>Myristica fragrans</i> (nutmeg)	Hallucinogen, GI upset
<i>Tribulus terrestris</i> (Puncturevine)	Gynecomastia
Yohimbine	Paresthesias, hypertension
<i>Topical</i>	
Cantharidin	Vesicant actions—GI mucositis and hemorrhage, hematuria
Bufotoxin	Cardioactive steroid
<i>Inhalation</i>	
Alkyl nitrites (amyl, butyl, isobutyl nitrites)	Hemolytic anemia, methemoglobinemia, orthostasis

Dopamine, NO, oxytocin, and ACTH facilitate sexual behavior. Dopamine stimulates the forebrain and midbrain and leads to an increase in sexual response and arousal. In animals, dopamine agonists, such as apomorphine and quinpirole, have proerectile effects through stimulation of dopamine pathways, increasing NO in the paraventricular nucleus in the hypothalamus, and releasing oxytocin.⁹⁰ Other preparations tested for the treatment of impotence include bromocriptine,^{1,22} nitroglycerin,⁹¹ zinc,¹⁰ oxytocin,⁷² and LH.⁷¹ Endogenous opioids, GABA, and norepinephrine are associated with decreased sexual behavior. Serotonin is generally inhibitory to sexual function, but the effects are dependent on the receptor subclass. Whereas 5-HT_{1A} receptor stimulation inhibits erection but facilitates ejaculation in rats, 5-HT_{2C} receptors facilitate male sexual behavior.⁹⁰ Various serotonergic drugs, including trazodone, nefazodone, bupropion, and clomipramine, are reported to improve sexual dysfunction.^{105,127}

URINARY SYSTEM

The urinary system is composed of the kidneys, ureters, bladder, and urethra (Chap. 28). Many xenobiotics are concentrated by the kidneys and eliminated in the urine. The following discusses the effect of xenobiotics on the bladder and urine.

Bladder Anatomy and Physiology. The bladder is a hollow, muscular reservoir composed of two parts—the body and the neck—and normally stores up to 350 to 450 mL of urine in adults. A smooth muscle, the detrusor muscle, makes up the bulk of the body and contracts during urination. Urine from the ureters enters the bladder at the uppermost part of the trigone, an area in the posterior wall of the bladder, and leaves via the neck and the posterior urethra. Surrounding the neck and posterior urethra is smooth muscle interlaced with elastic tissue to form the internal sphincter. Sympathetic innervation from the lumbar spinal cord to the internal sphincter maintains smooth muscle contraction. Distal to the internal sphincter is an area with voluntary skeletal muscle that forms the external sphincter and is innervated by somatic pudendal nerves.

The nerve supply and neurophysiology of urination involve interplay among lumbar sympathetic nerves, sacral parasympathetic nerves, and sacral somatic nerves. Figure 21–4 illustrates the physiology of micturition. With bladder filling, norepinephrine is released by sympathetic postganglionic fibers. α -Adrenergic receptors predominate in the internal sphincter and the bladder neck, and β -adrenergic receptors supply the detrusor wall of the bladder. Stimulation of α -

adrenergic receptors results in internal sphincter contraction and increased bladder outlet resistance, and stimulation of β -adrenergic receptors leads to detrusor relaxation and bladder filling.¹¹⁹ In micturition, parasympathetic pre- and postganglionic fibers release acetylcholine to M_2 and M_3 muscarinic receptors in the detrusor muscle. Stimulation of M_3 receptors is responsible for detrusor muscle contraction and bladder emptying.³⁰ Conversely, anticholinergics prevent bladder emptying and result in urinary retention.^{28,29,33,48,53,88}

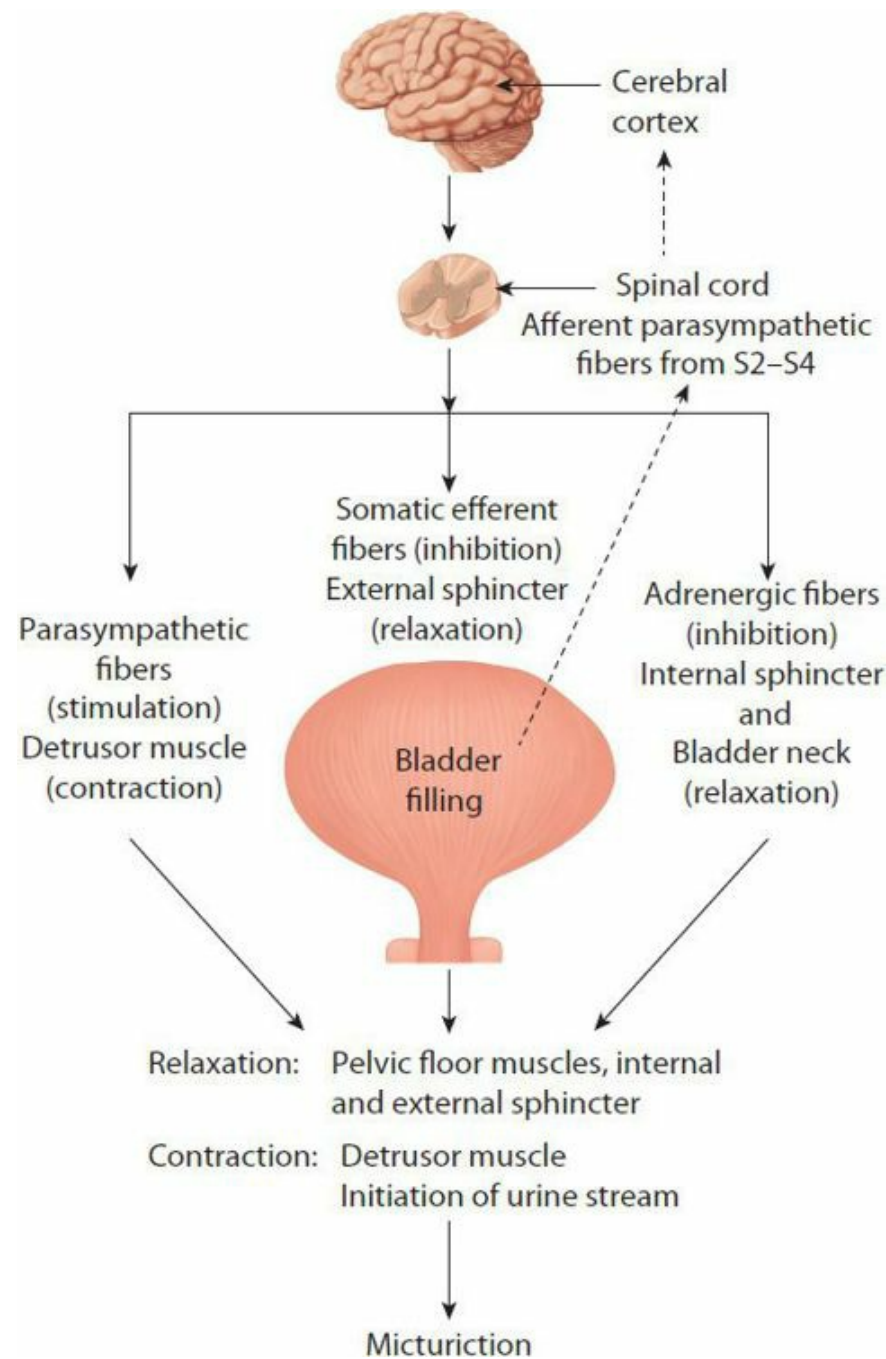


FIGURE 21–4. Schematic description of the physiology of micturition. (The dotted lines show the efferent pathway.)

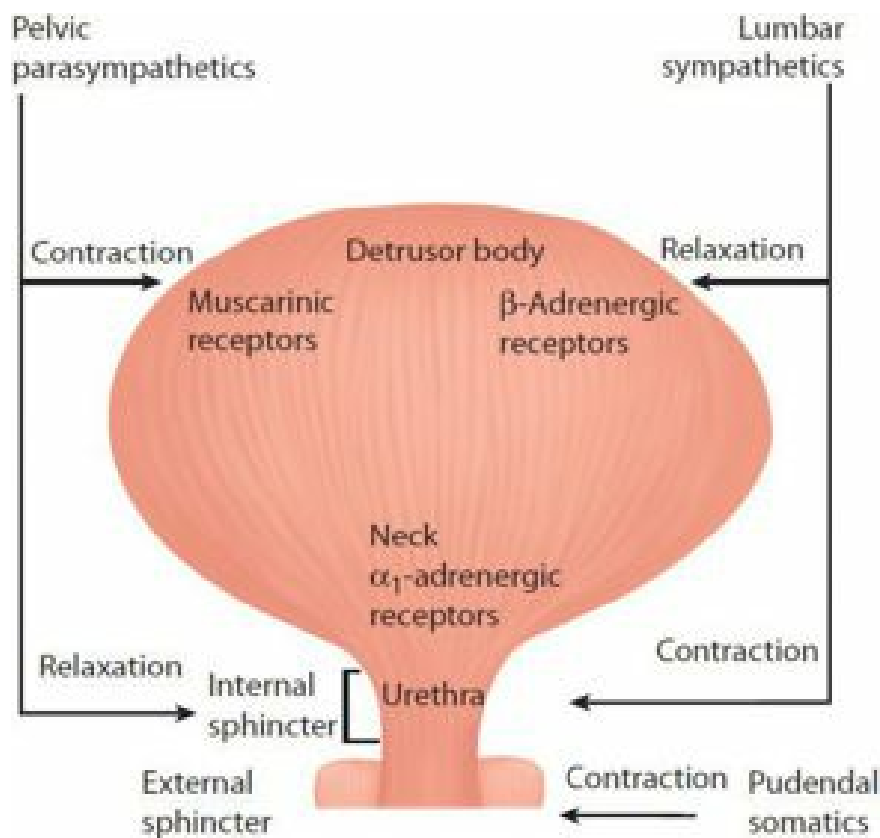
Urinary Abnormalities. Urinary incontinence is common in elderly adults. As age increases, bladder size decreases, resulting in more frequent emptying. Early detrusor contraction, even with low bladder volumes, occurs more commonly in elderly adults, causing a sense of urgency. There are many etiologies for urinary incontinence, including various xenobiotic exposures (Fig. 21–5). General or regional anesthesia, bladder instrumentation, and medications may produce bladder atony, leading to incontinence.³³ Functional incontinence can also result from use of any medication that causes impaired cognition or decreased mobility as recognized with the use of sedative–hypnotics and opioids.³³ Xenobiotics used in the treatment of urinary incontinence include the anticholinergics darifenacin, fesoterodine oxybutynin, solifenacin, tolterodine, trospium chloride, imipramine, botulinum toxin A, and venlafaxine. Venlafaxine is a serotonin and norepinephrine reuptake inhibitor that acts centrally at the sacral cord pudendal motor nucleus to stimulate urethral rhabdosphincter contraction.⁴² Urinary retention can be obstructive, neurogenic, psychogenic, or pharmacologic in origin. Medications associated with urinary retention include sympathomimetics, anticholinergics, antidysrhythmics (quinidine, procainamide, disopyramide), antidepressants, antipsychotics, hormonal agents (progesterone, estrogen, testosterone), and muscle relaxants.^{33,48} In men older than 50 years, benign prostatic hyperplasia is the most common cause of bladder outlet obstruction, leading to

decreased urinary output and urinary retention. Treatment of benign prostatic hyperplasia consists of 5 α -reductase inhibitors and α -adrenergic antagonists. 5 α -Reductase inhibitors (finasteride, dutasteride) block the conversion of testosterone to dihydrotestosterone to decrease prostate volume.⁸³ α_1 -Adrenergic antagonists (doxazosin, terazosin, alfuzosin, tamsulosin) decrease urethral α -adrenergic contraction.⁵⁰ Table 21–6 lists xenobiotics associated with urinary retention and incontinence.

TABLE 21–6. Xenobiotics That Cause Urinary Retention and Incontinence

<i>Retention</i>	<i>Incontinence</i>
α_1 -Adrenergic agonists	α_1 -Adrenergic antagonists
Amantadine	Antipsychotics
Antihistamines	Clozapine
Anticholinergics	Chlorpromazine
Atropine	Haloperidol
Dicyclomine	Thioridazine
Glycopyrrolate	Cholinesterase inhibitors
Hyoscyamine	Estrogen hormone replacement therapy
Ipratropium	Diuretics
Oxybutynin	Naloxone (for opioid-induced retention)
Tiotropium	SSRIs
Tolterodine	
Antipsychotics	
Aripiprazole	
Olanzapine	
Phenothiazines	
Risperidone	
Quetiapine	
Ziprasidone	
Atomoxetine	
Baclofen (intrathecal)	
Benzodiazepines	
Botulinum toxin	
Calcium channel blockers	
Carbamazepine	
Cyclic antidepressants	
Cyclopentolate	
Dantrolene	
Disopyramide	
Flecainide	
Imiquimod	
Kava	
MDMA	
Mirtazapine	
NSAIDs	
Opioids	
SSRIs	
Citalopram	
Duloxetine	
Escitalopram	
Fluoxetine	
Fluvoxamine	
Milnacipran	
Reboxetine	
Theophylline	

NSAID = nonsteroidal antiinflammatory drug; SSRI = selective serotonin reuptake inhibitor.



External sphincter (contraction)

Duloxetine
Reboxetine

Detrusor (contraction)

Bethanechol
Cholinesterase inhibitors
Carbamates
Donepezil
Galantamine
Organic phosphorus compounds
Rivastigmine

Internal sphincter (contraction)

α_1 -Adrenergic agonists
Ephedrine
Midodrine
Pseudoephedrine
Methamphetamine
MDMA

Internal sphincter (relaxation)

α -Adrenergic antagonists
Doxazosin
Phentolamine
Prazosin
Terazosin
Antipsychotics
Clozapine
Thioridazine

Detrusor (relaxation)

Anticholinergics
Amantadine
Antihistamines
Astemizole
Atropine
Cyclic antidepressants
Cyclopentolate
Dicyclomine
Hyoscyamine
Ipratropium
Dicyclomine
Oxybutynin
Propantheline
Tolteridine
Antipsychotics
Clozapine
Phenothiazines
Risperidone
Ziprasidone
 α_1 -Adrenergic antagonists
Botulinum toxin
Calcium channel blocker
Flunarizine
Type I antidysrhythmics
Cyclic antidepressants
Disopyramide
Flecainide

FIGURE 21–5. Graphic of the bladder and sites of xenobiotic effects. MDMA = 3,4-methylenedioxy-N-methylamphetamine.

Abnormalities in Urinalysis. Abnormalities of the urinalysis are often useful in identifying xenobiotic exposures. Crystalluria is a common finding and may be normal, but the presence of crystals may aid in diagnosis. Crystal formation is dependent on supersaturation of the urine and changes in the urine temperature or pH. The most common crystals are calcium oxalate, uric acid, and phosphate. However, crystals of various xenobiotics alone or in combination with other crystals may be seen in ingestions.⁴⁶ The urinalysis in patients who ingest ethylene glycol may reveal calcium oxalate or hippurate crystals in 50% of cases. Calcium oxalate crystals are monohydrates (prism or needlelike) or dihydrates (envelope shaped). Hippurate crystals are needle shaped.⁹⁷ Birefringent single or conglomerates of hexagonal crystals are noted after massive primidone poisoning and result from precipitation of primidone in the urine.¹¹⁸ Crystalluria may be present with therapeutic doses of salicylate, phenacetin, sulfonamide, and quinolones. Oral sodium phosphate preparations for bowel cleansing have caused calcium phosphate calcifications leading to acute phosphate nephropathy.⁷⁸ After large exposures, crystals can be seen with methotrexate, amoxicillin, cephalexin, ampicillin, and indinavir (Table 21–7).

TABLE 21–7. Xenobiotics That Cause Crystalluria

Antivirals
Acyclovir
Ganciclovir
Valacyclovir
Ampicillin
Amoxicillin
Ascorbic acid
Cephalexin
Ethylene glycol
Felbamate
Flucytosine
Foscarnet
Melamine
Methotrexate
Orlistat
Nitrofurantoin
Primidone
Protease inhibitors
Atazanavir
Indinavir
Quinolones
Salicylates
Sodium phosphate

Sulfonamides

Sulfadiazine

Sulfamethoxazole

Thiabendazole

Triamterene

Xylitol

Urine color is dependent on several factors, including pH, concentration, natural pigments, and length of time exposed to air. Normal urine specimens should be clear and yellow in coloration. Whereas dilute urine secondary to diuretic use, diabetes mellitus, diabetes insipidus, or simply hydration can appear colorless, concentrated urine is usually orange. Fluorescein, found in some antifreeze products, can be detected by illumination of the urine with a Wood lamp, although this diagnostic test has poor sensitivity and specificity.¹²⁰ One study used urine samples from a group of unpoisoned children and three urine samples with added sodium fluorescein to examine physicians’ ability to detect urinary fluorescence with a Wood lamp against a fluorometer. The fluorometer reported fluorescence in 100% of the urine samples, but the physicians reported fluorescence in 70% to 80% of the samples.⁹⁸ Urinary fluorescence, even when present, is not useful as a diagnostic test. [Table 21–8](#) lists other causes of colored urine.

TABLE 21–8. Common Causes of Colored Urine

Milky white

Chyle

Lipids

Neutrophils

Propofol

Reddish-brown

Anthraquinone

Bilirubin

Chloroquine

Ibuprofen

Levodopa

Methyldopa

Phenacetin

Phenazopyridine

Phenothiazines

Phenytoin

Porphyrins

Trinitrophenol

Reddish-orange

Aminopyrine
Aniline dyes
Antipyrine
Chlorzoxazone
Doxorubicin
Ibuprofen
Mannose
Phenacetin
Phenazopyridine
Phenothiazines
Phenytoin
Rifampin
Salicylazosulfapyridine
Sulfasalazine

Red

Anthraquinones
Beets
Blackberries
Eosin
Erythrocytes
Hemoglobin
Hydroxocobalamin
Myoglobin
Porphyrins
Rhubarb

Yellow-brown

Aloe
Anthraquinones
Chloroquine
Fava beans
Nitrofurantoin
Primaquine

Rhubarb

Sulfamethoxazole

Yellow

Fluorescein

Phenacetin

Quinacrine

Riboflavin

Santonin

Yellow-orange

Aminopyrine

Anisindione

Carrots

Sulfasalazine

Vitamin A

Warfarin

Black

Alcaptonuria

Homogentisic acid

Melanin

p-Hydroxyphenylpyruvic acid

Brown-black

Carbidopa/levodopa

Cascara

Iron

Methyldopa

Phenylhydrazine

Senna

Green or greenish-blue

Amitriptyline

Anthraquinones

Biliverdin

Flutamide

Chlorophyll breath mints
Flavin derivatives
Food dye and Color Blue No. 1
Indicans
Indigo blue
Magnesium salicylate
Methocarbamol
Methylene blue
Mitoxantrone
Phenol
Propofol
Thymol
Triamterene

There are multiple causes of hematuria⁷⁹ (Table 21–9). It can occur with xenobiotic-induced interstitial nephritis, a condition distinguished by fever, rash, eosinophilia, eosinophiluria, azotemia, and oliguria.⁴⁰ Hemorrhagic cystitis is a more frequent cause of hematuria and is associated with a number of xenobiotics. The clinical presentation of hemorrhagic cystitis includes hematuria, dysuria, and urinary frequency. Criteria for diagnosis of hemorrhagic cystitis¹⁰ include a history of gross hematuria, laboratory findings, of microscopic hematuria (>3 red blood cells/high-power field), platelet count above 50,000/mm³, and a negative urine culture result.¹⁰⁴ When in doubt, the diagnosis may be confirmed by cystoscopy, which reveals an inflamed, hyperemic, and sometimes ulcerated bladder mucosa.

TABLE 21–9. Xenobiotics That Cause Hematuria

Acyclovir
Amitraz
Anticoagulants
Brodifacoum
Clopidogrel
Heparin
Warfarin
Baclofen
BCG (intravesicular)
Cantharidin
Cefaclor
Chemotherapeutics
Bleomycin

Busulfan
Carboplatin
Cyclophosphamide
Dacarbazine
Doxorubicin
Ifosfamide
Methotrexate
Mitomycin
Pentostatin
Temozolomide
Chlordimeform
Clozapine
Colchicine
COX-2 inhibitors
Celecoxib
Rofecoxib
Crotaline envenomation
Danazol
Fibrinolytics
Fluoroquinolones
Ciprofloxacin
Gatifloxacin
Isoniazid
Ketamine
Mesalamine
NSAIDs
Indomethacin
Phenacetin
Tiaprofenic acid
Orthotoluidine
Penicillamine
Penicillins

Amoxicillin

Carbenicillin

Methicillin

Nafcillin

Penicillin G

Piperacillin

Pentamidine

Protease inhibitors

Radiation

Salicylates

Solvents

Cyclohexane

Toluene

Xylene

Statins

Atorvastatin

Rosuvastatin

BCG = Bacillus Calmette-Guerin; COX = cyclooxygenase; NSAID = nonsteroidal antiinflammatory drug.

Cyclophosphamide-related hemorrhagic cystitis was first described in 1959⁸⁶ and is the best-documented type of xenobiotic-induced hemorrhagic cystitis.⁵¹ As many as 46% of patients receiving cyclophosphamide develop hemorrhagic cystitis.^{43,61,67,70} Acrolein, the causative xenobiotic, is a metabolite of cyclophosphamide that damages the urothelium when excreted (Chap. 52).^{101,115} Cyclophosphamide- and ifosfamide-induced hemorrhagic cystitis may be prevented with mesna therapy.⁴

An outbreak of hemorrhagic cystitis occurred in workers in a packaging plant after exposure to chlordimeform, a formamidine insecticide used to control mites and insects on cotton. Nine workers developed abdominal pain, dysuria, urgency, and hematuria, with biopsy-proven hemorrhagic cystitis.⁴⁷ Eight young adults developed painful hematuria after consuming “bootleg” methaqualone. The cause was orthotoluidine, a compound used in the synthesis of methaqualone, and the symptoms occurred within 6 hours of ingestion.⁵⁴ Chronic ketamine and methoxetamine abuse is associated with the development of hemorrhagic ulcerative cystitis.¹¹¹ Rare cases of hemorrhagic cystitis have also been described with ticarcillin,⁸¹ nafcillin, penicillin G, carbenicillin, piperacillin, isoniazid, indomethacin, tiaprofenic acid, and busulphan.^{52,85,112}

Treatment for other causes of hemorrhagic cystitis includes bladder irrigation with saline, alum, PGs, silver nitrate, formalin, and phenol. Systemic therapy include estrogens, vasopressin, aminocaproic acid, and hyperbaric oxygen.¹²⁴ These therapies may have inherent adverse effects as well. Aluminum toxicity has been reported with alum bladder irrigation for hemorrhagic cystitis in patients with kidney failure.¹⁰⁰

SUMMARY

- Xenobiotics decrease fertility and fecundity by decreasing FSH and LH centrally or altering sperm production in men and altering ovarian function in women.
- Xenobiotics can cause sexual dysfunction by decreasing libido in men and women, increasing prolactin, decreasing dopamine, or causing erectile dysfunction in men.

- Therapies for male erectile dysfunction can lead to priapism.
- Abortifacients usually prevent embryo implantation or induce uterine contractions leading to increased vaginal bleeding and abdominal pain.
- Xenobiotics can alter bladder function to cause urinary retention or incontinence as well as changing the characteristics of urine in terms of color, hematuria, or crystal formation.

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22 HEMATOLOGIC PRINCIPLES

Marco L.A. Sivilotti

Blood is rightfully considered the vital fluid, because every organ system depends on the normal function of blood. Blood delivers oxygen and other essential substances throughout the body, removes waste products of metabolism, transports hormones from their origin to site of action, signals and defends against threatened infection, promotes healing via the inflammatory response, and maintains the vascular integrity of the circulatory system. It also serves as the central compartment in classical pharmacokinetics and thereby comes into direct contact with virtually every systemic xenobiotic that acts on the organism.⁸⁹ The ease and frequency with which blood is assayed, its central role in functions vital to the organism, and the ability to analyze its characteristics, at first by light microscopy and more recently with molecular techniques, have enabled a detailed understanding of blood that has advanced the frontier of molecular medicine.

In addition to transporting xenobiotics throughout the body, blood and the blood-forming organs can at times be directly affected by these same xenobiotics. For example, decreased blood cell production, increased blood cell destruction, alteration of hemoglobin, and impairment of coagulation can all result from exposure to many xenobiotics. The response in many cases depends on the nature and quantity of the xenobiotic as well as the capacity of the system to respond to the insult. In other cases, no clear and predictable dose–response relationship can be determined, especially when the interaction involves the immune system. These latter reactions are often termed idiosyncratic, reflecting an incomplete understanding of their causative mechanism. In general, such reactions can often be reclassified when advancing knowledge identifies the characteristics that render the individual vulnerable.

HEMATOPOIESIS

Hematopoiesis is the development of the cellular elements of blood. The majority of the cells of the blood system may be classified as either lymphoid (B, T, and natural killer lymphocytes) or myeloid (erythrocytes, megakaryocytes, granulocytes, and monocytes). All of these cells originate from a small common pool of totipotent cells called hematopoietic stem cells. Indeed, the study of this process and its regulation has provided fundamental insight into embryogenesis, stem cell pluripotency, and complex cell-to-cell signaling and interaction.

Bone Marrow

Marrow spaces within bone begin to form in humans at about the fifth fetal month and become the sole site of granulocyte and megakaryocyte proliferation. Erythropoiesis moves from the liver to the marrow by the end of the last trimester. At birth, all marrow contributes to blood cell formation and is red, containing very few fat cells. By adulthood, the same volume of hematopoietic marrow is normally restricted to the sternum, ribs, pelvis, upper sacrum, proximal femora and humeri, skull, vertebrae, clavicles and scapulae. Extramedullary hematopoiesis in the liver and spleen may reemerge as a compensatory mechanism under severe stimulation.

Progenitor cells must interact with a supportive microenvironment to sustain hematopoiesis. The hematopoietic stroma consists of macrophages, fibroblasts, adipocytes, and endothelial cells. The extracellular matrix is produced by the stromal cells and is composed of various fibrous proteins, glycoproteins, and proteoglycans, such as collagen, fibronectin, laminin, hemonectin, and thrombospondin. Hematopoietic progenitor cells have receptors to particular matrix molecules. The extracellular matrix provides a structural network to which the progenitors are anchored. As the cells approach maturity, they lose their surface receptors, allowing them to leave the hematopoietic space and enter the venous sinuses. Blood cell release depends upon the development of a pressure gradient that drives mature cells through channels in endothelial cell cytoplasm. This pressure is increased by erythropoietin and by granulocyte colony-stimulating factor.

Stem Cells

A stem cell is capable of self-renewal, as well as differentiation into a specific cell type. The pluripotent hematopoietic stem cells can therefore continuously replicate while awaiting the appropriate signal to differentiate into either a myeloid or a lymphoid stem cell (Fig. 22–1). Stem cells represent only 1 in 100,000 of the nucleated cells of the bone marrow, and most of these stem cells are usually quiescent. Nevertheless, these relatively few cells are directly responsible for the estimated 3 billion red cells, 2.5 billion platelets, and 1.5 billion leukocytes per kilogram of body weight produced each

day. In response to hemolysis or infection, substantially larger numbers of blood cells can be produced.⁷⁰ Multiple steps are involved in the commitment of less-differentiated cells to more mature cell lines. The final steps in the maturation of erythrocytes alone, for example, involve extensive remodeling, the restructuring of cellular membranes, the accumulation of hemoglobin, and the loss of nuclei and organelles.

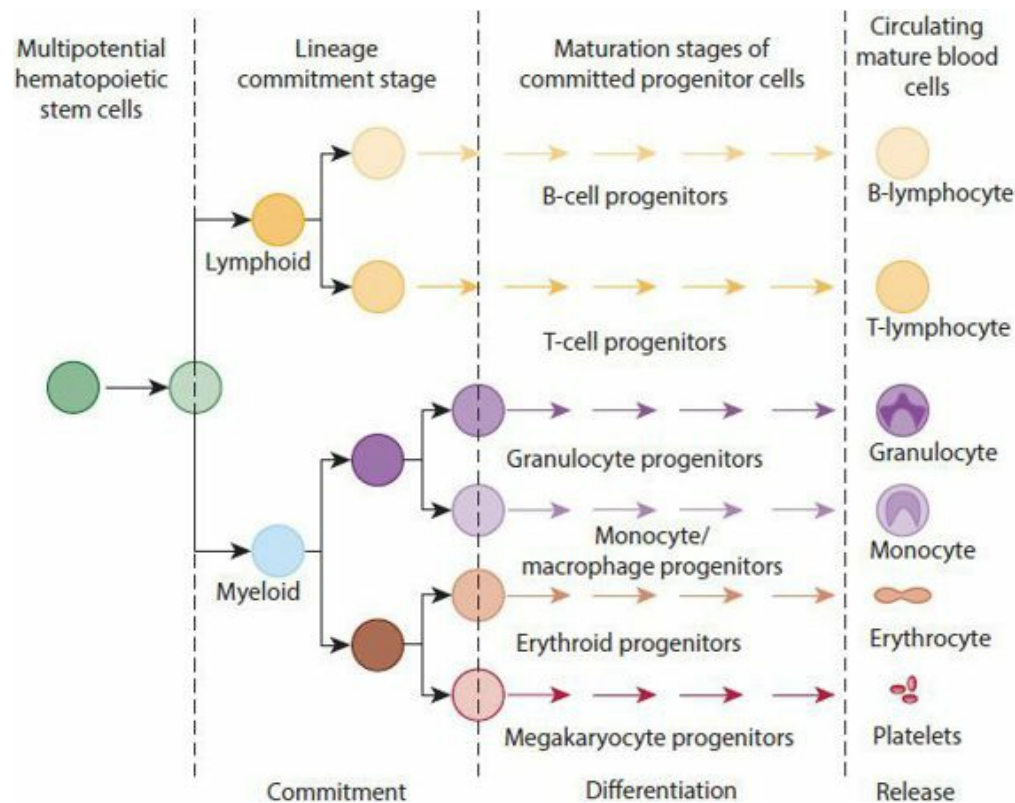


FIGURE 22–1. Principles of hematopoiesis. Commitment refers to the apparent inability of progenitor cells to generate hematopoietic stem cells. Following differentiation, the various mature blood cells are released into the circulation.

Multipotent mesenchymal stem cells capable of differentiating into other tissue lines, including hepatic, renal, muscle and perhaps neuronal, are also found in the bone marrow.⁴⁰ Furthermore, tissue-specific stem cells capable of self-renewal are believed to reside in numerous other organs and to play a fundamental role in repair and regeneration.²¹ A variety of strategies have likely evolved to protect the stem cell from injury due to xenobiotics and radiation, and a better understanding of these effects promises to improve our understanding of toxicity and treatment. The hematopoietic stem cell has provided fundamental insights into regenerative biology, and it remains a focus of intense research given the profound implications for organ homeostasis, tissue repair, and gene therapy.^{58,59}

Cytokines

Cytokines are soluble mediators secreted by cells for cell-to-cell communication. Initially termed growth factors, it is now recognized that not all cytokines are growth factors. Cytokines promote or inhibit the differentiation, proliferation, and trafficking of blood cells and their precursors. Importantly, they can also inhibit apoptosis, and their absence therefore results in the self-destruction of unwanted cells. They include growth factors or colony-stimulating factors (CSFs), interleukins, monokines, interferons, and chemokines. At baseline, these act in concert to maintain normal blood counts. In response to antigens or other stimuli, cytokines are released to combat perceived infection. Recombinant cytokines are being developed for therapeutic use in immunocompromised patients, transplant recipients, and those with sepsis and cancer. They have also been used in clinical toxicology for the treatment of colchicine and podophyllum toxicity.^{29,43}

The growth factors are glycoproteins necessary for the differentiation and maturation of individual or multiple cell lines. They fall into two families based on their target receptors. The ligands of the cytokine receptor family include growth hormone, interleukin-2 (IL-2), macrophage colony-stimulating factor-1 (CSF-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), γ -interferon, and granulocyte colony-stimulating factor (G-CSF), to name a few. The second group, the tyrosine kinase family, includes Kit ligand and insulinlike growth factor-1 receptor (IGF-1R), a member of the insulin family.

Cell Surface Antigens

Using monoclonal antibody technology, cell surface antigens are used to characterize cell types. The cluster designation (CD) nomenclature was introduced by immunologists to ensure a common language when confronted with multiple

antibodies to the same leukocyte cell-surface molecule, and hundreds of such unique molecules have been classified.¹⁰⁷ For example, the CD34 antigen is a 115-kilodalton (kDa) highly glycosylated transmembrane protein that is selectively expressed by primitive multipotent hematopoietic stem cells shortly after activation, but is absent from mature T and B lymphocytes.⁶¹ Advances in genomics and proteomics now complement the immunologic designation, but the ability to subtype blood cells phenotypically has transformed the approach to the leukemias, autoimmune disease, transplantation medicine, and thromboembolic disease.

The human leukocyte antigen (HLA) system denotes the major histocompatibility complex in humans, a group of genes involved in antigen presentation to T-lymphocytes, the complement system, cancer surveillance, and autoimmune disease. The rich variation in HLA genes, with more than 100 known alleles at six loci, is believed to be the result of selective pressure to deter individuals with similar HLA from mating. Such sexual selection enhancing diversity would protect a population from coevolving pathogens that attempted to mimic a specific human epitope and avoid immune attack. Indeed, humans appear to be able to distinguish and preferentially choose partners with HLA alleles different from their own using smell, promoting heterozygous diversity.⁶⁵ Exposure to blood transfusions, pregnancy, and organ grafts can generate antibodies against nonself HLAs.

Aplastic Anemia

Aplastic anemia is characterized by pancytopenia on peripheral smear, a hypocellular marrow, and delayed plasma iron clearance. Severe aplastic anemia denotes a granulocyte count of less than 500 cells/mm³, a platelet count of less than 20,000/mm³, and a reticulocyte count of less than 1% after correction for anemia. Following acute insult and depletion of extracirculatory reserves, cell line counts fall at a rate inversely proportional to their life span: granulocytes (half-life 6–12 hours in the circulation) disappear within days, platelets (life span of 7–10 days) decline by half in about one week, while erythrocytes (normal life span 120 days) decline over weeks in the absence of bleeding or hemolysis. Approximately 1000 new cases of aplastic anemia are diagnosed yearly in the United States. The incidence is two to three times higher in Asia, perhaps because of a combination of genetic, environmental, and infectious factors.¹⁰⁵ Aplastic anemia may be inborn (as in Fanconi anemia) or acquired. A variety of xenobiotics such as benzene, pesticides, and chloramphenicol are associated with acquired aplastic anemia (Table 22–1),^{20,106} but causality is uncertain given uncertain case ascertainment and other biases. More recent epidemiologic studies demonstrate that specific causes are identified in relatively few cases.⁵¹

TABLE 22–1. Xenobiotics Associated with Aplastic Anemia

Analgesics
Acetaminophen (APAP)
Diclofenac
Dipyrone
Indomethacin
Phenylbutazone
Salicylates
Antibiotics
Chloramphenicol
Mefloquine
Penicillin
Zidovudine
Anticonvulsants
Carbamazepine
Felbamate

Antidysrhythmics

Tocainide

Antihistamines

Cimetidine

Antiplatelets

Ticlopidine

Antipsychotics

Chlorpromazine

Clozapine

Antirheumatics

Gold salts

Methotrexate

d-Penicillamine

Antithyroids

Propylthiouracil

Chemotherapeutics^a

Adriamycin^a

Antimetabolites

Colchicine

Daunorubicin^a

Mustards

Vinblastine

Vincristine

Diuretics

Acetazolamide

Metolazone

Occupational

Arsenic^a

Benzene^a

Cadmium

Copper

Pesticides

Radiation^a

^aDenotes xenobiotics that predictably result in bone marrow aplasia following a sufficiently large exposure.

Generally speaking, the majority of cases of so-called idiosyncratic aplastic anemia are caused by autoimmune attack on CD34⁺ hematopoietic stem cells. Following an exposure to an inciting antigen, cytotoxic T-cells secrete interferon- γ and tumor necrosis factor α , which destroy progenitor cells, eventually depleting mature leukocytes, erythrocytes, and platelets in circulation.¹⁰⁶ As with other autoimmune diseases, certain HLA patterns are associated with a genetic predisposition for the condition, namely the HLA DR2. Clozapine-induced agranulocytosis is associated with the HLA B38, DR4, and DQ3 haplotypes.⁷¹ Immunosuppressive therapy or allogeneic stem cell transplantation allows recovery of hematopoiesis, and survival is now expected.¹⁰⁵

It is important to distinguish immunologic xenobiotic-induced aplastic anemia from the direct myelotoxic effects of radiation and chemotherapy. Following exposure to ionizing radiation, a pancytopenia ensues due to injury to stem and progenitor cells. While atom bomb survivors rarely developed aplastic anemia,⁴⁸ fractionated whole body radiation of at least 10 Gy is used to intentionally destroy bone marrow stem cells prior to hematopoietic stem cell transplantation. Cancer chemotherapy is often dosed to the end point of reversible hematopoietic toxicity. Vacuolated pronormoblasts can be found in the bone marrow when aplasia is due to a myelotoxic drug, and treatment consists primarily of stopping the offending xenobiotic while supporting cell lines and preventing infection and bleeding. Other nonimmunologic mechanisms of aplasia are identified in specific cases. For example, the severe pancytopenia that occasionally occurs following 5-fluorouracil therapy is caused by a deficiency of dihydropyrimidine dehydrogenase present in 3% to 5% of whites.¹⁰¹

THE ERYTHRON

The erythron can be considered to be a single yet dispersed tissue, defined as the entire mass of erythroid cells from the first committed progenitor cell to the mature circulating erythrocyte. This functional definition emphasizes the integrated regulation of the erythron, both in health and disease. The primary function of the erythron is to transport molecular oxygen throughout the organism. To accomplish this, adequate numbers of circulating erythrocytes (nearly half of the blood by volume) must be maintained. These erythrocytes must be able to preserve their structure and flexibility to circuit repeatedly through the microcirculation and to resist oxidant stress accumulated during their life span.⁸¹ The erythrocyte also plays a key role in modulating vascular tone. Interactions between oxyhemoglobin and nitric oxide help match vasomotor tone to local tissue oxygen demands.^{30,38,42,64,88}

Homeostasis of erythron proliferation is primarily maintained by the equilibrium between stimulation via the hormone erythropoietin and apoptosis controlled by two receptors, Fas and FasL, expressed on the membranes of erythroid precursors. At the other extreme, erythrocytes are culled from the circulation at the end of their life span primarily by the action of the spleen. With age, erythrocytes become less able to negotiate the narrow red pulp passages in the spleen and are phagocytosed by macrophages. By filtering out these senescent cells, the spleen minimizes entrapment in the microvasculature of other organs and prevents spillage of intracellular contents including hemoglobin into the intravascular circulation.

Erythropoietin

Erythropoietin (EPO) is a glycoprotein hormone of molecular weight 34,000 Da that is produced in the epithelial cells lining the peritubular capillaries of the kidney. Anemia and hypoxemia stimulate its synthesis. EPO receptors are found in human erythroid cells, megakaryocytes, and fetal liver. EPO promotes erythroid differentiation, the mobilization of marrow progenitor cells, and the premature release of marrow reticulocytes. The cell most sensitive to EPO is a cell between the erythroid colony-forming unit (CFU-E) and the proerythroblast. The absence of EPO results in DNA cleavage and erythroid cell death.

The Mature Erythrocyte

The mature erythrocyte (red blood cell) is a highly specialized cell, designed primarily for oxygen transport. Accordingly, it is densely packed with hemoglobin, which constitutes approximately 90% of the dry weight of the erythrocyte. During maturation, the erythrocyte loses its nucleus, mitochondria, and other organelles, rendering it incapable of synthesizing new protein, replicating, or using the oxygen being transported for oxidative phosphorylation. Its metabolic repertoire is severely limited and largely restricted to a few pathways (described below under Metabolism). In general, the enzymatic pathways are those required for optimizing oxygen and carbon dioxide exchange, transiting the microcirculation while maintaining cellular integrity and flexibility, and resisting oxidant stress on the iron and protein of the cell. The characteristic biconcave discocyte shape is dynamically maintained, increasing membrane surface-to-cell volume. This shape decreases intracellular diffusion distances to the cell membrane and allows plastic deformation when squeezing

through the microcirculation. The shape is the net sum of elastic and electrostatic forces within the membrane, surface tension, and osmotic and hydrostatic pressures. The cell membrane contains globular proteins floating within the phospholipid bilayer. The major blood group antigens are carried on membrane ceramide glycolipids and proteins, particularly glycophorin A and the Rh proteins. Membrane proteins generally serve to maintain the structure of the cell, to transport ions and other substances across the membrane, or to catalyze a limited number of specific chemical reactions for the cell.

Structural Proteins. The cell membrane is coupled to, and interacts dynamically with, the cytoskeleton, allowing changes in cell shape such as tank treading or rotation of the membrane relative to the cytoplasm. This cytoskeleton consists of a hexagonal lattice of proteins, especially spectrin, actin, and protein 4.1, which interact with ankyrin and band 3 in the membrane to provide a strong but flexible structure to the membrane. Other essential structural proteins include tropomyosin, tropomodulin, and adducin. Absence or abnormalities of these proteins can result in abnormal erythrocyte shapes such as spherocytes and elliptocytes.

Transport Proteins. Many specialized transport proteins are embedded in the erythrocyte membrane. These include anion and cation transporters, glucose and urea transporters, and water channels. The erythrocyte membrane is relatively impermeable to ion flux. Band 3 anion-exchange protein plays an important role in the chloride-bicarbonate exchanges that occur as the erythrocyte moves between the lung and tissues. Glucose, the sole source of energy of the erythrocyte, crosses the membrane by facilitated diffusion mediated by a transmembrane glucose transporter. Sodium-potassium adenosine triphosphatase ($\text{Na}^+\text{-K}^+\text{-ATPase}$) maintains the primary cation gradient by pumping sodium out of the erythrocyte in exchange for potassium.

Membrane-Associated Enzymes. At least 50 membrane-bound or membrane-associated enzymes are known to exist in the human erythrocyte. Acetylcholinesterase is an externally oriented enzyme whose role in the function of the erythrocyte remains obscure. Its function is inhibited by certain xenobiotics, most notably the organic phosphorus insecticides, and it can be conveniently assayed as a marker for such exposures ([Chap. 113](#)).

Metabolism. Lacking mitochondria and the ability to generate adenosine triphosphate (ATP) using molecular oxygen, the mature erythrocyte has a severely limited repertoire of intermediary metabolism compared to most mammalian cells. Having lost its nucleus, ribosomes, and translational apparatus, new enzymes cannot be synthesized and existing enzymes decline in function over the lifetime of the cell. Fortunately, the metabolic demands of the erythrocyte are usually modest, but under conditions of stress the capacity can be overwhelmed, especially among senescent cells. The greatest expenditure of energy under physiologic conditions is for the maintenance of transmembrane gradients and for the contraction of cytoskeletal elements. However, oxidant stress can put severe strain on the metabolic reserves of the erythrocyte, and lead ultimately to the premature destruction of the cell, a process termed hemolysis.

Figure 22–2 illustrates the main metabolic pathways and their purpose. Embden-Meyerhof glycolysis is the only source of ATP for the erythrocyte and consumes approximately 90% of the glucose imported by the cell. The reduced nicotinamide adenine dinucleotide (NADH) generated during glycolysis, which would ordinarily be used for oxidative phosphorylation in cells containing mitochondria, is directed toward the reduction of either methemoglobin to hemoglobin by cytochrome b5 reductase, or pyruvate to lactate. Both pyruvate and lactate are exported from the cell. During glycolysis, metabolism can be diverted into the Rapoport-Luebering shunt, generating 2,3-bisphosphoglycerate (2,3-BPG, formerly known as 2,3-diphosphoglycerate or 2,3-DPG) in lieu of ATP. 2,3-BPG binds to deoxyhemoglobin to modulate oxygen affinity and allow unloading of oxygen at the capillaries. In response to anemia, altitude, or changes in cellular pH, the activity of the shunt increases, thereby favoring synthesis of 2,3-BPG and increasing oxygen delivery considerably. Reduced [levels] of 2,3-BPG in stored blood result in impaired oxygen delivery following massive transfusion.⁹⁸

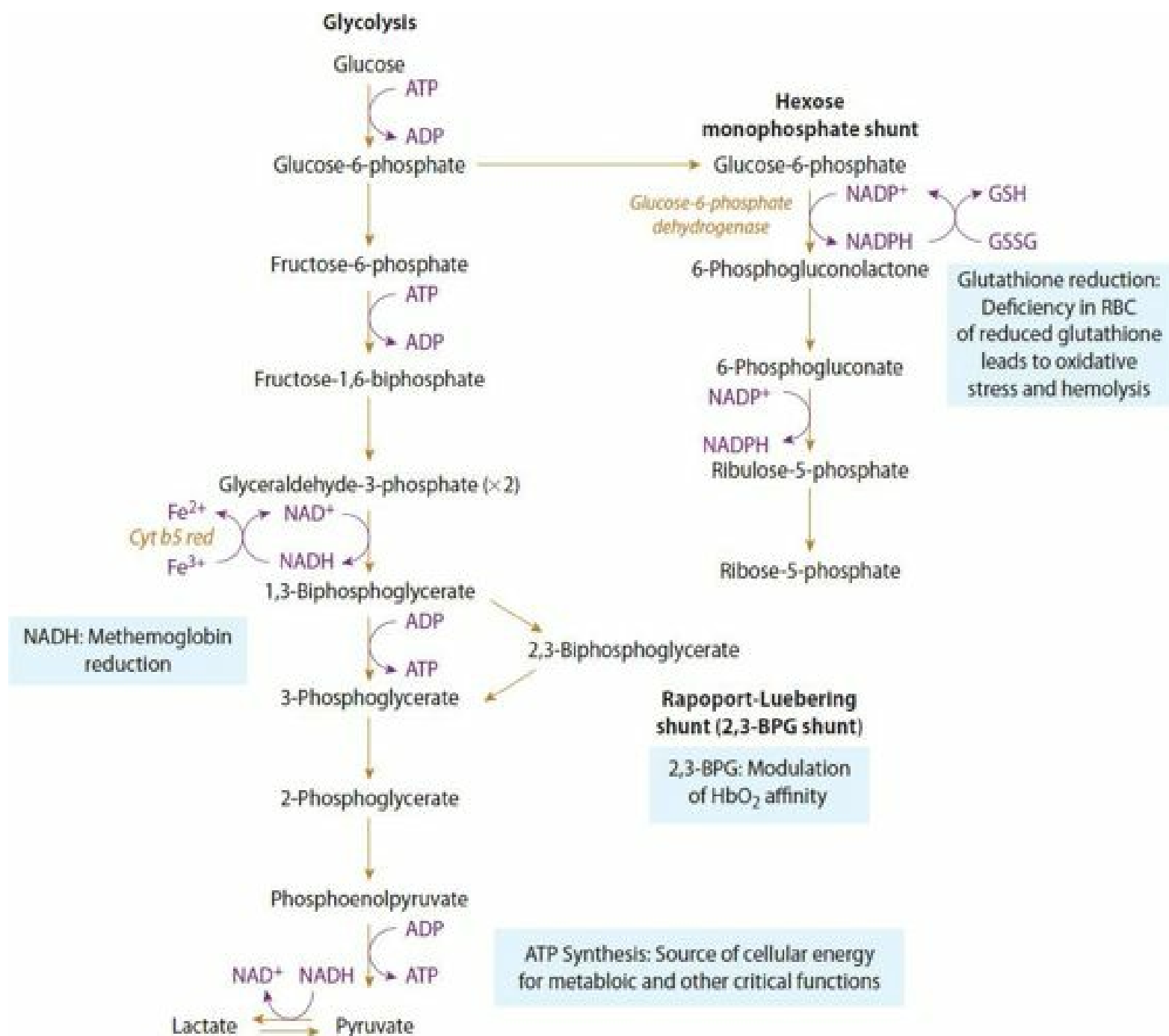


FIGURE 22–2. Metabolic pathways of the erythrocyte. The main metabolic pathways available to the mature erythrocyte are shown (rectangles). Glucose is imported into the cell, while pyruvate, lactate, and oxidized glutathione (GSSG) are exported. 2,3-BPG = 2,3-bisphosphoglycerate; ADP = adenosine diphosphate; ATP = adenosine triphosphate; cyt b5 red = cytochrome b5 reductase; G6PD = glucose-6-phosphate dehydrogenase; GSH = reduced glutathione; Hb = hemoglobin; NADH = reduced form of nicotinamide adenine dinucleotide (NAD⁺); NADPH = reduced form of nicotinamide adenine dinucleotide phosphate (NADP⁺); RBC = red blood cell (erythrocyte).

As an alternative to glycolysis, glucose can be directed toward the hexose monophosphate shunt during times of oxidant stress. This pathway results in the generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which the erythrocyte uses to maintain reduced glutathione which, in turn, inactivates oxidants and protects the sulfhydryl groups of hemoglobin and other proteins. The initial, rate-limiting step of this pathway is controlled by glucose-6-phosphate dehydrogenase (G6PD). Accordingly, cells deficient in this enzyme are less able to maintain glutathione in a reduced state, and are vulnerable to irreversible damage under oxidant stress. The consequences of this deficiency are discussed in greater detail below under Glucose-6-Phosphate Dehydrogenase Deficiencies.

The erythrocyte also contains enzymes to synthesize glutathione (γ -glutamyl-cysteine synthetase and glutathione synthetase), to convert CO₂ to bicarbonate ion (carbonic anhydrase I), to remove pyrimidines resulting from the degradation of RNA (pyrimidine 5'-nucleotidase), to protect against free radicals (catalase, superoxide dismutase, glutathione peroxidase), and to conjugate glutathione to electrophiles (ρ -glutathione-S-transferase).

Hemoglobin

Hemoglobin, the major constituent of the cytoplasm of the erythrocyte, is a conjugated protein with a molecular weight of

64,500 Da. To put things in perspective, the typical adult man has approximately 75 mL/kg of blood containing 15 g/100 mL of hemoglobin, or nearly 1 kg of hemoglobin. His 0.3-kg heart must pump this entire mass of hemoglobin every minute at rest, which is a substantial work expenditure. One molecule is composed of four protein (globin) chains, each attached to a prosthetic group called heme. Heme contains an iron molecule complexed at the center of a porphyrin ring. The globin chains are held together by noncovalent electrostatic attraction into a tetrahedral array. Hemoglobin is so efficient at binding and carrying oxygen that it enables blood to transport 100 times as much oxygen as could be carried by plasma alone (Chap. 29). In addition, the capacity of hemoglobin to modulate oxygen binding under different conditions allows adaptation to a wide variety of environments and demands. Three complex and integrated pathways are required for the formation of hemoglobin: globin synthesis, protoporphyrin synthesis, and iron metabolism.

Globin Synthesis. The protein chains of hemoglobin are produced with information from two different genetic loci. The α -globin gene cluster spans 30 kb on the short arm of chromosome 16, and codes for two identical adult α -chain genes, as well as the ζ -chain, an embryonic globulin. The β cluster is 50 kb on chromosome 11, and codes for the two adult globins β and α , as well as two nearly identical γ chains expressed in the fetus and an embryonic globulin ϵ . The expression of genes in each family changes during embryonic, fetal, neonatal, and adult development. Until 8 weeks of intrauterine life, ϵ , ζ , γ , and α chains are produced and assembled in various combinations in yolk sac–derived erythrocytes. With the shift in erythropoiesis from yolk sac to fetal liver and spleen, embryonic hemoglobin disappears, and the α and γ globin chains are paired into fetal hemoglobin (HbF = $\alpha_2\gamma_2$). Erythrocytes containing HbF have a higher O_2 affinity than those containing adult hemoglobin, which is important for oxygen transfer across the placenta into the relatively hypoxic uterine environment. Beginning shortly before birth, expression shifts to the α and β globins, which constitute the predominant adult hemoglobin termed hemoglobin A ($\alpha_2\beta_2$). Approximately 2.5% of normal adult hemoglobin is in the form of hemoglobin A₂ ($\alpha_2\delta_2$). The thalassemias, a group of inherited disorders, result from defective synthesis of one or more of the globin chains. Clinically this results in a hypochromic, microcytic anemia.

Heme Synthesis. Heme is the iron complex of protoporphyrin IX. Protoporphyrin IX is a tetramer composed of four porphyrin rings joined in a closed, flat-ring structure. The IX designation refers to the order in which it was first synthesized in Hans Fischer's laboratory. Of the 15 possible isomers, only protoporphyrin IX occurs in living organisms. Technically, only iron complexes with the iron in the Fe^{2+} state can be called heme, but the term is commonly used to refer to the prosthetic group of metalloproteins such as peroxidase (ferric) and cytochrome c (both ferric and ferrous), whether the iron is in the Fe^{2+} or Fe^{3+} state. The terms “hemoglobin” and “ferrihemoglobin” are synonymous with methemoglobin but rarely used. All animal cells can synthesize heme, with the notable exception of mature erythrocytes. Hemoproteins are involved in a multitude of biologic functions, including oxygen binding (hemoglobin, myoglobin), oxygen metabolism (oxidases, peroxidases, catalases, and hydroxylases), and electron transport (cytochromes), as well as metabolism of xenobiotics (cytochrome P450 family). Erythroid cells synthesize 85% of total body heme, with the liver synthesizing most of the balance. Hemoglobin is the most abundant hemoprotein, containing 70% of total body iron.

The first step in the synthesis of heme takes place in the mitochondrion and is the condensation of glycine and succinyl-coenzyme A (CoA) to form 5-aminolevulinic acid (ALA) (Fig. 22–3). The formation of 5-ALA is catalyzed by aminolevulinic acid synthase (ALAS), the rate-limiting step of the pathway. The rate of heme synthesis is closely controlled, given that free intracellular heme is toxic and that this first step is essentially irreversible.

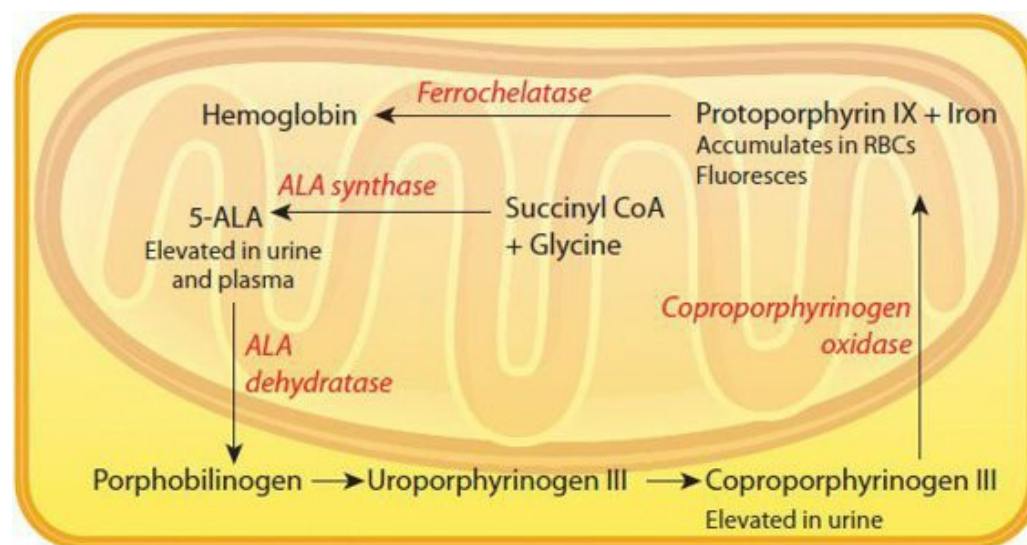


FIGURE 22–3. The heme synthesis pathway. The enzymatic steps inhibited by lead are marked in red. 5-ALA = 5-aminolevulinic acid; RBCs = red blood cells.

Of the two isoforms of ALAS known to exist in mammals, erythroid cells express the ALAS2 isoform, which resides on the X chromosome. Comparatively more is known about ALAS1 (chromosome 3), a housekeeping gene with a short half-

life expressed ubiquitously, allowing the synthesis of cellular and mitochondrial hemoproteins. ALAS1 activity is induced by many factors, which can increase its expression by two orders of magnitude. Moreover, it is strongly inhibited by heme in a classical negative feedback fashion. ALAS2 is constitutively expressed at very high concentrations in erythroid precursors, allowing sustained synthesis of heme during erythropoiesis. Pyridoxal phosphate (active vitamin B₆) serves as a cofactor to both isoforms of ALAS. The clinical consequences of pyridoxine deficiency include a hypochromic, microcytic anemia, iron overload, and neurologic impairment.

The next step in the synthesis of hemoglobin is the formation of the monopyrrole porphobilinogen via the condensation of two molecules of ALA. The subsequent steps in heme synthesis involve the condensation of four molecules of porphobilinogen into a flat ring, which is transported back into the mitochondrion by an unknown mechanism. The final step is the insertion of iron into protoporphyrin IX, a reaction that is catalyzed by ferrochelatase (also known as heme synthase) to form heme.

Understanding this carefully regulated synthetic pathway is relevant to understanding the laboratory evidence of lead toxicity ([Chap. 96](#)), and predicting the response of porphyric patients to a range of xenobiotics. Most steps in the heme biosynthetic pathway are inhibited by lead. ALA dehydratase is the most sensitive, followed by ferrochelatase, coproporphyrinogen oxidase, and porphobilinogen deaminase. As a consequence, ALA is increased in plasma and especially urine. With increasing exposure, ferrochelatase inhibition coupled with iron deficiency causes zinc protoporphyrin to accumulate in erythrocytes, which can easily be detected by fluorescence. Coproporphyrinogen III also appears in the urine. Historically, these effects have served as the basis for a number of tests of lead exposure.

The porphyrias are a group of disorders resulting from an inherited deficiency of any given enzyme that follows ALAS on the heme biosynthetic pathway. As such, when ALAS activity outpaces the activity of the deficient enzyme, the rate-limiting step shifts downstream, and intermediate metabolites accumulate. These metabolites can cause characteristic neuropsychiatric symptoms and palsies (caused by ALA and porphobilinogen), and cutaneous reactions, including photosensitivity (due to the fluorescence of the porphyrins). For example, porphobilinogen is excreted in large quantities by patients with acute intermittent porphyria (porphobilinogen deaminase deficiency), and the urine darkens with exposure to air and light due to oxidation to porphobilin and to nonenzymatic assembly into porphyrin rings. A variety of xenobiotics can precipitate a crisis in susceptible individuals, by inducing ALAS1 and overloading the deficient enzyme.⁹⁷ The molecular mechanisms that allow xenobiotics to induce the ALAS1 gene closely resemble those accounting for induction of the cytochrome P450 (CYP) genes, which also require heme synthesis. The xenobiotic typically interacts with either the constitutive androstane receptor (CAR) or the pregnane X receptor (PXR), the two main so-called orphan nuclear receptors.¹⁰⁴ These transcriptional factors are DNA-binding proteins that induce the expression of a range of drug metabolizing and transporting genes in response to the presence of a xenobiotic and are termed “xenosensors.” When activated, they associate with the 9-cis retinoic acid xenobiotic receptor (RXR), and then attach to enhancer sequences near the apoCYP or ALAS1 genes to enhance transcription.⁷⁸ The multifunctional inducers capable of activating a wide range of hepatic enzymes are therefore extremely porphyrogenic and include phenobarbital, phenytoin, carbamazepine, and primidone. Furthermore, because CYP 3A4 and 2C9 represent nearly half of the hepatic CYP pool, inducers of these isoforms also stimulate heme synthesis and can induce a porphyric crisis. Examples include the anticonvulsants; nifedipine; sulfamethoxazole; rifampicin; ketoconazole; and the reproductive steroids progesterone, medroxyprogesterone, and testosterone. Glucocorticoids, on the other hand, despite binding to PXR, suppress ALAS1 induction and translation, and they are not porphyrogenic.⁹⁷

Iron Metabolism. At equilibrium, approximately 1 to 2 mg of iron is absorbed from the diet, and a similar amount is shed from the intestinal epithelium each day. Unless appropriately chelated, free iron not bound by transport or storage proteins can generate harmful oxygen free radicals that damage cellular structures and metabolism ([Chaps. 12 and 46](#)). For this reason, serum iron circulates bound to a transfer protein, transferrin, and is stored in the tissues using ferritin ([Fig. 22–4](#)). Whereas each molecule of transferrin can bind two iron atoms, ferritin has a large internal cavity, approximately 80 Å in diameter, that can hold up to 4500 iron atoms per molecule. The amount of iron transported through plasma depends on total-body iron stores and the rate of erythropoiesis. Only about one-third of the iron-binding sites of circulating transferrin are normally saturated, as demonstrated by the usual serum iron content of 60 to 170 µg/dL (10–30 µmol/L) as compared to the total iron-binding capacity of 280 to 390 µg/dL (50–70 µmol/L).

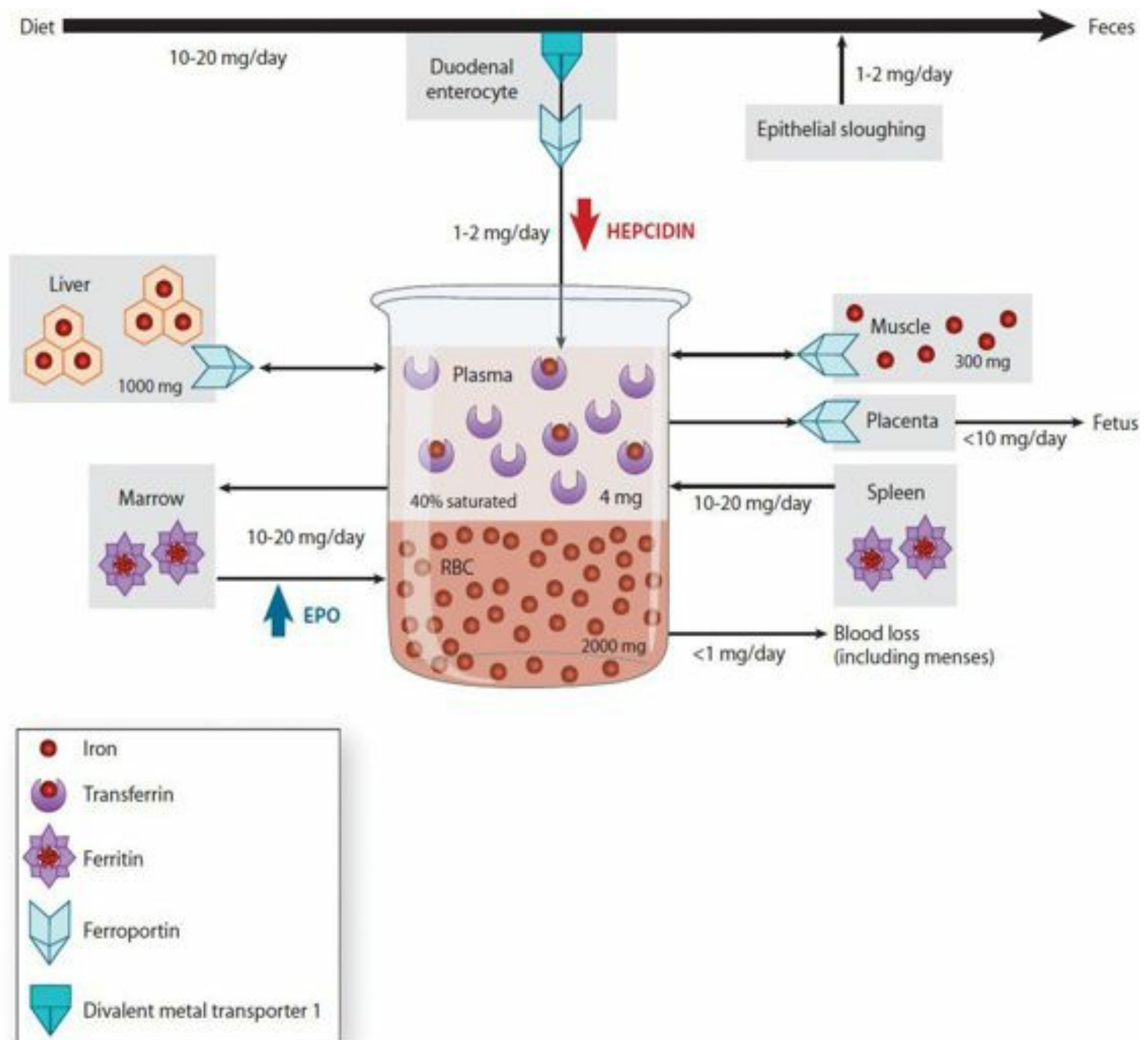


FIGURE 22–4. The iron cycle. The flow of iron is indicated by arrows, and average daily rates of flux are shown for an adult. Absorption at the duodenal enterocyte is tightly controlled, because there are few physiologic processes to regulate losses (other than pregnancy and menstruation). Atomic iron is absorbed via the divalent metal transporter 1, and heme-bound iron via heme carrier protein 1. Hepcidin is an important circulating peptide inhibitor of ferroportin, thereby limiting absorption when stores are adequate. Iron content (either atomic or heme-bound) of specific organs or compartments is shown in milligrams. The largest stores of atomic iron are contained by ferritin, mostly in liver and spleen macrophages, and erythrocyte precursors in the marrow. Only a relatively small amount circulates in the plasma bound to transferrin, which is usually only partially saturated. EPO = erythropoietin; RBC = red blood cell.

Only transferrin can directly supply iron for hemoglobin synthesis. The iron–transferrin complex binds to transferrin receptors on the surface of developing erythroid cells in bone marrow. Iron in the erythroid cell is used for hemoglobin synthesis or is stored in ferritin.

The absorption of nonheme, free ferrous iron from the diet occurs via the divalent metal transporter one of the duodenal enterocyte, which then passes it into the circulation via ferroportin. Iron then circulates in the ferric form bound to transferrin.⁴⁵ Dietary iron complexed with heme can be absorbed via the recently discovered heme carrier protein 1, which transports either iron or zinc protoporphyrin into the enterocyte.⁹¹ The iron may then be freed by microsomal heme oxygenase and follow the transport of atomic iron, or perhaps heme itself can be transferred to the circulation via specific export proteins and circulate bound to its carrier protein, hemopexin.⁵

When the erythrocyte is removed from the circulation by splenic macrophages, heme is degraded by heme oxygenase to

carbon monoxide and biliverdin, and the iron extracted. Some iron may remain in macrophages in the form of ferritin or hemosiderin. Most is delivered again by ferroportin back to the plasma and bound to transferrin.

Iron homeostasis is largely regulated at the level of absorption, with little physiologic control over its rate of loss. Excess absorption relative to body stores is the hallmark of hereditary hemochromatosis. The iron regulatory hormone hepcidin produced by the liver is now believed to play a central role in iron control, including the anemia of chronic disease caused by inflammatory signals.⁴⁵ Hepcidin is a 25-amino acid peptide that senses iron stores and controls the ferroportin-mediated release of iron from enterocytes, macrophages, and hepatocytes. The liver is an important reservoir of iron because it can store considerable amounts of iron taken from portal blood and release it when needed.

Oxygen-Carbon Dioxide Exchange

The evolutionary transition of organisms from anaerobic to aerobic life allowed the liberation of 18 times more energy from glucose. Vertebrates have developed two important systems to overcome the relatively small quantities of oxygen dissolved in aqueous solutions under atmospheric conditions: the circulatory system and hemoglobin. The circulatory system allows delivery of oxygen and removal of carbon dioxide throughout the organism. Hemoglobin plays an essential role in the transport and exchange of both gases. Moreover, the interactions between these gases and hemoglobin are directly linked in a remarkable story of molecular evolution. Understanding this interplay has allowed fundamental insight into protein conformation and the importance of allosteric interactions between molecules.

The binding of one oxygen molecule to each of the four iron atoms in heme results in conformational changes that affect binding of oxygen at the remaining sites. This phenomenon is known as cooperativity, and it is necessary to both the transport of relatively large quantities of oxygen and the unloading of most of this oxygen at tissue sites. Cooperativity results from the intramolecular interactions of the tetrameric hemoglobin, and is expressed in the sigmoidal shape of the oxyhemoglobin dissociation curve (Fig. 29–2). Conversely, the monomeric myoglobin has a hyperbolic oxygen binding curve. The partial pressure of oxygen at which 50% of the oxygen bindings sites of hemoglobin are occupied is about 26 mm Hg, in contrast with about 1 mm Hg for myoglobin. Moreover, hemoglobin is nearly 100% saturated at partial oxygen pressures of about 100 mm Hg in the pulmonary capillaries, transporting 1.34 mL of oxygen per gram of hemoglobin A. About one-third of this oxygen can be unloaded under normal conditions at tissue capillaries with partial oxygen pressures around 35 mm Hg. The proportion unloaded rises during exercise and sepsis, as well as with xenobiotics that uncouple oxidative phosphorylation. Elite athletes can extract up to 80% of the available oxygen under conditions of maximal aerobic effort.

The oxygen reserve, however, is only one of the benefits of the large quantity of hemoglobin in circulation. The ability of hemoglobin to buffer the acid equivalent of CO₂ in solution is equally vital to respiratory physiology, because it allows the removal of large quantities of CO₂ from metabolically active tissues with minimal changes in blood pH. Hemoglobin is by far the largest buffer in circulation, accounting for seven times the buffer capacity of the serum proteins combined (28 vs. 4 mEq H⁺/L of whole blood). For every 1 mole of oxygen unloaded in the tissue, about 0.5 mole of H⁺ is loaded onto hemoglobin.

The linked interaction between oxygen and carbon dioxide transport can be first considered from the perspective of oxygen binding to hemoglobin. The affinity of oxygen for hemoglobin is directly affected by pH, which is a function of the CO₂ content of the blood. The oxyhemoglobin dissociation curve shifts to the left in lungs, where the level of carbon dioxide, and thus carbonic acid, are kept relatively low as a result of ventilation, an effect that promotes oxygen binding. The curve shifts to the right in tissues where cellular respiration increases CO₂ concentrations. This phenomenon, known as the Bohr effect, promotes the uptake of oxygen in the lungs and the release of oxygen at tissue sites.

From the perspective of carbon dioxide transport, hemoglobin also plays an essential albeit indirect role. Carbon dioxide dissolves into plasma, and is slowly hydrated to carbonic acid which dissociates to H⁺ and HCO₃⁻ (pK_a 6.35). The speed of the hydration reaction is accelerated from about 40 seconds to 10 msec by the abundant enzyme carbonic anhydrase located within the erythrocyte. Most carbon dioxide collected at the tissues diffuses into erythrocytes, where it becomes H⁺ and HCO₃⁻. This HCO₃⁻ is then rapidly transported back to the serum in exchange for chloride ion via the band 3 anion exchange transporter located in the erythrocyte membrane, thereby shifting serum Cl⁻ into the erythrocyte (the chloride shift). The hydrogen ion is accepted by hemoglobin, largely at the imidazole ring of histidine residues, which have a pK_a of about 7.0. A small amount of CO₂ reacts directly with the amino terminal of the globin chains to form carbamino residues (HbNHCOO⁻). Thus, most of the transported carbon dioxide is transformed by the erythrocyte into bicarbonate ion that is returned to the serum and hydrogen ion that is buffered by hemoglobin. Each liter of venous blood typically carries 0.8 mEq dissolved CO₂ + 16 mEq HCO₃⁻ in the plasma, 0.4 mEq dissolved CO₂ + 4.6 mEq HCO₃⁻, + 1.2 mEq HbNHCOO⁻ in the erythrocyte (a total of 23 mEq CO₂, equivalent to 510 mL CO₂/L blood). Although two-thirds of the total CO₂ content is ultimately carried in the plasma, nearly all of the bicarbonate is generated within erythrocytes. In the capillaries of the lungs, the reverse reactions occur to eliminate CO₂. Because deoxyhemoglobin is better able to buffer

hydrogen ions, the release of oxygen from hemoglobin at the tissues facilitates the uptake of carbon dioxide into venous blood. This effect is known as the Haldane effect. In fact, 1 L of venous blood at 70% oxygen saturation can transport an additional 20 mL of CO₂ compared to arterial blood, which is nearly 100% saturated. Both the Bohr and Haldane effects can have important consequences at the extremes of acid–base perturbations, as can occur in a number of poisonings that interfere with oxygen metabolism.

Finally, in addition to inactivating nitric oxide, hemoglobin can also reversibly bind it as S-nitrosohemoglobin, thereby playing an important role in the regulation of microvascular circulation and oxygen delivery. The ability of hemoglobin to vasodilate the surrounding microvasculature in response to oxygen desaturation using nitric oxide provides new insight into oxygen delivery and may be pivotal in such disorders as septic shock, pulmonary hypertension, and senescence of stored red blood cells.⁹²

Abnormal Hemoglobins

Several alterations of the hemoglobin molecule are encountered in clinical toxicology. A detailed understanding of their molecular basis, clinical manifestations, and effects on gas exchange is essential. Unfortunately, the nomenclature can be ambiguous and overlaps with distinct clinical entities such as oxidant injury and hemolysis. Therefore, although a detailed discussion of these abnormal hemoglobins appears elsewhere ([Chaps. 125 and 127](#)), an overview of the subject is presented here. It is helpful to recall that the iron atom has six binding positions. Four of these positions are attached in a single plane to the protoporphyrin ring to form heme. The remaining two binding positions lie on opposite sides of this plane. One site is ordinarily bonded to the F8 proximal histidine residue of the globin chain. The remaining site is available for binding molecular oxygen, but it can also bind carbon monoxide, nitric oxide, cyanide, hydroxide ion, or water. The E7 distal histidine residue facilitates the binding of oxygen while sterically hindering carbon monoxide binding.

Methemoglobin. Methemoglobin (ferrihemoglobin or hemoglobin) is the oxidized form of deoxyhemoglobin in which at least one heme iron is in the oxidized (Fe³⁺) valence state. A number of valency hybrids can occur, depending on the number of ferric versus ferrous heme units within the tetramer. Methemoglobin therefore represents oxidation (loss of electrons) of the hemoglobin molecule at the iron atom. It occurs spontaneously as a consequence of interactions between the iron and oxygen. Normally, in deoxygenated hemoglobin, the heme iron is in the ferrous (Fe²⁺) valence state. In this state, there are six electrons in the outer shell, four of which are unpaired. When oxygen is bound, one of these electrons is partially transferred to it and the iron is reversibly oxidized. When O₂ is released, the electron is usually transferred back to heme iron, yielding the normal reduced state. Sometimes, the electron remains with the O₂ yielding a superoxide anion radical O₂[−] rather than molecular oxygen. In this case, heme iron is left in the Fe³⁺, or oxidized, state and is unable to release another electron to bind oxygen. This oxidation is primarily reversed via the action of cytochrome b5 reductase, also known as NADH methemoglobin reductase, which uses the electron carrier NADH generated by glycolysis (Metabolism discussion above and [Chap. 13](#)). Minor pathways are also involved in methemoglobin reduction, including NADPH methemoglobin reductase, which normally reduces only approximately 5% of the methemoglobin, and vitamin C, a nonenzymatic reducing agent. The activity of NADPH methemoglobin reductase may be significantly accelerated by the presence of the electron donor methylene blue (*Antidotes in Depth: A42* and [Chap. 127](#)) or riboflavin. Equilibrium is maintained with methemoglobin concentrations of 1% of total hemoglobin. Many xenobiotics increase the rate of methemoglobin formation by as much as 1000-fold. Nitrites, nitrates, chlorates, and quinones are capable of directly oxidizing hemoglobin.¹⁹ Certain individuals may be especially vulnerable resulting from deficient methemoglobin reduction.²⁸ The fetus and neonate are more susceptible to methemoglobinemia than the adult, because HbF is more susceptible to oxidation of the heme iron than adult hemoglobin. The newborn also has a limited capacity to reduce methemoglobin, because adult concentrations of cytochrome b5 reductase are only achieved at about 6 months of age.

Carboxyhemoglobin. Carbon monoxide (CO) can reversibly bind to heme iron in lieu of molecular oxygen. The affinity of CO for hemoglobin is 200–300 times that of oxygen, despite the steric hindrance of the E7 distal histidine. The presence of CO thereby precludes the binding of oxygen. In addition, CO binding within any one heme subunit degrades the cooperative binding of oxygen at the remaining heme groups of the same hemoglobin molecule. The oxyhemoglobin dissociation curve is therefore shifted to the left, reflecting the fact that oxygen is more tightly bound by hemoglobin and less able to be unloaded to the tissues. In addition, CO binds to the heme group of myoglobin and the cytochromes, interfering with cellular respiration and exacerbating the hypoxia ([Chap. 125](#)).⁴¹

Sulfhemoglobin. Sulfhemoglobin is a bright green molecule in which the hydrosulfide anion HS[−] irreversibly binds to ferrous hemoglobin. The sulfur atom is probably attached to a β carbon in the porphyrin ring and not at the normal oxygen-binding site.⁶⁷ It has a spectrophotometric absorption band at approximately 618 nm,¹⁶ is ineffective in oxygen transport, and clinically produces a condition that resembles cyanosis. The oxygen affinity of sulfhemoglobin is approximately 100 times less than that of oxyhemoglobin, shifting the oxyhemoglobin dissociation curve to the right, in favor of O₂ unbinding. Thus, the symptoms of hypoxia are not as severe with sulfhemoglobinemia as with carboxy- or methemoglobinemia.⁷⁴

Oxidation of the Globin Chain. Oxidation can also occur at the amino acid side chains of the globin protein. In

particular, sulfhydryl groups can oxidize to form disulfide links between cysteine residues, which leads to the unfolding of the protein chain, exposure of other side chains, and further oxidation. When these disulfide links join adjacent hemoglobin molecules, they cause the precipitation of the concentrated hemoglobin molecules out of solution. Covalent links can also form between hemoglobin and other cytoskeletal and membrane proteins.²⁵ Eventually, aggregates of denatured and insoluble protein are visible on light microscopy as Heinz bodies. The distortion of the cellular architecture and the loss of fluidity in particular signal reticuloendothelial macrophages to excise sections of erythrocyte membrane (“bite cells”) or to remove the entire erythrocyte from the circulation (see below). To guard against these oxidation reactions, the erythrocyte maintains a pool of reduced glutathione via the actions of the NADPH generated in the hexose monophosphate shunt (assuming adequate G6PD activity to initiate this pathway). This glutathione transfers electrons to break open disulfide links and to preserve sulfhydryl groups in their reduced state.

Hemolysis

Hemolysis is merely the acceleration of the normal process by which senescent or compromised erythrocytes are removed from the circulation.⁹³ The normal life span of a circulating erythrocyte is approximately 120 days, and any reduction in this life span represents some degree of hemolysis. If sufficiently rapid, hemolysis can overwhelm the regenerative capacity of the erythron, resulting in anemia. Intravascular hemolysis occurs when the rate of hemolysis exceeds the capacity of the reticuloendothelial macrophages to remove damaged erythrocytes, and free hemoglobin and other intracellular contents of the erythrocyte appear in the circulation.

Reticulocytosis, polychromasia, unconjugated hyperbilirubinemia, increased serum lactate dehydrogenase, and decreased serum haptoglobin are characteristic of hemolysis. A normal or elevated RBC distribution width and thrombocytosis are usually present. The presence of spherocytes on peripheral blood smear suggests an autoimmune or hereditary process and can be pursued with a Coombs’ test. Schistocytes suggest thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome, disseminated intravascular coagulation, or valvular hemolysis. TTP and hemolytic uremic syndrome are characterized by a microangiopathic anemia, thrombocytopenia, and normal coagulation parameters (unlike disseminated intravascular coagulation). TTP is discussed under platelet disorders below. Hemoglobinemia, hemoglobinuria, and hemosiderinuria can occur with intravascular hemolysis. Specialized tests to measure hemolysis detect shortened erythrocyte survival, increased endogenous carbon monoxide generation from heme oxygenase, and increased fecal urobilinogen.

Table 22–2 presents a brief classification of acquired causes of hemolysis relevant to toxicology. Oxidant injury following xenobiotic exposure is one of the triggers of hemolysis, as it may cause irreversible changes in the erythrocyte. Erythrocytes deficient in G6PD by virtue of cell age or enzyme mutations are particularly vulnerable to hemolysis following oxidant stress due to limited capacity to generate NADPH and reduced glutathione.⁹³ The immune-mediated hemolytic anemias occur when ingested xenobiotics trigger an antigen antibody reaction. In general, these molecules are too small to be sensitizing agents, but antigenicity can be acquired after binding to carrier proteins in blood. The particulars of the xenobiotic-carrier immune activation sequence form the basis for the classification of this group of hemolytic anemias.⁷

TABLE 22–2. Xenobiotics Causing Acquired Hemolysis

Immune-mediated

Type I: IgG against drug tightly bound to red cell

High-dose penicillin

Type II: Complement activated by antibodies against drug-membrane complex

Cefotaxime, cefotetan, ceftriaxone, quinidine, stibophen

Type III: True autoimmune response to red cell membrane

Chlorpromazine, cladribine, cyclosporine, fludarabine, levodopa, methyldopa, procainamide

Nonimmune-mediated

Oxidants

Aniline

Benzocaine

Chlorates
Dapsone
Hydrogen peroxide
Hydroxylamine
Methylene blue
Naphthalene
Nitrites
Nitrofurantoin
Oxygen
Phenacetin
Phenazopyridine
Phenol
Platinoids
Sulfonamides
Nonoxidants
Arsine (AsH_3)
Copper
Lead
Pyrogalllic acid
Stibine (SbH_3)
Hypophosphatemia
Microangiopathic (eg, ticlopidine, clopidogrel, cyclosporine, tacrolimus)
Osmotic agents (eg, water)
Venoms (snake, spider)

Nonimmune-Mediated Causes of Xenobiotic-Induced Hemolysis

A number of xenobiotics or their reactive metabolites can cause hemolysis via oxidant injury. A Heinz-body hemolytic anemia can result, which typically resolves within a few weeks of drug discontinuation. Some xenobiotics cause hemolysis in the absence of overt oxidant injury ([Table 22–2](#)). Copper sulfate hemolysis is described in [Chap. 95](#), while the delayed hemolysis following exposure to arsine or stibine is described here.

Arsine (AsH_3) is a colorless, odorless, nonirritating gas that is 2.5 times denser than air ([Chap. 89](#)). Clinical signs and symptoms appear after a latent period of up to 24 hours after exposure to concentrations above 30 ppm and may include headache, malaise, dyspnea, abdominal pain with nausea and vomiting, hepatomegaly, hemolysis with hemoglobinuric acute kidney injury, and death.^{23,34,53,57,77} The mechanism of hemolysis is believed to involve the fixation of arsine by sulfhydryl groups of hemoglobin and other essential proteins.^{39,103} Interestingly, hemolysis is prevented in vitro by conversion to carboxy- or methemoglobin.⁴⁴ Impairment of membrane proteins, including $\text{Na}^+\text{-K}^+\text{-ATPase}$, is another potential mechanism for arsine-induced hemolysis.⁸⁰ Chronic exposure to low levels of arsine can produce clinically significant disease.²³ Stibine (SbH_3), an antimony derivative, likely causes hemolysis via similar mechanisms ([Chap. 88](#)).

Glucose-6-Phosphate Dehydrogenase Deficiencies. G6PD is the enzyme that catalyzes the first step of the hexose monophosphate shunt: the conversion of glucose-6-phosphate to phosphogluconolactone (Fig. 13–7). In the process, NADP⁺ is reduced to NADPH, which the erythrocyte uses to maintain a supply of reduced glutathione and to defend against oxidation. It follows that erythrocytes deficient in G6PD activity are less able to resist oxidant attack and, in particular, to maintain sulfhydryl groups of hemoglobin in their reduced state, resulting in hemolysis. It is important to recognize that the term G6PD deficiency encompasses a wide range of differences in enzyme activities among individuals. These differences may result from decreased enzyme synthesis, altered catalytic activity, or reduced stability of the enzyme. Approximately 7.5% of the world population is affected to some degree, with more than 400 variants having been identified. Most cases involve relatively mild deficiency and minimal morbidity. Ethnic populations from tropical and subtropical countries (the so-called malaria belt) have a much higher prevalence of G6PD deficiency, possibly because that phenotype protects against malaria.⁶⁹

The gene that encodes for G6PD resides near the end of the long arm of the X-chromosome. Most mutations consist of a single amino acid substitution, as complete absence of this enzyme is lethal. Although men hemizygous for a deficient gene are more severely affected, women randomly inactivate one X-chromosome during cellular differentiation according to the Lyon hypothesis. Thus, women carriers heterozygous for a deficient G6PD gene have a mosaic of erythrocytes, some proportion of which expresses the deficient gene during maturation. Accordingly, approximately 10% of carrier women may be nearly as severely affected as males hemizygous for the same deficient gene. Because of the high gene frequency in certain ethnic groups, another approximately 10% of women may be homozygous for the deficient gene.

Normal G6PD has a half-life of about 60 days. Because the erythrocyte cannot synthesize new protein, the activity of G6PD normally declines by approximately 75% over its 120-day life span. Consequently, even in unaffected individuals, susceptibility to oxidant stress varies based on the age mix of circulating erythrocytes. In all cases, older erythrocytes are less likely to recover following exposure to an oxidant and will hemolyze first. Moreover, after an episode of hemolysis following acute exposure to an oxidant stress, the higher G6PD activity of surviving erythrocytes will confer some resistance against further hemolysis in most individuals with relatively mild deficiency, even if the offending xenobiotic is continued. For this reason, phenotypic testing for G6PD deficiency is best done 2 to 3 months after a hemolytic crisis, which is when the reticulocyte count has usually normalized.

The World Health Organization classification of G6PD is based on the degree of enzyme deficiency and severity of hemolysis.¹⁸ Both class I and class II patients are severely deficient, with less than 10% of normal G6PD activity. Class I individuals are prone to chronic hemolytic anemia, whereas class II patients experience intermittent hemolytic crises. Class III patients have only moderate (10%–60%) enzyme deficiency, and experience self-limiting hemolysis in response to certain xenobiotics and infections. Approximately 11% of African Americans have a class III deficiency, traditionally termed type A[−], and experience a decline of no more than 30% of the red blood cell mass during any single hemolytic episode. Another 20% of African Americans have type A⁺ G6PD enzyme, which is functionally normal, and therefore of no consequence despite a one-base substitution compared to wild-type B. The Mediterranean type found in Sardinia, Corsica, Greece, the Middle East, and India is a class II deficiency, and hemolysis can occur spontaneously or in response to ingestion of oxidants, such as the β-glycosides found in fava (*Vicia fava*) beans.

The most common clinical presentation of previously unrecognized G6PD deficiency is the acute hemolytic crisis. Typically, hemolysis begins 1 to 4 days following the exposure to an offending xenobiotic or infection (Table 22–3). Jaundice, pallor, and dark urine may occur with abdominal and back pain. A decrease in the concentration of hemoglobin occurs. The peripheral smear demonstrates cell fragments and cells that have had Heinz bodies excised. Bone marrow stimulation results in a reticulocytosis by day 5 and an increased erythrocyte mass. In general, a normal bone marrow can compensate for ongoing hemolysis and can return the hemoglobin concentration to normal. Most crises are self-limiting because of the higher G6PD activity of younger erythrocytes. Historically, the anemia observed when primaquine was administered to type A[−] military recruits for malaria prophylaxis resolved within 3 to 6 weeks in most cases.¹⁷ Some xenobiotics, including APAP, vitamin C, and sulfisoxazole, are safe at therapeutic doses but can cause hemolysis in G6PD-deficient patients following overdose.

TABLE 22–3. Representative Xenobiotics That Can Cause Hemolysis in Patients with Class I, II, or III G6PD Deficiency

Doxorubicin

Furazolidone

Isobutyl nitrite

Methylene blue

Nalidixic acid

Naphthalene
Nitrofurantoin
Phenazopyridine
Phenylhydrazine
Primaquine
Sulfacetamide
Sulfamethoxazole
Sulfanilamide
Sulfapyridine
Toluidine blue
Trinitrotoluene

Data adapted from Beutler E: Glucose-6-phosphate dehydrogenase deficiency. *N Engl J Med.* 1991;324: 169–174, and Beutler E: G6PD deficiency. *Blood.* 1994;84:3613–3636.

Other presentations of more severe variants of G6PD include neonatal jaundice and kernicterus, chronic hemolysis with splenomegaly and black pigment gallstones, megaloblastic crisis caused by folate deficiency, and aplastic crisis after parvovirus B19 infection.

Megaloblastic Anemia

Vitamin B₁₂ and folate are essential for one-carbon metabolism in mammals. One-carbon fragments are necessary for the biosynthesis of thymidine, purines, serotonin, and methionine; the methylation of DNA, histones, and other proteins; and the complete catabolism of branched chain fatty acids and histidine. Unable to synthesize vitamin B₁₂ or folate, mammals are dependent on dietary sources and microorganisms for these cofactors. The hematologic manifestation of vitamin B₁₂ or folate deficiency is a characteristic pancytopenia termed megaloblastic anemia. The hallmark nuclear-cytoplasmic asynchrony is due to disrupted DNA synthesis, halted interphase and ineffective erythropoiesis.⁷⁹ The hyperplastic bone marrow contains precursor cells with abnormal nuclei filled with incompletely condensed chromatin. Among circulating blood cells, macrocytic anemia (macro-ovalocytes) without reticulocytosis is followed by the appearance of granulocytes with an abnormally large, distorted nucleus (hypersegmented neutrophils with six or more lobes). Lymphocytes and platelets may appear normal but are also functionally impaired.

In addition to dietary deficiencies, which have become less common, macrocytic anemia with or without megaloblastosis in adults is usually caused by chronic ethanol abuse, chemotherapeutics, or antiretrovirals, especially when mean corpuscular volumes are only moderately elevated (100–120 fL).⁸⁷ The folate antagonists aminopterin, methotrexate, hydantoins, pyrimethamine, proguanil, sulfasalazine, trimethoprim sulfamethoxazole, and valproate can interfere with DNA synthesis. Ethanol affects folate metabolism and transport. Vitamin B₁₂ deficiency can be induced by chronic exposure to nitrous oxide, biguanides, colchicine, neomycin, and the proton pump inhibitors. Purine analogs (eg, azathioprine, 6-mercaptopurine, 6-thioguanine, acyclovir) and pyrimidine analogs (eg, 5-fluorouracil, floxuridine, 5-azacitidine, and zidovudine) also disrupt nucleic acid synthesis. Hydroxyurea and cytarabine, which inhibit ribonucleotide reductase, also delay nuclear maturation and function and frequently cause megaloblastosis.

Pure Red Cell Aplasia

Pure red cell aplasia is an uncommon condition in which erythrocyte precursors are absent from an otherwise normal bone marrow. It results in a normocytic anemia with inappropriately low reticulocyte count. The other blood cell lines are unaffected, unlike aplastic anemia. Pharmaceuticals cause fewer than 5% of cases of this uncommon condition, having been implicated in fewer than 100 human reports.⁹⁶ Only phenytoin, azathioprine, and isoniazid meet criteria for definite causality; chlorpropamide and valproic acid can be considered only as possible causes.⁹⁶ Most other xenobiotics are cited only in single case reports, and drug rechallenge was not used, making the association uncertain.

In part because of its rarity, a cluster of 13 cases in France of pure red cell aplasia in hemodialysis patients receiving subcutaneous recombinant EPO ultimately led to an international effort by researchers, regulatory authorities, and industry

to identify the etiology.^{14,26} To reduce theoretical concerns regarding transmission of variant Creutzfeldt-Jakob disease, human serum albumin was replaced with polysorbate 80 as the stabilizer in a formulation used in Europe and Canada. It is suspected that this change allowed rubber to leach from the uncoated stopper of prefilled syringes, triggering an immune response against both recombinant and endogenous EPO in some patients.⁶³ This episode not only serves as a recent example of successful pharmacovigilance for rare adverse drug effects but has also influenced safety assessments for an emerging class of biological therapies that include simple peptides, monoclonal antibodies, and recombinant DNA proteins.^{13,63}

Erythrocytosis

Erythrocytosis denotes an increase in the red cell mass, either in absolute terms or relative to a reduced plasma volume. An increasingly recognized cause of drug-induced absolute erythrocytosis is the abuse of recombinant human EPO by athletes to enhance aerobic capacity (Chap. 40). Autologous blood transfusions (doping) are also used in this population, and both can cause dangerous increases in blood viscosity. Cobalt was once considered for the treatment of chronic anemia³² due to its ability to cause a secondary erythrocytosis (Chap. 94). The mechanism may involve impaired degradation of the transcription factor hypoxia-inducible factor 1 α , thereby prolonging EPO transcription. This effect is more pronounced in high altitude dwellers, in whom elevated serum EPO concentrations persist despite hematocrits in excess of 75% and chronic mountain sickness is associated with increased serum cobalt concentrations.⁵²

THE LEUKON

The leukon represents all leukocytes (white blood cells), including precursor cells, cells in the circulation, and the large number of extravascular cells. It includes the granulocytes (neutrophils, eosinophils, and basophils), lymphocytes, and monocytes. Neutrophils (polymorphonuclear leukocytes) are highly specialized mediators of the inflammatory response, and are a primary focus of concern regarding hematologic toxicity of xenobiotics. B and T lymphocytes are involved in antibody production and cell-mediated immunity. Monocytes migrate out of the vascular compartment to become tissue macrophages and to regulate immune system function.

Immunity is generally divided into the innate and the adaptive responses. Innate immunity is an immediate but less specific defense that is highly conserved in evolutionary terms. It is centered on the neutrophil response, and it involves monocytes and macrophages as well as complement, cytokines, and acute phase proteins. The innate system responds primarily to extracellular pathogens, especially bacteria, by recognizing structures commonly found on pathogens, namely lipopolysaccharide (Gram-negative cell walls), lipoteichoic acid (Gram positive), and mannans (yeast). Adaptive immunity is demonstrated only in higher animals and is an antigen-specific response via T- and B-lymphocytes after antigen presentation and recognition. Although this reaction is more specific, it requires several days to develop, unless that antigen has previously triggered a response (so-called immune memory). This response can also at times be directed against self-antigens, resulting in autoimmune disorders.

The recruitment and activation of neutrophils provide the primary defense against the invasion of bacterial and fungal pathogens. They emerge from the bone marrow with the biochemical and metabolic machinery needed for the efficient killing of microorganisms. Activated macrophages release G-CSF and GM-CSF, which stimulate myeloid differentiation and can be recognized on blood testing as the classic neutrophil leukocytosis. Neutrophils are activated when circulating cells detect chemokines released from sites of inflammation. On activation, they undergo conformational and biochemical changes that transform them into powerful host defenders. These changes allow rolling along the endothelial lining of postcapillary venules, migration toward the site of inflammation, adherence to the endothelium, migration through the endothelium to tissue sites, ingestion, killing, and digestion of invading organisms.

Neutrophils migrate to sites of infection along gradients of chemoattractant mediators. An acute inflammatory stimulus leads to the accumulation of neutrophils along the endothelium of postcapillary venules. The major molecules involved in this process are adhesion molecules, chemoattractants, and chemokines. Loose adhesions between neutrophils and endothelium are made and broken, resulting in the slow movement of leukocytes along endothelium and a more intense exposure of neutrophils to activating factors. Chemotaxis requires responses involving actin polymerization–depolymerization adhesion events mediated by integrins and involving microfilament–membrane interactions. All leukocytes including lymphocytes localize infection using these same mediators. Colchicine depolymerizes microfilaments, causing the dissolution of the fibrillar microtubules in granulocytes and other motile cells, impairing this response.

Opsonized particles, immune complexes, and chemotactic factors activate neutrophils in tissues by binding to cell surface receptors. The neutrophil makes tight contact with its target, and the plasma membrane surrounds the organism completely enclosing it. Two mechanisms are then responsible for the destruction of the organism: the oxygen-dependent respiratory burst, and the oxygen-independent response involving cationic enzymes found in cytoplasmic granules. The respiratory burst is caused by an NADPH oxidase complex that assembles at the phagosomal membrane. Electrons are transferred from cytoplasmic NADPH to oxygen on the phagosomal side of the membrane, generating superoxide, hydrogen peroxide, hydroxyl radical, singlet oxygen, hypochlorous acid, chloramines, nitric oxide, and peroxynitrite. Cytoplasmic

granules within the neutrophil fuse with the phagosome and empty their contents into it. The components of these granules include myeloperoxidase (MPO), elastase, lipases, metalloproteinases, and a pool of CD11b/CD18 proteins required for adhesion and migration. Finally, the phagocytized organism is digested and eliminated by the neutrophil. Overstimulation of this complex and highly regulated but somewhat nonspecific system can at times become deleterious, as is postulated to occur with reperfusion injury or carbon monoxide poisoning, to cite two examples.⁹⁵ Vasculitis and the systemic inflammatory response syndrome are further examples of excessive activation of the innate response.

Neutropenia and Agranulocytosis

Neutropenia is a reduction in circulating neutrophils at least 2 standard deviations below the norm, but the threshold of $1500/\text{mm}^3$ ($1.5 \times 10^9/\text{L}$) is often used instead.⁴⁷ Severe neutropenia is termed agranulocytosis and is generally defined to be an absolute neutrophil count of less than $500/\text{mm}^3$ ($0.5 \times 10^9/\text{L}$). Neutropenia can result from decreased production, increased destruction, or retention of neutrophils in the various storage pools. Their high rate of turnover renders neutrophils vulnerable to any xenobiotic that inhibits cellular reproduction. As such, the various antineoplastics including antimetabolites, alkylating agents, and antimitotics will predictably cause neutropenia. This predictable, dose-dependent reaction represents an important dose-limiting adverse effect of therapy. On the other hand, a number of xenobiotics are implicated in idiosyncratic neutropenia.^{3,4} The parent drug or a metabolite usually acts as a hapten to trigger antineutrophil antibodies. Table 22–4 provides an abbreviated list.^{76,94} Cocaine users are at very high risk for agranulocytosis because of the common contamination of this drug with levamisole (Chap. 78).²²

TABLE 22–4. Selected Causes of Idiosyncratic Drug-Induced Agranulocytosis

Anticonvulsants

Carbamazepine

Phenytoin

Antiinflammatory

Aminopyrine

Ibuprofen

Indomethacin

Phenylbutazone

Antimicrobials

β-Lactams, including penicillin G^a

Cephalosporins

Chloramphenicol

Dapsone^a

Ganciclovir

Isoniazid

Rifampicin

Sulfonamides

Vancomycin

Antirheumatics

Gold salts

Levamisole^a
Penicillamine
Sulfasalazine^a
Antipsychotics
Clozapine^a
Phenothiazines
Antithyroid agents
Methimazole ^a
Propylthiouracil ^a
Cardiovascular agents
Hydralazine
Lidocaine
Procainamide^a
Quinidine
Ticlopidine^a
Vesnarinone
Diuretics
Acetazolamide
Hydrochlorothiazide
Hypoglycemics
Chlorpropamide
Tolbutamide
Sedative–hypnotics
Barbiturates
Flurazepam
Other
Deferiprone

^aDenotes at least 10 cases reported.²

Eosinophilia

Eosinophils are primarily responsible for protecting against parasitic infection. Allergic reactions and malignancies such as lymphoma are also common causes of eosinophilia, especially where nematode infection is rare.⁸⁵ Eosinophils bind to antigen-specific IgE and discharge their large granules, which contain major basic protein, peroxidase, and eosinophil-derived neurotoxin, onto the surface of the antibody-coated organism. Two unusual toxicologic outbreaks were characterized by eosinophilia, acute cough, fever, and pulmonary infiltrates, followed by severe myalgia, neuropathy, and

eosinophilia. The first outbreak, called the toxic oil syndrome, took place in central Spain in 1981, when industrial-use rapeseed oil denatured with 2% aniline was fraudulently sold as olive oil by door-to-door salesmen.³⁶ The precise causative agent remains uncertain but may include fatty acid esters of 3-(N-phenylamino)-1,2-propanediol.³⁶ The second outbreak, called the eosinophilia-myalgia syndrome, occurred during 1988 and 1989 in users of L-tryptophan supplements traced back to a single wholesaler in Japan.⁶ The causative contaminant has not been identified but is believed to have been present in only trace quantities in the L-tryptophan purified from microbial culture. Both syndromes appear to be mediated by immunologic mechanisms.

Leukemia

The leukemias represent the malignant, unregulated proliferation of hematopoietic cells. Although monoclonal in origin, they affect all cell lines derived from the progenitor cell. Acute myeloid leukemia (AML) and the myelodysplastic syndromes are the most common leukemias associated with xenobiotics. The long-recognized association between AML and occupational benzene exposure, radiation, or treatment with alkylating antineoplastics has helped to advance understanding of the molecular mechanisms underlying leukemogenesis.¹⁵ The necessary events are believed to involve several sequential genetic and epigenetic alterations, as evidenced by a distinct pattern of chromosomal deletions preceding the development of AML.^{49,50} Other recognized xenobiotics that can cause leukemia include topoisomerase II inhibitors, 1,3-butanediol, styrol, ethylene oxide, and vinyl chloride.^{54,75} In many cases, the latency period between exposure and illness is prolonged. For example, leukemia linked to benzene is preceded by several months of anemia, neutropenia, and thrombocytopenia.

HEMOSTASIS

In the absence of pathology, blood remains in a fluid form with cells in suspension. Injury triggers coagulation and thrombosis. The resulting clot formation, retraction, and dissolution involve an interaction between the vessel endothelium, soluble constituents of the coagulation system, and proteins located on and within platelets. Platelets respond to signals within their immediate environment and from injured components of the distant microcirculation. A dynamic balance must be maintained between coagulation and fibrinolysis to maintain the integrity of the circulatory system (Fig. 22–5).

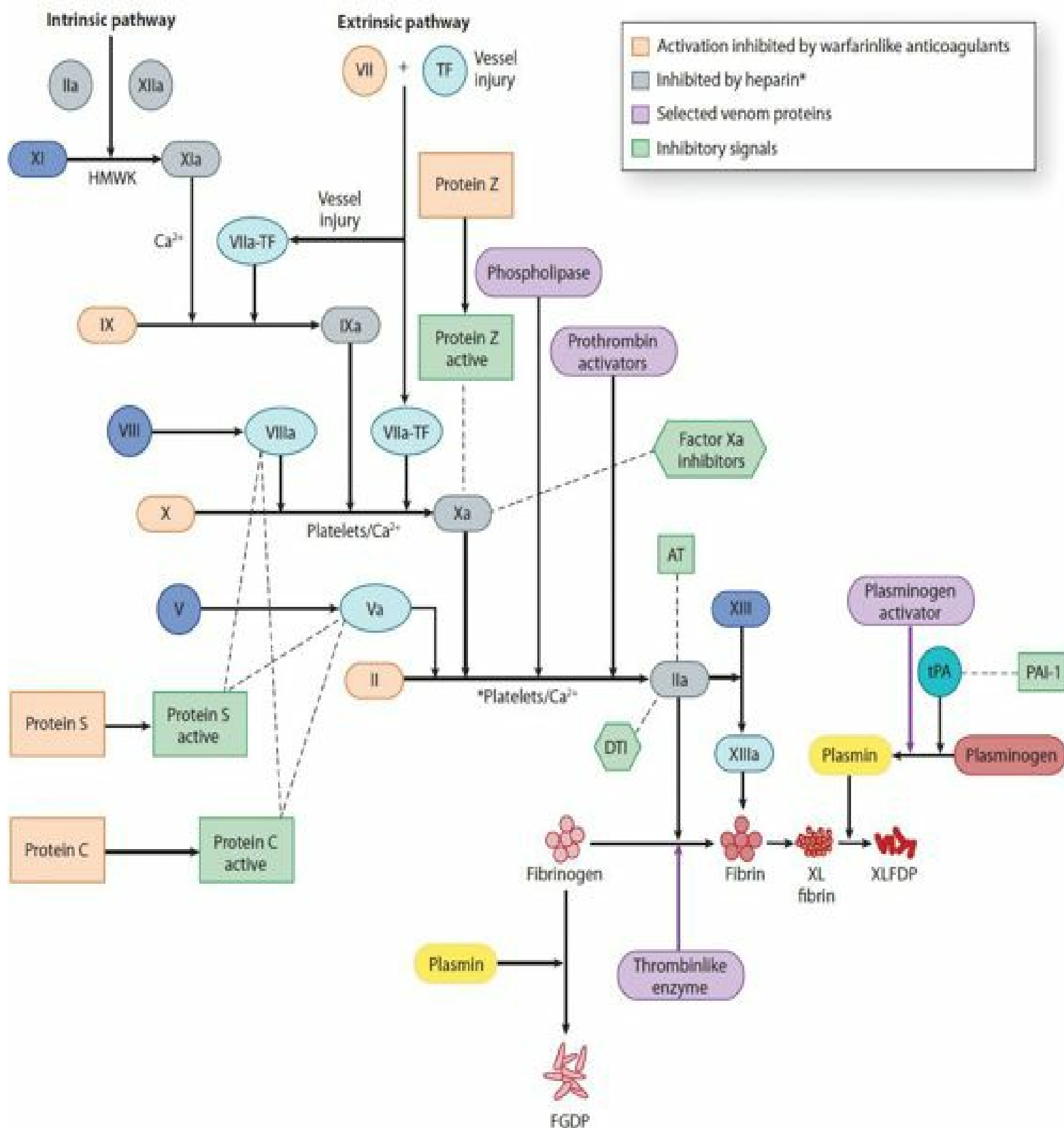


FIGURE 22–5. A schematic overview of the coagulation cascade and fibrinolytic pathway. Selected sites of interaction between phospholipids on the platelet surface and coagulation pathway intermediates are shown, with the exception of tissue factor/VIIa and IXa to VIIIa (to avoid confusion). Similarly, not all sites of interaction between various serine protease inhibitors are shown. Selected venom proteins are indicated by purple boxes. Dashed lines indicate inhibitory effects. FDP = fibrin degradation products; FGDP = fibrinogen degradation products; HMWK = high-molecular-weight kininogen; TF = tissue factor; tPA = tissue plasminogen activator; PAI = plasminogen activator inhibitor; XL = cross-linked.

Coagulation

Two basic pathways termed intrinsic and extrinsic are involved in the initiation of coagulation. The more important extrinsic, or tissue factor, pathway is activated when blood is exposed to tissue factor (also known as thromboplastin) which is normally expressed on subendothelial cells and fibroblasts not in direct contact with blood. Tissue factor activates factor VII and together form the extrinsic tenase complex activating both factors X and IX. The intrinsic, or

contact activation, pathway also activates factor IX, which forms the intrinsic tenase complex with factor VIIIa. Both extrinsic and intrinsic tenase (ie, “ten” –ase) with calcium activate factor X, which binds to factor Va on the surface of activated platelets, forming the prothrombinase complex. The prothrombinase complex activates prothrombin, which results in the generation of thrombin activity. Thrombin activates platelets, promotes its own generation by activation of factors V, VIII, and XI, and converts fibrinogen to fibrin (Chap. 60).⁴⁶

Laboratory Tests of Coagulation

An understanding of several widely available coagulation tests is important to the correct interpretation of the effects of xenobiotics on hemostasis, whether for therapeutic drug monitoring or following overdose. Four studies—prothrombin time (PT, or international normalized ratio {INR}), partial thromboplastin time (PTT), thrombin time, and fibrinogen concentration—are particularly important in the classification of coagulation disorders.

PT assesses the extrinsic coagulation pathway and is calculated by adding standardized thromboplastin reagent (phospholipid and tissue factor) to a sample of the patient’s citrated plasma (the citrate removes calcium to prevent clotting). Calcium is then introduced, and the time to clotting measured. With the exception of factor X, the PT is unaffected by the presence or absence of factors VIII to XIII, platelets, prekallikrein, and high-molecular-weight kininogen (HMWK). An individual’s PT was formerly expressed as a ratio (PT observed to PT control). Because this ratio is directly affected by both laboratory methodology and the source of the thromboplastin reagent used, the generated results suffered from significant variability between laboratories and countries. Thus, the INR was developed in an attempt to limit this variability. The INR is calculated by raising the PT ratio to an exponent known as the International Sensitivity Index (ISI): (PT ratio)^{ISI}. The ISI is calibrated against an international standard to measure responsiveness of the particular thromboplastin to the effects of warfarin.

Although the use of the INR does not completely eliminate variability,^{94,95} it improves warfarin dosing and comparison with international norms. It should be noted that the ISI, and thus the INR, is designed for greater consistency in measuring coagulation changes due to warfarin, and it may in fact be more variable than the PT ratio for patients with other coagulation defects. Specifically, replacing the PT with the INR for prognosis in the setting of fulminant hepatic failure, as may occur following APAP overdose, is controversial.^{24,84} In these patients, the INR may be more variable between laboratories, and the calculation of a substantially different ISI may be warranted.¹¹

The PTT tests both the intrinsic and common coagulation pathway. It is measured by adding calcium and an activator (kaolin, silica, or celite) to citrated plasma and the time to clotting observed. Some tests also use phospholipids in the reagent to activate the remaining coagulation factors, thereby giving rise to the term activated partial thromboplastin time (aPTT). Because the PTT and aPTT are essentially interchangeable, the term PTT is used hereafter to represent the concept. The PTT is not affected by alterations in factors VII, XIII, or platelets.

The thrombin time (or thrombin clotting time), determined by adding exogenous thrombin to citrated plasma, evaluates the ability to convert fibrinogen to fibrin, is thus unaffected by abnormalities of factors II, V, VII to XIII, platelets, prekallikrein, or HMWK. Finally, either a fibrinogen concentration or a determination of fibrin degradation products will help distinguish between problems with clot formation and consumptive coagulopathy (disseminated intravascular coagulation). An evaluation of the combination of normal and abnormal results of these tests usually determines a patient’s clotting abnormality (Table 22–5).

TABLE 22–5. Evaluation of Abnormal Coagulation Times

PT prolonged, PTT normal

Deficiency of factor VII

Warfarin therapy (early)

Vitamin K deficiency (mild)

Liver disease (mild)

PT normal, PTT prolonged, bleeding

Deficiencies of factors VIII, IX, XI

von Willebrand disease

PT normal, PTT prolonged, no bleeding

Deficiencies of factor XII, prekallikrein

High-molecular-weight kininogen inhibitor syndrome

PT and PTT prolonged, thrombin time normal, fibrinogen normal

Deficiencies of factors II, V, IX; vitamin K deficiency (severe) Warfarin therapy (late)

Factor Xa inhibitor therapy (eg, rivaroxaban, apixaban)^{a,b}

PT and PTT prolonged, thrombin time abnormal, fibrinogen normal

Heparin therapy^a

Direct thrombin inhibitor therapy (eg, dabigatran)^c

Dysfibrinogenemia

PT and PTT prolonged, thrombin time abnormal, fibrinogen abnormal

Liver disease

Disseminated intravascular coagulation

Fibrinolytic therapy

Crotaline envenomation

^aPTT insensitive to low-molecular weight heparin effects and less sensitive than PT to factor Xa inhibitor therapy. ^bNormal PT does not exclude effect. ^cProlongation of PTT is not linearly correlated with dabigatran concentration.

PT = prothrombin time; PTT = partial thromboplastin time.

Inhibitors can be diagnosed by “mixing studies,” because only a small percentage of the coagulation factors present in normal plasma are necessary to have normal clotting studies. Factor activity in blood can be as little as 25% of normal without affecting the PT or PTT. Thus, the presence of an abnormal PT or PTT that will not correct despite the addition of an equal volume of normal plasma demonstrates the presence of an inhibitor of coagulation as opposed to a factor deficiency. Heparin-induced anticoagulation results in an elevated PTT that does not correct when mixing studies are performed. More sophisticated studies can be used to identify specific coagulation factor deficiencies.

Xenobiotic-Induced Defects in Coagulation

A rapidly increasing number of xenobiotics are in therapeutic use to antagonize coagulation ([Chap. 60](#)). The recognition of a hemorrhagic disease in cattle in the 1920s and the isolation of the causative agent dicoumarol from spoiled sweet clover in the 1940s resulted in the development of the warfarin-type anticoagulants. This group of anticoagulants indirectly inhibits hepatic synthesis of coagulation factors II, VII, IX, X, and proteins C, S, and Z by inhibiting the reductase that is responsible for the regeneration of vitamin K quinone from vitamin K epoxide. Because warfarin is widely prescribed and has a narrow therapeutic index, efforts to improve our understanding of the pharmacology of warfarin are advancing the fields of pharmacogenomics and drug interactions.¹⁰²

Heparin is a highly sulfated glycosaminoglycan that is normally present in tissues. Commercial unfractionated heparin is either bovine or porcine in origin and consists of a mixture of polysaccharides with molecular weights ranging from 4000 to 30,000 Da. The anticoagulant activity of heparin is through its catalytic activation of antithrombin III, a suicide inhibitor of the serine proteases thrombin and factors IXa, Xa, XIa, and XIIa.⁶⁸

The low-molecular-weight heparins (LMWHs) have a mean molecular weight of 4000 to 6000 Da.⁴⁶ Their subcutaneous bioavailability, more predictable pharmacokinetics, lower protein binding, and longer half-life make them more convenient than unfractionated heparin.⁶⁸

Heparinoids are glycosaminoglycans not derived from heparin with anticoagulant effects. This class includes dermatan sulfate and danaparoid sodium. Fondaparinux is a synthetic pentasaccharide that also inhibits factor Xa by binding to antithrombin III and therefore acts upstream of thrombin. Recently, other oral factor Xa inhibitors have been approved for human use, including rivaroxaban and apixaban. Several direct thrombin inhibitors are also in clinical use, including parenterally administered lepirudin, argatroban, bivalirudin, desirudin, and more recently oral dabigatran. These agents can

prolong the INR, aPTT, thrombin clotting time, and whole-blood activated clotting time.

Fibrinolysis

The coagulation system is opposed by three major inhibitory systems. Components of the fibrinolytic system circulate as zymogens, activators, inhibitors, and cofactors.³³ Plasminogen can be activated to plasmin by an intrinsic pathway involving factor XII, prekallikrein, and HMWK. This produces the degradation products and fibrin monomers that are found in disseminated intravascular coagulation. The extrinsic pathway involves the release of tissue plasminogen activator (t-PA) from tissues and urokinase plasminogen activator (u-PA) from secretions.³³ Once activated, plasmin can degrade fibrinogen, fibrin, and coagulation factors V and VIII. The degradation of cross-linked fibrin strands results in the formation of D-dimers.

Several inhibitors oppose the fibrinolytic system, including α_2 -antiplasmin, α_2 -macroglobulin, both of which oppose plasmin activity, and plasminogen activator inhibitor (PAI) types 1 and 2, which oppose t-PA. PAI-1 and PAI-2 are opposed by activated protein C and protein S. Activated protein C is activated by thrombin. Another vitamin K–dependent glycoprotein, protein Z, accelerates the degradation of factor Xa. Congenital deficiencies of proteins C, S, and Z may result in pathologic venous thrombosis. Decreased fibrinolytic activity may result from decreased synthesis, release of t-PA, or from an elevation of the PAI-1 concentration. Both conditions have been observed postoperatively, with the use of oral contraceptives, in the third trimester of pregnancy, and in obesity. The activity of α_2 -antiplasmin and α_2 -macroglobulin are increased in pulmonary fibrosis, malignancy, infection, and myocardial infarction, and in thromboembolic disease.³³

Xenobiotic-Induced Defects in Fibrinolysis

Table 22–6 lists xenobiotics associated with an acquired defect of fibrinolysis. The chemotherapeutics may result in a reduction in serine protease inhibitors such as antithrombin. L-Asparaginase is associated with a reduction in circulating t-PA concentrations. Methotrexate can damage vascular endothelium, which may trigger thrombosis (Chap. 51).³³ Hemostatic drugs used therapeutically include the synthetic lysine derivatives aminocaproic acid and tranexamic acid, which bind reversibly to plasminogen; the bovine protease inhibitor aprotinin, which inhibits kallikrein; the vasopressin analog desmopressin, which increases plasma concentrations of factor VIII and vWF; and conjugated estrogens, which normalize bleeding times in uremia.⁶²

TABLE 22–6. Xenobiotics That Impair Fibrinolysis

Antifibrinolytics

Aminocaproic acid

Aprotinin

Desmopressin

Tranexamic acid

Chemotherapeutics

Anthracyclines

L-Asparaginase

Methotrexate

Mithramycin

Coagulation factors

Cytokines

Erythropoietin

Thrombopoietin

Hormones, including conjugated estrogens

Platelets

In the resting state, platelets maintain a discoid shape. The platelet membrane is a typical trilaminar membrane with glycoproteins, glycolipids, and cholesterol embedded in a phospholipid bilayer. The plasma membrane is in direct continuity with a series of channels, the surface-connected canalicular system (SCCS), which is sometimes referred to as the open canalicular system. The SCCS provides a route of entry and exit for various molecules, a storage pool for platelet glycoproteins, and an internal reservoir of membrane that may be recruited to increase platelet surface area. This facilitates platelet spreading and pseudopod formation during the process of cell adhesion.

The glycocalyx, or outer coat, is heavily invested with glycoproteins that serve as receptors for a wide variety of stimuli. The β_1 -integrin family includes receptors that mediate interactions between cells and mediators in the extracellular matrix, including collagen, laminin, and fibronectin. The β_2 -integrin receptors are present in inflammatory cells and platelets and are important in immune activation. The β_3 -integrin receptors (also known as cytoadhesins) include the glycoprotein (GP) IIb-IIIa fibrinogen receptor, as well as vitronectin.⁴⁶ Vitronectin has binding sites for other integrins, collagen, heparin, and components of complement. All of the integrins are active in the process of platelet adhesion to surfaces. Platelet aggregation is mediated by the GP IIb-IIIa receptors.⁴⁶

The submembrane region contains actin filaments that stabilize the platelets' discoid shape and are involved in the formation and stabilization of pseudopods. They also generate the force needed for the movement of receptor-ligand complexes from the outer plasma membrane to the SCCS. These mobile receptors are important in the spreading of platelets on surfaces, and for binding fibrin strands and other platelets. Platelet cytoplasm contains three types of membrane bound secretory granules.⁴⁶ The α granules contain β -thromboglobulin, which mediates inflammation, binds and inactivates heparin, and blocks the endothelial release of prostacyclin. In addition, platelet factor-4, which inactivates heparin, and fibrinogen are contained within the α granules. Dense granules store adenine nucleotides, serotonin, and calcium, which are secreted during the release reaction. Platelet lysosomes contain hydrolytic enzymes. Stimulation by platelet agonists causes the granules to fuse with the channels of the SCCS, driving the contents out of the platelets and into the surrounding media.

Platelet Adhesion. On the vessel wall, collagen, von Willebrand factor (vWF), and fibronectin are the adhesive proteins that play the most prominent role in the adhesion of platelets to vascular subendothelium. On the exposure of collagen (eg, following a laceration or the rupture of an atherosclerotic plaque), platelet adhesion is triggered. Under conditions of high shear (flowing blood), platelet adhesion is mediated by the binding of GP Ib-V-IX receptors on platelet membranes to vWF in the vascular subendothelium.⁴⁶ Following adherence of platelets to subendothelial vWF, a conformational change in GP IIb-IIIa on platelet membrane occurs, activating this receptor complex to ligate vWF and fibrinogen. The result is the amplification of platelet adhesion and aggregation. An important interaction occurs between thrombosis and inflammation. Platelet-activating factor is synthesized and coexpressed with P-selectin on the surface of the endothelium in response to mediators such as histamine or thrombin. Platelet-activating factor interacts with a receptor on the surface of neutrophils that activates the CD11/CD18 adhesion complex, and results in adhesion of neutrophils to endothelium and to platelets. This results in the synthesis of leukotrienes and other mediators of inflammation.

Platelet Activation. Thrombin, collagen, and epinephrine can activate platelets. In response to thrombin, granules fuse with each other and with elements of the SCCS to form secretory vesicles. These vesicles are believed to fuse with the surface membrane, releasing their contents into the surrounding medium. The membranes of the secretory granules become incorporated into the platelet surface membrane.

Platelet Aggregation. Following activation, GP IIb-IIIa is expressed in active form on platelet surface, serving as the final common pathway for platelet aggregation regardless of inciting stimulus. This receptor binds exogenous calcium and fibrinogen. GP IIb-IIIa ligates fibrinogen along with fibronectin, vitronectin, and vWF, resulting in the binding of platelets to other platelets, and ultimately the formation of the platelet plug. Collagen-induced platelet aggregation is mediated by adenosine diphosphate (ADP) and thromboxane A_2 . ADP binds to the metabotropic purine receptors P2Y1 and P2Y12, leading to transient and sustained aggregation, respectively.³⁵ Thromboxane A_2 is formed from arachidonic acid by the action of cyclooxygenase-1. It is a potent vasoconstrictor and inducer of platelet aggregation and release reactions.⁴⁶ Platelets participate in triggering the coagulation cascade by binding coagulation factors II, VII, IX, and X to membrane phospholipid, a calcium-dependent process.

Antiplatelet Xenobiotics

Aspirin. Aspirin inhibits prostaglandin H synthase (cyclooxygenase {COX}) by irreversibly acetylating a serine residue at the active site of the enzyme. Aspirin inhibition of the COX-1 isoform of this enzyme is 100–150 times more potent than its inhibition of the COX-2 isoform. The inhibition of COX-1 results in the irreversible inhibition of thromboxane A_2 formation. Because platelets can be activated by other mechanisms including thrombin, thrombosis can develop despite aspirin therapy (Chap. 39).⁹⁰

Selective COX-2 Inhibitors. Platelets express primarily COX-1 and use it to produce mostly thromboxane A_2 , which

leads to platelet aggregation and vasoconstriction. Endothelial cells express COX-2 and use it to produce prostaglandin I₂, an inhibitor of platelet aggregation and a vasodilator. Whereas aspirin and traditional (nonselective) nonsteroidal antiinflammatory medications inhibit the production of thromboxane A₂ and prostaglandin I₂ at both sites, the selective COX-2 inhibitors do not affect platelet-derived thromboxane A₂, perhaps accounting for the increase in cardiovascular events associated with long-term use of some of these xenobiotics.^{27,99}

Glycoprotein IIb-IIIa Antagonists. The GP IIb-IIIa antagonist abciximab is a chimeric human-murine monoclonal antibody that binds the GP IIb-IIIa receptor of platelets and megakaryocytes. Two synthetic ligand-mimetic antagonists have also been developed: eptifibatide and tirofiban. These parenteral antagonists are used primarily in patients undergoing percutaneous coronary interventions.⁴⁶ By blocking the fibrogen binding site of IIb-IIIa, platelet aggregation is blocked and even reversed regardless of the inciting activation. Reversible thrombocytopenia can occur within hours of initiation of these xenobiotics.⁸⁶

ADP Receptor Inhibitors. The thienopyridines clopidogrel, ticlopidine, and prasugrel antagonize platelet aggregation by irreversible inhibition of ADP binding to the P2Y₁₂ receptor. All three prodrugs are associated with TTP, as well as neutropenia and aplastic anemia.^{12,72,73} The purine analogs ticagrelor and cangrelor are direct-acting, reversible allosteric antagonists that bind to a different site on the P2Y₁₂ receptor.

Dipyridamole. The pyrimidopyrimidine derivative dipyridamole inhibits cyclic nucleotide phosphodiesterase in platelets, resulting in the accumulation of cyclic adenosine monophosphate and perhaps cyclic guanine monophosphate. It also inhibits cellular reuptake of adenosine, blocks thromboxane synthase, and inhibits the thromboxane receptor.

Xenobiotic-Induced Thrombocytopenia

Multiple xenobiotics are reported to cause thrombocytopenia, either via the formation of drug-dependent antiplatelet antibodies or as TTP. Drug-induced platelet antibodies are estimated to occur in 1 in 100,000 drug exposures. Reversible drug binding to platelet epitopes, such as GP Ib-V-IX, GP IIb-IIIa, and platelet-endothelial cell adhesion molecule-1, leads to a structural change that can form or expose a neoepitope target for antibody formation. The presence of the drug is required for antibody binding and increased platelet destruction, but there is no covalent bond (as occurs in the hapten model of penicillin binding to the erythrocyte membrane).

Thrombocytopenia can also occur as a result of spurious clumping, pregnancy, hypersplenism with cirrhosis, idiopathic thrombocytopenic purpura, heparin-induced thrombocytopenia ([Chap. 60](#)), bone marrow toxicity, and TTP. After excluding these conditions and nontherapeutic exposures, a systematic literature search updated annually lists more than 1000 cases reported in English involving more than 150 xenobiotics. [Table 22–7](#) lists the xenobiotics appearing in multiple cases, satisfying criteria for probable to definite causality including drug rechallenge. Nevertheless, a common clinical problem is to distinguish drug-induced thrombocytopenia from idiopathic thrombocytopenic purpura in a patient on multiple medications who develops thrombocytopenia. In the absence of validated laboratory assays for drug-dependent platelet antibodies other than heparin, diagnosis still depends on the clinical course following drug discontinuation and perhaps rechallenge. Large databases provide some guidance regarding past reported experience.^{37,60,82} Severe (<20,000 platelets/mm³), or acute transient thrombocytopenia are more likely to be drug-induced.¹⁰

TABLE 22–7. Xenobiotics Reported to Cause Thrombocytopenia as a Result of Antiplatelet Antibodies^a

Abciximab
APAP
Aminoglutethimide
Aminosalicylic acid
Amiodarone
Amphotericin B
Carbamazepine
Cimetidine
Danazol
Diclofenac

Digoxin
Dipyridamole
Eptifibatide
Famotidine
Furosemide
Gold salts
Heparin
Imipenem-cilastatin
Indinavir
Levamisole
Linezolid
Meclofenamic acid
Nalidixic acid
Orbofiban
Oxprenolol
Phenytoin
Piperacillin
Procainamide
Quinidine
Quinine
Rifampin
Tirofiban
Trimethoprim-sulfamethoxazole
Valproate
Vancomycin

^aXenobiotics reported in at least two cases to have definitely caused immune thrombocytopenia or in at least five cases to have probably caused immune thrombocytopenia following therapeutic use.

Data adapted from George JN, Raskob GE, Shah SR, et al: Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med.* 1998;129:886–890; Li X, Swisher KK, Vesely SK, George JN: Drug-induced thrombocytopenia: an updated systematic review. *Drug Safety.* 2007;30:185–186 and <http://w3.ouhsc.edu/platelets>; accessed June 24, 2013.

In patients administered the sensitizing agent de novo, 5 to 7 days are typically required for the development of the immune response. During rechallenge, thrombocytopenia can develop within 12 hours.¹⁰ Interestingly, the unique ability of GP IIb/IIIa inhibitors such as abciximab to cause thrombocytopenia within hours of first use suggests the presence of preformed antibodies directed against platelet epitopes, perhaps accounting for ex vivo clumping of platelets observed in

approximately one out of 500 normal patients.⁸³ Clinically, fever, chills, pruritus, and lethargy may occur. The onset of life-threatening bleeding may be abrupt. Hemorrhagic vesicles may be seen in the oral mucosa. Laboratory investigations will demonstrate an absence of platelets on peripheral smear, prolongation of the bleeding time, deficient clot retraction, and an abnormal prothrombin consumption test. Bone marrow aspiration will demonstrate normal or increased numbers of megakaryocytes and immature forms. Treatment includes the transfusion of blood products, glucocorticoids, and the withdrawal of the offending xenobiotic.¹⁰

Thrombotic Thrombocytopenic Purpura. TTP is characterized by the triad of microangiopathic hemolytic anemia, severe thrombocytopenia, and fluctuating neurologic abnormalities.⁶⁶ Fever and acute kidney injury are also common, although overt kidney failure is rare. The hallmark is the presence of platelet aggregates throughout the microvasculature, without fibrin clot, unlike the fibrin-rich thrombi seen in disseminated intravascular coagulation or the hemolytic uremic syndrome. In the acquired form, drug-induced autoantibodies inactivate a circulating zinc metalloprotease ADAMTS13, thereby blocking its ability to depolymerize large multimers of vWF and leading to platelet clumping.^{8,9,12,100} Plasma exchange with fresh frozen plasma replenishes ADAMTS13 and removes the inhibitory antibodies. Prior to understanding of the molecular mechanism, other causes of microvascular hemolysis with thrombocytopenia were often confused with TTP. These causes included hemolytic uremic syndrome due to shiga toxin, the HELLP syndrome of pregnancy, Rocky Mountain spotted fever, and paroxysmal nocturnal hemoglobinuria. Also included were cases secondary to xenobiotics such as cyclosporine, cocaine, gemcitabine, mitomycin C, and cisplatin, in which ADAMTS13 antibodies are not present.^{31,100}

Heparin-Induced Thrombocytopenia. An immune response to both unfractionated and low-molecular weight heparin, manifested clinically by the development of thrombocytopenia and, at times, venous thrombosis, is now recognized to result from IgG antibodies against platelet factor 4, a heparin-binding chemokine.¹ The diagnosis is confirmed by testing for these antibodies. The heparin–platelet factor 4 antibody complex results in the release of procoagulant microparticles which release tissue factor, provide an anionic phospholipid membrane surface on which clotting cascade complexes assemble, and can lead to paradoxical thrombosis, which can be limb- or life-threatening^{55,56} (Chap. 60).

SUMMARY

- The mechanisms of toxic injury to the blood are extremely varied, reflecting the complexity of this vital fluid.
- Virtually all xenobiotics come into contact with blood, and have the potential to disrupt its essential functions of oxygen transport, gas exchange, signaling, host defense, and hemostasis.
- Xenobiotics may directly injure mature cells, or prohibit their development by injuring the stem cell pool.
- Oxygen transport can be disrupted in several distinct ways, including oxidation of the heme iron, protein globin chain disruption, and shift of the oxygen-hemoglobin dissociation curve and hemolysis.
- A common theme in hematologic toxicity is the perturbation of homeostatic equilibria that exist between cell proliferation and apoptosis, between immune activation and suppression, or between thrombophilia and thrombolysis.

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23 HEPATIC PRINCIPLES

Kathleen A. Delaney

The liver plays an essential role in metabolic homeostasis. Hepatic functions include the synthesis, storage, and breakdown of glycogen. In addition, the liver is important in the metabolism of lipids; the synthesis of albumin, clotting factors, and other important proteins; the synthesis of the bile acids necessary for absorption of lipids and lipid soluble vitamins; and the metabolism of cholesterol.^{64,159} Hepatocytes facilitate the excretion of metals, most importantly iron, copper, zinc, manganese, mercury, and aluminum, as well as the detoxification of products of metabolism, such as bilirubin and ammonia.^{32,74} Generalized disruption of these important functions results in manifestations of liver failure: hyperbilirubinemia, coagulopathy, hypoalbuminemia, hyperammonemia, and hypoglycemia.^{86,89,137} Disturbances of more specific functions result in accumulation of lipids, metals, and bilirubin, and the development of lipid-soluble vitamin deficiencies.^{64,159}

The liver is also the primary site of biotransformation and detoxification of xenobiotics. Its interposition between the gut and systemic circulation makes it the first-pass recipient of xenobiotics absorbed from the gastrointestinal tract. The liver receives blood from the systemic circulation and participates in the detoxification and elimination of xenobiotics that reach the bloodstream through other routes, such as inhalation or cutaneous absorption.^{142,159,160}

Many xenobiotics are lipophilic and inert and require chemical modification followed by conjugation to make them sufficiently water-soluble to be eliminated. The liver contains the highest concentration of enzymes involved in phase I oxidation-reduction reactions, the first stage of detoxification for many lipophilic xenobiotics. Conjugation of the reactive products of phase I biotransformation with molecules such as glucuronide facilitates excretion (**Chap. 13**). Although many xenobiotics that are detoxified in the liver are subsequently excreted in the urine, the biliary tract provides a second essential route for the elimination of detoxified xenobiotics and products of metabolism.^{32,56,160} Although phase I activation of xenobiotics is usually followed by phase II conjugation that results in detoxification, it can also lead to the production of xenobiotics with increased toxicity, which may cause injury to hepatocytes at the site of their synthesis.^{142,160}

MORPHOLOGY AND FUNCTION OF THE LIVER

Two pathologic concepts are used to describe the appearance and function of the liver: a structural one represented by the hepatic lobule and a functional one represented by the acinus. The basic structural unit of the liver as characterized by light microscopy is the hepatic lobule, a hexagon with the central hepatic vein at the center and the portal triads at the angles. The portal triad consists of the portal vein, the common bile duct, and the hepatic artery. Cords of hepatocytes are oriented radially around the central hepatic vein, forming sinusoids. In contrast, the acinus, or “metabolic lobule” is the functional unit of the liver. Located between two central hepatic veins, it is bisected by terminal branches of the hepatic artery and portal vein that extend from the bases of the acini toward hepatic venules at the apices. The acinus is subdivided into three metabolically distinct zones. Zone 1 lies near the portal triad, zone 3 lies near the central hepatic vein, and zone 2 is intermediate.^{64,159} **Figure 23–1** illustrates the relationship of the structural and functional concepts of the liver.

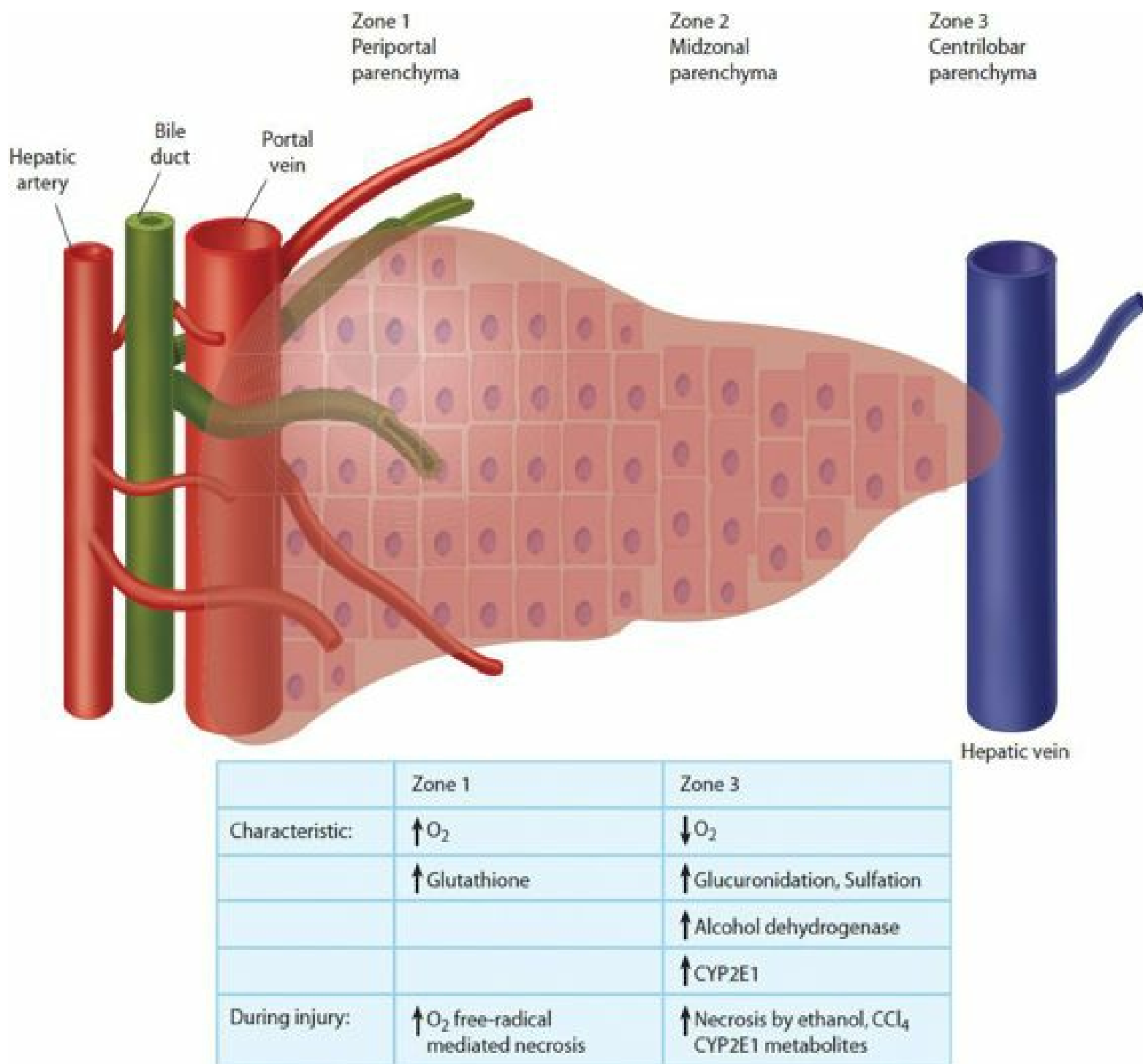


FIGURE 23–1. The acinus is defined by three functional zones. Specific contributions of each zone to the biotransformation of xenobiotics reflect various metabolic factors that include differences in oxygen content of blood as it flows from the oxygen-rich portal area to the central hepatic vein, differences in glutathione content, different capacities for glucuronidation and sulfation, and variations in content of metabolic enzymes such as CYP2E1. The hepatic lobule (not shown) is a structural concept, a hexagon with the central vein at the center surrounded by six portal areas that contain branches of the hepatic artery, bile duct, and portal vein. Injury to hepatocytes that is confined to zone 3 is called “centrilobular” because in the structure of the lobule, zone 3 encircles the central vein, which is the center of the hepatic lobule.

Approximately 75% of the blood supply to the liver is derived from the portal vein, which drains the alimentary tract, spleen, and pancreas. This blood is enriched with nutrients and other absorbed xenobiotics and is poor in oxygen. The remainder of the hepatic blood flow comes from the hepatic artery, which delivers well-oxygenated blood from the systemic circulation. Blood from the hepatic artery and portal vein mixes in the sinusoids, coming in close contact with cords of hepatocytes before it exits through small fenestrations in the wall of the vein.¹⁷⁵ Oxygen content diminishes several fold as blood flows from the portal area to the central hepatic vein.⁶⁴

There are six types of cells in the liver. Hepatocytes and bile duct epithelia make up the parenchyma. Cells found in the vicinity of the sinusoids include endothelial cells, fixed macrophages (Kupffer cells), hepatic stellate cells (so-called Ito cells), and a large population of lymphocytes that roam the sinusoids. The sinusoidal lining formed by endothelial cells is thin and fenestrated, allowing transfer of fluid, chylomicrons, and proteins across the space of Disse, an extrasinusoidal

space filled with microvilli.¹⁷⁵ Kupffer cells remove particles and cell debris that include bacteria and endotoxin from the portal circulation. They also clear many biologically active substances from the systemic circulation.¹⁶ When immunologically activated by xenobiotics, Kupffer cells contribute to the generation of oxygen free radicals^{141,178} and may also participate in the production of autoimmune injury to hepatocytes, including activation of hepatic stellate cells.^{36,73,141} Hepatic stellate cells are primary sites for the storage of fat and vitamin A.^{48,58} In a quiescent state they spread out between the sinusoidal endothelium and hepatic parenchymal cells. Filled with microtubules and microfilaments, they project cytoplasmic extensions that contact several cell types.^{48,58} Activated stellate cells produce collagen, proteoglycans, and adhesive glycoproteins, which are crucial to the development of hepatic fibrosis.^{10,46} The liver lymphocyte population is enriched with natural killer (NK) or pit cells, which play a key role in host defense by actively lysing tumor cells and cells infected by viruses^{23,47} (Fig. 23–2). Evidence from animal models suggests that NK cells selectively kill activated stellate cells, inhibiting the development of liver fibrosis.^{46,47}

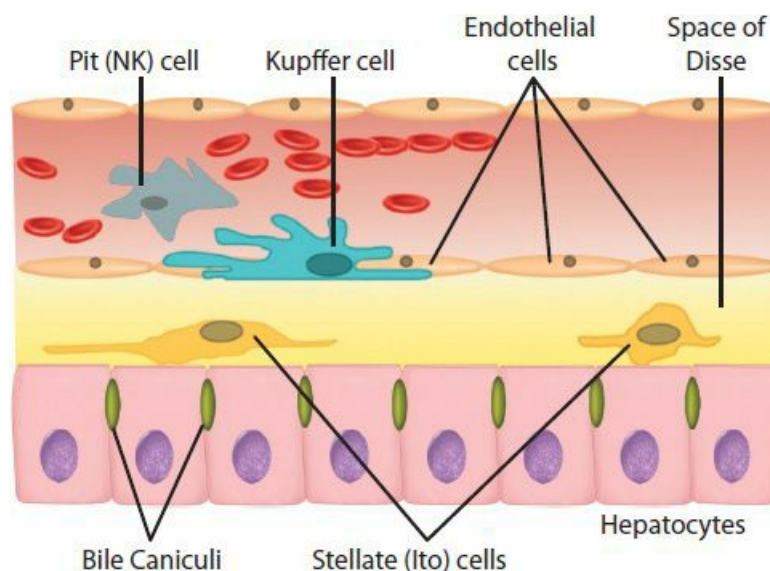


FIGURE 23–2. Blood flowing through the hepatic sinusoids is separated from hepatocytes by fenestrated endothelium that allows passage of many substances across the space of Disse. This figure shows six types of cells found in the liver and their localization in relation to the sinusoid. Stellate cells are fat storage cells that promote fibrosis when activated.⁴⁶ Kupffer cells are fixed macrophages that participate in immune surveillance and are a source of free radicals when activated. Natural killer cells are lymphocytes that float freely in the sinusoids, scavenging tumor and virus infected cells.²³ Hepatocytes and bile epithelial cells form the hepatic parenchyma.

Bile acids, organic anions, bilirubin, phospholipids, xenobiotics, and other molecules excreted in bile are actively transported across the hepatocyte plasma membrane into the bile canaliculi at sites that have specificity for acids, bases, and neutral xenobiotics.¹²¹ Tight junctions separate the contents of the bile canaliculi from the sinusoids and hepatocytes, maintaining a rigid and functionally necessary compartmentalization. Bile acids use three active transport systems: a sodium-dependent bile salt transporter in the sinusoidal membrane, an adenosine triphosphate (ATP)-dependent bile salt carrier in the canalicular membrane, and a canalicular membrane transport site driven by the membrane voltage potential.^{79,121} Xenobiotics bound to glucuronide are substrates for the bile acid transport systems and are actively secreted into bile. Xenobiotics with molecular weights greater than 500 Da are also preferentially secreted into bile. Like the transport and concentration of constituents from the sinusoids and hepatocytes, the flow of bile through the canaliculi is also an active process facilitated by ATP-dependent contractions of actin filaments that encircle the canaliculi.^{79,121,171}

The enterohepatic circulation of bile acids and some vitamins plays a crucial role in their conservation. Unfortunately, this physiologically important process impedes the fecal elimination of some xenobiotics by reabsorbing and returning them back into the systemic circulation, prolonging their apparent half-lives and toxicity. Xenobiotics that have low molecular weights and are not ionized at intestinal pH, such as methylmercury, phencyclidine, and nortriptyline, are most likely to be reabsorbed.^{32,140}

TYPES OF HEPATIC INJURY

Due to its location at the end of the portal system and its substantial complement of biotransformation enzymes, the liver is especially vulnerable to toxic injury. The pathological spectrum of liver injury includes combinations of hepatocellular necrosis with focal or generalized lysis of hepatocytes and elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT); hepatitis associated with inflammatory cellular infiltrates and varied elevation of hepatocellular

enzymes; cholestasis with pruritus, jaundice, and insignificant elevations of hepatocellular enzymes; steatosis caused by intracellular deposits of fat; apoptosis, the formation of shrunken, nonfunctioning, eosinophilic bodies; and fibrosis.¹⁵⁹

FACTORS THAT AFFECT THE ANATOMIC LOCALIZATION OF HEPATIC INJURY

Hepatocellular necrosis that occurs near the portal vein is called periportal, or zone 1 necrosis. The term centrilobular or zone 3 necrosis refers to injury that surrounds the central hepatic vein. **Figure 23–3** shows centrilobular necrosis caused by exposure to bromobenzene. Metabolic characteristics of the zones of the acinus have important relevance to the anatomic distribution of toxic liver injury. Because of its location in the periportal area, zone 1 has a two-fold higher oxygen content than zone 3. Hepatic injury that results from the metabolic production of oxygen free radicals predominates in zone 1. Allyl alcohol, an industrial chemical that is metabolized to a highly reactive aldehyde, is associated with oxygen dependent lipid peroxidation injury to hepatocytes in zone 1.⁶ The tendency for centrilobular or zone 3 accumulation of fat in patients with alcoholic steatosis is attributed to the effect of relative hypoxia in the central vein area on the oxidation potential of the hepatocyte.^{9,95} The availability of substrates for detoxification and the localization of enzymes involved in biotransformation also affect the site of injury. Zone 1 has a higher concentration of glutathione, whereas zone 3 has a greater capacity for glucuronidation and sulfation.¹⁶³ Zone 3 has higher concentrations of alcohol dehydrogenase, which may lead to increased production of its toxic metabolite acetaldehyde at centrilobular sites.^{31,95,101} Zone 3 also has high concentrations of cytochrome oxidase CYP2E1, which converts many xenobiotics including acetaminophen (APAP), nitrosamines, benzene, and carbon tetrachloride (CCl_4) to reactive intermediates that may cause centrilobular injury. Although CCl_4 can be metabolized to a highly reactive oxygen free radical in zone 1, it primarily injures zone 3 for the following reasons:^{18,36,96} CCl_4 is metabolized by CYP2E1 in zone 3 to a trichloromethyl free radical ($\cdot\text{CCl}_3$) that can form covalent bonds with cellular proteins, cause lipid peroxidation, or spontaneously react with oxygen to form the more highly reactive trichloromethyl peroxy radical ($\text{CCl}_3\text{OO}\cdot$).^{18,36,96} Higher oxygen tension in zone 1 fosters the formation of $\text{CCl}_3\text{OO}\cdot$, which is rapidly detoxified by glutathione. Since the less reactive $\cdot\text{CCl}_3$ that predominates in zone 3 is not readily detoxified by glutathione, zone 3 incurs the greater amount of injury. Hyperbaric oxygen increases the oxygen tension throughout the liver and decreases liver injury caused by CCl_4 , possibly by increasing the formation of $\text{CCl}_3\text{OO}\cdot$ in zone 3, which is then efficiently detoxified by glutathione.^{18,160} The observed effects of isoniazid (an inhibitor of the enzyme CYP2E1) and chronic ethanol intake (an inducer of the CYP2E1 gene) on injury in cell cultures from periportal and centrilobular areas exposed to CCl_4 support the association of CCl_4 injury with the localization of CYP2E1 activity. Acute exposure to isoniazid significantly decreases the injury associated with exposure of zone 3 cells to CCl_4 , whereas chronic treatment with ethanol significantly enhances injury.⁹⁶

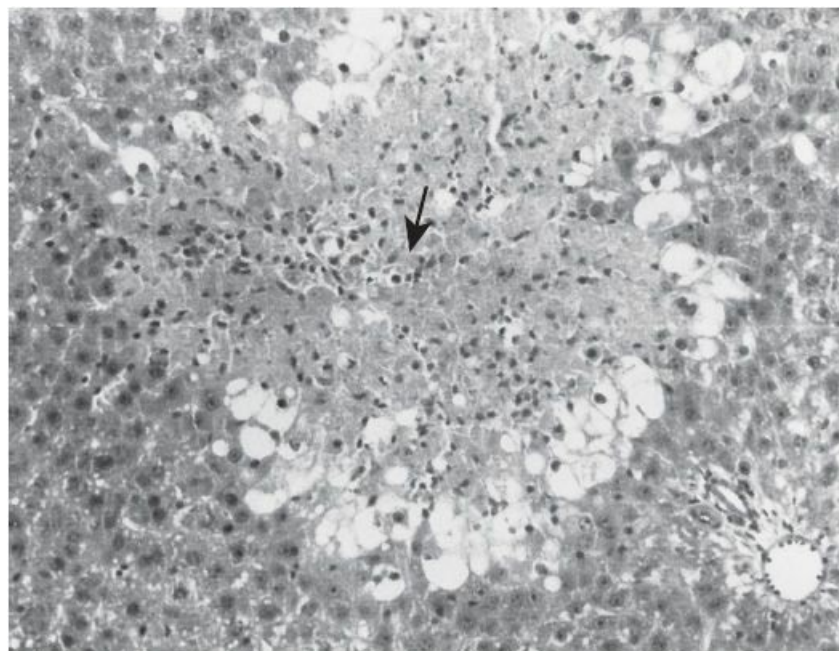


FIGURE 23–3. Centrilobular necrosis in a rat liver caused by bromobenzene administration. Note the polymorphonuclear leukocyte infiltration (arrow) surrounded by vacuolated hepatocytes in the necrotic area. (Reprinted, with permission, from Hetu C, Dumont A, Joly JG, et al: Effect of chronic ethanol administration on bromobenzene liver toxicity in the rat. *Toxicol Appl Pharm.* 1983;67:166.)

FACTORS THAT AFFECT THE DEVELOPMENT OF HEPATOTOXICITY

Xenobiotics that produce liver damage in all humans in a predictable and dose-dependent manner are called intrinsic hepatotoxins. They include APAP, CCl₄, and yellow phosphorous. Those that cause liver damage in a small number of individuals and whose effect is not apparently predictable or dose dependent are called idiosyncratic hepatotoxins.^{50,88}

Prediction of Drug-Induced Liver Injury

Drug-induced liver injury (DILI) refers to the production of liver injury by pharmaceuticals. It is the most common apparent cause of acute liver failure in the United States.^{20,134} DILI causes 33% of terminations of clinical trials of new drugs and accounts for a majority of post-marketing withdrawals of marketed drugs.¹⁶⁹ Recent studies of DILI question the lack of dose dependency of some apparently idiosyncratic hepatotoxins.^{1,20,50,84} Analysis of a Swedish data base of patients with DILI demonstrated dose dependency, as more reported cases were associated with higher doses of drugs metabolized in the liver.⁸⁴

Prediction of DILI in any individual patient based on clinical trials is difficult because the incidence is rare.^{102,169} DILI depends largely on factors that affect host susceptibility.^{5,156} These include age, gender, diet, underlying diseases, and concurrent exposure to other xenobiotics.²⁰ Genetic factors are increasingly elucidated. Many enzymes involved in biotransformation show genetic polymorphism. Inherited variations in CYP enzymes affect susceptibility to DILI.^{55,62,87,97} Approximately 8% of Caucasians are deficient in CYP2D6, which is responsible for the metabolism of a number of pharmaceuticals, including debrisoquine (an antihypertensive first identified as the substrate of this enzyme), several antidepressants and antidysrhythmics, some opioids, and phenformin.^{87,150} Perhexiline, an antianginal marketed in Europe in the 1980s, caused severe liver injury and peripheral neuropathy in persons with an inability to metabolize debrisoquine.¹⁵⁰ The congenital disorder that results in Gilbert syndrome is characterized by impaired glucuronyltransferase. Patients demonstrate decreased glucuronidation and increased bioactivation of APAP during chronic therapeutic dosing, suggesting an increased risk of hepatic injury following ingestion of APAP.²⁹ Gastrointestinal toxicity due to irinotecan, an antineoplastic used in the treatment of colon cancer, is associated with deficiency of glucuronyltransferase.¹¹¹

Studies that compare the genomes of patients who develop hypersensitivity reactions to various drugs with those who do not show significant associations with human leukocyte antigen (HLA) alleles.^{5,27,53,99,156,164,169} Hypersensitivity reactions to abacavir are significantly associated with HLA-B*5701, such that the Food and Drug Administration now recommends HLA screening prior to the initiation of abacavir.¹⁰⁴ HLA-B*5701 is also associated with cholestatic DILI in patients taking flucloxacillin, an antibiotic marketed in Europe.²⁷ Severe hypersensitivity reactions to carbamazepine are associated with the HLA allele HLA-A*3101.¹⁰⁶ Specific HLA phenotypes are implicated in the development of cholestatic liver injury in patients exposed to amoxicillin-clavulanate.^{5,99,156} DILI in the form of elevation of the ALT occurred in 15% of patients exposed to the first-generation direct thrombin inhibitor ximelagatran, with some developing clinically significant hepatitis. This was associated with two specific HLA phenotypes DRB1*07 and DQA1*02.^{69,72}

Effects of Xenobiotics on Enzyme Function

Some xenobiotic combinations increase the possibility of hepatotoxic reactions because one xenobiotic alters the metabolism of the other, leading to the production of toxic metabolites. This is the case with combinations of rifampin and isoniazid,^{65,143} amoxicillin and clavulanic acid,^{85,128} and trimethoprim and sulfamethoxazole.² Changes in the activities of biotransformation enzymes that result in increased formation of hepatotoxic metabolites suggest increased susceptibility to hepatic injury. Chronic administration of isoniazid induces CYP2E1 activity.^{143,179} During chronic ethanol exposure, proliferation of the smooth endoplasmic reticulum in the centrilobular areas is associated with increased activity of CYP2E1.^{77,96,98} In one rat study, the administration of an average of 9.2 g/kg of ethanol in increasing doses for 4 weeks resulted in a significant increase in the extent of injury to cultured zone 3 hepatocytes when exposed to CCl₄. This was associated with a higher expression of CYP2E1 in the livers of ethanol-treated rats.⁹⁶ Bromobenzene is a xenobiotic whose metabolism and hepatotoxicity are similar to that of APAP. When administered to rats chronically exposed to ethanol, the onset of hepatotoxicity occurs more rapidly in study animals, with only a small increase in the extent of hepatic necrosis. The dose of bromobenzene required for hepatic injury to occur is not altered by pretreatment with ethanol.⁵⁹ Chronic administration of phenobarbital to rats results in a significant increase in the hepatotoxic effects of bromobenzene.¹³² In humans, hepatic toxicity caused by solvents such as CCl₄, dimethylformamide, and bromobenzene may be exacerbated by chronic exposure to ethanol.^{96,105,129,130} Whether ethanol increases the clinical risk of APAP hepatotoxicity in humans has been debated.^{80,125,145,149,182}

Availability of Substrates

The availability of substrates for detoxification may significantly affect both the likelihood and localization of hepatic injury. The metabolism of APAP illustrates the effect of glutathione concentration on the delicate balance between detoxification and the production of injurious metabolites. In healthy adults taking therapeutic amounts of APAP, approximately 90% of hepatic metabolism results in formation of the glucuronide or sulfate metabolites.¹⁶⁰ Most of the remainder undergoes oxidative metabolism to the toxic electrophile N-acetyl-p-benzoquinone imine (NAPQI) and is rapidly detoxified by conjugation with glutathione.^{21,64} Glutathione may be depleted during the course of metabolism of APAP by otherwise normal livers, or it may be decreased by inadequate nutrition or liver disease.^{87,88} Excessive amounts of APAP result in increased synthesis of NAPQI, which, in the absence of glutathione, reacts avidly with hepatocellular macromolecules. The cellular concentration of glutathione correlates inversely with the demonstrable covalent binding of NAPQI to liver cells.²¹ Centrilobular (zone 3) necrosis predominates in APAP induced hepatic injury, likely related both to the centrilobular localization of CYP2E1 and to the relatively low glutathione concentrations in zone 3 compared to the periportal areas (zone 1).⁶⁴

MECHANISMS OF HEPATIC INJURY

Several pathologic mechanisms of injury that are associated with various hepatocyte “targets” are described.^{88,159}

Immune-Mediated Liver Injury

Immune-mediated liver injury is an idiosyncratic and host-dependent hypersensitivity response to exposure to xenobiotics.^{11,20,97} Damage to the hepatocyte may be mediated by complement- or antibody-directed lysis, by specific cell-mediated cytotoxicity, or by an inflammatory response stimulated by immune complexes and complement.^{10,14,15,34,70,73,110} The antibody or cell-mediated response may be precipitated by a covalently bound xenobiotic-cell protein adduct that acts as a haptén.⁵⁶ The resultant inflammatory response provokes secondary cytokine release that may promote further cell injury by neutrophils.⁵⁶ Subsequent apoptosis appears to be partly mediated by tumor necrosis factor (TNF).¹³¹ Immune-mediated toxic hepatitis is differentiated from liver injury caused by other autoimmune disorders by the absence of self-perpetuation; that is, there is a need for continuous exposure to the xenobiotic to perpetuate the injury.^{11,97} It is also less likely to recur following withdrawal of immune suppression therapy.^{11,97}

Hypersensitivity reactions result in forms of liver injury that include hepatitis, cholestasis, and mixed disorders. Whether autoantibodies stimulated by the xenobiotic–protein adducts are in all cases the actual mediators of cell injury is not clear.^{11,91} Adducts and associated autoantibodies are demonstrated for APAP,²¹ halothane,^{14,34,154} dihydralazine,¹⁵ phenytoin,⁹¹ and germander.⁸³ In cases where the metabolite is highly unstable, an electrophilic attack may be directed against the CYP enzyme at the site of formation of the metabolite.^{14,15,95,97} Autoantibodies against the CYP2E1 enzyme have been demonstrated in halothane liver injury (Chap. 68).^{14,70} The most severe form of idiosyncratic halothane liver injury is manifest as fulminant hepatic necrosis associated with formation of adducts of its trifluoroacetyl chloride (TFA) metabolite with numerous hepatoproteins that include CYP2E1 and pyruvate dehydrogenase.^{34,70,154} Autoantibodies specifically directed against CYP enzymes are also demonstrated for dihydralazine¹⁵ and phenytoin.⁹¹ A trifluoroacetyl protein adduct similar to that associated with halothane hepatitis was detected in workers who developed hepatic necrosis following exposure to hydrochlorofluorocarbons.⁶⁰ Early reports of lymphocyte sensitization in cases of xenobiotic-mediated liver toxicity suggested that cell-mediated immunity may play a role.¹⁶⁷ Cell-mediated autoimmune mechanisms are implicated in the idiosyncratic type of halothane hepatitis and are suspected in an increasing number of models of experimental xenobiotic-mediated liver injury.^{35,167} Polymorphonucleocyte (PMN) activation and infiltration appear to be important factors in the production of cholangitis in a rat model of α -naphthyl-isothiocyanate (ANIT) liver injury. ANIT stimulates the release of cytotoxic lysosomal enzymes and oxygen free radicals by activated PMNs.¹¹⁰ Antibodies directed against circulating neutrophils decrease the extent of liver damage caused by ANIT.²⁵ NK T-cells are ubiquitous in the liver, and their possible role in the facilitation of cell-mediated autoimmune liver injury is being investigated.^{23,24,52}

Pharmaceuticals most commonly involved in autoimmune injury are nitrofurantoin and minocycline.¹¹ Drugs with hypersensitivity reactions that typically present with hepatitis include halothane,^{14,70,154} trimethoprim-sulfamethoxazole,^{2,117} anticonvulsants,⁹¹ and allopurinol.^{3,153} Drugs associated with hypersensitivity that typically present with cholestatic signs include chlorpromazine, erythromycin, penicillins, rifampin, and sulfonamides.^{79,121,167} Signs of injury typically begin 1 to 8 weeks following the initiation of the drug, although they may begin as late as 20 weeks for drugs such as isoniazid or dantrolene. The onset of signs of injury associated with the oxypenicillins may occur as late as 2 weeks after the drug is stopped.⁹⁷ In all cases, the onset is earlier when the patient is rechallenged with the drug. Antinuclear antibodies and smooth muscle antibodies are frequently present, as are eosinophilia, atypical lymphocytosis, fever, and rash. Their absence does not exclude an autoimmune mechanism of drug-associated liver injury.^{11,76,97} Liver injury characterized by the formation of hepatic granulomas may also be a consequence of hypersensitivity reactions.¹⁰⁹

Xenobiotics That Target the Biliary Tract

Xenobiotics that undergo biliary excretion are most commonly associated with jaundice in patients with hepatotoxicity.¹²¹ Xenobiotics induce cholestasis by targeting specific mechanisms of bile synthesis and flow or by damaging canalicular cells.^{54,79} Elucidations of various bile transport proteins have led to better understanding of mechanisms of cholestasis in toxic liver injury.¹²¹ Cholestasis may occur with or without associated hepatitis. The development of jaundice following hepatic necrosis is a manifestation of general failure of liver function. More discrete mechanisms that result in intrahepatic cholestasis include (a) impairment of the integrity of tight membrane junctions that functionally isolate the canaliculus from the hepatocyte and sinusoids, (b) failure of transport of bile components across the hepatocytes, (c) blockade of specific membrane active transport sites, (d) decreased membrane fluidity resulting in altered transport, and (e) decreased canalicular contractility resulting in decreased bile flow.^{13,79,121,146} Xenobiotics that specifically target bile canaliculi may lead to irreversible injury, the so-called “vanishing bile duct syndrome.”¹⁶¹ Estrogens cause intrahepatic cholestasis by altering the composition of the lipid membrane and inhibiting the rate of secretion of bile into the canaliculi.^{79,146} Rifampin impedes the uptake of bilirubin into hepatocytes. Methyltestosterone and C-17 alkylated anabolic steroids impair the secretion of bilirubin into canaliculi.⁹⁴ Cyclosporine inhibits sodium-dependent uptake of bile salts across the sinusoidal membrane and blocks ATP-dependent bile salt transport across the canalicular membrane.¹³ Floxacillin causes cholestasis with minimal inflammation or evidence of hepatocellular injury.¹⁶⁷ Exposure of rats to ANIT causes a specific injury localized to the tight junctions that separate the hepatocyte from the canaliculi. This results in reflux of bile constituents into the sinusoidal space and increased access of sinusoidal molecules to the biliary tree.^{25,79,110}

Mitochondrial Injury

Direct mitochondrial injury impairs cellular respiration and is associated with fat accumulation, diminution of ATP production, and metabolic acidosis with elevated lactate.^{82,89,122} This may involve attacks by xenobiotics on structural components of the mitochondria such as DNA, respiratory chain enzymes, and membranes. Nucleoside analogs that inhibit viral reverse transcriptase also inhibit mitochondrial DNA synthesis, leading to depletion of mitochondria.^{22,82,108,144}

Other Targets

Stimulation of Kupffer cells enhances hepatic injury. When immunologically activated by xenobiotics, Kupffer cells contribute to the generation of oxygen free radicals^{141,178} and may also participate in the production of autoimmune injury to hepatocytes, including activation of hepatic stellate cells.^{36,73,141} Activated stellate cells produce collagen, proteoglycans, and adhesive glycoproteins, which are crucial to the development of hepatic fibrosis.^{9,46} Hepatic venoocclusive disease is caused by xenobiotics that injure the endothelium of terminal hepatic venules, resulting in intimal thickening, edema, and nonthrombotic obstruction.^{81,107,113,174,176}

MORPHOLOGIC MANIFESTATIONS OF TOXIC HEPATIC INJURY

The liver responds to injury in a limited number of ways.^{67,68,88,118,159} Cells may swell (ballooning degeneration) and accumulate fat (steatosis) or biliary material. They may necrose and lyse or undergo the slower process of apoptosis, forming shrunken, nonfunctioning, eosinophilic bodies. Necrosis may be focal or bridging, linking the periportal or centrilobular areas; zonal or panacinar; or it may be massive.^{59,86,108} An autoimmune type of injury is characterized by hepatitis with a prominent plasma cell infiltrate.^{11,97,164} Injury to the bile ducts results in cholestasis.^{79,121,167} Xenobiotics that target canalicular transport proteins may cause cholestasis in the absence of injury to hepatocytes.¹²¹ Direct mitochondrial injury impairs cellular respiration and is associated with fat accumulation, diminution of ATP production, and metabolic acidosis.^{82,122} Injuries to the intima of postsinusoidal veins cause obstruction to venous flow.^{81,176} The vascular effects of cocaine may cause ischemic liver injury.^{87,165} Table 23–1 lists characteristic morphologies of hepatic injury and associated xenobiotics.

TABLE 23–1. Morphology of Liver Injury by Selected Xenobiotics

Acute Hepatocellular Necrosis

APAP^a

Allopurinol

Amatoxin^a

Arsenic

Carbamazepine

Carbon tetrachloride^a

Chlordecone (less severe)

Clove oil

Hydralazine

Iron

Isoniazid

Methotrexate^a

Methyldopa

Nitrofurantoin

Phenytoin

Phosphorus (yellow)^a

Procainamide

Propylthiouracil

Quinine

Sulfonamides

Tetrachlorethane

Tetracycline

Trinitrotoluene

Troglitazone

Valproic acid

Vinyl Chloride

Steatohepatitis

Amiodarone

Dimethyl formamide

Microvesicular Steatosis

Aflatoxin

Cereulide

Fialuridine

Hypoglycin

Margosa oil

Nucleoside analogs (antiretrovirals)

Tetracycline

Valproic acid

Granulomatous Hepatitis

Allopurinol

Beryllium

Carbamazepine

Copper salts

Diltiazem

Halothane

Hydralazine

Isoniazid

Methyldopa

Metolazone

Nitrofurantoin

Penicillins

Phenytoin

Procainamide

Quinidine

Quinine

Salicylates

Sulfonamides

Sulfonylureas

Cholestasis

Allopurinol

Amoxicillin/clavulanic acid

Androgens

Chlorpromazine

Chlorpropamide

Erythromycin estolate

Hydralazine

Nitrofurantoin

Oral contraceptives

Rifampin

Tetracycline

Trimethoprim-sulfamethoxazole

Fibrosis and Cirrhosis

Ethanol

Methotrexate

Vitamin A

Neoplasms

Androgens

Contraceptive steroids

Vinyl chloride

Venoocclusive Disease

Cyclophosphamide

Pyrrolizidine alkaloids

Cannicular Cholestasis

Chlorpromazine

Cyclosporine

Estrogens

Methylene dianiline

Bile Duct Damage

α -Naphthylisothiocyanate

Amoxicillin

Carbamazepine

Nitrofurantoin

Oral contraceptives

Autoimmune Hepatitis

Dantrolene

Diclofenac

Methyldopa

Nafcillin

Nitrofurantoin

Propylthiouracil

^aIntrinsic hepatotoxin.

Acute Hepatocellular Necrosis

Numerous xenobiotics are associated with hepatocellular necrosis (Table 23–1). APAP is a common cause, as are herbal remedies that contain hepatotoxins, whose risks are increasingly recognized.^{37,61,116} Many halogenated hydrocarbons that include carbon tetrachloride,^{18,96} bromobenzene,^{59,132} hydrochlorofluorocarbons,⁶⁰ halothane,^{15,70,154} and antituberculous medications^{19,112,143} also produce hepatocellular necrosis. A study of more than 11,000 patients exposed to isoniazid during preventive treatment showed that the risk of hepatocellular necrosis was low, occurring in 0.1% of those starting treatment, and in 0.15% of those completing treatment.^{19,120} Risk factors for the development of hepatotoxicity from isoniazid exposure are female sex, increasing age, coadministration with rifampin, and alcoholism¹⁹ (Chap. 58). The thiazolidinedione antidiabetics troglitazone and rosiglitazone are associated with acute hepatocellular necrosis.^{44,51} Occupational exposure to solvents including dimethylformamide and CCl₄ causes dose-related hepatocellular necrosis.^{129,130}

Acute necrosis of a hepatocyte disrupts all aspects of its function. Because there is a great deal of functional reserve in the liver, hepatic function may be preserved despite the development of focal necrosis.¹⁵⁹ Extensive necrosis results in functional liver failure. The processes that lead to cell necrosis are not well known. Cell lysis is preceded by the formation of blebs in the lipid membrane and leakage of cytosolic enzymes, primarily aminotransferases and lactate dehydrogenase. Coalescence of blebs leads to rupture of the cellular membrane and acute irreversible cell death, with disintegration of the nucleus and termination of all cellular function. Prior to membrane rupture, this injury is reversible by membrane repair processes.¹¹⁰ The release of intracellular constituents attracts circulating leukocytes and results in an inflammatory response in the hepatic parenchyma. A proposed mechanism of rapid injury to the cell membrane is the initiation of a cascading lipid peroxidation reaction following attack by a free radical. The CYP2E1 enzyme has a significant potential to produce oxygen free radicals, as do activated PMNs and Kupffer cells.^{26,36,46,110,141,178} Oxidant stress is an important cause of liver injury during the metabolism of ethanol by CYP2E1. This results in cell death and the stimulation of stellate cells, which promotes fibrosis.^{31,46,159} In addition to peroxidation of membrane lipids, the oxidation of proteins, phospholipid fatty acyl side chains, and nucleosides appears to be widespread. Mitochondrial injury and resultant ATP depletion may also be associated with necrosis.^{67,103} Xenobiotics known to cause mitochondrial injury include antiretroviral drugs that inhibit the replication of mitochondrial DNA,^{22,28,108} tetracycline,¹⁴⁷ valproic acid,¹⁸⁰ hypoglycin, margosa oil, and cereulide.^{103,144}

Steatosis

Steatosis is the abnormal accumulation of fat in hepatocytes. It reflects abnormal cellular metabolism in conditions that include responses to xenobiotics. Cell injury depends on the severity of the underlying metabolic disturbance. Steatosis per se is normally well tolerated and reversible in many cases, although approximately one-third of patients with nonalcoholic steatosis may develop steatohepatitis.^{41,82} Nonalcoholic steatosis associated with obesity, insulin resistance, and the metabolic syndrome may account for many cases of cryptogenic cirrhosis.⁴¹ The β -oxidation of fatty acids depends on a steady synthesis of cellular energy in the form of ATP and takes place in the mitochondria. Mechanisms of impaired β -oxidation of fatty acids include direct inhibition or sequestration of critical cofactors such as coenzyme-A and L-carnitine.^{82,122}

Intracellular fat accumulation may also occur as a result of any one or more of the following mechanisms: impaired synthesis of lipoproteins, increased mobilization of peripheral adipose stores, increased uptake of circulating lipids, increased triglyceride production, decreased binding of triglycerides to lipoprotein, and decreased release of very-low-density lipoproteins from the hepatocytes.^{82,95} There are two light microscopic manifestations of steatosis: macrovesicular steatosis, in which the nucleus is displaced by large droplets of intracellular fat, and microvesicular steatosis, which is characterized by tiny cytoplasmic fat droplets that do not displace the nucleus. Xenobiotics associated with macrovesicular steatosis include ethanol and amiodarone. Ethanol increases the uptake of fatty acids into hepatocytes and decreases lipoprotein secretion. In addition, the increased ratio of the reduced form of nicotinamide adenine dinucleotide (NADH) to the oxidized form of nicotinamide adenine dinucleotide (NAD⁺), associated with hepatic metabolism of ethanol, decreases oxidation of fatty acids and promotes fatty acid synthesis.⁹⁵ An early pathologic lesion that occurs in alcoholic liver disease is reversible macrovesicular steatosis. Steatohepatitis is a more virulent form, characterized by ballooning degeneration of hepatocytes and apoptosis that may progress to cirrhosis.^{92,177} Mallory bodies, eosinophilic cytoplasmic deposits of keratin

filaments in degenerating hepatocytes, are also common microscopic findings in alcoholic liver disease.^{9,95,100,101} Amiodarone hepatic toxicity resembles that of alcoholic hepatitis, with steatosis, Mallory bodies, and potential for progression to cirrhosis.⁸⁷ Lamellated intralysosomal phospholipid inclusion bodies are specific for amiodarone toxicity.¹³⁶ Figure 23–4 shows macrovesicular steatosis with Mallory bodies caused by amiodarone.

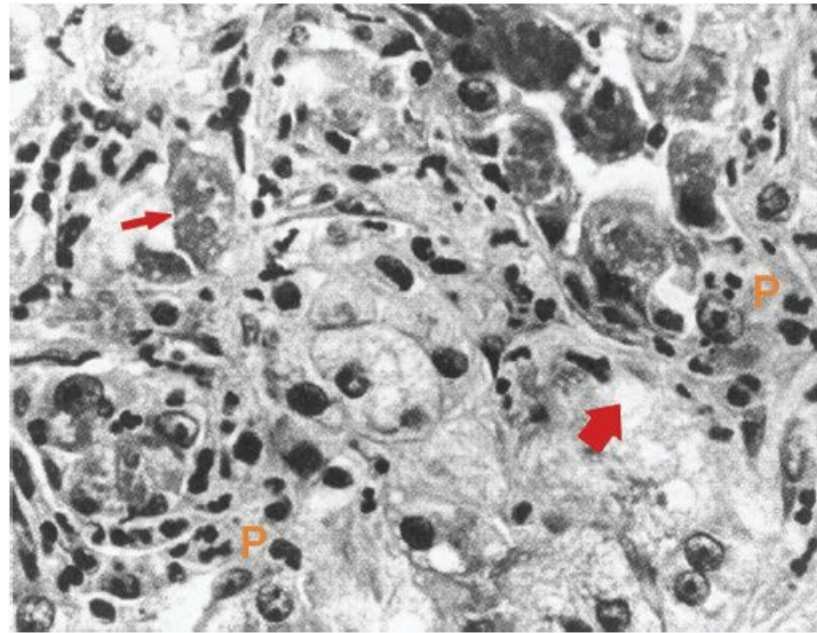


FIGURE 23–4. Macrovesicular steatosis associated with administration of amiodarone. The small arrow indicates the presence of Mallory bodies. The large arrow points to accumulated intracellular fat. (Note that the nuclei are displaced.) Polymorphonuclear leukocytes (P) are also present. (Reprinted, with permission, from Lee WM. Drug-induced hepatotoxicity. *N Engl J Med.* 1995;333:1118.)

Steatosis Associated with Mitochondrial Dysfunction. Microvesicular steatosis is caused by severe impairment of β -oxidation of fatty acids. Valproic acid causes mild elevations of aminotransferases in approximately 11% of patients, usually during the first few months of therapy. The earliest pathologic lesion that signals progression of liver injury is microvesicular steatosis, which occurs in the absence of necrosis. An association between deficiency of carnitine, microsteatosis, and the development of hyperammonemia is observed in children treated with valproic acid.^{12,126,166} A small percentage of patients progress to fulminant hepatic failure characterized by centrilobular necrosis.¹⁸⁰ The incidence of fatal hepatocellular injury is highest in children, approaching 1 in 800 children younger than 2 years of age.¹²⁶ Other mechanisms of impaired β -oxidation of fatty acids include processes that disrupt cellular ATP production, either directly by xenobiotics such as sodium azide or cyanide that inhibit electron transport in the respiratory chain, by xenobiotics that increase permeability of mitochondrial membranes and degrade the proton gradient that is critical to ATP synthesis, or by xenobiotics that uncouple oxidative phosphorylation.^{93,144,147} Microvesicular steatosis is described in patients taking antiretrovirals such as zidovudine, zalcitabine, and didanosine.^{28,155,158} In all cases, metabolic acidosis with elevated lactate is a prominent biochemical feature.^{28,144} The nucleoside analog fialuridine caused severe hepatotoxicity during a study of its use in the treatment of chronic hepatitis B infection. Microscopic examinations of liver specimens in these cases showed marked accumulation of fat with minimal necrosis or structural injury. Severe acidosis and failure of hepatic synthetic function suggested failure of cellular energy production. Mitochondria examined under the electron microscope were demonstrably abnormal.¹⁰⁸ Figure 23–5 demonstrates microvesicular steatosis in a patient with fialuridine hepatotoxicity. High doses of tetracycline produce microvesicular steatosis associated with moderate elevations of aminotransferases, markedly prolonged prothrombin time (PT), and progression to fulminant hepatic failure.¹⁴⁷ Microvesicular steatosis attributed to failure of mitochondrial energy production was reported in a fatal case of *Bacillus cereus* food poisoning, where high concentrations of the bacterial emetic toxin cereulide are found in the bile and liver. In this case, microvesicular steatosis is associated with extensive hepatocellular necrosis.¹⁰³ Other xenobiotics that cause mitochondrial failure are hypoglycin, the cause of Jamaican vomiting sickness, aflatoxin, and margosa oil.¹⁴⁴ Steatosis is also observed following exposure to the industrial solvent dimethylformamide. Liver biopsies in patients with acute illness show focal hepatocellular necrosis and microvesicular steatosis. More prolonged, less symptomatic exposures result in significant macrovesicular steatosis with mild aminotransferase elevations.^{129,130}

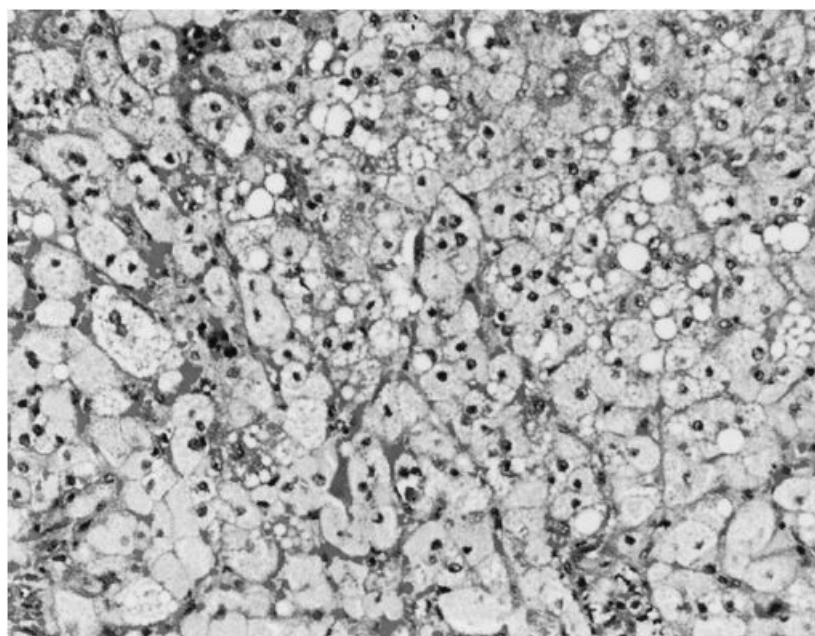


FIGURE 23–5. This figure shows severe microvesicular steatosis in a patient treated with fialuridine. Note the central location of the nuclei. (Reprinted, with permission, from McKenzie R, Fried MW, Sallie R, et al. Hepatic failure and lactic acidosis due to fialuridine, an investigational nucleoside analogue for chronic hepatitis B. *N Engl J Med.* 1995;333:1099.)

Venoocclusive Disease

Hepatic venoocclusive disease is caused by xenobiotics that injure the endothelium of terminal hepatic venules, resulting in intimal thickening, edema, and nonthrombotic obstruction. Central and sublobular hepatic veins may also become edematous and fibrosed. There is intense sinusoidal dilation in the centrilobular areas that is associated with liver cell atrophy and necrosis.¹⁷⁴ The gross pathologic appearance is that of a “nutmeg” liver.^{81,176} Massive hepatic congestion and ascites ensue.^{81,135} Hepatic venoocclusive disease is rapidly fatal in 15% to 20% of cases. It is associated with exposure to pyrrolizidine alkaloids found in many plant species including *Symphytum* (comfrey tea),^{172,176} *Heliotrope*, *Senecio*, and *Crotalaria*.⁸¹ It has occurred in epidemic proportions, in South Africa after the ingestion of flour contaminated with ragwort (*Senecio*), in Jamaica after the ingestion of “bush teas” (*Crotalaria* spp), and in India and Afghanistan when food was contaminated with *Heliotropium lasiocarpine* and *Crotalaria*.^{17,113} A rapidly progressive form has been reported in bone marrow transplant patients following high-dose treatment with cyclophosphamide.¹⁰⁷

Chronic Hepatitis

A form of toxic hepatitis that clinically resembles autoimmune hepatitis occurs with the chronic administration of drugs such as methyldopa, allopurinol, nitrofurantoin, propylthiouracil, nafcillin, dantrolene, and diclofenac.^{3,7,11,71,89,133,148,157} Many cases are associated with positive antinuclear antibody (ANA), smooth muscle antibody (SMA), and hyperglobulinemia. Jaundice is prominent and hepatocellular enzymes are elevated 5- to 60-fold. Liver biopsy commonly reveals intrahepatic cholestasis, as well as centrilobular inflammation.^{11,97}

Granulomatous hepatitis is characterized by infiltration of the hepatic parenchyma with caseating granulomata. At least 60 drugs are associated with this disorder. Fever and systemic symptoms are common, and 25% of patients have splenomegaly. Liver enzymes are mixed, reflecting variable degrees of cholestasis and hepatocellular injury. Eosinophilia occurs in 30% as an extrahepatic manifestation of drug hypersensitivity. Continued exposure may result in a more severe form of liver disease. Small vessel vasculitis, which may involve the skin, lungs, and kidney, is a disturbing sign associated with increased mortality.^{88,109,181} Table 23–1 lists a number of the xenobiotics that are implicated in this disorder.

Cirrhosis

Cirrhosis is caused by progressive fibrosis and scarring of the liver, which results in irreversible hepatic dysfunction and portal hypertension. This causes shunting of blood away from hepatocytes and subsequent hepatocellular dysfunction. Activated stellate cells produce collagen, proteoglycans, and adhesive glycoproteins, which are deposited in the space of Disse and are crucial to the development of hepatic fibrosis.^{46,159} The development of fibrosis requires inflammation. Reactive oxygen species derived from lipid peroxidation, reduced NADPH, and apoptotic cells are important inflammatory stimuli that activate stellate cells.⁴⁶ In alcoholic cirrhosis, acetaldehyde and tumor necrosis factor provide a cytokine-mediated inflammatory stimulus.^{9,95,159} Chronic ingestion of excessive amounts of vitamin A (25,000 units/day for 6 years or 100,000 units/day for 2.5 years) results in cirrhosis. An increase in the fat content of the sinusoidal stellate cells with

increasing degrees of collagen formation are characteristic lesions that occur early in vitamin A toxicity (Chap. 47). Portal hypertension may be early and striking.⁴⁹ Like vitamin A, methyldopa and methotrexate also cause a slow progressive development of cirrhosis with few clinical symptoms.^{90,173} Methotrexate-induced hepatic fibrosis is dose dependent. Risk factors include associated alcohol intake and preexisting liver disease. Reduced dosing has largely eliminated the risk of the development of cirrhosis in patients receiving methotrexate.^{67,173}

Hepatic Tumors

There is persuasive evidence that the use of oral contraceptive steroids increases the risk of hepatic adenomas.⁷⁵ Oral contraceptives also increase the overall risk of hepatocellular carcinoma; however, the number of cases associated with estrogen therapy is low.⁶³ Anabolic steroids are rarely associated with the development of both benign and malignant hepatic tumors.⁴⁰ Angiosarcoma is strongly associated with exposure to vinyl chloride, in addition to arsenic, thorium dioxide, and androgenic hormones.³⁸

Hepatic Injury Associated with Plants and Herbs

In addition to the venoocclusive disease associated with pyrrolizidine alkaloids described above, herbal remedies are increasingly recognized as a cause of acute hepatocellular injury. Numerous plants or plant products are known or suspected to cause hepatic injury (Chaps. 45 and 121).^{33,37,61,83,116}

CLINICAL PRESENTATION OF TOXIC LIVER INJURY

Clinical presentations of toxic liver injury range from indolent, often asymptomatic progression of impairment of hepatic function to rapid development of hepatic failure. Jaundice and pruritus are due to increased concentrations of bile acids and bilirubin in the blood. Failure of hepatocellular synthetic function results in bleeding due to coagulopathy and edema due to hypoalbuminemia. Encephalopathy may be due to hypoglycemia, impaired neurotransmission, or accumulation of toxic products of metabolism such as ammonia. Fever may occur with autoimmune-mediated liver injury. Impaired hepatic blood flow results in familiar manifestations of portal hypertension such as caput medusa, splenomegaly, ascites, and varices. Spider angiomas and gynecomastia also occur due to altered estrogen metabolism.¹⁵⁹

Acute Liver Failure

Acute liver failure is defined as a rapid onset of liver injury progressing over 2 to 3 weeks that results in altered mental status, vasodilation, kidney and pulmonary failure, frequent infection, and a poor outcome without transplantation.^{45,90,137,159} Complications from acute liver failure include encephalopathy, cerebral edema, coagulopathy, kidney dysfunction, hypoglycemia, hypotension, acute respiratory distress syndrome, sepsis, and death. The encephalopathy associated with chronic liver disease should be considered separately from the rapidly progressive disorder of acute liver failure.^{38,137} In some cases, a patient may progress from health to death in as little as 2 to 10 days.^{42,87,103,119,137} Table 23–2 emphasizes the clinical progression of encephalopathy as acute liver failure develops. The prognosis of acute liver failure is related to the time that passes between the onset of jaundice and the onset of encephalopathy. Perhaps surprisingly, a better prognosis is associated with shorter (2 to 4 weeks) jaundice-to-encephalopathy intervals.^{137,138} Most cases are caused by xenobiotics or viral hepatitis. Acute liver failure is usually associated with extensive necrosis, although it may occur in the absence of demonstrable necrosis following exposures to xenobiotics that injure mitochondria.^{103,108,158} Some xenobiotics that are associated with acute liver failure are shown in Table 23–1.

TABLE 23–2. Stages of Hepatic Encephalopathy

<i>Clinical Stage</i>	<i>Mental Status</i>	<i>Neuromotor Function</i>
Subclinical	Normal physical examination	Subtle impairment of neuromuscular function → driving or work injury hazard
I	Euphoric, irritable, depressed, fluctuating mild confusion, poor attention, sleep disturbance	Poor coordination; asterixis alone
II	Impaired memory, cognition, or simple mathematical tasks	Slurred speech, tremor, ataxia
III	Difficult to arouse, persistent confusion, incoherent	Hyperactive reflexes, clonus, nystagmus
IV	Coma; may respond to noxious stimuli	Decerebrate posturing; Cheyne-Stokes respirations; pupils are reactive and the oculoccephalic reflex is intact; signs of ↑ intracranial pressure

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a complex disorder that affects both cognitive and neuromuscular functions of the central nervous system.^{8,138,139} Cognitive changes range from barely discernible impairment evident only on psychometric testing to confusion, stupor and coma. Neuromuscular signs include slowed motor responses, asterixis, myoclonus, and rigidity.^{8,139} HE is potentially fully reversible, even in cases of deep coma.^{43,139} Table 23–2 lists the clinical stages of acute HE. Ammonia concentrations are elevated in 60% to 80% of patients with HE.¹³⁹ The demonstration that ammonia is not elevated in many cases suggests that there are other pathogenic etiologies and the etiology is multifactorial.¹³⁸ Disruption of central neurotransmitter regulation including dopamine receptor binding may contribute.¹⁷⁰ There is evidence that liver failure is associated with the accumulation of substances that stimulate central benzodiazepine receptors, leading to enhancement of γ -aminobutyric acid transmission.^{4,139} Other toxins that include mercaptans, phenol, and manganese may also play a role.¹³⁹ Inflammation and infection is also proposed as an important precipitant.¹⁵² Ammonia is produced in the colon by bacterial breakdown of ingested proteins then transported to the liver via the portal circulation where it is detoxified to glutamine and urea by urea cycle enzymes.^{8,123,138} Processes that raise central nervous system ammonia concentrations include infection, hypokalemia, alkalosis, increased muscle wasting, volume depletion, azotemia, and gastrointestinal bleeding.^{8,138,139,152} Alkalosis and hypokalemia facilitate conversion of NH_4^+ to NH_3 , which moves more easily across the bowel wall and the blood–brain barrier. Acidification of the bowel by bacterial breakdown of lactulose creates a hostile environment for ammonia-producing bacteria and constructs a gradient that favors entrapment of ammonia in the bowel.^{123,138} In a study of lactulose alone versus placebo, over a 14-month period 19.6% of patients on lactulose had recurrent HE, compared with 48.6% of patients on placebo.¹⁵¹ A nonabsorbed broad-spectrum antibiotic rifaximin has been shown to decrease the recurrence of HE in cirrhotic patients, presumably by decreasing the numbers of urease-containing colonic bacteria that produce ammonia. Recurrence rates at 6 months were 22.1% in the rifaximin groups versus 46.8% in the placebo group. In this study, 90% of the patients in each group were also on lactulose.⁸

Flumazenil has been proposed to treat HE. Although it is clear that benzodiazepines can make encephalopathy worse, studies of the use of flumazenil to reverse encephalopathy show conflicting results.^{4,137} Although there is no clear evidence that all patients will benefit from flumazenil, some individuals may benefit for a short time. Certainly, the administration of benzodiazepines should be avoided.⁴

EVALUATION OF THE PATIENT WITH LIVER DISEASE

The history is critical in establishing the etiologic diagnosis of the patient with liver disease. A medication history should include careful investigation of nonprescription xenobiotics, especially APAP and the possible use of alternative or complementary therapies including herbal therapies. Nearly any chronically used medications should be suspect. An occupational history may indicate exposure to vinyl chloride (plastics industry), dimethylformamide (leather industry), or other industrial solvents. Table 23–3 lists occupational exposures that result in liver injury. Alcohol abuse is a common cause of acute hepatitis and the most common cause of cirrhosis in the USA.^{9,95,101} A history of male homosexual contacts, health care occupation, or intravenous drug use indicates the possibility of hepatitis B and C. Recent travel to a developing

country suggests the possibility of hepatitis A. In patients with significant pain, the possibility of cholelithiasis should be considered.¹⁵⁹

TABLE 23–3. Occupational Exposures Associated with Liver Injury

<i>Xenobiotic</i>	<i>Type of Injury</i>
Arsenic	Cirrhosis, angiosarcoma
Beryllium	Granulomatous hepatitis
Carbon tetrachloride	Acute necrosis
Chlordecone	Minor hepatocellular
Copper salts	Granulomatous hepatitis, angiosarcoma
Dimethylformamide	Steatohepatitis
Methylenedianiline	Acute cholestasis
Phosphorus	Acute necrosis
Tetrachloroethane	Acute, subacute necrosis
Tetrachloroethylene	Acute necrosis
Toluene	Steatosis, minor hepatocellular
Trichloroethane	Steatosis, minor hepatocellular
Trinitrotoluene	Acute necrosis
Vinyl chloride	Acute necrosis, fibrosis, angiosarcoma
Xylene	Steatosis, minor hepatocellular

Biochemical Patterns of Liver Injury

There are two basic biochemical patterns associated with liver injury induced by xenobiotics. The hepatocellular pattern is characterized by elevation of liver aminotransferases due to the injury of hepatocytes by apoptosis or necrosis.¹¹⁸ The cholestatic pattern is characterized by elevation of the serum alkaline phosphatase concentration and bilirubin and usually results from injury or functional impairment of the bile ductules.⁵⁴ Processes associated with intrahepatic cholestasis in the absence of hepatitis may not lead to significant aminotransferase elevation.^{117,128,181}

Aminotransferases. Laboratory tests are helpful, and certain patterns may be suggestive of specific etiologies (Table 23–4). Elevation of hepatocellular enzymes, especially the AST and ALT, indicates hepatocellular injury, and within a given clinical context, has useful diagnostic significance. Aminotransferases may be increased up to 500 times normal when hepatic necrosis is extensive, such as in severe acute viral or toxic hepatitis.^{86,124} The degree of elevation does not always reflect the severity of injury because concentrations may decline as liver failure progresses. Only moderately elevated, or occasionally normal, aminotransferase concentrations occur in some patients with hepatic failure caused by mitochondrial failure, cirrhosis, or venoocclusive disease.^{49,81,108,180} Aminotransferase concentrations may be normal or only slightly elevated in processes associated with intrahepatic cholestasis in the absence of hepatitis.^{117,128,181} In alcoholic liver disease, in contrast to other forms of hepatitis, the AST concentration is typically two to three times greater than the ALT. Elevation of either of these enzymes greater than 300 IU/L is inconsistent with injury caused by ethanol.^{100,124} During acute extrahepatic obstruction of the biliary tract, the AST or ALT may be as high as 1000 IU/L, indicating inflammation caused by reflux of bile acids into the biliary tree.¹²⁴ The measurement of γ -glutamyl transpeptidase (GGTP) is not very useful because it is present throughout the liver and its elevation is often nonspecific.¹²⁴

TABLE 23–4. Laboratory Tests That Evaluate the Liver

Disorder	Alkaline Phosphatase	AST, ALT	Albumin	Prothrombin Time	Bilirubin	Ammonia	Anion Gap
Hepatocellular necrosis, acute focal (hepatitis)	N or ↑	↑↑↑	N	N or ↑	↑↑	N	N
Hepatocellular necrosis, acute massive	N or ↑	↑↑↑	N	↑↑	↑↑↑	↑↑	↑
Chronic infiltrative disease (tumor, fatty liver)	↑↑↑	↑	N	N	N	N	N
Acute mitochondrial failure	N or ↑	N or ↑	N	↑↑	↑	↑↑	↑↑↑
Cholelithiasis	↑	N or ↑	N	N	N or ↑	N	N
Cholestasis	↑↑	N or ↑	N	N	↑	N	N
Chronic hepatitis	N or ↑	↑	N or ↓	N	N or ↑	N or ↑	N
Cirrhosis	N or ↑	↑	↓	N or ↑	N or ↑	N or ↑	N

↑ = increase; ↓ = decrease; N = normal.

Alkaline Phosphatase. In patients with cholestasis, bile acids stimulate the synthesis of alkaline phosphatase by hepatocytes and biliary epithelium in response to a number of pathologic processes in the liver. Elevations of the alkaline phosphatase as great as 10-fold may occur with infiltrative liver diseases but are most commonly associated with extrahepatic obstruction.¹²⁴ Although the alkaline phosphatase may be normal or elevated only minimally in hepatocellular injury, it is unusual for obstruction to occur without some elevation of the alkaline phosphatase. Elevations of alkaline phosphatase and GGTP parallel each other in diseases of the biliary tract.¹²⁴

Bilirubin. Elevation of conjugated (direct) bilirubin implies impairment of secretion into bile, whereas elevation of unconjugated (indirect) bilirubin implies impairment of conjugation. Unconjugated hyperbilirubinemia also occurs during hemolysis and in rare disorders of hepatic conjugation such as Gilbert or Crigler-Najjar syndromes. Except in cases of pure unconjugated hyperbilirubinemia, the fractionation of bilirubin in the case of hepatobiliary disorders does not have any important diagnostic utility, and it will not distinguish patients with parenchymal disorders of the liver from intrinsic or extrinsic cholestasis. The presence of bilirubin in the urine implies elevation of conjugated (direct) bilirubin, which is water soluble and filtered by the glomerulus, obviating the need for laboratory fractionation.^{124,159}

Urobilinogen is produced by the bacterial metabolism of bilirubin in the bowel lumen. It is absorbed and excreted in the urine. Its presence in the urine indicates the normal excretion of bilirubin in bile, while its absence is associated with complete biliary obstruction. As a result of more modern methods of detection of complete obstruction of the biliary tract, this test is mainly of historical interest.

Serum Albumin. Quantitatively, albumin is the most important protein that is made in the liver. With a half-life as great as 20 days, the albumin is usually normal in the previously healthy patient with acute liver injury. In the absence of disorders that affect albumin, such as nephrotic syndrome, protein-losing enteropathy, or starvation, a low serum albumin concentration is a useful marker for the severity of chronic liver disease.^{124,159}

Coagulation Factors. Impairment of coagulation is a marker of the severity of hepatic dysfunction in both acute and chronic liver disease. Elevation of the PT in acute hepatitis is associated with a higher risk of hepatic failure.^{57,87,108} Unlike the case with serum albumin, the onset of coagulopathy as a consequence of impaired synthesis of coagulation factors produced in the liver is rapid. Acute changes in coagulation reflect the concentration of factor VII, which has the shortest half-life.⁶⁶ The extrinsic coagulation pathway, as measured by the PT, is affected by reductions in factors VII, IX, and X. In addition to failure of hepatic synthesis, inadequate concentrations of factors II, VII, IX, and X may also result from ingestion of warfarin anticoagulants or malabsorption of vitamin K (**Chap. 60**).

Because different thromboplastin reagents give different PT values on the same sample, the international normalized ratio (INR) was developed to normalize PT measurements in patients treated with warfarin, allowing comparisons of therapeutic outcomes across different care settings and across the literature. The INR uses the International Sensitivity Index (ISI) that is derived from a cohort of patients on stable anticoagulant therapy. It normalizes the responsiveness of a given thromboplastin reagent in comparison to a WHO reference standard that is assigned a value of 1.0.⁷⁸ There is little controversy regarding the value of the INR in comparison with the PT ratio for measuring the extent of warfarin-induced anticoagulation. In patients with liver disease, use of the INR implies a normalized correlation that does not exist and is therefore potentially misleading. Because factor deficiencies in patients with liver disease are different from those in patients on warfarin, there is considerable controversy regarding which measurement is best for patients with liver disease.^{30,66,78} Although comparison of factor concentrations in warfarin-treated patients with those with liver disease showed no difference in factor VII, there are significant differences in factors II, V, X, and fibrinogen. Comparison of the PT with INR in the evaluation of test results with three different thromboplastin reagents showed consistency among the control groups of warfarin-treated patients, but no consistency among PT or INR measurements using the same

thromboplastin reagents in patients with liver disease.⁷⁸ Because of a failure to demonstrate an advantage, liver specialists have supported the continued use of the PT to describe the degree of liver injury, lacking the availability of a single reliable standard that would help predict operative risk.^{30,78} The implication for toxicologists is that caution should be exercised in relying too heavily on published INR values that purportedly predict the severity of illness in patients with acute liver failure.

A thoughtful review of bleeding risk due to coagulopathy in chronic liver disease discussed the balance of procoagulation forces (elevated factor VIII concentrations, elevated von Willebrand factor, decreased protein C and antithrombin) and anticoagulation forces (decreased fibrinogen and other clotting factors, high tissue plasminogen activator, low platelet count). The balance is simply characterized as a seesaw effect between stimulation of thrombin generation by factor VIII and the suppression of thrombin generation by protein C. This fragile balance between procoagulation and anticoagulation may be tipped by events such as kidney failure or infection. It is not effectively characterized by the INR or the PT. The review proposed that the standard belief that patients with liver failure are “auto-anticoagulated” and not at risk of venous or arterial thrombosis is erroneous. The authors suggested that neither the PT nor the INR could predict bleeding risk in the cirrhotic patient and proposed further investigations to help identify bleeding risk and prevent or manage thrombotic events in cirrhotic patients.¹⁶²

Ammonia. Severe generalized impairment of hepatic function leads to a rise in the serum ammonia concentration as a result of impairment of hepatic detoxification of ammonia produced during catabolism of proteins.^{8,123,138} Urease-containing bacteria within the bowel, especially *Klebsiella* and *Proteus* species, are the most prominent producers of ammonia.¹³⁸ Some patients treated with valproic acid develop alterations in mental status associated with elevated ammonia concentrations in the absence of other laboratory indicators of hepatic injury.^{37,127,168} Hyperammonemia in patients on valproic acid is also commonly asymptomatic.¹¹⁵ This has been attributed to selective impairment of urea cycle enzymes ornithine transcarbamylase or carbamyl phosphate synthetase by pentanoic acid metabolites ([Chap. 48](#)). As noted above, an association between deficiency of carnitine, microsteatosis, and the development of hyperammonemia in the setting of liver failure is observed in children treated with valproic acid. This is attributed to impairment of carnitine-dependent β -oxidation of sodium valproate and free fatty acids in the mitochondria.^{12,126,166}

Other Laboratory Tests

Serologic studies for the presence of markers of hepatitis A, B, and C should be obtained routinely in patients with hepatitis. In the patient with severe liver injury, hypoglycemia is a major concern because of impairment of glycogen storage and gluconeogenesis. Hyperglycemia also occurs as a result of the inability of the liver to handle a large glucose load. The arterial or venous blood gas commonly shows a respiratory alkalosis. Severe metabolic acidosis with elevated lactate occurs in patients with hepatic failure caused by mitochondrial injury. Measurements of serum lactate concentration may be useful in identifying the cause of acidosis in a patient with suspected toxic liver injury.^{103,108,144,159}

Computed tomography and magnetic resonance imaging scans are useful tests for evaluation of parenchymal disease of the liver. An ultrasound examination reliably demonstrates dilation of the extrahepatic bile ducts. Liver biopsy may be helpful but is not specifically diagnostic of xenobiotic-induced hepatic injury.

MANAGEMENT

In many patients, toxic liver injury resolves with simple withdrawal of the offending xenobiotic. In patients with severe injury, significant improvement in survival is associated with good supportive care in an intensive care environment.⁸⁷ Transplantation may be lifesaving for critically ill patients with acute liver failure. Early referral to a transplant center for patients with evidence of severe or rapidly progressive toxic injury is indicated.^{45,102} For discussion of indications for the use of N-acetylcysteine and discussion of indications for transplantation ([Antidotes in Depth: A3](#)).

SUMMARY

The primary role of the liver in the biotransformation of xenobiotics results in an increased risk of hepatotoxicity. Xenobiotic-induced liver injury can be dose-dependent and predictable or idiosyncratic and unpredictable.

- Predictability is evolving with the science of genome analysis. Injury that is apparently idiosyncratic is affected by host characteristics that include genetic makeup, concomitant or previous exposure to xenobiotics, and the underlying condition of the liver. The ability to predict this susceptibility is increasing.
- The pathological spectrum of liver injury includes combinations of hepatocellular necrosis, hepatitis, cholestasis, steatosis, apoptosis, and fibrosis.
- Mechanisms of hepatic injury include cell-mediated immune mechanisms that result in inflammation and fibrosis; antibody-mediated immune mechanisms that attack various hepatocyte targets including critical cellular enzymes; lipid

peroxidation initiated by free radicals; and mitochondrial injury.

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24 NEUROLOGIC PRINCIPLES

Rama B. Rao

INTRODUCTION

The central nervous system (CNS) coordinates responses to the fluctuating metabolic requirements of the body and modulates behavior, memory, and higher levels of thinking. These functions require a diversity of cells: astrocytes, neurons, ependymal cells, and vascular endothelial cells. Disruption or death of any one cell type can cause critical changes in the function or viability of another. This cellular interdependence, along with the high metabolic demands of the CNS, makes neurons especially vulnerable to injury from both endogenous neurotoxins and xenobiotics. Endogenous neurotoxins, such as the metals iron, copper, and manganese, are substances that may be critical to CNS function but are harmful when their penetration into the CNS is poorly controlled.

The understanding of the normal chemical and molecular functions of the CNS is limited at best. Interestingly, cellular mechanisms have sometimes been revealed by investigating xenobiotic-induced neuronal injuries.^{38,68} For example, the pathophysiology of Parkinson disease, which affects movement and motor tone, was elucidated by the inadvertent exposure of individuals to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The mechanisms of axonal transport were elucidated by investigations of the effects of acrylamide exposures in human and animal models.⁵⁸ The neurodegenerative changes of amyotrophic lateral sclerosis have a promising xenobiotic model in β -methylamino-L-alanine (BMAA), a neurotoxin found in the cyanobacteria associated with cycad plants ingested by the Chamorro people of Guam (Chap. 14).

There are few minimally invasive methods available to investigate xenobiotic-induced CNS injury. Biomarkers are usually nonspecific and not readily available. Xenobiotic concentrations of blood and urine rarely reflect tissue concentrations of the CNS.⁶⁰ Cerebrospinal fluid (CSF) may be useful in excluding CNS injury from infection, hemorrhage and inflammatory processes, but is, with few exceptions, poorly reflective of the etiology of neuronal injuries.⁹⁰ Similarly, electroencephalograms and electromyelograms are useful in only a few types of xenobiotic exposures, and neuroimaging, while progressively evolving,⁵⁴ is a poor substitute for neuroanatomical evaluations that are usually available only on autopsy. Much of the current study to elucidate the mechanisms of CNS injury uses animal models, cultured astrocytes, and other tissue, or postmortem investigations. Less commonly, occupational evaluations, such as the enzyme activity of cholinesterases in pesticide exposed workers, are used.

This chapter reviews some basic anatomic and physiologic principles of the nervous system and the common mechanisms by which xenobiotics exploit the functional and protective components of the CNS with a few relevant examples. The multiple factors determining the clinical expression of neurotoxicity are reviewed.

CELLS OF THE NERVOUS SYSTEM: AN OVERVIEW

Neurons

Neurons are the major pathway of cellular communication in the CNS. Having one of the highest metabolic rates in the body, these cells are especially sensitive to changes in the microenvironment and are dependent on astrocytes, choroidal epithelium, and capillary endothelium to confer protection and deliver glucose and other sources of energy.

Although each neuron is capable of receiving information through different neurotransmitters and receptor subtypes at the dendrite, neurons typically produce and release a single type of neurotransmitter at the axonal terminal. This specificity allows for cellular classification of neurons based on the neurotransmitter released, for example, serotonergic, cholinergic, and dopaminergic neurons (Chap. 14). Other substances such as adenosine may be produced and released that are less specific to the neuron type.

The anatomic structure of neurons facilitates their function. Dendrites located on the cell body are lined with receptors that bind neurotransmitters and affect cellular changes via several mechanisms. The soma, or cell body, is responsible for coordination and production of multiple proteins required to carry out normal physiological functions. This synthesis occurs at a rate several times greater than the liver or kidney. These proteins, organelles, and substrates must then be transported across long distances to the terminal axon. This energy-dependent function is supported by a cytoskeleton comprised of neurofilaments, microfilaments, microtubules, and complex transport proteins. Fast anterograde transport of membrane-bound organelles occurs through kinesin, a transport protein, at a rate of 200 to 400 mm/d. Channel proteins,

synaptic vesicles, mitochondria, $\text{Na}^+\text{-K}^+\text{-ATPase}$, glycolipids, and other substances are transported by kinesin. Slow anterograde transport also occurs at a substantially slower rate (0.5–4 mm/d). The retrograde transport protein, dynein, is produced in the soma and delivered to the nerve terminal for the movement of larger vesicles and reusable proteins back to the cell body.

In the CNS, groups of neurons are organized into complex functional pathways, with a single class of neuron regulating different functions and clinical effects depending on the brain region. As an example, dopaminergic neurons regulate cravings, movement, and resting muscle tone, each of which is determined not only by dopaminergic neurons and receptor subtype, but the location in the cortex or basal ganglia ([Chap. 14](#)).

Neurons must be able to respond to changes in the local environment and alter the expression of different receptors in response to signaling from neurotrophic factors, variations in metabolic requirements, and xenobiotic interactions. This “neuroplasticity” accounts for the diversity of clinical responses to xenobiotics that induce tolerance such as ethanol ([Chap. 15](#)).

Glial Cells

Glial cells are comprised of astrocytes, oligodendrocytes, Schwann cells, and microglia. These cells serve to support the neurons both structurally and functionally.

Astrocytes comprise between 25% and 50% of the brain volume.^{1,3,4,11} In addition to the anatomic contribution to the blood–brain barrier (BBB), astrocytes play a critical role in maintaining neuronal function.^{1,2,93} They contribute to three major areas: homeostasis of the extraneuronal environment, provision of energy substrates, and limitation of oxidative stress. In addition, astrocytes contribute to the “plasticity” of cells and receptor expression in the CNS (see later discussion).

In order for cells of all types to function in the CNS, membrane potentials must be adequately maintained. Astrocytes contribute to this by closely regulating the extracellular pH, water, and, like brain capillaries, the extracellular potassium concentration. Metallothioneins, which control the entry of metals necessary for CNS function, are produced by astrocytes.^{28,93} Astrocytes also release energy substrates such as lactate, citrate, alanine, glutathione, and α -ketoglutarate for utilization by neurons.¹¹

Astrocytes metabolize glutamate, the main excitatory amino acid (EAA) neurotransmitter in the CNS, as well as ammonia. These cells also produce superoxide dismutase and glutathione peroxidase to reduce free radical propagation. Glutathione, the major antioxidant for the brain, is predominantly located in the astrocytes. It can be released into the extracellular space or cleaved for neuronal uptake and intracellular reformulation.¹¹

Through the release of complex trophic factors, astrocytes control the expression of endothelial transporters of the BBB and the production of tight junctions in both the blood–CSF barrier and BBB. Angiogenesis is similarly astrocyte regulated, as is detection of neuronal injury, immune mediation, and neurotransmitter production. The growth of neurites, the branches of neuronal cell bodies that eventually become dendrites or axons, is similarly modulated by astrocytes.

Oligodendrocytes are a type of glial cell that provide anatomical support, protective insulation, and facilitate rapid neuronal depolarization by the production of myelin. Myelin is the primary constituent of white matter in the CNS. The production of myelin in the peripheral nervous system (PNS) is performed by the Schwann cells. Although oligodendrocytes support several axons, each Schwann cell is anatomically dedicated to a single axon.

Finally, microglial cells modulate immune response, inflammation, and tissue repair from a variety of CNS injuries. Like neurons, microglia are dependent on signaling from astrocytes.

MECHANISMS OF NEUROPROTECTION

The nervous system has multiple protective mechanisms. Xenobiotics are prevented from accessing the CNS by the blood–brain and blood–CSF barriers. For xenobiotics that enter the CNS, there are multiple cellular specializations to limit oxidant stress as reviewed below.

Blood–Brain Barrier

The BBB confers an anatomic and enzymatic barrier to xenobiotic entry into the CNS. Brain capillaries are surrounded by the foot processes of adjacent astrocytes. The potential spaces between endothelial cells are limited by tight junctions, or zonulae occludentes, which are between 50 and 100 times tighter than those found on peripheral capillaries.^{1,2,4,52,63} This anatomic barrier prevents movement of substances between cells, also known as the paracellular aqueous pathway, due to osmotic and oncotic forces.^{1,2,4,52,63}

Transendothelial movement of critical substrates and, potentially, xenobiotics occurs through three major mechanisms: diffusion, transport proteins, and endocytosis.^{1,4} These routes allow carefully controlled entry of critical substrates and cofactors while limiting the potential for injury from either endogenous or exogenous neurotoxins.

Lipophilic substances may move directly across the luminal and abluminal endothelial membranes abutting the CNS. Other substances may enter the endothelium through bidirectional transport proteins on the luminal surface. These proteins may be specific, such as the glucose transporter 1 (GLUT1) protein for uptake of glucose, or less specific large neutral amino acid transporters that move amino acids and xenobiotics, such as baclofen, intracellularly. These transporters also line the abluminal surface of the endothelial cell for movement of substrates and xenobiotics into the CNS. The third line of entry for larger proteins is via endocytosis. This can be adsorptive, or mediated through specific receptors such as those for insulin or transferrin.^{1,3,4,52,63,93}

Endothelial cells have other protective properties, including intracellular enzymes, to metabolize xenobiotics and efflux proteins to transport certain xenobiotics back into the capillary lumen. These efflux proteins include energy-dependent P-glycoproteins that are ATP-binding cassette transporters and are sometimes referred to as multidrug-resistant (MDR) proteins (Chap. 9). Several hydrophobic xenobiotics are prevented from accumulating in the CNS through these transporters, including vinca alkaloids, digoxin, cyclosporine A, and protease inhibitors. Nonsedating antihistamines may have limited sedative properties due, in part, to efflux through P-glycoproteins.²⁵ Another type of saturable transporter, known as organic acid transport (OAT) protein, facilitates the efflux of hydrophilic xenobiotics such as valproic acid or baclofen. The expression of each of these transporters may be upregulated under certain conditions such as intermittent disruptions in the BBB from seizures. This expression upregulation is theorized to account for the resistance of anticonvulsant medications in patients with epilepsy. Comprehensive lists of xenobiotics that are substrates for these transporters are available elsewhere.^{2,52,53}

Blood–Cerebrospinal Fluid Barrier

The ventricles of the brain are lined by the epithelial cells of the choroid. These cells also have tight junctions but not as extensive as those of the BBB. They are, however, rich in glutathione peroxidase and other xenobiotic-metabolizing enzymes in concentrations approximating those of the liver. Similar to brain capillary cells, the choroid contains efflux transporters for organic anions and cations, as well as MDR efflux proteins (P-glycoproteins) to limit entry of xenobiotics into the CSF.^{1,4,52,93}

NEUROTOXIC PRINCIPLES

Excitotoxicity

Neuronal function is strictly dependent on aerobic metabolism. When energy expenditure exceeds production, cellular dysfunction and ultimately cell death, or apoptosis, results. The specific cascade of molecular events relating to this process is termed excitotoxicity.^{10,73}

The initial event is traced to an oxidant stress and excessive stimulation of N-methyl-D-aspartate (NMDA) receptors by glutamate, an EAA neurotransmitter. An influx of intracellular calcium changes membrane potentials across the cellular and mitochondrial membranes. The mitochondria become progressively more inefficient at ATP production and handling the resulting reactive oxygen species. As membrane damage is propagated, calcium further depolarizes the mitochondria, activating a permeability transition pore across the mitochondrial membrane. Gradients are further disrupted, precipitating more injury, energy failure, and ultimately cell death.

Excitotoxicity is considered a common mechanism of cell death due to xenobiotic, ischemic, traumatic, infectious, neoplastic, or neurodegenerative injury. It is the subject of study for many therapeutic interventions in CNS injury.

Determinants of Neurotoxicity

The clinical expression of neurotoxicity is related to many factors. These include the chemical properties of the xenobiotic, the dose and route of administration, xenobiotic interactions, and underlying patient characteristics including age, gender, and comorbid conditions.

Chemical Properties of Xenobiotics

One of the most important determinants of neurotoxicity is the ability of a xenobiotic to penetrate the BBB. Water-soluble molecules larger than M_r 200 to 400 (molecular weight ratio, or mass of a molecule relative to the mass of an atom) are unable to bypass the tight junctions.⁴ Xenobiotics with a high octanol/water partition coefficient are more likely to passively penetrate the capillary endothelium, and potentially the BBB, whereas those with a low partition coefficient may require energy-dependent facilitated transport.⁶³ Xenobiotics that are substrates for capillary endothelial efflux mechanisms will have limited penetration regardless of the coefficient.^{1,4,52,63}

Route of Administration

The route of xenobiotic administration may also be consequential. Although most xenobiotics gain access to the nervous system through the circulatory system, aerosolized solvent and heavy metals in industrial and occupational exposures gain CNS access through inhalation, traveling via olfactory and circulatory routes. Alternatively, some substances may move from the PNS via retrograde axonal transport to the CNS. Naturally occurring proteins such as tetanospasmin, as well as rabies, polio, and herpes virus may use this mechanism to access the PNS and CNS.^{13,16,47} The toxalbumins ricin and abrin as well as bismuth salts may also use this mechanism to a limited extent.^{85,91} This understanding may prove beneficial from a therapeutic perspective. For example, in one small experimental series of patients experiencing severe pain, doxorubicin was injected into the involved peripheral nerves. Therapeutically, a chemical ganglionectomy occurred through retrograde “suicide” transport of doxorubicin, which provided substantial relief for these patients.⁵⁰

Some xenobiotics may be delivered directly into the CSF (intrathecally), the consequences of which are variable (Special Considerations: SC3).

Xenobiotic Interactions

Coadministration of xenobiotics may precipitate neurotoxicity by several mechanisms.⁴⁵ Extraaxially (outside of the CNS), xenobiotic interactions that result in an increase of the blood concentration of one or both may overwhelm the protective mechanisms of the BBB.²⁰ Similar effects may occur in the PNS where elevated blood concentrations may enhance clinical effects resulting in peripheral neuropathies.⁹³

Xenobiotic interactions can be synergistic, acting on the same neuroreceptor. Benzodiazepines and ethanol, for example, both stimulate the γ -aminobutyric acid type A (GABA_A) receptor. The excessive neuroinhibition can result in deep coma and even respiratory depression when these xenobiotics are administered simultaneously.

In some circumstances, xenobiotic interactions result in excessive neurotransmitter availability.⁹ This neurotransmitter excess is demonstrated in patients with the serotonin toxicity, which results from the coadministration of a monoamine oxidase inhibitor and a serotonin reuptake inhibitor or other serotonergics as an example (Chap. 75).

Access to the CNS may be altered by one of the xenobiotics, allowing the other to bypass the BBB. For example, mannitol causes transient opening of the BBB; as a result, therapeutic use of mannitol is under investigation for the delivery of chemotherapeutics that might otherwise be unable to access the nervous system.⁵³ Similarly, some xenobiotics, such as verapamil, cyclosporine, and probenecid, are blockers of capillary endothelium efflux.^{4,93} These theoretically limit efflux of other substrates of P-glycoprotein or OAT. The clinical utility of employing such efflux blockers is under investigation as was done in a study in which primates received intrathecal methotrexate. The CSF clearance of methotrexate was reduced in animals administered intrathecal probenecid.^{12,76}

Patient Characteristics

Patient-specific variables may affect the ability of a xenobiotic to penetrate the BBB and/or the clinical effects of a given exposure. For example, age of the patient at the time of exposure is critical, especially in the fetus and neonates.⁷⁸ The structural and enzymatic development of the BBB is incomplete, and synaptogenesis, or formation of intercellular relationships, is especially sensitive to impaired protein synthesis or other excitotoxic events. This is demonstrated classically by maternal exposure to methylmercury. The mother may be minimally affected, but the developing fetus suffers profound neurological and developmental consequences (Chaps. 31 and 98).

In neonates, immature liver function may lead to the accumulation of circulating bilirubin. Due to incomplete formation of the BBB, the bilirubin may access the CNS and produce a form of encephalopathy known as kernicterus.

Elderly patients may also have increased susceptibility to neurotoxins as a result of relatively impaired circulation or age-related changes in mitochondrial function that predispose to excitotoxicity.⁸¹ Xenobiotic-induced parkinsonism, or the unmasking of subclinical idiopathic Parkinson disease, may occur more readily than in younger patients. Animal models also suggest age-related sensitivity with one study noting increased manganese toxicity with advanced age.³⁶

Gender may be contributory to the expression of xenobiotic-induced neurological injury. In animal models, the presence of estrogen-related and progesterone-related compounds may be neuroprotective for some xenobiotic injuries.^{64,71} In humans, women are more susceptible to some movement disorders such as xenobiotic-induced parkinsonism and tardive dyskinesia, whereas dystonias and bruxism are more prevalent in young men.⁷⁴ The etiologies of these gender-related differences are incompletely understood.

Neurologic Comorbidities

Conditions affecting the integrity of the BBB can affect CNS penetration of xenobiotics and endogenous neurotoxins. For example, glutamate concentrations are normally higher in the circulatory system than the CNS.⁵⁷ Patients with trauma, ischemia, or lupus vasculitis³ may experience neuropsychiatric disorders as a result of increased penetration of glutamate

or sensitivity to additional xenobiotics. Similarly, inflammation associated with meningitis and encephalitis causes openings in the BBB, which may be exploited therapeutically. Intravenous penicillin achieves a higher CSF concentration in animals with meningitis than in those without meningitis.⁷⁷

In some patients, previously undiagnosed diseases become evident on exposure to xenobiotics. This is especially true in patients with peripheral neuropathies. For example, patients being treated with therapeutic doses of vincristine suffered a severe polyneuropathy due to unmasking of a previously undiagnosed Charcot-Marie-Tooth disease.^{9,22} Similarly, patients with diabetes mellitus, the commonest cause of peripheral neuropathy, or human immunodeficiency virus disease may have exacerbation of symptoms in the presence of antiretrovirals.^{24,72} Patients with myasthenia gravis may have exacerbation of weakness with aminoglycoside administration, which can affect transmission at the neuromuscular junction (NMJ).⁹²

Chronic exposures to some neuroinhibitory xenobiotics such as ethanol may alter neuronal receptor expression and upregulate or increase the amount of receptors for EAAs. In addition to receptor augmentation, neurotransmitter concentrations of the excitatory neurotransmitters glutamate and aspartate are increased, as is homocysteine. These changes induce a tolerance to neuroinhibitory xenobiotics acting on the same receptor, and patients require escalating doses to achieve the same clinical effect. In such patients, cessation of ethanol intake results in a relative deficiency of exogenous inhibitory tone. The patient experiences neuroexcitability and the clinical syndrome of withdrawal^{17,18} (Chap. 15).

Adequate nutritional status is important for the maintenance of normal neurological function. The BBB may not be adequately maintained in patients with malnutrition. Deficiencies of metal cofactors such as manganese, copper, zinc, and iron can affect neurological function. In some cases, the deficiencies enhance absorption of other xenobiotics. For example, iron deficiency enhances lead and manganese absorption in the gastrointestinal tract, which can ultimately overwhelm neuroprotective mechanisms. Vitamins serve as enzymatic cofactors in modulating the production of glutamate, homocysteine, and other amino acids. Specific vitamin deficiencies can precipitate neurological syndromes such as Wernicke encephalopathy in thiamine-depleted patients (Antidotes in Depth: A24 and Chap. 47). The toxicity of xenobiotics may also be enhanced. For example, a relative pyridoxine deficiency in patients with acute isoniazid overdose may result in seizures as a result of a relative excess of EAAs (Antidotes in Depth: A14 and Chap. 58). Glucose is a critical energy substrate that can cause profound neurological impairment when delivery is inadequate (Antidotes in Depth: A12 and Chap. 53).

Interestingly, certain conditions such as temperature may affect the toxicity of xenobiotics. For example, cooling may limit the impedance of acetylcholine neurotransmission caused by botulinum toxin.⁴¹

Extraaxial Organ Dysfunction

Kidney failure may impair metabolism or elimination of xenobiotics or endogenous neurotoxins such as urea, rendering it more available to the CNS. Hyperglycemia in patients with diabetes mellitus may also increase formation of CNS reactive oxygen species. Similarly, patients with liver failure may have elevations in CNS manganese resulting in Parkinsonism.^{51,79}

Hepatic encephalopathy illustrates the concept of excitotoxicity from endogenous neurotoxins. Hyperammonemia increases oxidative stress and free radical formation in astrocytes. Ammonia potentially decreases critical metabolic enzymes such as catalases, superoxide dismutase, and glutathione peroxidase. Nitric oxide (NO) production is increased due to elevations in NO synthetase. Under these conditions, astrocytes upregulate the expression of the peripheral benzodiazepine receptor (PBR) on the outer mitochondrial membrane. The PBR modulates the production of neurosteroids and, in turn, the GABA_A receptor. Continued CNS exposure to ammonia and other endogenous solutes propagates this oxidative and nitrosative stress to the mitochondrial membrane, potentially opening the mitochondrial permeability transition pore. Osmotic swelling of the mitochondrial membrane followed by excitotoxicity results in cerebral edema and hepatic encephalopathy.^{64–66}

SPECIFIC MECHANISMS OF NEUROTOXICTY

Alteration of Endogenous Neurotransmission

Xenobiotics can induce neurotoxicity by triggering changes in neurotransmission in either the CNS or PNS. In some cases xenobiotics enhance neurotransmission through a specific receptor subtype. This enhanced transmission can occur through inhibition of presynaptic metabolism (monoamine oxidase inhibitors), stimulation of neurotransmitter release (amphetamines), impairment of neurotransmitter reuptake (cocaine), or inhibition of synaptic degradation (acetylcholinesterase inhibitors).

Alternatively, synaptic neurotransmission may be impaired.⁸⁰ Xenobiotics may inhibit the presynaptic release of neurotransmitters (botulinum toxin), block receptors (antimuscarinics), or alter membrane potentials at the postsynaptic membrane (tetrodotoxin).^{32,33} Patients may present with a clinical syndrome of toxicity associated with altered neurotransmission of the specific receptor (Chap. 3).

Direct Receptor Interaction

Some xenobiotics are able to directly stimulate receptors. Both kainate and α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) are subclasses of the glutamate receptor, which are targeted by some naturally occurring xenobiotics.⁴² An example is β -N-oxalylamino-L-alanine (BOAA) found in the grass pea, *Lathyrus sativus*. BOAA stimulates the AMPA receptor and inhibits specific mitochondrial enzymes resulting in the spastic paraparesis of lathyrism.⁶⁹ Domoic acid stimulates the kainate receptor and causes the neuroexcitation associated with neurotoxic shellfish poisoning (Chap. 44). Direct inhibition is also possible, as exemplified by phencyclidine, an NMDA receptor antagonist.

Enzyme and Transporter Exploitation

The classic example of xenobiotics that exploit endogenous enzymes and or transporters is MPTP.³⁸ Once MPTP crosses the BBB, it is converted by monoamine oxidase to the neurotoxic compound 1-methyl-4-phenylpyridine (MPP⁺) in astrocytes. MPP⁺ is taken up by dopamine transporters into the neurons of the substantia nigra pars compacta. MPP⁺ inhibits complex I of the mitochondrial electron transport chain resulting in dopaminergic excitotoxicity and the clinical syndrome similar to Parkinson disease (Disorders of Movement and Tone, below, and Chap. 38).

Altered Conduction along Membranes:Demyelinating Neurotoxins

Aside from xenobiotics that affect neurotransmission at the postsynaptic membrane, some affect the production or maintenance of myelin by oligodendrocytes and Schwann cells.^{23,34,37,48} In the CNS these are often associated with white matter abnormalities and a leukoencephalopathy.³⁴ Xenobiotics such as hexachlorophene, arsenic, inhibitors of tumor necrosis factor α , neural tissue-derived rabies vaccine, and the act of “chasing the dragon” or inhaling volatilized heroin are associated with a demyelinating neurotoxicity.²³ In the PNS, nitrous oxide, suramin, and tacrolimus are associated with peripheral demyelination.⁴⁶

Inhibition of Intracellular Functions

Some xenobiotics are nonspecific inhibitors of cellular function.²⁹ For example, the neurotoxicity of carbon monoxide (CO) or cyanide that may appear as a diffuse impairment of neuropsychiatric dysfunction or, depending on the dose and specific vulnerabilities of an exposed patient, be more focal. Patients surviving acute CO exposure may experience delayed neurological sequelae that may include a diffuse impairment of neuropsychiatric function, or more focally, present with a xenobiotic-induced Parkinson syndrome (see later and Chap. 125).

Antineoplastics can affect the production of critical proteins required for cellular maintenance. These can be very specific such as the ability of vincristine to impair cytoskeletal transport in the peripheral nervous system (Chap. 36).

CLINICALLY RELEVANT XENOBIOTIC-MEDIATED CONDITIONS

Alterations in Consciousness

The toxicological differential diagnosis of xenobiotics that induce alterations in mental status or consciousness is expansive. These xenobiotics can be broadly divided into those that produce some form of neuroexcitation and those that produce neuroinhibition. Although some xenobiotics such as phencyclidine have elements of both depending on dose, this categorization facilitates a general clinical understanding of neurotoxic alterations in mental status.

Xenobiotics resulting in neuroexcitation enhance neurotransmission of EAAs, or diminish inhibitory input from GABAergic neurons. The clinical presentation of the patient may vary; some patients may be alert and confused, or suffering from an agitated delirium, hallucinations, or a seizure.

Neuroinhibitory xenobiotics typically enhance GABA-mediated neurotransmission. These patients may be somnolent or in deep coma. Benzodiazepines hyperpolarize cells by increasing inward movement of Cl⁻ ions through the chloride channel of the GABA_A receptor. This hyperpolarization limits subsequent neurotransmission (Chap. 14). Less commonly, neuroinhibition is a result of diminution of EAA. Patients presenting the day after bingeing on cocaine may be sleepy but arousable and oriented in what is termed cocaine “washout,” theoretically related to depletion of EAA and dopamine. Xenobiotics that cause diffuse cortical dysfunction through impairment in the delivery or utilization of oxygen or glucose can also present with depressed or altered consciousness.

Clinical evaluation of patients with altered consciousness includes obtaining complete history, including medications, comorbid conditions, occupation, and suicidal intent when relevant or available. Patients should have a complete physical examination, with particular attention paid to vital sign abnormalities or findings that may indicate a toxic syndrome. Assessment and correction of hypoxia or hypoglycemia should be performed. An electrocardiogram may be useful in some circumstances (Chap. 16).

Xenobiotic-Induced Seizures

Seizures are the most extreme form of neuroexcitation. As with alterations of consciousness, this may be due to enhanced EAA neurotransmission (domoic acid, sympathomimetics) or inhibition of GABAergic tone (isoniazid). Unlike in traumatic or idiopathic seizure disorders with an identifiable seizure focus, the initiation and propagation of xenobiotic-induced seizures is diffuse. It is for this reason that most non-sedative-hypnotic anticonvulsants such as phenytoin are unlikely to be effective in terminating xenobiotic-induced seizures.

Seizures may be idiopathic as described with tramadol and bupropion, or they may be concentration-dependent events as described with theophylline and isoniazid toxicity. Alternatively, seizures may be a result of withdrawal from GABAergic substances.

Status epilepticus is variably defined but involves two or more seizures without a lucid interval, or continuous seizure activity for greater than 5 minutes.⁵⁹ True xenobiotic-induced status epilepticus is rare. Cicutoxin, the toxin in water hemlock, *Cicuta maculata*, is a potent inhibitor of GABA_A neurotransmission and may cause status epilepticus.

Theophylline toxicity precipitates seizures and status epilepticus through a different mechanism. Normally, endogenous termination of seizures is mediated through presynaptic release of adenosine during the release of the primary neurotransmitter at the terminal axon. Adenosine functions as a feedback inhibitor of the presynaptic neuron, disrupting propagation of excitatory neurotransmission. Theophylline is an adenosine antagonist. Adenosine administration is not a useful therapy for theophylline-induced seizures as adenosine is unable to cross the BBB. Generally high-dose sedative-hypnotics, affecting GABA_A receptors, are required for seizure control.

Some clinical conditions appear to be centrally mediated tonic-clonic movements but are due to glycine inhibition in the spinal cord. Glycine is the major inhibitory neurotransmitter of motor neurons of the spinal cord. Under normal conditions, glycine contributes to termination of reflex arcs. Glycine inhibition results in myoclonus, hyperreflexia, and opisthotonos, often without alteration in consciousness. Presynaptic glycine release inhibition is caused by tetanospasmin, the major neurotoxin from *Clostridium tetani*. Postsynaptic glycine inhibition is caused by strychnine, the toxin in *Strychnos nux-vomica*. Patients with exposures to tetanospasmin or strychnine are often treated in quiet environments where the stimuli to initiate hyperreflexia are minimized ([Chap. 117](#) and [Table 24-1](#)).

TABLE 24-1. Xenobiotics That Commonly Induce Seizures

<i>Concentration Related</i>	<i>Idiosyncratic</i>	<i>Withdrawal Related</i>	<i>Tonic-Clonic Seizurelike</i>
Antihistamines	Bupropion ^a	Baclofen	Strychnine
Baclofen	Carbamazepine	Barbiturates	Tetanospasmin
Camphor ^a	Ergotamines	Benzodiazepines	
Carbon monoxide	GHB	Ethanol	
Chloroquine ^a	Mefenamic acid	GHB	
Cicutoxin ^a	Phenylbutazone		
CNS stimulants	Tramadol		
Cyanide			
Diphenhydramine ^a			
Domoic acid			
Isoniazid ^a			
Hypoglycemics			
Gyromitrin ^a			
Lidocaine			
Meperidine			
Organic chlorines			
Organic phosphorus compounds			
Propoxyphene			
Strychnine			
Tetramethylenedisulfotetramine (TETS) ^a			
Thallium			
Theophylline ^a			
Zinc phosphide			

^aHigh concentrations may result in status epilepticus.

CNS = central nervous system; GHB = γ -hydroxybutyric acid.

Xenobiotic-Induced Mood Disorders

Certain xenobiotics are inconsistently associated with alterations in mood.^{5,19} What predisposes individuals to xenobiotic-induced mood alterations is unclear. In some circumstances, patients with previously undiagnosed bipolar disorder are given a xenobiotic that unmasks their disease. Interestingly antibiotic-induced mania is found in some patients without a previous psychiatric history. The symptoms of mania are usually evident within the first week of therapy and, unlike the mania of purely psychiatric origin, readily abate within 48 to 72 hours of the last antibiotic dose. Some patients with clarithromycin-induced mania have documented recurrence on rechallenge.⁵ In general, xenobiotic-induced manias are idiopathic and very rare. More common are either psychosis from chronic CNS stimulant use or depression from ethanol or the xenobiotics listed in [Table 24–2](#).

TABLE 24–2. Xenobiotics Commonly Inducing Mood and Neuropsychiatric Disorders

<i>Mania</i>	<i>Depression</i>	<i>Psychosis</i>
Acyclovir	β-Adrenergic antagonists	Amantadine
Amantadine	Amiodarone	Corticosteroids
Caffeine	Interferon	CNS stimulants
Chloroquine	Isotretinoin acid	
Clarithromycin	Ribavirin	
CNS stimulants		
Corticosteroids		
Dextromethorphan		
Dehydroepiandrosterone		
Efavirenz		
Fenfluramine		
Fluoroquinolones		
Gabapentin		
Ginseng		
Interferon-α		
Isoniazid		
Isophosphamide		
L-dopa		
Mefloquine		
Phentermine		
Phenylpropanolamine		
Pseudoephedrine		
Quetiapine		
St. John's wort		
Testosterone		
Tramadol		

CNS = central nervous system.

Disorders of Movement and Tone

Central Nervous System–Mediated Disorders. Most movement disorders, including akathisia, bradykinesia, tics, chorea, and dystonias, are mediated by the complex dopaminergic pathways of the basal ganglia. Different dopamine receptor subtypes are modulated by serotonergic, GABAergic, glutaminergic, and cholinergic neurons ([Chap. 14](#)).

Chorea occurs in some cases of carbamazepine overdose, therapeutic oral contraceptive use,³¹ and after cocaine use when the stimulant effects have subsided.⁷⁴

Dopamine receptor antagonists can precipitate acute dystonic reactions. The D₂ receptor antagonists, in conjunction with alterations in muscarinic cholinergic tone, are usually implicated. Animal models suggest possible mediation through σ receptors, the craniofacial distribution of which corresponds to the common clinical manifestations of acute dystonias.⁴⁹

Diffusely increased motor tone may occur with glycine antagonists such as tetanospasmin and strychnine, and in adrenergic states such as acute toxicity with CNS stimulants, or withdrawal from sedative-hypnotics. The rare complication of bone fractures associated with severe muscle spasm and myoclonus is reported with chronic bismuth toxicity and inadvertent intrathecal administration of hyperosmolar contrast dye ([Chap. 90](#) and Special Considerations: SC3).

Other centrally mediated disorders of tone include serotonin toxicity and neuroleptic malignant syndrome (NMS). Both of these potentially life-threatening disorders consist of altered consciousness, hyperthermia, rigidity, and autonomic instability. NMS may occur in patients taking dopamine receptor antagonists such as antipsychotics or in those with idiopathic Parkinson disease who abruptly stop their dopamine agonist therapy. Dopamine receptor agonists such as bromocriptine or restoration of antiparkinson medications are used therapeutically in these circumstances ([Chap. 70](#)). The diagnosis and management of serotonin toxicity is reviewed in [Chap. 75](#).

Parkinsonism. Xenobiotic-induced parkinsonism is a syndrome of unstable posture, rigidity, gait disturbance, loss of facial expression, hypokinesia, and variable presence of tremor.⁷ The common neuroanatomic target involves the dopaminergic neurons of the basal ganglia, specifically the substantia nigra.^{26,86} In some circumstances, the toxicity is

transient and the mechanism inadequately understood.

Some xenobiotics such as carbon monoxide and heroin produce tissue hypoxia and ischemia in the basal ganglia that occasionally results in xenobiotic-induced Parkinson syndrome.

Other xenobiotics such as MPTP, carbon disulfide, manganese, and the endogenous neurotoxin copper in patients with Wilson disease produce predictable mitochondrial impairment of the basal ganglia neurons. Viscose rayon workers exposed to carbon disulfide may present with a Parkinson syndrome refractory to L-dopa administration^{43,44} (see Enzyme and Transporter Exploitation earlier).

Manganese is a critical substrate for production and metabolism of several neurotransmitters including glutamate. Excessive manganese interferes with normal uptake of glutamate and is critical to the function of superoxide dismutase and glutamine synthetase.^{30,35} In patients with liver failure who accumulate manganese from occupational exposure, reversal or treatment of liver disease may result in resolution of parkinsonism.^{36,79}

A recent review of patients who intravenously injected the illicit methcathinone described a Parkinson syndrome thought to be secondary to contamination with manganese from a precursor, potassium permanganate, which is used in methcathinone production. Unlike patients with idiopathic parkinsonism, these patients did not suffer from a resting tremor, and they had a specific gait abnormality in which they walked on the balls of their feet.⁸⁴ Like those with occupational manganese exposures and normal liver function, these patients did not respond to L-dopa (Table 24–3).

TABLE 24–3. Xenobiotics Commonly Inducing Parkinsonism

Reversible ^a	Irreversible
Amlodipine	Carbon disulfide
Antipsychotics	Carbon monoxide
Cyclosporine	Copper
Calcium channel blockers	Cyanide
Chemotherapeutics	Heroin
Dopaminergic agonists (withdrawal)	Manganese
Kava kava	MPTP
Progesterone	
Valproate	
Trazodone	

^aMay improve with removal of xenobiotic, sometimes requiring persistent administration of dopaminergic therapy.

MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Tremors. Tremors may be observed with adrenergic excess, with specific xenobiotics such as lithium, or as a result of sedative–hypnotic withdrawal. These are well reviewed elsewhere.⁶²

The Neuromuscular Junction. Flaccid paralysis usually occurs as a result of impaired transmission at the NMJ^{14,15,80} or from xenobiotics causing demyelination.⁵⁵ Mechanisms of NMJ transmission impairment include impeded propagation of the action potential on the terminal neuron, impaired release of acetylcholine, depression of motor end-plate potential with failure of depolarization, and impedance of myofibril excitation^{55,80} (Chap. 69).

Rarely xenobiotics can enhance transmission at the NMJ. Latrotoxin, the toxic compound in the black widow spider (*Latrodectus* spp) venom causes enhanced release of acetylcholine at the NMJ with severe, painful muscle contractions. Some types of scorpion venom act similarly (Chap. 118).

NEUROPATHIES AND MYOPATHIES

Cranial Nerves

Xenobiotics are a relatively rare cause of cranial nerve impairment. Some neuropathies are a result of direct delivery of the xenobiotic to the affected cranial nerve. For example, some patients may have optic nerve impairment from intraorbital installation of silicone oil⁶ or inadvertent deep space injection of a local anesthetic during dental anesthesia with a resultant abducens palsy.⁶¹ In some cases, a xenobiotic, methanol is converted into a toxic substance such as formic acid in the retina.

The neuromuscular junction of the cranial nerves is sensitive to disruptions in neurotransmission. When xenobiotics affect the oculomotor nerves (cranial nerves (CN) III, IV, VI), patients may describe diplopia or have gaze palsies on

examination. Botulinum toxin, diethylene glycol toxicity, elapid snake venom, and the cranial neuropathy associated with the organic phosphorus insecticide-induced intermediate syndrome are some examples.

Absence of critical substrates such as glucose or thiamine can result in ophthalmoplegia. In most cases, however, the mechanisms underlying the cranial neuropathy are poorly understood, such as is the case with antineoplastics. Similarly, some patients who survive ethylene glycol poisoning experience transient ophthalmoplegia days after the initial exposure^{56,83} (Table 24-4 and Chap. 25).

TABLE 24-4. Cranial Neuropathies

Cranial Nerve	Sign	Symptom	Xenobiotic
I		Failure to detect odor	Hydrogen sulfide; olfactory fatigue
II	Pupil unresponsive to light	Blindness	Amiodarone, ammonia, cisplatin, cloquinal, deferioxamine, DEG, dimethyl mercury, holocyclotoxin, interferon α , methadone, methotrexate, methyl iodide, oxaliplatin, quinine, solvents
III	In paralysis: ptosis, pupil unresponsive to light In excess: miosis	Photophobia Dim vision Muscarnic cholinergics	Amiodarone, antimuscarinics, botulinum toxin, DEG, holocyclotoxin, hypoglycemics, interferon α , methyl iodide, thallium, venoms (Eupidae, scorpion)
IV	Paralysis of the superior oblique muscle of eye with weakness of downward gaze, slight upward gaze of affected eye	Vertical and torsional diplopia that worsens on adduction and may improve with tilt of head	Barbiturates, botulinum toxin, DEG, holocyclotoxin, thallium, venoms
V	Diminished facial sensation, weakness in chewing and swallowing Excessive contraction: trismus	Paresthesia face, weakness in chewing Difficulty opening mouth/jaw	Botulinum toxin, ethylene glycol, holocyclotoxin, oxaliplatin, vincristine Tetanus toxin and strychnine ^b
VI	Failure to abduct eye on lateral gaze	Diplopia	Botulinum toxin, DEG, holocyclotoxin, intrathecal water-soluble contrast agents, lithium, local anesthetics, MDMA, nitroglycerin, ornithine-ketoacid transaminase, oxaliplatin, thallium, thiamine deficiency, venoms (elapid), vitamin A
VII ^a	Weakness of facial muscles, impaired expression	Facial droop, impaired taste	Botulinum toxin, DEG, ethylene glycol, holocyclotoxin
VIII ^a	Impaired hearing on auditory testing, nystagmus	Alterations in hearing, potential alterations in balance	Cisplatin, DEG, ethylene glycol, oxalosis, quinine, salicylates, solvents
IX	Impaired gag reflex	Impaired taste	Botulinum toxin, cholinergic compounds, ethylene glycol, stibarsite ^c
X ^d	Decreased gag reflex when paralyzed May be enhanced with cholinergic or impaired with anticholinergic; autonomic instability, altered bowel sounds	Choking, change in voice	Botulinum toxin, cholinergic compounds, ethylene glycol, stibarsite ^c
XI	Weakness shoulder shrug	Weakness neck/shoulders	Botulinum toxin, cholinergic compounds
XII	Impaired speech, tongue deviation	Dysarthria	Botulinum toxin, cholinergic compounds

^aSee also Chap. 26. ^bTetanus causes indirect effects on muscular muscles; see section on xenobiotic-induced seizures in Chap. 112. ^cWeakness of cranial nerves IX–XII is often referred to as bulbar palsy and can be seen in the intermediate syndrome after acute organic phosphorus compound poisoning. This syndrome is often accompanied by paralysis of extraocular muscles (Chap. 113). ^dSee Chap. 3.

DEG = diethylene glycol; MDMA = methylenedioxymethamphetamine.

Peripheral Nerves

Complaints of pain, paresthesias, numbness, or weakness of extremities are clinically termed neuropathies. The mechanisms of evolution are variable. Common to most xenobiotic-induced neuropathies is early symmetrical involvement of the lower extremities. This may be due in part to the patient's rapid recognition of impairment during an attempt to ambulate. Additionally, the axons serving the lower extremities are longer. Maintenance and transportation of substrates is more energy dependent and sensitive to xenobiotic-induced disruptions.

In some cases, the anatomic structure of the nerve is maintained, but the xenobiotic affects neurotransmission. This may be due to direct impairment of specific enzymes at the NMJ, such as cholinesterase inhibitors.²⁷ Tri-ortho-cresyl phosphate (TOCP) is an inhibitor of neuropathic target esterase. Contamination of food and the beverage Ginger Jake with TOCP resulted in irreversible lower extremity paralysis in several epidemic exposures.^{70,88} Indirectly, the extracellular environment may be altered as in the case of hypermagnesemia, or hypokalemia which can be induced by multiple xenobiotics ([Chap. 19](#)). Ciguatoxin, a sodium channel opener, affects neurotransmission, causing paresthesias and the unusual symptom of temperature reversal in which the perception of temperature is opposite to the stimulus.

Xenobiotics such as amiodarone and tacrolimus induce peripheral demyelination. Patients present with weakness and flaccidity. Nitrous oxide impairs the production of S-adenosyl methionine essential to the production of myelin and is additive to the nitrous oxide disruptions of vitamin B₁₂, which further impair axonal function.⁸⁹

Other xenobiotics affect the structure or intracellular function of the peripheral nerves. Those that induce death of the cell body are termed neuronopathies, and they may be clinically indistinguishable from those that affect the axon, or axonopathies.

Peripheral nerve cell death is usually linked to injury at the spinal cord as was described above by the doxorubicin injection of the peripheral nerves.⁵⁰ Pyridoxine overdose is another cause of neuronopathy. However, neuronopathies are an unusual mechanism of peripheral nerve toxicity.

Unlike neuronopathies, axonopathies are potentially reversible and are the most common mechanism of xenobiotic-induced peripheral neuropathy. Xenobiotic-induced axonal injuries to the peripheral nerves are usually diffuse and bilateral, with preservation of the proximal cell body. These often target the cytoskeleton and impair the capacity for the microtubule system to deliver functional substrates.^{21,40} Patients with occupational exposure to 2,5-hexanedione, a diketone metabolite of n-hexane present in certain glues, suffer from a sensorimotor axonopathy due to cross-linking of neurofilaments and impaired substrate transport.⁶⁷ Progressive neuropathy may occur long after the initial exposure. Vincristine similarly affects axonal transport. Acrylamide impairs fast anterograde and retrograde transport in animal models, suggesting effects on both kinesin and dynein. Nucleoside reverse transcriptase inhibitors cause peripheral neuropathy by decreasing the production of mitochondrial DNA.

Myopathies

Some patients experience local muscle damage as a result of direct injury from extravasation of tissue toxic substances or enzymatic degradation associated with crotalid snake envenomations.

Most xenobiotic-induced muscle injuries or myopathies are more diffuse.^{39,75,82,87} 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG Co-A) reductase inhibitors can cause myalgias, cramping, myositis, or rhabdomyolysis. The incidence appears to be higher in patients taking other medications that share the same liver metabolic enzymes. The mechanism underlying the myopathy may be related to impaired cholesterol synthesis in myocytes or diminished production of regulatory proteins such as ubiquinone and GTP-binding proteins required for mitochondrial function.

Another myopathy that presents predominantly with weakness is the acute quadriplegic myopathy of intensive care patients. This syndrome was originally described in ventilated patients with asthma who received glucocorticoids and nondepolarizing neuromuscular blockers, but is also reported in other critically ill patients⁸ ([Chap. 69](#)). The mechanisms underlying quadriplegic myopathy, eosinophilia myalgia syndrome, and toxic oil syndrome are poorly described. Xenobiotics associated with muscle injury can be found in [Table 24–5](#).

TABLE 24–5. Xenobiotics Associated with Muscle Toxicity

ε-Aminocaproic acid
Amiodarone
Chloroquine
Cimetidine
Clofibrate
Clostridium toxins
Cocaine
Colchine

Cyclosporine
Doxylamine
Ethanol
Ethchlorvynol
Glucocorticoids
Heroin
HMG-CoA reductase inhibitors
Hydroxychloroquine
Loxosceles spp venom
Niacin
Organic phosphorous compounds
D-Penicillamine
Phencyclidine
Procainamide
Propylthiouracil
Rifampin
Snake venoms
Succinylcholine
Sulfonamides
Syrup of ipecac
Toxic oil syndrome
Tricholoma equestre (mushroom)
L-Tryptophan
Vincristine
Zidovudine

SUMMARY

- With improved understanding of these neurotoxic principles, therapeutic medications can be better delivered to the CNS while limiting the entry of potentially toxic xenobiotics.
- Toxicological models for the investigation of neurodegenerative disorders can be further developed as can new and creative therapies for mood disorders, hepatic encephalopathy, and injuries from infections, trauma, and ischemia.
- Elucidation of neurotoxicologic principles shows promise for the treatment of many nervous system disorders.
- The chemical properties of the xenobiotic and the characteristics of the patient exposed are critical to the clinical expression of neurotoxicity.

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25 OPHTHALMIC PRINCIPLES

Adhi Sharma

While it is arguable that the eyes are the mirror to the soul, it is certain that the eyes can reveal a great deal of information with regard to toxicology. In addition to exhibiting findings of systemic toxicity, they are also subject to the direct effects of xenobiotics and can serve as a portal of entry for systemic absorption. An understanding of ophthalmic principles will allow the clinician to make timely and more accurate diagnoses that can be sight-saving or lifesaving and is essential to efficient, organized patient care.

OPHTHALMIC EXAMINATION

As a matter of convention, the routine eye examination is performed in the following sequence: visual acuity, pupillary response, extraocular muscle function, funduscopy, and, when indicated, a slit-lamp examination. Examination of the pupillary size and response to light can help determine the presence of a toxic syndrome. For example, opioids and cholinergics may produce miosis, whereas anticholinergics and sympathomimetics may produce mydriasis. Assessment of the extraocular muscles can reveal xenobiotic-induced nystagmus or cranial nerve abnormalities. Funduscopy can reveal pink discs characteristic of poisoning by methanol or carbon monoxide. The slit-lamp examination allows for evaluation of toxic exposure to the lids, lacrimal systems, conjunctiva, sclera, cornea, and anterior chamber. However, before considering specific xenobiotic exposures in detail, it is important to review the anatomy and physiology of the visual pathways and how alteration of the normal physiology and anatomy correlate with clinical signs and symptoms.

OCULAR ANATOMY AND PHYSIOLOGY

The eye is a roughly spherical structure referred to as a globe. The globe is divided into anterior and posterior structures ([Fig. 25–1](#)). The most anterior structures are the cornea, conjunctiva, and sclera. Posterior to the cornea are the iris, the lens, and the ciliary body. The space between the cornea and the iris is the anterior chamber, and the space between the iris and the retina is the posterior chamber. The anterior chamber contains aqueous humor, which is produced by the ciliary processes; this fluid nourishes the cornea, iris, and lens. The iris, the ciliary processes, and the choroid compose the uvea. The posterior chamber is filled with a transparent gelatinous mass termed the vitreous humor. The vitreous humor is an important body fluid in forensic toxicology as it is less susceptible to postmortem redistribution ([Chaps. 7 and 34](#)). The fundus is the most posterior structure and includes the retina, retinal vessels, and the head of the optic nerve or disc.

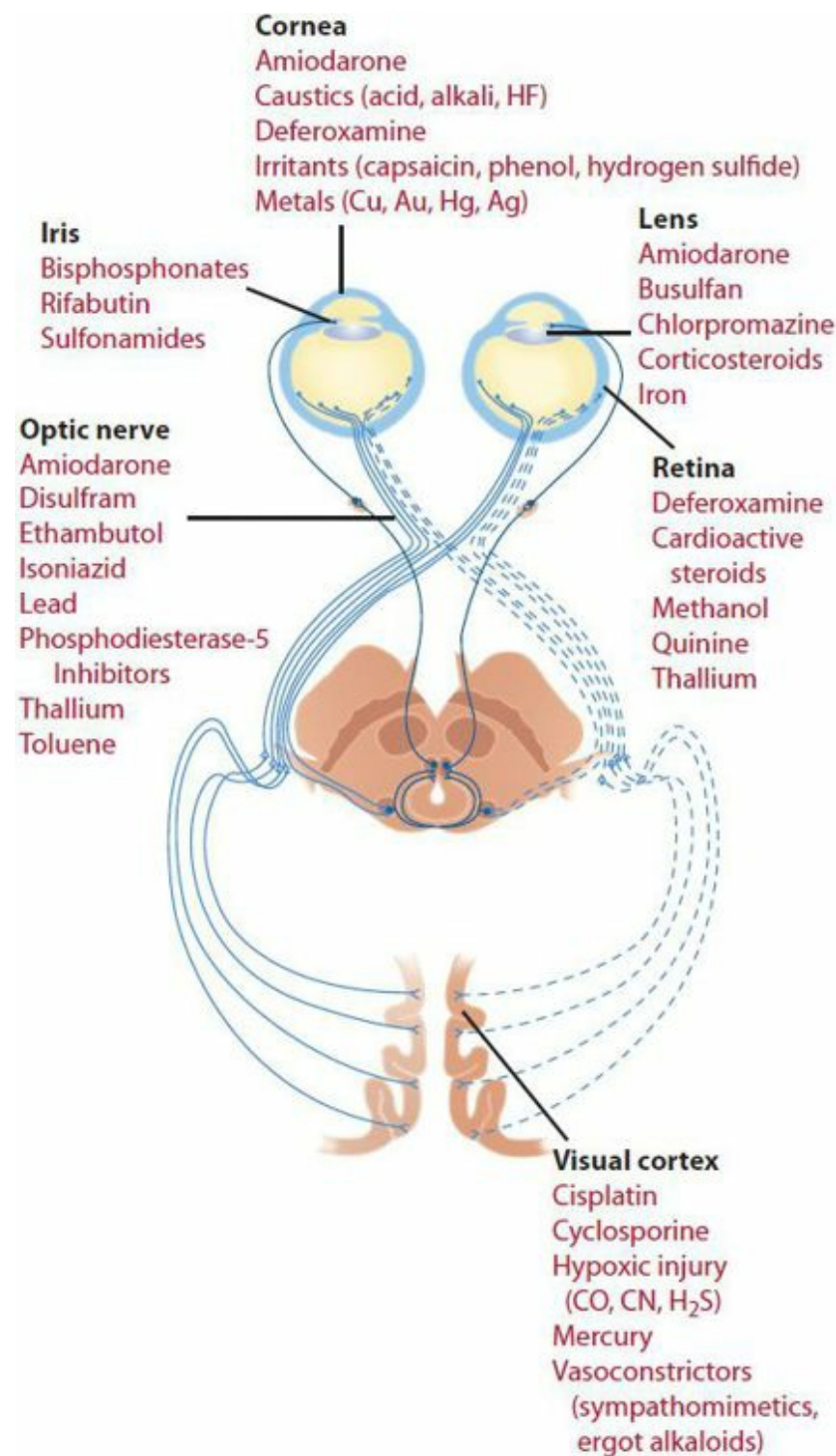


FIGURE 25–1. The major xenobiotics that cause ophthalmic toxicity and their areas of ophthalmic injury.

Visual Acuity and Color Perception

Normal vision is dependent on light transmission through the globe reaching intact posterior neural elements. As such, appropriate light transmission requires a clear cornea, clear aqueous humor, proper pupil size, an unclouded lens, and clear vitreous. The posterior neural elements include the retina, optic nerve, and the optic cortex; in turn, all of these structures require intact blood circulation for proper function. Decreased acuity can result from abnormalities anywhere in the visual system that affect either light transmission or the neural elements.^{4,12,21} Corneal injury or edema may result in blurring of vision, characteristically described as “halos” around lights. Toxicologic causes of corneal abnormalities include direct exposure to chemicals, failure of corneal protective reflexes because of local anesthetic effects or a profoundly decreased level of consciousness, and incomplete eyelid closure during coma. Mydriasis (Table 25–1) may interfere with the pupillary constriction necessary for accommodation, thereby resulting in decreased acuity for near objects. Lens clouding or cataract formation causes blurred vision and decreased light perception, as does blood (hyphema), pus (hypopyon), or other deposits in the aqueous humor or vitreous humor (vitreous hemorrhage). Xenobiotic-induced lens abnormalities caused by chronic exposures are well described (Table 25–2)^{17,21,27} but are unimportant in the evaluation of an acute toxicologic emergency. Even if light reaches the retina without distortion, abnormal reception or transmission can result from ischemia or injury to any neural element from the retina to the optic cortex. Direct, acute, visual neurotoxic injury is rare and is caused almost exclusively by methanol or quinine. Indirect injury following xenobiotic-induced central nervous system (CNS) ischemia or hypoxia is far more common. Alterations in color perception generally result from abnormalities

in retinal or optic nerve function. Color-vision abnormalities are attributed to hundreds of xenobiotics, but unlike those caused by chronic xenobiotic exposure such abnormalities are rare and inconsistent features of acute toxicity.^{16,21}

TABLE 25–1. Ophthalmic Findings Caused by Acute Xenobiotic Exposures

Disconjugate gaze

Botulism

Elapid envenomation

Neuromuscular blockers

Paralytic shellfish poisoning

Secondary to decreased level of consciousness (many causes)

Tetrodotoxin

Thiamine deficiency

Funduscopy abnormalities

Carbon monoxide (red)

Cocaine (vasoconstriction)

Cyanide (retinal vein arterialization)

Ergot alkaloids (vasoconstriction; disc pallor)

Intravenous drug use (attenuation or loss of small vessels due to emboli)

Methanol (disc and retinal pallor or hyperemia)

Methemoglobin (cyanosis)

Miosis

Cholinesterase inhibitors (carbamates, organic phosphorus compounds)

Coma from sedative–hypnotics (barbiturates, benzodiazepines, ethanol)

Decreased sympathetic tone (clonidine, opioids, valproic acid)

Increased cholinergic tone (pilocarpine, nicotine)

Mydriasis

Decreased cholinergic tone (antihistamines, atropine, cyclic antidepressants)

Nicotine

Increased sympathetic tone (cocaine, sedative-hypnotic withdrawal, lysergic acid diethylamide, monoamine oxidase inhibitors)

Nystagmus

Carbamazepine

Dextromethorphan

Ethanol

Ketamine and methoxetamine

Lithium

Monoamine oxidase inhibitors (oscillopsia or ping-pong nystagmus)

Phencyclidine (usually rotary nystagmus)

Phenytoin

Sedative–hypnotics

Scorpion venom

Thiamine deficiency

Opsoclonus

Diphenhydramine

Monoamine oxidase inhibitors

Scorpion venom

Papilledema

Amiodarone

Lead

Phenytoin

Vitamin A

TABLE 25–2. Examples of Ocular Abnormalities Caused by Chronic Systemic Xenobiotic Exposures^a

Alteration of color vision

Alkylamines (dimethylamine) (glauropsia)

Ethyl chloride

Digoxin

Ethambutol

Sildenafil citrate (cyanopsia)

Styrene (color blindness)

Cataracts

Busulfan^c

Corticosteroids^b

Deferoxamine

Dinitrophenol (internal use)^d

Trinitrotoluene^d

Corneal deposits

Amiodarone^b

Chloroquine

Chlorpromazine

Copper^d

Gold

Mercury^d

Retinoids

Silver (argyria)^d

Vitamin D

Corneal/Conjunctival inflammation

Cytosine arabinoside (Ara-C)

Isotretinoin^b

Mercury (acrodynia)

Practolol^c

Cortical blindness

Cisplatin

Cyclosporine

Glycine

Interleukin^c

Methylmercury compounds^d

Tacrolimus

Lens deposits

Amiodarone^b

Chlorpromazine

Copper^d

Iron

Mercury^d

Silver^d

Macular edema

Atorvastatin/Simvastatin

Sildenafil

Thiazolidinediones

Myopia^c

Acetazolamide

Diuretics (chlorthalidone, thiazides, spironolactone)

Retinoids

Sulfonamides

Topiramate

Retinal injury

Carbon disulfide^d

Carmustine^c

Chloramphenicol^c

Chloroquine

Cinchona alkaloids (quinine)

Deferoxamine^c

Ethambutol

Methanol

Thallium

Vigabatrin

Vincristine^c

Retrobulbar and optic neuropathy

Carbon disulfide^d

Chloramphenicol^d

Dinitrobenzene^d

Dinitrochlorobenzene^d

Dinitrotoluene^d

Disulfiram

Ethambutol^b

Ethyl chloride

Isoniazid^c

Lead^c

Thallium

Vincristine^c

Uveitis

Bisphosphonates

Pamidronate

Rifabutin

Sulfonamides

^aThis list includes only selected examples and is not intended to be comprehensive. ^bParticularly important example.

^cReported, but extremely rare from this exposure. ^dMostly of historical interest; associated with patterns of use that are no longer common.

Pupil Size and Reactivity

Generally, pupils are round and symmetric with an average diameter of 3 to 4 mm under typical light conditions. Physiologic anisocoria (unequal pupils) is a normal variant and is defined as a difference in pupil size of 1 mm or less. However, in the absence of a history of physiologic anisocoria, any asymmetry in pupil size should be considered an abnormal finding. Pupils react directly and consensually to light intensity by either constricting or dilating. Constriction is also a component of the near reflex (accommodation) that occurs when the eye focuses on near objects. The iris controls pupil size through a balance of cholinergic innervation of the sphincter (constrictor) muscle by cranial nerve III and sympathetic innervation of the radial (dilator) muscle.¹²

Pupillary dilation (mydriasis) can result from increased sympathetic stimulation of the radial muscle by endogenous catecholamines, or from xenobiotics such as cocaine, amphetamines, and other sympathomimetics as well as ophthalmic instillation of sympathomimetics such as phenylephrine. Mydriasis can also result from inhibition of muscarinic cholinergic-mediated innervation of the sphincter secondary to systemic or ophthalmic exposure to anticholinergics ([Chap. 49](#)). Because pupillary constriction in response to light is a major determinant of normal pupil size, blindness from ocular, retinal, or optic nerve disorders also leads to mydriasis as exemplified by methanol and quinine toxicity. As such, the reactivity of mydriatic pupils to light varies with the etiology of the mydriasis.²¹ Although often difficult to appreciate, constriction to light can usually be elicited after sympathomimetic exposures because constrictor function is preserved, whereas this is often not the case when mydriasis results from anticholinergic excess since constrictor function is potentially antagonized. Light reactivity is absent in cases of complete blindness but may be preserved if there is some remaining light perception.

Miosis can result from increased cholinergic stimulation such as opioids, pilocarpine, and cholinesterase inhibitors, such as organic phosphorus compounds, or inhibition of sympathetic dilation caused by clonidine. Miosis was the most common finding in victims of the Tokyo subway sarin attack of 1995 and was used to distinguish between mild and moderate exposure.³³

There are conflicting reports regarding the pupillary reactions to many xenobiotics. Depending on the stage and severity of toxicity, the presence of coingestants or coexistent hypoxemia, and numerous other factors, many individual xenobiotics (eg, clonidine, nicotine, phencyclidine, and barbiturates) are reported to cause either mydriasis, miosis, or hippus, which is defined as a fluctuation between miosis and mydriasis.^{21,28} For some xenobiotics, the pupillary examination provides consistent information ([Table 25–1](#)), but many factors are involved and the significance of the pupil size and reactivity must always be considered in the context of the remainder of the patient evaluation.

Extraocular Movement, Diplopia, and Nystagmus

Maintenance of normal eye position and movement requires a coordinated function of a complex circuit involving bilateral frontal and occipital cortices, multiple brainstem nuclei, cranial nerves, and extraocular muscles.^{2,12} Because of the many elements necessary for normal function, abnormalities of eye movement can result from several causes and are extremely common.²¹ Probably the most common abnormality is reversible nystagmus or rhythmic oscillations of the globes ([Table 25–1](#)). Nystagmus is divided into two types: jerk nystagmus, which has a slow phase and a fast phase, and pendular nystagmus which has rhythmic oscillation. Either type can be torsional (rotary) or in a horizontal or vertical direction. Xenobiotic-induced nystagmus can take many forms but is most commonly jerk nystagmus, as opposed to pendular. The nystagmus may be evident at rest but is accentuated by visual pursuit and extreme lateral gaze. Although nystagmus with extreme lateral gaze is a normal finding, it extinguishes within 2 to 5 beats; if nystagmus persists, it is evidence of

underlying pathology. Vertical nystagmus in other settings is usually associated with a structural lesion of the CNS. However, xenobiotic-induced vertical nystagmus occurs with phencyclidine, ketamine, dextromethorphan, or phenytoin toxicity. Loss of conjugate gaze commonly results from CNS depression of any etiology, typically after sedative-hypnotic or ethanol poisoning. Except after extremely rare exposures to neurotoxins (Table 25–1), diplopia without a decreased level of consciousness should not be attributed to an acute toxicologic etiology. In addition to the transient effects of some xenobiotics, thallium, carbon disulfide, and carbon monoxide may cause sustained gaze disorders as a consequence of residual cranial nerve and CNS injury.²¹ Nystagmus and ophthalmoplegia caused by thiamine deficiency (Wernicke encephalopathy) usually improves after therapy, but the nystagmus may not completely resolve.⁴³

DIRECT OCULAR TOXINS

Caustics

The initial approach to all patients with ocular caustic exposures should be immediate decontamination by irrigating with copious amounts of fluids.^{9,44} Water, 0.9% sodium chloride solution, lactated Ringer solution, and balanced salt solution (BSS) are all appropriate choices. In theory, BSS is ideal, because it is both isotonic and buffered to physiologic pH. Lactated Ringer solution (pH 6–7.5) and 0.9% sodium chloride solution (pH 4.5–7) are also isotonic and therefore theoretically preferable to water.²² The use of an ocular anesthetic is usually required to perform irrigation properly. Irrigation is intended to accomplish at least four objectives: immediate dilution of the offending xenobiotic; removal of the xenobiotic; removal of any foreign body; and, in some cases, normalization of anterior chamber pH. Because delays of even seconds can dramatically affect outcome,²¹ there is no justification for waiting for any specific solution if water is the first available therapy. Irrigation must include the external and internal palpebral surfaces, as well as the cornea and bulbar conjunctiva and its recesses. Effective irrigation includes lid retraction and eversion or use of a scleral shell or other irrigating device. After irrigation, visual acuity testing, inspection of the eye, and slit-lamp examination should be performed. The immediacy with which an ophthalmologic consultation must be obtained will depend on the degree of injury.

Sulfur Mustard

This alkylating agent reacts with ocular tissues resulting in early and late toxic effects. Of note, there is a latency of 30 minutes to 8 hours, during which time victims are asymptomatic. Initial effects include pain, foreign body sensation (grittiness), lacrimation, photophobia, blepharospasm, corneal ulceration, and blindness.²⁴ Generally, injury is limited to the anterior chamber. More than 90% of exposed victims will experience late complications associated with conjunctival sensitivity to irritants with resultant recurrent blepharoconjunctivitis. Fewer than 1% of severely toxic victims will suffer delayed keratopathy, resulting in thinning, neovascularization, and epithelial defects of the cornea.²⁴

Management is directed at removal from the exposure and aggressive decontamination of the skin and eyes. Any of the irrigation solutions mentioned above will suffice. The goal is to provide irrigation as soon as possible; to this end, even tap water is an acceptable solution. Animal studies suggest that topical antiinflammatories are helpful; as such, a short course of ocular steroids may be beneficial.⁵ Steroid treatment should only be rendered in consultation with an ophthalmologist. Late complications are best managed by an ophthalmologist.

Exposure-Specific Irrigating Solutions

Despite theoretical concern, there is probably no toxic exposure for which standard aqueous solutions are contraindicated. Of greatest concern are xenobiotics such as white or yellow phosphorus, metallic sodium, metallic potassium, and calcium oxide (cement) that may react violently in the presence of water, leading to heat or mechanical injury, or resulting in the generation of sodium hydroxide, potassium hydroxide, and calcium hydroxide.²¹ Although not well studied, irrigation with large amounts of water probably dissipates the heat of the initial hydration reaction with conjunctival moisture more than it initiates a thermochemical reaction. In addition to removing the offending material, irrigation serves to dilute and remove the alkaline by-products formed by reaction with conjunctival water. Table 25–3 summarizes irrigation solutions for various xenobiotics.

TABLE 25–3. Irrigation Solutions for Various Xenobiotics

<i>Xenobiotic</i>	<i>Irrigation Solution</i>	<i>Duration of Irrigation^a</i>
Caustics (acids/alkalis)	NS, LR, BSS	1–2 hours
Hydrofluoric acid	NS	1–2 hours ^a
Phenol	NS, LR, BSS	15–20 minutes
Cyanoacrylate adhesives	Typically none needed	N/A
Capsaicin (pepper spray)	NS, LR, BSS	15–20 minutes

^aDuration of irrigation can also be determined by other endpoints, including symptoms or conjunctival pH. BSS = balanced saline solution (pH ~7.4); LR = lactated Ringer solution (pH 6.0–7.5); NS = 0.9% sodium chloride (pH ~5.5).

The use of special irrigating solutions for more uncommon exposures, including hydrofluoric acid and phenols, is also debated. Animal models of alkaline injury suggest irrigation with amphoteric or buffered solutions rapidly restores anterior chamber pH.³⁸ Some authors have gone further to conclude that 0.9% sodium chloride solution should be avoided as an irrigation solution.³⁵ Unfortunately, these were all ex vivo models, and the majority of the published human data have been case reports. Therefore, at this time these solutions are probably best suited for first aid treatment at worksite eyewash stations and are neither practical nor proven in the emergency department setting for prolonged irrigation.

Hydrofluoric Acid. For hydrofluoric acid exposures ([Chap. 107](#)), experimental irrigation with calcium salt solutions was too irritating to the eye, but isotonic magnesium chloride solutions appear effective and not irritating.^{29,30} From a practical standpoint, however, 0.9% sodium chloride solution remains readily available, well studied, and effective. In one animal model, it was suggested that irrigation beyond the initial liter yielded worse outcomes; however, this has not been demonstrated in humans.²⁹

Phenol. For dermal exposure, topical low-molecular-weight polyethylene glycol (PEG) solutions are effective for treatment of experimental skin exposure; for eyes, copious water irrigation appears to be as effective as PEG.⁷ There is, however, a report of superior efficacy of PEG-400 over water in treatment of actual phenol eye burns.²⁶ Although PEG-400 may be readily available at worksites where phenols are used, it is not a realistic option in the emergency department, and there should be no hesitation to use water, 0.9% sodium chloride solution, lactated Ringer solution, or BSS as lavage solutions.

Cyanoacrylate Adhesives. Ocular exposures to cyanoacrylate adhesives such as Dermabond and Krazy Glue occasionally result in rapid adherence between the upper and lower eyelids that may persist for days. Such occurrences may be associated with corneal abrasions¹³ but are otherwise relatively harmless. In fact, cyanoacrylate has been safely used for decades to treat corneal perforations.⁴⁶ Solvents such as acetone or ethanol, which are often effective treatment for dermal-to-dermal adhesions caused by cyanoacrylates, should never be used in or around the eyes because they can result in a severe keratitis. Expectant management is the safest approach, because spontaneous rejection of the glue will occur over time. Application of gauze pads coated with antibiotic ophthalmic ointment may speed recovery.²⁵ A thorough eye examination should be performed once the eyelids can be fully opened.

Other xenobiotic-specific treatments have been tried experimentally or clinically,²² but none should be considered prior to, or instead of copious irrigation. Most are not advocated, and consideration of such therapies should be vanishingly rare.

Duration of Irrigation

To accomplish the desired goals of irrigation, the appropriate duration varies with the exposure. Most solvents, for example, do not penetrate deeper than the superficial cornea, and brief (10–20 minutes) irrigation is generally sufficient.²¹ After exposure to acids or alkalis, normalization of the conjunctival pH is often suggested as a useful end point. Testing of pH should be done in every case of acid or alkali exposure, but the limitations of testing must be understood. When measured by sensitive experimental methods, normal pH of the conjunctival surface is 6.5 to 7.6.¹ This is highly method dependent, however, and normal values in the literature range from 5.2 to 8.6.¹⁰ When measured by touching pH-sensitive paper to the moist surface of the conjunctival cul-de-sac, normal pH is most often near 8.³ Therefore, after irrigation following alkali burns, pH should not be expected to reach 7 and is more likely to stabilize near 8.²¹ In this setting, lower pH values may indicate the pH of the irrigant rather than of the ocular surface. Waiting for an interval of several minutes between irrigation and pH testing allows washout of any residual irrigant.¹¹ Choice of testing paper is important, because some are intended for use at extremes of pH and lack sensitivity in the clinically useful range.

Despite these limitations, a logical role for pH assessment can be described. Probably a minimum of 500 to 1000 mL of irrigant should be used for each affected eye before any assessment of pH, and after 7 to 10 minutes, the pH of the lower

fornix conjunctiva should be checked. Thereafter, cycles of 10 to 15 minutes of irrigation followed by rechecks should be continued until the pH is 7.5 to 8. This is certainly adequate for exposures to weak acids, which do not penetrate well, and for alkaline exposures where the pH is less than 12.

For strong or concentrated acid or alkali exposures normal surface pH is not an adequate end point. After these burns, irrigation should be continued for at least 1 to 2 hours, regardless of surface pH, in an attempt to correct anterior chamber pH.^{21,36,44} In addition, immediate ophthalmologic consultation is mandatory. Following this lengthy irrigation, it is important to verify that conjunctival pH has normalized. If not, irrigation must be continued, sometimes for 24 to 48 hours.

Others

Most solvents cause immediate pain and superficial injury because of dissolution of corneal epithelial lipid membranes but do not penetrate or react significantly with deeper tissue.²¹ The epithelial defect may be large or complete, but the limited depth of injury usually allows rapid regeneration of normal epithelium. Detergents and surfactants cause variable injury, ranging from minor irritation from soaps to extensive injury from cationic detergents such as concentrated benzalkonium chloride.²¹ Ocular exposure to A-200 Pyrinate pediculicide shampoo causes typical detergent–surfactant injury, leading to extensive loss of corneal epithelium but with normal underlying stroma; therefore, complete healing within days. Lacrimators (tear gases), such as chloroacetophenone, stimulate corneal nerve endings and cause pain, burning, and tearing, but produce no structural injury at low concentrations. At high concentrations, these xenobiotics can produce significant corneal injury.

Pepper spray, often used for self-protection by civilians or to defuse a potentially violent event by law enforcement contains the active ingredient oleoresin capsicum (OC). OC results in rapid depolarization of nociceptors containing substance P, resulting in immediate pain, blepharospasm, tearing, and blurred vision. In general, ocular injury is uncommon, although corneal erosions can occur. The solvent used for the spray can be more injurious to the eye than the OC itself. Although most sprays use a water-based or oil-based solvent, some use alcohol, which can result in significant corneal damage.⁴⁷ Management of pepper spray exposure consists of rapid irrigation and pain control. Corneal erosions can be treated with artificial tears but corneal abrasions should be treated with topical antistaphylococcal antibiotics. Specific information on thousands of other xenobiotics is readily available if needed.²¹

General Measures

There is a wide array of options for adjunctive therapy of chemical burns of the eye. In all cases in which serious injury is evident, the treatment plan must include consultation with an ophthalmologist. Generally, patients with corneal injury should be treated with an ocular topical antibiotic providing antistaphylococcal and antipseudomonal coverage. Cycloplegics not only reduce pain from ciliary spasm, but also decrease the likelihood of posterior synechiae (scar) formation. Topical nonsteroidal antiinflammatory drugs and systemic analgesics also improve patient comfort. It is never appropriate to dispense topical ophthalmic anesthetics, because repeated use leads to further corneal disruption both by direct chemical effects and by eliminating corneal protective reflex sensation.

DISPOSITION

Disposition of patients with chemical burns of the cornea can be challenging. Patients with extensive burns to other parts of the body should be evaluated for transfer to a burn center. Grading the degree of injury in patients with isolated ocular injury can guide disposition. The most commonly used grading system is the Roper-Hall modification of the Ballen classification system. Injury is graded on a four-tier scale. Patients with mild conjunctival injection with corneal epithelial loss and minimal corneal haziness are classified as grades 1 and 2 (mild to moderate). These patients can be safely discharged from the emergency department with ophthalmology follow-up within 24 to 48 hours. Patients with severe corneal haziness or opacification with significant limbal ischemia are classified as grades 3 or 4 (moderate to severe) and should receive immediate consultation with an ophthalmologist; transfer to a burn unit should be considered.

SYSTEMIC ABSORPTION AND TOXICITY FROM OCULAR EXPOSURES

Systemic absorption from ocular exposure has caused serious toxicity, morbidity, and even death.^{14,23} Although the patterns of toxicity are characteristic of the xenobiotics involved, recognition may be delayed as a result of a failure to appreciate the eye as a significant route of absorption. Although transcorneal diffusion of xenobiotics is limited, there is substantial nasal mucosal absorption after nasolacrimal drainage, and absorption via conjunctival capillaries and lymphatics, which is markedly increased during conjunctival inflammation. Unlike the gastrointestinal route of absorption, there is no significant first-pass hepatic removal after ocular absorption; consequently, bioavailability is much greater.^{20,23,39} If nasolacrimal outflow is normal, up to 80% of instilled drug may be absorbed systemically.¹⁴ Unfortunately, by the time toxicity is apparent, there is no role for ocular decontamination to prevent further absorption. After instillation of eyedrops,

absorption is generally complete within 7 minutes.

Children appear to be at greatest risk, possibly because of the higher relative drug dose they experience when systemic absorption does occur.^{14,34,39} Diligent attempts to comply with prescribed dosing in a struggling, crying infant may also result in excessive dosing. As eyedrop size (40–50 μL) exceeds ocular cul-de-sac capacity (30 μL), overflow often occurs and is assumed to represent a failed instillation, which leads to unnecessary reinstallation. Also, as doses of ocular medications are typically not adjusted based on patient weight, the consequences of equivalent degrees of systemic absorption are much greater for an infant than for an adult. Toxicity from eyedrops is also a problem among the immunocompromised, probably because of the combination of greater use of potentially toxic ophthalmic medications and the presence of comorbid conditions.

Prevention of systemic toxicity from topical ophthalmic medications requires recognition of the risk, a careful history, use of the lowest effective concentration and dose, and patient education including proper administration instructions. To minimize inadvertent absorption, no more than one drop of any eyedrop solution should be instilled at one time in the superolateral corner of the eye while using gentle finger compression of the medial canthus to limit nasolacrimal drainage.^{14,23}

Mydriatics

Mydriatics are used almost exclusively to dilate the pupils prior to diagnostic evaluation of the eyes. This common practice is not generally considered to be potentially dangerous; however, the risk may be substantial if the precautions outlined are not considered. Anticholinergic poisoning (Chap. 49), is well described after ocular use of atropine, cyclopentolate, or scopolamine eyedrops, especially in infants.

The use of the α -adrenergic agonist phenylephrine eyedrops in a 10% solution may cause severe hypertension, subarachnoid hemorrhage, ventricular dysrhythmias, and myocardial infarction.¹⁷ Fortunately, these effects are rare if the 2.5% ocular phenylephrine is used. Mydriatics can also precipitate acute angle closure glaucoma in susceptible individuals.

Miotics and Other Antiglaucoma Drugs

Miosis can be induced by the cholinesterase inhibitor echothiophate (sometimes used to treat glaucoma or accommodative esotropia) which can also exacerbate asthma, parkinsonism, and cardiac disease, and prolong the metabolism of certain medications such as succinylcholine.²³ Miosis can also be produced by use of direct cholinergic agonists, such as pilocarpine. Although absorption is limited, nausea and abdominal cramps can occur at recommended doses. After excessive dosing, salivation, diaphoresis, bradycardia, and hypotension may occur.

β -Adrenergic antagonists, such as timolol, levobunolol, metipranolol, carteolol, and betaxolol, are used to lower intraocular pressure but may cause a variety of adverse effects, including bradycardia, hypotension, myocardial infarction, syncope, transient ischemic attacks, congestive heart failure, exacerbation of asthma, and respiratory arrest. Timolol can exacerbate weakness in patients with myasthenia gravis and is implicated in both causing and masking symptoms of hypoglycemia in diabetics.^{41,42} Nonspecific complaints of anorexia, anxiety, depression, fatigue, hallucinations, headache, and nausea are also described after use of timolol eye drops. Despite the cardioselectivity of betaxolol, respiratory effects occur.¹⁴

Dipivefrin, an esterified epinephrine derivative sometimes used to treat glaucoma, can cause systemic adrenergic effects, although much fewer than those caused by epinephrine. Ophthalmic formulations of highly selective α_2 -adrenergic agonists, brimonidine (Alphagan) and apraclonidine (Iopidine), were introduced to treat glaucoma.^{14,45} Apraclonidine is expected to have a lower potential for toxicity because of limited CNS penetration. Systemic absorption of brimonidine eye drops in a child has led to bradycardia, hypotension, and a decreased level of consciousness, similar to the central effects of other α_2 -adrenoceptor agonists (eg, clonidine),⁶ apparently mediated through both α_2 -adrenoceptors and imidazoline receptors⁸ (Chap. 63).

Antimicrobials

Life-threatening reactions to ophthalmic antimicrobials are unusual. Aplastic anemia has occurred after prolonged use of chloramphenicol eye preparations,¹⁵ and Stevens-Johnson syndrome was reported after short-term use of ophthalmic sulfacetamide in a patient with a history of allergy to sulfa drugs.²⁰

TOXICITY TO OCULAR STRUCTURES FROM NONOCULAR EXPOSURES

Ocular toxicity from systemic xenobiotics is almost always the result of chronic exposure, and the manifestations develop over a prolonged period of time. Thousands of xenobiotics are implicated, affecting every element of the visual system

from the cornea to the optic cortex. Thorough discussion of this topic is beyond the scope of this text, but [Table 25–2](#) lists examples of causative xenobiotics.^{17,21} Many topical and systemic medications are associated with inflammation of the eye, such as uveitis (inflammation of the iris, ciliary process, or choroid membrane).¹⁸ Unlike many other ocular abnormalities caused by xenobiotics, uveitis should prompt immediate ophthalmologic consultation. Because in many cases the etiology is related to commonly prescribed medications, adverse drug effects should always be considered when patients present with visual abnormalities or unusual ocular findings.

In the setting of emergency care, xenobiotic-induced disturbances of normal vision from systemic exposures take many forms. Impaired near-vision from mydriasis, and diplopia or nystagmus from interference with normal control of extraocular movements, are examples of common, usually harmless visual effects. Serious effects generally result from injury or dysfunction of the neural elements from the retina to the cortex. Such toxicity can be direct (neurotoxic) or indirect (hypoxia, ischemia). Many xenobiotics historically reported to cause acute visual loss directly are no longer available.²¹ Methanol and quinine are currently the most important xenobiotics that cause direct visual toxicity after acute oral poisoning. Many xenobiotics capable of causing vasospasm, hypotension, or embolization also cause acute visual loss ([Table 25–4](#)).⁴⁰ Blindness and other visual defects are described following recovery from severe toxicity with barbiturates and other sedative–hypnotics, opioids, carbon monoxide, and many others.²¹

TABLE 25–4. Xenobiotics Reported to Cause Visual Loss after Acute Exposures	
Direct Causes	Indirect Causes ^b
Caustics	Vasoactive xenobiotics
Methanol	Amphetamines
Quinine	Cocaine
Lead ^a	Ergot alkaloids
Mercuric chloride ^a	Hypotension (eg, calcium channel blockers)
	Cisplatin
	Combined endocrine xenobiotics (thyrotropin-releasing hormone with gonadotropin-releasing hormone and glucagon)
	Embolization of foreign material (intravenous injection)

^aDistinctly rare with poisoning. ^bDistinctly rare with use of these xenobiotics; visual loss often instantaneous, secondary to sudden hypotension, vascular spasm, or embolization.

OCULAR COMPLICATIONS OF DRUG ABUSE

In addition to the well-known ocular pupillary signs of opioid, cocaine, amphetamine, and phencyclidine toxicity, a number of complications may result from short-term or long-term use of these and other xenobiotics.³¹ Quinine amblyopia ([Chap. 59](#)) caused by intravenous use of quinine-containing heroin is one of many ocular complications caused by injection of contaminants. Talc contaminants have resulted in talc retinopathy, which was first described after prolonged intravenous use of adulterated methylphenidate¹⁹ but was also noted after intravenous use of heroin, methadone,³² codeine, meperidine, and pentazocine. Talc retinopathy develops only after extensive intravenous drug use. In one study of intravenous methadone abusers, only patients who had injected more than 9000 tablets developed this complication.³² Infectious complications, such as fungal (*Candida*, *Aspergillus*) or bacterial (*Staphylococcus* spp, *Bacillus cereus*) endophthalmitis, are well known as both direct effects of intravenous drug use and secondary complications of acquired immunodeficiency syndrome (AIDS). In addition to AIDS-related ophthalmic infections such as cytomegalovirus, cryptococcus, toxoplasmosis retinitis, and choroidal *Mycobacterium avium-intracellulare* complex (MAC), other disorders include retinal cotton-wool spots, conjunctival Kaposi sarcoma, and ocular motility disorders caused by infectious or neoplastic meningitis. Corneal defects are reported after smoking cocaine alkaloid (“crack eye”).³⁷ Cocaine that is either volatilized or inadvertently introduced by direct contact probably results in corneal anesthesia and loss of corneal protective reflex sensation. Minor trauma, such as eye rubbing, then leads to corneal epithelial defects. In addition, there appears to be an increased incidence of infectious keratitis and corneal ulceration in these patients. The ability of local anesthetics to interfere with corneal epithelial adhesion may also play a role.

SUMMARY

- Systemic and local toxicologic emergencies are manifest in the ophthalmic system.

- Although the obvious physical injuries are apparent to the clinician, the more subtle clues to toxicologic mechanisms that involve the ophthalmic and neurologic systems are made only by a meticulous examination of the eye.
- Direct ocular toxins should be washed out immediately without delays for determining visual acuity or locating toxin specific irrigation solutions.
- After initial management, patients with moderate-severe injury should be promptly referred to an ophthalmologist for further evaluation.

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26 OTOLARYNGOLOGIC PRINCIPLES

William K. Chiang

Many xenobiotics adversely affect the senses of olfaction, gustation, and cochlear-vestibular functions. These toxic effects are not life-threatening but may pose significant distress to patients. Health care providers are often not familiar with the pathophysiology of these special senses. Furthermore, because of the lack of standardized diagnostic techniques and normal parameters, such adverse effects may be overlooked and dismissed by health care providers, despite significant patient distress and dysfunction. This is particularly true for disorders of olfaction and gustation. This chapter reviews the anatomy and physiology of these senses, describes the effects of xenobiotics on these senses, and examines the significant diagnostic information these senses contribute to identifying the presence of xenobiotics. Understanding the effects of xenobiotics on these senses may allow for early detection, removal, appropriate referral, treatment, and prevention of future events. In occupational settings, understanding these principles may prevent permanent and life-threatening injuries.

OLFACTION

Anatomy and Physiology

Olfactory receptors are bipolar neurons located in the superior nasal turbinates and the adjacent septum. There are 10 to 20 million receptor cells per nasal chamber, and the receptor portion of the cell undergoes continuous renewal from the olfactory epithelium.^{114,118} Renewed olfactory receptors regenerate neural connections to the olfactory bulb. These olfactory receptor neurons are distinctive in their ability to regenerate.²⁴ The axons of these cells form small bundles that traverse the fenestrations of the cribriform plate of the ethmoid bone to the dura. Within the dura, these bundles form connections with the olfactory bulb from which neural projections then connect to the olfactory cortex. There are extensive interconnections to other parts of the brain, such as the hippocampus, thalamus, hypothalamus, and frontal lobe, suggesting effects on other biologic functions.¹¹⁴ Although primary odor detection is a function of the olfactory nerve (CN I), some irritant odors, such as ammonia and acetone, are transmitted through the trigeminal nerve (CN V) and its receptors.^{45,153}

The actual olfactory receptor sites are structurally similar to the taste receptors of the mouth and the photoreceptors of the retina. The receptor is a single polypeptide chain consisting of approximately 350 amino acids, which folds back and forth onto itself to traverse the cellular membrane seven times. The outer end of the polypeptide contains an amine group (N-terminal) and the cytosolic end contains a carboxyl group (C-terminal). The transmembranous portions determine the receptor shape and characteristics of the binding site. When a molecule binds to a specific receptor site, the resultant conformational change leads to the activation of the G protein system and calcium and/or sodium channel activation and neurotransmission.⁷⁹

Smelling is an extremely sensitive mechanism of detecting xenobiotics. Olfactory receptors can detect the presence of a few molecules of certain xenobiotics with a sensitivity that is superior to some of the most sophisticated laboratory detection instruments.⁷²

Clinical Use of Odor Recognition

The sense of smell can be extremely useful as a toxicologic warning system. Human olfaction is a variable trait.^{5,126,187} For example, 40% to 45% of people have specific anosmia (inability or loss of smell) for the bitter almond odor of cyanide.^{46,94,126} There are limited data on the inheritance characteristics or genetic basis of these specific forms of anosmia. While some studies suggest that the ability to detect the odor of cyanide is a sex-linked recessive trait,⁶² other studies yield conflicting results.^{5,19,96} Women have a greater ability to detect androsterone, which is prominent in human underarm secretion.⁷² Human olfaction usually can distinguish a mixture of no more than four xenobiotics¹⁰⁰; therefore, specific odors may be masked by other stimuli.

Olfactory fatigue is the process of olfactory adaptation following exposure to a stimulus for a variable period of time. This leads to a temporal diminution of the smell. Unfortunately, this adaptation may provide a false sense of security during continued exposure to a xenobiotic. For example, hydrogen sulfide, which inhibits cytochrome oxidase, is readily detectable as distinct and offensive at the very low concentration of 0.025 ppm. At the higher and potentially toxic

concentration of 50 ppm, the odor is less offensive, and recognition may disappear after 2 to 15 minutes of exposure.^{8,160} At even higher concentrations when toxicity is likely, the onset of olfactory fatigue is even more rapid. The combination of the rapid onset of olfactory fatigue and systemic toxicity at high concentrations of hydrogen sulfide exposure has contributed to numerous fatalities (Chap. 126).^{1,25,174}

In industrial settings, it is important to be aware of impaired olfactory function in any worker who may be exposed to chemical vapors or gases.^{77,166} Such workers are at increased risk for toxic injury. The National Institute for Occupational Safety and Health (NIOSH) requires that an individual using an air-purifying respirator be capable of detecting the odor of a xenobiotic at concentrations below those producing toxicity.^{6,166} Sensory perception at this concentration ensures that the individual can detect filter cartridge “breakthrough” or failure at a safe concentration.¹⁶⁶ The odor safety factor refers to the ratio of the time-weighted average (TWA) threshold limit value (TLV) to the odor threshold for a given xenobiotic. A xenobiotic with a high odor safety factor can be detected despite prolonged exposure.⁶ Nontoxic xenobiotics with a very high odor safety factor, such as ethyl mercaptan, can be added to xenobiotics that are odorless with lower safety factors so that olfactory detection is predictable. This enhanced sensory awareness is the basis for the addition of mercaptans to the odorless natural gases used in the home so as to limit the potential for unrecognized hazardous exposure.

The recognition of odors has traditionally been considered an important diagnostic skill in clinical medicine. Some diseases can be diagnosed accurately by recognizable associated odors of various affected parts of the body such as the breath, sweat, urine, and wounds: diabetic ketoacidosis as a characteristically fruity odor; diphtheria as sweet; scurvy as putrid; typhoid fever as fresh-baked brown bread; and scrofula as stale beer.³⁹ Odors are also described for disorders of amino acid and fatty acid metabolism, such as phenylketonuria, maple syrup urine disease, hypermethioninemia, and isovaleric acidemia.³⁹

The recognition of odors continues to be an important diagnostic skill for the rapid detection of some xenobiotics (Table 26–1). To increase awareness of odors of toxic xenobiotics, a “sniffing bar” of commonly available odors may be prepared.⁶⁷ Nontoxic xenobiotics that simulate the odors of toxic xenobiotics are placed in test tubes, numbered, and inserted in a test tube rack for circulation among staff. The sniffing bar, brief descriptions of clinical presentations, and a table of diagnostic odors (Table 26–1) may be used to teach the recognition of odors in medical toxicology.⁶⁷

TABLE 26–1. Odors Suggestive of a Xenobiotic

<i>Odor</i>	<i>Xenobiotic</i>
Bitter almond	Cyanide
Carrots	Cicutoxin (water hemlock)
Disinfectants	Creosote, phenol
Eggs (rotten)	Carbon disulfide, disulfiram, hydrogen sulfide, mercaptans, <i>N</i> -acetylcysteine
Fish or raw liver (musty)	Aluminum phosphide, zinc phosphide
Fruity	Nitrites (amyl, butyl)
Garlic	Arsenic, dimethyl sulfoxide, organic phosphorus compounds, phosphorus, selenium, tellurium, thallium
Hay	Phosgene
Mothballs	Camphor, naphthalene, <i>p</i> -dichlorobenzene
Pepper	<i>O</i> -chlorobenzylidene malononitrile
Rope (burnt)	Marijuana, opium
Shoe polish	Nitrobenzene
Sweet fruity	Acetone, chloral hydrate, chloroform, ethanol, isopropanol, lacquer, methylbromide, paraldehyde, trichloroethane
Tobacco	Nicotine
Vinegar	Acetic acid
Violets	Turpentine (metabolites excreted in urine)
Wintergreen	Methyl salicylate

Classification of Olfactory Impairment

There are different types of olfactory dysfunction. Anosmia, the inability to detect odors, and hyposmia, a decrease in the perception of certain odors, are the most common forms of olfactory impairment. The etiology of olfactory impairment may be classified as conductive, from anatomic obstruction of inspired air, or perceptive, from dysfunction of the olfactory receptors or signal transmission. Most conductive olfactory dysfunction results in hyposmia, because the obstruction is usually incomplete.^{114,150}

The most common causes of anosmia and hyposmia are viral infections, trauma, xenobiotics, tumors, and congenital and psychiatric disorders (Table 26–2).^{45,136,142,150} Viral infections may result in olfactory impairment either by obstructing nasal airflow or by causing damage to the olfactory epithelium.⁸⁰ Trauma to the head or nose can shear fragile olfactory nerves crossing the cribriform plate.^{153,176}

TABLE 26–2. Xenobiotics Responsible for Disorders of Smell

<i>Hyposmia/Anosmia</i>	<i>Dysosmia/Cacosmia/Phantosmia</i>
Acrylic acid	β-Adrenergic antagonists
Antihyperlipidemics: cholestyramine, clofibrate, gemfibrozil, HMG-CoA reductase inhibitors	Amebicides/antihelminthics: metronidazole
Cadmium	Anesthetics, local
Chlorhexidine	Anticonvulsants: carbamazepine, phenytoin
Cocaine	Antihistamines
Formaldehyde	Antihypertensives: angiotensin-converting enzyme inhibitors, diazoxide
Gentamicin nose drops	Antimicrobials
Hydrocyanic acid	Antiinflammatory
Hydrocarbons (volatile)	Antirheumatics: allopurinol, colchicine, gold, D-penicillamine
Hydrogen sulfide	Antiparkinsonians: levodopa, bromocriptine
Methylbromide	Antithyroid drugs: methimazole, methylthio- uracil, propylthiouracil
Nutritional	Calcium channel blockers
Vitamin B ₁₂ deficiency	Dimethylsulfoxide
Zinc deficiency	Ethacrynic acid
Pentamidine	Insecticides
Sulfur dioxide	Lithium
	Nicotine
	Opioids
	Sympathomimetics
	Toothpastes
	Vitamin D

Anosmia = the loss of smell; cacosmia = sensation of a foul smell; dysosmia = a distorted perception of smell; hyposmia = a decreased perception of smell; phantosmia = sensation of smell without stimulus.

Chronic exposures to numerous xenobiotics are associated with olfactory dysfunction (Table 26–2). The most common toxic mechanism related is perceptive olfactory dysfunction. This may be a result of a direct injury, or of a structural alteration of the receptor or its components such as G proteins, adenylate cyclase, or receptor kinase.^{78,79} Anosmia or hyposmia from hydrocarbons, formaldehyde, cadmium, and chemotherapeutics such as cytarabine results from direct effects on the receptor sites.^{49,79,84} Local effects on the epithelium and the receptors from antibiotic nose drops may lead to temporary anosmia and hyposmia.^{90,186} Inhaled corticosteroids may have local effects on the epithelium, as well as direct effects on both G proteins and adenylate cyclase.⁸¹ Cocaine insufflation causes direct local effects as well as effects on receptor functions.^{68,70} Because of the limited local effects of most xenobiotics and the regenerative ability of the olfactory receptor neurons, most xenobiotic-induced olfactory dysfunction is reversible.

Many individuals determined to have anosmia actually have congenital anosmia for select molecules, such as hydrogen cyanide, n-butyl mercaptan, trimethylamine, and isovaleric acid.^{7,45} Some extreme forms of congenital anosmia are associated with other abnormalities, such as Kallmann syndrome, a hereditary form of anosmia associated with hypogonadotropic hypogonadism where agenesis of the olfactory bulbs and incomplete development of the hypothalamus are responsible for the anosmia.^{45,153}

Dysosmia or parosmia is the distorted perception of smell (Table 26–2). Subclassifications of dysosmia include the perception of foul smell or cacosmia, the sensation of smell without a stimulus, or phantosmia, and the sensation of the smell of a burnt or metallic material, torquosmia.¹⁵⁰ The etiologies are classified as peripheral or central. Peripheral etiologies include abnormalities of the nose, sinuses, and upper respiratory tract. Central etiologies may be related to disorders such as Addison disease, hypothyroidism, temporal lobe epilepsy, psychosis, or pregnancy.^{45,114,151} How these conditions actually alter the perception of smell is unclear. A number of xenobiotics with similar effects are listed in Table 26–2. Bromocriptine alters dopaminergic transmission and inhibits adenylate cyclase. Levodopa affects the dopaminergic transmission and also chelates zinc, which is important in the maintenance of normal receptor functions.^{79,81}

Evaluation of Olfactory Impairment

General evaluation of olfactory function should include a detailed history, focusing on types, duration, and progression of symptoms, recent illnesses, head and nose trauma, sinus problems, family history, occupational history, hobbies, and xenobiotic history.^{41,71} A physical examination with a detailed examination of the nasopharynx and sinuses should be performed to assess the potential for inflammation or structural abnormality. A simple set of olfactory stimulants, such as ground coffee, almond extract, peppermint extract, and musk, should be used to test each nostril individually with the patient's eyes closed.^{71,153} Standardized smell tests such as the UPSIT (University of Pennsylvania Smell Identification Test) and the CCCRC (Connecticut Chemosensory Clinical Research Center) tests are commercially available, and a composite score based on a panel of tests can determine the degree of olfactory dysfunction.¹⁰⁶ Pungent odors or stimulation associated with ammonia, capsaicin, acetone, and menthol are dependent on the trigeminal nerve (CN V) olfactory function, which is mainly responsible for tactile pressure, pain, and temperature sensation in the mouth and nasal cavity. A patient who has olfactory nerve damage should be able to detect these substances; conversely, a person with hysteria may deny detection of these substances that should physiologically be recognized.^{71,153,186} If a xenobiotic-mediated mechanism is suspected, the offending xenobiotic should be discontinued. Coronal computed tomography of the sinuses and nose or magnetic resonance imaging of the brain should be obtained if structural abnormalities are suspected.^{153,186} Gas chromatographic analysis of the urine may be useful in patients with fish odor syndrome associated with trimethylaminuria.^{101,163} Complicated cases and patients with significant impairment should be referred to an otolaryngologist or neurologist.

GUSTATION

Anatomy and Physiology

Taste, the sensory interpretation of oral materials, is determined by taste buds on the tongue, palate, throat, and upper third of the esophagus. The cells in the taste buds have a life span of 10 days and are constantly renewed.^{11,153} The taste buds on the anterior two-thirds of the tongue and the palate are innervated by the facial (CN VII) nerve, those on the posterior one-third of the tongue by the glossopharyngeal (CN IX) nerve, and those on the laryngeal and epiglottal regions by the vagus (CN X) nerve. The signals are sent to the solitary nucleus in the brainstem, where they are processed and distributed to various regions of the brain. There are at least 13 known chemical taste receptors responsible for the five primary taste sensations—sweet, sour, bitter, umami (savory) and salty: two sodium receptor types; two potassium receptor types; one chloride receptor; one adenosine receptor; two inosine receptor; two sweet receptor types; two bitter receptor types; one glutamate receptor; and one hydrogen ion receptor.⁷³ One substrate will typically activate multiple taste receptors; the combined effects of these stimulated receptors determine the taste of the substance.⁶⁰

The structure of the taste receptors is similar to that of the olfactory receptors, in that they are coupled to G proteins and sodium and calcium channels permitting neural stimulation. Each receptor is capable of interacting with various classes of xenobiotics, of varying sizes. The pH of the xenobiotic determines sour (acid taste), whereas sodium or potassium concentrations determine salty taste. Many xenobiotics such as sugars, glycols, aldehydes, ketones, amides, amino acids, inorganic salts of lead, and bretylium activate the sweet receptors. Bitter taste may result from long-chain organic substances containing nitrogen, or alkaloids, including quinine, strychnine, caffeine, and nicotine.^{13,73} The threshold for bitter receptor stimulation is several orders of magnitudes lower than other taste receptors.¹³ Umami taste is a more recently accepted primary taste, best defined as a pleasant savory taste. The primary xenobiotic that stimulates umami receptor is glutamate, such as monosodium-L-glutamate. Umami receptor stimulation can be enhanced by 5'-ribonucleotide monophosphates such as inosine and guanosine.¹⁹⁰ Salivary proteins, such as zinc-containing gustin and ebnerin, are important in the regulation of taste sensation.^{79,83,103,161} These molecules may serve as binding proteins and growth factors for the regeneration of taste receptors. Taste is also affected significantly by the appreciation of aromas or odors and, to a lesser extent, by visual perception.¹⁵¹

Classification of Gustatory Dysfunction

Types of gustatory dysfunction include ageusia, the inability to perceive taste; hypogeusia, the diminished sensitivity of taste; and dysgeusia, the distortion of normal taste. There are several variations of dysgeusia, such as cacogeusia, which is a perceived foul, perverted, or metallic taste.^{71,111} Taste impairment is commonly related to direct damage to the taste receptors, adverse effects on their regeneration, or effects on receptor mechanisms.⁸⁰ These effects can result from a xenobiotic, disease, aging, and nutritional disorder (Table 26–3).^{66,73,141,172} Any abnormality that interferes with either the direct contact of a xenobiotic with the gustatory cells of the tongue or cranial nerves VII, IX, or X dramatically affects taste.¹⁵⁰ Most common forms of xenobiotic-induced dysgeusia are related to direct effects on the taste receptor site or effects related to receptor mechanisms such as G proteins, adenylate cyclase, and calcium channels.⁹⁹ Other forms of dysgeusia may result from direct stimulation of chemical receptors by xenobiotics.^{73,79}

TABLE 26–3. Xenobiotics Responsible for Alterations of Taste

<i>Hypogeusia/Ageusia</i>	<i>Dysgeusia</i>	<i>Metallic Taste</i>
Local	Local	ACE inhibitors
Chemical and thermal burns	Chemical burn	Acetaldehyde
Radiation therapy	Radiation therapy	Allopurinol
Systemic	Systemic	Arsenicals
ACE inhibitors	ACE inhibitors	Cadmium
Amiloride	Adriamycin	Ciguatoxin
Amrinone	Amphotericin B	Copper
Carbon monoxide	Botulism (in recovery)	<i>Coprinus</i> spp
Cocaine	Carbamazepine	Dipyridamole
Dimethylsulfoxide	Dimethylsulfoxide	Disulfiram
Gasoline	5-Fluorouracil	Ethambutol
Hydrochlorothiazide	Griseofulvin	Ferrous salts
Methylthiouracil	Isotretinoin	Flurazepam
Nitroglycerin	Levodopa	Iodine
NSAIDs	Nicotine	Lead
Penicillamine	Nifedipine	Levamisole
Propranolol	NSAIDs	Lithium
Pyrethrins	Phenylthiourea (hereditary)	Mercury
Smoking	Quinine	Methotrexate
Spironolactone	Zinc deficiency	Metformin
Triazolam		Metoclopramide
		Metronidazole
		Pentamidine
		Pine nuts
		Procaine penicillin
		Propafenone
		Snake venom
		Tetracycline

ACE = angiotensin-converting enzyme; NSAID = nonsteroidal antiinflammatory drug.

Angiotensin-converting enzyme (ACE) inhibitors commonly cause gustatory impairment, usually hypogeusia and dysgeusia.^{18,68,113,188} ACE inhibitors work by inhibiting zinc-dependent ACE, and chelating zinc from taste receptors and salivary proteins results in gustatory dysfunction. Calcium channel blockers act by inhibiting calcium channels of the taste receptor mechanisms.⁷³ Many diuretics cause zinc depletion by enhancing zinc elimination in the urine,⁷⁹ whereas furosemide and spironolactone may also chelate zinc. Numerous xenobiotics also cause gustatory dysfunction through variable degrees of zinc chelation: amrinone, ethambutol, hydralazine, methyl dopa, the nonsteroidal antiinflammatory drugs (NSAIDs), antithyroid agents, penicillamine, and phenytoin.^{73,79,189} Arsenic, mercury, chromium, and lead may either chelate zinc or replace zinc in salivary proteins because of a higher level of affinity. Chemotherapeutics and colchicine inhibit cellular division and taste-receptor regeneration. The oral antiseptic chlorhexidine directly alters taste-receptor function.⁵⁸ Acetazolamide causes cacogeusia when carbonated beverages are consumed. The exact mechanism is unclear, but is postulated to be a result of the inhibition of carbonic anhydrase causing carbon dioxide accumulation and an increased tissue bicarbonate.^{79,92,115}

HEARING

Anatomy and Physiology

Normal hearing begins when sound waves are captured by the external auricle, traverse the external auditory canal, and are conducted to the tympanic membrane, the three auditory ossicles of the middle ear, and move through the oval window to the perilymph in the scala vestibuli of the cochlea (Figs. 26–1 and 26–2). The sound wave is then transferred through the Reissner membrane at the roof of the cochlear duct, to the endolymph and the organ of Corti.^{54,167} The specialized hair cells

of the organ of Corti convert mechanical waves into neurologic signals. The hair cells contain cross-linked stereocilia projections that detect transmitted shear forces, which lead to the influx of potassium from the endolymph through opened potassium channels.^{43,104} Depolarization of the hair cells results in calcium influx and neurotransmitter release to the cochlear nerve. Neurologic signals from the cochlear nerve are conducted to the cochlear nucleus of the pons; bilateral projections are then sent to the superior olivary nucleus of the midbrain, nuclei of lateral lemnisci, inferior colliculus, medial geniculate body of the thalamus, and then to the auditory cortex of the temporal lobe.¹⁶⁷ Interruption or damage to any part of the hearing mechanism may lead to auditory impairment.

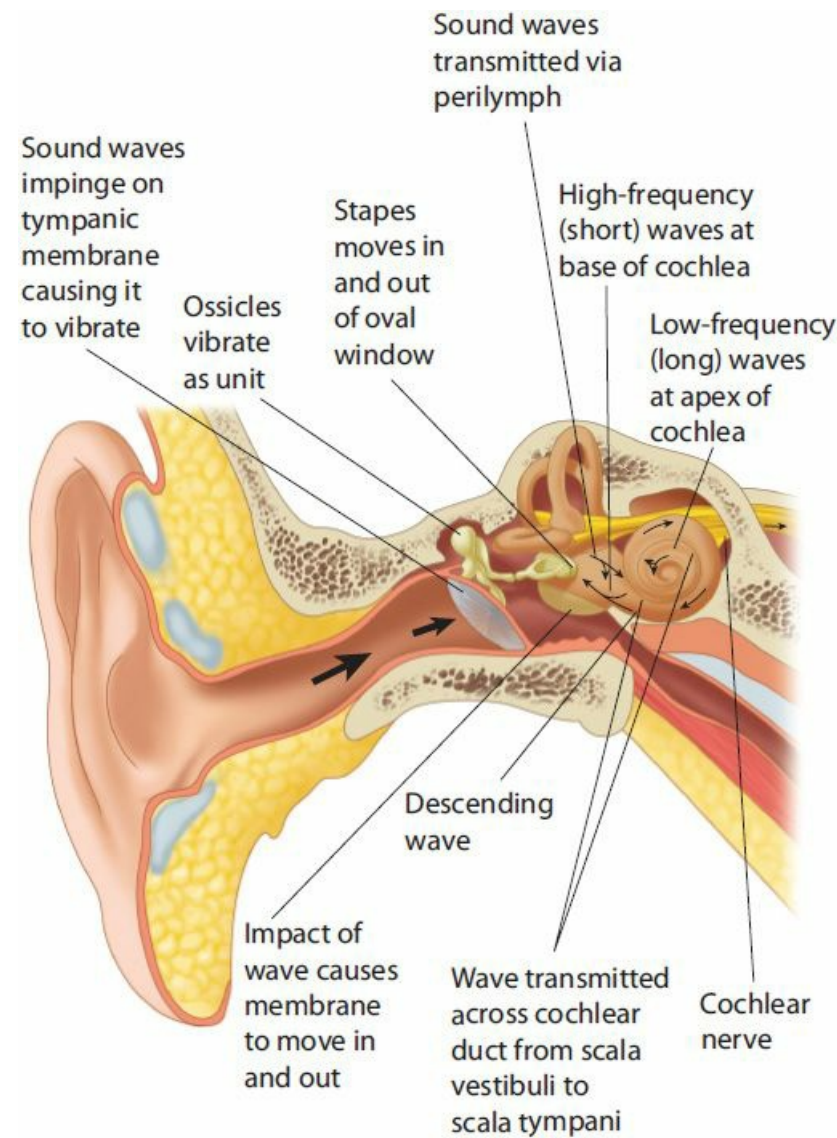


FIGURE 26–1. Pathways of sound conduction in the ear.

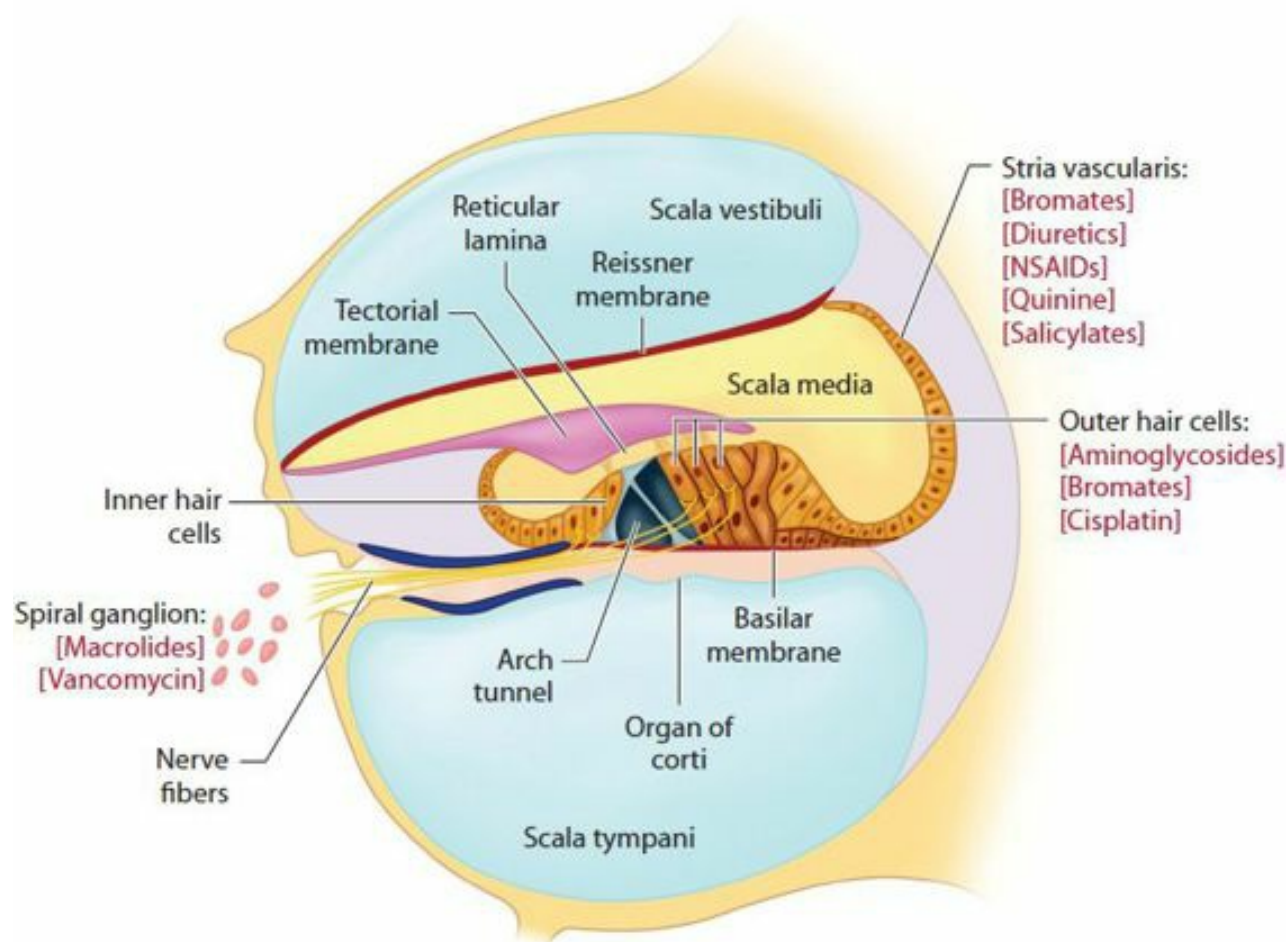


FIGURE 26–2. Cross-section of the organ of Corti showing sites of xenobiotic effect.

The anatomy and physiology of the cochlea and its importance in the biomechanics of hearing are reviewed in order to better understand the potential for xenobiotic injury. The word cochlea is derived from the Greek word *kochlias*, meaning snail, and describes its general structure—a 2.5-turn, spirally wound tube. The cochlea is further divided into three inner tubular structures: the upper tube or scala vestibuli, the middle tube or cochlear duct, and the lower tube or scala tympani. The scala vestibuli and the scala tympani contain the perilymph fluid. The cochlear duct contains endolymph fluid, the Reissner membrane at the roof, and the organ of Corti.¹⁶⁷ The cochlear fluids serve multiple functions: to conduct sound waves to the hair cells; to provide nutrients for and remove waste from the cells lining the cochlear duct; to control pressure distribution in the cochlea; and to maintain an electrochemical gradient for the function of the hair cells. The sodium concentration of the perilymph is similar to that of the extracellular fluid, and the potassium concentration of the endolymph is similar to that of the intracellular fluid.⁵⁶ Any significant alterations of the sodium or potassium concentrations will depress the cochlear potential and function. The stria vascularis controls the production of the cochlear fluids and the repolarization of the hair cells, and maintains the electrochemical gradient between the endolymph and the perilymph. The stria vascularis contains a high concentration of the oxidative enzymes, $\text{Na}^+\text{-K}^+$ -adenosine triphosphatase (ATPase), adenylate cyclase, and carbonic anhydrase, which are all highly susceptible to xenobiotics.^{20,84,148}

Although human speech is composed of sounds in the frequency of 250 to 3000 Hz, humans can normally detect sounds in the frequency range of 20 to 20,000 Hz.¹²⁵ The cochlea is a “tuned” structure with varying width and stiffness, such that different regions can receive different sound waves. The stiffer and wider base of the cochlea serves as a receptacle for higher-frequency sounds, whereas the apex is responsible for receiving the lower-frequency sounds.⁵⁴ Because various regions of the cochlea are susceptible to different forms of injury, appropriate audiologic testing should be tailored specifically to each patient.²⁷

Xenobiotic-Induced Ototoxicity

Ototoxicity includes effects on the cochlear and vestibular system. This section focuses on cochlear toxicity. Quinine and salicylates were widely recognized in the 1800s and streptomycin in the 1940s as causes of ototoxicity.^{85,143} Several hundred xenobiotics are implicated as causes of either reversible or irreversible ototoxicity (Table 26–4).^{23,89,97,121} Ototoxic xenobiotics primarily affect two different sites in the cochlea: the organ of Corti—specifically the outer hair cells—and the stria vascularis. Because of the limited regenerative capacity of the sensory hair cells and other supporting cells, when significant cellular damage occurs, the loss is often permanent.^{47,54,85,165} Although cell death of the outer hair cells

from inflammation and necrosis is expected when sufficient insults occur, apoptotic cell death is now postulated to be a major mechanism of ototoxicity from certain xenobiotics such as cisplatin and aminoglycosides.^{20,23,44,85,89,140} Inhibition of caspases and calpain associated with apoptosis of the hair cells is demonstrated to decrease ototoxicity from cisplatin and aminoglycosides in animals.^{140,164} Heat shock proteins are endogenous molecules that respond to cellular stress and inhibit apoptosis. Xenobiotics that can up-regulate heat shock proteins such as celestrol prevent cisplatin and aminoglycoside toxicity in animal models.^{40,59} Further studies are required to demonstrate clinical utility. Evidence supports the concept that otic injury can be potentiated by loud noises. Although the actual cellular mechanisms for many forms of ototoxicity remain unclear,¹⁸⁵ some of the mechanisms are known.⁶³ Loop diuretics, such as furosemide, bumetanide, and ethacrynic acid, cause physiologic dysfunction and edema at the stria vascularis, resulting in reversible hearing loss.^{85,109,181} The underlying mechanisms appear to be the inhibition of potassium pumps and G proteins associated with adenylate cyclase.⁹ Studies of loop diuretics demonstrate decreased potassium activity in the endolymph and a decreased endocochlear potential.¹⁴⁵ Permanent hearing loss associated with furosemide and ethacrynic acid is also reported, and may be related to direct interference with oxidative metabolism in the outer hair cells.^{98,109,145}

TABLE 26–4. Etiologies of Xenobiotic-Induced Hearing Loss

<i>Reversible</i>	<i>Irreversible</i>
Antimicrobials: chloroquine, erythromycin, quinine	Aminoglycosides
Carbon monoxide	Chemotherapeutics: bleomycin, cisplatin, nitrogen mustard, vincristine, vinblastine
Cocaine	Bromates
Diuretics: acetazolamide, bumetanide, ethacrynic acid, furosemide, mannitol	Hydrocarbons: styrene, toluene, xylene
Nonsteroidal antiinflammatory drugs	Metals: arsenic, lead, mercury
Opioids (frequently)	Opioids (infrequently)
Salicylates	

Salicylates are a well-known cause of ototoxicity. Aspirin (acetylsalicylic acid)-induced hearing impairment was first reported in 1877.⁹³ Salicylate-induced hearing loss is generally mild to moderate (a loss of 20–40 decibels {dB}) and reversible.^{17,87} Animal studies demonstrate immediate hearing impairment with the use of high doses of salicylates.^{16,110,111,132} The mechanism of salicylate-induced ototoxicity is unclear, although multiple factors are postulated. Salicylates and other NSAIDs inhibit cyclooxygenase, which converts arachidonic acid to prostaglandin G₂ and prostaglandin H₂. These effects may interfere with Na⁺-K⁺-ATPase pump function at the stria vascularis, and also decrease cochlear blood flow.^{29,50,93} A reversible decrease in outer hair cell turgor secondary to membrane permeability changes may impair otoacoustic emissions.^{131,135} In support of these theories, pretreatment of animals with leukotriene antagonists and α -adrenergic receptor antagonists attenuates or prevents salicylate-induced ototoxicity.⁹³

NSAIDs and quinine also cause reversible hearing loss, particularly at the higher frequencies.^{31,85} Occasionally, quinine-induced hearing loss may be permanent.^{85,149} The primary mechanism is related to prostaglandin inhibition.⁹³ Quinine inhibits the enzyme phospholipase A₂, which converts phospholipids to arachidonic acid. Quinine also inhibits calcium channels that interact with prostaglandins.⁹³

Certain chemotherapeutics, such as cisplatin, vinblastine, and vincristine, can cause permanent ototoxicity.⁸⁵ Cisplatin is the most toxic of the group, with clinically apparent hearing loss noted in 30% to 70% of the patients receiving doses of 50 to 100 mg/m². These antineoplastics typically damage the outer hair cells but may also affect the stria vascularis.⁸⁵ The underlying mechanisms may be related to the inhibition of adenylate cyclase in the stria vascularis, the inhibition of protein synthesis, and the formation of oxygen free radicals.^{9,85,155} The generation of oxygen free radicals and the depletion of antioxidants result in the irreversible damage to the hair cells.⁵² Furthermore, cranial radiation will cause synergistic toxicity if radiation precedes cisplatin therapy. Various antioxidants and free radical scavengers prevent cisplatin-induced ototoxicity in animals, perhaps preventing oxidative injury–induced apoptosis to hair cells.^{102,116,119,137,140,144,169,184} Amifostine, a precursor to a thiol free radical scavenger, prevents cisplatin-induced nephrotoxicity, but does not appear to prevent cisplatin-induced ototoxicity.¹⁴⁷

The aminoglycosides are best known for their association with irreversible ototoxicity,¹³⁰ but they are not concentrated in the cochlea. The endolymph concentration of gentamicin is approximately 10% of that in the serum. It is postulated that toxicity is related to the metabolites of aminoglycosides and not the parent compounds because toxicity can be reproduced

in vivo, but not in vitro.¹⁴⁸ Neomycin and kanamycin are the most ototoxic, although all aminoglycosides are potentially toxic.⁹⁸ With the development of the newer aminoglycosides and therapeutic drug monitoring, the incidence of aminoglycoside-related ototoxicity appears to be decreasing. The reported rates of ototoxicity for the more commonly used aminoglycosides gentamicin and tobramycin are between 5% and 8%.¹⁰⁸ In China, where aminoglycosides are readily available as nonprescription medications, as much as 66% of deafness may be directly related to aminoglycoside toxicity.^{61,105} Several uncommon genetic mutations that predispose to aminoglycoside-induced ototoxicity are identified, including A1555G and C1494T mutations.^{57,75} The genetic transmission appears to be maternal via mitochondrial DNA and the defects increase aminoglycoside binding to mitochondrial 12S ribosomal RNA.⁵⁷ These patients may experience rapid and severe hearing loss compared with normal people with a similar aminoglycoside exposure.¹⁴⁰

Several mechanisms of aminoglycoside ototoxicity are postulated, including antagonism of calcium channels of the outer hair cells of the cochlea, blocking transduction of the hair cells and resulting in acute, reversible hearing deficits as well as binding to polyphosphoinositides of cell membranes to alter their functions. Polyphosphoinositides are essential for the generation of the second messengers diacylglycerol and inositol triphosphate and their ultimate cellular function, for the maintenance of lipid membrane structure and permeability, and as a source for arachidonic acid.^{85,140} However, the most important mechanism is that aminoglycosides interact with iron and copper to generate free radicals, damaging the hair cells. Aminoglycosides also inhibit ornithine decarboxylase which is important for cellular recovery following an injury and makes the cell more susceptible to toxicity.¹⁴⁸ The outer hair cells of the cochlea are increasingly susceptible to aminoglycosides and damage progresses from the inner row of the outer hair cells to the basal turn of the cochlea, and, ultimately, to the apex.^{4,7,98,140}

The risks of ototoxicity are increased with a duration of therapy of more than 10 days, concomitant use of other ototoxic xenobiotics, and the development of elevated serum concentrations.^{7,55,146} There is no evidence that single daily dosing of aminoglycosides alters the risk of ototoxicity.^{127,179} Loop diuretics increase aminoglycoside toxicity by increasing aminoglycoside penetration into the endolymph. In animal models, certain free radical scavengers, such as glutathione, amifostine, and deferoxamine, decrease aminoglycoside-induced ototoxicity.^{64,149,170,177,180} Fosfomycin, a phosphonic antibiotic, has limited efficacy in reducing aminoglycoside-induced ototoxicity.¹²⁴ Leupeptin and Z-DEVD-FMK, calpain and caspase inhibitors, respectively, that affect the apoptotic pathway, decrease ototoxicity in animal models.^{32,63,159,164} Further studies are required to determine their applicability to humans. Salicylates, which may act as free radical scavengers in therapeutic concentration, were effective in preventing gentamicin ototoxicity in animals. Two randomized human trials using concomitant salicylate therapy at 1.5 and 3 g/day significantly attenuated gentamicin-induced ototoxicity.^{12,160} Gastric adverse effects, including bleeding, were also more common in the salicylate group. Confirmation of these findings and determining safer alternatives are warranted.

Erythromycin, vancomycin, and their respective analogs are ototoxic. There are a number of reports of hearing loss following erythromycin therapy in humans and an animal study supporting the ototoxic potential. Most deficits in humans are transient, although several cases of permanent hearing loss are reported.^{21,22} The mechanisms of toxicity remain unclear, although the proposed effects are on the central auditory pathways. Erythromycin-induced hearing loss occurs at both lower and higher frequencies for speech, allowing for recognition in the early stages of ototoxicity.²¹ Similarly, both reversible and irreversible ototoxicities from the newer macrolide antibiotics clarithromycin and azithromycin were also reported.

The evidence for vancomycin-induced ototoxicity is less convincing. Although numerous cases of presumed vancomycin-related ototoxicity are reported, concomitant use of other ototoxic antibiotics was common or audiometric studies were not performed. In limited animal studies, vancomycin alone does not induce ototoxicity, but it increases ototoxicity when administered concomitantly with an aminoglycoside. Vancomycin analogs such as teicoplanin and daptomycin probably have similar ototoxic potentials.

Bromates are among the most extensively studied ototoxic xenobiotics.^{31,36,107,133} Bromates are used in hair “neutralizers,” bread preservatives, and as fuses in explosive devices.^{86,133,173} Following bromate administration the stria vascularis and hair cells of the organ of Corti are irreversibly damaged.¹³³ Substantial exposure to bromates may also cause acute kidney injury, which decreases bromate elimination and, in turn, increases its ototoxic potential.^{86,133}

It is intriguing that xenobiotics, such as the bromates, loop diuretics, and aminoglycosides, primarily affect both the cochlea and the kidneys. One possible explanation is that the stria vascularis and the renal tubules have similar functions in maintaining electrochemical gradients.^{124,125} However, renal tubules may regenerate, while damage to the hair cells and the stria vascularis of the cochlea is more likely to be permanent.

Sudden hearing loss is reported with recreational drug use, particularly with cocaine and opioids. For cocaine, the mechanism of injury may be related to cochlear hemorrhage and hypoxia from vasoconstriction.^{37,123,171} While other mechanisms such as a direct effect on the potassium channels in the hair cells and sodium channels of the auditory nerve have been postulated, they are not well elucidated in animal models. Concomitant opioid use and adulterants should be

considered. Various opioids, including heroin, methadone, and hydrocodone, are associated with hearing loss.^{34,154,156,162} Neither the route of use nor the presence of adulterants such as quinine can adequately explain the hearing loss. Most cases of opioid associated hearing loss are reversible, but some are permanent. The mechanisms of opioid associated hearing loss are unclear. One potential mechanism is that the stimulation of opioid receptors in the cochlea inhibits adenylate cyclase activity, leading to hearing loss.⁵³ Various opioid receptors have been identified in the cochlea, such as in the inner hair cells, outer hair cells, and the spiral ganglion. Others postulate that opioids have potential roles as neurotransmitters or neuromodulators that affect auditory function.⁹¹

Other xenobiotics implicated as ototoxins are carbon monoxide, lead, arsenic, mercury, toluene, xylene, and styrene.^{82,166} However, both human and animal data are quite limited. Carbon disulfide, carbon tetrachloride, and trichloroethylene are also suspected of being ototoxic, but toxicity has not been demonstrated in humans.^{82,156} Because exposures to xenobiotics are frequently occupational, they are of great concern as they may potentiate or be additive to other types of occupational hearing impairments.^{95,138}

High-frequency hearing is most vulnerable, and early or limited impairment may not be noticeable unless audiometry, especially at 8000 kHz and above, is performed.¹⁷⁸ These hearing tests can be performed in infants using the measurement of auditory brainstem response.¹⁴

Noise-Induced Hearing Impairment

Noise-induced hearing impairment has been recognized for hundreds of years, but became a great concern and increasingly prevalent with the industrial revolution and the discovery of gunpowder.⁵⁴ Some of the anatomic changes in the organ of Corti and the audiometric features of noise-induced hearing impairment were well described by 1900.^{2,3,112} Unfortunately, few longitudinal studies on noise-induced hearing impairment have been performed.

Although noises of sufficient magnitude may cause hearing impairment with limited exposure, most noise-induced hearing losses result from preventable prolonged cumulative occupational exposure. NIOSH has estimated that up to 1.7 million workers in the United States between 50 and 59 years of age have significant occupation-related hearing loss.¹²⁵ Noise can be defined as any unwanted sound, which can be further characterized by duration, time pattern (continuous, intermittent, or impulsive), frequency, and intensity. Although loud sounds from concerts and personal listening devices may not be classified as noise, they are included as noise for the purpose of the discussion. The intensity is measured in sound pressure levels (SPLs) and expressed in a logarithmic scale in decibels (dB). The intensity of a normal conversation is approximately 65 dB (Table 26–5).¹²⁵ The risk of noise-induced hearing loss is related to cumulative duration of exposure, intensity, and individual susceptibility.^{122,128,183} Much of the risk assessment of noise-induced hearing loss is inexact. Most authorities agree that sounds with maximal intensity below 75 to 80 dB will not cause hearing impairment, regardless of the duration of exposure.¹²² At higher intensity, the risk of hearing impairment increases with increased duration of exposure. Continued occupational exposure at 90 to 94 dB typically causes some high-frequency hearing loss in approximately 10 years.^{2,128} Further exposure results in hearing loss in the lower-frequency range. The Occupational Safety and Health Administration (OSHA) established guidelines for permissible occupational noise exposure based on an analysis of the average intensity and duration of exposure (Table 26–6).^{2,183}

TABLE 26–5. Typical Sound Levels on the Decibel Scale

<i>Sound</i>	<i>Decibels</i>
Weakest sound that humans can detect	10
Quiet bedroom, soft whisper	20
Broadcast studio	25–30
Insulated lounge	50
Normal conversation	65
Television-audio	70
Vacuum cleaner	80
Machine press, subway car (35 mph)	95
Spray painting, snowmobile	105
Power saw	110
Maximum volume of MP3 players	100–115
Loud rock concert, car horn	115
Armored personnel carrier; ear pain begins	120
Jet plane engine, gunshot	145
Highest sound level that can occur	194

TABLE 26–6. OSHA Standard for Permissible Noise Exposure

<i>dBA^a</i>	<i>Duration of Exposure Per Day in Hours</i>
85	16
90	8
92	6
95	4
97	3
100	2
102	1.5
105	1
110	0.5
115	≤0.25

^aDecibels using the A-scale filter.

The pathophysiology of noise-induced hearing impairment is related to an excessive energy impact on the cochlea, but the exact biochemical changes are unclear. Apoptotic death of the hair cells can be demonstrated and inhibition of apoptosis pathways mitigates noise-induced toxicity in animal models. A limited exposure to excessive noise results in a temporary hearing impairment or temporary threshold shift with a duration of hours to weeks. However, prolonged exposure results in a permanent threshold shift or hearing impairment.^{3,54,183} Initially, outer hair cells are lost, but more significant exposures result in damage to both inner and outer hair cells and all supporting structures in the organ of Corti. Cochlear nerve fibers degenerate after hair cell damage.^{54,183} The section of the cochlea most at risk from loud noises is at the region of 9 to 13 mm (total length is 32 mm).¹¹² This region is responsible for hearing at the range of 3000 to 6000 kHz, corresponding to the typical noise-induced hearing loss pattern.

Much of the clinical assessment and monitoring of noise-induced hearing loss is based on pure tone hearing loss, demonstrating an audiometric deficit at 3000 to 6000 kHz.^{125,128,183} Although human speech is composed mainly of low frequency sounds, the ability to perceive the higher frequency sounds is extremely important in speech recognition. For this reason, the major impairment in patients with noise-induced hearing loss is an inability to discriminate speech, particularly from background noise.^{2,42} Currently, the science of the investigation of speech discrimination is limited with extensive areas for research.

Blast injury to the ear results from exposure of extremely short duration, but very high-intensity sound waves, usually greater than 140 dB. Military personnel are particularly at risk.^{30,129,175,178} Hearing loss from blast injury may be related to rupture of the tympanic membrane, disruption of the ossicles, temporary cochlear dysfunction, and permanent cochlear dysfunction from labyrinthine fistulae and basilar membrane rupture.²⁸ When a large tympanic membrane rupture or disruption of the ossicles occurs, surgical intervention may be required to treat hearing impairment.²⁸

Prevention of any type of noise-induced hearing loss remains the best solution. Various hearing-protection devices are available if the noise exposure cannot be reduced. Better monitoring and more longitudinal studies are required on noise-induced hearing loss. Exposures to xenobiotics that can impair hearing may have synergistic effects with noise-induced hearing loss.^{95,97} These factors should be considered when noise exposure is evaluated. Furthermore, noise exposure is not limited to the workplace. Significant noise exposure may occur at home or from leisure activities, such as the use of power tools, loud music, and ambient exposure.^{15,38,74,128} The impact of noise exposure outside of the workplace has only recently attracted the attention of investigators.

Tinnitus

Tinnitus is the sensation of sound not resulting from mechanoacoustic or electric signals. Virtually all humans experience tinnitus during their lives. The exact mechanism or mechanisms resulting in tinnitus are largely unknown.¹⁵² Tinnitus may or may not be associated with hearing loss. Several theories are proposed, but none is completely satisfactory. Tinnitus may result from spontaneous neurologic discharges when the hair cells or cochlear nerve is injured. Altered sound perception may result from local or central effects when feedback mechanisms are interrupted.^{45,51,88,111} Severing the cochlear nerve terminates tinnitus in less than half of affected patients, suggesting important central mechanisms.¹⁰ Furthermore, certain etiologies of tinnitus, such as migraine headache and temporal lobe seizures, do not affect hearing directly. N-methyl-D-aspartate (NMDA) glutamate receptor activation (and enhanced cochlear signal transmission) is implicated as a mechanism for tinnitus in animal models; NMDA receptor activation may result from cyclooxygenase inhibition or neurologic injuries.^{76,131} Xenobiotics, including salicylate, may cause hair cell dysfunction and may modify neurotransmission centrally in both the cochlear nucleus and the inferior colliculus.^{65,182} Although the probable sites involved in tinnitus may be classified as peripheral (external ear, middle ear, or cochlear {CN VIII}), central, or extra-auditory (vascular, nasopharyngeal), some etiologies may affect peripheral and central sites, and many etiologies remain unknown.^{35,51,111}

Numerous xenobiotics are associated with tinnitus (Table 26–7), but the incidence is probably low and the implied relationships are usually supported only by case reports.^{33,157,158} Tinnitus may or may not be associated with transient or permanent hearing loss. It is probable that the xenobiotics associated with hearing loss affect cochlear function, while those that produce tinnitus without hearing loss probably act on signal transmission at the cochlea in the CNS. Xenobiotics that frequently produce tinnitus include streptomycin, neomycin, indomethacin, doxycycline, ethacrynic acid, furosemide, heavy metals, and high doses of caffeine.^{69,157,158} Only a few xenobiotics, such as quinine and salicylates, consistently cause tinnitus at toxic doses.^{16,51} These two xenobiotics also serve as examples of how the presence of tinnitus may be an indicator of drug toxicity.

TABLE 26–7. Xenobiotics That Cause Tinnitus

β-Adrenergic antagonists
Anticonvulsants: carbamazepine
Antidepressants: cyclic antidepressants, amoxapine, lithium, trancylcypromine
Antifungals: amphotericin B
Antihistamines
Antimicrobials: aminoglycosides, vancomycin, dapson, tetracyclines, sulpha drugs, metronidazole, thiabendazole, clindamycin

Antiparasitics: chloroquine, hydroxychloroquine

Antipsychotics: haloperidol, molindone

Bromates

Chemotherapeutics: cisplatin, nitrogen mustard, 6-aminonicotinamide, methotrexate, vinblastine

Cinchona alkaloids: quinine, quinidine

Diuretics: furosemide, ethacrynic acid, bumetanide

Hydrocarbons: benzene

Local anesthetics: mepivacaine, bupivacaine, lidocaine

Nonsteroidal antiinflammatory drugs

Oral contraceptives

Salicylates

Sympathomimetics: caffeine, theophylline, metaproterenol, albuterol, methylphenidate

Tinnitus associated with salicylates usually begins when serum concentrations are in the high therapeutic or low toxic range of approximately 20 to 40 mg/dL.¹¹⁷ Membrane permeability changes cause a loss of outer hair cell turgor in the organ of Corti which may impair acoustic emissions, explaining tinnitus to some extent.^{131,132,135} NMDA-receptor activation from cyclooxygenase inhibition may also cause tinnitus.¹³¹ Before the wide availability of serum salicylate measurements, physicians treating gout or rheumatoid arthritis often titrated the salicylate dosage until tinnitus developed.¹¹⁷ Tinnitus and other signs and symptoms of salicylism ([Chap. 39](#)) should be sufficient for physicians to diagnose salicylate toxicity before serum salicylate concentrations are available. However, tinnitus may not be evident in patients with hearing impairment despite significantly elevated salicylate concentrations.¹¹⁷ The classic constellation of symptoms of quinine and salicylate toxicity, called cinchonism, includes nausea, vomiting, tinnitus, and visual disturbances.^{4,26,120} Because serum quinine concentrations are not readily available, symptoms of quinine toxicity define the clinical diagnosis ([Chap. 59](#)).¹⁶⁸

SUMMARY

- Numerous xenobiotics commonly affect the sense of smell, taste, and hearing, thus causing significant morbidity.
- Some of the events may be predictable, whereas others will require monitoring and appropriate testing.
- Current knowledge about the pathophysiology of xenobiotics and these special organs at the molecular level is rapidly expanding.
- Although no definitive antidote is available for the prevention or treatment of xenobiotic-induced ototoxicity in humans, substantial progress has been achieved in both in vitro and in vivo animal models.

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27 PSYCHIATRIC PRINCIPLES

Erin A. Zerbo and Andrea M. Kondracke

Psychiatric problems may be the cause or the effect of many toxicologic presentations. Suicide attempts and aggressive behaviors are commonly associated with toxicity and can be uniquely difficult to assess and manage. Patient behaviors are often viewed dichotomously as either totally intentional and deliberate or totally “out of control” and irrational. The truth is usually more complex, with some aspects occurring within the awareness and control of the patient and other aspects either unknown or overwhelming to the patient. Neuropsychological conceptions of “behavioral disinhibition” as a baseline personality trait that is relatively fixed are complementary to presumed organic etiologies of disinhibition such as intoxication or brain injury; in the latter cases, frontal lobe dysfunction is directly implicated. Yet more subtle frontal lobe dysfunction is likely occurring in many patients without such a direct neurological insult: patients with psychosis or mania, personality disorders, attention-deficit/hyperactivity disorder, or even agitation in the context of psychological distress. A patient’s innate capacity for self-restraint can vary widely, and some will present with behavioral disturbances much more readily than others.¹¹²

Issues of capacity often arise with intoxicated or impaired patients, and the basic approach to capacity assessment will be covered. “Medical clearance” is usually requested prior to a patient’s transfer to psychiatric care, yet this has proven to be a rather vague concept that lacks a standard protocol; however, there are practice guidelines addressing this issue, which will be discussed. This chapter also explores the topics of suicide/self-harm and violence to enable the physician to adopt the appropriate role of both diagnostician and medical decision-maker. Finally, substance use disorders (SUDs) will be addressed, given that they are problematic in the emergency setting and highly comorbid with suicidality and violence.

CAPACITY

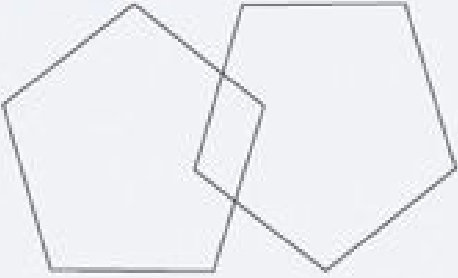
Physicians are legally and ethically required to obtain informed consent before treating a patient to allow the patient to make a voluntary choice about his or her care. However, if a patient is cognitively impaired, the physician must make a careful assessment of capacity and proceed as medically necessary should the patient be found to lack capacity. It does not matter whether the cognitive impairment is due to psychiatric illness, medical illness, or a transient xenobiotic-induced delirium; if the patient is unable to make a logical and rational decision stemming from his or her personal value system, the physician can override the patient’s autonomy to provide necessary care.⁷ Traditionally, the term “competence” denotes a legal status determined by a court of law, whereas “capacity” is assessed by a physician in a clinical setting. The distinction between these terms has become blurred in both the medical and legal literature, but it is a helpful framework nonetheless.⁷

It is important to note that capacity assessments occur at a specific moment in time regarding a specific medical decision. The assessment is not a “global” determination that persists throughout the hospitalization or even the length of an emergency department (ED) visit, but rather a temporary determination that requires reassessment as factors change. Capacity may fluctuate with a change in the patient’s mental status, medical or psychiatric condition, the time of day, amount of pain, level of anxiety, perceived support, recent medication administration or in the context of withdrawal from a xenobiotic.

While disease status cannot be used to determine capacity, some correlations have been noted in the literature. Fifty percent of patients with schizophrenia who are hospitalized with an acute psychotic episode will not have capacity; more than 50% of patients with mild-to-moderate dementia will also lack capacity, and this increases to 100% with severe dementia. If the Mini-Mental State Exam (MMSE) (Table 27–1) score is lower than 19 out of 30 possible points, it is highly unlikely the patient will have capacity.⁵¹ Most patients with mild-to-moderate depression do not have impaired capacity, yet 20% to 25% of hospitalized patients admitted with severe depression do lack capacity.⁷ Nonetheless, capacity should always be carefully assessed, since active psychiatric symptoms or long-standing cognitive impairment do not invariably lead to a lack of capacity.

TABLE 27–1. The Mini-Mental State Exam

Patient _____	Examiner _____	Date _____
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Maximum	Score	
		Orientation
5	()	What is the (year) (season) (date) (day) (month)?
5	()	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	()	Name three objects: one second to say each. Then ask the patient all three after you have said them. Give one point for each correct answer. Then repeat them until he/she learns all three. Count trials and record. Trials _____
		Attention and Calculation
5	()	Serial "7's". One point for each correct answer. Stop after five answers. Alternatively, spell "world" backward.
		Recall
3	()	Ask for the three objects repeated above. Give one point for each correct answer.
		Language
2	()	Name a pencil and watch.
1	()	Repeat the following "No ifs, ands, or buts"
3	()	Follow a three-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	()	Read and obey the following: CLOSE YOUR EYES
1	()	Write a sentence.
1	()	Copy the design shown.
		
		Total Score _____
		ASSESS level of consciousness along a continuum _____
		Alert Drowsy Stupor Coma

Reproduced with permission from Folstein MF, Folstein SE, McHugh PR: Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975 Nov;12(3):189-98.

Depriving a patient of his decision-making rights is a serious infringement on liberty. While physicians are implicitly assessing patients' capacity on a regular basis, they often have little formal training and may not have a systematic approach. This limitation leads to difficulty determining capacity in murky ethical situations, confusing clinical scenarios or when a patient is making "bad" decisions (such as refusing treatment of clear benefit or refusing life-sustaining measures). Patients refusing treatment in the setting of a recent suicide attempt, such as refusing an antidote for a potentially lethal ingestion, is one frequently encountered scenario (see Suicide).

Intricacies of capacity assessment may be dictated by individual jurisdiction and it is important to know the laws in the area within which you practice. For example, some states require two separate assessments by physicians that are separated in time. The assessment should be done by a physician familiar with the procedure and able to discuss risks and benefits, and should include assessment of the patient's mental status, educational level, and any cultural factors that may be relevant. A well-researched scale for determining decisional capacity is the MacArthur Competence Assessment Tool for Treatment (MacCAT-T), a semi-structured interview that requires 15 to 20 minutes to administer and is designed for use in a clinical setting (Table 27-2).⁵⁹

Interview Process (15–20 minutes):

- Clinician discloses patient’s disorder, recommended treatment, risks, benefits, and alternative treatments
- Patient expresses a treatment choice and explains how the choice was made

Questions embedded in the interview process assess patient’s abilities in 3 areas:

1. Understanding

- Ask the patient to paraphrase what has been disclosed about the disorder, the recommended treatment, and the risks/benefits.
- If a patient demonstrates poor understanding, redisclose the information and reassess (if a patient wasn’t paying attention or found the concepts unfamiliar, his or her understanding should improve with redisclosure).

2. Appreciation

- Does the patient acknowledge that the information applies to him or her? That treatment might have at least some benefit?
- A reasonable difference of opinion is permissible; however, if a patient’s opinion is derived from delusional or distorted perceptions, these patients are lacking appreciation.

3. Reasoning

- Has the patient expressed a preference? What are his or her explanations for making that choice? Does he or she mention any consequences of treatment alternatives, how alternatives compare, or any thoughts about consequences besides those offered in the disclosure? Does the patient’s final choice follow logically from the explanation?
- If the patient is not able to logically explain how he/she arrived at a choice, or is inconsistent in the choice, this indicates a failure of reasoning.

Data from Grisso T, Appelbaum PS, Hill-Fotouhi C: The MacCAT-T: a clinical tool to assess patients’ capacities to make treatment decisions. *Psychiatr Serv.* 1997;Nov;48(11):1415–1419.

The general legal standard for capacity requires assessment of four basic skills, which should be clearly documented:⁷

1. Communicate a Choice. The patient must be able to indicate a choice, and to be consistent long enough for the choice to be implemented. A patient may alter the decision over time or with new information, but repeated reversals of a decision suggest a lack of capacity. Difficulties in this first measure can occur in patients who have a high degree of ambivalence, patients with poor short-term memory or a thought disorder, or patients who are unconscious or delirious.

2. Understand Relevant Information. As a first step, the physician should provide all the relevant information in a patient’s primary language and in an understandable manner. In addition to describing the medical condition, the proposed intervention(s) and the risks and benefits, the physician should be certain to address the possibility of “doing nothing” and the associated risks/benefits with this decision.

Physicians often feel that this step is the key to capacity assessment, and that if a patient can verbally repeat the details of the procedure and the risks/benefits/alternatives that capacity has been established. However, the assessment is more nuanced than this. The patient should be able to understand and manipulate the information independently, which can be demonstrated by asking the patient to paraphrase the physician’s explanations rather than repeat verbatim. The patient should understand that probabilities, not certainties, are being discussed, and that he or she has an autonomous role as a decision-maker. Difficulties in this domain can arise from deficits in attention, intelligence, or memory.

3. Appreciate the Situation and Its Consequences. The patient may be able to comprehend the relevant information, yet it is important to ensure that the patient is also able to apply the facts to the individual’s particular situation. The medical condition in question must be acknowledged, and the individual must demonstrate awareness that the risk and benefits being discussed apply to this unique personal situation. Courts have clarified that patients who do not acknowledge their illness do not have capacity. Difficulties in this area often arise from pathologic denial, mistrust of the motivation of the physician, cognitive or affective impairment, or delusional thinking.

4. Reason about Treatment Options. This final step describes the patient’s ability to comprehend and incorporate the relevant information as applied to this particular situation in order to logically reach a decision about his or her treatment. The physician should ask the patient to compare treatment options and consequences, and should inquire about how the choice was selected; the patient should be able to explain the reasoning involved and discuss the major factors considered. If a patient is unable or unwilling to explain the personal reasoning process, as sometimes can occur in the setting of anger or irritability, the capacity assessment is not complete and this suggests a lack of capacity until proven otherwise. Patients are allowed to make “unreasonable” choices, but they should be able to explain their reasoning process. Difficulties in this

domain often occur in patients with delirium, dementia, extreme phobia, panic, anxiety, psychosis, depression, or anger. Patients with SUDs might be experiencing withdrawal or intense craving and therefore demanding to leave and unwilling to participate in a discussion about their reasoning; addressing their withdrawal or cravings directly can often result in significant relief and rapid re-establishment of capacity.

Once a patient is deemed not to have capacity at a specific time to make a specific decision, the evaluation should proceed to determine the reason for this lack of capacity and the route through which it might be restored. Every effort should be made to assist in the restoration of patient capacity in order to protect autonomy. Individual state laws may mandate when court proceedings should be pursued, often depending on the level of invasiveness of a procedure: For example, a venipuncture is much less invasive than a surgical procedure, and would not require a special court order. However, for a procedure such as a limb amputation, the physician should likely pursue a court decision. In unclear circumstances, the physician can consult with the hospital's risk management department. Every effort to find an alternative decision-maker should be made. When there is no designated health care proxy and family members are not in agreement about the best treatment choice, most states have determined a specific hierarchy to determine which family member should make the decision.⁸

Complexities of Capacity Determination in Clinical Settings

Decisional capacity is often part of a larger question about how to proceed with treatment for a particular patient. If a patient is found to lack capacity, ethical questions arise about the appropriateness and practicality of imposing treatment; such as the consideration of sedating a patient to obtain a blood sample. Sedating a patient has its own inherent risks, and psychological distress to the patient cannot be discounted. In these situations it is often helpful to have a discussion involving the psychiatrist, and a general consensus can usually be reached about the balance of costs and benefits to proceeding with treatment against a patient's will. Life-threatening refusal of treatment is always clear, but the physician often quickly encounters a "gray area" in which the medical necessity of a treatment is less urgent. The physician has a responsibility to petition the court for invasive procedures such as surgery if the patient's medical condition is stable enough to allow this, but if the situation becomes urgent, the physician can proceed without involving the court. In these cases, it is often helpful to have a team approach involving psychiatry, risk management, and a bioethics consultation if available.

Another important concept is the sliding scale of capacity, which has been supported by both expert consensus guidelines and the legal system. This "sliding scale" concept indicates that the threshold for deeming a patient to lack capacity changes depending upon the seriousness of the consequences. For example, a patient refusing treatment in a life- or limb-threatening situation would be held to a higher standard of capacity than for a patient refusing a venipuncture. A life-threatening situation requires the patient to clearly demonstrate a thorough understanding of the relevant information, its application to the situation and the individual's reasoning process in order to be deemed to have capacity. On the other hand, even if a patient doesn't technically have capacity to refuse a blood draw, if it is not medically necessary at that moment, the patient might be allowed to refuse. This philosophy stems in part from our conception of a modern democracy in the United States, in which the vast majority of persons are considered capable to make their own decisions. We would like to preserve this autonomy when it is not dangerous to the patient's health.⁷

MEDICAL CLEARANCE

Not all patients who present with psychiatric symptoms have mental illness. Intoxication, withdrawal syndromes, medical illness, and organic brain disease can often mimic mental illness. Patients with behavioral disturbances present unique challenges to diagnostic assessment given that they are unlikely to be cooperative and it can be difficult to achieve a comprehensive medical history. Emergency physicians are usually asked to "medically clear" the patient before transfer to psychiatric care, yet there is no standard process for this.

In general, psychiatrists request that ED physicians: (1) determine if presenting symptoms are caused or exacerbated by a medical illness, (2) assess and treat any acute medical issue necessitating urgent or emergent intervention, and (3) determine if the patient's symptoms are primarily related to a xenobiotic, which would preclude an accurate psychiatric evaluation.⁸⁰ Obvious signs of need for further evaluation include abnormal vital signs, delirium, altered cognition, or an abnormal physical examination. Four other groups are identified as high risk for medical instability: the elderly, patients with substance abuse, patients without any prior psychiatric history, and those with preexisting medical disorders or current medical complaints.⁵⁸

While routine laboratory testing is often requested by the psychiatrist for medical clearance, a number of studies demonstrate that selective testing based on history and physical examination is probably the correct strategy. There is a strong consensus among ED physicians that routine laboratory testing is unnecessary, and without any clinical suspicion, the probability of false positive laboratory results begins to outweigh true positives.^{16,42} The American College of Emergency Physicians (ACEP) provides a level B recommendation that diagnostic evaluation be directed by the history and physical

examination, and that routine laboratory testing is low yield and not necessary as part of the ED assessment.⁸⁰

ACEP also provides a level C recommendation against routine urine toxicology testing and blood alcohol concentrations in alert, awake and cooperative patients, and specifies that transfer to psychiatric care should not be delayed to await collection of samples for toxicologic analysis.⁸⁰ However, from the psychiatrist's perspective, this testing is time-sensitive and can change psychiatric management and disposition considerably. If the emergency physician knows the patient will be transferred for psychiatric care and suspects substance abuse, it would be helpful to obtain toxicologic results as early as possible in the hospital course, but also can be done after transfer if necessary.

A final issue is if the patient is intoxicated with alcohol. At what point is it appropriate to "medically clear" the patient for a psychiatric evaluation? There are no evidence-based data to support that patients regain decision-making capacity at a particular blood alcohol concentration. Depending upon tolerance, cognition can vary widely, and patients often develop ethanol withdrawal while consequential blood alcohol concentrations persist.³⁹ Therefore, ACEP provides a level C recommendation that the patient's cognitive abilities should be the basis on which the psychiatric assessment is begun, and a period of observation can be used to see if psychiatric symptoms resolve with intoxication and a psychiatric assessment is no longer needed.⁸⁰

SUICIDE AND SELF-INJURIOUS BEHAVIOR

Suicide was the tenth leading cause of death in the United States, accounting for 38,364 deaths in 2010.²⁸ It was the third leading cause of death among 15 to 24 year olds, and accounts for 20% of deaths in this age group annually. Although suicide may be attempted or accomplished in a variety of settings and by a variety of means, it is most typically associated with psychiatric disorders and/or substance abuse, especially ethanol, and is frequently accomplished with psychoactive xenobiotics alone or in combination.

Terminology

The terms and definitions of suicide and suicidal behaviors used in this chapter have been outlined in several reports on the subject. The term suicide refers to self-inflicted death with either explicit or implicit evidence that the person intended to die. The term suicidal ideation refers to thoughts of serving as the agent of one's own death, and suicidal ideation may vary in seriousness depending on the degree of suicidal intent and the specificity of suicide plans. Suicidal intent refers to the subjective expectation and desire for a self-destructive act to end in death, and suicidal plan refers to the formulation of a specific method through which one intends to die.

A suicide attempt is a self-injurious behavior with a nonfatal outcome accompanied by either explicit or implicit evidence that the person intended to die. The related term suicide gesture generally refers to an attempt which is not felt to be medically serious, and often implies that the patient is making a "cry for help" rather than truly attempting to die; such a gesture can still result in death, even if unintentional. As defined in the literature, "serious" suicide attempts meet one of the following criteria: (1) treatment in a specialized unit (such as an intensive care unit), (2) surgery under general anesthesia, (3) medical treatment beyond gastric lavage, activated charcoal, or routine neurologic observation, (4) method with high risk of fatality (such as hanging or firearm), or (5) hospital admission longer than 24 hours.¹²

Self-harm or self-injurious behavior refers to the self-infliction of painful, destructive, or injurious acts without the intent to die. An example is the superficial cutting that occurs in a patient with a borderline personality disorder, which is actually a coping mechanism that provides psychological relief; one hypothesis is that relief is mediated by the endogenous release of opioids.⁹⁹ However, the distinction of suicidal and "parasuicidal" behaviors such as these is outside of the scope of the medical toxicologist, and a mental health professional should be consulted to help make such a distinction.

Finally, the lethality of suicidal behavior is an objective measure of the "danger to life" associated with self-injurious behavior. It is important to note that objective lethality may be distinct from subjective lethality. This occurs when a patient does not truly expect a behavior to be as medically dangerous as it turns out to be, or vice versa. For example, a patient may not be aware that an acetaminophen (APAP) overdose can be fatal, believing that its status as a "nonprescription" medication indicates that it is less likely to be fatal in overdose than a prescribed medication.

Epidemiology

Suicidal thoughts and behaviors are common. An estimated 8.3 million adults in the United States reported having suicidal thoughts in 2008, and approximately 1 million actually made an attempt that year.³⁵ Studies have consistently found that self-poisoning accounts for more than 70% of all serious suicide attempts.⁸³ While there is reportedly one suicide completion for every 25 attempts, this ratio dramatically decreases for adolescents and young adults. Among 15 to 24 year-olds, there are approximately 100 to 200 attempts for every completed suicide.⁴³

Ninety percent of suicide completers and attempters meet criteria for a diagnosable psychiatric illness, 70% have mood disorders, and 30% have alcohol abuse or dependence.⁶⁴ On average, one-third of suicide decedents test positive for

alcohol, and 65% of them have a blood alcohol concentration higher than 80 mg/dL.⁷³ Many individuals who complete suicide do so on the first attempt. Although a prior suicide attempt is still the strongest predictor of a future completed suicide, only about one in 10 attempters is successful.^{62,88} Multiple attempters also appear to have higher risk than those who make a single attempt.^{57,103} Medically serious attempts, defined as involving treatment in a specialized unit, surgery, or medical treatment beyond stomach evacuation, may be a more robust marker of risk. Those who make serious attempts tend to share with completers a higher rate of serious mental illness such as schizophrenia, bipolar disorder, or severe major depressive disorder.¹²

Suicidal or self-injurious patients are often encountered in EDs. Approximately 70% of all self-inflicted, nonfatal injuries seen in an ED are the result of a suicide attempt, and an ED visit for self-harm is predictive of a completed suicide in the future.^{23,94} Anywhere from 1% to 2.7% will commit suicide within the next year or two.^{65,94} The average annual number of ED visits for attempted suicide and self-injury has nearly doubled over the last 15 years: from 244,000 in the early 1990s to 538,000 in the mid-2000s.¹⁰⁷ Self-poisoning was the most common method at 68%, followed by cutting or piercing at 20%.⁴⁴ Increases occurred in all major demographic groups: males, females, Caucasians and African Americans. ED visits were most common among those aged 15 to 19 years.¹⁰⁷

Although the prevalence of suicide and suicidal behaviors shows significant overlap, one notable area of difference is the consistent pattern of higher rates of suicide attempts among women and of completed suicides among men.^{22,26} Men account for 80% of completed U.S. suicides at a rate highest among men greater than 75 years of age. Men are more likely to use a firearm, at rate of 57% versus 34% in women; some authors suggest this difference in method leads to the disparity in completed suicide rates as compared with women, who are more likely to self-poison.^{28,73}

Self-Poisonings

According to the National Electronic Injury Surveillance System, which surveys a select number of nationally representative hospitals, an estimated 170,000 people were treated in ED for poisonings in 2000. Sixty percent of these were classified as “probable” suicide attempts, 10% were “possible” suicide attempts, and the intent for the remaining 30% was “unclear/unknown.” Women were more likely to self-poison than men (72% vs 55%), and the highest rate of self-inflicted injury occurred in adolescents aged 15 to 19 years (especially women), followed by young adults aged 20 to 24 years. Ethnically, rates were highest among non-Hispanic Caucasians of both sexes.²³

In the 16 states participating in the National Violent Death Reporting System in 2009, self-poisoning was the third leading method of suicide (following firearms and hanging/suffocation).⁷² Detailed data from 2005 to 2007 indicates that 75% of individuals poisoned themselves with a substance (either illicit or licit, including alcohol) as opposed to other types of poison such as carbon monoxide. Seventy percent of individuals ingested just one “drug type,” defined as prescription drugs versus nonprescription drugs versus alcohol/illicit drugs. Out of poisoning deaths due to a single “drug type,” 80% were due to prescription drugs such as opioids, benzodiazepines, or antidepressants, and 10% were due to nonprescription drugs such as APAP. When individuals consumed more than one “drug type,” 45% involved alcohol or illicit drugs as part of the combination.^{25,28,72} It was estimated that for every self-poisoning death in the United States, there were 33 intentional overdoses reported to poison centers ([Chap. 136](#)), of which two ultimately went untreated.²⁹

There is a large body of literature about self-poisoning in the United Kingdom, and their data indicate proportionally higher death rates among poisonings with tricyclic antidepressants (TCAs) versus selective serotonin reuptake inhibitors (SSRIs), which is not surprising given the cardiac toxicity of TCAs. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is more toxic in overdose than SSRIs. Poisoning deaths with atypical antipsychotics such as clozapine, olanzapine, and quetiapine were increasing, especially as of the early 2000s.⁴⁹

Given that the act of suicide is a statistically rare event in the overall population, it is virtually impossible to predict who will actually commit suicide. Therefore, it is critical to identify risk factors that increase the likelihood that any individual might attempt suicide, and to identify risk factors that are modifiable ([Tables 27–3 and 27–4](#)). The identification of modifiable risk factors provides opportunities for interventions that may decrease suicide risk. Additionally, there are protective factors that mitigate the risk for suicide, and it is important to assess for the presence or absence of these factors in determining the overall risk for suicide in a patient.

TABLE 27–3. Factors Associated with an Increased Risk for Suicide

<i>Psychiatric Risk Factors</i>	<i>Neurological and Medical Factors</i>	<i>Sociodemographic Factors</i>	<i>Genetic and Familial Factors</i>
Major depressive disorder	Diseases of the nervous system	Access to firearms	Family history of suicide (particularly in first-degree relatives)
Bipolar disorder	Multiple sclerosis	Male sex (suicide completion)	Family history of mental illness, including substance use disorders
Schizophrenia	Huntington disease	Female sex (suicide attempts)	
Alcohol use disorder	Brain and spinal cord injury	Widowed, divorced, or single marital status, particularly among elderly men	
Other substance use disorders	Seizure disorders	Elderly age group	
Alcohol intoxication	Malignant neoplasms	Adolescent and young adult age groups	
Personality disorders	HIV/AIDS	Gay, lesbian, or bisexual orientation	
Bulimia or anorexia nervosa	Chronic pain syndromes	Recent lack of social support (including living alone)	
Post-traumatic stress disorder	Caucasian race	Unemployment	
Helplessness	Functional impairment	Decrease in socioeconomic status	
Hopelessness	Low concentration of serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid—(Research)	Domestic partner violence	
Impulsivity		Recent stressful life event	
Aggression, including violence against others		Childhood sexual abuse	
Agitation		Childhood physical abuse	
Factors related to current or past suicidal behavior:			
Prior suicide attempts			
Suicidal ideation			
Suicidal plans			
Suicidal intent and lethality			

TABLE 27–4. Factors Associated with Protective Effects for Suicide

Children in the home

Effective clinical care for mental, physical, and substance use disorders

Pregnancy

Family and community support (connectedness)

Religious beliefs and cultural practices

Positive social support

Skills in problem solving and conflict resolution

PSYCHIATRIC MANAGEMENT OF SELF-POISONING

Table 27–5 depicts a case of suspected self-poisoning from the starting point of prehospital care through the completion of a comprehensive assessment and treatment planning.

TABLE 27–5. Case Presentation: Suspected Self-Poisoning

	<i>Case</i>		<i>Evolution</i>		<i>Disposition</i>
Patient course	Patient found in the community unresponsive	Patient monitored in the emergency department; vital signs stable; still unresponsive	Patient lethargic but cooperative; answers simple questions	Patient fully awake and alert	Evaluation complete
Treatment course	Prehospital	Triage medical assessment	Observation and monitoring	Formal psychiatric evaluation	Treatment planning
Physician course	Patient identification Search for prescription drugs, drug paraphernalia Assessment of cardiac and respiratory function	Orogastric lavage (?) Activated charcoal (?) Diagnostic testing (blood studies, electrocardiography, urine toxicology) Contact collateral sources for history Prior records	Focused psychiatric assessment: elopement aggressive behavior decisional capacity addressing confidentiality immediate suicide risk	Comprehensive psychiatric assessment: diagnostic interviewing risk factors future risk	Treatments: medication hospitalization substance abuse counseling crisis intervention family therapy

Initial Psychiatric Management

In any case of suspected self-poisoning, a thorough psychiatric assessment is warranted. It can be helpful to call a psychiatric consult immediately after medical stabilization, even if the patient is unable to communicate, since important information such as pill bottles, ambulance reports, and the ability to call the patient's family and outside providers may be lost if the consult is delayed. Although not required for an ED assessment unless clinically indicated, it should be helpful for the psychiatrist if urine toxicology and blood alcohol concentration is obtained as early as possible.

An early, focused assessment is necessary to ascertain elopement risk and decisional capacity. Subacute residual central nervous system (CNS) effects of ingestions, such as confusion, fatigue, and fear, can dispose patients to wander or elope. The patient should be searched for weapons, pills, and other potentially toxic materials to prevent additional self-harm or ingestion in the hospital. Given that the patient's intentions remain unclear at this point, the question of unintentional versus intentional exposure to a xenobiotic cannot be completely resolved. For this reason, a high level of supervision should be maintained, and a patient should not be allowed to leave or be left unattended until an adequate assessment of the patient's mental status is completed. Depending on the architecture and organization of the ED and its personnel, it may be sufficient to place the patient in an open area in the direct line of sight of the medical staff. If such an arrangement is not possible, or if the patient is agitated and disruptive, it may be necessary to separate the patient from the general population. Under these circumstances, an individual aide should be assigned to observe the patient on a one-to-one basis. Safe physical and/or chemical restraints may be necessary to prevent further injury to both the patient and the staff.

At a relatively early point in the patient's course, when the patient can be cooperative, a more detailed psychiatric assessment is critical to address specific clinical concerns. Both history-taking and collateral contacts can help to establish the patient's preingestion mental status and baseline, as it may be difficult in an initial, time-limited assessment to differentiate a xenobiotic-induced delirium from mental illness and therefore ensure that any delirium has fully resolved. The determination that the patient is stable is not solely established on the basis of blood concentrations of a xenobiotic or ancillary medical tests, but rather when the emergency physician or medical toxicologist with an understanding of toxicokinetics and toxicodynamics deems it appropriate.⁶⁶ Although a thorough psychiatric examination is not possible until an altered mental status has cleared, it is reasonable to have the psychiatrist involved earlier for the above-mentioned reasons.

The physician should not unequivocally attribute altered mental status to poisoning or toxicity until the signs of altered consciousness have resolved and cognitive functions have returned to normal. Until that time, other toxic-metabolic and structural conditions that might coexist with, or masquerade as, toxicity cannot be excluded. If the patient's cognitive functioning is impaired by xenobiotics, then critical historical details may be unreliable.³³ It should be understood that much of what the patient reports may be ephemeral, caused by the predictable temporary and reversible effects on mood of these xenobiotics.¹⁴ However, any patient utterances about intended overdose or self-harm should be documented in the record, since it is important information to consider if the patient becomes guarded and evasive after returning to baseline mental status.

In addition to routine laboratory studies, such as complete blood count, electrolytes, renal function, and liver function tests, psychiatrists usually request thyroid function tests, B12, folate, HIV testing, and syphilis immunoglobulin G antibody or RPR; abnormalities in these laboratory values can be associated with medical disorders producing psychiatric manifestations that would affect management and disposition. However, these laboratory tests have proven to be low yield when obtained routinely and without clinical suspicion, and are not necessary as part of the ED work-up.⁸⁰

Special Issues of Capacity in Suspected Self-Poisonings. Patients may request to be discharged, refuse care, or become

aggressive. Aggression may arise from lingering effects of ingestion or withdrawal, severe anxiety, fear, anger at the loss of autonomy, or the discomfort associated with unpleasant procedures.⁸⁶ Although patients may respond to verbal limit-setting and repeated explanations of their care, they may also require pharmacologic or physical restraint and involuntary treatment. Patients are not allowed to make poor health care decisions if their ability to weigh the risks and benefits of the proposed care is limited by cognitive deficits or mental illness. In the setting of toxicity, appropriate care may be provided under the doctrine of implied consent.

The emergency exception to the doctrine of informed consent may also apply in circumstances where self-injury is suspected. The emergency exception permits forcible detention, restraint, medication over objection, and necessary medical care until psychiatric assessment can be accomplished. This includes collecting information from collateral sources without the patient's consent. After the management of the immediate medical emergency and resolution of toxicity, suspected self-injury is sufficient evidence of impaired decisional capacity for the emergency physician to hold a patient for further psychiatric assessment. The emergency physician should document the patient's objections in the medical record and indicate the basis for the determination of diminished capacity.

After the intentionally self-poisoned patient is stabilized, there may be a need for a more thorough assessment of decisional capacity. Psychiatric consultation is appropriate at this stage to help document the degree of impairment, determine the etiology, and predict the likely course.

Immediate Risk of Self-Harm. After these safety considerations are addressed, the aim of the focused psychiatric assessment moves toward a determination of immediate suicide risk. This examination should answer the following questions: What is the patient's attitude toward lifesaving care? What are the patient's current wishes with regard to living or dying? What are the patient's thoughts about his or her rescue and likely recovery?

These questions can only be answered in the course of a frank discussion between the patient and the emergency physician. The physician should not be concerned about "provoking" further self-injurious impulses by having this vital discussion; many patients will be relieved that the health care professional is speaking directly about their distress.

Reliability and Confidentiality. Mention should be made here about the difficult issues of reliability and confidentiality with regard to gathering history. Evasiveness, lack of detail, inconsistency, and improbability may lead to an unreliable history. It is appropriate to confront the patient with the implausible aspects of this history and offer an opportunity for the patient to rethink the history. This is often successful, although subsequent reports are, of course, equally suspect.

The most important step from the standpoint of both clinical care and risk management is to locate other sources of information to clarify the patient's situation. A careful review of any previous medical and psychiatric records is critical. Any pattern to a patient's presentations such as increasing frequency, more aggravated behavior, or disheveled appearance should be noted.

Collateral contacts are another important source of information, although the level of involvement, sophistication, and reliability of the collateral contacts must also be taken into account. In the interest of providing necessary medical and psychiatric care for a patient in an emergent situation, the ED staff is legally permitted to solicit information from collateral contacts without the patient's consent. However, an effort should be made to obtain consent for any broader discussion of the patient's situation with family, friends, or other physicians. The patient may express concern about the ED staff contacting a family member or counselor. Any information to be imparted to third parties can be discussed in advance with the patient. The patient may restrict consent to receiving information only and may withhold consent to impart certain information. More caution is indicated in contacting an employer. Although disclosing information about the patient without the patient's consent is a breach of confidentiality, a physician may do so in the interest of protecting the patient ([Chap. 141](#)).⁵

Comprehensive Psychiatric Assessment

The goal of comprehensive psychiatric assessment is to: (1) characterize the nature of the attempt and any ongoing suicidal ideation that might be present, (2) explore risk factors for another suicide attempt, and (3) formulate a diagnostic impression. These three elements help to determine the level of risk and guide immediate treatment and disposition planning.¹¹⁰

The best understanding of suicide at this time is that it results from intrinsic vulnerability factors interacting with external circumstances, which can be termed the "stress vulnerability." Intrinsic vulnerability may be conferred by a variety of traits such as impulsivity or conditions such as depression, anxiety, low self-esteem, low self-efficacy, loneliness, and hopelessness. External factors include stressful life events, access to lethal means, and a host of other factors, positive and negative. Poor interpersonal problem-solving skills and a perceived lack of problem-solving ability also appear to increase risk.⁴⁰

Assessing Suicide Attempts and Suicidal Ideation. The core of the suicide risk assessment is a detailed discussion of the patient's suicide attempt and any ongoing suicidal thoughts and urges. It is important to establish rapport and introduce these topics in an appropriate context in order to improve the patient's candor. This evaluation requires significant time and skillful interviewing, for which there is no substitute. This approach will enhance both the therapeutic quality of the

interview and its reliability.

The clinician should explore the exact details of the attempt, including precipitating factors that may have begun days or weeks prior to the actual act. It is critical to determine the level of actual and intended lethality, along with the seriousness of the intent. Why did the patient make an attempt on that day or time? Understanding the patient's thought process can help to gauge the extent of impulsivity versus planning involved in the attempt. Signs of premeditation and planning are concerning, such as organizing one's affairs (giving away possessions, ensuring a will is updated) or writing goodbye letters (such as a phone call, internet posting or text message). It is crucial to determine if the patient expected to be found, and if any effort was made to notify someone about the impending attempt such as a phone call, internet posting, or text message. How was the patient discovered, and by whom? A patient who overdoses alone in a hotel room is very different from someone who overdoses in the bedroom while the family is at home. Current feelings about surviving should also be assessed: Is the patient relieved or upset to be alive? Is there currently active or passive suicidal ideation? How forthcoming does the patient appear to be when discussing this? Other important information includes prior suicide attempts and their lethality and circumstances, the frequency and duration of suicidal ideation in the past, prior psychiatric treatment, prior and current medication trials, and a detailed substance abuse history. Psychological factors such as reactivity to positive and negative external events and subjective distress are also important to explore. The social history should focus on interpersonal conflict, stressors within romantic or family relationships, and employment or financial concerns. Current support systems or lack thereof are important to note, as are feelings of isolation and abandonment, which can all be contributing factors.⁶⁷

The communication of suicidal ideas either directly or indirectly should not be misconstrued as a "cry for help" and hence evidence of lower risk. Communication is probably related to the degree of preoccupation with morbid thoughts and to personality characteristics that dispose individuals to revealing their thoughts to various degrees.⁷⁴ In psychological autopsy studies, approximately 50% to 70% of those who completed suicides gave some warning of their intention, and 30% to 40% disclosed a direct and specific intent to kill themselves.^{10,91}

Risk Factors for Suicide

The goal of assessing suicide risk factors is to identify factors that may increase or decrease the level of suicide risk in a particular patient, which will enable the clinician to develop a plan that addresses the modifiable factors. For example, hopelessness is one such modifiable risk factor, which would likely improve with time and treatment; when risk factors such as hopelessness can be modified on the inpatient psychiatric ward, an inpatient admission is warranted to help decrease the risk of suicide. Unfortunately, to date no study has ever identified one specific risk factor or set of risk factors as specifically predictive of suicide or other suicidal behavior; therefore, the assessment is ultimately based on clinical judgment. Despite the lack of such predictive factors for suicide, there is a large body of evidence on the multiple risk factors that contribute to suicide risk, and a growing body of evidence on protective factors (Tables 27–3 and 27–4). Knowledge of this evidence is critical to informing the clinical determination of suicide risk.

Risk factors are additive, with suicide risk increasing with the number of risk factors that are present, but certain risk factors interact synergistically to increase suicide risk. The combined risk of concomitant depression and alcohol intoxication may be greater than the sum of the risk associated with each in isolation. Certain risk factors, such as a recent suicide attempt associated with a high degree of lethality or the presence of a suicide note, should be considered serious on its own, regardless of whether other risk factors are present.³⁴

A number of avenues of inquiry suggest that violent suicide attempts are associated with a persistent deficiency in brain serotonin concentrations. Impulsive types of aggression and impulsive suicidal behavior have been linked to serotonergic dysfunction in prefrontal cortical regions of the brain.³⁶ This deficiency has been measured in the postmortem brains and spinal fluid of suicide victims and survivors of violent attempts as compared to nonviolent attempts and to other patients. Hopelessness has also received a significant amount of study as a potential predictor of suicide; unfortunately, it appears to have a high sensitivity but a low specificity.¹³ However, identifying hopelessness does provide for an intervention.

While much is known about the risk of suicide for various groups over time, little can be said with certainty about an individual patient at a particular point in time. The risk of suicide increases 50 to 100 times within the first 12 months after an episode of self-harm as compared to the general population risk. About one-half of all people who commit suicide have a history of self-harm, and this increases to 60% in juveniles.⁶ Unfortunately, there is no "typical" suicidal patient or clinically useful test or rating scale at this time. Albeit, while one investigator was able to prospectively identify almost all of those who ultimately died by suicide (97% sensitivity), the investigator overpredicted suicide by almost one-half (56% specificity).⁸⁸ However, there is also no patient in distress for whom the risk of suicide is so remote that it need not be considered.

Ultimately, most persons belonging to a high-risk group do not commit suicide, and some individuals with no apparent risk factors do. Many risk factors are not modifiable. This type of information, then, weighs most heavily in the assessment in the absence of other more specific data, early in the hospital course, or in the case of the uncooperative or hostile patient. The best foundation for treatment planning and clinical decision making is direct examination and clinical diagnosis.⁴³

Psychiatric Illness and Suicide. One major consideration in suicide risk assessment is the occurrence of severe mental illness. Suicide risk for individuals with severe mental illness is 20 to 40 times higher than it is for the general population.⁷⁵ Psychological autopsy studies, which focus historically on the decedent's intentions and mental state prior to death, have consistently revealed major psychiatric illness to be a factor in suicide and present in 93% of adult suicides.^{68,75,89,92} This is also true of those who make medically serious suicide attempts.^{13,68} In particular, prospective cohort studies and retrospective case control investigations have revealed clinical depression and bipolar disorder to dramatically increase suicide risk.^{60,74,109} For mood disorders, factors correlated with current suicidality include current depression, severe anxiety, anhedonia, panic, insomnia, ambivalence, and acute alcohol abuse.⁷⁴

After mood disorders, chronic alcoholism is the most commonly reported disorder and is present in approximately 20% of cases. Moreover, alcoholic patients who also experience episodes of depression are at a higher risk for suicide than patients who present with either disorder separately. There are considerable data that other types of substance use such as heroin, cocaine, or polydrug use also increase the risk of suicidality when psychiatric illness is present, and this seems to be especially true in depressive or dysphoric mood disorders (unipolar, bipolar II, and mixed types of bipolar I disorders).^{15,108} As a result, any assessment conducted on a patient with a substance use history must include an examination of symptoms of major depression or bipolar illness.^{47,111}

Patients with schizophrenia are at risk for suicide at rates comparable to major depression and are 20 times more likely to attempt suicide than the general population.¹⁰⁶ Approximately 50% of patients with schizophrenia will attempt suicide and 13% of schizophrenic patients will successfully complete suicide.^{17,106} Additionally, between 5% and 18% of patients with severe borderline personality disorder (especially those patients with comorbid depression) ultimately kill themselves.^{52,68,102}

The ability to treat psychiatric disorders such as mood disorders, schizophrenia, borderline personality disorder, and alcoholism suggests that most suicides are preventable. Indeed, a suicide prevention program designed for general practitioners in Sweden demonstrated evidence for prevention based on the detection and treatment of depression.⁹⁰ The Centers for Disease Control and Prevention reported that psychiatric problems in US EDs represented approximately 3% of mental illness visits, which is significantly lower than the national psychiatric rate of 20% to 28%.²⁷ This suggests that significant psychiatric underdiagnosis is occurring in the ED. Consequently, emergency physicians must enhance the comprehensive nature of their psychiatric screening to identify suicidality and concomitant mental disorders in patients presenting with self-injury.

Treatment

Following a comprehensive psychiatric assessment, the next step is deciding on treatment alternatives. Any patient who has made a suicide attempt must be considered to be at risk for another attempt and some further intervention is warranted. The risk of a subsequent lethal attempt is approximately 1% per year over the first 10 years. The risk is highest during the first year. Suicide is most commonly a symptom of an underlying disease process, so the goal is to diagnose and treat the underlying disease in the setting that is the least restrictive while also ensuring safety for the patient. The treatment alternatives available will depend on the psychiatric sophistication of staff available to the ED at any given time. This section describes the commonly used interventions in the ED; they can be employed singly or in combination.

Psychotropic medications can be used acutely in the treatment of severe anxiety or psychosis; however, in the case of antidepressants, several weeks are required for therapeutic effect, so their immediate use is not indicated in the ED. However, if the patient is to be discharged to the community with follow-up, it is reasonable for a psychiatrist to start an antidepressant in the ED setting. There are concerns about prescribing medications with relatively high potential for lethality in overdose, such as the TCAs and nonselective monoamine oxidase inhibitors, to persons who have recently attempted suicide. Medications for medical illnesses, such as insulin, should also be considered for risk of overdose. However, newer antidepressants, particularly the SSRIs, can be used as first-line drugs for treatment of most depressions and are relatively safe in overdose.

In 2007, the US Food and Drug Administration (FDA) ordered that all antidepressants should include a black box warning stating that there is an increased risk of suicidality in children, adolescents, and adults younger than 24 years of age. This risk was not increased in adults 25 to 64 years of age, and was actually decreased in adults older than 65 years of age. Further studies have confirmed this age-related difference.^{18,101} Proposed explanations include an ascertainment bias, activation and/or akathisia as an adverse event in the first few weeks, or increased energy resulting in increased ability to carry out suicidal plans. Nonetheless, the FDA and other authors emphasize that untreated depression also carries a risk of suicide, and treatment options should be carefully weighed with regard to their risks and benefits. Therefore, the initiation of antidepressant therapy by the nonpsychiatric physician is not recommended unless a tight linkage can be made between discharge and immediate (within days) aftercare by either a community outreach team or a crisis clinic.

Patients with depressive disorders may suffer from significant anxiety, as may patients with overwhelming situational stressors such as job loss, new financial hardship, bereavement, or divorce. The prescription of a short course (days to weeks) of a benzodiazepine may provide significant relief to the patient in crisis. Yet again, close psychiatric follow-up is

essential.

After the patient's immediate symptoms have been treated in the ED, the next treatment decision is determining the setting in which further treatment may safely be provided. Not all patients with suicidal ideation or even significant attempts necessarily require hospitalization, and there is still a substantial stigma attached to psychiatric hospitalization. In general, hospitalization should be used if less restrictive measures cannot ensure the patient's safety. If significant doubt exists about the safety of outpatient treatment, then the patient should be observed in the ED for further evaluation, admitted to a general hospital with close nursing supervision, or admitted to a psychiatric unit. "Holding beds," now available in some larger psychiatric EDs, are ideal for this purpose. Some localities may also have crisis outreach services that follow the patient after discharge from the ED and can provide appropriate monitoring and continuity of care.

Patients most likely to respond to interventions in the ED are individuals who have been stable, until recently but now, as a result of some external event, may find their way of life threatened. This acute change results in a painful state of anxiety and the mobilization of some combination of adaptive and maladaptive coping strategies. Finally, a second event, the precipitant, intensifies the anxiety to the point that the patient cannot tolerate the instability and is thrown into crisis. The patient then feels desperate and may be completely immobilized or vulnerable to various strong impulses including the impulse to run away, strike out at someone else, or kill him or herself. Reality testing is preserved, and no major psychiatric syndrome is present. The patient accurately perceives his or her situation, understands that the current reaction is a psychological problem, and is highly motivated to obtain help. The crisis may last for a matter of hours or weeks prior to the ED presentation and will ultimately resolve. Such patients respond well to crisis intervention and may actually undergo some positive development in the course of treatment.

By contrast, patients whose condition has been deteriorating for some time in the absence of significant stressors, and who appear on examination to be suffering from severe depressive symptoms, are unlikely to benefit rapidly from supportive techniques. If such patients present with suicidal ideation or attempts, it will be difficult, although not impossible, to manage them outside the hospital.

Outpatient settings have the advantage of maintaining the patient's functioning as much as possible. Work and childcare responsibilities, financial obligations, and social relationships are not disrupted. Unnecessary regression is halted. The patient can assume more responsibility for his or her outcome, and independence helps preserve self-esteem. These individuals remain closer to and more engaged with the people and situations with whom and with which they must learn to cope. Their morale may be rapidly improved by the combination of support, planning, and modest early treatment successes.

However, in some cases, these same factors may be disadvantageous. Routine tasks may seem overwhelming. High levels of conflict may render major relationships at least temporarily unworkable. Inpatient settings offer the advantage of respite, high levels of structure, more intensive professional and peer support, constant supervision, and, usually, more rapid pharmacologic and psychosocial intervention.

The choice of inpatient or outpatient setting will depend on the balance of strengths and weaknesses of the patient, the involvement and competence of family or friends, the availability of a therapist in the community, and the ongoing stresses in the patient's life. This decision is best made by a psychiatrist. Because a psychiatrist is not always present in many facilities, a trained mental health professional should optimally be on call to every ED. This may be a psychiatric social worker, nurse clinician, or psychologist. When such services are not available, it is appropriate to detain patients in the ED until a practitioner with specific competence is available or to transfer the patient to another facility for evaluation. Every U.S. state has laws that provide for the involuntary commitment of the mentally ill under circumstances that vary from state to state ([Chap. 141](#)). Any acute, deliberately self-injurious behavior would generally qualify. Chronic, repetitive dangerous behavior that is not deliberate, such as frequent unintentional opioid, alcohol, sedative-hypnotic, or illicit "recreational" psychoactive drug overdoses, warrants careful evaluation. In the absence of psychiatric illness, involuntary treatment is usually not necessary, but should be considered carefully if a patient appears unable to achieve self-care. The practitioner should be familiar with the criteria for commitment and the classes of health care professionals so empowered under state law.

There are other treatment interventions that can be provided in the emergency setting, including crisis intervention, substance abuse counseling, and family therapy. A single session in the ED may be sufficient to defuse a crisis or to spur the drug-abusing patient to seek help. Alternatively, the intervention may be initiated in the ED and continued as an outpatient.

Crisis intervention is a brief, highly focused therapy that seeks to deconstruct how a crisis occurred, with the intent of examining the patient's role. Often, patients have distorted perceptions of the crisis, and a gentle "correction" of catastrophic thinking can be extremely helpful. The crisis is presented to the patient as an unfortunate and perhaps tragic experience that the patient can overcome. Ideally, the patient should have a relief of symptoms and learn how crises may be avoided in the future. This insight intervention will likely fail for patients with severe depression because of the presence of profound hopelessness. It is most successful for patients who give a history of high functioning just prior to the crisis.

Interestingly, sustained contact with patients via letters, postcards, or telephone calls can reduce suicidal behavior in the months after their presentation. A toxicology service in Australia found that a "postcard intervention" significantly

reduced the rate of repeated self-poisoning by patients who presented to their ED for self-poisoning.²¹ The postcard was mailed to patients in a sealed envelope eight times over the 12 months after their initial presentation, and simply stated: “It has been a short time since you were here, and we hope things are going well for you. If you wish to drop us a note we would be happy to hear from you. Best wishes.” Although the proportion of patients who self-poisoned again did not differ in the experimental versus control group, the total number of self-poisoning episodes were halved for the experimental group on follow-up 24 months later.²¹ Follow-up data at 5 years indicated that this benefit was sustained, and that psychiatric admissions were reduced by one-third.²⁰ Other studies examining letter-writing or postcard interventions in various clinical settings have also shown some benefit when examining rates of attempted or completed suicide or psychiatric emergency department visits.^{63,71,84} Given that such interventions do not require many resources and are quite cost effective, they appear promising.

“Contracting for safety” was a popular technique in the past, and consists of patients being asked whether they can remain safe and agree not to engage in self-harm. However, there are no empirical data to show that it is effective, and in court cases it has not been protective in terms of liability for the clinician. It is not recognized as part of the standard of care for the suicidal patient, and if anything, it seems to provide the clinician with a false sense of security. Its use is not recommended except as a technique to engage in a larger discussion of a safety plan that delineates scenarios the patient might face after leaving the hospital, and possible coping strategies.⁵³

VIOLENCE

Aggression presents unique challenges to the emergency physician, the psychiatrist, the nurses, and the other staff. Moreover, aggression is intimately related to suicidal behavior. Chronic aggression and impulsivity are risk factors for suicidality. Like suicidal patients, aggressive patients are difficult to treat and they tend to elicit strong negative reactions in ED personnel.⁹⁶ In one study of violence in the ED, directors of emergency medicine residency programs were surveyed as to the frequency of verbal threats, physical attacks, and the presence of weaponry in the area. Of the 127 institutions surveyed, 74.7% of the residency directors responded; 41 (32%) reported receiving at least one verbal threat each day; moreover, 23 (18%) reported that weapons were displayed as a threat at least once each month. Fifty-five program directors (43%) noted that a physical attack on medical staff members occurred at least once a month.⁷⁷

Another study involved a retrospective review of university police log records and ED staff incident reports to examine the problem of violence in the ED setting. Almost 75% of the incidents occurred during the evening or night. Of the 686 episodes of violence in this study, more than 25% required physical restraint or removal from the premises. In addition, it was found that the hospital security responded to the ED nearly twice daily.⁸⁷ These studies underscore the need for timely identification of the violent patient, as well as appropriate management for this diagnostically heterogeneous group.³⁸ The assessment and management of the violent patient should include provisions for patient and staff safety as well as a thorough search for the cause of violent behavior.^{69,96}

This section addresses the differential diagnosis of violent behavior, the pharmacotherapy of aggressive and/or agitated behavior (often termed “chemical restraint”), and the use of seclusion and physical restraint. It also provides an overview of potential risk factors for violent behavior.

Stress-Vulnerability Model of Aggression

As in the case of suicide, there are many and varied causes of violent behavior, some more social and some more medical in nature. The stress-vulnerability model suggests that violence should be considered as the outcome of a dynamic interaction among numerous factors both intrinsic and extrinsic to the individual, some of which promote and some of which ameliorate the potential for violent behavior at any given moment. Education may provide alternatives to violence, but a xenobiotic-induced delirium will render any education ineffective since delirium prevents patients from reasoning or exercising impulse control. Once confused, the patient may misinterpret health care efforts in a paranoid manner, and become violent under circumstances that would not normally be sufficient to provoke a violent outburst. Some patients, on the other hand, come from cultures in which aggressive behavior is more acceptable, and these patients require little stress or provocation before responding in what can be perceived as aggression by Western cultural standards.

In the ED, likely medical sources of vulnerability include metabolic derangements, exposure to xenobiotic (both licit and illicit) withdrawal syndromes, seizure disorders, head trauma, psychosis, and personality disorders. Additionally, patients with severe pain, delirium, or extreme anxiety can respond to the efforts of emergency personnel with resistance, hostility, or frank aggression.

Prediction of Violence

Research on risk factors for community violence may not apply to the prediction of inpatient violence. Some researchers have postulated that violence committed outside the hospital may not be predictive of inpatient violence and that hospital

violence may result from the interaction of patients with specific factors found in the hospital environment.^{41,96} Other studies are contradictory.⁹⁸ Consequently, prior violence is not a perfect predictor of future violence. Other factors, such as mental illness and substance abuse, need to be examined to make meaningful predictions of inpatient violence for each individual case.⁹⁶ One study found that the most common types of hospital violence were incidents of aggression against objects in the hospital (57%), violence directed against the hospital staff (28%), and violence directed against other patients (14%).⁹⁷ In this study, men did not commit significantly greater incidents of violence than women. Other studies concur that men are not necessarily more of a risk for inpatient violence than women. For example, researchers examining inpatient violence found that close to half of the violent incidents were committed by women, and the number of violence-related injuries committed by men and women inpatients were almost proportional to the ratio of men and women inpatients on the unit.^{76,89} The conclusion was that gender should not be considered a risk factor for inpatient violence. Long hospitalization was not considered a factor predictive of violence for the majority of inpatients. As with outpatient violence, the correlation of violence with younger age appears to hold true in the inpatient setting.^{82,89,90}

Substance Use

The association between substance use and violence is well established. Alcohol is found in the offender, the victim, or both in one-half to two-thirds of homicides and serious assaults.^{30,89} Substance use is seldom the sole cause, but it may contribute to violence in a number of ways. The direct pharmacologic effects include disinhibition and misinterpretation, suspiciousness, or paranoia. Psychological effects of substance use include cultural expectations of appropriate behavior under the influence and the ability to excuse or disavow inappropriate behavior that occurs while intoxicated. Substance use then interacts with other physiologic, cognitive, psychological, situational, and cultural factors including any underlying mental illness. A tripartite model has been described: (1) systemic violence related to drug distribution, (2) economic compulsive violence associated with the criminal activity necessary to sustain a drug habit, and (3) psychopharmacologic violence resulting from the direct effects of the particular xenobiotic.^{55,56}

Mental Illness

The relationship between mental illness and violence is also complex. Efforts made to destigmatize mental illness have confused the issue, but it seems clear that mental illness is associated with an increased risk for violence.⁸⁹ In one large epidemiologic study, the prevalence of violence for those with no mental illness was 2%. Schizophrenia was associated with an 8% rate of violent behavior, and other mental disorders all had similar prevalence of approximately 12%. But of all respondents reporting violent behaviors, 42% had an SUD. Substance use more than tripled the rate of violence for individuals with schizophrenia. Mental illness appears to reduce the threshold for aggression, and the more comorbid conditions present, the greater the risk.^{85,104,105}

Researchers consistently find a greater prevalence of personality disorders among violent inpatients than among nonviolent inpatients.²⁴ However, antisocial personality is the condition most strongly associated with both substance use and aggression. In one study, when the history of juvenile deviant behavior was controlled for alcohol, the drug most commonly associated with violence, it accounted for only 2% of the violent behavior.

In conclusion, some aggressive behavior is attributable to the direct pharmacologic effects of xenobiotics, but probably represents only a modest fraction. Substance use is often implicated in violent behavior in the community, it can occur as a coincidental part of the lifestyle of violent individuals, and both substance use and violence are related to common underlying characteristics such as a personality disorder.

Additional Factors in Aggressive Behavior

Many of the factors correlated with aggression are easy to observe and monitor in the hospital, yet some additional factors may not be as easy to detect. For example, one study found that most violent incidents in the hospital occur on Mondays and Fridays, with very few incidents on weekends. Furthermore, researchers have postulated a seasonal variation of violence.³² There is an increase in the frequency of assaults by inpatients during the winter months, and it has been hypothesized that increased population density, cold temperature, and less sunlight during the day could account for the increased violence. This finding is in contrast to the literature on outpatient violence, which has reported greater incidence of violence during the warmer months.⁶ However, this same review conceded that any extreme temperature could evoke aggressive feelings and frustration. Yet another study examined the relationship between temperature and violence and found that more aggressive acts occur during the summer months, both in the hospital and in the community.⁵⁰ They cited several explanations, one of which was that the high rate of staff turnover (eg, vacations) disrupts the social networks that the patients have established, and evokes aggressive feelings.

Although it is unclear whether cold temperatures can provoke aggression as much as it has been established that heat can, it does seem clear that overcrowding and social stressors can lead to violent behavior. If the effects of temperature and social stressors (eg, holidays) correlate so drastically with violence in the community, it is likely that such effects would

have even more impact when comorbid with severe mental illness, substance use, or any of the other risk factors of aggression.

Assessment of the Violent Patient

The comprehensive evaluation of the violent patient should include a complete physical examination. The examination may reveal the underlying cause of the violent behavior as well as ensuring the treatment of any secondary patient injuries. Laboratory analysis may include blood chemistries (glucose, electrolytes, including sodium and calcium), a complete blood count, liver function tests, thyroid function tests, lumbar puncture and/or neuroimaging as guided by the examination and clinical history.

Substance Intoxication and Withdrawal. Illicit xenobiotic and alcohol use often present with symptoms of violence. Please refer to subsequent chapters for details on presentations of acute intoxication for specific substances.

Withdrawal syndromes can also promote aggressive behavior as a consequence of physical discomfort or anticipatory anxiety. Patients experiencing any of these symptoms may become aggressive, verbally abusive, or threatening. Prompt recognition of these syndromes and immediate treatment can prevent some aggressive outbursts. Because drug use is often concealed, is difficult to ascertain on clinical grounds, and frequently contributes to violent behavior, urine and blood toxicological studies may be useful to enhance the understanding and long-range treatment of some patients.⁸⁹

Alternative Etiologies. Delirium can be a cause of aggression. Patients are often suddenly confused, frightened, or frankly psychotic as a result of impaired perception. Patients may require sedation or physical restraint in order to prevent injury to themselves as well as staff members.

Although persons with psychotic disorders are not generally aggressive, there are aspects of their psychosis that place them at risk for aggressive behavior. Paranoid ideation can serve to promote misperceptions of impending bodily harm (“They’re trying to kill me”), sexual victimization (“Men and women are raping me”), or humiliation (“Everyone is laughing at me”). It follows that these fearful perceptions might provoke violent reactions in a patient. Hallucinations can lead to aggression, either when patients explicitly follow the instructions of a command auditory hallucination or in reaction to the anxiety and fear that patients can experience with loud or persistent auditory hallucinations (“hearing voices”). Patients with either borderline or antisocial personality disorder are at risk for violent acting out as a result of poor impulse control and impaired frustration tolerance in the context of poor coping skills.

Violence risk is also associated with cognitive dysfunction. Both acute mental illness and chronic substance use can result in neurologic impairment. Psychiatric patients with compromised cognitive abilities such as impaired attention, memory, or executive functioning, such as reasoning and planning, are found to be at increased risk for violence.⁸⁹ Patients presenting with cognitive impairment may also be at increased risk for committing acts of violence in the ED.

Treatment

The acute pharmacotherapy of violent behavior is directed simply at reducing the level of arousal. If agitation and violent outbursts are viewed as transient disturbances of the usual treatment relationship between the physician and patient, then pharmacotherapy, seclusion, and restraint are to be used as needed to restore that relationship for the benefit of the patient as well as staff.² Sleep delays rather than promotes assessment, may further frighten or anger the patient, and does not guarantee elimination of the agitated state on awakening. There are two main approaches to controlling aggressive behavior: chemical restraint and physical restraint.

Chemical Restraint. Chemical restraint is defined as “chemical measures for confining a patient’s bodily movements, thereby preventing injury to self or others and reducing agitation.”³⁷ Given that aggression can result from multiple etiologies, there is much debate about the specific sedative and route of administration that should be used. Overall, it has been found that both benzodiazepines and antipsychotics resulted in rapid control of agitation and aggression.^{19,45,74,76}

Haloperidol has been safely used in the treatment of agitation and aggression in patients with psychoses, acute alcohol intoxication, and delirium.^{1,19,74,76} It can be administered orally, intravenously, or intramuscularly. Dosing intervals range from 30 minutes to 2 hours, with a usual regimen of haloperidol 5 mg given every 30 to 60 minutes; most patients respond after one to three doses. Older studies indicated that the dose of haloperidol needed to achieve sedation rarely exceeded a total of 50 mg in acute management, but it is unusual that more than 20 mg is used today.^{78,79} Most psychiatrists would switch to a second-generation antipsychotic such as olanzapine or add a mood stabilizer such as valproic acid rather than continue to titrate haloperidol.

Benzodiazepines are also quite effective for sedation; their use has been examined in patients with psychoses, stimulant intoxication, sedative-hypnotic and alcohol withdrawal, and postoperative agitation.^{54,81} Diazepam may be given as intravenous (IV) 5 to 10 mg, with rapid repeat dosing titrated to desired effect. Because diazepam is poorly absorbed from intramuscular (IM) sites, its preferred route of administration is either IV or oral. Lorazepam 1 to 2 mg or midazolam 5 to 10 mg may be given orally or parenterally and repeated at 30- or 15-minutes intervals, respectively, until the patient is calm (Antidotes in Depth: A23). Midazolam is frequently used in the ED due to its quick onset of action and short half-life

of 1 to 4 hours, but it has a significant amnestic effect; lorazepam may be preferable since it is less amnestic and will provide longer anxiolysis given its slower elimination half-life of 10 to 20 hours.

If a patient is agitated in the context of alcohol intoxication, antipsychotics can be used but benzodiazepines should be avoided due to the potential to cause additive respiratory depression. Benzodiazepines may have a unique role in the treatment of agitation secondary to cocaine intoxication ([Chap. 78](#)). Antipsychotics, particularly low-potency antipsychotics (such as chlorpromazine), lower the seizure threshold in animals, so their use for patients with cocaine/amphetamine toxicity or alcohol/sedative-hypnotic withdrawal should be avoided. Some studies suggest that the combined use of lorazepam with antipsychotics in patients with known psychiatric illness and delirium afforded relief of psychotic symptoms while allowing for a reduced dose of antipsychotic medications.^{1,31,95} On psychiatric services, the combination of haloperidol and lorazepam is still the most frequently used IM pharmacotherapeutic intervention, likely due to the relative lack of data for second-generation antipsychotics combined with lorazepam.⁶¹

Special concern has been raised about oversedation and respiratory depression with IM olanzapine, given that eight fatalities were reported in the European literature when olanzapine was used in excessive dosages or combined with benzodiazepines and/or other antipsychotics; although significant comorbidities were present in the patients who died, it is now recommended that IM olanzapine should not be coadministered with other CNS depressants.¹¹ In general, concerns regarding respiratory depression mandate careful observation and monitoring of patients receiving sedation with any xenobiotic.

Physical Restraint. Isolation and mechanical restraints are also used in the treatment of violent behavior. Isolation or seclusion can help to diminish environmental stimuli and thereby reduce hyper-reactivity. However, a few aspects are worth mentioning: Because seclusion is defined by a condition of very limited interactive and environmental cues, it is not indicated for patients with unstable medical conditions, delirium, dementia, self-injurious behavior (cutting, head banging), or those who are experiencing extrapyramidal reactions as a consequence of antipsychotic medication (such as an acute dystonic reaction).³ Mechanical restraint is used to prevent patient and staff injury, although it does occasionally lead to patient and staff injury itself.^{9,61} All facilities should have clear, written policy guidelines for restraint that address monitoring, documentation, and provisions for patient comfort. Frequent reassessment of the patient and documentation of the need for continued restraint are essential, and should be performed according to state law. The Joint Commission standards require a renewed restraint order every 4 hours, but the physician (or licensed independent practitioner) is only required to evaluate the patient within the first hour and then every 24 hours. Other staff members provide ongoing monitoring at time intervals specified by the institution. The Joint Commission notes that state laws should be followed when they are more restrictive. Although there are limited controlled data at this point, numerous interventions are being considered in psychiatric settings as alternatives to de-escalate a patient before restraints are employed, and there is a general trend to attempt to reduce the use of mechanical restraints, although it seems doubtful that such restraints can be eliminated entirely.¹⁰⁰

Training. Finally, training in the management of aggression helps to reduce violence and injuries through the early identification of impending episodes of violence, use of verbal techniques to defuse incidents, and appropriate physical techniques to minimize injuries in those that occur. It is necessary for health care providers to maintain their skills through training and to advocate for continuing medical education on this topic at the workplace.^{17,93} See [Tables 27–6 and 27–7](#) for violence warning signs and the S.A.F.E.S.T. Approach.

TABLE 27–6. Violence Warning Signs

- Threatening statements
- Clenched fists
- Loud vocalizations
- Body posturing, rapid/shallow breathing
- Agitated movements
- Pacing
- Staring
- Striking at inanimate objects

TABLE 27–7. S.A.F.E.S.T. Approach⁴⁸

Spacing	Maintain a safe distance Allow both patient and you to have equal access to the door (but you should be closest) Do not touch the patient
Appearance	Maintain empathetic and professional detachment Use one primary person to build rapport Have security available as a show of strength
Focus	Watch the patient's hands Look for potential weapons Watch for escalating agitation
Exchange	Attempt to de-escalate by use of calm/continuous talking Avoid punitive or judgmental statements Use good listening skills Elicit patient cooperation by targeting the current problem
Stabilization	By the least restrictive means possible: Physical restraints Sedation (benzodiazepines) Antipsychotics
Treatment	Treat underlying cause May need to treat involuntarily

SUBSTANCE USE DISORDERS

SUDs are characterized by compulsive drug seeking and drug taking in a setting of loss of control, continued use despite negative consequences, and functional impairment in several areas of a person's life. They are highly comorbid with suicidality, violence, and mental illness as described above in previous sections. Prevalence rates of substance use in the ED range from 9% to 47%, depending on the sample.⁴⁶ ED physicians and medical toxicologists are in a unique position to identify substance use disorders and refer patients to additional treatment services. There is an extensive array of evidence-based treatment for SUDs, but fewer than 10% of persons with SUDs in the United States receive substance abuse treatment.

DSM-5 Diagnoses

The psychiatrist's diagnostic handbook, the Diagnostic and Statistical Manual of Mental Disorders (DSM), codifies various diagnoses involving the use of substances. The latest version is the 5th edition, DSM-5, which was released in 2013.⁴ While previous versions of the DSM differentiated "substance abuse" and "substance dependence," the DSM-5 combines these categories into an overarching "substance use disorder" diagnosis with mild, moderate, and severe specifiers. "Substance abuse" was considered to be a milder or earlier phase of an addictive disorder, while "substance dependence" was the more severe manifestation; however, in practice, substance abuse criteria were sometimes quite severe, and the distinction was not found to be clinically helpful. In the combined "substance use disorder" criteria found in DSM-5, the criterion of recurrent legal problems has been eliminated, and a new criterion for "craving" has been introduced. Table 27-8 shows the criteria for an alcohol use disorder, and the reader can use this as a template to substitute other substances of abuse as well.

TABLE 27-8. DSM-5: Criteria for Alcohol Use Disorder (2013)

Alcohol Use Disorder

Diagnostic Criteria

A. A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.

4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, as defined by either of the following:
 - a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
 - b. A markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following:
 - a. The characteristic withdrawal syndrome for alcohol (refer to Criteria A and B of the criteria set for alcohol withdrawal).
 - b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

Specify if:

- **In early remission:** After full criteria for alcohol use disorder were previously met, none of the criteria for alcohol use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, “Craving, or a strong desire or urge to use alcohol,” may be met).
- **In sustained remission:** After full criteria for alcohol use disorder were previously met, none of the criteria for alcohol use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, “Craving, or a strong desire or urge to use alcohol,” may be met).

Specify if:

- **In a controlled environment:** This additional specifier is used if the individual is in an environment where access to alcohol is restricted.

Code based on current severity: Note for ICD-10-CM codes: If an alcohol intoxication, alcohol withdrawal, or another alcohol-induced mental disorder is also present, do not use the codes below for alcohol use disorder. Instead, the comorbid alcohol use disorder is indicated in the 4th character of the alcohol-induced disorder code (see the coding note for alcohol intoxication, alcohol withdrawal, or a specific alcohol-induced mental disorder). For example, if there is comorbid alcohol intoxication and alcohol use disorder, only the alcohol intoxication code is given, with the 4th character indicating whether the comorbid alcohol use disorder is mild, moderate, or severe: F10.129 for mild alcohol use disorder with alcohol intoxication or F10.229 for a moderate or severe alcohol use disorder with alcohol intoxication.

Specify current severity:

- **305.00 (F10.10) Mild:** Presence of 2–3 symptoms.
- **303.90 (F10.20) Moderate:** Presence of 4–5 symptoms.
- **303.90 (F10.20) Severe:** Presence of 6 or more symptoms.

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Neurobiology of Substance Use Disorders

It is helpful for the emergency physician to be able to recognize the signs and symptoms of an SUD. Although the DSM-5 criteria are straightforward, many patients may not be forthcoming and may not share the extent of their drug use and its

effect on their lives. In those cases, one can look for inconsistencies in either the history or the presentation. Denial is often prominent. For example, a patient might present intoxicated with an arm injury, but is unconcerned and dismissive about the incident when no longer intoxicated. One would expect a patient to demonstrate appropriate concern, rather than just “wanting to leave.”

One of the more vexing aspects of substance-dependent patients is the frequency with which they minimize the dangerousness of their actions or the severity of their presentation. This can be interpreted as a sign of prefrontal cortex dysfunction due to the addiction. The patient is incorrectly processing risks/benefits, and is increasingly driven to compulsive drug use at the cost of natural rewards such as food, sex, love, or safety. Initial drug use results in relaxation, euphoria, stress relief, or a variety of other psychological effects, as mediated by the dopaminergic “reward pathway.” It was traditionally taught that dopamine release in this pathway was synonymous with experiencing “pleasure,” but it has become apparent that the function of dopamine is more accurately portrayed as indicating “salience” (or importance). A burst of dopamine in this pathway confers enhanced salience onto a particular stimulus or aspect of the environment, which means that this stimulus now appears more important and there is greater motivation to pay attention to it. One can see how this works well as a survival system, with natural rewards such as food and sex resulting in increased dopamine and subsequently greater salience. Drugs of abuse essentially “hijack” this pathway by directly producing supraphysiologic dopamine increases that would normally not occur.⁷⁰

However, activity in the reward pathway only explains the acute effects of drugs, and does not mediate any enduring behavioral changes. The cravings and compulsive behavior that occur in addiction result from glutamate-mediated circuits that develop in the prefrontal cortex and establish aberrant connections to the limbic system. Areas affected include the orbitofrontal cortex, which regulates salience attribution, and the anterior cingulate gyrus, which regulates inhibitory control. Late-stage addiction is characterized by derangements in these areas of the prefrontal cortex, which lend increased salience to drugs of abuse coupled with reduced ability to inhibit behavior. Environmental “triggers” established by classical conditioning can subsequently act to induce powerful states of craving and motivation to find and use a particular drug.⁷⁰

Despite our sophistication in describing the neurobiology of addiction, it can be challenging for an individual clinician to act accordingly when dealing with an addicted patient; we are used to assuming that behavior is voluntary, especially if a person is coherent and oriented. It can be difficult to recall that a patient who is hostile and in denial actually has true neurobiologic dysfunction, not unlike a patient with dementia or psychosis. Unfortunately, our current civil commitment laws and society’s perception of these patients have not “caught up” with this neurobiological understanding.

Suicidality

Substance use itself (not necessarily as part of an SUD) is frequently comorbid with self-injurious behavior. Based on data from 16 reporting states in the National Violent Death Reporting System in 2009, 33.3% of suicide decedents tested positive for alcohol, 23% for antidepressants, 20.8% for opiates (including heroin and prescription analgesics).⁷³ As described earlier, patients often combine alcohol or illicit substances with prescription medication when multiple substances are used to self-poison.^{25,72} It is hypothesized that substance use can lead to disinhibition and the resultant ability to carry out an act of self-harm that may not have happened if the person had remained sober.

Treatment

Substance abuse treatment is ultimately an intermediate (weeks to months) to long-term (months to years) intervention. However, there are powerful initial steps that the emergency physician can take. Central among these is confronting the patient about the medical consequences of substance use. This can take the form of discussion only, or the physician can invite the patient to examine clinical laboratory results or view remarkable clinical diagnostic findings (hepatomegaly, repeated fractures from falls, liver enzyme abnormalities, or evidence of “silent” past myocardial infarction). There is little to be lost from a respectful but blunt confrontation of the patient’s deterioration, and the patient may listen to a physician rather than family or friends. “Physician advice” in this manner is shown to be useful for patients who do not yet meet criteria for substance dependence, and therefore still have sufficient control of their substance use to make a logical decision about the risks versus benefits of continued use.

Patients who are further along the addictive spectrum and who display behavioral or physiologic signs of substance dependence are much less likely to curb their substance use in the face of adverse medical sequelae. For these patients, more intensive intervention is warranted, often in the form of a consultation. For most hospitals, this type of consultation would be fulfilled by a psychiatrist, but some institutions have a separate substance abuse consult service. Ideally, all patients suspected to have an SUD should be referred to some type of aftercare when possible: inpatient or outpatient detoxification, inpatient or outpatient rehabilitation, or even follow-up with primary care.

In a busy ED this can be quite cumbersome logistically, depending upon the demographics of the patient population and the percentage of patients suspected to have an SUD. Regulatory agencies at the state and federal levels are increasingly mandating substance abuse screening, brief interventions, and referrals, so hopefully this will result in increased resources

for additional ancillary staff to assist with such tasks.

It is helpful to note that peer counseling is particularly useful in addictive disorders, and community 12-step programs like Narcotics Anonymous (NA) and Alcoholics Anonymous (AA) are ubiquitous worldwide. AA has its own website and specific phone lines in some cities that are staffed by AA members with the express purpose of orienting potential new members and assisting them in getting to their first meeting. Even if there is insufficient infrastructure in the ED to provide the more intensive intervention that might be needed for a patient who is substance-dependent, the physician can at least refer directly to AA. Patients with repeated presentations for substance intoxication/withdrawal should be considered for a higher level of care, since they may be demonstrating an inability to care for themselves. Such a decision would be made in conjunction with the psychiatrist and would have to comply with the local civil commitment laws. Finally, it is important to note that substance abuse treatment is quite effective, and that coerced treatment has been found to be just as effective as voluntary treatment. Given the remarkably high comorbidity of SUDs in the ED setting, it behooves us to attempt to connect these patients with the appropriate treatment.

SUMMARY

- Capacity assessment should be approached systematically, and such an approach is helpful in more complex situations. A “sliding scale” is a useful concept; when refusing an intervention would have serious consequences, a patient is held to a higher standard to demonstrate capacity.
- “Medical clearance” does not have a standard protocol, but in general the ED assessment should be guided by the history and physical examination.
- Both violent and suicidal behavior in the ED may be the cause or the effect of many toxicologic presentations.
- It is incumbent on all emergency physicians to screen patients for psychiatric emergency presentations as part of a comprehensive screening for self-harm.
- Identifying risk factors for suicide and aggression can aid the clinician in employing preventive or early intervention strategies in the ED.
- Important risk factors for both suicidal and violent behavior include past history of the behavior, comorbid mental illness, drug and alcohol intoxication, and young age.
- Mental status examination for suicidality should focus on extrinsic factors such as current ideation, intent, lethality of plan, current life stressors, as well as intrinsic vulnerability factors such as comorbid mental illness, feelings of hopelessness, and impulsivity.
- In terms of violence risk assessment, drug and alcohol intoxication, mental illness, and psychiatric medication noncompliance (alone or in combination) are robust predictors of aggressive behavior in the ED and other inpatient settings.
- Substance use disorders are highly prevalent in patients who present with psychiatric issues in the ED, and there are possibilities for identification and referral even in busy ED settings.

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28 RENAL PRINCIPLES

Marc Ghannoum and David S. Goldfarb

ANATOMY AND BASIC PHYSIOLOGY

The kidneys lie in the paravertebral grooves at the level of the T12 to L3 vertebrae. The medial margin of each is concave, whereas the lateral margins are convex, giving the organ a bean-shaped appearance. In the adult, each kidney measures 10 to 12 cm in length, 5 to 7.5 cm in width, and 2.5 to 3.0 cm in thickness. In an adult man, each kidney weighs 125 to 170 g; in an adult woman, each kidney weighs 115 to 155 g.

On the medial surface of the kidney is the hilum, through which the renal artery, vein, renal pelvis, a nerve plexus, and lymphatics pass. On the convex surface, the kidney is surrounded by a fibrous capsule, which protects it, and a fatty capsule with a fibroareolar capsule called the renal fascia, which offers further protection and serves to anchor it in place.

The arterial supply begins with the renal arteries, which are direct branches of the aorta. On entering the hilum, the arteries subdivide into branches supplying the five major segments of each kidney: the apical pole, the anterosuperior segment, the anteroinferior segment, the posterior segment, and the inferior pole. These arteries subsequently divide within each segment to become lobar arteries. In turn, these vessels give rise to arcuate arteries that diverge into the sharply branching interlobular arteries, which directly supply the glomerular tufts.

The cut surface of the kidney reveals a pale outer rim and a dark inner region corresponding to the cortex and medulla, respectively. The cortex is 1 cm thick and surrounds the base of each medullary pyramid. The medulla consists of between 8 and 18 cone-shaped areas called medullary pyramids; the apex of each area forms a papilla containing the ends of the collecting ducts. Urine empties from each papilla into a calyx and the calyces join together to form the renal pelvis. Urine is drained from the pelvis into the ureters, and, subsequently, into the urinary bladder.

The kidneys serve three major functions: (1) homeostasis of fluids, acid-base balance, and electrolytes, (2) excretion of nitrogen, as urea, and other waste products, and (3) endocrine production (eg, 1,25-dihydroxy vitamin D, renin, erythropoietin).

The kidneys maintain the constancy of the extracellular fluid by creating an ultrafiltrate of the plasma that is virtually free of cells and larger macromolecules, and then processing that filtrate, reclaiming what the body needs and letting the rest escape as urine. Every 24 hours, an adult's glomeruli filter nearly 180 L of water (total body water is ~ 25–60 L) and 25,000 mEq of sodium (total body Na^+ content is 1200–2800 mEq). Under normal circumstances, the kidneys regulate salt and water excretion, depending on intake and extrarenal losses. Approximately 1% of the filtered water and 0.5% to 1% of the filtered Na^+ are excreted.

Renal function begins with filtration at the glomerulus, a highly permeable capillary network connecting two arterioles in series. The relative constriction or dilation of these vessels normally controls the glomerular filtration rate (GFR). Under healthy circumstances, the filtration fraction, the proportion of renal plasma that is filtered, is approximately 20%. Plasma water crosses the filter, along with electrolytes, small solutes such as glucose, amino acids, lactate, and urea; blood cells and most of the larger proteins, including albumin and globulins do not typically cross the filter, although recent observations suggest that more plasma proteins than previously thought are filtered and reclaimed by the proximal tubule. The filtrate then enters the tubules, the serial segments of which have varying roles to metabolize, reabsorb, and secrete various solutes.

The proximal tubule performs the bulk of reabsorption, isotonicly reclaiming 65% to 70% of the filtrate. Distal to the proximal tubule is the loop of Henle, which controls concentration and dilution of the urine and plays an important role in the balance of Na^+ , Ca^{2+} and Mg^{2+} . The distal convoluted tubules also reabsorb Na^+ and Ca^{2+} and are joined by the connecting tubules to form the collecting ducts, which do the fine-tuning in the balance between excretion and reclamation of water, urea, K^+ , and H^+ . Paracellular reabsorption of sodium is controlled proximally by hydrostatic and oncotic pressures between the peritubular capillaries and the tubule while transcellular reabsorption is stimulated by angiotensin II. In the distal tubule, hormones such as aldosterone, and a variety of kinases control sodium transport. Control of water balance, dilution, and concentration depends first on function of the ascending limb of the loop of Henle, which absorbs solute without water. This produces a dilute tubular fluid and at the same time makes the medullary interstitium hypertonic. Final regulation of water reabsorption is related to the concentration of antidiuretic hormone (ADH; or vasopressin), which moves water-reabsorbing channels (aquaporins) into the membranes of the collecting ducts. The kidneys also regulate the

balance of potassium and hydrogen ions (which are influenced by the effect of aldosterone on the distal nephron), and calcium and phosphate via circulating parathyroid hormone, activated vitamin D, and fibroblast growth factor 23.

XENOBIOTICS AND THE KIDNEYS

Xenobiotics may affect kidney function in various ways and, conversely, renal disease may influence drug pharmacokinetics and lead to dangerous underdosing or overdosing. In the latter case, renal failure, whether acute or chronic, reduces the clearance of drugs eliminated by the kidneys. This may lead to drug accumulation and potential toxicity. The ideal dosing of drugs such as gabapentin, digoxin, baclofen, and vancomycin can vary several fold in patients with kidney failure compared to those with intact renal function. Some non-therapeutic xenobiotics may be potentially toxic in patients with kidney impairment while being relatively benign in patients with normal GFR. This is the case for gadolinium-based contrast used for magnetic resonance imaging, which carries the risk of nephrogenic systemic fibrosis.⁴⁶

Drug dosing in patients dependent on hemodialysis or peritoneal dialysis further complicates pharmacokinetics; in particular, the behavior of many antimicrobials can be severely altered in critically ill patients with kidney failure, whether acute or chronic. In this setting, the risk of underdosing with subsequent therapeutic failure and breakthrough resistance acquired by microorganisms may surpass that of drug accumulation. A notable example is fluconazole: the required dosage in patients undergoing continuous renal replacement therapy may surpass drug requirement in patients with intact renal function.⁵¹ For those drugs of which a substantial fraction is removed by hemodialysis, drug dosing after dialysis is often recommended. The use of therapeutic guides is encouraged to ensure proper drug prescription in patients with a history of kidney disease.³

Many xenobiotics cause or aggravate renal dysfunction. The kidneys are particularly susceptible to toxic injury for four reasons²⁶: (1) they receive 20% to 25% of cardiac output, yet make up less than 1% of total body mass implying a relatively large exposure to circulating xenobiotics, (2) they are metabolically active, and thus vulnerable to xenobiotics that disrupt metabolism or are activated by metabolism, such as acetaminophen (APAP), (3) they remove water from the filtrate which increases tubular concentration of xenobiotics, and (4) the glomeruli and interstitium are susceptible to attack by the immune system. Many factors, such as renal perfusion, can affect an individual's reaction to a particular nephrotoxin.⁴ Clinicians should be aware of these factors and, when possible, alter them to minimize the adverse effect after a toxic exposure.

Xenobiotics can affect any part of the nephron (Fig. 28–1), although not every type of toxic renal exposure will result in loss of GFR. The following will be described: (1) acute kidney injury, (2) chronic kidney disease, and (3) functional kidney disorders.

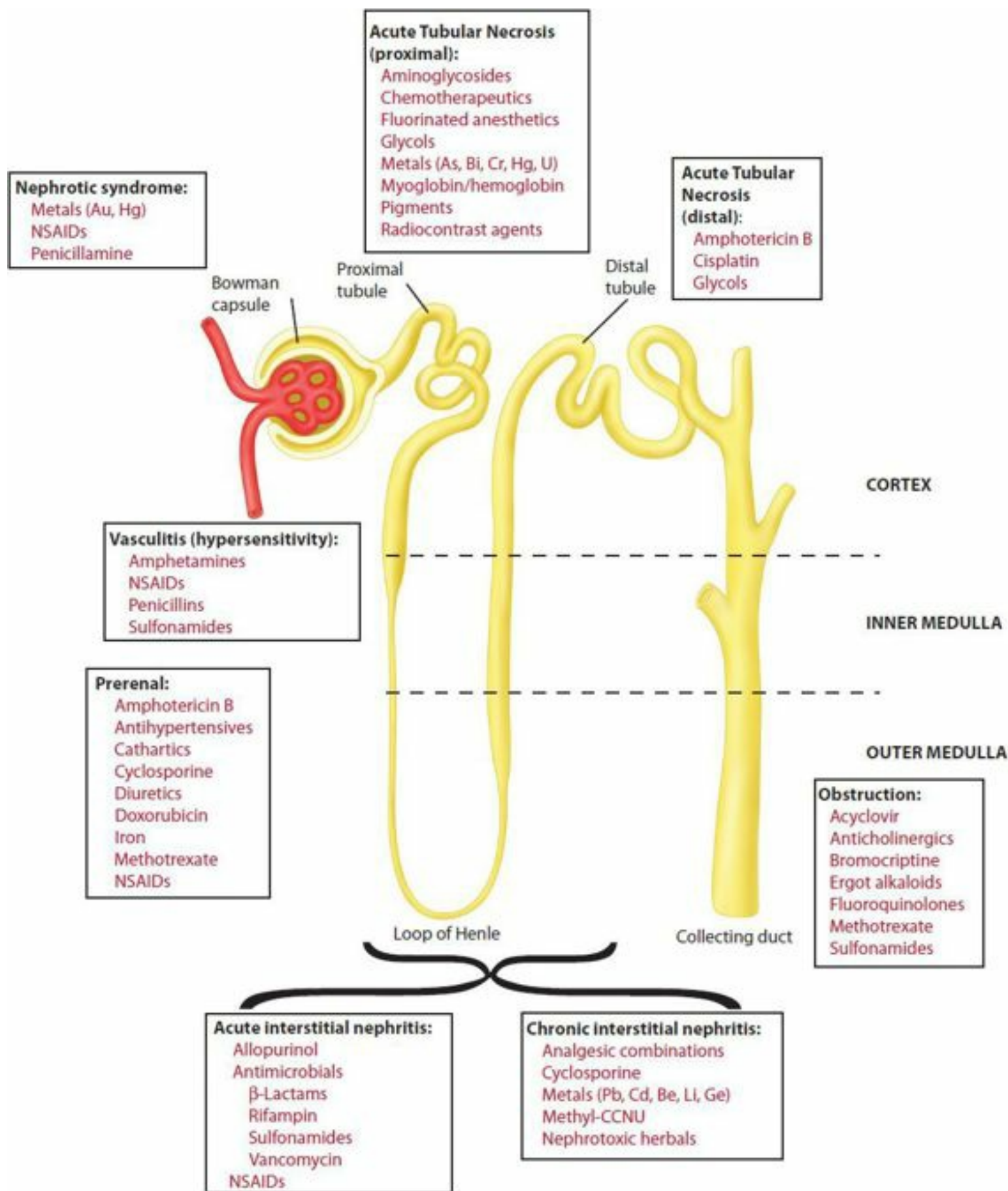


FIGURE 28–1. Schematic showing the major nephrotoxic processes and the sites on the nephron that they chiefly affect.

Acute Kidney Injury

Acute kidney injury (AKI; formerly called “acute renal failure”) relates to an abrupt decline in renal function that impairs the capacity of the kidney to maintain metabolic balance.

Several recent definitions of AKI have now been proposed, although they will likely be revised with the advent of newer and more specific biomarkers of kidney injury. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines introduced staging criteria for AKI, based on prior work from Acute Dialysis Quality Initiative (ADQI) and Acute Kidney Injury Network (AKIN) (Table 28–1).

TABLE 28–1. Kidney Disease Improving Global Outcomes (KDGO) Staging Criteria of Acute Kidney Injury

Stage 1	Creatinine of 1.5–1.9 times baseline
	OR
	≥ 0.3 mg/dL (≥ 26.5 μmol/L) increase in the serum creatinine
Stage 2	OR
	urine output < 0.5 mL/kg/h for 6–12 hours
	Creatinine of 2.0–2.9 times baseline increase in the serum creatinine
Stage 3	OR
	urine output < 0.5 mL/kg/h for ≥ 12 hours
	Creatinine of 3.0 times baseline increase in the serum creatinine
	OR
	increase in serum creatinine to ≥ 4.0 mg/dL (≥ 353.6 μmol/L)
	OR
	urine output of < 0.3 mL/kg/h for ≥ 24 hours
	OR
	anuria for ≥ 12 hours
	OR
	initiation of renal replacement therapy
	OR
in patients < 18 years, decrease in estimated GFR to < 35 mL/min per 1.73 m ²	

The three main categories of acute kidney injury are prerenal, postrenal, and intrinsic AKI.

Prerenal AKI. Prerenal AKI implies impaired renal perfusion, which can occur with volume depletion, systemic vasodilation, heart failure, or preglomerular vasoconstriction. Renal hypoperfusion initiates a sequence of events leading to renal salt and water reabsorption.⁴ Renin is released, causing production of angiotensin II, which enhances proximal tubular sodium reabsorption and stimulates adrenal aldosterone release, thus increasing distal sodium reabsorption. Therefore, prerenal AKI is usually accompanied by low urinary sodium excretion. Release of ADH increases water and urea retention. Histologically, the kidney appears normal. However, recent data showing elevated urinary content of molecules thought to represent kidney injury suggest a less benign course.

Any toxic exposure that compromises renal perfusion may contribute to prerenal AKI including bleeding (eg, overdose of anticoagulants), volume depletion (diuretics, cathartics, or emetics), cardiac dysfunction (β-adrenergic antagonists), or hypotension from any cause can lead to acute prerenal AKI.⁹ Nonsteroidal antiinflammatory drugs (NSAIDs) lower filtration rate by inhibiting production of vasodilatory prostaglandins in the afferent arteriole. Finally, cardiotoxins, such as doxorubicin, can cause severe heart failure (Fig. 28–1). Calcineurin inhibitors (cyclosporine, tacrolimus) may cause prerenal vasoconstriction by their effect on both afferent and efferent arterioles, possibly induced by endothelin. Calcineurin nephrotoxicity is usually dose-dependent and especially occurs when trough concentrations remain supratherapeutic for an extended period of time. Nephrotoxicity is often reversible after temporary discontinuation or decrease in the calcineurin dose if identified relatively quickly.

Prerenal AKI can also be caused by the hepatorenal syndrome, which is characterized by progressive renal hypoperfusion in the context of severe acute or chronic liver failure, marked constriction of the renal arterial vasculature and systemic hypotension. Circulating mediators of vasoconstriction that are subsequently increased include angiotensin, norepinephrine, vasopressin, endothelin, and isoprostane F₂ all contribute to an extreme cortical vasoconstriction. That the cause of AKI is extrarenal is best illustrated by the fact that when a kidney from a patient with hepatorenal syndrome is transplanted into a uremic patient, the function of the graft promptly returns to normal.

Finally, the entity known as the abdominal compartment syndrome is becoming increasingly recognized as a potential cause of renal hypoperfusion. Abdominal compartment syndrome is usually defined as new organ dysfunction induced by intraabdominal hypertension. Abdominal compartment syndrome may be observed when the intraabdominal pressure exceeds 20 mm Hg, especially if sustained. This abdominal hypertension may then induce renal artery vasoconstriction and impede venous drainage. Abdominal compartment syndrome can be caused by several entities, but usually requires some abdominal event, especially with concomitant aggressive fluid resuscitation. Surgical decompression is life-saving in this context.

Renal AKI. Renal AKI implies intrinsic damage to the renal parenchyma, which can be divided into vascular, glomerular, and tubulointerstitial etiologies.

Vascular etiologies of AKI includes vasculitis, malignant hypertension, atheroemboli, scleroderma, and hemolytic-

uremic syndrome or thrombotic thrombocytopenic purpura (HUS/TTP), the latter of which can sometimes be associated with use of certain xenobiotics (Table 28–2).

TABLE 28–2. Xenobiotics Causing Thrombotic Microangiopathy

Anticalcineurins (cyclosporine, tacrolimus)

Cisplatin

Gemcitabine

Mitomycin C

Quinine

Clopidogrel

Ticlopidine

Glomerular diseases infrequently cause acute AKI, but more commonly either chronic or subacute decline in kidney function. Glomerular lesions can present with the nephrotic or nephritic syndrome. A nephritic pattern is associated with histological inflammation, an active urine sediment with proteinuria and hematuria, and impaired kidney function. Hypertension is common. Nephrotic syndrome is characterized by massive proteinuria (>3.5 g/day), hypoalbuminemia, hyperlipidemia, and pitting pedal edema that usually prompts the patient to seek medical attention. Although the relationships among these findings are not completely understood, the underlying event is injury to the glomerular barrier that normally prevents macromolecules from passing from the capillary lumen into the urinary space. Xenobiotics induce nephrotic syndrome (Table 28–3) in two ways. First, they may release hidden antigens into the blood, which leads to antigen–antibody complex formation after the immune response is elicited. These complexes subsequently deposit in the glomerular basement membrane, thereby changing its properties (eg, gold)¹⁶ (Fig. 28–2). Second, they can upset the immunoregulatory balance.

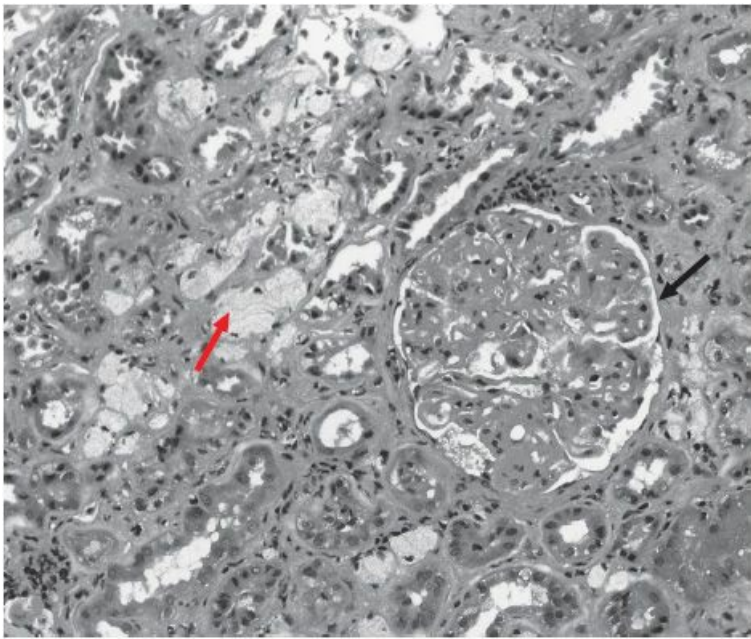


FIGURE 28–2. Membranous glomerulonephropathy (secondary to gold), a cause of nephrotic syndrome. Globally thickened glomerular capillaries (red arrow) and interstitial foam cells (black arrow) are seen. Hematoxylin and eosin stain $\times 450$. (Used with permission of Dr. Rabia Mir.)

TABLE 28–3. Xenobiotics Causing Nephrotic Syndrome

Anabolic steroids

Antimicrobials (cefixime, rifampicin)

Captopril

Chemotherapeutics (bevacizumab, sunitinib, sorafenib)

Drugs of abuse (heroin, cocaine)

Insect venom

Interferon α

Metals (gold, mercury, lithium)

Nonsteroidal antiinflammatory drugs

Pamidronate

Penicillamine

Probenecid

Sirolimus

Kidney biopsy will permit identification of the characteristic pathologic pattern, either minimal glomerular change disease, membranous glomerulopathy, or focal segmental glomerulosclerosis. Hypoalbuminemia usually is worse than urinary excretion of albumin would suggest, as a result of renal tubular catabolism of filtered protein. The tubules also retain sodium, causing expansion of the extracellular space and edema. The glomerular lesion may progress to end-stage renal disease (ESRD) if the pathologic process continues.

The major causes of acute tubulointerstitial diseases include acute tubular necrosis (ATN), acute interstitial nephritis (AIN), and tumor lysis syndrome. Although there is controversy about how a tubular lesion leads to glomerular shutdown, it is generally felt that tubular obstruction, back-leak of filtrate across injured epithelium, renal hypoperfusion, and decreased glomerular filtering surface combine to impair glomerular filtration.⁴⁴ Additionally, filtration pressure is diminished by neutrophil infiltration into the interstitium and vasa recta.⁴⁸ Evidence also suggests that prolonged medullary ischemia, perhaps caused by an imbalance in the production of vasoconstrictors such as endothelin and vasodilators such as nitric oxide, is important in prolonging the renal dysfunction after the tubular injury develops.²³

ATN is the most common cause of AKI in hospitalized patients (Table 28–4).²⁷ ATN is manifested pathologically by patchy necrosis of the tubular epithelium and occlusion of the lumen by casts and cellular debris (Fig. 28–3). Clinically, ATN presents as a rapid deterioration of renal function. Muddy brown casts or renal tubular cells may be seen in the urinary sediment, but hematuria and leukocyturia are unusual. Disorders of metabolic balance, such as hyperkalemia and metabolic acidosis, are also common. The abrupt fall in GFR usually leads to positive sodium and water balance.³⁰

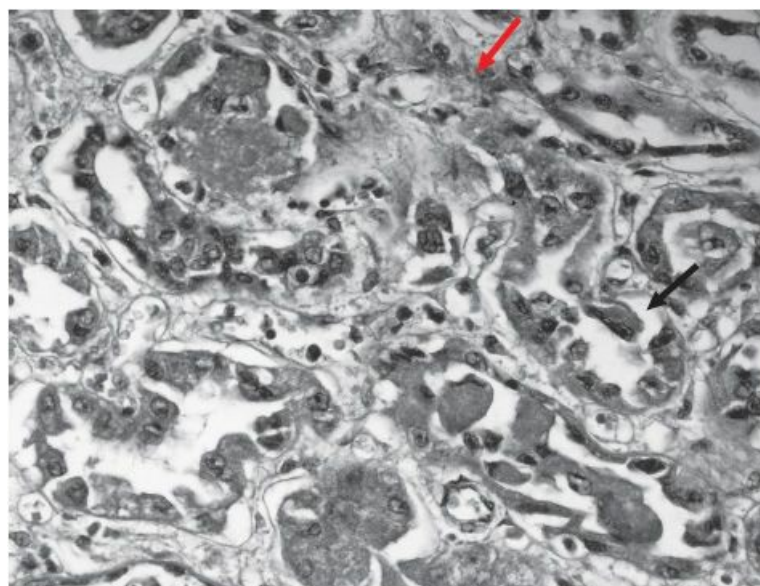


FIGURE 28–3. Acute tubular necrosis (secondary to mercury). Proximal tubular epithelial necrosis (↙) and sloughing are associated with interstitial edema (↗). Hematoxylin and eosin stain $\times 450$. (Used with permission of Dr. Rabia Mir.)

TABLE 28–4. Xenobiotics Causing Acute Tubular Necrosis

APAP

Aluminum phosphide

Antibacterials (aminoglycosides, ciprofloxacin, levofloxacin, colistin)

Antifungals (amphotericin B, pentamidine)

Antivirals (acyclovir, foscarnet, ritonavir, tenofovir, cidofovir, adefovir)

Chemotherapeutics (cisplatin, ifosfamide, mithramycin, streptozotocin)

Deferoxamine

Etidronate

Grass carp gallbladder

Halothane

Mannitol/hydroxyethyl starch/dextran

Metals (arsenic, bismuth, chromium, mercury, uranium)

Mushrooms (*Amanita* {especially *A. smithian*}), *Cortinarius* spp)

Paraquat, diquat

Radiocontrast agents (iodinated contrast, gadolinium)

ATN occurs following an ischemic or toxic injury.³⁵ Direct toxicity accounts for approximately 35% of all cases of ATN.⁴⁵ Xenobiotics can affect different segments of the renal tubules; for example, uranium attacks the proximal tubule and amphotericin the distal tubule⁴⁰ (Fig. 28–1). Certain xenobiotics cause a sudden or progressive decrease in GFR with concomitant prominent tubular wasting for electrolytes, though mechanisms of injury vary; this is the case of ifosfamide,¹⁷ amphotericin B,⁴⁰ aminoglycosides,³⁹ pentamidine,²⁹ and cisplatin.² Poisoning may also lead to ischemic tubular necrosis if hypotension or cardiac failure causes prolonged ischemia of nephron segments (proximal straight tubule and inner medullary collecting duct) that are particularly vulnerable to hypoxia. Patients who receive significant amounts of colloids (specifically mannitol, dextran, or hydroxyethyl starch)¹⁴ can occasionally develop AKI, characterized by tubular vacuolization or “osmotic nephrosis.” Iodinated contrast can cause AKI by mediating medullary vasoconstriction and inducing reactive oxygen species in tubules. Whatever the clinical pattern of rapidly declining renal function, all forms of ATN usually present with oliguria. Aminoglycosides are one exception: kidney failure, which may appear after several days of exposure, is nonoliguric.²⁵

Pigmenturia (myoglobinuria following rhabdomyolysis or hemoglobinuria from massive hemolysis) may also cause tubular injury and necrosis by precipitating in the tubular lumen.^{11,35} Myoglobin is normally excreted without causing toxicity. A study of patients with rhabdomyolysis suggests that the concentration of myoglobin in the urine may affect the development of AKI.¹¹ If myoglobin inspissates in the tubular lumen because of renal hypoperfusion and high urinary concentration, it dissociates in the relatively acidic environment as H⁺ is secreted, releasing tubulotoxic hematin. This toxicity may stem from the iron-catalyzing production of oxygen free radicals.

Rhabdomyolysis is most often caused by direct muscle injury following trauma or prolonged immobilization (Table 28–5). Any poisoning causing extended unconsciousness (eg, opioids and sedative-hypnotics), hyperthermia (neuroleptic malignant syndrome), excessive muscle contraction (cocaine, amphetamines),^{24,33} or tonic-clonic seizures (alcohol withdrawal, theophylline, isoniazid) may therefore lead to muscle breakdown.¹³ Other xenobiotics are directly myotoxic in some individuals, such as alcohol,²⁰ HMG-CoA reductase inhibitors (statins),¹⁸ carbon monoxide, copper sulfate, and zinc phosphate.^{28,50} Rhabdomyolysis can also occur after extensive bee or wasp stings¹⁹ or fire ant bites.²² Hypokalemia and hypophosphatemia (which may follow diuretics and laxatives abuse) can also induce rhabdomyolysis.

TABLE 28–5. Xenobiotics Causing Rhabdomyolysis

Alcohol

Antipsychotics

Carbon monoxide

Colchicine

Doxylamine

Drugs of abuse (heroin, cocaine, amphetamines, D-lysergic acid diethylamide, phencyclidine)

Drugs causing hypokalemia or hypophosphatemia

Selective serotonin reuptake inhibitors

Drugs causing prolonged central nervous system depression (immobilization) or seizures

Snake and insect venoms

Statins (especially when prescribed with fibrates)

Zidovudine

Hemoglobinuria follows hemolysis, which can be caused by a number of xenobiotics, including snake and spider venoms, cresol, dapsone, phenol, aniline, arsine, stibine, naphthalene, dichromate, and methylene chloride. Sensitivity reactions to drugs (hydralazine, quinine) can also cause hemolysis.²¹ The pathophysiology of hemoglobinuric ATN resembles that of myoglobinuria. The pigment deposits in the tubules and dissociates, causing necrosis to occur.³⁵ Volume depletion and acidosis precipitate the disorder; therefore, volume expansion and alkalinization may help prevent kidney injury.

Differentiation of ATN and prerenal AKI may be difficult clinically especially in critically ill patients; [Table 28–6](#) illustrates empiric criteria to separate them, although there are numerous exceptions to these. These exceptions should always be considered and correlated with clinical status. For example, fractional sodium excretion (the proportion of filtered sodium that appears in the urine, FE_{Na}) can be paradoxically high in prerenal AKI associated with metabolic alkalosis, diuretics, or adrenal insufficiency ([Table 28–7](#)). FE_{Na} can also be low in renal AKI secondary to rhabdomyolysis or contrast-induced AKI. Furthermore, distinction between both entities is difficult when there is exposure to xenobiotics capable of affecting the kidneys in various ways. NSAIDs, for example, can cause prerenal AKI, ATN, acute interstitial nephritis, analgesic nephropathy, or membranous nephropathy.

TABLE 28–6. Differentiation between Prerenal Acute Kidney Injury and Acute Tubular Necrosis

	<i>Prerenal Acute Kidney Injury</i>	<i>Acute Tubular Necrosis</i>
Fractional excretion of sodium (FE_{Na})	< 1%	> 2%
Fractional excretion of urea (FE_{Urea})	< 35%	> 50%
Serum urea/creatinine	> 20	10–15
Urine osmolality	> 400 mOsm/kg H ₂ O	Equivalent to plasma (isosthenuric)
Urine sodium	< 20 mEq/L	> 40 mEq/L
Urine sediment	Bland	Muddy “dirty” brown casts

TABLE 28–7. Calculations

Fractional Na ⁺ excretion (FE _{Na}) =	$\frac{([Na]_{urine}/[Na]_{plasma}) \times 100}{([Creat]_{urine}/[Creat]_{plasma})}$
Fractional Urea excretion (FE _{Urea}) =	$\frac{([Urea]_{urine}/[Urea]_{plasma}) \times 100}{([Creat]_{urine}/[Creat]_{plasma})}$
Creatinine clearance (by urine collection) =	$\frac{([Creat]_{urine} \times \text{urine flow})}{([Creat]_{plasma})}$
Estimated creatinine clearance (by Cockcroft-Gault formula) =	$\frac{(140 - \text{age}) \times \text{ideal body weight}}{(72 \times [Creat]_{plasma})(\times 0.85 \text{ if female})}$
Estimated glomerular filtration rate = (MDRD formula)	$\frac{186 \times [Creat]_{plasma}^{-1.154} \times \text{Age}^{-0.203}}{(\times 0.74 \text{ if female}) \times (1.21 \text{ if African American})}$

Units: urine flow (mL/min), creatinine concentration (mg/dL), weight (kg), age (years). N.B. these formulae are only applicable in a steady state (ie, if renal function is stable). MDMR = Modification of Diet in Renal Disease.

The other major tubulointerstitial cause of AKI is AIN (Table 28–8), which is characteristically distinguished from ATN by a dense cellular infiltrate separating tubular structures on renal biopsy (Fig. 28–4). Nearly all cases of acute interstitial nephritis are caused by hypersensitivity.⁴⁷ The diagnosis may be clear and kidney biopsy not necessary if kidney failure follows exposure to culpable drugs and is accompanied by classic manifestations of systemic allergy such as fever, rash, or eosinophilia, although only 10% of patients typically present with this classic triad.⁵ Flank pain or arthralgia may also be present. Unlike those with ATN, most patients with AIN have hematuria and leukocyturia,¹ particularly eosinophiluria, which is specific to this disorder.³⁴ The development of AIN is not dose-dependent and usually improves after cessation of the offending xenobiotic, although corticosteroids may hasten recovery in severe cases.

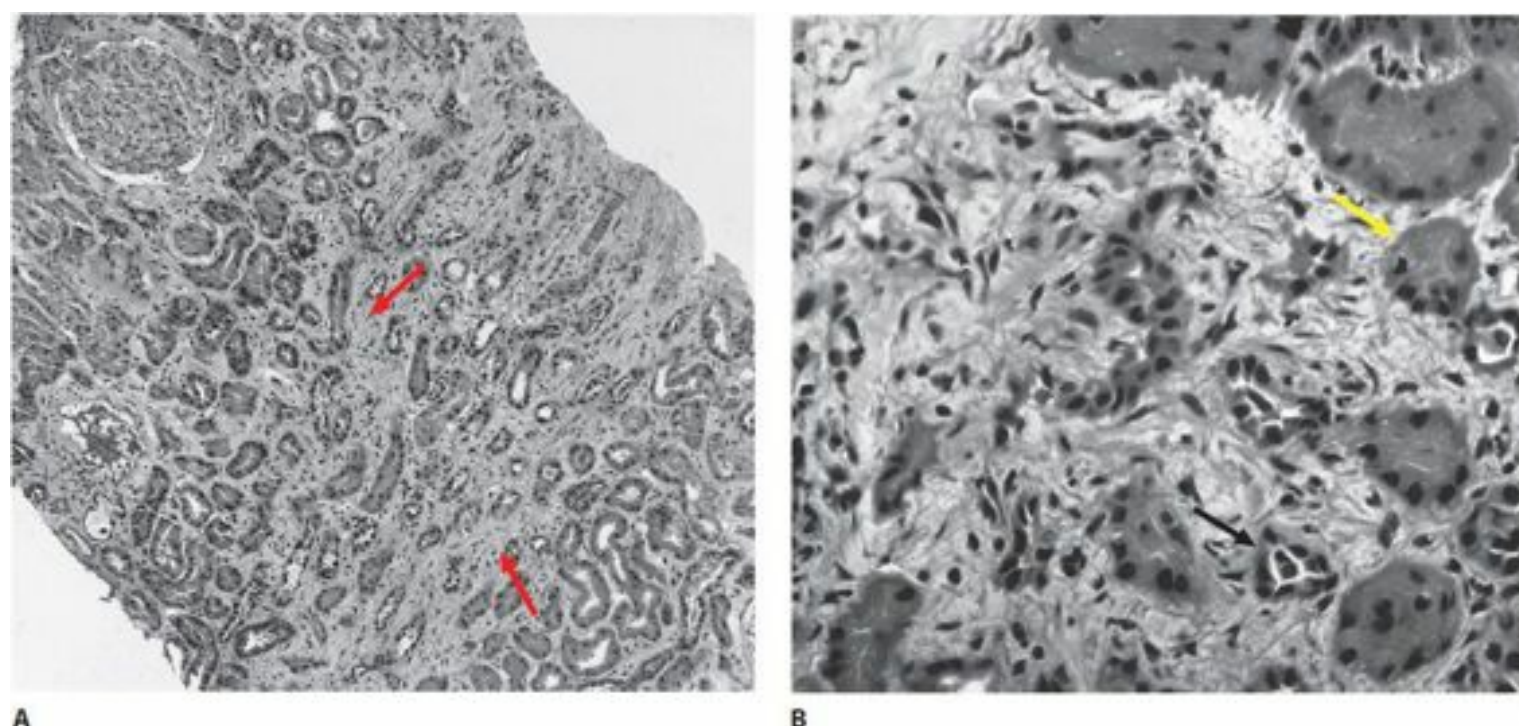


FIGURE 28–4. Acute interstitial nephritis (secondary to rifampin). Interstitial edema and patchy lymphocyte, plasma cell, and eosinophil infiltration occur without fibrosis (↗). Tubular epithelium shows degenerative and regenerative changes (↘) and mononuclear cell infiltration (tubulitis) (↖). (A) Hematoxylin and eosin stain × 112; (B) Hematoxylin and eosin stain × 450. (Used with permission of Dr. Rabia Mir.)

TABLE 28–8. Xenobiotics Causing Acute Interstitial Nephritis

Allopurinol

Anticonvulsants (carbamazepine, phenobarbital, phenytoin)

Antimicrobials (β -lactams, especially methicillin and cloxacillin, ciprofloxacin, sulfonamides, vancomycin, rifampin, nitrofurantoin, aminoglycosides, tetracyclines, colistin)

Azathioprine

Chinese herbs (*Stephania tetrandra*, *Magnolia officinalis*)

Diuretics (furosemide, thiazides)

H₁-antagonists (cimetidine, ranitidine)

Nonsteroidal antiinflammatory drugs (including selective cyclooxygenase-2 inhibitors)

Proton-pump inhibitors

Sulfinpyrazone

Zoledronate

Tumor lysis syndrome also affects the tubulointerstitium and usually occurs following chemotherapy for large bulk tumors. The incidence of tumor lysis has decreased with better procedural hydration and premedication with allopurinol or rasburicase.

Postrenal AKI. Postrenal AKI implies obstruction of urine flow anywhere from the renal pelvis to the urethra. Regardless of the cause of urinary tract obstruction, there are characteristic histologic and pathophysiologic alterations in the kidney: tubular dilation, predominantly in the distal tubule and collecting ducts, occurs initially and glomerular structure is preserved; subsequently dilation of the Bowman space occurs, and finally periglomerular fibrosis develops. Tubular function is impaired such that concentrating ability, potassium secretory function, and urinary acidification mechanisms are all altered.

Urinary tract obstruction should always be considered when the kidneys fail rapidly. Other risk factors include having a solitary kidney or a history of abdominal or genitourinary malignancy. Sudden anuria is a classical but rare feature of obstructive nephropathy; alternating phases of oliguria and polyuria are more common. Continued production of urine in the presence of obstruction leads to distension of the urinary tract above the blockage. Calyceal dilation is common. Obstruction of the bladder outlet or urethra may distend the bladder.

Obstruction may be caused by xenobiotics (Table 28–9). Most do so by impairing contraction of the bladder through anticholinergic action (atropine, antidepressants). Rarely, certain xenobiotics, particularly methysergide,⁴³ cause retroperitoneal fibrosis and ureteral constriction. Finally, a few xenobiotics lead to crystalluria and intratubular obstruction (eg, oxalosis in ethylene glycol poisoning³⁷). Sometimes the xenobiotic itself forms precipitates (sulfonamides, atazanavir, or methotrexate).^{7,42,49}

TABLE 28–9. Xenobiotics Causing Postrenal Acute Kidney Injury

<i>Bladder Dysfunction</i>	<i>Crystals</i>	<i>Retroperitoneal Fibrosis</i>
Anticholinergics (antihistamines, atropine, cyclic antidepressants, scopolamine)	Acyclovir	β -Adrenergic antagonists
Antipsychotics (butyrophenones, phenothiazines)	Ciprofloxacin	Bromocriptine
Bromocriptine	Diethylene glycol	Herbals (<i>Stephania</i> spp, <i>Aristolochia</i> spp)
Central nervous system depressants	Ethylene glycol	Hydralazine
	Fluorinated anesthetics	Methyldopa
	Fluoroquinolones	Methysergide
	Heme pigments	Pergolide
	Indinavir, nelfinavir, saquinavir, atazanavir	
	Melamine	
	Methotrexate	
	Phenylbutazone	
	Sulfonamides	
	Vitamin C	

Patients who present with acutely deteriorating kidney function often represent a difficult diagnostic challenge. Not only are there three major etiologic categories, each category has several subdivisions; and more than one factor may be present. For example, a patient with an opioid overdose may have neurogenic hypotension (prerenal), together with muscle necrosis causing myoglobinuric renal failure (intrinsic renal), and opioid-induced urinary retention (postrenal). Because renal, prerenal, and postrenal processes are not mutually exclusive and require different interventions, all three should always be considered, even when one appears to be the most obvious cause of the kidney failure.

Chronic Kidney Disease

Chronic kidney disease (CKD) refers to a disease process of a minimum duration of 3 months that often causes progressive decline of renal function. There is usually a gradual rise in blood urea nitrogen (BUN) and serum creatinine concentration as the GFR falls; unless advanced, there are often no clinical manifestations other than hypertension and nocturia (indicating loss of urinary concentrating ability). Classification of various stages of CKD, presently endorsed by KDIGO, is presented in [Table 28–10](#).

TABLE 28–10. Classification of Chronic Kidney Disease as Defined by the Kidney Disease Outcomes Quality Initiative and Modified and Endorsed by the Kidney Disease Improving Global Outcomes⁸

Stage	GFR	Description
1	≥ 90	Any kidney damage with normal or ↑ in GFR
2	60–89	Kidney damage with mild ↓ in GFR
3a	45–59	Mild to moderate ↓ in GFR
3b	30–44	Moderate to severe ↓ in GFR
4	15–29	Severe ↓ in GFR
5	< 15 or on dialysis	Kidney failure

GFR = glomerular filtration rate.

Reproduced with permission from Eckardt KU, Berns JS, Rocco MV, Kasiske BL. Definition and classification of CKD: the debate should be about patient prognosis—a position statement from KDOQI and KDIGO. *Am J Kidney Dis*. 2009;June;53(6):915–920.

In industrialized countries, most of the cases of CKD are caused by diabetes, hypertension, or glomerulonephritis. Nevertheless, many xenobiotics are implicated as nephrotoxins in long-term exposures. The most common lesion of nephrotoxic CKD is chronic interstitial nephritis ([Fig. 28–5](#)), which involves destruction of tubules over a prolonged period,¹² with tubular atrophy, fibrosis, and a variable cellular infiltrate ([Fig. 28–5](#)), sometimes accompanied by papillary necrosis. This then leads to ureteral colic via papillary sloughing. Acute interstitial nephritis may progress to chronic interstitial nephritis, if exposure is prolonged.⁴¹ Analgesic nephropathy was a common etiology of CKD until certain analgesics (such as phenacetin) were discontinued.³⁶ Chronic interstitial nephritis presents with mild to moderate proteinuria that remains well under the nephrotic range. Unlike other chronic renal disorders, it is characterized by failure of the diseased tubules to adapt to the renal impairment, resulting in metabolic imbalances such as hyperchloremic metabolic acidosis, sodium wasting, and hyperkalemia early in the disease course.¹⁰ Injury to erythropoietin-secreting cells may produce a disproportionate anemia.

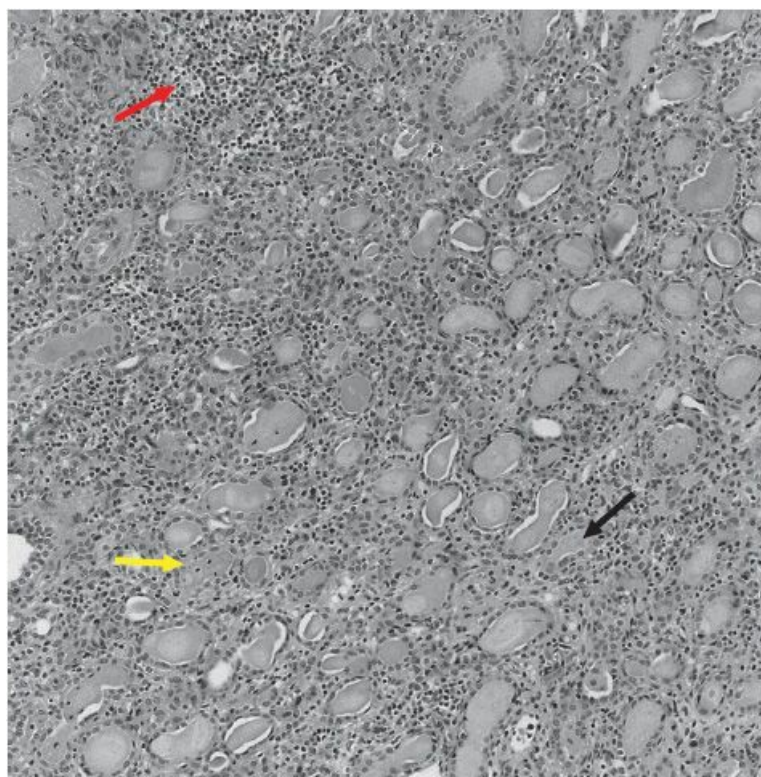


FIGURE 28–5. Chronic interstitial nephritis (secondary to NSAIDs). Interstitial fibrosis (→), lymphocytic infiltration (→), and tubular atrophy (↙). Hematoxylin and eosin stain $\times 225$. (Used with permission of Dr. Rabia Mir.)

Functional Toxic Renal Disorders

Although most toxic renal injury results in decreased renal function, certain functional disorders can also upset systemic balance despite normal GFR in anatomically normal kidneys. Three examples are presented here: renal tubular acidosis (RTA), syndrome of inappropriate secretion of ADH (SIADH), and diabetes insipidus.

RTA is a loss of ability to reclaim the filtered bicarbonate (proximal type 2 RTA) or a decreased ability to secrete protons and generate new bicarbonate to replace that lost in buffering the daily acid load (distal type I RTA). In either case, there is a nonanion gap hyperchloremic metabolic acidosis (Chap. 19).

The primary defect in distal RTA (also called type 1 RTA) involves the decreased secretion of protons (H^+) from the intercalated cells of the distal tubule. This defect is most frequently the result of a defect in the H^+ -translocating adenosine triphosphatase (ATPase) on the luminal surface of these cells. Less frequently occurring mechanisms include abnormalities of the chloride-bicarbonate exchanger, which is responsible for returning bicarbonate generated within the cell to the systemic circulation. Also, given the voltage dependence of proton secretion, a decrease in the luminal electronegative charge will cause a decrease in its secretion. Most of this voltage is created by the activity of the Na^+-K^+ -ATPase on the peritubular capillary side of the adjacent cell. (Note: Cells adjacent to the intercalated cells are called principal cells and primarily control water absorption and K^+ secretion.) As this pump malfunctions, less sodium is returned to the capillaries, creating a decreased gradient from the lumen to the cell. Thus, the lumen becomes more electropositive, diminishing the transmembrane potential. Amphotericin B and some analgesics can cause distal RTA by allowing secreted H^+ to leak back into the tubular cells.⁶

The primary defect in proximal type 2 RTA is incompletely understood. Normally, the Na^+-H^+ exchanger in the luminal membrane, the Na^+-K^+ -ATPase in the basolateral membrane, and the enzyme carbonic anhydrase are the key systems necessary for proximal tubular bicarbonate reabsorption. If one or more of these mechanisms becomes disordered, then the resorptive capacity of the proximal tubule is diminished. Proximal RTA often occurs as part of the Fanconi syndrome, a generalized failure of proximal tubular transport (proximal RTA plus aminoaciduria, glycosuria, and hyperphosphaturia). Xenobiotics associated with type 2 RTA include aminoglycosides, lead, ifosfamide, mercury, and acetazolamide.

What was once known as type 3 RTA is recognized to be a combination of features of both distal and proximal RTA and affects infants as part of an autosomal recessive syndrome. Type 4 RTA is caused by a deficiency of aldosterone or by tubular resistance to its action. It most often occurs in adult patients with both diabetes and CKD who have hyporeninemic hypoaldosteronism. Hyperkalemia is the most prominent electrolyte disturbance while the metabolic acidosis itself is usually mild.

SIADH occurs when the posterior pituitary gland or abnormal, unregulated sources such as lungs or tumors, secrete ADH despite the absence of physiological conditions that normally stimulate ADH secretion. The two usual stimuli for ADH release are elevated plasma osmolality and contraction of the effective arterial blood volume (eg, volume depletion,

congestive heart failure, cirrhosis). ADH primarily affects the collecting tubule and causes increased water reabsorption by increasing the permeability of the collecting duct by causing movement of aquaporins from intracellular lysosomes to the apical membranes. The hormonal effect of ADH augments normal free water retention, which subsequently leads to the main clinical manifestations of SIADH, namely, inappropriately concentrated urine (as reflected in a failure to decrease urine osmolality to 50–100 mOsm/kg) and hyponatremia in the setting of euvolemia. Although this manifestation most often occurs as a complication of intracranial lesions or from ectopic ADH production by a tumor or a diseased lung, many xenobiotics (eg, carbamazepine, chlorpropamide, antidepressants, vincristine, opioids, methylenedioxymethamphetamine {MDMA or Ecstasy}) can also cause inappropriate ADH release ([Chap. 19](#)).

Diabetes insipidus (DI) is the inability of the kidneys to maximally concentrate the urine and retain water leading to inappropriate loss of urine. Its two causes are the absence of pituitary ADH secretion (central DI) or by the absence of an appropriate renal response to ADH stimulation (nephrogenic DI). DI will typically present with polyuria or hypernatremia if water intake is limited, in the presence of inappropriately dilute urine. Central DI can be due to autoimmune destruction of the pituitary or trauma but often is the result of a space-occupying lesion affecting the posterior hypophysis. NDI can be caused by a variety of factors, including genetic disorders, kidney failure, disease states, or electrolyte perturbations, but xenobiotics are often implicated. Lithium, demeclocycline, foscarnet, and clozapine are drugs that can cause this syndrome ([Chap. 19](#)). NDI from lithium toxicity is thought to result from impaired aquaporin-2 synthesis and transport despite normal ADH binding to vasopressin type 2 receptors at the basolateral membranes of the collecting ducts.³⁸

PATIENT EVALUATION

Evaluation of a patient with suspected toxic renal injury should include consideration of extrarenal as well as renal factors. The kidney's response to xenobiotics is affected by baseline renal function, renal blood flow, and the presence of urinary tract obstruction, all of which must be considered.

History

A past history of renal disease or conditions that can affect the kidney (eg, diabetes, hypertension, cardiovascular disease, stones, urinary tract infection, prior chemotherapy) should be noted. Pertinent family history of kidney disease, glomerulopathy, kidney stones, and polycystic kidney disease needs to be recorded. Flank pain, hematuria, urine discoloration, or an abnormal pattern of urine output are important findings. Acute loss of kidney function may be suspected if urine output decreases, but oliguria is not universal. The patient's intravascular volume status affects renal perfusion. Thus, a recent history of heart disease, vomiting, or diarrhea is important. Symptoms of kidney failure are usually only present when severe but include anorexia, nausea and vomiting, leg cramps, fatigue, edema, and mental status changes. Systemic symptoms such as arthralgias, weight loss, and fever may suggest vasculitis.

All current xenobiotics should be evaluated for potential renal effects.¹⁵ The patient's intake of alcohol and drugs of abuse, as well intake of natural products and medicinal herbs, should be explored. A careful occupational history and assessment of hobbies and lifestyle are crucial, with emphasis on exposure to nephrotoxic xenobiotics.

Physical Examination

The patient's hemodynamic status should be carefully assessed. Postural changes in pulse and blood pressure, and either engorgement or decreased filling of the neck veins, give important information about the intravascular volume. The skin should be examined for lesions. Funduscopy may reveal evidence of chronic hypertension or diabetes. All aspects of cardiac function should be noted, including presence or absence of edema. Bluish discoloration of toes can suggest recent cholesterol emboli. Injuries or scars in the suprapubic area or evidence of past urologic or retroperitoneal surgery may suggest obstruction, as may a palpable or percussible bladder.

Laboratory Evaluation

Although history and physical examination may suggest nephrotoxic injury, laboratory testing is indispensable to confirm the degree of renal dysfunction. The approach to a patient with renal disease usually combines both assessment of GFR and urinalysis. Both are noninvasive, inexpensive, and have considerable predictive value for patients with renal disease.

Because creatinine is freely filtered by the glomerulus and not significantly reabsorbed or metabolized in the tubule, serum creatinine concentration is used as the preeminent marker of overall kidney function; because a small proportion of total excreted creatinine in urine appears as the result of tubular secretion, creatinine clearance always overestimates GFR. As the kidneys fail, creatinine concentration increases. However, the relationship between its concentration and GFR is hyperbolic, not linear; therefore, a small initial elevation in serum concentration denotes a large decrease in kidney function. By the time the serum creatinine concentration exceeds the upper limit of normal, GFR is reduced by up to 50%. Furthermore, creatinine secretion becomes a significantly greater proportion of creatinine excretion as GFR fails. Renal hypoperfusion and prerenal states are associated with a disproportionate rise in urea in comparison with the rise in

creatinine, because urea is partially reabsorbed in the proximal tubule along with salt and water. However, this often cited increase in the BUN–creatinine ratio may fail to occur in patients with chronic kidney disease, including the elderly. There are other limitations of their use as markers of renal injury; decreased production of urea (starvation or liver failure) or creatinine (amputation, muscle wasting) may result in a normal BUN or creatinine in the presence of significant renal impairment. Certain xenobiotics alter measured concentrations of urea and creatinine in the absence of any change in renal function.³² The most obvious is exogenous creatine taken to build muscle mass. Drugs that block renal creatinine secretion, such as cimetidine and trimethoprim, may also increase serum creatinine. BUN may be raised independently of renal function by corticosteroids (increased protein catabolism), tetracycline and by gastrointestinal bleeding due to digestion of hemoglobin.

Recently, more sensitive serum or urine markers of early AKI have been proposed, such as serum cystatin C, urinary kidney injury molecule-1, neutrophil gelatinase-associated lipocalin (NGAL), and N-acetyl- β -glucosaminidase. Early studies suggest they may help discriminate between ATN and prerenal AKI although they are costly and unavailable in most centers. Renal function can also be estimated by nuclear medicine and inulin clearance but these tests are impractical.

In patients with stable chronic kidney disease, a more precise estimation of the glomerular filtration rate is available. The Cockcroft-Gault formula and 24-hour urine collection for creatinine clearance are commonly used to assess renal function. More recently, the estimated GFR (eGFR) has been validated in several populations of kidney disease populations (Table 28–10). Using these measurements in AKI is not helpful, as the accuracy of the measurement of clearance implies a steady state. Changing GFR during a clearance time period distorts the resulting estimation. There is also a lag period between changes in kidney function and changes in BUN or creatinine concentrations. An extreme example would be a patient undergoing bilateral nephrectomy: although GFR immediately postoperatively equals 0 mL/min, the increase in serum creatinine will only be evident after a few hours. Any clearance calculation would yield an estimated GFR very different from true GFR. In general, a patient with AKI and rapidly changing creatinine concentration should be managed as if GFR were less than 10 mL/min until serum creatinine concentration stabilizes and GFR can more accurately be estimated. Estimation of GFR is most important in prescribing drugs. Since much of the relevant pharmacology literature predates the current equations used to estimate GFR, many recommendations for drug dosing are still based on the Cockcroft-Gault formula, which estimates creatinine clearance.

Most patients presenting with AKI should have their urine examined. Standard automated dipsticks will detect albumin and glucose. The presence of a positive dipstick for blood when the urine contains no or few RBCs suggests either rhabdomyolysis or hemolysis. A simple urine spot test may help discriminate prerenal azotemia from ATN (Table 28–6); this is suggested by a fractional sodium excretion below 1% and urine osmolality above 400 mOsm/kg. Direct microscopic examination of the urine sediment also provides useful clues. Dysmorphic red cells suggest glomerular hematuria but are neither sensitive nor specific. If acute interstitial nephritis is a consideration, a fresh urine sample should be stained for eosinophils.³¹ Crystalluria may suggest an obstructive cause to AKI and may reveal exposure to xenobiotics such as ethylene glycol.

Measurement of postvoiding residual urine volume, preferably by suprapubic ultrasonography or by passage of a urinary catheter with complete bladder emptying, can demonstrate lower urinary tract obstruction; if the volume is in excess of 75 to 100 mL, then bladder dysfunction or obstruction should be suspected. Among the many radiologic studies used in patients with kidney diseases, renal ultrasonography is the most useful and is indicated in all patients with AKI or CKD of unknown etiology; postrenal AKI is suggested by obstruction of the urinary tree, characteristically by swelling of one or two kidneys (hydronephrosis). Asymmetry between kidney diameters may suggest vascular stenosis. Cortex thinning and poorly differentiated corticomedullary junction are consistent with long-standing kidney failure of any etiology. When the etiology of kidney disease remains elusive, a percutaneous renal biopsy can establish the final diagnosis. Table 28–11 summarizes the nephrotoxic effect of various metals to demonstrate some of the complexities of the issue.

TABLE 28–11. Nephrotoxic Effects of Metals

	<i>Toxic ATN</i>	<i>Shock ATN</i>	<i>Hemolysis</i>	<i>Acute Interstitial Nephritis</i>	<i>Chronic Interstitial Nephritis</i>	<i>Tubular Dysfunction</i>	<i>Nephrotic Syndrome</i>
<i>Antimony</i>	+						
<i>Arsenic</i>	+++	+++	++	+	+		
<i>Barium</i>	+						
<i>Beryllium</i>					++		
<i>Bismuth</i>	++					+	+
<i>Cadmium</i>					+++	+++	
<i>Chromium</i>	+++						
<i>Copper</i>		+	+				
<i>Gadolinium</i>	+						
<i>Germanium</i>					+		
<i>Gold</i>	+						+++
<i>Iron</i>		++			+		
<i>Lead</i>	+		+		+++	+++	
<i>Lithium</i>	+				+++	++	+
<i>Mercury</i>	+++	+				+	+
<i>Platinum</i>	++				++	++	
<i>Silicon</i>							+
<i>Silver</i>	+						
<i>Thallium</i>	+			+			
<i>Uranium</i>	+						

+++ = common; + = uncommon. ATN = acute tubular necrosis.

SUMMARY

- The kidneys are exposed to exogenous or endogenous xenobiotics in their role as primary defenders against harmful xenobiotics entering the bloodstream.
- The environment, the workplace, and, especially, the administration of medications represent potential sources of nephrotoxicity. Consequently, it is important to determine, by history and observation, to which xenobiotics a patient may have been exposed and to be aware of their potential to harm the kidneys.
- It is equally crucial to work the other way when a patient presents with renal dysfunction: review all xenobiotics, both conventional and complementary, all xenobiotic exposures, and any conditions that can adversely affect the kidneys.

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29 RESPIRATORY PRINCIPLES

Andrew Stolbach and Robert S. Hoffman

The primary function of the lungs is to exchange gases. Specifically, this involves the transport of oxygen (O_2) into the blood, and the elimination of carbon dioxide (CO_2) from the blood. In addition, the lungs serve as minor organs of metabolism and elimination for a number of xenobiotics, a source of insensible water loss, and a means of temperature regulation.

Cellular oxygen use is dependent on many factors, including respiratory drive; percent of oxygen in inspired air; airway patency; chest wall and pulmonary compliance; diffusing capacity; ventilation–perfusion mismatch; hemoglobin content; hemoglobin oxygen loading and unloading; cellular oxygen uptake; and cardiac output. Xenobiotics have the unique ability to impair each of these factors necessary for oxygen use and result in respiratory dysfunction. This chapter illustrates how xenobiotics interact with the mechanisms of gas exchange and oxygen use. Discussion of chronic occupational lung injury is beyond the scope of this text; the reader is referred to a number of reviews for further information.⁵

PULMONARY MANIFESTATIONS OF XENOBIOTIC EXPOSURES

Respiratory Drive

Respiratory rate and depth are regulated by the need to maintain a normal partial pressure of carbon dioxide (PCO_2) and pH. Most of the control for ventilation occurs at the level of the medulla, although it is modulated both by involuntary input from the pons and voluntary input from the higher cortices. Changes in PCO_2 are measured primarily by a central chemoreceptor, which measures cerebral spinal fluid pH, and secondarily by peripheral chemoreceptors in the carotid and aortic bodies, which measure PCO_2 . Input with regard to partial pressure of oxygen (PO_2) is obtained from carotid and aortic chemoreceptors. Stretch receptors in the chest relay information about pulmonary dynamics, such as the volume and pressure.

Xenobiotics can affect respiratory drive in one of several ways: direct suppression of the respiratory center; alteration in the response of chemoreceptors to changes in PCO_2 ; direct stimulation of the respiratory center; increase in metabolic demands such as those resulting from agitation or fever, which, in turn, increases total body oxygen consumption; or indirectly, as a result of the creation of acid–base disorders. For example, opioids ([Chap. 38](#)) depress respiration by decreasing the responsiveness of chemoreceptors to CO_2 and by direct suppression of the pontine and medullary respiratory centers.^{35,80,102} Any xenobiotic that causes a decreased respiratory drive or a decreased level of consciousness can produce bradypnea (a decreased respiratory rate), hypopnea (a decreased tidal volume), or both, resulting in hypoventilation ([Chap. 3](#)).

Methylxanthines and sympathomimetics may cause an increase in both respiratory drive and oxygen consumption. Salicylates produce hyperventilation by both central and peripheral effects via respiratory alkalosis and metabolic acidosis. The net consequence of increased respiratory drive, increased oxygen consumption, or metabolic acidosis is the generation of either tachypnea (an elevated respiratory rate), hyperpnea (an increased tidal volume), or both. Either alone or in combination, tachypnea and hyperpnea produce hyperventilation. [Tables 29–1 and 29–2](#) both list xenobiotics that commonly produce hypoventilation and hyperventilation.

TABLE 29–1. Xenobiotics Producing Hypoventilation

Baclofen

Barbiturates

Botulinum toxin

Carbamates

Clonidine

Conium maculatum (poison hemlock)

Colchicine

Cyclic antidepressants

Elapid venom

Electrolyte abnormalities

Ethanol

Ethylene glycol

γ -Hydroxybutyrate and analogs

Isopropanol

Methanol

Neuromuscular blockers

Nicotine

Opioids

Organic phosphorus compounds

Sedative-hypnotics

Strychnine

Tetanus toxin

Tetrodotoxin

TABLE 29–2. Xenobiotics Producing Hyperventilation

Amphetamines

Anticholinergics

Camphor

Carbon monoxide

Cocaine

Cyanide

Dinitrophenol

Ethanol (ketoacidosis)

Ethylene glycol

Gyromitra spp (Mushroom)

Hydrogen sulfide

Iron

Isoniazid

Isopropanol

Methanol

Metformin

Methemoglobin inducers

Methylxanthines

Nucleoside reverse transcriptase inhibitors

Paraldehyde

Pentachlorophenol

Phenformin

Progesterone

Salicylates

Sodium monofluoroacetate

Decreased Inspired FIO₂

Barometric pressure at sea level ranges near 760 mm Hg. At this pressure, 21% of ambient air is comprised of oxygen (the fraction of inspired oxygen {FiO₂} = 21%), and, after subtracting for the water vapor normally present in the lungs, the alveolar partial pressure of oxygen (PAO₂) is about 150 mm Hg. Any reduction in FiO₂ decreases the PAO₂, thereby producing signs and symptoms of hypoxemia (a low arterial partial pressure of oxygen {PaO₂}). At an FiO₂ of 12% to 16%, patients experience tachypnea, tachycardia, headache, mild confusion, and impaired coordination. A further decrease to an FiO₂ of 10% to 14% produces severe fatigue and cognitive impairment and when the FiO₂ decreases to between 6% and 10%, nausea, vomiting, and lethargy develop. An FiO₂ < 6% is incompatible with life.⁶³

This effect on PAO₂ is typically observed as elevation increases above sea level, because while FiO₂ remains 21%, barometric pressure falls. At 18,000 feet, barometric pressure is only 380 mm Hg, and the PAO₂ falls to below 70 mm Hg. At 63,000 feet, the barometric pressure falls to 47 mm Hg, a level where the PAO₂ equals 0 mm Hg. Although it is important to remember this relationship, altitude-induced decreases in PAO₂ are rarely important in clinical medicine, even in commercial airline flights, where the cabins are pressurized to a maximum of several thousand feet above sea level. However, in closed or low-lying spaces, oxygen may be replaced or displaced by other gases that have no intrinsic toxicity. Common examples of these gases, referred to as simple asphyxiants (Table 29–3), are found alone or in combination with more toxic gases. Because they have little or no toxicity other than their ability to replace oxygen, removal of the victim from exposure and administration of supplemental oxygen are curative if permanent injury as a consequence of hypoxia has not already developed (Chap. 124).

TABLE 29–3. Simple Asphyxiants

Argon

Carbon dioxide

Ethane

Helium

Hydrogen

Methane

Nitrogen

Propane

The potential magnitude of toxicity from simple asphyxiants is best exemplified by disasters in Cameroon near Lake Mounoun and Lake Nyos, in 1984 and 1986, respectively. Following an earthquake, Lake Nyos, a volcanic lake, released a

cloud of CO₂ gas of approximately one quarter million tons. Because CO₂ is 1.5 times heavier than air, the gas cloud flowed into the surrounding low-lying valleys, killing by asphyxia more than 1700 people, and affecting countless more people because of hypoxia. Most survivors recovered without complications.^{11,39} Smaller scale, but equally serious, toxicity from CO₂ results from improper handling of dry ice or release into a closed space.^{40,45}

Chest Wall

Hypoventilation can result from a decrease in either respiratory rate or tidal volume. Thus, even when the stimulus to breathe is normal, adequate ventilation is dependent on the coordination and function of the muscles of the diaphragm and chest wall. Changes in this function can result in hypoventilation by two separate mechanisms; both muscle weakness and muscle rigidity may impair the patient’s ability to expand the chest wall. Some examples of toxicologic causes of muscle weakness include botulinum toxin,⁸⁷ electrolyte abnormalities, such as hypokalemia,^{57,103} or hypermagnesemia,^{2,32} organic phosphorus compounds,^{70,88} and neuromuscular blockers.^{14,50} Patients with hypoventilation caused by muscle weakness respond well to assisted ventilation and correction of the underlying problem (Chaps. 19, 41, 69, and 113). Chest-wall rigidity impairing ventilation can occur in strychnine poisoning,^{16,55,62} tetanus,^{23,55,93} and fentanyl use^{22,24} (Chaps. 38 and 117). Often these patients are difficult to ventilate despite tracheal intubation and may require muscle relaxants, neuromuscular blockers, or naloxone (for fentanyl).

Airway Patency

The airway may be compromised in several ways. As a patient’s mental status becomes impaired, the airway is often obstructed by the tongue.⁴² Alternatively, vomitus, or aspiration of activated charcoal or a foreign body, can directly obstruct the trachea or major bronchi with resultant hypoxia.^{52,65,83} Obstruction may also result from increased secretions produced during organic phosphorus compound poisoning. Laryngospasm may occur either as a manifestation of systemic reactions, such as anaphylaxis, as a result of edema from thermal or caustic injury (Chaps. 106 and 128), or as a direct response to an irritant gas (Chap. 124). Similarly, the tongue can become swollen in response to thermal or caustic injury or toxic exposure to plants such as *Dieffenbachia* spp, or as a result of angioedema from drugs such as angiotensin-converting enzyme inhibitors (Chaps. 63, 106, 121, and 128).³⁵ Regardless of the mechanism, upper airway obstruction results in hypoventilation, hypoxemia, and hypercapnia (hypercarbia) with the persistence of a normal alveolar–arterial (A–a) gradient (see discussion of A–a gradients). Upper airway obstruction is often acute and severe and requires immediate therapy to prevent further clinical compromise. Bronchospasm may be a manifestation of anaphylaxis, as well as exposure to pyrolyzed cocaine,⁸⁶ smoke, irritant gases⁴⁴ (Table 29–4), dust (eg, cotton in byssinosis), or as a result of work-related asthma⁶¹ and hypersensitivity pneumonitis¹⁰⁷ (Chaps. 124 and 128).

TABLE 29–4. Irritant Gases

Ammonia
Chloramine
Chlorine
Chloroacetophenone
Chlorobenzylidene-malononitrile
Fluorine
Hydrogen chloride
Isocyanates
Nitrogen dioxide
Ozone
Phosgene
Phosphine
Sulfur dioxide

Airway collapse may result from pneumothorax caused by barotrauma, which more commonly results from the manner of administration of illicit xenobiotics than from actual drug overdose. Barotrauma may also result from nasal insufflation or inhalation of drugs. This form of barotrauma occurs most often in cocaine (particularly in the form of “crack”) and marijuana users, who either smoke or insufflate these xenobiotics and then perform prolonged Valsalva maneuvers in an attempt to enhance the effects of these xenobiotics (Chaps. 77 and 78).^{12,90,104} The increased airway pressure leads to rupture of an alveolar bleb, and free air dissects along the peribronchial paths into the mediastinum and pleural cavities. Nitrous oxide abuse also causes barotrauma.⁵³ Siphoning of nitrous oxide from low-pressure tanks meant for inhalation is

not typically associated with barotrauma. By contrast, inhalation of nitrous oxide, used as a propellant in whipped cream cans, generates tremendous pressure that sometimes results in severe barotrauma (Chaps. 68 and 84).

Ventilation–Perfusion Mismatch

Ventilation–perfusion (V/Q) mismatch is manifested at the extremes by aeration of the lung without arterial blood supply (as in pulmonary embolism from injected contaminants) and by a normal blood supply to the lung without any ventilation. Impaired blood supply to a normal lung and normal blood supply to an inadequately ventilated lung constitute an infinite number of gradations that exist between the extremes. The normal response to regional variations in ventilation is to shunt blood away from an area of lung poorly ventilated, thereby preferentially delivering blood to an area of the lung where gas exchange is more efficient. An hypoxia-induced reduction in local nitric oxide production appears to be responsible for the regional vasoconstriction that occurs.¹ This effect, commonly known as hypoxic pulmonary vasoconstriction, is best described in patients with chronic obstructive lung disease and facilitates compensation for the V/Q mismatch associated with that disorder. It is unclear whether xenobiotic-induced alterations in pulmonary nitric oxide production are significant determinants in the V/Q mismatch that occurs in poisoning.

In toxicology, V/Q mismatch most commonly results from perfusion of an abnormally ventilated lung, as may occur following aspiration of gastric contents, a frequent complication of many types of poisoning.^{52,71} Although alterations in consciousness and loss of protective airway reflexes are predisposing factors, certain xenobiotics, such as hydrocarbons, directly result in aspiration pneumonitis because of their specific characteristics of high volatility, low viscosity, and low surface tension (Chap. 108).

The diagnosis of aspiration pneumonitis often relies on chest radiography for confirmation. The location of the infiltrate depends on the patient's position when the aspiration occurred. Most commonly, aspiration occurs in the right mainstem bronchus, because the angle with the carina is not as acute as it is for entry into the left mainstem bronchus. When aspiration occurs in the supine position, the subsequent infiltrate is usually manifest in the posterior segments of the upper lobe and superior segments of the lower lobe. Aspiration typically involves vomitus; however, secretions, activated charcoal, teeth, dentures, food, and other foreign bodies are also frequently aspirated.

Diffusing Capacity Abnormalities

Severe impairment in diffusing capacity commonly results from local injury to the lungs in disorders such as interstitial pneumonia, aspiration, toxic inhalations, and near drowning, and from systemic effects of sepsis, trauma, and various other medical disorders.¹⁰ When this process is acute and associated with clinical criteria, including crackles, hypoxemia, and bilateral infiltrates on a chest radiograph demonstrating a normal heart size, it has been historically referred to as noncardiogenic pulmonary edema or, more recently, acute lung injury (ALI).¹⁰ The most severe manifestation of these processes was described as acute respiratory distress syndrome (ARDS). However, a task force of pulmonary specialists has determined that all of these conditions are best classified as gradations of ARDS. According to the 2012 Berlin definition, ARDS consists of bilateral pulmonary infiltrates (by radiography or computed tomography), which occur within 7 days of an inciting event and are not explained by heart failure or fluid overload. Severity of ARDS is determined by the $\text{PaO}_2/\text{FiO}_2$ ratio. ARDS may be classified as mild ($200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$), moderate ($100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$), and severe ($\text{PaO}_2 \leq 100 \text{ mm Hg}$). Cases that once were described as ALI may now fit under the mild ARDS classification.

Throughout this chapter and text, this newer nomenclature will be used. Using the older definition, it was estimated that approximately 150,000 Americans developed ARDS annually, many as a result of xenobiotics; severe ARDS has a fatality rate near 50%.^{4,34}

Commonly, patients are chronically exposed to xenobiotics associated with reduced diffusing capacity by smoking tobacco and other xenobiotics or working with asbestos, silica, and coal, which slowly causes pulmonary fibrosis or promotes emphysema. More recent work also emphasizes the ability of chronically smoked cocaine to alter pulmonary function.⁹⁴ Acutely, ARDS from opioids, salicylates, or phosgene and delayed severe fibrosis from paraquat can cause profound alterations in diffusion (Chaps. 38, 39, 112, and 132).^{76,84,108} Associated parenchymal damage is almost always present and causes both reduction in lung volumes and V/Q mismatch. Intravenous injection of talc, a common contaminant found in drugs of abuse,⁷⁸ and septic emboli from right-sided endocarditis^{77,92} may result in isolated vascular defects with reduction in diffusion capacity. Similarly, cocaine-induced pulmonary spasm can obstruct vascular channels and alter pulmonary function, creating V/Q mismatch.²⁸

ARDS commonly occurs in cases of poisoning. The edema fluid (and the resulting hypoxia, pulmonary crackles, and radiographic abnormalities) may develop in part because of increased permeability of the alveolar and capillary basement membrane.^{21,25,64,84} Proteinaceous fluid leaks from the capillaries into the alveoli and interstitium of the lung. Several mechanisms are proposed as the cause of ARDS, although no single unifying mechanism exists for all of the xenobiotics implicated. ARDS may result from exposure to xenobiotics that produce hypoventilation by at least three different

mechanisms: (1) hypoxia may injure the vascular endothelial cells, (2) autoregulatory vascular redistribution may cause localized capillary hypertension, or (3) alveolar microtrauma may occur as alveolar units collapse, only to be reopened suddenly during reventilation.⁸⁴ These and other events may activate neutrophils and release inflammatory cytokines.^{3,101} Other xenobiotics may be directly toxic to the capillary epithelial cells or may be partly responsible for the release of vasoactive substances.³ The effects of salicylates and other nonsteroidal antiinflammatory drugs may be mediated via effects on prostaglandin synthesis. Finally, sympathomimetic stimulants may cause “neurogenic” pulmonary edema, which may be mediated by massive catecholamine discharge. Elevated catecholamine concentrations are also noted in experimental opioid overdose, possibly representing support for a link between hypoxia, hypercarbia, and the catecholamine hypothesis of ARDS.⁶⁹

In the 1880s, William Osler described “oedema of left lung” in a morphine user. The opioids are still among the most common causes of ARDS ([Chap. 38](#)), but it is now recognized that there are many types of xenobiotics that can cause or are associated with ARDS, such as the sedative-hypnotics, salicylates, cocaine, carbon monoxide, diuretics, and calcium channel blockers ([Table 29–5](#)).^{29,31,33,37,38,43,46,49,56,79,81,91,92,108} The route of xenobiotic administration is not usually the determining factor; ARDS can result from oral, intravenous, and inhalational exposure. Because the source of the problem is increased pulmonary capillary permeability, patients with ARDS have a normal pulmonary-capillary wedge pressure, unlike patients with cardiogenic pulmonary edema.

TABLE 29–5. Common Xenobiotic Causes of Acute Respiratory Distress Syndrome

Amiodarone
Amphetamines
Amphotericin
Bleomycin
Calcium channel blockers
Carbon monoxide
Cocaine
Colchicine
Cyclic antidepressants
Cytosine arabinoside
Ethchlorvynol
Irritant gases
Lidocaine
Opioids
Protamine
Salicylates
Sedative-hypnotics
Smoke inhalation
Streptokinase
Vinca alkaloids

Cardiogenic pulmonary edema may also occur as the result of poisoning. Etiologies for this phenomenon include the ingestion of large amounts of a xenobiotic with negative inotropy (eg, β -adrenergic antagonists, type 1A antidysrhythmics),

myocardial ischemia, or infarction (from cocaine). Because many overdoses are mixed overdoses, the distinction between cardiogenic pulmonary edema and ARDS is often difficult to establish by physical examination and requires invasive monitoring techniques.

Although the treatments for cardiogenic pulmonary edema and ARDS have many similarities, critical aspects of the therapy differ; therefore, an accurate diagnosis must be established. Most diagnostic tests are not helpful in differentiating between the two diseases. Physical examination reveals the presence of crackles with both entities. An S₃ gallop, if present, suggests a cardiac cause, but its absence does not establish the diagnosis of ARDS. In both entities, the arterial blood–gas analysis demonstrates hypoxia and chest radiography shows perihilar, basilar, or diffuse alveolar infiltrates. However, the presence of “vascular redistribution” on chest radiography is suggestive of a cardiogenic etiology; a normal-sized heart is more commonly associated with ARDS, whereas an enlarged heart is more typical of cardiogenic pulmonary edema. The diagnostic tests that may be useful in establishing the correct diagnosis include echocardiography, transcutaneous bioimpedance, pulmonary artery catheter pressure measurements, and radionuclide ventriculography (“gated-pool” scan). Although the radionuclide scan accurately measures cardiac output, it is not routinely available in the emergency department or intensive care unit and usually requires the transport of a critically ill patient to the nuclear medicine suite. Although echocardiography can be performed as a portable “bedside” technique, it is less sensitive and less specific for determinations of cardiac output. Therefore, the most definitive diagnostic procedure in the emergency setting is the insertion of a pulmonary artery catheter for hemodynamic monitoring. Cardiogenic pulmonary edema results from an elevated left-atrial filling pressure (elevated pulmonary-capillary wedge pressure) and a decreased cardiac output. In patients with ARDS, the pulmonary artery wedge pressure and the cardiac output are normal. Although not specifically well investigated in poisoning, experiences with transcutaneous bioimpedance measurements of cardiac output show promise for this portable noninvasive technique.^{10,26,68,72}

The basic treatment for ARDS is supportive care while the xenobiotic is eliminated and healing occurs in the pulmonary capillaries.^{3,59} The most important specific therapeutic maneuver in patients with ARDS requiring mechanical ventilation involves the use of low tidal-volume ventilation (≤ 6 mL/kg predicted body weight).^{1,41,101}

This results in reduced airway pressures, which seem to decrease the chance for alveolar distension and subsequent injury. The efficacy of jet ventilators or membrane oxygenators is inadequately studied. Some studies suggested a potential role for extracorporeal membrane oxygenation in the treatment of ARDS.⁵⁴ Positive end-expiratory pressure (PEEP), which may derive its benefit from keeping alveoli open, is considered an essential component in the management of ARDS.^{30,41}

PEEP should be maintained in the range of 5 to 12 cm H₂O, to maintain a PO₂ of at least 55 mm Hg, or an oxygen saturation of 88%, with an inspired oxygen concentration of $\leq 40\%$. Higher PEEP settings are not always beneficial and can cause an increased incidence of pneumothorax or hypotension. An increase in PEEP may result in a modest increase in PO₂, but a larger decrease in venous return and decreased cardiac output. Therefore, with each change in PEEP, the resulting increase (or perhaps decrease) in oxygen delivery to the body should be determined.⁴

A conservative fluid strategy improves oxygenation and decreases stays in the intensive care unit without increasing the incidence of shock or the need for hemodialysis. A conservative fluid management strategy is recommended for patients with ARDS not in shock, have not been in shock for at least 12 hours, and do not have other reasons to require liberal fluid administration.⁷⁴

Hemoglobin and Chemical Asphyxiants

Disorders of hemoglobin oxygen content, and of hemoglobin loading and unloading, result in cellular hypoxia, which, in turn, results in hyperventilation. Anemia is a common complication of the infectious diseases associated with injection drug use. In addition, many xenobiotics result in hemolysis or direct bone marrow suppression. Among the latter group are the metals, lead, benzene, and ethanol. Hemolysis may occur in individuals exposed to lead, copper, or arsine gas, and in patients with glucose-6-phosphate dehydrogenase deficiency exposed to oxidants (Chap. 22).

The oxygen-carrying capacity of blood declines in almost direct proportion to hemoglobin content,⁹⁶ as seen in Fig. 29–1. As shown in Fig. 29–1A, under most normal conditions the dissolved oxygen content of the blood contributes little; thus, the last portion of the equation can be eliminated. Anemia resulting in a decrease of the hemoglobin content to 7.5 g/dL (a hematocrit of $\sim 22\%$) decreases the oxygen content of the blood to about 10.2 mL O₂/dL (Fig. 29–1B). Because central cyanosis is only visible with a concentration of reduced deoxyhemoglobin of at least 5 g/dL, unless an abnormal hemoglobin concentration is present, anemia can significantly impair oxygen-carrying capacity without the development of this common physical manifestation (Chap. 127).

Oxygen content (O_2 content) = hemoglobin bound oxygen + dissolved oxygen

A. Normal conditions: hemoglobin (Hb) = 15 g/dL; PO_2 = 100 mm Hg,

oxygen saturation (O_2 sat) = 95%

$$\begin{aligned} O_2 \text{ content} &= [(Hb)(O_2 \text{ sat}) (\text{constant}) + (\text{another constant})(PO_2)] \\ &= [(Hb)(O_2 \text{ sat})(1.39 \text{ mL } O_2/\text{g}\%) \\ &\quad + (0.003 \text{ mL } O_2/\text{dL/mm Hg})(PO_2)] \\ &= [(15 \text{ g/dL})(95\%)(1.39 \text{ mL } O_2/\text{g}\%) \\ &\quad + (0.003 \text{ mL } O_2/\text{dL/mm Hg})(100 \text{ mm Hg})] \\ &= [(19.8 \text{ mL } O_2/\text{dL}) + (0.3 \text{ mL } O_2/\text{dL})] \\ &= \mathbf{20.1 \text{ mL } O_2/\text{dL} = 20.1 \text{ vol}\%} \end{aligned}$$

B. Anemia: Hb = 7.5 g/dL; PO_2 = 100 mm Hg, O_2 Sat = 95%

$$\begin{aligned} O_2 \text{ content} &= [(Hb)(O_2 \text{ sat})(1.39 \text{ mL } O_2/\text{g}\%) \\ &\quad + (0.003 \text{ mL } O_2/\text{dL/mm Hg})(PO_2)] \\ &= [(7.5 \text{ g/dL})(95\%)(1.39 \text{ mL } O_2/\text{g}\%) \\ &\quad + (0.003 \text{ mL } O_2/\text{dL/mm Hg})(100 \text{ mm Hg})] \\ &= [(9.9 \text{ mL } O_2/\text{dL}) + (0.3 \text{ mL } O_2/\text{dL})] \\ &= \mathbf{10.2 \text{ mL } O_2/\text{dL} = 10.2 \text{ vol}\%} \end{aligned}$$

C. Hyperbaric oxygen: Hb = 15 g/dL; PO_2 = 1500 mm Hg, O_2 Sat = 100%

$$\begin{aligned} O_2 \text{ content} &= [(Hb)(O_2 \text{ sat})(1.39 \text{ mL } O_2/\text{g}\%) \\ &\quad + (0.003 \text{ mL } O_2/\text{dL/mm Hg})(PO_2)] \\ &= [(15 \text{ g/dL})(100\%)(1.39 \text{ mL } O_2/\text{g}\%) \\ &\quad + (0.003 \text{ mL } O_2/\text{dL/mm Hg})(1500 \text{ mm Hg})] \\ &= [(20.9 \text{ mL } O_2/\text{dL}) + (4.5 \text{ mL } O_2/\text{dL})] \\ &= \mathbf{25.4 \text{ mL } O_2/\text{dL} = 25.4 \text{ vol}\%} \end{aligned}$$

FIGURE 29–1. Examples of calculations of the oxygen content of the blood under various conditions.

By contrast, as the PO_2 reaches higher values (as in hyperbaric oxygen chambers), the dissolved oxygen content becomes significant and may be of therapeutic value, particularly when the oxygen-carrying content of hemoglobin is compromised. The PO_2 corresponding to an FiO_2 of 100% at 1 atm is approximately 575 mm Hg. By contrast, with hyperbaric oxygen at 3 atm and 100% oxygen, PO_2 values in excess of 1500 mm Hg can be achieved.⁶³ Under these conditions, the dissolved oxygen content of the blood rises dramatically (to as much as 4.5 mL O_2 /dL) and may be adequate to sustain life, even in the absence of any contribution from hemoglobin (Fig. 29–1C).

The chemical asphyxiants that produce methemoglobin, carboxyhemoglobin, and sulfhemoglobin interfere with oxygen loading and/or unloading to various degrees. Methemoglobin inhibits oxygen loading, producing cyanosis unresponsive to supplemental oxygen (Chap. 127). In addition, the oxyhemoglobin saturation curve is shifted to the left, interfering with unloading (Fig. 29–2). Carboxyhemoglobin has similar effects on oxygen loading and unloading, but carboxyhemoglobin is not associated with cyanosis (Chap. 125). While sulfhemoglobin also impairs oxygen loading, it shifts the oxyhemoglobin saturation curve to the right, favoring unloading of the remaining normal hemoglobin. Cyanide, hydrogen sulfide, and sodium azide primarily affect oxygen use by interfering with the cytochrome oxidase system (Chap. 126).

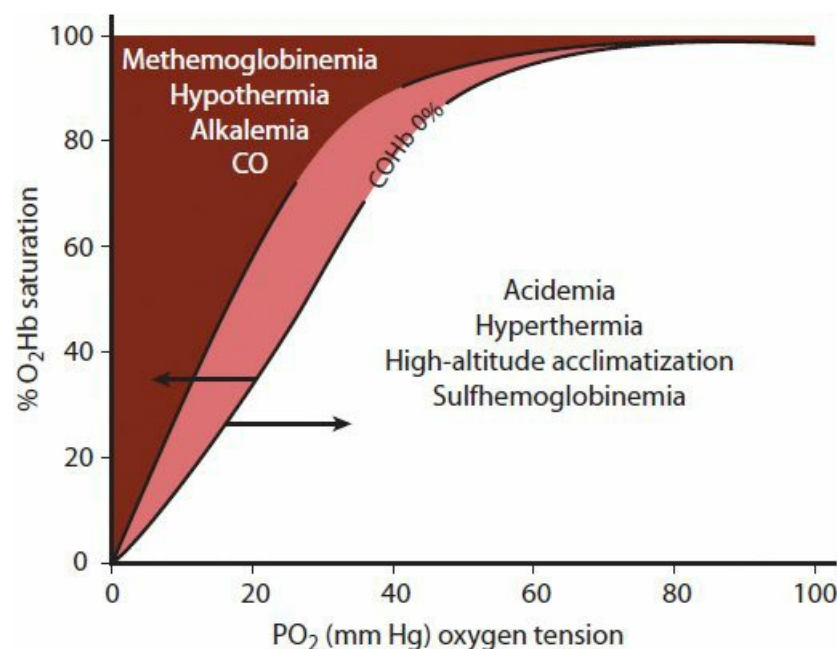


FIGURE 29–2. Oxyhemoglobin dissociation curve at 98.6°F (37°C) and pH 7.40. Hematocrit does not alter this relationship.

Cardiac Output

Any xenobiotic that causes a decreased cardiac output or hypotension may result in tissue hypoxia and tachypnea. This occurs most frequently with overdoses of β -adrenergic antagonists and calcium channel blockers, antidysrhythmics, cyclic antidepressants, and phenothiazines ([Chap. 17](#)).

Asthma and Occupational Exposures

Usually considered a cause of morbidity more than mortality, work-related asthma is frequently encountered by the practitioner. The pathophysiology of these illnesses is still being elucidated, and appears to result from both immunoglobulin (Ig) E and non-IgE-related mechanisms.¹⁵

Work-related asthma can be divided into three distinct clinical entities:

1. Work-aggravated asthma: Preexisting asthma worsened by allergens in the workplace.
2. Occupational asthma: Asthma caused by workplace exposure and not factors outside the workplace. There is a latency period between the symptoms and the first exposure, possibly as long as several years.
3. Reactive airway dysfunction syndrome (RADS): Asthma caused by nonimmunogenic stimuli in the workplace, occurring for the first time within 24 hours of exposure to an inhaled irritant xenobiotic.^{6,20,100}

Occupational exposures are thought to be responsible for a substantial proportion of adult-onset asthma, estimated at 10% to 25% in one international prospective study.¹⁹

A large number of xenobiotics and occupations are associated with the development of work-aggravated and work-related asthma. Because researchers rely on surveys and interviews, the latency period between exposure and symptoms makes identification of these associations a challenge.

Many high molecular weight xenobiotics, usually plant or animal derived, are known etiologies, such as arthropod and mite-related materials, latex, flour, molds, endotoxins, and biological enzymes. Lower molecular weight xenobiotics associated with work-related asthma include isocyanates (used in spray paints and foam manufacturing), cleaning agents, anhydrides, amines, dyes, and glues. For more information on specific xenobiotics, see [Chap. 124](#).

In one study, the following occupations were found, in decreasing order, to be associated with the development of occupational asthma: printing, woodworking, nursing, agriculture and forestry, cleaning and caretaking, and electrical processors.⁵⁸

By contrast to occupational asthma and work-related asthma, the latency period between exposure and symptoms in RADS is short or absent, so the health care professional may more easily identify the precipitant from history. Xenobiotics frequently associated with RADS include cleaning materials (including chlorine, hypochlorite, ammonia, and chloramines), solvents, toluene diisocyanate, acids, alkali, nitrogen oxides, smoke, and diesel exhaust.^{47,89}

APPROACH TO THE POISONED PATIENT

The initial assessment of each patient must involve the evaluation of upper airway patency. Adequacy of ventilation should

then be determined. If concomitant injury is suspected, then care must be taken to protect the cervical spine. When airway patency is in question, maneuvers to establish and protect the airway are of prime importance. Often this may simply involve repositioning the chin, jaw, or head, or suctioning secretions or vomitus from the airway. However, insertion of an oral or nasopharyngeal airway, or nasopharyngeal or endotracheal intubation, or surgical cricothyroidotomy may be required as clinically indicated. After the airway is secured, high-flow supplemental oxygen if needed should be provided and the depth, rate, and rhythm of respirations evaluated. An acceptable tidal breath is one that transports 10 to 15 mL of air/kg of body weight.⁴

Hypoventilation that results from an inadequate respiratory rate or tidal volume is arbitrarily defined as a PCO_2 higher than 44 mm Hg and leads to hypoxia and ventilatory failure if uncorrected.¹⁰⁵ The symptoms of hypoxia and or hypercarbia are nonspecific and resemble toxicity from many xenobiotics. Initially, patients appear restless and confused. Signs of sympathetic discharge, such as tachycardia and diaphoresis, may be noted. Later, patients may complain of headache, only to become sedated and subsequently comatose, as further deterioration occurs. These signs and symptoms are often nonspecific. We recommend early determination of oxygenation and ventilation when there is concern for respiratory failure in patients following xenobiotic overdose. Arterial blood gas or pulse oximetry may be used to identify hypoxia, while capnography or blood gas (venous or arterial) are good modalities for determining ventilation.

A trial of naloxone, hypertonic dextrose, and thiamine may be indicated for the patient with an altered mental status and or respiratory compromise ([Chap. 4](#)). Because opioid overdose and hypoglycemia are rapidly reversible, potential causes of respiratory failure, these diagnoses should be addressed before most other interventions are considered. Failure to identify and reverse these conditions may result in unnecessary diagnostic and therapeutic interventions in addition to irreversible neurologic sequelae.

Having assured an acceptable airway, the remainder of the evaluation can proceed. A rapid assessment of the remainder of the vital signs ([Chap. 3](#)) should then occur. Obtaining a history and physical examination, measured oxygen saturation, measured ventilation, and chest radiography are sufficient to determine the diagnosis of pulmonary pathology in most cases. However, adjuncts, such as measurement of negative inspiratory force (NIF), invasive hemodynamic monitoring, evaluation of the arterial–venous oxygen difference, xenon ventilation and technetium scanning, and computed tomographic scanning may be required.

History

A directed history must include questions on the nature, onset, and duration of symptoms; substance use and abuse; home and occupational exposures; and underlying pulmonary pathology. If the patient has a significant degree of respiratory compromise, most or all of the history may have to be obtained from friends, relatives, paramedics, coworkers, or others.

Physical Examination

The physical evaluation must include a detailed assessment of depth, rate, and rhythm of respirations, use of accessory muscles, direct evaluation of the oropharynx, position of the trachea, and presence and quality of breathing sounds. Skin, nail bed, and conjunctival color must be observed for pallor or cyanosis. Funduscopic examination is a useful adjunct to the examination. Papilledema may be noted in the presence of acute hypercapnia. Additionally, because cyanide poisoning interferes with oxygen delivery to tissue, the venous oxygen saturation remains high. During the funduscopic examination, this may appear as arteriolization of the retinal veins, where the veins take on a color more characteristic of arteries ([Chap. 126](#)). A general assessment of muscle tone, with a specific emphasis on ocular and neck muscles, may give clues to flaccidity or rigidity syndromes that interfere with respiration. When in doubt, a determination of the negative inspiratory force will provide a rapid, objective, quantifiable bedside assessment of respiratory strength.

Pulse Oximetry

Pulse oximeters have gained widespread acceptance as rapid, noninvasive indicators of hemoglobin oxygen saturation. As defined, hemoglobin oxygen saturation is the ratio of oxyhemoglobin to total hemoglobin. By using two light-emitting diodes, the pulse oximeter is able to measure absorbance at the peak wavelengths for oxyhemoglobin and deoxyhemoglobin (typically at 940 and 660 nm). Thus, the ratio of oxyhemoglobin to oxyhemoglobin plus deoxyhemoglobin (total hemoglobin) can be calculated. The clinician may then estimate the PO_2 from the oxygen saturation.

Limitations of this approach require elaboration. Because the oxyhemoglobin saturation curve becomes quite flat above 90% saturation ([Fig. 29–2](#)), small changes in saturation greater than 90% may represent very large changes in PO_2 . Thus, a decrease from 97% saturation to 95% saturation may represent a substantial decrease in PO_2 . Although a low saturation is an early indicator of hypoxic hypoxia, this is only one of many causes of tissue hypoxia. If total hemoglobin is low, then oxygen-carrying capacity is inadequate even with excellent saturation ([Fig. 29–1](#)). Dyshemoglobinemias, such as carboxyhemoglobin, methemoglobin, and possibly sulfhemoglobin, interfere with the accuracy of pulse oximeter determinations and are of particular concern in the poisoned patient. Specifically, using a standard pulse oximeter, the

presence of elevated concentrations of methemoglobin will tend to make the saturation approach 84% to 86% (Chap. 127).^{8,77} Carboxyhemoglobin is falsely interpreted by the pulse oximeter as mostly oxyhemoglobin, thus readings tend to appear normal even with significant carbon monoxide poisoning (Table 29–6).⁹⁷ Accurate response by the pulse oximeter also requires adequate blood pressure, lack of strong venous pulsations (as might occur in a patient with tricuspid regurgitation), translucent nails (some shades of nail polish may interfere), absence of circulating dyes (methylene blue), and a near-normal temperature. If the pulse oximeter does not produce an accurate reading, then arterial blood gas may be obtained to assess oxygenation. Finally, we are often more interested in PCO₂ than PO₂, which is not a direct measure of ventilation. The pulse oximeter gives no information with regard to PCO₂. Although the pulse oximeter may give early clues to the presence of hypoxic hypoxia, extrapolation of oxygen saturation to standard arterial blood–gas values may be difficult because of the many possible sources of error.

TABLE 29–6. Sample Interpretations of Oxygen Saturations Reported by Various Sources of Measurement

Condition	Percent Oxygen Saturation			
	PO ₂ (mm Hg)	Arterial Blood Gas	Pulse Oximeter	Cooximeter
Normal	95	95	95	95
Anemia	95	95	95	95*
Methemoglobinemia (30%)	95	95	85	70
Carboxyhemoglobinemia (30%)	95	95	95	70
Hypoxemia	60	90	90	90

The table demonstrates limitations of the various methods for determining oxygen saturation (O₂ saturation). The arterial blood gas calculates the O₂ saturation from the dissolved oxygen content (PO₂) and becomes abnormal only when the PO₂ falls. The pulse oximeter uses only two wavelengths of light and produces substantial errors in the presence of a dyshemoglobinemia. Because the cooximeter uses more wavelengths of light than the pulse oximeter, it can correctly identify the presence of carboxyhemoglobin and methemoglobin. The cooximeter has the additional advantage (*) of calculating the total hemoglobin and oxygen content, so that it is useful in the setting of anemia. All techniques are acceptable for the assessment of hypoxemia.

Pulse–cooximeters (noninvasive spectral analysis cooximeter), designed to measure carboxyhemoglobin and methemoglobin, in addition to hemoglobin oxygen saturation, are entering clinical practice. Use of these devices can potentially facilitate early, noninvasive diagnosis of carbon monoxide poisoning and methemoglobinemia, as well as minimize erroneous interpretations of standard pulse oximetry caused by the presence of these abnormal hemoglobins. A volunteer study, sponsored by the manufacturer of the device, demonstrated the ability to measure carboxyhemoglobin with an uncertainty of $\pm 2\%$ within the range of 0% to 15% and methemoglobin with an uncertainty of 0.5% within the range of 0% to 12%.⁷ In a large study of screening for carboxyhemoglobin, the noninvasive cooximeter was 94% sensitive (95% confidence interval {CI}: 71%–100%) and 77% specific (95% CI: 75%–79%) for identification of a carboxyhemoglobin rate above 6.6%.⁸⁵ Other authors have found high rates of false negatives when using the noninvasive cooximeter to screen for carbon monoxide poisoning.⁹⁵

Because of these limitations, the best role for this device is as a rapid screening tool. Positive results should be confirmed with a blood carboxyhemoglobin concentration, as should normal results whenever carbon monoxide poisoning is highly suspected, or when the result from the machine is not consistent with the clinical appearance of the patient.

Capnography

Capnography is the noninvasive measurement of PCO₂ from the airway. Both the numerical value of CO₂ and the shape of the tracing, the capnogram, provide information to the clinician (Fig. 29–3). Measurements are obtained constantly during inhalation and exhalation. End-tidal CO₂ (EtCO₂) is the maximum partial pressure of CO₂ at the end of exhalation. EtCO₂ underestimates PaCO₂ because exhaled air consists mostly of CO₂–poor air from dead space, in addition to air expired from alveoli. Anatomic dead space, always present, is from the nonventilated upper airways, whereas physiologic dead space results from underperfused areas of the lung. Therefore, a high EtCO₂ always correlates with an elevated PaCO₂, whereas a low value may be spurious. In patients without pulmonary disease, EtCO₂ is 2 to 5 mm Hg less than PaCO₂.⁷³ In nonintubated emergency department patients with metabolic acidosis, the mean difference was 6 mm Hg.⁹ EtCO₂ can be

used to confirm endotracheal intubation, monitor endotracheal tube placement, monitor patients during procedural sedation, and assess patients with pulmonary illness. EtCO₂ has been used as a tool to assess ventilation in patients obtunded from a xenobiotic (Fig. 29–3).²⁷

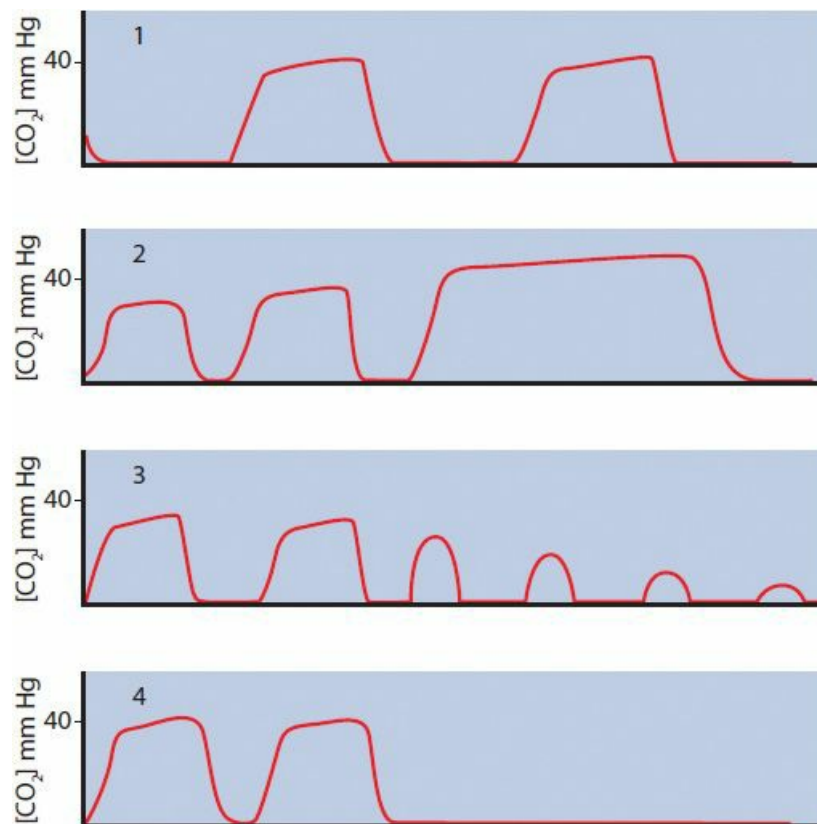


FIGURE 29–3. Capnograms. (1) Normal capnogram. (2) Bradypnea and hypoventilation. The tidal volumes are the same as (1) but the rate is slowing down. (3) Hypopnea and hypoventilation. The amplitude of the waveforms is decreasing. (4) Complete laryngospasm or apnea. After initial waveforms, there is no expired CO₂.

Blood–Gas Analysis

Arterial blood–gas analysis is an easy and rapid means of evaluating both acid–base status and gas exchange. Attention must be paid to the method for determining oxygen saturation, specifically whether it is measured or calculated from the PO₂. If the measured O₂ saturation is lower than would be predicted from the PO₂ (the calculated O₂ saturation), then the presence of an abnormal hemoglobin concentration (such as carboxyhemoglobin or methemoglobin) must be suspected. A normal calculated O₂ saturation does not exclude these disorders (see Use of the Cooximeter).

Because it is easier to obtain, venous blood–gas analysis is often used as a substitute for arterial blood–gas analysis.¹⁷ In comparison with arterial values, venous pH and PO₂ are lower, whereas PCO₂ is higher. Errors can be introduced by increased muscle activity of the extremity being tested (eg, seizures.) In most cases, a venous blood gas can be used to evaluate PCO₂ and pH, but not PO₂. However, mixed venous blood (defined as right-heart blood) is required for accurate determination of the arterial–venous oxygen extraction and is an excellent indicator of acid–base status, cardiovascular function, and oxygen use. Unfortunately, a central venous catheter is required for sampling. When performing a peripheral venous blood–gas analysis, it is usually assumed that this is only an approximation of mixed venous blood.

The arterial PO₂ is generally considered adequate only if it lies within the flat portion at the upper right of the sigmoidal-shaped oxyhemoglobin dissociation curve (Fig. 29–2). That portion of the curve includes the PO₂ range from 60 to 100 mm Hg, which corresponds to oxygen saturations higher than 90%. As mentioned earlier, within this flat portion there can be discernible changes in PO₂ with little change in oxygen saturation. For instance, an arterial PO₂ of 80 mm Hg corresponds roughly to an oxygen saturation of 95%. If the PO₂ falls to 60 mm Hg, then the oxygen saturation falls to 90%. This insignificant decrease in the oxygen-carrying capacity of the blood is of minimal clinical concern. However, if the PO₂ falls another 20 mm Hg, then there is a more significant reduction in oxygen saturation, to approximately 70%. Thus, changes in PO₂ higher than 60 mm Hg are usually not of acute therapeutic significance, because the O₂ saturation is higher than 90%. However, these changes are frequently of diagnostic significance.

An exception to this concept applies to the patient who is under metabolic stress, as might result from low cardiac output, impaired vascular flow, anemia, or dyshemoglobinemia. Under these circumstances even the modest gain achieved by increasing both dissolved oxygen content and hemoglobin saturation higher than 90% may be desirable, as discussed

earlier (see Hemoglobin and Chemical Asphyxiants). Also, even if a PO_2 higher than 60 mm Hg or an O_2 saturation higher than 90% is considered acceptable in most acute settings, it is still desirable to achieve greater values, when feasible, to create a safety zone in case of clinical deterioration.

Significance of a Decreased PO_2

In a patient with a diminished PO_2 , five clinically relevant mechanisms for the hypoxemia should be considered: (1) alveolar hypoventilation, (2) V/Q mismatch, (3) shunting, (4) diffusion abnormality, and, rarely, (5) a decrease in FiO_2 . In most clinical circumstances, diffusion defects cannot be distinguished from V/Q mismatch. Usually the responsible mechanism can be identified by calculating the A–a oxygen gradient. In patients with alveolar hypoventilation, the A–a gradient is completely normal (≤ 15 mm Hg when breathing room air). Patients with V/Q mismatch have an A–a gradient that is increased but which normalizes when 100% oxygen is administered for at least 20 minutes. A normal A–a gradient is defined as less than 100 mm Hg on 100% oxygen. The arterial PO_2 on 100% oxygen reaches approximately 575 mm Hg. By contrast, a patient with a shunt will also have an increased A–a gradient while breathing room air, but when 100% oxygen is administered, the arterial PO_2 falls to substantially less than 575 mm Hg and the A–a gradient does not normalize. Finally, in the case of a patient with hypoxia resulting from breathing in an environment in which the FiO_2 is less than 21%, the PO_2 should correct rapidly when the patient is removed from the environment or supplemental oxygen is delivered.

In general, a low PO_2 can be improved by supplying supplemental oxygen. Although in this instance the patient's laboratory values may be corrected, the underlying process persists. It is important to remember that the laboratory correlate of hypoventilation is hypercapnia on the arterial blood–gas analysis. If hypercapnia is associated with acidemia, then assisted ventilation should be considered, regardless of whether the PO_2 corrects with supplemental oxygen.

Use of the Cooximeter

Routine analysis of an arterial blood gas yields a measured pH, a measured PO_2 , and a measured PCO_2 . Ordinarily, the serum bicarbonate, base excess, and percent oxygen saturation of hemoglobin are all calculated values. The oxygen saturation is of clinical significance because it usually correlates with the oxygen content of the blood; thus, the oxygen available to the tissues. However, implied in this relationship is a normal amount of functional hemoglobin. Because the oxygen saturation is calculated from the measured PO_2 using the oxyhemoglobin dissociation curve, it represents only the saturation of normal hemoglobin. Thus, in the presence of even a small percentage of abnormal hemoglobin, the calculated oxygen saturation overestimates the total oxygen content of the blood. For example, a patient with PO_2 of 95 mm Hg has a calculated oxygen saturation of 95%. If the patient also has a 30% methemoglobinemia, only 70% of the total hemoglobin is saturated to 95% and the actual saturation is only 67%. This gap is clinically important because hemoglobin saturations of less than 90% do not provide adequate oxygen delivery to the tissues.

As discussed above, despite the development of bedside noninvasive pulse-cooximetry, most clinicians still depend on laboratory cooximeters for measurement of carboxyhemoglobin and methemoglobin. Most cooximeters spectrophotometrically measure total hemoglobin, oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin. Newer models measure fetal hemoglobin and sulfhemoglobin as well (Fig. 29–4). The resultant saturation is a measured oxygen saturation of the total hemoglobin by including four common hemoglobin variants, and thus correlates with the total oxygen content of the blood.

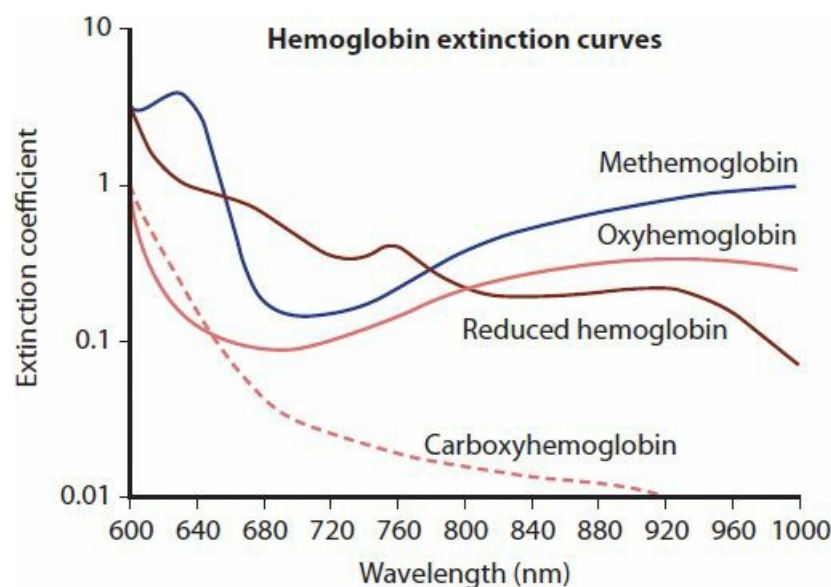


FIGURE 29–4. Cooximetry curves for normal and abnormal hemoglobin variants. Transmitted light absorbance spectra are shown for four hemoglobin species: oxyhemoglobin, reduced (deoxy) hemoglobin, carboxyhemoglobin, and methemoglobin.

The difference between measured and calculated oxygen saturation represents the percentage of abnormal hemoglobin present. This gap is helpful in the diagnosis of methemoglobin and carboxyhemoglobin, and is useful in assessing the adequacy of therapy for these disorders. Common indications for cooximetry include cyanosis that is unresponsive to oxygen (methemoglobin and sulfhemoglobin), known use of methemoglobin-forming xenobiotics (such as dapsone), smoke inhalation (carboxyhemoglobin and possibly methemoglobin), and evaluation of therapy for cyanide toxicity (methemoglobin).

Like so many other tools, the cooximeter is not perfect. Its biggest limitation occurs when dealing with uncommon hemoglobins. Older cooximeters use four wavelengths of light and have the ability to define only four hemoglobin variants. Consequently, rare dyshemoglobinemias, such as sulfhemoglobin, have been interpreted as one or a combination of the four common hemoglobin variants, giving erroneous results. This phenomenon is commonly noted in neonates in whom fetal hemoglobin may be interpreted as carboxyhemoglobin.^{99,106} Although this error rarely adds greater than 10% to the true carboxyhemoglobin value, this amount can be significant because of the difficulties in assessing the neuropsychiatric status of infants possibly exposed to carbon monoxide. Newer cooximeters use at least six wavelengths of light and are designed to measure fetal hemoglobin and sulfhemoglobin directly, avoiding these interference problems.⁵¹ Another source of interference with cooximetry has been the use of hydroxocobalamin, which has a deep red color. Hydroxocobalamin administration has resulted in falsely low carboxyhemoglobin by laboratory cooximetry.⁶⁶ Clinicians should use caution in interpreting carboxyhemoglobin concentrations in patients who have received hydroxocobalamin. When available, a sample obtained before hydroxocobalamin administration should be sent for cooximeter analysis.

Additionally, cooximeters tend to inconsistently interpret low levels (< 2.5%) of carboxyhemoglobin.⁶⁷ Fortunately, this rarely has clinical implications.

Chest Radiography

Radiographic detection of a pneumothorax or pneumomediastinum, cardiogenic pulmonary edema, ARDS, aspiration pneumonia, or the presence of a foreign body is crucial, but can usually be delayed until the initial evaluation is completed. Confirmation of endotracheal tube placement is necessary but initially can be ascertained by auscultating bilateral breath sounds following compression of a bag valve mask, or using a variety of marketed devices such as EtCO₂ detectors designed to help confirm tube placement. For patients with occupational disorders, chest radiography is essential to confirm and stage exposures to asbestos, silica, coal, and other causes of pneumoconiosis.

THERAPEUTIC OPTIONS

Supplemental Oxygen

Supplemental oxygen is indicated for all patients with suspected or confirmed respiratory insufficiency. Although it is generally advisable to begin with high flow (12 L/min) via a nonrebreather mask, lower concentrations of oxygen can be used in more stable patients. Supplemental oxygen can be titrated lower to the minimum flow rate required to achieve adequate oxygen saturation. Pulse oximetry is a good modality for monitoring oxygenation especially if used in conjunction with EtCO₂ recognizing the limitations of both modalities. The clinician may opt to obtain either a venous or an arterial blood gas if there is concern that pulse oximetry saturation and the EtCO₂ are not reflective of the true saturation.

Hyperbaric oxygen is indicated for carbon monoxide poisoning and rarely other exposures (Antidotes in Depth: A38).

Initially, there should be limited concern over worsening hypercapnia in patients with chronic obstructive pulmonary disease and respiratory failure. This concern should not deter clinicians from providing needed oxygen, because many of these patients will require intubation for their hypoventilation. It is important to appreciate that supplemental oxygen will improve hypoxia but not hypercarbia.

Additional respiratory support can be offered from bilevel positive airway pressure (BiPAP). Some experimental evidence supports the use of BiPAP for patients with acute respiratory dysfunction in the emergency department.⁸² Although this technique may be useful in overdosed patients, it should be considered only as a temporizing measure for patients who are expected to recover rapidly, or while preparing for intubation.

Intubation

After the decision for mechanical ventilation has been made, the route needs to be selected. The editors of this text prefer oral intubation because it permits the use of a larger endotracheal tube—usually 8 mm or even larger in adults—than does nasal intubation. If the patient later needs bronchoscopy, then it can be performed through the endotracheal tube. Some data

suggest that bronchoscopy with bronchoalveolar lavage may be of both diagnostic⁹⁸ and therapeutic⁶⁰ benefit for selected poisoned patients. However, in a patient who is awake, nasotracheal intubation done blindly or with the aid of a flexible fiberoptic laryngoscope may be more easily performed. Newer fiberoptic devices facilitate oral intubation in difficult cases making nasotracheal intubation almost obsolete. An advantage of nasotracheal intubation over oral intubation is that orogastric lavage can be performed more easily when the oral cavity is unimpeded. After the trachea is intubated, the tube should be checked to ensure that it is correctly positioned.

All patients who sustain overdoses and show signs or symptoms of respiratory insufficiency should have chest radiography performed. Unfortunately, intubated patients usually have portable radiography performed and the carina may be difficult to visualize because of the poor quality of the study. When seen, the carina is visualized between T-5 and T-7 in most patients. Thus, the tip of the endotracheal tube should be above T-5 for proper (safe) placement. When portable chest radiography is obtained, the patient's neck may be extended or flexed, altering the location of the endotracheal tube tip. For this reason it is essential to note the position of the neck during radiography, because the tip of the endotracheal tube may move up (with flexion) or down (with extension) by almost 2 cm.¹³

Mechanical Ventilation

After a patient is intubated for ventilatory support, the respirator mode is selected. Patients with pure hypoventilation usually require a controlled fixed rate that can be easily adjusted based on pulse oximetry, EtCO₂ and or serial venous or arterial blood–gas analyses. Patients with pulmonary parenchymal processes, such as ARDS or pneumonia, usually do best when placed on either assist control (AC) or intermittent mechanical ventilation (IMV) mode. Both of these modes are volume-controlled, meaning the clinicians set a volume and a minimal rate. In each of these modes the patient may take additional breaths. In AC, the additional patient breaths trigger a ventilator-delivered breath at the preset tidal volume. With the IMV mode, the tidal volume of extra patient-initiated breaths is determined by the patient. This may permit lower mean airway pressure, which theoretically may reduce the risk of barotrauma and hemodynamic compromise. Although the lower airway pressures associated with IMV are desirable, many authorities recommend the use of the assist mode because it eliminates the patient's work of breathing.⁵⁹

The next step is to determine the appropriate FiO₂ to be delivered to the patient. A number of formulas have been devised. One simple approach is to intubate a patient, control breathing, administer 100% oxygen, and decrease to an FiO₂ of less than 50% as quickly as possible in an attempt to prevent oxygen toxicity.³ Although the toxic effects of oxygen are well known for paraquat ([Chap. 112](#)), evidence suggests that oxygen may be an important mediator of other xenobiotic-induced pulmonary injuries such as with iron.⁴⁸ A PO₂ of 55 mm Hg or a measured oxygen saturation > 88% is generally acceptable; thus, there is little reason to expose patients to much higher concentrations of oxygen once these conditions are met.^{1,101} Many clinicians feel more comfortable establishing a “buffer” against deterioration by increasing the PO₂ to somewhat greater than 55 mm Hg, but prolonged exposure to higher values is rarely indicated. Tidal volumes should be set on the order of 6 mL/kg/breath. These lower, “protective” tidal volumes cause less barotrauma, lung injury, and cytokine release. Lower tidal volumes decrease mortality and ventilator days for patients with ARDS and to improve clinical outcomes in patients without ARDS.^{1,75} If oxygenation cannot be maintained with FiO₂ at or less than 50%, PEEP may be used, with careful reassessment of serial arterial blood–gas analyses, changes in effective compliance, and hemodynamic data with each increment in PEEP.

Pharmacologic Interventions: Antidotes

Only a few antidotes have a significant role in reversing xenobiotic-induced respiratory dysfunction. Naloxone may have the greatest role. Atropine and pralidoxime may be useful for respiratory dysfunction from cholinesterase inhibitors (Antidotes in Depth: A32 and A33, and [Chap. 113](#)). Elapid antivenom and botulinum antitoxin are rarely used but may be lifesaving. Neostigmine can reverse muscle weakness from nondepolarizing neuromuscular blockers ([Chap. 69](#)). More commonly, clinicians are required to treat bronchospasm from exposure to pulmonary irritants. The use of β_2 -selective adrenergic-agonist bronchodilators are effective in these patients.³⁶ The role of corticosteroids remains controversial.³

When treating patients with bronchospasm from one of the work-related asthma syndromes, it is reasonable that management should be similar to that of any patient with pulmonary bronchospasm, ie, emphasizing inhaled bronchodilators and corticosteroids ([Fig. 29–5](#)).

Two 30 year old patients who overdosed were brought to the ED. Each had ingested substantial amounts of barbiturates and diazepam. An arterial blood gas drawn from patient 1 while he was breathing room air revealed a pH of 7.18, PCO_2 of 70 mm Hg, PO_2 of 50 mm Hg, and a calculated bicarbonate of 24 mEq/L. An arterial blood gas drawn from patient 2, also breathing room air, revealed a pH of 7.31 PCO_2 of 50 mm Hg, PO_2 of 50 mm Hg, and a calculated bicarbonate of 25 mEq/L. Quick analysis showed that patient 1 was hypercapnic with a significant respiratory acidosis. Patient 2 did not appear as ill; his PCO_2 was not very elevated and his pH was not significantly reduced. The A-a gradients were calculated to be 12.5 mm Hg for patient 1 and 37.5 mm Hg for patient 2.

A. Arterial PCO_2 approximates alveolar PCO_2 and is substituted as:

$$\text{PAO}_2 = \text{PIO}_2 - \frac{\text{PCO}_2}{R}$$

$$\text{PIO}_2 = (\text{FIO}_2)(\text{PB} - \text{PH}_2\text{O})$$

where PAO_2 is alveolar PO_2 , PIO_2 is partial pressure of inspired O_2 , PaCO_2 is arterial PCO_2 , and R is the respiratory exchange ratio. Therefore:

$$\text{PAO}_2 = [(\text{FIO}_2)(\text{PB} - \text{PH}_2\text{O})] - \frac{\text{PCO}_2}{R}$$

where FIO_2 is the inspired O_2 fraction PH_2O is water vapor pressure, and PB is barometric pressure. On room air at sea level, $\text{FIO}_2 = 21\%$. At steady state, $R = 0.8$. At sea level, $\text{PB} = 760$ mm Hg, and $\text{PH}_2\text{O} = 47$ mm Hg. Therefore:

$$\text{PAO}_2 = [(\text{FIO}_2)(\text{PB} - \text{PH}_2\text{O})] - \frac{\text{PCO}_2}{R}$$

$$= [(0.21)(760 - 47)] - \frac{\text{PCO}_2}{R}$$

$$= 150 - [(1.25)(\text{PCO}_2)]$$

Because the A-a gradient is equal to $\text{PAO}_2 - \text{PaO}_2$, it can be expressed as:

$$150 - [(1.25)(\text{PCO}_2)] - \text{PaO}_2 \text{ or } 150 - [(1.25)(\text{PCO}_2) + \text{PaO}_2]$$

A normal A-a gradient on room air is 10–15 mm Hg, but this increases with age. A rough estimate of the normal A-a gradient is one-third the patient's age.

B. Referring to the two overdosed patients above, the A-a gradient for patient 1 is:

$$150 - [(1.25)(70) + 50] = 12.5 \text{ mm Hg}$$

This calculation reveals a normal gradient, indicating that the etiology for hypoxemia and hypoventilation is extrinsic to the lung itself. In patient 2, the A-a gradient is:

$$150 - [(1.25)(50) + 50] = 37.5 \text{ mm Hg}$$

This abnormally high A-a gradient is consistent with the aspiration which was pneumonia seen on the patient's chest radiograph.

FIGURE 29–5. (A) Derivation of the definition of alveolar–arterial (A–a) oxygen gradients. (B) Using the A–a gradients

An inhaled solution of 2% sodium bicarbonate may provide symptomatic relief for patients with pulmonary exposure to hydrogen chloride or to chlorine (Antidotes in Depth: A5).

Exogenous nitric oxide has been considered for a variety of pulmonary conditions. Specifically, nitric oxide may be useful as a bronchodilator,¹⁸ a means to reverse hypoxic pulmonary vasoconstriction,³ and as treatment for ARDS.² Unfortunately, controlled studies fail to demonstrate a benefit for nitric oxide in patients with ARDS.^{3,101} Similarly, the results are disappointing for corticosteroids, surfactants, and a variety of antiinflammatory agents.^{4,101}

SUMMARY

- Xenobiotics may adversely affect tissue oxygenation at every step required for ventilation, oxygen delivery, and cellular respiration.
- Hypoxia and hypercarbia should be addressed as soon as they are suspected clinically. The use of supplemental oxygen or assisted ventilation should not be delayed.
- Although the clinical manifestations of hypoxia are constant regardless of etiology, the history, physical examination, and diagnostic testing often help to identify the specific mechanism of hypoxia.
- Invasive and noninvasive measures of oxygenation and ventilation may be used to assess response to therapy and need for further therapy. Clinicians should familiarize themselves with the strengths and limitations of pulse oximetry, end-tidal carbon dioxide capnography, venous and arterial blood-gas analyses, and cooximetry.
- In most cases of xenobiotic-induced respiratory depression, general supportive measures are favored over specific antidotal therapy.

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30 THERMOREGULATORY PRINCIPLES

Susi U. Vassallo and Kathleen A. Delaney

Despite exposure to wide fluctuations of environmental temperatures, human body temperature is maintained within a narrow range.^{17,126} Elevation or depression of body temperature occurs when (1) thermoregulatory mechanisms are overwhelmed by exposure to extremes of environmental heat or cold; (2) endogenous heat production is either inadequate, resulting in hypothermia, or exceeds the physiologic capacity for dissipation, resulting in hyperthermia; or (3) disease processes or xenobiotic effects interfere with normal thermoregulatory responses to heat or cold exposure.

METHODS OF HEAT TRANSFER

Heat is transferred to or away from the body through radiation, conduction, convection, and evaporation. Radiation involves the transfer of heat from a body to the environment and from warm objects in the environment, for example, from the sun to a body. Conduction involves the transfer of heat to solid or liquid media in direct contact with the body. Water immersion conducts significant amounts of heat away from the body. This effect facilitates cooling in a swimming pool on a hot summer day or may lead to hypothermia despite moderate ambient temperatures on a rainy day. The amount of heat lost through conduction and radiation depends on the temperature gradient between the skin and its surroundings; cutaneous blood flow; and insulation such as subcutaneous fat, hair, clothing, or fur in lower animals.¹⁴³ In the respiratory tract, heat is lost by conduction to water vapor or gas. In animals unable to sweat, this represents the primary method of heat loss. The amount of heat lost through the respiratory tract depends on the temperature gradient between inspired air and the environment and the rate and depth of breathing.¹⁴³ Convection is the transfer of heat to the air surrounding the body. Wind velocity and ambient air temperature are the major determinants of convective heat loss. Evaporation is the process of vaporization of water, or sweat. Large amounts of heat are dissipated from the skin during this process, resulting in cooling. Ambient temperature, rate of sweating, air velocity, and relative humidity are important factors in determining how much heat is lost through evaporation. On a very hot and humid day, sweat may pour off an exercising person who rather than evaporating and initiating heat loss is accomplishing little heat loss. In very warm environments, thermal gradients may be reversed, leading to transfer of heat to the body by radiation, conduction, or convection.¹⁵⁶

PHYSIOLOGY OF THERMOREGULATION

In a normal human, stimulation of peripheral and hypothalamic temperature-sensitive neurons results in autonomic, somatic, and behavioral responses that lead to the dissipation or conservation of heat. Thermoregulation is the complex physiologic process that serves to maintain hypothalamic temperature within a narrow range of $98.6 \pm 0.8^{\circ}\text{F}$ ($37 \pm 0.4^{\circ}\text{C}$), known as the set point.¹²⁶ This hypothalamic set point is influenced by factors such as diurnal variation, the menstrual cycle, and others. Maintaining, raising, or lowering the set point results in many outwardly visible physiologic manifestations of thermoregulation such as sweating, shivering, flushing, or panting. In the central nervous system (CNS), thermosensitive neurons are located predominantly in the preoptic area of the anterior hypothalamus, but to a lesser extent in the posterior hypothalamus. These neurons may be divided into those that are warm sensitive, cold sensitive, or temperature insensitive. Approximately 30% of preoptic neurons are warm sensitive. These increase their firing rate during warming and decrease their firing rate during cooling.³⁰ Warming of the hypothalamus in conscious animals results in vasodilation, hyperventilation, salivation, and increases in evaporative water loss, as well as a reduction of cold-induced shivering and vasoconstriction.¹²⁶ Cooling of the hypothalamus in conscious animals causes shivering, vasoconstriction, and increased metabolic rate even if the environment is hot.¹¹⁷ How these temperature-sensitive neurons of the hypothalamus detect temperature changes and effect neuronal transmission is unclear. Altered action potential initiation and propagation caused by temperature-dependent membrane potential changes associated with the ratios of Na^{+} to Ca^{2+} ions that alter neuronal excitability and neurotransmitter release, or effects on the $\text{Na}^{+}\text{-K}^{+}\text{-ATPase}$ (adenosine triphosphatase) pump.¹⁴³ Xenobiotics that increase intracellular cyclic adenosine monophosphate (cAMP) concentrations increase the thermosensitivity of warm-sensitive neurons.³⁰ In the brainstem, warm- and cold-sensitive neurons are located in the medullary reticular formation, where information from cutaneous receptors, spinal cord, and preoptic area of the anterior hypothalamus is integrated.¹³²

The spinal cord is thermosensitive. Heat and cold sensitive ascending spinal impulses are conducted in the spinothalamic tract. As in the hypothalamus, local heating or cooling of the spinal cord results in thermoregulatory responses.¹²⁶ In addition to the hypothalamus, brainstem, and spinal cord, there is evidence of thermosensitivity in the deep abdominal viscera.^{113,126,228} Intraabdominal heating or cooling results in thermoregulatory responses. Cold and warm sensitive afferent impulses can be recorded from the splanchnic nerves in animals.^{113,230} Finally, the skin also contains heat and cold thermosensitive neurons. Whereas cold receptors are free nerve endings that protrude into the basal epidermis, warm sensitive receptors protrude into the dermis.^{125,127} Cutaneous thermoreceptor output is affected by the absolute temperature of the skin, rate of temperature change, and area of stimulation.¹²⁶ Cutaneous cold receptors are A- δ and C nociceptor afferent fibers. A δ fibers are small-diameter, thinly myelinated fibers that conduct at 5 to 30 m/sec, and C fibers are small-diameter, unmyelinated fibers that conduct at 0.5 to 2 m/sec.¹²¹ Afferents from heat receptors are primarily C fibers. Cutaneous thermoreceptive neurons respond to external temperature change as well as rate of temperature change, sending early warning to the CNS via afferent impulses, allowing rapid and transient thermoregulatory responses before brain temperature changes (Fig. 30–1).

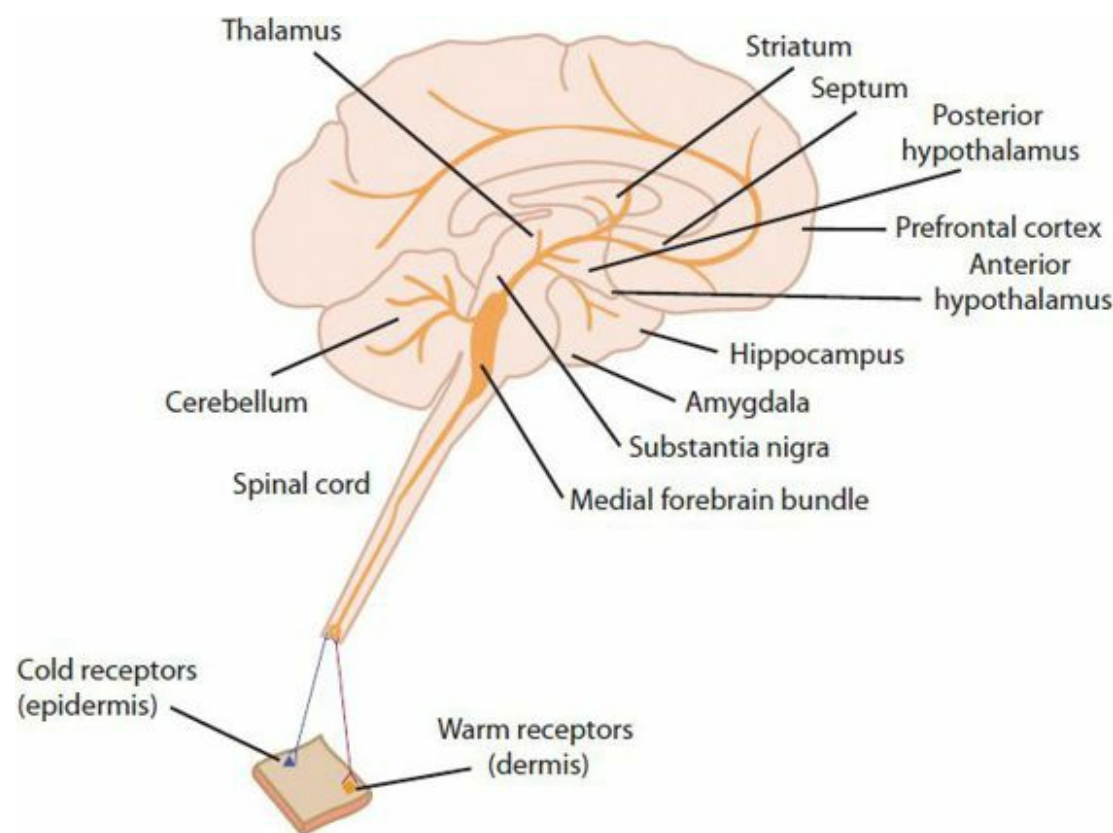


FIGURE 30–1. A representation of the response of cutaneous thermoreceptive neurons to external temperature change as an early warning to the central nervous system.

Vasomotor and Sweat Gland Function

Vasomotor responses to thermoregulatory input differ according to location. The normal thermoregulatory response to heat stress is mediated primarily by heat-sensitive neurons in the hypothalamus. Increased body-core temperature results in active vasodilation in the extremities and is under noradrenergic control; increasing sympathetic stimulation results in vasoconstriction, and decreasing sympathetic control results in vasodilation. Vasodilation in the head, trunk, and proximal limbs is not a result of decreased sympathetic tone; instead, it is a result of an active process that is under the influence of cholinergic sudomotor nerves and local effects of temperature on vasomotor tone. Sweat glands release local transmitters, such as vasoactive intestinal polypeptide (VIP) or bradykinins, and vasodilation results. Areas of the body such as the forehead, where sweating is most prominent during heat stress, correspond to areas where active vasodilation is greatest. The neurotransmitters involved in the regulation of relationships between vasodilation and sweating as a response to heat stress are not fully elucidated, but animal evidence suggests the presence of specific vasodilator nerves.¹²⁶

Sweat glands are controlled by postganglionic nerve fibers, which are cholinergic, and large amounts of acetylcholinesterase as well as other peptides are involved in neural transmission.^{125,126}

Neurotransmitters and Thermoregulation

The neurotransmitters involved in thermoregulation include serotonin, norepinephrine, acetylcholine, dopamine, prostaglandins, β -endorphins, and intrinsic hypothalamic peptides such as arginine vasopressin, adrenocorticotrophic

hormone, thyrotropin-releasing hormone, and melanocyte–stimulating hormone.^{51,217} Studies on the effects of individual neurotransmitters in thermoregulation yield contradictory results, depending on the animal species and the route of administration of the exogenous neurotransmitter. Refinements in techniques of microinjection of neurotransmitters into the hypothalamus of animals, rather than intraventricular instillation, have elucidated microanatomic sites where neurotransmitters are active. More research is needed, however, because interspecies variations and theoretical differences in response to exogenous versus endogenous peptides make this area of study complex.

Apomorphine is a mixed dopamine agonist that causes hypothermia in animals; studies using selective D₁- and D₂-receptor agonists and antagonists suggest that the hypothermic effect of apomorphine is a result of its effects on D₂ receptors, with some modulation by D₁ receptors in the hypothalamus.¹⁹⁵ Stimulation of D₂ receptors appears to mediate the hypothermia induced by the peptide sauvagine.³³ Stimulation of D₃ by specific agonists caused hypothermia in an animal model.^{196,197} There appears to be a link between dopamine D₂ receptors and norepinephrine receptors in the hypothalamus, perhaps leading to vasodilation and hypothermia. The effect of clozapine in producing hypothermia in rats is caused by D₁ and D₃ stimulation.^{196,241} Lesser known peptides appear to be involved in thermoregulation. For example, neuropeptide Y is an amino acid neurotransmitter that occurs in high concentrations in the preoptic area of the anterior hypothalamus. Administration of neuropeptide Y caused a reduction in core temperature when administered with adrenergic receptor antagonists such as prazosin, an α_1 -adrenergic antagonist; propranolol, a β -adrenergic antagonist; and clonidine, a central α_2 -adrenergic agonist.^{84,239} Studies on muscarinic receptors suggest the involvement of muscarinic M₂ and M₃ receptors in the production of hypothermia when agonists to these receptors are administered centrally.²⁴² Blockers of ATP–sensitive K⁺ channels can reverse the effect of cholinomimetic drugs in producing hypothermia.²²⁵

DRUG EFFECTS ON THERMOREGULATION

Many xenobiotics have pharmacologic effects that interfere with thermoregulatory responses (Tables 30–1 and 30–2).^{180,182,281} α -Adrenergic agonists prevent vasodilation in response to heat stress. Increased endogenous heat production in the setting of increased motor activity also occurs in patients poisoned with cocaine or amphetamines. Life-threatening hyperthermia is associated with the use of these xenobiotics. Whereas adrenergic antagonists and calcium channel blockers diminish the cardiac reserve available to compensate for heat-induced vasodilation, diuretics decrease cardiac reserve through their effects on intravascular volume.⁶⁴ β -Adrenergic antagonists also interfere with the capacity to maintain normothermia under conditions of cold stress, possibly related to their interference with the mobilization of substrates required for thermogenesis.^{126,182} Opioids and diverse sedative–hypnotics depress hypothalamic function and predispose to hypothermia in the overdose setting.⁸⁶ Carbon monoxide poisoning must also be considered in hypothermic patients. Organic phosphorous insecticides and other xenobiotics that cause cholinergic stimulation cause hypothermia by stimulation of inappropriate sweating and possibly through depression of the endogenous use of calorogenic substrates.¹⁸² Xenobiotics with anticholinergic effects decrease sweating and predispose to hyperthermia during environmental heat exposure or exercise. Phenothiazines appear to interfere with normal response to both heat and cold. Severe hyperthermia associated with the absence of sweating is frequently described in patients using phenothiazines and may be a consequence of their anticholinergic effects.^{243,297} Effects on cold tolerance are attributed to their α -adrenergic antagonist effects, which prevent vasoconstriction in response to cold stress.¹⁸¹ In addition, hyperthermia associated with severe extrapyramidal rigidity may occur in patients taking antipsychotics.¹⁷³ This rigidity is attributed to the dopamine-blocking effects of this class of drugs.

TABLE 30–1. Effects of Xenobiotics That Predispose to Hyperthermia

I. Impaired cutaneous heat loss

- A. Vasoconstriction through α -adrenergic stimulation
 - Amphetamines
 - Cocaine
 - Ephedrine
 - Phenylpropanolamine
 - Pseudoephedrine
- B. Sweat gland dysfunction
 - Antihistamines
 - Belladonna alkaloids

Cyclic antidepressants
Topiramate
Zonisamide

II. Myocardial depression

- A. Decreased cardiac output
 - Antidysrhythmics
 - β -Adrenergic antagonists
 - Calcium channel blockers
- B. Reduced cardiac filling by salt and water depletion
 - Diuretics
 - Ethanol

III. Hypothalamic depression

Antipsychotics

IV. Impaired behavioral response

Cocaine
Ethanol
Opioids
Phencyclidine
Sedative–hypnotics

V. Uncoupling of oxidative phosphorylation

Dinitrophenol
Pentachlorophenol
Salicylates

VI. Increased muscle activity through agitation, seizures, or rigidity

Amphetamines
Caffeine
Cocaine
Isoniazid
Lithium
Monoamine oxidase inhibitors
Phencyclidine
Strychnine

VII. Dystonia

Butyrophenones
Phenothiazines

VIII. Withdrawal

Dopamine agonists
Ethanol
Sedative–hypnotics

TABLE 30–2. Effects of Xenobiotics That Predispose to Hypothermia

Impaired nonshivering thermogenesis

β -Adrenergic antagonists

Cholinergics

Hypoglycemics

Impaired perception of cold

Carbon monoxide

Ethanol

Hypoglycemics

Opioids

Sedative–hypnotics

Impaired shivering by hypothalamic depression

Carbon monoxide

Ethanol

General anesthetics

Opioids

Phenothiazines

Sedative–hypnotics

Impaired vasoconstriction

α -Adrenergic antagonists

Ethanol

Phenothiazines

Ethanol is the xenobiotic most commonly related to the occurrence of hypothermia in an urban setting.^{62,288,289} The mechanism by which ethanol predisposes to hypothermia is said to be by virtue of its effects on CNS depression, vasodilation, and blunting of behavioral responses to cold. However, thermoregulatory dysfunction associated with ethanol intoxication is undoubtedly more complex.

In animal models, ethanol leads to hypothermia, the extent of which is partly dependent on ambient temperature.^{211,231,232} In mice, as the dose of ethanol increased, body temperature decreased, and the rate of this decline in body temperature was faster at higher ethanol doses.²⁰⁶ The decline in body temperature could be reversed by increasing ambient temperature; increasing ambient temperature to 96.8°F (36°C) caused an immediate rise in the body temperature.²⁰⁶ The poikilothermic effect of ethanol was not a result of hypoglycemia. Poikilothermia is the variation in body temperature greater than $\pm 3.6^\circ\text{F}$ ($\pm 2^\circ\text{C}$) on exposure to environmental temperature changes. Rats treated with equipotent amounts of sodium pentobarbital showed the same effects on body temperature as rats treated with ethanol, suggesting a similar central mechanism of CNS depression resulting in altered thermoregulation.²⁰⁶

Numerous mechanisms are involved in the ethanol-induced depression of CNS function.²³⁶ Genetic factors influence the role of ethanol in the production of hypothermia. Mice can be selectively bred for genetic sensitivity or insensitivity to acute ethanol-induced hypothermia, and the differences appear to be mediated by the serotonergic systems.^{87,101,200,206} Cyclo His-Pro DKP, another neurotransmitter that is found in many animal species, acts at the preoptic-anterior hypothalamus to modulate body temperature.^{41,136} Exogenous administration of this neuropeptide produced a dose-dependent decrease in ethanol-induced hypothermia. Attenuation of hypothermia resulted from passive immunization with CHP antibody.^{41,136} Ethanol effects may be mediated through modulation of endogenous opioid peptides because high-dose (10 mg/kg) naloxone reverses ethanol-induced hypothermia in animals.²²¹

Pharmacokinetic characteristics of ethanol metabolism change in the presence of hypothermia. Hypothermic piglets

infused with ethanol showed slower ethanol metabolism and a smaller volume of distribution (Vd) and, as a result, higher ethanol concentrations than normothermic control piglets. Ethanol elimination and metabolism decreased as temperature fell.¹⁶³

Tolerance develops to the effect of ethanol in producing hypothermia in all species.^{89,211} The degree of tolerance is proportional to the dose and duration of treatment with ethanol and is not explained by the increased rate of metabolism with chronic exposure.¹⁴³ Age is a factor in the development of tolerance; older animals do not display the same degree of tolerance to the hypothermic effects of chronic ethanol administration as do younger animals.^{203,220,296} The development of tolerance to ethanol-induced hypothermia is affected by genetic factors. Experimentally, tolerance to ethanol-induced hypothermia increases the incorporation of certain amino acids into proteins in the rat brain. The formation of new proteins in ethanol-tolerant rats suggests stimulation of gene expression related to the tolerant state.^{143,284} Deficits in N-methyl-D-aspartate (NMDA) receptor systems may also be implicated in the development of ethanol tolerance. In addition, altered nicotinamide adenine dinucleotide (NADH) oxidation to NAD⁺, diminished blood flow to the liver, or slowing of metabolism through the microsomal enzyme system may be involved.²³⁶

Hypothermia alters the breath-ethanol partition in the alveolus, and the temperature of expired breath alters breath-ethanol analysis results. In patients with mild hypothermia, ethanol-breath analysis results in lower values by 7.3% per degree centigrade (or 1.8°F) decrease in body temperature.⁹² Whether breath-ethanol analysis is also affected by hyperthermia remains to be studied.⁹²

DISEASE PROCESSES AND THERMOREGULATION

Many disease processes interfere with normal thermoregulation, limiting an individual's capacity to prevent hypothermia or hyperthermia. Extensive dermatologic disease or cutaneous burns impair sweating and vasomotor responses to heat stress.³⁶ Patients with autonomic disturbances such as diabetes mellitus or peripheral vascular disease also have altered vasomotor responses that impair vasodilation and sweating.²²⁹ Extensive surgical dressings may preclude the evaporation of sweat in an otherwise normal patient. Heat stressed persons with poor cardiac reserve may not be able to sustain skin blood flow rates high enough to maintain normothermia.^{76,264} Intense motor activity may lead to excessive heat production in patients with Parkinson disease or hyperthyroidism. Patients with agitated delirium or seizures also have significantly elevated rates of endogenous heat production. Hypothalamic injury caused by cerebrovascular accidents, trauma, or infection may disturb thermoregulation.^{75,177} Hypothalamic dysfunction can lead to high, unremitting fevers and insufficient stimulation of heat loss mechanisms such as sweating. Hypothalamic damage may predispose to hypothermia by interference with centrally mediated heat conservation.^{75,177,244,245} Fever, the normal response to stimulation of the hypothalamus by pyrogens, results in an elevated physiologic temperature set point and is a disadvantage in the heat-stressed individual.¹²⁶

HYPOTHERMIA

Epidemiology

Hypothermia is defined as a lowering of the core body temperature to below 95°F (<35°C). Between 1999 and 2002, 4607 people had hypothermia-related diagnoses listed on their death certificates as the underlying cause of death.⁴⁶ Most of these, 2622, were caused by exposure to excessive cold; in the remainder, hypothermia resulted from some reason other than exposure, such as medical illness^{43,44,130,159} (Table 30–3).

TABLE 30–3. Factors Predisposing to Hypothermia

Advanced age

Decreased ability to shiver

Decreased metabolic rate

Decreased temperature discrimination

Reduced peripheral blood flow

Central nervous system depression

Cerebrovascular accident

Ethanol

Hypothalamic dysfunction

Infection

Xenobiotics, diverse

Endocrine

Diabetic ketoacidosis

Hyperosmolar coma

Hypopituitarism

Hypothyroidism

Environmental

Homelessness

Unintentional

Hepatic failure

Immobilization

Central nervous system dysfunction

Illness

Spinal cord injury

Trauma

Nutritional

Glycogen depletion

Hypoglycemia

Starvation

Thiamine deficiency

Sepsis

Social

Failure to use indoor heating

Homelessness

Inadequate indoor heating

Poverty

Social isolation

Uremia

Most hypothermic deaths occur in the winter months; however, mildly cool environments and windy wet conditions are also frequently associated with hypothermia. From 1999 to 2011, a total of 16,911 deaths in the United States were associated with exposure to excessive natural cold. Alaska, Montana, Wyoming, and New Mexico had the greatest overall death rates from hypothermia. States with milder climates and rapid fluctuations in temperature, such as North and South Carolina, and western states, such as Arizona, with high elevations and cold nighttime temperatures, report hypothermia-related deaths.⁴⁶

Response to Cold

The normal physiologic response to cold is initiated by stimulation of cold-sensitive neurons in the skin, so that the onset of the body response to cold occurs before cooling of central blood. Cold-sensitive neurons in the skin send afferent impulses to the hypothalamus, resulting in shivering and piloerection. Shivering is the main thermoregulatory response to cold in humans, except in neonates, in whom nonshivering thermogenesis prevails. Shivering is initiated in the posterior hypothalamus when impulses from cold-sensitive thermoreceptors are integrated in the anterior hypothalamus and communicated to the posterior hypothalamus or when cold-sensitive neurons in the posterior hypothalamus are activated directly. Efferent stimuli from the posterior hypothalamus travel through the midbrain tegmentum, pons, and lateral medullary reticular formation to the motor pathways of the tectospinal and rubrospinal tracts, resulting in shivering.²² A mechanism of stimulation of shivering that usually occurs later when core temperature drops is the local cooling of the spinal cord, which leads to shivering by increasing excitability of motor neurons.

Heat produced without muscle contraction is known as nonshivering thermogenesis.^{34,126} Nonshivering thermogenesis is mediated by the sympathetic nervous system.⁵⁶ Catecholamines activate adenylate cyclase, increasing cAMP, resulting in mobilization of fat and glucose stores (β -adrenergic receptors).^{183,238} Nonshivering thermogenesis is blocked by α -adrenergic receptor antagonism and increased by administration of norepinephrine. Brown adipose tissue is the most important site of nonshivering thermogenesis. In humans, brown fat is found primarily in neonates, although in cold-acclimatized people, there may be small amounts found on autopsy.³⁴ Brown adipose tissue functions as a thermoregulatory effector organ, producing heat by the oxidation of fatty acids when the tissue is stimulated by norepinephrine.⁴⁰

In addition to shivering and nonshivering thermogenesis, efferent sympathetic fibers from the hypothalamus stimulate peripheral vasoconstriction (α -adrenergic receptors). Piloerection and vasoconstriction result in decreased heat loss from the body. Intense vasoconstriction shunts blood away from the periphery to the core and antidiuretic hormone antagonism results in increased urine output and hemoconcentration.

Several disease processes commonly result in an inability to maintain a normal body temperature in a cool environment (Table 30–3). Hypothermia may develop in association with sepsis, hypothyroidism, hypoglycemia, uremia, hepatic failure, or poor nutrition.^{68,175} Hypothalamic injury may result in chronic poikilothermia.¹⁸¹ Thiamine deficiency adversely affects the hypothalamus, perhaps because of inefficient glucose metabolism, and leads to hypothermia.¹⁶¹ Spinal cord transection above the first thoracic segment interrupts hypothalamic–sympathetic outflow pathways, resulting in hypothermia.²²⁹ Frail elderly adults are at greater risk of hypothermia because of decreased vasomotor responses and a decreased capacity to shiver.^{56,59} Mentally and physically compromised patients may be unable to make appropriate behavioral responses to hot or cold environments.

Evaluations to determine the presence of underlying diseases are often difficult in a patient with hypothermia.^{90,175} The mental status may be markedly altered by hypothermia but is not usually abnormal until the temperature falls below 90°F (32.2°C). If normal mental status is not regained when the temperature reaches 90°F (32.2°C) during rewarming, underlying CNS structural, toxic, or metabolic problems must be considered.^{90,175,226} Failure of the patient to rewarm quickly suggests the presence of underlying disease⁶⁸ (Fig. 30–2). In one study, whereas hypothermic patients without underlying disease are reported to rewarm at a rate of 1.0 to 3.7°F/h (0.6–2.1°C/h) (average, 2.1°F/h; 1.2°C/h), patients with significant underlying disease (sepsis, gastrointestinal {GI} hemorrhage, diabetic ketoacidosis, pulmonary embolus, myocardial infarction) warmed at a rate of 0.25 to 1.8°F/h (0.1–1.0°C/h) (average, 1°F/h; 0.6°C/h).²⁸⁸

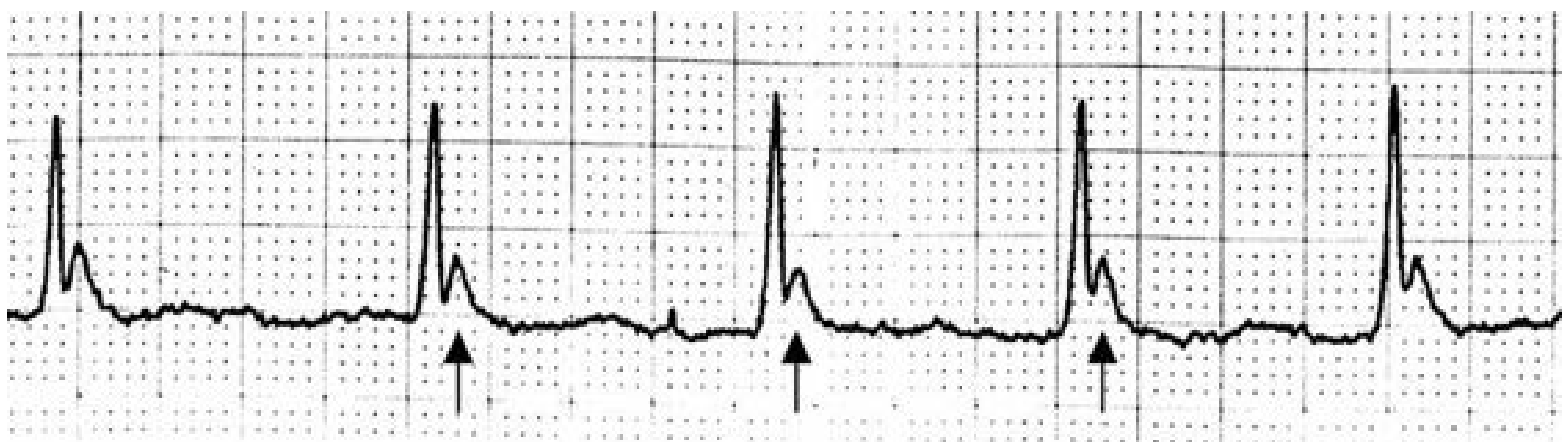


FIGURE 30–2. A characteristic electrocardiographic finding in a patient with profound hypothermia. The terminal phase of the QRS complex shows a typical elevation of the J-point Osborn wave (↑). (Reproduced with permission from Delaney KA, Vassallo SU, Larkin GL, et al. Rewarming rates in urban patients with hypothermia: prediction of underlying infection. *Academic emergency medicine: official journal of the Society for Academic Emergency Medicine*. 2006;Sep;13(9):913–921.)

Alteration of Pharmacology in Hypothermia

The pharmacology of certain xenobiotics is altered in the setting of hypothermia. In hypothermic piglets, the V_d and the clearance of fentanyl are decreased.¹⁶³ Similarly, in piglets given gentamicin, the V_d and clearance rate decreased in direct proportion to the decrease in cardiac output and glomerular filtration rate (GFR).¹⁶² Hypothermic puppies given intravenous (IV) lidocaine showed slower rates of disappearance of the drug than when normothermic.²⁰¹ Humans and animals given propranolol showed a reduced V_d and decreased total body clearance, resulting in higher than expected propranolol concentrations.^{35,188,189,209} Decreased hepatic metabolism of propranolol during hypothermia has been shown in vitro.¹⁸⁹ Hypothermia prolongs neuromuscular blockade with d-tubocurarine¹¹⁵ and increases neuromuscular blockade with suxamethonium.²⁹³ Phenobarbital metabolism and V_d decreased with hypothermia in children.¹⁴² The lethal dose of digoxin was doubled in hypothermic dogs.¹⁸ Digoxinlike substances are present during hypothermia.^{97,129}

Reasons for altered metabolism in hypothermia include delayed distribution of the drug and altered enzyme function with temperature and pH changes. Cardiac output decreases, leading to decreased liver perfusion and decreased delivery of drug to hepatic microsomal enzymes.^{115,145–147,218} Plasma volume decreases as free water moves intracellularly, causing hemoconcentration and further decreasing organ perfusion.¹¹⁶ Biliary excretion of atropine, procaine, and sulfanilamide decreases in vitro.^{145–147} The GFR decreases in hypothermia.³¹ In vitro, the activity of metabolic pathways, including acetylation and hydrolysis, decrease with cooling.^{145,146}

Xenobiotic Metabolism in Therapeutic Hypothermia. Hypothermia is induced for its neuroprotective effects but requires attention to alterations in pharmacokinetics and pharmacodynamics of xenobiotics administered during hypothermia. Physiological changes during induced hypothermia are similar to those of unintentional hypothermia and include slowed enzymatic reactions, vasoconstriction, decreased cardiac output, and hemoconcentration. Studies support a decrease in the V_d of pancuronium, midazolam, morphine, and gentamicin.⁶⁵ Clearance of xenobiotics is affected by organ perfusion, enzyme activity, and xenobiotic characteristics such as the degree of protein binding and the pK_a . Hepatic and renal clearance is affected by regional blood flow, which is decreased during hypothermia. In general, the decrease in the V_d and the decrease in clearance result in increased serum xenobiotic concentrations.²³ Experimental studies in animals demonstrate a 25% increase in fentanyl concentrations at a core temperature of 32°C.⁹³ Concurrent supportive modalities during hypothermia such as cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO) further alter the kinetics of xenobiotics during hypothermia.²⁹⁰ In neonates, asphyxia treated with induced hypothermia presents the additional complication of rapidly changing neonatal physiology and the effects of supportive measures such as ECMO.⁶⁵

Clinical Findings

The clinical effects of hypothermia are related to the membrane depressant effects of cold, which result in ionic and electrical conduction disturbances in the brain, heart, peripheral nerves, and other major organs (Table 30–4).¹³¹ Cold tissues are protected by decreases in tissue oxygen requirements. As body temperature decreases, metabolic activity declines at a rate of approximately 7% per 1.8°F (1°C).²⁹⁵ This effect provides significant protection to vital organs despite the potentially deleterious effects of membrane suppression.

TABLE 30–4. Physiologic and Clinical Manifestations of Hypothermia

Cardiovascular

Normal, decreased, or increased cardiac output

Normal heart rate or tachycardia, then bradycardia as hypothermia increases

Vasoconstriction and central shunting of blood

Electrocardiogram

Prolongation of intervals

Atrial fibrillation

Increased ventricular irritability

J-point elevation “Osborn waves”

Central nervous system

Mild: 90°–95°F (32°–35°C)

Normal mental status or slightly slowed

Moderate: 80°–90°F (27°–32°C)

Lethargic but verbally responsive

Severe: 68°–80°F (20°–27°C)

Unlikely to respond verbally or purposefully to noxious stimuli

Profound: <68°F (<20°C)

Unresponsive; may “appear dead”

Gastrointestinal tract

Decreased motility

Depressed hepatic metabolism

Hematologic

Hemoconcentration

Left shift of oxyhemoglobin dissociation curve

Kidneys

Cold-induced diuresis

Antidiuretic hormone antagonism

Lungs

Hyperventilation to hypoventilation with increasing hypothermia

Bronchorrhea

Metabolic

Metabolic acidosis

Increased glycogenolysis

Increased serum free fatty acids

Normal thyroid and adrenal function

Effects on the CNS are temperature dependent and predictable. Mild hypothermia (90–95°F; 32.2–35°C) usually results in relatively benign clinical manifestations. Ataxia, clumsiness, slowed response to stimuli, and dysarthria are common.⁹⁰ As cooling continues, the mental status slowly deteriorates. In moderate hypothermia (80–90°F; 27–32.2°C), the patient is usually lethargic but still likely to respond verbally. In severe hypothermia (68–80°F; 20–26.6°C), the patient is unlikely to respond verbally but will react purposefully to noxious stimuli.^{90,122} In profound hypothermia (<68°F; <20°C), the patient is unresponsive to stimuli. The pupils may be fixed and dilated and the patient may appear dead.¹²² However, standard criteria for brain death do not apply to hypothermic patients. The hypothermia itself protects against cerebral hypoxic damage.¹³¹ Temperature drop inhibits the release of the excitatory neurotransmitter glutamate and attenuates the release of dopamine in animal models of brain ischemia, suggesting a protective effect of hypothermia in brain injury.³⁹ Cerebrospinal fluid (CSF) glutamate concentrations were lower in patients showing benefit from mild induced hypothermia after brain injury compared with brain-injured patients kept normothermic.¹⁸⁵

Patients have survived with body temperatures as low as 48.2°F (9°C).⁹⁴ Vigorous resuscitation is required for these patients. This approach may lead to hours of cardiopulmonary resuscitation (CPR) of hypothermic patients with ventricular fibrillation, ventricular tachycardia, or asystole but may be ultimately successful in resuscitating patients initially presumed to be dead.²⁶²

For field rescue work, the Swiss distinguish between five stages of hypothermia and provide guidelines for rescue in dangerous environmental conditions. These stages are based on the degree of consciousness, the presence or absence of shivering, cardiac activity, and core temperature.^{74,35} The adage that a patient cannot be considered dead until the patient is warm and dead is further refined by the Swiss guidelines for field rescue attempts under avalanche conditions.

The cardiac and hemodynamic effects of cold correlate closely with body temperature. As cooling begins, there is a transient increase in cardiac output. Tachycardia develops secondary to shivering and sympathetic stimulation. At about 81°F (27.2°C), shivering ceases. Bradycardia develops with maintenance of a normal cardiac stroke volume.³⁷ This bradycardia is responsible for the decreased myocardial oxygen demand, which may be protective in the setting of hypothermia.³⁷ In profound hypothermia, bradycardia may progress to asystole and death.

Unlike cerebral circulation, in which autoregulation is preserved during cooling, coronary autoregulation is disturbed during hypothermia, and myocardial injury may ensue.³⁷ Attempts to maximize myocardial oxygenation through administration of oxygen and volume replacement to increase diastolic filling pressures are appropriate.

The initial response to cold is hyperventilation; however, as temperature continues to decrease, hypoventilation develops, which may progress to apnea and death. In animal models, this has been attributed to cold-induced failure of phrenic nerve conduction.¹⁵⁴

The Electrocardiogram

The most common electrocardiographic (ECG) abnormality in hypothermia is generalized, progressive depression of myocardial conduction. PR, QRS, and QT intervals are all prolonged, and increasingly profound hypothermia may lead to gradual progression to asystole.^{73,277} Ventricular fibrillation occurs in an irritable myocardium most commonly at temperatures less than 86°F (30°C), resulting in a high O₂ consumption dysrhythmia. Atrial fibrillation is the most common dysrhythmia occurring in the presence of hypothermia.^{91,219} Shivering may not be clinically evident, but the characteristic fine muscular tremor frequently produces a mechanical artifact in the baseline of the ECG.⁷⁸ A deflection occurring at the junction of the QRS and ST segment is invariably present in patients with temperatures <86°F (<30°C) (Fig. 30–3). First described in a single patient in 1938, the J-point deflection is commonly known as the Osborn wave.^{79,222,273} The J-point deflection, thought to be a “current of injury” associated with CO₂ retention under hypothermic conditions, was believed to be a poor prognostic sign.²²² Subsequent study does not support any prognostic significance because the J-point deflection is invariably found in hypothermic patients when multiple ECG leads are obtained.^{78,79,275,282} The size of the J-point deflection increases as body temperature decreases.^{219,282} Atrial dysrhythmias that occur in the absence of underlying heart disease invariably disappear solely with rewarming.

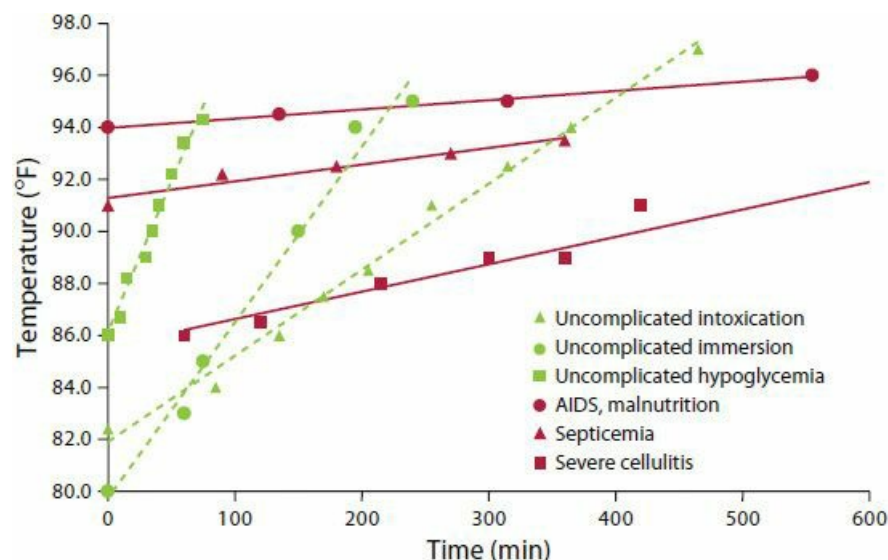


FIGURE 30–3. Relation of rewarming rate to underlying illness. (Reprinted with permission from Academic Emergency Medicine.⁶⁸)

Management

After blood specimens are drawn, the hypothermic patient in whom hypoglycemia is present should be given 0.5 to 1.0 g of dextrose/kg of body weight as D₅₀W (50% dextrose in water in adults or D₂₀W or D₁₀W as appropriate for children) and 100 mg of IV thiamine. If hypoglycemia is the cause of the hypothermia, the response to dextrose may be dramatic, heralded by the onset of shivering and rapid return to normal body temperature. Wernicke encephalopathy is uncommon but may be associated with mild hypothermia; thermoregulation and normal ocular motion may return after the initiation of thiamine therapy.¹⁶¹

Hypothermia shifts the oxygen dissociation curve to the left (Chap. 29), resulting in decreased oxygen unloading to tissues; therefore, oxygen administration may be of benefit.⁶⁷ If clinically indicated, endotracheal intubation should be performed for airway protection or inadequate ventilation or oxygenation.^{62,168,198} However, there are case reports of ventricular fibrillation occurring during endotracheal intubation.^{15,100,122,223,291} Every effort should be made to limit patient activity and stimulation during the acute rewarming period because activity may increase myocardial oxygen demand or alter myocardial temperature gradients, increasing the risk of iatrogenic ventricular fibrillation. Although pulmonary artery catheters and central venous lines have been inserted without complications, they should be avoided unless absolutely essential so as not to precipitate ventricular dysrhythmias.^{120,169,274} If a central venous catheter is considered necessary, it should not be allowed to touch the endocardium.²⁷⁶ Patients who develop ventricular fibrillation or asystole are difficult to manage because of the many supportive therapies required at once and the often lengthy resuscitation efforts. In these instances, CPR should be initiated and the patient intubated and ventilated to maintain a pH of 7.40, uncorrected for temperature. Active internal rewarming (see later discussion) should be instituted in the patient in cardiac arrest because standard therapy for ventricular fibrillation or asystole may be unsuccessful until rewarming is achieved. There is a risk of toxicity if multiple doses of drugs are administered in the hypothermic patient in whom drug metabolism is altered and circulation is arrested. However, based on current research discussed later, it is reasonable to incorporate pharmacotherapy into the management of hypothermic cardiac arrest. A vasopressor, either epinephrine or vasopressin, may be given to increase the coronary perfusion pressure.²⁹² Amiodarone or lidocaine may then be administered if ventricular fibrillation is present. Defibrillation may not be successful until the temperature exceeds 86°F (30°C); however, defibrillation can be successfully accomplished in animals and patients with temperatures of less than 86°F (30°C).^{5,15,63,292} A reasonable approach is that if defibrillation is unsuccessful, defibrillation should not be attempted again until the patient has been warmed several degrees centigrade. Individuals presenting with cardiac arrest and hypothermia may appear dead yet respond to rewarming and resuscitative efforts. Pneumatically powered devices capable of mechanical chest compression and cardiopulmonary bypass are used successfully during prolonged hypothermic cardiopulmonary arrests.^{15,55,172,263,274}

Arterial Blood Gas Physiochemistry in Hypothermia

Assessment of the adequacy of ventilation and oxygenation in the hypothermic patient often poses a dilemma to clinicians because the chemical effects of cold on arterial pH and blood gases lead to confusion in the interpretation of arterial blood gas values. Cold inhibits the dissociation of water molecules, causing pH to increase as cooling occurs. In vitro, the pH change of blood as it is cooled increases parallel to the pH change of neutral water. The partial pressures of CO₂ and O₂ decrease as cooling occurs even as the blood content of those gases remains unchanged. Blood in a syringe taken from a

patient whose body temperature is 98.6°F (37°C) yields a pH of 7.40 and a PCO₂ of 40 mm Hg in the blood gas machine at 98.6°F (37°C) but yields a pH of 7.72 and a PCO₂ of 14 mm Hg if the blood is cooled to 61°F (16°C) and the values are measured at that temperature. Specially calibrated laboratory equipment, not routinely available, is required to measure blood gas values directly at other than normal body temperature. A patient whose body temperature is 61°F (16°C) and whose actual in vivo blood gas values are a pH of 7.72 and PCO₂ of 14 mm Hg will have a pH of 7.40 and PCO₂ of 40 mm Hg when the blood is warmed to 98.6°F (37°C) and measured in the standard laboratory blood gas machine. Because the machine measures pH and blood gas pressures only in blood warmed to 98.6°F (37°C) (the uncorrected values), the actual in vivo values in hypothermic patients can be approximated using mathematically derived corrected values. Because the pH of neutrality has also increased, it is unclear what clinical meanings these corrected values have. The uncorrected values indicate what the pH and PCO₂ would be if the patient were normothermic. At first glance, the clinician might be content to learn that a hypothermic patient at 61°F (16°C) has a corrected pH of 7.47 and PCO₂ of 40 mm Hg. However, the uncorrected values in the blood gas machine at 98.6°F (37°C) of pH of 7.18 and PCO₂ of 111 mm Hg indicate that the patient has a significant respiratory acidosis. Attempts to maintain a corrected pH of 7.40 may lead to hypoventilation and risk alveolar collapse and impairment of oxygenation. The preponderance of evidence in the anesthesia and cardiovascular surgery literature suggests that maintenance of ventilation is associated with a decreased incidence of myocardial injury and a decreased incidence of ventricular fibrillation.⁶⁷ Thus, the pH and PCO₂ blood gas values should be left uncorrected after the blood sample is warmed in the blood gas machine and interpreted in the same way as in a normothermic patient.⁶⁷

Hypotension

When hypotension occurs in a patient with hypothermia, it may be a result of the presence of bradycardia and volume depletion. However, hypotension may be a predictor of infection, particularly when associated with a slow rewarming rate. Fluid depletion in hypothermia occurs as a result of a variety of mechanisms, including central shunting of blood by vasoconstriction and cold-induced diuresis. Cold diuresis occurs when increases in central blood volume result in inhibition of the release of antidiuretic hormone. Impairment of renal enzyme activity and decreased renal tubular reabsorption contribute to the large quantities of dilute urine known as cold diuresis.^{116,121,169,295} 0.9% NaCl should be given to expand intravascular volume. Urine output is an important indicator of organ perfusion and the adequacy of intravascular volume in hypothermic patients, although the initial cold diuresis may lead to underestimation of fluid needs.²⁹⁵

Pharmacologic Interventions

The best means to effect resuscitation of a hypothermic victim in ventricular fibrillation is controversial. The most recent recommendations of the American Heart Association (AHA) for the treatment of cardiac arrest when the core body temperature is below 86°F (<30°C) states that the administration of a vasopressor or antidysrhythmic according to standard Advanced Cardiac Life Support algorithm concurrent with rewarming may be reasonable.²⁷⁹ A metaanalysis of animal studies of antidysrhythmic and vasopressor therapy for ventricular fibrillation in the setting of hypothermia found that there was significant improvement in the return of spontaneous circulation (ROSC) in animals that received epinephrine or vasopressin.²⁹² In this report, the authors could not identify a benefit to the use of amiodarone administered without a vasopressor. They postulated that this is most likely due to the improvement in coronary perfusion pressure caused by vasopressors during cardiac arrest.²⁹²

Epinephrine and Vasopressin. The administration of vasopressin to pigs in hypothermic cardiac arrest increased coronary perfusion pressure and improved defibrillation success.²⁵² In a pig model, when warmed thoracic lavage was used, vasopressin increased coronary perfusion pressure and increased the 1-hour survival.²⁵¹ In this study, the administration of 0.9% NaCl resulted in zero episodes of successful defibrillation, but all eight vasopressin-treated pigs had restoration of spontaneous circulation after electrical defibrillation and improved short-term survival. The whole-body temperature was not increased, but the authors postulated that myocardial warming may have occurred.²⁵¹ In another study in which epinephrine was given to one group of pigs and vasopressin to another, increased coronary perfusion pressure and ROSC resulted in both groups.^{165,166} In contrast, body temperature significantly increased during CPR with thoracic lavage, and epinephrine increased coronary perfusion pressure, but no improvement in ROSC occurred.¹⁶⁴ The length of time of cardiac arrest, the doses of drug, and the efforts to rewarm differed in these studies. A 19 year-old patient who had a prolonged hypothermic cardiopulmonary arrest showed no improvement after 2 mg of epinephrine but had immediate restoration of spontaneous circulation after the administration of vasopressin.²⁶⁹ Interactions with epinephrine, vasopressin, and ischemia during CPR are complex and incompletely understood.¹⁶⁷

Amiodarone. Amiodarone is recommended in the current AHA algorithm for ventricular fibrillation in normothermia. In one study comparing the use of amiodarone, bretylium, and placebo in a hypothermic dog model, amiodarone showed no statistical improvement in causing ROSC. There was no significant difference among the groups; only one of 10

amiodarone-treated dogs demonstrated ROSC versus three of 10 in the placebo group and four of 10 in the bretylium-treated dogs.²⁶⁷ However, in a study in which hypothermic dogs in ventricular fibrillation were treated with epinephrine before administration of 10 mg/kg of amiodarone, there was a significantly higher rate of ROSC.²⁹²

Dopamine. Dopamine increases cardiac output, mean arterial pressure, heart rate, and stroke volume in dogs cooled to 77°F (25°C) and stabilizes pulmonary arterial wedge pressure.²⁰⁸ In a canine hypothermia model, dopamine infusions provided some protection from ventricular fibrillation. Dopamine lowered the temperature at which ventricular fibrillation occurred and reduced the incidence of ventricular fibrillation, as did infusion of norepinephrine.⁹ The added benefit of dopamine in hypothermia may be a result of its renal and splanchnic vasodilating properties, increasing renal perfusion and supporting urine output.¹⁰⁴ Dopamine increases myocardial oxygen demand and decreases peripheral perfusion, potentially detrimental effects in hypothermic patients.⁹

Rewarming

Three types of rewarming modalities are used in the management of hypothermic patients.^{58,79} Passive external rewarming involves covering the patient with blankets and protecting the patient from further heat loss. Passive external rewarming uses the patient's own endogenous heat production for rewarming and is most successful in healthy patients with mild to moderate hypothermia whose capacity for endogenous heat production is intact.¹²¹ Passive external rewarming is reported to be successful in hypothermic patients with temperatures as low as 69°F (20.6°C).^{272,282,289} Advocates of passive external rewarming argue that it allows vasoconstriction to persist and decreases the afterdrop and shock from vasodilation associated with active skin rewarming.^{121,198,272}

Active external rewarming involves the external application of heat to the patient. There is disagreement about the possible detrimental effects of active external rewarming. For example, skin warming may lead to a physiologically detrimental suppression of shivering.¹²¹ Acute vasodilation of peripheral vessels could cause hypotension and an increased peripheral demand on the persistently cold myocardium. The return of cold blood from the extremities to the heart is suggested to exacerbate intramyocardial temperature gradients, which could cause ventricular irritability during hypothermia.¹⁸⁶ However, in pigs, blood returning to the heart was found to be warm before warming of central organs occurred.¹⁰⁵

Afterdrop is the continuing decrease in temperature after rewarming begins. There is no evidence that it occurs in humans.²⁶⁸ In one study of 33 patients with core temperature below 82.4°F (<28°C), no patient experienced afterdrop during peripheral rewarming.²³⁴ There is no evidence of pooling of blood in the periphery nor of increased flow during surface rewarming.^{179,247} Flow studies in the hand, arm, calf, and foot demonstrate that afterdrop has already occurred and is completed before any increase in blood flow occurs in the limbs.^{179,286} Initial experiments demonstrating afterdrop were done in inanimate objects and reflected continued cooling of central structures before heat from external sources reached the core.^{105,179,286}

Mortality rates for active external rewarming are frequently reported to be higher than for passive external rewarming,²²⁹ but case selection is not controlled in these series. Sicker patients with stable cardiac rhythms who fail to rewarm passively and are then actively rewarmed have a higher mortality rate directly correlated with their underlying disease rather than by the method of therapy.⁶⁸ Selection of either passive or active external rewarming in treatment of mild to moderate hypothermic patients with perfusing cardiac rhythms does not appear to influence the prognosis as much as the presence or absence of underlying disease.^{68,134,198,288} In our experience, active external rewarming has not resulted in death except in patients with severe underlying disease.⁶⁸

Active internal rewarming involves attempts to increase central core temperature directly by warming the heart before the extremities or periphery. Minimally invasive modalities of active internal rewarming include the administration of heated, humidified oxygen delivered by face mask or endotracheal tube¹²³ and gastric lavage with warmed fluids. More invasive modalities, procedures that are fundamental to the rewarming controversy, include peritoneal lavage with warmed dialysate^{140,213} and the rerouting of blood through external blood rewarming equipment via cardiopulmonary or femoral–femoral bypass and hemodialysis.^{42,128,204} Heparin-coated bypass systems are available that avoid systemic anticoagulation, thus decreasing the risk of bleeding complications. It is suggested that extracorporeal venovenous rewarming and continuous arteriovenous rewarming show improved rewarming rates compared with standard techniques such as saline lavage of the bladder, stomach, or peritoneal cavity.⁹⁸ Extracorporeal methods of active internal rewarming should be reserved for severely hypothermic patients (<80°F or <27°C) or those with unstable cardiac rhythms (ventricular fibrillation, ventricular tachycardia, or asystole) attributed to hypothermia.^{5,66,117} In patients with stable rhythms, studies are essential to resolve the debate over the merits of passive or active external rewarming versus active internal rewarming. Transcutaneous pacing was successful in improving hemodynamic parameters and speeding rewarming in an animal model.⁷⁵

Many patients with temperatures below 86°F (30°C) have been successfully treated with passive external rewarming

with, at most, the addition of warm, humidified oxygen.^{68,259,289} Patient temperature correlates poorly with outcome.^{5,63,168,274,277} Treatment recommendations should not be based solely on temperature. Stability of the vital signs and cardiac rhythm and the underlying cause of hypothermia are much more critical considerations in management.

Hyperkalemia is not described as a consequence of rewarming.⁶² In all of the evidence collected with regard to hyperkalemia, this abnormality was present as a consequence of the hypothermia and not the rewarming.^{122,183,248}

Prognosis in Hypothermia

Except in cases of profound hypothermia,¹²² the prognosis is most closely correlated with the presence or absence of underlying disease.^{134,198,216,288,289} In patients with hypothermia alone, in the absence of underlying disease, the mortality rate is 0% to 10%. In the presence of a severe underlying disease such as sepsis, the mortality rate is much greater.⁶⁸ Morbidity results from associated frostbite and trauma.

Prolonged cardiopulmonary arrest and absolute temperature are not predictive of poor outcome.^{5,63,168,274,277} In severely hypothermic patients, profound hyperkalemia ($K^+ > 10$ mEq/L) is associated with unsuccessful resuscitation.^{122,183,248}

Frostbite. Hypothermia may be accompanied by frostbite when patients are exposed to environmental temperatures that are lower than 20°F (6.7°C).¹⁹⁹ Frostbite should be managed by rapid rewarming of the frozen part of the affected person. The extremity involved may be placed in a large, soft basin of warm water (100–108°F; 38–43°C) for 30 minutes. The water temperature must be frequently adjusted because the frozen extremity will cool the water in the basin. Parenteral analgesics may be necessary because the rewarming process is often painful. Frostbitten areas should never be rubbed because the tissue is particularly sensitive to trauma.

HYPERTHERMIA

Definition of Heatstroke

Heatstroke is defined by a rectal temperature greater than 106°F (41.1°C) in the setting of a neurologic disturbance manifested by mental status changes, including confusion, delirium, stupor, coma, or convulsions.¹⁵⁶ Temperature criteria cannot be absolute because information regarding the patient's temperature is rarely available at the time of onset of heatstroke. In some instances, the temperature may not be measured for several hours, during which time cooling may have been instituted or occurred spontaneously.^{150,151} When appropriate environmental conditions prevail, the diagnosis of heatstroke should be made liberally. Although the absence of sweating was once thought to be an essential component of the definition of heatstroke,^{53,214} many patients with heatstroke maintain the ability to sweat.^{61,184,256,283}

Epidemiology of Heatstroke

Hundreds of people die annually of heatstroke in the United States, 80% of whom are older than age 50 years. When counting heat-related fatalities, the number is underestimated if only death certificates are included in which hyperthermia is listed as the underlying cause of death. Including hyperthermia as a contributing factor to death increased the total number of heat-related deaths by 54% from 1993 to 2003.⁴⁴ Several studies show mortality rates from heatstroke to be 5.6% to 80%. Thousands of other victims survive with significant heat-related morbidity.^{8,260} The high morbidity and mortality of heatstroke markedly contrast with those of profound hypothermia, in which the prognosis is related not to the temperature itself but to the underlying etiology. The overall prognosis in heatstroke depends primarily on how long the temperature has been elevated before cooling, the maximum temperature reached, and the affected individual's premorbid health.

Heat-related deaths are preventable, and the public health preparedness of cities, health care workers, and the community is essential.^{16,45} The mortality rate during heat waves are increased in urban areas where a heat wave has not occurred for several years.^{52,77,141,250} The mortality rate is decreased when public health interventions improve preparedness. The city of Milwaukee experienced a heat wave in 1995 that resulted in numerous public health and preparedness responses. These efforts may have resulted in a diminution by 49% of the number of heat-related deaths and emergency medical service runs in the heat wave of 1999.²⁸⁷ After the Chicago heat wave of 1995, public policies targeting the elderly adults of Chicago may have contributed to a change in the demographics of those who succumbed during a subsequent heat wave in Chicago in 1999. The dead in 1999 were younger; more than 50% of those who died were younger than age 65 years. More than half of the dead were seen or spoken to on either the day of or the day before their death. Psychiatric illness was almost twice as common in the younger victims compared with those older than 65 years of age.²⁰⁷

Heat waves are meteorological events characterized by air temperatures that are 90°F or above ($\geq 32.2^\circ\text{C}$) for 3 or more consecutive days.⁴⁴ During the summer of 2003, Europe experienced record high temperatures for many consecutive days. The prolonged heat caused extreme increases in mortality rates across Europe. In France, there were 14,800 excess deaths caused by heat. This is equivalent to a total mortality rate increase of 60% between August 1 and August 20,

2003.^{170,280} In a follow-up report of 83 of these victims, the mortality rate at 2 years was 71%.¹⁰ Survivors had dramatic decreases in their ability to function.¹⁰ From June to August 2003, Italy reported 1094 excess deaths, a 23% increase compared with the average annual number of deaths from 1995 to 2002.⁴⁵ An increased mortality rate was associated with risk factors previously reported, including old age, limited access to care, poor living conditions, and social isolation.²⁵³

Socially isolated individuals, people with preexisting illnesses, physically compromised individuals, and frail elderly adults are at greatest risk of death during heat waves. Confinement to bed was the strongest predictor of death in the Chicago heat wave of 1995, and living alone doubled the risk of death. There were fewer deaths among people with working air conditioners or who had access to an air-conditioned environment.^{235,253} Although fans may seem to improve comfort, they do not prevent heat-related illness and may contribute to heat stress when temperatures and humidity exceed approximately 100°F (37.8°C).^{148,152,153,207,253,294} Prisoners incarcerated in hot conditions die of heatstroke.³⁸ In times of heat waves, preventive public health programs should encourage visiting nurses, housekeepers, and community service programs to increase the awareness of the danger of heat and identify individuals most at risk.²⁵³ A decreased risk of death was found among people with contacts from these agencies during the Chicago heat wave.²⁵³ The media must alert the public and provide information on avoiding heat illness, as well as encourage individuals to help others to stay cool by ensuring access to cooling measures.

The number of deaths from exposure-related illness has increased threefold in foreign transients attempting to enter the United States from Mexico. Because urban areas are more tightly patrolled, individuals attempting to cross into the United States illegally have turned to the harsh deserts and mountain ranges of the southwestern United States, increasing prolonged exposure and resulting in death from heat, cold, and dehydration. Although many more bodies remain undiscovered, 99 individuals' deaths were attributed to environmental causes in the year 2000, many of them caused by heat.⁸²

From 1995 to 2002, 233 children died from heatstroke when left unattended in cars, 75% of whom were either forgotten or left by caretakers who did not expect the temperature to rise dangerously within the automobile. In 25% of the incidents, children were trapped inadvertently while playing. Most of these deaths occurred during the summer months.¹¹¹

Infants may suffer heatstroke under environmental conditions that would not be expected to place a child in danger. Well-meaning parents sometimes overinsulate children with clothing and blankets, inhibiting their cutaneous heat loss and placing them at risk.^{14,137,138}

During 2002, the US military reported 1816 heat-related injuries of active duty soldiers.⁶ During Operation Iraqi Freedom, six soldiers died from heat-related causes. There were 30 other cases of heatstroke and many other heat-related casualties. During the period from 1997 to 2002, 8084 soldiers were treated as outpatients for heat injuries.⁶ The US military actively promotes heat illness prevention and exhorts its personnel to not repeat history. In comparison, in 1917, 425 British soldiers on active duty in the area on the Persian Gulf (formerly known as Mesopotamia; presently known as Iraq) died of heatstroke during 1 month, and 524 died in 1 year.²⁹¹

There were 114 heatstroke deaths among football players from 1960 to 2007. From 1995 to 2007, 33 football players died of heatstroke—25 high school, five college, two professional, and one sandlot.²⁷⁸

High ambient temperature is associated with an increase in mortality from cocaine overdose. The mean daily number of deaths from cocaine overdose was 33% higher when the ambient temperature exceeded 88°F (31°C).¹⁸⁶

Thermoregulation and Heat Stress

The normal thermoregulatory response to heat stress is mediated primarily by heat-sensitive neurons in the hypothalamus. Increased body core temperature results in active dilation of cutaneous vessels, and skin blood flow increases.^{126,238} Because increased skin blood flow is attained primarily by an increase in heart rate and stroke volume, the capacity to increase cardiac output is critical to cooling. Compensatory shifting of blood flow from the splanchnic and renal vessels to the skin further increases skin blood flow.^{133,238} The combination of vasodilation, increased skin blood flow, and increased sweating results in heat loss through convection and evaporation. Dehydration after profuse sweating increases plasma osmolality. Heat-sensitive neurons in the preoptic anterior hypothalamus are inhibited by locally increased osmolality and by input from distal hepatportal osmoreceptors. The inhibition of heat sensitive neurons results in decreased heat dissipation response.^{51,217}

Types of Heatstroke

Heatstroke is commonly divided into two types, exertional and nonexertional. Nonexertional, or classic, heatstroke describes heatstroke occurring in the absence of extreme exertion. Nonexertional heatstroke is most commonly described during heat waves, and the victims are predominantly those persons least able to tolerate heat: infants,¹⁴ older adults,⁵⁷ individuals with psychiatric disorders, and chronically ill individuals.

Exertional heatstroke occurs as a result of increased motor activity. It may occur in young, healthy individuals who are

exercising or in individuals whose increased motor activity results from other causes, such as seizures or agitation. Often a period of significant heat stress in exercising individuals precedes the development of heatstroke. Military recruits who develop heatstroke may sometimes present to the camp infirmary with vague complaints before collapse.²⁵⁶ Published studies of heatstroke in miners, athletes, and military recruits describe several precipitating factors in heatstroke, including fatigue associated with a recent deficit in sleep, poor physical conditioning, a recent febrile illness, recent heat-related symptoms such as thirst or weakness, relative volume depletion, failure to allow for acclimatization, and obesity. Symptoms of nausea, weakness, headache, diarrhea, or irritability often precede the development of heatstroke. Although rapid onset of symptoms and acute loss of consciousness are frequently reported in exertional heatstroke, the preceding period of heat stress and insidious symptoms may go unrecognized. Although exertional heatstroke is more likely to occur during intense exertion in a hot, humid environment, it may also occur with moderately intense exercise early in the morning, when environmental conditions do not usually represent a thermoregulatory stress.¹²

Differential Diagnosis of Hyperthermia

In addition to exposure and exertion, conditions that predispose to severe hyperthermia include primary hypothalamic lesions, intracranial hemorrhage, agitation, alcohol and sedative-hypnotic withdrawal, seizures, and the use of therapeutic and illicit xenobiotics (Table 30–5).^{102,107–109,165,187,270} The differential diagnosis may include serotonin toxicity, malignant hyperthermia, or the neuroleptic malignant syndrome, conditions causing high temperature, altered mental status, and increased muscle tone. These conditions are much less common than classical or exertional heatstroke resulting from impaired thermoregulation caused by the effects of therapeutic xenobiotics.

TABLE 30–5. Differential Diagnosis of Hyperthermia

I. Increased heat production

- Increased muscle activity
 - Agitation
 - Catatonia
 - Ethanol withdrawal
 - Exercise
 - Infectious diseases
 - Malignant hyperthermia
 - Monoamine oxidase inhibitor drug interactions
 - Neuroleptic malignant syndrome
 - Parkinson disease
 - Sedative-hypnotic withdrawal
 - Seizures
 - Serotonin toxicity
 - Xenobiotics
- Increased metabolic rate
 - Hyperthyroidism
 - Pheochromocytoma
 - Sympathomimetics

II. Impaired heat loss

- Environmental
 - Heat
 - Humidity
 - Lack of acclimatization
- Social disadvantage
 - Confinement to bed
 - Isolation
 - Lack of air conditioning
 - Poverty

- Medical illness
 - Cardiac insufficiency
 - CNS dysfunction
 - Diabetes
 - Hypertension
 - Pulmonary
- Dehydration
- Fatigue
- Limited behavioral response
 - Extremes of age
 - Intellectual disability
 - Psychiatric impairment
 - Xenobiotics

Serotonin Toxicity. Serotonin toxicity, results from excess stimulation of the serotonin receptors, primarily the 5-HT_{1A} subtype.²⁶⁶ Drug interactions are most commonly the cause. Monoamine oxidase inhibitors used in conjunction with tricyclic antidepressants,¹⁶ selective serotonin reuptake inhibitors,⁸⁵ L-tryptophan,^{85,271} meperidine,¹¹⁸ dextromethorphan,²³³ and amphetamines,¹⁶⁵ are reported to lead to serotonergic hyperstimulation and severe symptoms.^{103,266} The clinical condition resulting from excess serotonin includes alterations in consciousness, restlessness, increased muscle tone, tremor, GI disturbances, and hyperthermia. Treatment focuses on control of hyperthermia by using aggressive cooling; muscle relaxation primarily by using benzodiazepines; or, in severe cases, endotracheal intubation and paralysis (Chap. 75).

Malignant Hyperthermia. Malignant hyperthermia is a very rare disorder, that is associated with a congenital disturbance of calcium regulation in striated muscle. Malignant hyperthermia was first reported in 1960. Ten deaths occurred in a single family after general anesthesia.⁷² Exposure to anesthetics; depolarizing muscle relaxants; or, rarely, severe exertion precipitates uncontrolled calcium efflux from the sarcoplasmic reticulum, leading to severe muscle rigidity and hyperthermia.^{110,139} The clinical setting of severe muscle rigidity and hyperthermia after general anesthesia usually is adequate to define the syndrome (Chap. 69). In other words, malignant hyperthermia is a pharmacogenetic disorder of the ryanodine receptor causing increased sensitivity to certain xenobiotics.^{119,246}

Neuroleptic Malignant Syndrome. Neuroleptic malignant syndrome, a severe extrapyramidal syndrome associated with muscle rigidity, autonomic dysfunction, and altered mental status, was first described in 1968.⁶⁹ This disorder develops during the administration of antipsychotics or the withdrawal of dopaminergic xenobiotics. Increased muscle tone because of dopaminergic blockade of the striatum as well as central altered hypothalamic thermoregulation leads to hyperthermia.¹²⁴ Temperature elevation and alteration of mental status occur after the onset of “lead pipe” muscle rigidity.^{21,114} Laboratory findings are not specific and include a marked elevation of creatine phosphokinase (CPK) in some patients and leukocytosis with a left shift. Neuroleptic malignant syndrome must be distinguished from the much more common cases of heatstroke in psychiatric patients that are caused by heat intolerance resulting from the anticholinergic effects of antipsychotics or antihistamines prescribed to control extrapyramidal symptoms (Chap. 70).^{243,297}

Inflammatory Mediators in Heatstroke

The response to heat stress is a coordinated interplay between the mediators of inflammation, including endothelial cells, leukocytes, inflammatory cytokines, and endotoxins. These are important mediators of the systemic immune response. However, in heatstroke, they are responsible for systemic inflammation and activation of the coagulation cascade, similar to the systemic inflammatory response syndrome (SIRS). Many proinflammatory cytokines are identified in heatstroke, including tumor necrosis factor (TNF); interleukins-2, -6, -8, -10, and -12; interferon- α and - β ; and granulocyte colony-stimulating factors.²⁸ In one study of 18 heatstroke patients, circulating cytokine concentrations correlated with clinical indices of heatstroke severity.¹³⁵ Cooling delays the release of interleukin-1 β , interleukin-6, and TNF in vitro.¹⁵⁵ Studies in hyperthermic animals focus on the modulation of the mediators of inflammation as possible future adjuncts to cooling. In another study, recombinant human activated protein C provided cytoprotection by decreasing release of inflammatory cytokines but did not improve survival.²⁹ Whole-body cooling restored appropriate concentrations of cardiac tissue protein associated with loss of structural integrity of the cardiac myocytes and reversed cardiac dysfunction.⁴⁸

Heat stress causes increased gene transcription of heat shock proteins, which render the organism more resistant to heat injury, protecting cells from injury and increasing cell survival. Heat shock protein 72 is protective against injury and from heat stress, and the extent of protection correlates with the concentration of heat shock protein.¹⁸⁰

During exercise, splanchnic hypoperfusion increases the translocation of bacteria from the gut into the bloodstream,

establishing the cascade of inflammation and injury that perpetuates tissue injury after normothermia is established.⁸³

Pathophysiologic Characteristics of Heatstroke

In heatstroke, hypotension and tachycardia are caused by a number of factors. The patient with heatstroke may have a reduced plasma volume secondary to salt and water depletion. Peripheral pooling of blood is associated with an increase in cutaneous blood flow from 0.5 L/min to 7 to 8 L/min.^{133,238} In addition, patients may manifest primary myocardial insufficiency.¹⁵⁷ Clinically, patients exhibit either a hypo- or hyperdynamic circulatory response. The observed circulatory response to heat stress is a function of the patient's cardiac reserve, volume status, and degree of myocardial heat injury. The hyperdynamic condition is characterized by increased cardiac index and decreased systemic vascular resistance.²¹⁵ These hemodynamic characteristics occur in patients who are able to maintain a significantly increased cardiac output in response to the circulatory demand of heat stress.

Volume-depleted patients and those patients with primary myocardial insufficiency may exhibit a hypodynamic response. These patients have a decreased cardiac index and increased systemic vascular resistance.^{215,265} Whether pulmonary vascular resistance is affected is unclear. High central venous pressures (CVPs) have been found in some patients, with evidence of right heart failure and right heart dilation on autopsy.¹⁸⁴ These findings have led to the suggestion that pulmonary vascular resistance may be elevated.²¹⁵ In 22 of 34 patients with heatstroke, CVPs were greater than 3 cm H₂O. Twelve patients had a CVP of 0 cm H₂O, and 10 had a CVP that exceeded 10 cm H₂O. These authors cautioned against injudicious infusion of large quantities of IV fluids that can result in complications of congestive heart failure and fluid overload. In the study, only three patients required more than 2 L of 0.9% sodium chloride solution during cooling. Crystalloid infusion ranged from 500 to 2500 mL, and none of the patients developed problems associated with fluid overload.²⁵⁴

A study of compromised elderly patients with heatstroke using pulmonary artery catheters showed that pulmonary vascular resistance was low or normal. Pulmonary capillary wedge pressures were not elevated.²⁶⁴ A study of 13 cases of heatstroke in pilgrims to Mecca, Saudi Arabia, monitored with pulmonary artery catheters demonstrated a good correlation of CVP with pulmonary capillary wedge pressures.² Serial ECGs in 51 of these pilgrims with heatstroke showed normal sinus rhythm in 25%, sinus tachycardia in 52%, atrial fibrillation in 16%, and sinus bradycardia in 6%. ST segment depression and other ST-T wave changes were reported. The QT interval showed no abnormality.³ ST changes suggestive of acute coronary syndrome may occur and normal coronary arteries are noted on coronary catheterization.²⁰² In some patients, echocardiography showed pericardial effusions and regional wall motion abnormalities, asymmetric septal hypertrophy, right ventricular dilation, and left ventricular dilation with impaired function.³

Autopsy studies of the heart demonstrate right heart dilation, pericardial effusions, interstitial edema, degeneration and necrosis of myocardial fibers, and subendocardial hemorrhages.^{151,184} Postmortem examination of the lungs revealed vascular congestion, pleural effusions, and parenchymal hemorrhages.^{184,215}

Gastrointestinal hemorrhage, vomiting, and diarrhea occur frequently.²⁵⁶ At autopsy, edema and hemorrhage of the bowel wall occur.⁴⁷ These changes may be partly a result of the regional ischemia of splanchnic blood vessels and resultant hypoperfusion and hypoxia. Increased bowel wall edema and bleeding predispose to the release of bacteria into the bloodstream from the gut, causing focal microvascular changes in the intestinal villi, leading to bowel wall anoxia and further injury.⁸⁶ Liver injury occurs commonly and is not clinically manifest until the second or third day after the temperature increase.^{150,256} Centrilobular changes, such as widening of central veins and adjacent sinusoids and pooling of blood, and varying degrees of hepatocellular degeneration are demonstrated on liver biopsy. Repeat biopsies demonstrated that these changes resolve as the patient recovers.¹⁵⁰ In other cases, only congestion and fatty infiltration are reported.⁴⁷

Neuropsychiatric impairment is, by definition, present in all cases of heatstroke, the duration of altered consciousness correlates significantly with mortality.^{13,256} Autopsy studies demonstrate a variety of structural and microscopic CNS injuries. Edema and venous congestion are evident. The number of cortical neurons is reduced, with concomitant glial proliferation. Cerebellar Purkinje cell deterioration is marked. The hypothalamus appears to be relatively spared, with limited edema of the neuronal nuclei. Hemorrhages occur throughout the brain.^{47,184,256} Carotid artery vasoconstriction occurs in response to heating in an in vitro model using the carotid arteries of rabbits to elucidate the mechanism of ischemia and injury in heatstroke.²⁰⁵ Heatstroke-induced cerebral ischemia is associated with increased glutamate release, activation of cerebral dopaminergic neurons causing dopamine overload, and gliosis. These changes are attenuated by induction of hypothermia in an animal model.⁵⁰

Reports of magnetic resonance imaging (MRI) of brains of patients recovering from heatstroke describe radiographic findings, including hemorrhagic and ischemic abnormalities of the cerebrum and cerebellum, delayed cerebellar atrophy, central pontine myelinolysis, vascular infarcts, and medial thalamic lesions, which correspond anatomically to the paraventricular nucleus.^{20,191,192} The paraventricular nucleus is involved with core temperature regulation via the hypothalamic–pituitary–adrenal axis.¹⁹ The clinical symptoms of dysphagia, quadriparesis, wasting extrapyramidal

syndrome, and pancerebellar syndrome have corresponding MRI findings.⁴ Persistent cerebellar dysfunction occurs, as does lower motor neuron damage, manifested by areflexia and muscle wasting.^{70,171} Abnormal nerve conduction studies are documented.¹⁴⁴ Higher cortical functions may be spared in survivors or may be reversible when they occur.^{83,174,194} Permanent neurologic sequelae are correlated with the degree and duration of hyperthermia.

Acute kidney injury (AKI) was a major cause of death in heatstroke victims before the advent of hemodialysis.^{249,283} In addition to the direct effects of heat, volume depletion, and hypotension, myoglobinuria secondary to rhabdomyolysis results in further renal tubular injury. This is especially common in an agitated or exercising patient.^{54,102,224} The mechanism by which myoglobin contributes to AKI remains controversial. At autopsy, the kidneys are enlarged, with extensive petechial hemorrhage.¹⁸⁴ Acute tubular necrosis is demonstrated on biopsy. In exertional heatstroke with AKI, renal hemodynamics are compromised because of increased vasoconstrictive hormones, such as catecholamines, renin, aldosterone, and endothelin-1, and decreased vasodilatory hormones, such as prostaglandin E₂.¹⁷⁶

Bleeding is associated with significant morbidity and mortality in many cases of heatstroke. The etiology of coagulation disturbances in patients with heatstroke appear to be multifactorial. Elevation of the prothrombin time may occur within 30 minutes of temperature elevation and is attributed to direct heat injury of clotting factors.¹⁶ Liver damage may significantly contribute to the coagulation disturbances, although this does not manifest as rapidly.^{16,206,227} Two patients with severe liver failure secondary to heatstroke received liver transplantation; both died after chronic rejection.²⁴⁰ A third patient with extensive liver cell necrosis as a consequence of heatstroke was referred for consideration of liver transplantation but recovered completely with supportive therapy.⁹⁹ Evidence of diffuse capillary basement membrane injury is demonstrable by electron microscopy and is thought to precipitate consumptive coagulopathy in severe cases of heatstroke.^{47,261} Thrombocytopenia is very common and occurs within 30 minutes of onset of heatstroke, frequently in the absence of other evidence of disseminated intravascular coagulation. Direct thermal injury leading to decreased platelet survival and megakaryocyte damage may play a role (Table 30–6).^{184,206}

TABLE 30–6. Physiologic and Clinical Manifestations of Heatstroke

Cardiovascular

- Hypodynamic states in elderly adults
- Hyperdynamic states in young, healthy individuals
- Electrocardiogram
- Nonspecific
- Widening of QRS because of an underlying abnormality (cocaine toxicity, hyperkalemia associated with rhabdomyolysis)

Central nervous system

- Altered mental status
- Irritability, confusion, ataxia, seizures, coma
- Weakness, dizziness, headache
- Plantar extension, pupillary abnormalities, decorticate posturing
- Electroencephalogram
- Normal or diffuse slowing
- Cerebrospinal fluid
- Normal or increased protein
- Lymphocytosis

Gastrointestinal

Vomiting, diarrhea, hematemesis

Hematologic

Bleeding diathesis

Prolonged PT and PTT

Disseminated intravascular coagulation

Thrombocytopenia

Petechiae

Purpura

Leukocytosis

Hepatic

Hepatic insufficiency at 12–36 hours

Elevated AST, ALT, LDH

Metabolic

Metabolic acidosis and respiratory alkalosis

Electrolyte disturbance

Hypernatremia

Hypokalemia

Hypocalcemia

Hypophosphatemia

Muscle

Rhabdomyolysis

Elevated CPK

Renal

Decreased renal perfusion

Myoglobinuria

Proteinuria

Oliguria

Acute tubular necrosis

Interstitial necrosis

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time.

Clinical Findings in Heatstroke

Clinical evaluation of a hyperthermic patient begins with careful assessment of the vital signs. Vital sign abnormalities

commonly include tachycardia with heart rates greater than 130 beats/min, hypotension, and tachypnea with the respiratory rates often above 30 breaths/min. Most importantly, temperature is elevated. After cooling, there is often a secondary rise in temperature that suggests persistent disturbances of thermoregulation.¹⁸⁴

Neurologic examination reveals a delirious, comatose, or seizing patient. Pupils may be normal, fixed and dilated, or pinpoint. Decerebrate or decorticate posturing may be evident. Muscle tone is increased, normal, or flaccid. The skin may be hot and dry or diaphoretic. Nasal and oropharyngeal bleeding may be present as a consequence of the acute coagulopathy. Examination of the lungs is often nonspecific, although heatstroke victims are at risk of acute respiratory distress syndrome (ARDS) as a primary event associated with capillary endothelial damage or after overly aggressive fluid resuscitation. Cardiac auscultation may reveal a flow murmur secondary to high cardiac output or a right ventricular gallop. Neck vein distension indicates increased CVP. Jaundice suggests hepatic injury and occurs on the second or third day after the onset of heatstroke.⁴⁹ Nasogastric aspiration or rectal examination may demonstrate gross bleeding. A petechial rash develops, probably secondary to capillary endothelial damage.

Laboratory Findings of Heatstroke

Lactate dehydrogenase (LDH) rises as a consequence of diffuse tissue injury. Early rises in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which peak at 48 hours, are indicators of the liver damage that occurs during heatstroke.¹⁵⁰ Muscle enzymes were elevated in all patients in a study of exertional heatstroke²⁵⁶ and in 86% of patients in one study of nonexertional heatstroke.¹⁰⁸ Nonspecific ST- and T-wave changes on ECG are common. Myocardial enzyme elevation occurs and correlates with ECG changes.¹⁵¹ Results of lumbar puncture are nonspecific, are often normal, or may demonstrate elevated CSF protein and lymphocytosis.²⁵⁶

Other laboratory parameters are affected by heatstroke. Salt and water depletion leads to hemoconcentration in patients exposed to elevated temperatures for a period of time. Hypokalemia is common, with potassium deficits as great as 500 mEq occurring during the early period of heat exposure. Arterial blood gas analysis may show a respiratory alkalosis secondary to direct stimulation of the respiratory center by heat or a metabolic acidosis with an elevated lactate concentration.^{61,265} Metabolic acidosis is the most frequent acid–base disturbance, either alone or part of a mixed picture. The prevalence of metabolic acidosis correlates with the degree of hyperthermia; 95% of patients demonstrated metabolic acidosis when the body temperature exceeded 107.6°F (42°C).²⁸

Hypophosphatemia is common and is attributed to respiratory alkalosis, which causes intracellular shifts of phosphate. However, eight of ten heatstroke patients developed hypophosphatemia, and none was alkalemic.²⁷ The hypophosphatemia in these patients was associated with increased phosphaturia and decreased tubular reabsorption of phosphorus, a finding that reversed after cooling.¹⁵⁸ Renal tubular damage may also lead to phosphate depletion.¹¹² Phosphate and potassium are elevated when significant muscle injury has occurred. Calcium is normal or low, the latter secondary to binding to damaged muscle tissue. Later, hypercalcemia occurs, possibly as a result of release of this bound calcium.^{95,178}

Significant alterations occur in lymphocyte subsets in heatstroke victims. One study reported an increased ratio of T-suppressor to T-cytotoxic cells, as well as increased natural killer cells. There was a significant decrease in the percentages of T and B cells and T-helper cells. These changes correlate with the degree of hyperthermia.^{25,29} Catecholamines are increased in heatstroke¹ and may affect the distribution of the lymphocyte subsets.²⁵ It is possible that the increased susceptibility to infection described in heatstroke and the alterations in lymphocyte populations are related.²⁵

Effects of Xenobiotics in Heatstroke

Xenobiotics predispose the individual to heatstroke by two primary mechanisms: increased production of heat as a result of xenobiotic action and interference with the body's ability to dissipate heat because of pharmacologic or toxicologic effects on thermoregulatory centers (Table 30–5). Xenobiotic interactions may cause life-threatening increases in temperature, such as the combination of monoamine oxidase inhibitors with meperidine or dextromethorphan resulting in serotonin toxicity. The uncoupling of oxidative phosphorylation by salicylate, pentachlorophenol, or dinitrophenol leads to the release of metabolic energy as heat rather than trapping that energy in the form of high energy phosphate bonds in ATP. Sympathomimetics may increase heat production by increasing physical activity.

During heat stress, vasodilation leads to increased cutaneous blood flow, resulting in an increased cardiac output. Parasympathetic stimulation results in increased sweating. Xenobiotics that impair these physiologic mechanisms for heat dissipation predispose the individual to heatstroke. Xenobiotics with anticholinergic effects, such as antihistamines, cyclic antidepressants, and antipsychotics, interfere with sweating. Heatstroke as a result of oligohidrosis is reported for zonisamide and topiramate.^{160,210} The mechanism is postulated to concern the inhibition of carbonic anhydrase, an enzyme associated with eccrine sweat gland function. Sympathomimetics stimulate α -adrenergic receptors, impairing vasodilation. Antihypertensives and antianginals (most notably calcium channel blockers and β -adrenergic antagonists) with negative inotropic and chronotropic effects impair the ability of the heart to meet the output requirements of increased skin blood flow. Diuretic-induced salt and water depletion also limits cardiac output. Antipsychotics cause hypothalamic depression,

altering the normal CNS response to heat stress. Finally, xenobiotics such as ethanol, opioids, and sedative–hypnotics impair normal behavioral responses, and heat-related discomfort may go unnoticed.²⁹²

Heatstroke and Subsequent Heat Intolerance

Whether heatstroke victims are subsequently unable to adapt to exercise in a hot environment remains unclear. Is the heatstroke victim genetically predisposed to heat intolerance, or does heatstroke occur as a result of environmental and host factors? Several studies suggest that heatstroke leads to persistent heat intolerance. These studies often use a single heat intolerance test.^{81,255,257,258} A study of 10 previous heatstroke victims showed no difference in acclimatization responses, thermoregulation, whole-body sodium and potassium balance, sweat gland function, and blood values when compared with control participants.¹² The rate of recovery from exertional heatstroke probably differs among individuals. In this study, one of 10 patients was found to have recurrent heat intolerance 12 months after the study.¹² Resolution of heat intolerance was delayed for 5 months in an individual who had experienced heatstroke twice.¹⁴⁹

Treatment of Heatstroke

Management must focus on the early recognition of hyperthermia. Body temperatures above 106°F (>41.1°C) place the patient at great risk for end-organ injury. Rapid cooling is the first priority and is associated with improved outcomes. Cooling that is delayed allowing body temperatures to remain above 102.2°F (38.9°C) for more than 30 minutes is associated with a high morbidity and mortality. In one report of the Chicago heat wave of 1995, only one patient of 58 victims was cooled within 30 minutes, resulting in an in-hospital mortality rate of 21% and an additional 28% mortality rate within 1 year.⁷¹ Cooling by covering in ice water was twice as rapid in lowering the core temperature as was cooling by using an evaporative spray.¹¹ Ice water immersion results in faster cooling compared with all of the evaporative cooling methods in some studies.^{60,88,96} A more recent report of endovascular cooling using a heat exchange balloon catheter demonstrated dangerously lengthy cooling times and inadequate cooling measures.¹⁹³

Successful treatment requires adequate preparation. Equipment needed for rapid cooling should always be readily available in the emergency department and includes fans, ice, and tubs for immersion. En route to the hospital, the patient's clothes should be removed, and the patient should be covered with ice, if available, and water-soaked sheets. Respiration and cardiovascular status should be stabilized and monitored. Oxygen should be administered. The cause of the heatstroke should be determined and appropriate measures initiated immediately. Xenobiotics, such as antihistamines, butyrophenones, and phenothiazines, and physical restraints that interfere with heat dissipation, such as camisoles and strait jackets, should not be used.¹⁰⁹ Light hand and foot restraints should be used to protect the patient from self-harm. If light restraints are used, the patient should be monitored continuously. A patient who is hyperthermic in the setting of ethanol or sedative–hypnotic withdrawal should be treated with a benzodiazepine.¹⁰⁸ The patient should never be confined to a small, unventilated seclusion room. Adequate cooling, hydration, sedation, and electrolytes and substrate repletion should be ensured.¹⁰⁶

In the emergency department, appropriate laboratory studies should be performed and an IV line inserted. Administration of 100 mg of thiamine should be considered. A rectal probe should be placed for continuous temperature monitoring. The patient should be immersed in an ice bath with a fan blowing over the patient if possible. In addition to the ice bath, iced gastric lavage may be effective.

Agitation, seizures, and cardiac dysrhythmias must be managed while cooling is accomplished. Benzodiazepines are the treatment of choice for agitation and seizures. Heatstroke patients may have significant volume needs, depending on the amount of fluid lost before the onset of heatstroke. Hypotension should be treated with fluids and cooling. Volume repletion should be monitored carefully by parameters such as blood pressure, pulse, CVP, and urine output. As the temperature returns to normal, the hypotension may resolve if significant volume deficits are not present.^{53,157,159} In patients with myoglobinuria, an attempt should be made to increase renal blood flow and urine output. The use of sodium bicarbonate and mannitol in the prevention of acute tubular necrosis in these cases is controversial.^{80,95,237}

Phenothiazines and butyrophenones should not be used because they may depress an already altered mental status, may produce hepatotoxicity in a compromised liver, lower the seizure threshold,²⁴ cause acute dystonic reactions, exacerbate hypotension, and interfere with thermoregulation and cooling by affecting the hypothalamus. However, although phenothiazines and butyrophenones may theoretically reduce shivering and the possibility of rebound hyperthermia, their onset of action is slow.²¹⁴ When shivering occurs during cooling, we recommend the judicious use of a benzodiazepine. In addition, benzodiazepines treat ethanol and sedative–hypnotic withdrawal and cocaine toxicity, common causes of hyperthermia.

There is no role for antipyretics in the management of heatstroke. Aspirin and acetaminophen lower temperature by reducing the hypothalamic set point, which is only altered in a patient febrile from inflammation or endogenous pyrogens.^{72,126} Heatstroke, however, occurs when cooling mechanisms are overwhelmed and the hypothalamic

thermoregulatory set point is not disturbed.¹⁷

Dantrolene is the preferred drug in the treatment of malignant hyperthermia (Antidotes in Depth: A21).^{139,285} It acts directly on skeletal muscle and either inhibits the release of calcium or increases calcium uptake through the sarcoplasmic reticulum.³² Its usefulness has not been demonstrated in other conditions associated with hyperthermia, and there is no evidence to support its administration for other conditions.⁷ In a prospective, randomized, double-blind, placebo-controlled study of 52 patients with heatstroke, IV dantrolene at 2 mg/kg of body weight did not alter cooling time.²⁶ There was no significant difference in the mean number of hospital days necessitated by heatstroke victims who received dantrolene and cooling versus those who received cooling alone. Dantrolene may influence central dopaminergic metabolism in patients with neuroleptic malignant syndrome by affecting calcium-triggered neurotransmitter release in the CNS; however, further study is required.²¹² Anecdotal reports of the efficacy of dopamine agonists such as bromocriptine and amantadine have appeared in descriptions of neuroleptic malignant syndrome.¹⁹⁰ No drug therapy should delay the institution of aggressive external cooling (Table 30–7).

TABLE 30–7. Management of Heatstroke

Preparation

Ice and cooling fans available in emergency department

Monitor weather reports

Alert media

On arrival

Rapid cooling

Clear airway and administer oxygen

Cover with ice and water-soaked sheets

Stabilize respiratory and cardiovascular status

Cool as rapidly as possible

Intravenous access

Consideration of 0.5–1.0 g/kg of dextrose and 100 mg of thiamine

Benzodiazepines for agitation, shivering, seizures

Continuous monitoring

Remove from ice bath at 101°F (38.3°C)

Watch for rebound hyperthermia

Cautions

Antipsychotics may have serious adverse effects

Antipyretics do not work

Cooling blankets alone are inadequate

SUMMARY

- Xenobiotics may disturb normal thermoregulation and result in the abnormal conditions of hyperthermia or hypothermia. These disturbances of homeostasis present significant clinical management challenges.
- Hypothermia and heatstroke are preventable conditions.

- Immediate and aggressive cooling is imperative in heatstroke. Near-normal body temperature should be achieved within 30 minutes from onset of heatstroke.
- Rewarming of the patient with hypothermia and a stable cardiac rhythm can often be successfully accomplished with patience and without extracorporeal methods.
- Climate change causing increasingly hot weather demands municipal preparedness and public education efforts to prevent deaths during hot conditions.

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SECTION III

SPECIAL POPULATIONS

SECTION III

SPECIAL POPULATIONS

31 REPRODUCTIVE AND PERINATAL PRINCIPLES

Jeffrey S. Fine

Reproductive and perinatal principles in toxicology are derived from basic science and are applied to clinical practice. This chapter reviews several principles of reproductive medicine that have implications for toxicology, including the physiology of pregnancy and placental xenobiotic transfer, the effects of xenobiotics on the developing fetus and the neonate, and the management of overdose in pregnant women.

One of the most dramatic effects of exposure to a xenobiotic during pregnancy is the birth of a child with congenital malformations. Teratology, the study of birth defects, has principally been concerned with the study of physical malformations. A broader view of teratology includes “developmental” teratogens—xenobiotics that induce structural malformations, metabolic or physiologic dysfunction, or psychological or behavioral alterations or deficits in the offspring, either at or after birth.²⁷⁴ Only 4% to 6% of birth defects are attributable to known pharmaceuticals or occupational and environmental exposures.^{44,274}

Reproductive effects of xenobiotics may occur before conception. Female germ cells are formed in utero; adverse effects from xenobiotic exposure can theoretically occur from the time of a woman’s own intrauterine development to the end of her reproductive years. An example of a xenobiotic that had both teratogenic and reproductive effects is diethylstilbestrol (DES), which caused vaginal or cervical adenocarcinoma (or both) in some women who had been exposed to DES in utero and also had effects on fertility and pregnancy outcome.^{26,33}

Men generally receive less attention with respect to reproductive risks. Male gametes are formed after puberty; only from that time on are they susceptible to xenobiotic injury. An example of a xenobiotic affecting male reproduction is dibromochloropropane, which reduces spermatogenesis and, consequently, fertility. In general, much less is known about the paternal contribution to teratogenesis.³³⁶

Occupational exposures to xenobiotics are potentially important but are often poorly defined. In 2004, it was estimated that there were 41 million women of reproductive age in the workforce.³¹³ Although approximately 90,000 chemicals are used commercially in the United States, only a few thousand of them have been specifically evaluated for reproductive toxicity. Many xenobiotics have teratogenic effects when tested in animal models, but relatively few well-defined human teratogens have been identified (Table 31–1).²⁸⁶ Thus, most tested xenobiotics do not appear to present a human teratogenic risk, but most xenobiotics have not been tested. Some of the presumed safe xenobiotics may have other reproductive, nonteratogenic toxicities. Several excellent reviews and online resources are available.^{45,104,238,249,274,286}

TABLE 31–1. Known and Possible Human Teratogens

<i>Teratogenic</i>	<i>Reported Effects</i>	<i>Comments</i>
Alkylating agents (eg, busulfan, chlorambucil, cyclophosphamide, mechlorethamine, nitrogen mustard)	Growth retardation, cleft palate, microphthalmia, hypoplastic ovaries, cloudy corneas, renal agenesis, malformations of digits, cardiac defects, other anomalies	10–50% malformation rate, depending on the agent. Cyclophosphamide-induced damage requires cytochrome P450 oxidation.
Aminopterin, methotrexate (amethopterin)	Hydro- or microcephaly, meningoencephalocele, anencephaly, abnormal cranial ossification; cerebral hypoplasia; growth retardation; eye, ear, and nose malformations; cleft palate; malformed extremities or fingers; reduction in derivatives of first branchial arch; developmental delay ¹²²	Folate antagonists inhibit dihydrofolate reductase. High rate of malformations.
Amiodarone	Transient neonatal hypothyroidism, with or without goiter; hyperthyroidism	Amiodarone contains 39% iodine by weight. Small to moderate risk from 10 weeks to term for thyroid dysfunction.
Androgens	Virilization of the female external genitalia; clitoromegaly, labioscrotal fusion	Dose dependent. Stimulates growth of sex steroid receptor-containing tissue.
Angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor inhibitors	Fetal or neonatal death, prematurity, oligohydramnios, neonatal anuria, IUGR, secondary skull hypoplasia, limb contractures, pulmonary hypoplasia	Significant risk of effects related to chronic fetal hypotension during second or third trimester. If used during early pregnancy, can be switched during first trimester. ^{10,11,44}
Carbamazepine	Upwarding palpebral fissures, epicanthal folds, short nose with long philtrum, fingernail hypoplasia, developmental delay, NTD ¹⁴⁴	1% risk for NTD. Risk of other malformations is unquantified but may be significant for minor anomalies. Risk is increased in setting of therapy with multiple anticonvulsants, particularly valproic acid. Mechanism may involve an epoxide intermediate. High-dose folate is recommended to prevent NTDs.
Carbon monoxide	Cerebral atrophy, intellectual disability, microcephaly, convulsions, spastic disorders, intrauterine death	With severe maternal poisoning, high risk for neurologic sequelae; no increased risk in mild exposures.
Cocaine	IUGR, microcephaly, neurobehavioral abnormalities, vascular disruptive phenomenon (limb amputation, cerebral infarction, visceral or urinary tract abnormalities)	Vascular disruptive effects because of decreased uterine blood flow and fetal vascular effects from first trimester through the end of pregnancy. Risk for major disruptive effects is low.
Corticosteroids	Cleft palate, decreased birth weight (up to 9%) and head circumference (up to 4%)	Low risk. Most information related to prednisone or methylprednisolone.
Coumadin	Fetal warfarin syndrome: nasal hypoplasia, chondrodysplasia punctata, brachydactyly, skull defects, abnormal ears, malformed eyes, CNS malformations, microcephaly, hydrocephalus, skeletal deformities, intellectual disability, spasticity	10%–25% risk of malformation for first trimester exposure, 3% risk of hemorrhage, 8% risk of stillbirth. Bleeding is an unlikely explanation for effects produced in the first trimester. CNS defects may occur during the second or third trimesters and may be related to bleeding. ^{140,143}
Diazepam	Cleft palate, other anomalies	Controversial association, probably low risk. ^{45,46,145} Risk may extend to other benzodiazepines. Also risk for neonatal sedation or withdrawal after maternal use near delivery.
Diethylstilbestrol (DES)	Female offspring: vaginal adenosis, clear cell carcinoma, irregular menses, reduced pregnancy rates, increased rate of preterm deliveries, increased perinatal mortality and spontaneous abortion Male offspring: epididymal cysts, cryptorchidism, hypogonadism, diminished spermatogenesis	A synthetic nonsteroidal estrogen that stimulates estrogen receptor-containing tissue and may cause misplaced genital tissue with a propensity to develop cancer. A 40%–70% risk of morphologic changes in vaginal epithelium. Risk of carcinoma is approximately one in 1000 for exposure before the 18th gestational week. Most patients exposed to DES in utero can conceive and deliver normal children.
Ethanol	FAS: pre- or postnatal growth retardation, intellectual disability, fine motor dysfunction, hyperactivity, microcephaly, maxillary hypoplasia, short palpebral fissures, hypoplastic philtrum, thinned upper lips, joint, digit anomalies	FAS in 4% of offspring of women with alcoholism consuming ethanol above 2 g/kg/d (6 oz/d) over the first trimester. There may be a threshold for effects, but a safe dose has not been identified. Partial expression or other congenital anomalies. Increased incidence of spontaneous abortion, premature delivery, and stillbirth; neonatal withdrawal.
Fluoxazole	Brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease	Risk related to high-dose (400–800 mg/d), chronic, parenteral use. Single 150-mg oral dose probably safe.
Indomethacin	Premature closure of the ductus arteriosus; in premature infants, oligohydramnios, anuria, intestinal ischemia	NSAIDs generally labeled as category B. However, there is concern when used after 31–32 weeks gestation and for more than 48 hours or immediately before delivery. Risk may extend to other NSAIDs.

Iodine and iodine-containing products	Thyroid hypoplasia after the 8th week of development	High doses of radioiodine isotopes can additionally produce cell death and mitotic delay. Tissue and organ-specific damage depends on the specific radioisotope, dose, distribution, metabolism, and localization.
Lead	Lower scores on developmental tests	Higher risk when maternal lead is >5 µg/dL. ¹⁶
Lithium carbonate	Ebstein anomaly	Low risk.
Methimazole	Aplasia cutis, skull hypoplasia, dystrophic nails, nipple abnormalities, hypo- or hyperthyroidism	Small risk of anomalies or goiter with first trimester exposure. Hypothyroidism risk after 10 weeks of gestation.
Methyl mercury, mercuric sulfide	Normal appearance at birth; cerebral palsylike syndrome after several months; microcephaly, intellectual disability, cerebellar symptoms, eye or dental anomalies	Inhibits enzymes, particularly those with sulfhydryl groups. Of 220 babies born after the Minamata Bay exposure, 13 had severe disease. Mothers of affected babies ingested 9–27 ppm of mercury; greater risk with ingestion at 6–8 months' gestation. In acute poisoning, the fetus is four to 10 times more sensitive than an adult. Pathologically, there are atrophy and hypoplasia of the brain cortex and abnormalities in cytoarchitecture. ^{12,18}
Methylene blue (intraamniotic injection)	Intestinal atresia, hemolytic anemia, neonatal jaundice	This xenobiotic was used to identify twin amniotic sacs during amniocentesis. ¹⁹
Misoprostol	Vascular disruptive phenomena (eg, limb reduction defects); Moebius syndrome (paralysis of 6th and 7th facial nerves)	Synthetic prostaglandin E ₁ analog. Effects mostly observed in women after unsuccessful attempts to induce abortion.
Mycophenolate mofetil	Microtia, orofacial cleft, coloboma, hypertelorism, micrognathia, conotruncal CHD, agenesis of the corpus callosum, esophageal atresia, digital hypoplasia	Immunosuppressive xenobiotic used in transplant recipients, inhibits inosine monophosphate dehydrogenase and blocks de novo purine synthesis in T and B lymphocytes. ^{15,20}
Oxazolidinone-2,4-diones (trimethadione, paramethadione)	Fetal trimethadione syndrome: V-shaped eyebrows; low-set ears with anteriorly folded helix; high-arched palate; irregular teeth; CNS anomalies; severe developmental delay, cardiovascular, genitourinary, and other anomalies	An 83% risk of at least one major malformation with any exposure; 32% die. Characteristic facial features are associated with chronic exposure.
Paroxetine	Cardiovascular malformations, mostly VSD and ASD	Possible small (1%) increased risk. Risk may extend to other member of SSRI class.
Penicillamine	Cutis laxa, hyperflexibility of joints	Copper chelator—copper deficiency inhibits collagen synthesis or maturation. Few case reports; low risk.
Phenytoin	Fetal hydantoin syndrome: microcephaly, intellectual disability, cleft lip or palate, hypoplastic nails or phalanges, characteristic facies—low nasal bridge, inner epicanthal folds, ptosis, strabismus, hypertelorism, low-set ears, wide mouth	Phenytoin has a direct effect on cell membranes and on folate and vitamin K metabolism. May reduce the availability of retinoic acid derivatives or alter the genetic expression of retinoic acid. Epoxide intermediate may play a role in teratogenesis. Effects seen with chronic exposure. A 5%–10% risk of typical syndrome, 30% risk of partial syndrome. Risks confounded by those associated with epilepsy itself and use of other anticonvulsants. Possible increased risk of developing tumors, in particular, neuroblastoma, although the absolute risk is very low.
Polychlorinated biphenyls	Cola-colored children; pigmentation of gums, nails, and groin; hypoplastic, deformed nails; IUGR; abnormal skull calcifications	Cytotoxic xenobiotic. Body residue can affect subsequent offspring for up to 4 years after exposure. Most cases followed high consumption of PCB-contaminated rice oil; 4%–20% of offspring were affected. ¹⁴
Progestins (eg, ethisterone, norethindrone)	Masculinization of female external genitalia	Progestogens are converted into androgens or may have weak androgenic activity. Stimulates or interferes with sex steroid receptors. Effects occur only after exposure to high doses of some testosterone-derived progestins and may be at the rate of <1% of those exposed. Oral contraceptives containing these agents are not thought to present teratogenic risk despite their category X designation.
Quinine	Hypoplasia of lith nerve, deafness, abortion	Effects related to high doses used as abortifacients.
Radiation, ionizing	Microcephaly, intellectual disability, eye anomalies, growth retardation, visceral malformations	Significant doses of radiation from diagnostic or therapeutic sources produce cell death and mitotic delay. There is no measurable risk with X-ray exposures of 5 rads or less at any stage of pregnancy. ^{11,15}
Retinoids (isotretinoin, etretinate, high-dose vitamin A)	Spontaneous abortions; micro- or hydrocephalus; deformities of cranium, ears, face, heart, limbs, liver	Retinoids can cause direct cytotoxicity, alter apoptosis, and inhibit migration of neural crest cells. For isotretinoin, 38% risk of malformations; 80% are CNS malformations. Effects are associated with vitamin A doses of 25,000–100,000 units/day. Exposures below 10,000 units/day present no risk to fetuses. Topical retinoids are not considered a reproductive risk. ²⁴
Smoking	Placental lesions, IUGR, increased perinatal mortality, increased risk of SIDS, neurobehavioral effects such as learning deficits and hyperactivity ^{15,22}	Possible mechanisms include vasoconstriction (nicotine effect); hypoxia secondary to hypoperfusion, CO, and CN; and altered development of neurons and neural pathways via stimulation of nicotinic acetylcholine receptors. ^{23,24}

Streptomycin	Hearing loss	Rare reports. A low-risk phenomenon that could be associated with long-duration maternal therapy during pregnancy.
Tetracycline	Yellow, gray-brown, or brown staining of deciduous teeth, hypoplastic tooth enamel	Effects seen after 4 months of gestation because tetracyclines must interact with calcified tissue. Effects occur in 50% of fetuses exposed to tetracycline and in 12.5% of fetuses exposed to oxytetracycline.
Thalidomide	Limb phocomelia, amelia, hypoplasia, congenital heart defects, renal malformations, cryptorchidism, abducens paralysis, deafness, microtia, anotia	~20% risk for exposure during days 34–50 of gestation.
Trimethoprim	NTD, oral clefts, hypospadias, and cardiovascular defects	~1% risk of NTD for first trimester exposure. Mechanism is folic acid inhibition.
Valproic acid	Spina bifida, ASD, cleft palate, hypospadias, polydactyly, craniosynostosis, cognitive deficits, autism ^{42,100,101}	Risk for spina bifida is ~1%, but the risk for dysmorphic facies may be greater. The mechanism of teratogenicity is unknown. Possible explanations include interference with glutathione, folate, or zinc metabolism or regulation of intracellular pH. Risk is confounded by risks associated with epilepsy itself or use of other anticonvulsants.
Vitamin D	Possible association with supravalvular aortic stenosis, elfin facies, and intellectual disability	Large doses of vitamin D may disrupt cellular calcium regulation. Genetic susceptibility may play a role.

ASD = atrial septal defect; CHD = congenital heart disease; CN = cyanide; CNS = central nervous system; CO = carbon monoxide; FAS = fetal alcohol syndrome; IUGR = intrauterine growth restriction; NSAID = nonsteroidal antiinflammatory drug; NTD = neural tube defect; PCB = polychlorinated biphenyl; SIDS = sudden infant death syndrome; SSRI = selective serotonin reuptake inhibitor; VSD = ventricular septal defect.

Data from Brent RL: Environmental causes of human congenital malformations: The pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics*. 2004;113:957–968; Nulman I, Litovskoy Y, Stancovski A, Koren G: Teratogenic drugs and chemicals in humans. In: Koren G, ed. *Medication Safety in Pregnancy and Breastfeeding*. New York: McGraw-Hill; 2007:21–35; and Profka JE, Friedman JM: Medical genetics: 1. Clinical teratology in the age of genomics. *CMAJ*. 2002;167:265–271.

Another type of xenobiotic exposure for a pregnant woman is intentional overdose. Although a xenobiotic taken in overdose may have direct toxicity to the fetus, fetal toxicity frequently results from maternal pulmonary or hemodynamic compromise, further emphasizing the critical nature of the maternal–fetal dyad.

Xenobiotic exposures before and during pregnancy can have effects throughout gestation and may extend into and beyond the newborn period. In addition, the effects of xenobiotic administration in the perinatal period and the special case of delivering xenobiotics to an infant via breast milk deserve particular consideration.

PHYSIOLOGIC CHANGES DURING PREGNANCY THAT AFFECT DRUG PHARMACOKINETICS

Many physical and physiologic changes that occur during pregnancy affect both the absorption and distribution of xenobiotics in the pregnant woman and consequently affect the amount of xenobiotics delivered to the fetus.³⁰⁹

Delayed gastric emptying, decreased gastrointestinal (GI) motility, and increased transit time through the GI tract occur during pregnancy. These changes result in delayed but more complete GI absorption of xenobiotics and, consequently, lower peak plasma concentrations. Because blood flow to the skin and mucous membranes is increased, absorption from dermal exposure may be increased. Similarly, absorption of inhaled xenobiotics may be increased because of increased tidal volume and decreased residual lung volume.

An increased free xenobiotic concentration in the pregnant woman can be caused by several factors, including decreased plasma albumin, increased binding competition, and decreased hepatic biotransformation, during the later stages of pregnancy. Fat stores increase throughout pregnancy and are maximal at about 30 weeks; near term, free fatty acids are released, and along with them the lipophilic xenobiotics that may have accumulated in the lipid compartment are released. The increased concentration of circulating free fatty acids can compete with circulating free xenobiotic for binding sites on albumin.

Other factors may lead to decreased free xenobiotic concentrations. Early in pregnancy, increased fat stores, as well as the increased plasma and extracellular fluid volume, lead to a greater volume of distribution. Increased renal blood flow and glomerular filtration may result in increased renal elimination.

Cardiac output increases throughout pregnancy, with the placenta receiving a gradually increasing proportion of total blood volume. Xenobiotic delivery to the placenta may therefore increase over the course of pregnancy.

These processes interact dynamically, and it is difficult to predict their net effect. The concentrations of many xenobiotics, such as lithium, gentamicin, and carbamazepine, decrease during pregnancy even if the dose administered is unchanged.¹⁰⁸

Although not specifically related to the physiologic changes occurring during pregnancy, the fetus may be exposed to xenobiotics that accumulated in adipose tissue before pregnancy. For example, malformations typically ascribed to retinoid

use occurred in a baby born to a woman whose pregnancy began one year after she discontinued use of the xenobiotic etretinate (retinoic acid).¹⁷¹

XENOBIOTIC EXPOSURE IN PREGNANT WOMEN

Exposure to xenobiotics during pregnancy is common. At some time during pregnancy, as many as 90% of pregnant women take prescription or nonprescription medications other than vitamins and mineral supplements. The most commonly used are analgesics, antipyretics, antimicrobials, and antiemetics.^{17,36,78,217,265} In addition, use of caffeine, tobacco, and alcohol is common. Some pregnant women use xenobiotics to treat a preexisting chronic disease such as epilepsy or a newly diagnosed disease such as deep vein thrombosis. Many women use various prescription and nonprescription xenobiotics before recognizing that they are pregnant.

Pharmaceutical manufacturers are required by law to label their products with respect to use in pregnancy according to standards promulgated by the US Food and Drug Administration (FDA) (Table 31–2).³¹⁴ Similar classification systems have been developed in Sweden and Australia.^{8,255,272} The original intent of the US regulations was to inform practitioners about the nature of the available evidence regarding risk in pregnancy. However, the general impression among prescribing health care practitioners is that the categories refer to teratogenic risk, a hierarchy of harmful effects according to the letter categories and an equivalence of risk within each letter category.^{85,279,280} For example, in the US system, a category C medication is generally considered more dangerous than a category B medication in pregnancy even though category C is the default category for medications about which there is little or no specific information available and for which the risk is unknown. Approximately 90% of medications are classified as category C.¹⁸⁶

TABLE 31–2. Food and Drug Administration Use-in-Pregnancy Ratings^a

Category	Risk to Human Fetus	Example(s)	Basis
A	No known risk	Multiple vitamins	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women do not demonstrate a risk to the fetus, and if animal studies exist, they do not demonstrate a risk.
B	Unlikely risk	Acetaminophen, penicillin	No evidence of risk in humans. Either animal studies show risk but human studies do not, or if no adequate human studies have been done, animal studies show no risk.
C	Unknown risk	Albuterol	Risk cannot be excluded. Animal studies may or may not show risk, but human studies do not exist. However, benefits may justify the potential or unknown risk.
D	Known risk but benefit may outweigh risk	Tetracycline	Positive evidence of risk. Investigational or postmarketing data or human studies show risk to fetuses. Nevertheless, potential benefits may outweigh the potential risk (eg, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Known risk but risk significantly outweighs benefit	Isotretinoin	Contraindicated in pregnancy. Studies in animals or humans or investigational or postmarketing reports have shown fetal risk that clearly outweighs any possible benefit to the patient.

^aBased on US Food and Drug Administration. *Specific Requirements on Content and Format of Labeling for Human Prescription Drugs*. 21 CFR Ch. I (4–1–04 ed.) § 301.57.

There is significant discordance between the use-in-pregnancy labeling and the teratogenic risk as determined by clinical teratologists,¹⁸⁶ and the FDA system has been criticized for being too conservative.¹⁰³ Manufacturers may label certain medications as category X even when there is only limited information associating the medication with any adverse fetal or neonatal effects. For example, oral contraceptives generally carry a category X classification even though they are not considered teratogenic; category X is assigned because there is no indication for use of oral contraceptives in pregnancy.¹⁶⁹ Certain medications with a category D classification may cause problems only at certain times during pregnancy. Approximately 6% of pregnant women are prescribed medications that carry a category D or X classification, and 1% are prescribed medications that are definitively considered teratogenic.¹⁸ Even medications that are classified as category D or X may only have a very low risk of teratogenicity or other adverse effect, and exposure to these xenobiotics, even during the first trimester, may not be a sufficient indication to terminate a pregnancy.⁹¹

The difficulty regarding appropriate drug labeling reflects many complex questions regarding the use of medications during pregnancy. How should animal data in general be evaluated? How should animal data be extrapolated to humans? How should the teratogenic risk be defined and quantified for any particular xenobiotic? How should the risk of not treating a particular disease be compared with the risk of using a particular medication to treat that disease? Finally, how should the answers to these questions be communicated to practitioners and the public?²⁸⁰

In an attempt to address many of these problems, the FDA has proposed changes to the labeling of medications for use

in pregnancy and lactation.^{134,169,316} These changes include (1) a concise description and estimate of risk of structural teratogenesis, fetal or infant mortality, and impaired growth or physiologic function; (2) details of animal and human data, in particular information from registries, cohort studies, and case-control studies; and (3) clinical considerations such as risk of the disease (treated or untreated) versus risk of the medication, need for dose adjustment in pregnancy, adverse drug reactions specific to pregnancy, monitoring of drug use and effect, effects on labor and delivery, and neonatal complications. Similar labeling rules are proposed for medication effects in the setting of lactation.

Specific current information on individual xenobiotics can be obtained from local and regional teratogen information services⁷ and published books,^{45,104,274,285} some of which also have online versions.^{219,249,307} Motherisk is a Canadian program that uses accumulated evidence and experience to advise women about their actual risk of using a particular medication or being exposed to a particular xenobiotic in a current or planned pregnancy.^{218,219}

Although most women are concerned about the teratogenic effects of medications, in utero exposure to therapeutic medications can have other pharmacologic effects on newborn infants, such as hyperbilirubinemia or withdrawal syndromes.^{45,81}

Estimates of substance use in pregnancy vary tremendously, depending on the geographic location, practice environment, patient population, and screening method.^{56,174} In the National Survey on Drug Use and Health, approximately 16% of pregnant women smoked cigarettes, 11% drank ethanol, 5% used marijuana, 0.25% used cocaine, and 0.1% used heroin.²⁶⁹ Women tend to decrease their exposure to xenobiotics after they know they are pregnant.^{37,141,145}

PLACENTAL REGULATION OF XENOBIOTIC TRANSFER TO FETUSES

With respect to the transfer of xenobiotics from mother to fetus, the placenta functions in a manner similar to other lipoprotein membranes. Most xenobiotics enter the fetal circulation by passive diffusion down a concentration gradient across the placental membranes. The characteristics of a substance that favor this passive diffusion are low molecular weight (MW), lipid solubility, neutral polarity, and low protein binding.²⁴² Polar molecules and ions may be transported through interstitial pores.³¹⁰

Xenobiotics with an MW greater than 1000 Da do not diffuse passively across the placenta, and this characteristic is used to therapeutic advantage. For example, warfarin (MW, 1000 Da) easily crosses the placenta and causes specific fetal malformations.³²² However, heparin (MW, 20,000 Da), which is too large to cross the placenta, is not teratogenic and, consequently, is the preferred anticoagulant during pregnancy. Most therapeutic medications have MWs between 250 and 400 Da and easily cross the placenta. For example, thiopental is highly lipid soluble and crosses the placenta rapidly. Fetal plasma concentrations reach maternal concentrations within a few minutes. Neuromuscular blockers such as vecuronium are more polar and cross the placenta slowly.⁸⁸

Although ionization is a limiting factor for diffusion, some highly charged molecules can still diffuse across the placenta. Valproic acid (pK_a of 4.7) is nearly completely ionized at physiologic pH, yet there is rapid equilibration across the placental membrane. The small amount of xenobiotic that exists in the nonionized form rapidly crosses the placenta, and as the equilibrium is reestablished, a new, small amount of nonionized xenobiotic becomes available for diffusion.²²³

Fetal blood pH changes during gestation. Embryonic intracellular pH is high relative to the intracellular pH of the pregnant woman. During this developmental stage, weak acids diffuse across the placenta to the embryo and remain there because of “ion trapping.” Many teratogens, such as valproic acid, trimethadione, phenytoin, thalidomide, warfarin, and isotretinoin, are weak acids. Although ion trapping does not explain the mechanism of teratogenesis, it may explain how xenobiotics accumulate in an embryo. Late in gestation, the fetal blood is 0.10 to 0.15 pH units more acidic than the maternal blood; this pH differential may permit weakly basic xenobiotics to concentrate in the fetus during this period.²⁴²

The relative concentrations of protein binding sites in the pregnant woman and fetus also have an impact on the extent of xenobiotic transfer to the fetus.²⁴² As maternal free fatty acid concentrations increase near term, these fatty acids can displace xenobiotics such as valproic acid or diazepam from maternal protein binding sites and make more free xenobiotic available for transfer to the fetus. Fetal albumin concentrations increase during gestation and exceed maternal albumin concentrations by term. Because the fetus does not have high concentrations of free fatty acids to compete for protein binding sites, these sites are available for binding the xenobiotics. At birth, when neonatal free fatty acid concentrations increase two- to threefold, they displace stored xenobiotic from the binding protein. In the cases of valproic acid and diazepam, the elevated concentrations of free xenobiotic have adverse effects on the newborn infant.^{111,143,223,248}

The placenta may also affect xenobiotic presentation to the fetus by ion trapping and xenobiotic metabolism. The placenta blocks the transfer of some positively charged ions such as cadmium and mercury¹²² and may even accumulate them. This barrier does not necessarily protect the fetus, however, because these metal ions interfere with normal placental function and may lead to placental necrosis and subsequent fetal death.²¹⁶

The placenta contains xenobiotic-metabolizing enzymes capable of performing both phase I and phase II reactions (Chaps. 13 and 23). However, the concentration of biotransforming enzymes in the placenta is significantly lower than that

in the liver, and it is unlikely that the level of enzymatic activity is protective for the fetus. Moreover, the fetus may be exposed to reactive intermediates that form during these processes. On the other hand, glutathione may also be present in the placenta and detoxify some of these reactive intermediates.¹⁵⁰

Placental transfer of xenobiotics can have a positive effect when it delivers desired therapies to the fetus. For example, if a fetus is found to have a supraventricular tachycardia or atrial flutter, digoxin can be given to the mother to treat the tachydysrhythmia in the fetus.^{162,263}

EFFECTS OF XENOBIOTICS ON THE DEVELOPING ORGANISM

A basic premise of teratogenicity is that the particular toxic effects of a xenobiotic are determined by the stage of development of the embryo or fetus.^{41,281} Although the fertilized ovum is generally thought to be resistant to toxic insult before implantation,⁴¹ xenobiotics in the fallopian or uterine secretions may prevent implantation of the embryo. Xenobiotic exposure leading to cell loss or chromosomal abnormalities may also lead to loss of the embryo, possibly even before pregnancy has been detected. If the preimplantation embryo survives a xenobiotic exposure, the functional cells usually proceed to normal development.²⁸¹ Teratogens that act in such a manner elicit an “all-or-none response”; that is, the exposed embryo will either die or go on to normal development.

The dose–response curve of environmental xenobiotics can have deterministic (threshold) or stochastic (no threshold) effects.⁴² Mutagenic and carcinogenic events are stochastic phenomena. Teratogenesis is a deterministic phenomenon with a threshold dose below which no effects occur. As the dose of the teratogen increases above the threshold, the magnitude of the effect increases. The effects might be the number of offspring that die or develop malformations or the extent or severity of malformations. Radiation is one agent that has both deterministic effects (eg, microcephaly and growth retardation) and stochastic effects (induction of leukemia). Strictly speaking, teratogenic effects are those that occur at doses that do not cause maternal toxicity because maternal toxicity itself might be responsible for an observed adverse or teratogenic effect on the developing organism.⁴¹

Organogenesis occurs during the embryonic stage of development between days 18 and 60 of gestation. Most gross malformations are determined before day 36, although genitourinary and craniofacial anomalies occur later.⁴¹ The period of susceptibility to teratogenic effects varies for each organ system (Fig. 31–1). For instance, whereas the palate has a very short period of sensitivity, lasting approximately 3 weeks, the complete development of the central nervous system (CNS), including neurogenesis and differentiation, arborization, synaptogenesis and synaptic organization, and myelination and gliogenesis, remains susceptible throughout the fetal period and into the neonatal period and infancy.

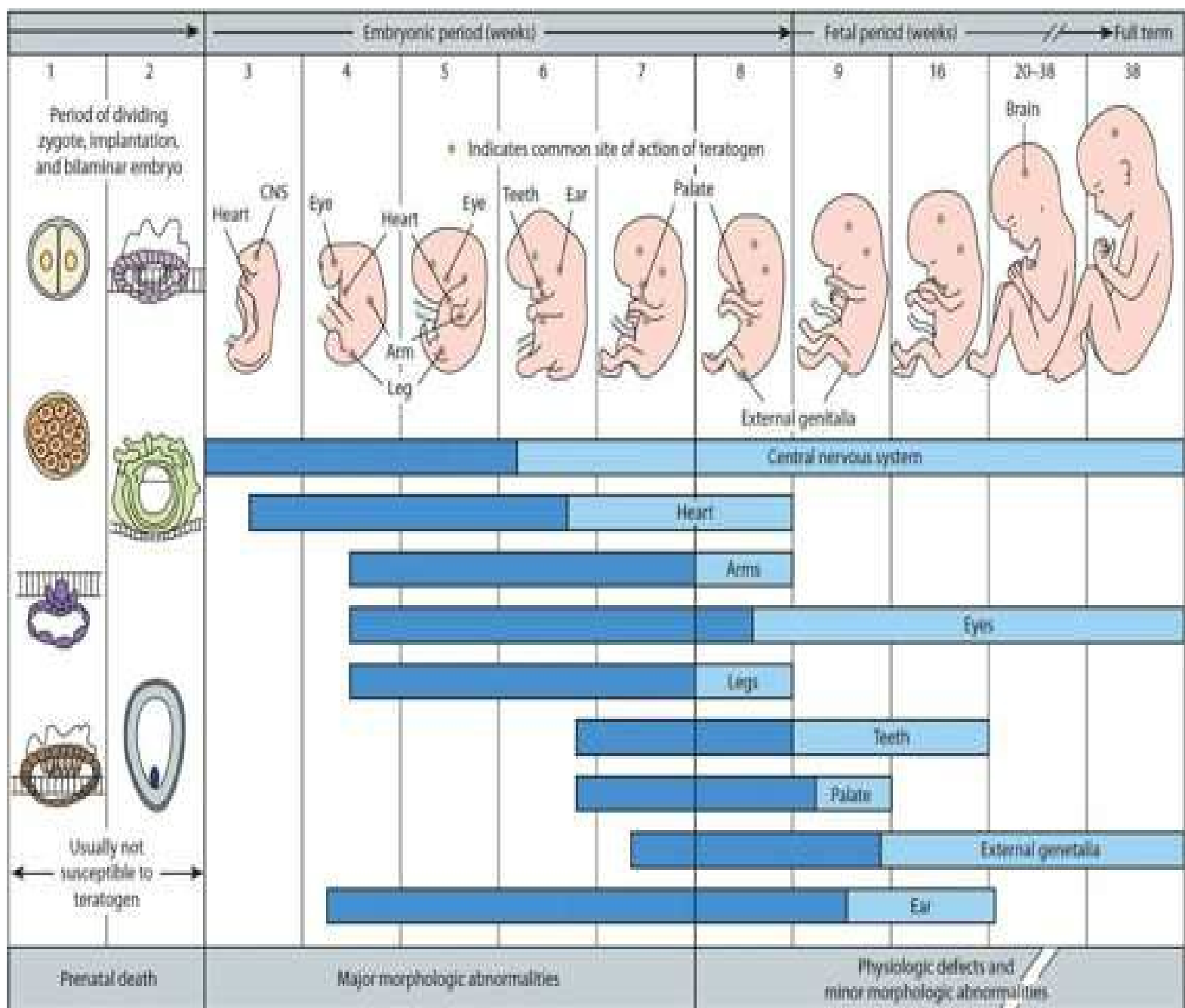


FIGURE 31-1. Critical periods of human prenatal development. CNS, central nervous system. (Modified with permission from Moore KL, Persaud TVN, Torchia MG: *Before We Are Born: Essentials of Embryology and Birth Defects*. 8th ed. Philadelphia: Saunders; 2013.)

Theoretically, knowing the exact time of teratogen exposure during gestation would allow prediction of a teratogenic effect; this is true in animal models, where the dose and time of exposure can be strictly controlled. It is also true for thalidomide in which different limb anomalies are specifically related to exposures on particular days of gestation.²⁸¹ In many clinical situations, for xenobiotics administered either for a short course or chronically, relating teratogenicity to a particular xenobiotic exposure is difficult because the exact time of conception and the exact time of exposure are unknown. This is particularly true when the primary exposure precedes the identification of pregnancy but there is secondary or ongoing exposure during pregnancy as xenobiotic is redistributed from tissue storage sites.¹⁷¹

During the fetal period, formed organs continue their cellular differentiation and grow to functional maturity. Exposure to xenobiotics such as cigarettes and their toxic constituents during this period generally lead to growth retardation. Teratogenic malformations or death may still occur as a result of disruption or destruction of growing organs, as has resulted from exposure to angiotensin-converting enzyme inhibitors during the second and third trimesters.³⁰

Another concern during the fetal period is the initiation of carcinogenesis. Significant cellular replication and proliferation lead to a dramatic growth in size of the organism. At the same time, when the fetus is exposed to xenobiotics, development of biotransformation systems may expose the organism to reactive metabolites that might initiate tumor formation. Some tumors, such as neuroblastoma, appear so early in postnatal life that their prenatal origin is suggested. In pregnant rats given ethylnitrosourea during the embryonic period, lethal or teratogenic effects occur.²⁵⁰ If ethylnitrosourea is administered during the fetal period, there is an increased incidence of tumors in the offspring. Clear cell vaginal and cervical adenocarcinomas occur in the female offspring of women exposed to DES during pregnancy.³³

MECHANISMS OF TERATOGENESIS

Cytotoxicity is one mechanism of teratogenesis and is the characteristic result of exposure to alkylating or chemotherapeutic agents. Aminopterin, for example, inhibits dihydrofolate reductase activity and leads to suppression of mitosis and cell death. If exposure to a cytotoxic xenobiotic occurs very early in development, the conceptus may die, but sublethal exposure during organogenesis may result in maldevelopment of particular structures. There is evidence that after cell death, the remaining cells in an affected region may try to repair the damage caused by the missing cellular elements. This “restorative growth” may lead to uncoordinated growth and exacerbate the original malformation.

In the case of the cytotoxics, the mechanism of action is understood, although it is not always clear why particular xenobiotics affect particular structures. With other xenobiotics, the structural effects have a clearer relationship to the site of action. For instance, when corticosteroids are administered in large doses to some experimental animals during the period of organogenesis, malformations of the palate occur. Glucocorticoid receptors are found in high concentrations in the palate of the developing mouse embryo.²⁴³ Corticosteroid exposure can also cause cleft palate in humans at a low frequency.^{236,285}

Caloric deficiency is not considered teratogenic during the period of organogenesis; however, specific nutritional or vitamin deficiencies can be. In particular, there is an increased incidence of neural tube defects (anencephaly and spina bifida) associated with dietary folate deficiency, although the specific mechanism of teratogenesis is unknown. To ensure that all women of childbearing age have adequate folate stores by the time they become pregnant and during their pregnancy and to reduce the number of severe birth defects, it is important for women to have folate supplementation either as vitamin or dietary supplements even before they become pregnant. Because fortification of grain products is considered critical to help accomplish this goal, the FDA requires US manufacturers to add folic acid to enriched breads, cereals, flours, corn meals, pastas, rice, and other grain products.²³⁰

Ethanol affects fetuses both directly and indirectly. The craniofacial malformations that occur in fetal alcohol syndrome (FAS) probably result from the effects of ethanol during the period of organogenesis. Growth retardation may result from direct effects of ethanol on fetal growth or from indirect effects resulting from ethanol-induced maternal nutritional deficiencies.

MANAGEMENT OF ACUTE POISONING IN PREGNANT WOMEN

For most women, pregnancy and the postpartum period are a period of emotional happiness. However, women have a lifetime prevalence of depression that is two to three times higher than men, and for some women, psychiatric illness during pregnancy, particularly depression and anxiety, represents a significant complication. A new first episode or recurrence of major depression occurs in approximately 3% to 5% of pregnant women and 1% to 6% of postpartum women; an additional 5% to 6% of women in each period will have minor symptoms of depression.¹⁰⁷ Overall, these rates of depression are about the same in pregnant and nonpregnant women; however, during the postpartum period, the onset of new episodes of depression may be three times higher than for nonpregnant women. Pregnant teenagers may also be at higher risk of depression in pregnancy.¹⁸⁴

Postpartum “baby blues” are common; typically involve relatively mild symptoms including mood swings, irritability, anxiety and crying spells; and generally resolve by 2 weeks postpartum.¹⁹¹ Postpartum blues do not include suicidal ideation. True depression is manifested by feelings of hopelessness or helplessness and may include suicidal ideation.¹⁹¹ Postpartum psychosis, typically associated with bipolar disorder, is uncommon, but it represents a true psychiatric emergency because there is a high risk of suicide, infanticide, or both.¹⁹¹

Risk factors for perinatal depression include an unplanned pregnancy, ambivalence about the pregnancy, poor social support, marital difficulties, adverse life events, and chronic stressors such as financial problems.^{65,173,319} Of substantial importance is a personal or family history of depression, particularly previous perinatal depression. Discontinuation of antidepressant represents a significant risk for relapse of disease, although relapse is possible even while a woman is receiving an antidepressant. Additional risk factors for depression include miscarriage, stillbirth, and preterm delivery.²⁷⁶

Depression in pregnancy has adverse effects on both the mother and the fetus.³⁵ For the pregnant woman, adverse effects include noncompliance with prenatal care; self-medication with tobacco, alcohol, and drugs; poor sleep; poor appetite; and poor weight gain. In addition, there may be an increased risk of spontaneous abortion, preeclampsia, preterm delivery, and growth retardation. For many of these outcomes, it is difficult to differentiate the contributions from multiple confounding and interacting factors, including psychopathology, socioeconomic status, acute and chronic stressors, smoking, and the use of alcohol and other drugs of abuse. Infants born to women being treated with antidepressant medications are also at risk for neonatal withdrawal symptoms.¹⁵⁸

One of the most extreme outcomes of depression is suicide. Suicidal ideation occurs in about 5% of pregnant women in community samples and up to 20% in women with underlying psychiatric illness.^{184,226} Even so, suicide and suicide attempts during pregnancy are uncommon. Each year a small number of women die during pregnancy or the postpartum

period; 1% to 5% of these pregnancy-related deaths may be the result of suicide.^{54,76,231} Between 2% and 12% of women who attempt or commit suicide may be pregnant.^{157,240,332} Overall, completed suicide occurs less frequently during pregnancy.^{19,184,205} Psychiatric illness, including previous suicide attempts, predisposes to suicide attempts in pregnancy. Acute stressors leading to impulsive acts account for most of the uncompleted suicide attempts; these reasons include loss of a lover, economic crisis, prior loss of children, and unwanted pregnancy, and desire for an abortion.^{72,180,332} Fewer than half of the suicide attempts are specifically related to a pregnancy-related problem.

Women who complete suicide typically have more severe psychiatric illness. In particular, these women are likely to use more violent means of suicide such as hanging or self-inflicted gunshot wounds, although poisonings are a significant contributor to these deaths.²³¹ In addition, substance and alcohol use is a significant contributing factor in many cases; additionally, some pregnancy-related deaths may be secondary to complications of substance use, such as overdose.²³¹ Initiation of child-protection proceedings, particularly in the setting of maternal substance use, may be an additional risk factor for postpartum suicide.²³¹

Ingestion of xenobiotics is the most common method of attempted suicide during pregnancy and the postpartum period.^{65,240,245} There are about 9000 xenobiotic exposures in pregnant women reported to the AAPCC annually, which account for less than 1% of the approximately 1 million reported adolescent and adult exposures. The patterns of xenobiotic exposure are similar to those of adult exposures in general with analgesics being the most common exposure. However, according to AAPCC data, there are relatively more exposures to cleaning substances, pesticides, fumes, and vitamins, but there are relatively fewer exposures to sedative-hypnotics, antidepressants, and cardiovascular agents; the absolute differences are small (Chap. 136). Some of these xenobiotic exposures may be attempts to terminate pregnancy (Chap. 21).²⁴⁰ As with most poisonings overall, the severity of poisoning in pregnant women is typically minor.^{226,231}

In one US national sample, 1659 pregnant women had poisoning-related hospitalizations, representing 0.04% of all hospitalized pregnant women and approximately 10% of injury-related admissions of pregnant women. A total of 244 of these women (15%) delivered their babies during these hospitalizations related to poisoning.¹⁶⁶

In national samples from both the United States and England, approximately 2% to 3% of deaths in pregnancy and the immediate postpartum period follow suicidal poisoning.^{54,231} The AAPCC reports approximately one to two deaths per year in pregnant women, which represents approximately one to two per 1000 AAPCC-reported adult deaths overall, two to four per 1000 deaths in adult women, and approximately one death per 10000 xenobiotic exposures in pregnancy (Chap. 136). In a combined Hungarian series of pregnant women who had suicidal poisonings, 19 of 1044 (1.8%) died.⁷³

Any woman who attempts suicide during pregnancy or the postpartum period should have a psychiatric evaluation after she is medically stabilized. In particular, a growing number of specialized units or teams focus on pregnant and postpartum women and attempt to keep women and infants together in the postpartum period.^{191,231}

Managing any acute overdose during pregnancy provokes discussion of several questions. Is the general management different? Do altered metabolism and pharmacokinetics increase or decrease the woman's risk of morbidity or mortality from a xenobiotic overdose? Is the fetus at risk of poisoning from a maternal overdose? Is there a teratogenic risk to the fetus from an acute overdose or poisoning? Is the use of an antidote contraindicated, or should use be modified? When should a potentially viable fetus be emergently delivered to prevent toxicity? When should termination of a pregnancy be recommended?

As described earlier, physiologic changes during pregnancy affect pharmacokinetics; xenobiotics taken in overdose also have unpredictable toxicokinetics. In any significant overdose during pregnancy, pregnancy-related alterations in pharmacokinetics are unlikely to protect the woman from significant morbidity or mortality.

Although a single high-dose exposure to a xenobiotic during the period of organogenesis might seem analogous to an experimental model to induce teratogenesis, most xenobiotics ingested as a single, acute overdose do not induce physical deformities.⁷⁴ Anticonvulsants are teratogenic and may be ingested in toxic doses, but their teratogenicity is probably related more to chronic exposure. Acute acetaminophen (APAP) toxicity in the first trimester may lead to an increased risk of spontaneous abortion,²⁵³ suggesting a teratogenic effect similar to the all-or-none response described earlier. In general, however, it is extremely difficult to ascribe teratogenicity to a particular xenobiotic exposure based on a single case report. There is, for example, a report of multiple severe congenital malformations in the stillborn fetus of a woman who overdosed on isoniazid during the 12th week of pregnancy.¹⁷⁸ However, because the background incidence of congenital malformations is 3% to 6%, it is almost impossible to determine for a single individual whether a particular exposure is the etiology of observed malformations.⁷⁵ The Budapest Registry of Self-Poisoned Patients uses this construct to screen for possible teratogenic effects of xenobiotics in overdose.^{73,74} Considering the successful outcome of most pregnancies that progress to term after an acute overdose, it is very unlikely that the small risk of teratogenesis would lead to a recommendation for termination of pregnancy after an acute overdose of most xenobiotics.

In general, any condition that leads to a severe metabolic derangement in a pregnant woman is likely to have an adverse impact on her developing fetus. Therefore, the management of overdose in a pregnant woman usually follows the principles outlined in Chap. 4, with close attention paid to the airway, oxygenation, and hemodynamic stability. The use of naloxone

or dextrose has not been specifically assessed in pregnancy but should be guided by the same considerations raised in managing the nonpregnant patient with alterations in respiratory or neurologic function. Opioid-induced respiratory failure in a pregnant patient will lead to fetal hypoxia and adverse effects; opioid withdrawal in a pregnant woman, whether induced by abstinence or the use of naloxone, may adversely affect the fetus or the pregnancy. Consideration of the benefits and risks of the use of naloxone for an opioid-poisoned woman in respiratory distress or coma suggests that reduced morbidity, for both the mother and fetus, may be achieved by the use of carefully titrated doses of naloxone to minimize the likelihood of maternal withdrawal ([Chap. 38](#) and *Antidotes in Depth: A4*).

Gastrointestinal decontamination is frequently a part of the early management of acute poisoning in nonpregnant patients. Gastric lavage is not specifically contraindicated for pregnant patients, and the usual concerns about protecting the airway apply.

There is no specific contraindication to the use of activated charcoal in a pregnant woman. There may be a specific role for whole-bowel irrigation (WBI) in the management of several xenobiotic exposures, particularly in the treatment of iron overdose in pregnancy.³¹⁷ The use of oral polyethylene glycol is safe in pregnant women.²²⁴

Almost all antidotes are designated as FDA pregnancy-risk category C; that is, there is little specific information to guide their use. Ethanol is labeled as category D (positive evidence of risk), although this is presumably related to chronic use throughout pregnancy. Fomepizole, which has replaced ethanol as the preferred antidote for toxic alcohol poisoning, is labeled as category C. Pyridoxine and thiamine are category A xenobiotics; N-acetylcysteine (NAC), magnesium, glucagon, and naloxone are category B xenobiotics.

Thus far, there are no reports of adverse effects on a fetus from antidotal treatment of a poisoned pregnant woman. Conversely, in at least one case, withholding deferoxamine therapy may have contributed to the death of both a woman and her fetus.^{201,302}

ACETAMINOPHEN

APAP is the most common analgesic and antipyretic agents used during pregnancy and is also one of the most common xenobiotic overdoses during pregnancy. There are two published series of acute APAP overdose during all trimesters of pregnancy in addition to multiple casereports.^{24,50,105,119,133,165,177,190,211,239,253,257,258,264,267,270,299,320} Overall, most pregnant women recover from an APAP ingestion without adverse effects to themselves or their babies.

Of 28 women with first trimester exposures who continued their pregnancies, five women with toxic serum APAP concentrations and 14 with nontoxic concentrations delivered full-term newborns; in one case, both the mother and fetus died; and eight women had spontaneous abortions. Five of these eight had toxic serum concentrations and received NAC (one within 8 hours and four between 12 and 17 hours after ingestion).

Of 31 women with second trimester exposures who continued their pregnancies, seven women with toxic serum APAP concentrations and 20 with nontoxic concentrations delivered full-term babies; one woman with a nontoxic serum concentration and one woman who developed hepatotoxicity delivered premature infants; and two women with nontoxic serum APAP concentrations had spontaneous abortions probably unrelated to the overdose.

Of 54 women with third trimester exposures, 15 women with toxic serum APAP concentrations and 26 with nontoxic concentrations delivered full-term babies; eight woman with a toxic serum concentration, four of whom developed hepatotoxicity, and two women with nontoxic concentrations delivered premature infants; two women with severe hepatotoxicity delivered stillborn infants who also showed signs of hepatotoxicity; and one woman with severe hepatotoxicity delivered an infant who died at 34 hours of life.

There are also several case reports of adverse pregnancy outcome in the setting of chronic use of APAP or acute overdose associated with chronic substance use.^{55,133,167,192,253,311} It is difficult to interpret these reports with respect to specific APAP effect because of the confounders of chronic disease, chronic use, or use of additional medications or substances.

Although APAP at recommended doses is considered safe in pregnancy,¹⁸¹ in overdose, it puts the developing fetus at risk. As the cases demonstrate, APAP crosses the placenta to reach the fetus. There may be an increased risk of spontaneous abortion after overdose during the first trimester, particularly in the setting of toxic serum APAP concentrations and delayed NAC therapy.²⁵³ There is also a question about whether overdose during the first trimester can lead to late sequelae, for instance, premature labor.

Some experimental work might explain early pregnancy loss after overdose. APAP prevented the development of preimplantation (two-cell stage) mouse embryos in culture, an effect that was not associated with alterations in glutathione concentrations,¹⁷⁵ and led to abnormal neuropore development in cultured rat embryos.²⁹⁸ These data suggest that APAP may be directly toxic to the immature organism. However, other work reported that similar embryotoxic effects were associated with reductions in glutathione concentrations³²⁷ and that N-acetyl-p-benzoquinoneimine (NAPQI) produced nonspecific toxicity when added to the rat embryo culture medium.²⁹⁸

The fetal liver has some ability to metabolize APAP to a reactive intermediate in vitro. Cytochrome P450 (CYP) activity was detected in intact hepatocytes, as well as in microsomal fractions isolated from the livers of fetuses aborted between 18 and 23 weeks of gestation. This fetal hepatic CYP activity increased between 18 and 23 weeks (the only period studied) but was maximally only 10% of the activity of hepatocytes isolated from adults after brain death.²⁶¹ In two clinical cases, cysteine and mercapturate conjugates were identified in newborns exposed to APAP in utero, suggesting that the fetus and neonate can metabolize APAP through the CYP system.^{177,257} These data suggest that the fetus in utero and the neonate can generate a toxic metabolite. The clinical cases suggest that the fetal liver is susceptible to injury, although whether this fetal hepatotoxicity is related to fetal APAP toxicity, maternal toxicity, or postmortem changes is unclear.

This CYP activity has not been further characterized. However, CYP2E1, one of the cytochromes responsible for APAP metabolism, is present in human fetal tissues as early as 16 weeks of gestation.²¹⁴ CYP3A4 and CYP1A2 are also involved in APAP metabolism but are not present in fetal liver. CYP3A7 is a functional fetal form of the CYP3 family, but its metabolic activity with respect to APAP has not been studied.¹²⁰

The most relevant clinical questions relate to management of overdose during the third trimester. Can APAP overdose lead to premature labor even if a pregnant woman does not have a toxic serum concentration or develop hepatotoxicity? Should a woman be emergently delivered following overdose? Does NAC treatment of the mother help the fetus? What is the appropriate treatment of a neonate exposed to APAP in utero?

The clinical cases may help address the last two questions (Table 31–3). Seven women whose pregnancies were all at less than 36 weeks of gestation, developed hepatotoxicity. Two infants died in utero, and one infant died on the second day of life with evidence of hepatotoxicity. The other four infants experienced problems associated with prematurity but did not develop obvious hepatotoxicity. One of these four had an exchange transfusion and an unexplained death at 3 months of age. Five women whose pregnancies were all at 36 or more weeks of gestation did not develop hepatotoxicity. One infant had an exchange transfusion and did not develop hepatotoxicity but died of sudden infant death syndrome (SIDS) at 5 months of age. One infant received intravenous (IV) NAC and had a transient elevation of aspartate aminotransferase (AST) and prothrombin time. Two infants were not treated, and both did well, although one had a transient elevation of AST. One infant was born 6 weeks after the overdose and was normal.

TABLE 31–3. Reported Cases of Third Trimester APAP Overdose

Gestational Age (wk)	Maternal		Infant		Comment	Reference
	APAP Concentration ($\mu\text{g/mL}$)(time ^a)	AST Peak (IU/L) (time ^a)	APAP Concentration ($\mu\text{g/mL}$)(time ^a)	Hepatotoxicity (Yes/No)		
27	0 (36 hours)	1226 (36 hours)	ND	No	C/S for fetal distress. Infant: mild respiratory distress syndrome.	105
27–28	56 (16 hours)	6226 (96 hours)	ND	Yes	Ingestion over 24 hours. No fetal movements at presentation. PO NAC started at 20 hours. Induced labor at 4 days. Infant: stillborn with diffuse hepatic necrosis. Hepatic APAP 250 $\mu\text{g/g}$.	119
29	160 (10 hours)	4300 (50 hours)	76 (16 hours, cord)	No	Ingestion of aspirin, caffeine, and quinine followed 17 hours later by APAP. Presented in labor. Treated with oral methionine. Spontaneous delivery at 16 hours. Infant: moderate hyaline membrane disease. Peak AST of 86 IU/L (cord). Four whole-blood exchange transfusions. Discharge home at 54 days of life. Died at 106 days; no apparent cause.	177
30	55 (18 hours)	4000 (48 hours)	ND	ND	Maternal chorioamnionitis with delivery at 31 weeks. Respiratory distress syndrome and hyperbilirubinemia.	239
31	40 (26 hours)	13320 (60 hours)	41 (27)	Yes	APAP only. C/S for fetal distress one hour after initial maternal evaluation. Infant's birth weight was 1620 g. Apgar scores 0, 0, 1. ^b Infant died at 34 hours of life. Mother died at 34 hours postingestion. No autopsy of mother or child.	320
32	448 (12 hours)	5269 (48 hours)	0 (84 hours, cord)	No	IV NAC started at 12 hours. Induced delivery at 84 hours. Infant: transient hypoglycemia, mild respiratory distress, mild jaundice. Peak AST of 56 IU/L (day 1 of life).	211, 264
32	166 (4 hours)	"Normal"	ND	ND	Vaginal delivery at term without complications.	70
33	135 (28 hours)	6237 (66 hours)	330 (3 days, cord)	Yes	Oral NAC at 12 hours. Fetal death at 2 days; spontaneous delivery at 3 days. Infant: stillborn with diffuse hepatic necrosis.	253
36	280 (3–4 hours)	"Normal"	217 (6–7 hours, cord)	No	Ingestion of APAP, ethanol, barbiturates. Elective C/S at 6–7 hours. Infant: double-volume exchange transfusion at 18 hours. Discharge at 40 days, "cot death" at 157 days.	257
36	200 (5 hours)	25 (24 hours)	ND	No	Oral NAC (7 time). Infant: spontaneous delivery 6 weeks after ingestion. Normal neonatal course.	50
38	216 (4 hours)	"Normal"	13 (17 hours, cord)	No	NAC (7 route). Infant: normal neonatal course.	165, 267
"Term"	147 (9 hours)	28 (9 hours)	133 (9 hours, 4 hours of life)	No	Infant PT of 44 at 4 hours of life. IV NAC. No problems. AST of 56 IU/L at 4 hours of life.	24
"Term"	89 (11 hours)	326 (35 hours)	144 (11 hours, 4 hours of life)	No	Mother presented in labor at 6 hours. Infant received IV NAC at 4 hours of life. AST of 55 IU/L at 4 hours of life.	270

^aTime after maternal ingestion. ^bApgar scores are at 1, 5, and 10 minutes.

APAP = acetaminophen; AST = aspartate aminotransferase; C/S = cesarean section; IV = intravenous; NAC = N-acetylcysteine; ND = not done or not reported; PO = oral; PT = prothrombin time.

Severe maternal hepatotoxicity that is associated with any sign of fetal distress is an indication for urgent delivery. Although a fetus with prolonged exposure to APAP in utero is at risk of developing severe hepatotoxicity, not all at-risk infants are affected. What role gestational age, maternal disease state, or other maternal factors may play is unknown. Although there are insufficient case data to suggest that APAP overdose per se is an indication for urgent delivery, there may be an indication for urgent delivery when the maternal serum APAP concentration is in the toxic range but hepatotoxicity has not yet developed.³⁰⁶ The clinical cases suggest that significant APAP overdose with or without hepatotoxicity may precipitate premature labor and that even women with nontoxic serum concentrations may be at an increased risk.

In two cases, exchange transfusion was used to treat the exposed neonate. In both cases, the APAP half-life was prolonged, and in neither case was this affected by the transfusion. Disturbingly, these two infants had unexplained deaths at

several months of age. There are currently no data supporting exchange transfusion as therapy for prenatal exposure.

A pregnant woman with acute toxic APAP ingestion should be treated with NAC ([Chap. 35](#) and Antidotes in Depth: A3). This therapy is designed to treat the mother. Maternal hepatotoxicity and delayed NAC therapy are associated with fetal toxicity²⁵³; whether NAC therapy can prevent later sequelae such as premature delivery is unclear. Although NAC did not cross the sheep placenta in vivo²⁸² or the perfused human placenta in vitro,¹⁴¹ NAC was found in cord blood after administration to four mothers before delivery.¹³³ Even if NAC does cross the placenta, whether it prevents fetal hepatotoxicity is unknown because not all exposed fetuses develop hepatotoxicity.

IRON

Iron is also commonly ingested during pregnancy; maternal toxicity is generally greater than fetal toxicity. In two reported cases, normal babies were delivered, although the mothers died.^{233,251} In another case, the mother had severe iron toxicity with acidosis, shock, kidney failure, and disseminated intravascular coagulation but was not treated with deferoxamine because of concerns about its teratogenic risks. Instead, the mother received an exchange transfusion followed 45 minutes later by a spontaneous abortion of the 16-week fetus.^{201,302} Neonatal and cord blood iron concentrations were not elevated. In several cases, pregnant women who had signs and symptoms of iron poisoning and elevated serum iron concentrations were treated with deferoxamine and subsequently delivered normal babies.^{34,155,170,246,275,312}

Although the placenta transports iron to the fetus efficiently,²³ it also blocks the transfer of large quantities of iron. In a sheep model of iron poisoning, only a small amount of iron was transferred across the placenta despite significantly elevated serum iron concentrations.⁷¹

Deferoxamine is an effective antidote for iron poisoning ([Chap. 46](#) and Antidotes in Depth: A7), but it is reported to be an animal teratogen that causes skeletal deformities and abnormalities of ossification (FDA class C pregnancy risk). An animal model observed similar effects but only with doses of deferoxamine that caused maternal toxicity.³⁸ Experimentally, in sheep, deferoxamine was minimally transported across the placenta⁷¹; therefore, the reported fetal effects may be secondary to chelation of essential nutrients (eg, trace metals) on the maternal side of the placenta.³⁰⁶

In clinical case reports of iron overdose for which deferoxamine was used, there have been no adverse effects on the fetus, although most have been either second or third trimester poisonings.^{34,155,170,233,246,275,312} In a case series of 49 patients with iron poisoning during pregnancy, few of the patients exhibited any clinical toxicity other than vomiting and diarrhea; 25 received deferoxamine, most by the oral route.²¹⁰ One woman with a first trimester overdose, eight women with second trimester overdoses, and 12 women with third trimester overdoses were treated with deferoxamine and subsequently delivered full-term infants. One infant whose mother overdosed at 30 weeks of gestation had webbed fingers on one hand. One woman overdosed at 20 weeks had minimal clinical toxicity, received deferoxamine, and delivered a 2.5-kg male infant at 34 weeks of gestation. One woman with a first trimester overdose and two women with second trimester overdoses elected to terminate their pregnancies.

Further support for the safe use of deferoxamine in pregnancy is the experience with its use for pregnant women with thalassemia major. For many years, deferoxamine has been administered as part of the therapy for posttransfusion iron overload without adverse effects.²⁸⁹

Deferoxamine is probably safe for use in pregnant women. Considering the potentially fatal nature of severe iron poisoning, deferoxamine should be administered when signs and symptoms indicate significant poisoning.

Iron overdose may be one of the few specific indications for WBI because iron is not adsorbed to activated charcoal (Antidotes in Depth: A1 and A2). A case report demonstrated elimination of pill fragments after treatment of a pregnant woman with WBI.³¹⁷

CARBON MONOXIDE

Carbon monoxide is the leading cause of poisoning fatalities in the United States. In contrast to iron and most other xenobiotics, when pregnant women are exposed to carbon monoxide, the fetus may be at greater risk of toxicity than the expectant woman. There are reports of both the mother and fetus dying; the mother surviving but the fetus dying; and both the mother and fetus surviving but with an adverse neonatal outcome, primarily brain damage resembling that seen after severe cerebral ischemia.^{51,69,163,187,202,228,317,335} Similar clinical effects have also been observed in animal models.^{87,112,188}

The case literature suggests an increased risk of poor fetal outcome with clinically severe maternal poisoning or significantly elevated carboxyhemoglobin concentrations.^{163,228} Women with minimal symptoms or low concentrations of carboxyhemoglobin have a low risk of fetal toxicity, but a lower limit of exposure without effect has not been specifically defined.¹⁶³

In animal models, under experimental conditions, the fetus has a carboxyhemoglobin concentration 10% to 15% higher

than the mother.^{128,188} After exposure to carbon monoxide, the fetus achieves peak carboxyhemoglobin concentrations 58% higher than those achieved by the mother at steady state, and the time to peak concentration is also delayed compared with that of the mother. Similarly, the elimination of carbon monoxide occurs more slowly in the fetus than in the mother.^{128,187,188} One case report describes such a phenomenon: after 1 hour of supplemental oxygen, the maternal carboxyhemoglobin concentration was 7% and the fetal carboxyhemoglobin concentration was 61% at the time of death in utero.⁹³

Carbon monoxide leads to fetal hypoxia by several mechanisms: (1) maternal carboxyhemoglobin leads to a decrease in the oxygen content of maternal blood, and therefore less oxygen is delivered across the placenta to the fetus, which normally has an arterial PO₂ of only 20 to 30 mm Hg; (2) fetal carboxyhemoglobin causes a decrease in fetal PO₂; (3) carbon monoxide shifts the oxyhemoglobin dissociation curve to the left and decreases the release of oxygen to the fetal tissues (an exacerbation of the physiologic left shift found with normal fetal hemoglobin); and (4) carbon monoxide may inhibit cytochrome oxidase or other mitochondrial functions (Chap. 125).

The treatment for severe carbon monoxide poisoning is hyperbaric oxygen therapy (HBO) (Chap. 125 and Antidotes in Depth: A38). There are questions about the use of HBO in pregnant women because animal models suggest HBO adversely affects the embryo or fetus.^{99,215,273,305} The applicability of these animal models to humans is difficult to assess; many of the animal models used hyperbaric conditions of greater pressures and duration than those clinically used for humans.

Hyperbaric oxygen therapy has been used therapeutically for carbon monoxide poisoning in pregnancy with good results reported, although there are limited data on the long-term follow-up of the children.^{47,98,106,116,129,163,318} One large series reported 44 women who were exposed to carbon monoxide during pregnancy and were treated with HBO, regardless of clinical severity or gestational age: 33 had term births, one had a premature delivery 22 weeks after HBO during an episode of maternal fever, two had spontaneous miscarriages (one 12 hours after severe poisoning and one 15 days after mild poisoning), one delivered a child with Down syndrome, one had an elective abortion, and six were lost to follow-up.⁹³ Details regarding trimester of exposure, maternal carboxyhemoglobin concentration, and severity of symptoms are not available, making it difficult to interpret the reported adverse outcomes. Although HBO appears safe for pregnant women and seems to present little risk to the fetus, it is not clear whether HBO prevents carbon monoxide–related fetal toxicity.

Hyperbaric oxygen therapy should be considered for any pregnant woman exposed to carbon monoxide, especially for a woman with an elevated serum carboxyhemoglobin concentration or any evidence of fetal distress. To allow the fetal carboxyhemoglobin to be eliminated, if HBO therapy is not available, 100% oxygen should be administered to a pregnant woman for five times as long as the time needed for her carboxyhemoglobin concentration to return to the normal range. Thus, if a pregnant woman's carboxyhemoglobin concentration returns to normal in 30 minutes, she should continue to receive 100% oxygen for a total of 150 minutes.

SUBSTANCE USE DURING PREGNANCY

Illicit and licit substance use during pregnancy and its effects on the woman, on the pregnancy, and on the fetal and postnatal development are complex.

With the increased use of cocaine during the latter half of the 1980s and 1990s, there was great interest in determining the effects of cocaine use during pregnancy. As research in this area progressed, many of the critical methodologic issues related to substance use research were highlighted.^{100,140,179,225,337}

Substance-using women often have multiple risk factors for adverse pregnancy outcomes, such as low socioeconomic status, polysubstance use, ethanol and cigarette use, sexually transmitted infections, AIDS, malnutrition, and lack of prenatal care. Lack of prenatal care is highly correlated with premature birth, and smoking is associated with spontaneous abortion, growth retardation, and SIDS.^{152,330} Other factors not specifically related to substance use such as age, race, gravidity, and prior pregnancies also affect pregnancy outcome. Each of these factors represents a significant potential confounding variable when the effects of a particular xenobiotic such as cocaine or marijuana are evaluated during pregnancy and must be controlled for in research design. Many of these factors are also significant confounders in evaluation of postnatal growth and development.

There may be bias in the selection of study subjects. For example, if all the patients are selected from an inner-city hospital obstetrics service, there is potential for overestimating the effects of the xenobiotic being studied. If cohorts are followed over a long time, study subjects are frequently lost to follow-up. Are the ones who continue more motivated, or do they have more problems that need attention?

Categorizing patients into substance-use groups is difficult. Self-reporting of substance use is frequently unreliable or inaccurate, and making determinations about the nature, frequency, quantity (dose), or timing (with respect to gestation) of xenobiotic exposure is difficult. Because substance users frequently use multiple xenobiotics, it may be difficult to categorize subjects into particular xenobiotic-use groups, and patients using different xenobiotics may be grouped together. In fact, there may be no actual xenobiotic-free control groups.

When urine drug screens are used to identify substance users, there is a high probability of false negatives because drug screens reflect only recent use. This factor is particularly important because substance use tends to decrease later in pregnancy, and a negative urine drug screen in the third trimester or at delivery may fail to identify a woman who was using xenobiotics early in pregnancy. Testing for xenobiotics in hair or meconium may improve the accuracy of the analysis with regard to the entire pregnancy.^{39,160}

Another bias involves selection of infants who are exposed to xenobiotics. Evaluating newborns who are “at risk,” show signs of withdrawal, or have positive urine drug screens will miss some exposed infants. When research concerns the neurobehavioral development of children exposed in utero to substances, it is important that the examiners performing the evaluation be blinded to the infants’ xenobiotic exposure category.

Finally, there may be a bias against publishing research that shows a negative or no significant effect.¹⁶¹

Ethanol

Chronic ethanol use during pregnancy produces a constellation of fetal effects. The most severe effects occur in the FAS, which is characterized by (1) intrauterine or postnatal growth retardation; (2) intellectual disability or behavioral abnormalities; and (3) facial dysmorphogenesis, particularly microcephaly, short palpebral fissures, epicanthal folds, maxillary hypoplasia, cleft palate, a hypoplastic philtrum, and micrognathia.^{32,200} A child can be diagnosed with FAS even when a history of regular gestational alcohol use cannot be confirmed.

In an attempt to formalize diagnostic criteria for FAS and other gestational alcohol-related effects, the Institute of Medicine proposed some additional descriptors that are in common use.³⁰⁰ Partial FAS is applied to a child with some of the characteristic facial features and with growth retardation, neurodevelopmental abnormalities, or other behavioral problems. Alcohol-related birth defects are congenital anomalies other than the characteristic facial features described earlier, for example, cleft palate, which sometimes occurs with regular gestational alcohol use. Alcohol-related neurodevelopmental disorder describes neurodevelopmental abnormalities or other behavioral problems, which sometimes occur with regular gestational alcohol use. Fetal alcohol spectrum disorders (FASDs) is an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy.^{32,294}

Differential expression of the syndrome may reflect the effects of varying quantities of ethanol ingested at critical periods specific for particular effects. The craniofacial anomalies probably represent teratogenic effects during organogenesis, but some CNS abnormalities and growth retardation may result from adverse effects later in gestation.

There is considerable controversy about what amount of alcohol consumption can cause FASD.^{221,229} Approximately 10% of women consume some alcohol during pregnancy, 2% are frequent users, and 2% binge. Of women who might become pregnant, about 50% drink some alcohol, 13% drink frequently, and 12% binge.⁵² Some researchers believe that the FASD is a result of alcoholism—chronic regular use or frequent bingeing—rather than to low concentrations of gestational ethanol exposure, no matter how little or how infrequent.^{4,115} A high level of consumption would be in the range of 50 to 100 mL of 100% ethanol (four to six “standard” drinks of hard liquor) regularly throughout pregnancy³⁰⁰ or binge drinking (at least five standard drinks per occasion), with a significantly elevated peak blood ethanol concentration.^{3,197} Literature suggests that behavioral abnormalities are associated with the reported consumption of as little as one drink per week.²⁹⁵ In this regard, neither a no-effect amount nor a safe amount of ethanol use in pregnancy has been determined,¹⁴⁹ and therefore the US Surgeon General recommends no alcohol consumption during pregnancy.²³²

The incidence of FAS is 0.5 to 3 per 1000 live births; 4% of women who drink heavily may give birth to children with FAS.^{2,207} This means that several hundred children with FAS and several thousand with fetal alcohol effects will be born each year; thus, ethanol use is considered the leading preventable cause of intellectual disability in this country.³⁰⁰ Although the primary determinant of FAS and its effects is the amount of maternal ethanol consumption, there is some evidence that paternal ethanol exposure may play a contributing role.¹

Ethanol use during pregnancy may lead to an increased incidence of spontaneous abortion, premature deliveries, stillbirths,¹⁹⁸ neonatal ethanol withdrawal,^{28,227} and possibly carcinogenesis.¹⁵⁶ Infants may be irritable or hypertonic and may have problems with habituation and arousal. Long-term behavioral and intellectual effects include decreased IQ, learning disabilities, memory deficits, speech and language disorders, hyperactivity, and dysfunctional behavior in school.^{206,295,301}

Brain autopsies of children with FAS demonstrate malformations of gray and white matter, a failure of certain regions such as the corpus callosum to develop, a failure of certain cells such as the cerebellar astrocytes to migrate, and a tendency for tissue in certain regions to die.⁹⁷ The mechanisms of ethanol-induced teratogenesis are not fully elucidated.^{29,121} Much of the work in animals has focused on the developing nervous system, where ethanol adversely affects nerve cell growth, differentiation, and migration, particularly in areas of the neocortex, hippocampus, sensory nucleus, and cerebellum.^{117,303}

Several mechanisms are potential contributors to the effects of ethanol.¹¹⁴ Ethanol interferes with a number of different

growth factors, which may affect neuronal migration and development.³³¹ In addition, ethanol interferes with the development and function of both serotonin and N-methyl-D-aspartate (NMDA) receptors. Ethanol, or its metabolite acetaldehyde, may also cause cell necrosis directly or through the generation of free radicals and excessive apoptosis.^{64,97,125} In particular, craniofacial abnormalities may be related to apoptosis of neural crest cells through the formation of free radicals, a deficiency of retinoic acid, or the altered expression of homeobox genes that regulate growth and development.³⁰³

One integrative model of ethanol-induced teratogenesis proposes that sociobehavioral risk factors, such as drinking behavior, smoking behavior, low socioeconomic status, and cultural or ethnic influences, create provocative biologic conditions, such as high peak blood ethanol concentrations, circulating tobacco constituents, and undernutrition. These provocative factors exacerbate fetal vulnerability to potential teratogenic mechanisms, such as ethanol-related hypoxia or free radical-induced cell damage.⁵

Opioids

Opioid use in pregnancy remains a significant cause of both maternal and neonatal morbidity. In past month surveys, approximately 0.2% of pregnant women report heroin use, 0.9% report the illicit use of prescription pain relievers, and 0.1% report the use of oxycodone (OxyContin).²⁶⁹ Up to 75,000 babies per year may be exposed to methadone or heroin in utero.²²² Most clinical research regarding opioid toxicity during pregnancy relates to the use of heroin or methadone.

Pregnant opioid users are at increased risk for many medical complications of pregnancy, such as hepatitis, sepsis, endocarditis, sexually transmitted infections, and AIDS, and may be at increased risk for obstetric complications, such as miscarriage, premature delivery, or stillbirth.^{100,113} Some of the obstetric complications may be related to associated risk factors in addition to the opioid use. Maternal opioid use most commonly affects fetal growth.^{100,113,337} There is an increased incidence of low birth weight in babies born to opioid-using mothers compared with control participants, and the effect is greater for heroin than for methadone.

There is extensive clinical experience with methadone maintenance during pregnancy. Compared with untreated heroin use, methadone maintenance during pregnancy is associated with better obstetric care, decreased risk of maternal withdrawal, increased fetal growth, decreased fetal mortality, decreased risk of HIV infection, and increased likelihood that a child will be discharged home with his or her parents.¹⁴⁶ Women who receive low-dose methadone and good prenatal care are at increased risk for pregnancy-related complications but have birth outcomes similar to nonusers.¹⁰⁰ For these reasons, methadone maintenance has become the standard opioid replacement therapy during pregnancy.¹³⁵

Nonetheless, alternatives to methadone are being explored. Just as alternative opioid replacement strategies with buprenorphine have been introduced for opioid users in general, new strategies using buprenorphine in pregnancy are being tested. In one large trial, obstetric outcomes were similar after buprenorphine treatment compared with methadone, although more women in the buprenorphine arm dropped out of the study because they did not feel well during the induction of therapy.^{146,147} One group in Australia is using implantable naltrexone in pregnant patients after opioid detoxification.^{137,138}

The most significant acute neonatal complication of opioid use during pregnancy is the neonatal withdrawal syndrome (NWS), which is characterized by hyperirritability; GI dysfunction; respiratory distress; and vague autonomic symptoms, including yawning, sneezing, mottling, and fever.¹³⁵ Myoclonic jerks or seizures may also signify neurologic irritability. Withdrawing infants are recognizable by their extreme jitteriness despite efforts at consolation; ecchymoses and contusions may be found on the tips of their fingers or toes as a result of trauma from striking the sides of the bassinet. Approximately 50% to 90% of methadone, heroin, buprenorphine, and probably other chronic opioid-exposed newborns show some signs of withdrawal.^{100,146}

Opioid withdrawal symptoms typically occur within one week of birth. Heroin withdrawal usually occurs within the first 24 hours, but methadone and buprenorphine withdrawal usually occur within 2 to 3 days of age. The onset of methadone withdrawal is delayed because methadone has a larger volume of distribution and slower metabolism in the neonate and therefore an increased half-life. The onset and severity of methadone withdrawal may be related to absolute neonatal serum concentration or the rate of decline in concentration.^{83,168} In one study, methadone withdrawal occurred when the plasma concentration fell below 0.06 mg/mL.²⁶²

The onset and severity of symptoms may also be related to which opioid(s) as well as other licit and illicit substances were used; how much was used chronically; how much was used near the time of delivery; the character of the labor; whether analgesics or anesthetics were used; and the maturity, nutrition, and medical condition of the neonate.⁸⁰ Acute neonatal withdrawal symptoms generally last from days to weeks, but as many as 80% of infants have been reported to have recurrence of some symptoms such as restlessness, agitation, tremors, wakefulness, hyperphagia, colic, or vomiting for 3 to 6 months.⁵⁸ In general, the incidence and severity of withdrawal are thought to be greater from methadone than from either heroin or buprenorphine.¹³⁵ When methadone was compared with buprenorphine, buprenorphine-exposed infants

required lower total doses of morphine to control symptoms, had shorter courses of treatment, and had shorter hospitalizations overall.^{146,147}

From 5% to 7% of babies showing signs of withdrawal experience seizures, generally by 10 days after birth.¹²⁷ Seizures may be more likely after methadone withdrawal than after heroin withdrawal. These seizures do not necessarily predispose to idiopathic epilepsy; in one small study, children who had withdrawal seizures were without seizures and had normal neurologic examination findings and psychometric testing at one-year follow-up.⁸⁴

Treatment of withdrawal begins by providing a comforting environment: swaddling or tightly wrapping the infant, minimal handling or stimulation, and demand feeding. More severe symptoms may require pharmacologic therapy. The severity of withdrawal as measured by a standardized scoring scale determines the need for therapy; several scales are in use.^{100,185} In general, babies who are extremely irritable; have feeding difficulties, diarrhea, or significant tremors; or cry continuously are candidates for pharmacologic therapy.¹³⁵

Opioid agonists such as morphine, methadone, tincture of opium, and paregoric; sedative-hypnotic agents such as diazepam and phenobarbital; and clonidine have all been used both individually and in various combinations to treat withdrawal symptoms. Few well-controlled trials have evaluated the relative efficacy of the different interventions or examining long-term effects of therapy.^{234,235} Oral morphine is preferred to treat withdrawal symptoms because it is a short-acting pure opioid agonist, and the formulation has no additives.²⁴⁴ Clonidine and phenobarbital are beneficial as adjunctive therapies.

Opioid agonists may be more effective at preventing withdrawal seizures from heroin or methadone than from phenobarbital or diazepam.^{127,151} However, sedative-hypnotic agents are commonly used by heroin users or adults maintained on methadone, and sedative-hypnotic withdrawal seizures may contribute to the overall neonatal abstinence symptomatology. In this setting, there may be a role for phenobarbital.

Infants of opioid-using mothers have a two to three times increased risk for SIDS compared with control participants.^{152,153} The mechanism may be related to a decreased medullary responsiveness to CO₂, or the effect may be related to some condition of the postnatal environment.¹⁰⁰

Although young children born to opioid users do not seem to have significant differences in behavior compared to control participants, older children have increased learning problems and school dysfunction particularly related to behavior difficulties.³³⁷

Cocaine

Approximately 1% of pregnant women in the United States use cocaine at some time during their pregnancy.²²² The rate may be as high as 15% in certain populations,⁷⁷ and it is estimated that more than 100,000 infants born in the United States each year may be exposed to cocaine in utero.⁵⁶ The consequences of cocaine use during pregnancy have been extensively reviewed.^{131,241,283}

The incidence of abruptio placentae may be significant when related to acute cocaine use.²⁸⁷ Some uncommon perinatal problems include seizures, cerebral infarctions, and intraventricular hemorrhage.^{61,241}

Cocaine use is significantly related to decreases in gestational age, birth weight, length, and head circumference, although these growth parameters generally correct by several years of age.²⁸³ In addition, these growth effects are exacerbated by concomitant alcohol, tobacco, and opioid use.²⁸³ Good prenatal care can mitigate many of these adverse effects of cocaine.^{193,252,337}

Significant congenital malformations were reported among some infants who were exposed to cocaine in utero, specifically genitourinary malformations, cardiovascular malformations, and limb-reduction defects.^{49,104} However, in one large population-based study, there was no increase in the incidence of malformations.²⁰³

Teratogenic effects are observed in animal models of in utero cocaine exposure. Decreased maternal and fetal weight gain and an increased frequency of fetal resorption were demonstrated in rats⁹⁶; sporadic physical anomalies are also observed.⁶³ Teratogenic effects similar to those observed in humans were reported in mice, including bony defects of the skull, cryptorchidism, hydronephrosis, ileal atresia, cardiac defects, limb deformities, and eye abnormalities.^{101,194,195,213} Cocaine caused hemorrhage and edema of the extremities, and, subsequently, limb-reduction defects in rats when administered during midgestation in the postorganogenic period.³²⁴

The perinatal effects of cocaine are probably mediated through a vascular mechanism. Cocaine administration in the pregnant ovine model causes increased uterine vascular resistance, decreased uterine blood flow, increased fetal heart rate and arterial blood pressure, and decreased fetal PO₂ and O₂ content.^{22,333} Similar effects are reported in rats.²³⁷ Fetal hypoxia may cause rupture of fetal blood vessels and infarction in developing organ systems such as the genitourinary system^{60,213,293} or the CNS.^{57,82,325} Hyperthermia or direct effects of cocaine in the fetus may exacerbate these effects.⁴⁰

Limb-reduction defects similar to those attributed to cocaine can be produced after mechanical clamping of the uterine vessels.^{40,326} A developing concept is that after vasospasm and ischemia, reperfusion occurs with the generation of oxygen free radicals and subsequent injury.^{333,334}

Despite the reported malformations and a possible mechanism, neither the human epidemiology nor the effects observed in animal models suggest a specific teratogenic syndrome. The risk of a significant malformation from prenatal cocaine exposure is low, but the effect, if one occurs, may be severe.^{41,89,104}

One of the greatest concerns about prenatal cocaine exposure is the potential adverse effect on the developing child, and this is an intensive area of epidemiologic research. The most common findings in early infancy are lability of behavior and autonomic regulation; decreased alertness and orientation; and abnormal reflexes, tone, and motor maturity; however, many studies show no effect, especially after controlling for confounding variables.^{95,283} For some children, effects may manifest in later infancy as difficulty with information processing and learning. For school-age children, observed cognitive deficits may also be related to the home environment even for children who showed some of the typical neonatal behaviors.^{102,283} Nonetheless, there is evidence of impairment in modulating attention and impulsivity, which makes handling unfamiliar, complex, and stressful tasks more difficult,^{209,283} and these effects are also observed in animal models of prenatal cocaine exposure.^{89,123,182,296}

The mechanism of neurotoxicity has not been specifically elucidated. As described earlier, for many of the maternal and fetal physical defects, cocaine may have direct toxicity or, alternatively, effects may be mediated through hypoxia or oxygen free radicals. Because cocaine interferes with neurotransmitter reuptake, it is likely that cocaine also disrupts normal neural ontogeny by interfering with the trophic functions of neurotransmitters on the developing brain, in particular dysfunction of signal transduction via the dopamine D₁ receptor.^{123,182,199,208} These mechanisms may be more important in the etiology of neurobehavioral effects.

BREASTFEEDING

In the United States, breastfeeding is the recommended method of infant nutrition because it offers nutritional, immunologic, and psychological benefits without additional costs. Many women use prescription and nonprescription xenobiotics while breastfeeding and are concerned about the possible ill effects on their infants of these xenobiotics in the breast milk. This concern extends to the possible exposure of infants to occupational and environmental xenobiotics via breast milk.^{259,278} The response to many of these concerns can be determined by the answer to the following question: Does the risk to an infant from a xenobiotic exposure via breast milk exceed the benefit of being breastfed?¹⁷⁶

Pharmacokinetic factors determine the amount of xenobiotic available for transfer from maternal plasma into breast milk; only free xenobiotic can traverse the mammary alveolar membrane. Most xenobiotics are transported by passive diffusion. A few xenobiotics, such as ethanol and lithium, are transported through aqueous-filled pores. The factors that determine how well a xenobiotic diffuses across the membrane are similar to those for other biologic membranes such as the placenta: MW, lipid solubility, and degree of ionization.

Large-molecular-weight xenobiotics, such as heparin and insulin, do not pass into breast milk. Lipid solubility is important not only for diffusion but also for xenobiotic accumulation in breast milk because breast milk is rich in fat, especially breast milk that is produced in the postcolostral period (~ 3–4 days postpartum). With a pH near 7.0, breast milk is slightly more acidic than plasma. Consequently, xenobiotics that are weak acids in plasma exist largely as ionized molecules and cannot be easily transported into milk. Conversely, xenobiotics that are weak bases exist in plasma largely as nonionized molecules and are available for transport into breast milk. In breast milk, ionization of the weak base xenobiotics occurs, and the xenobiotics are concentrated as a result of ion trapping. In other words, xenobiotics that are weak bases may concentrate in breast milk. Whereas sulfacetamide (pK_a of 5.4, a weak acid) has a concentration in plasma 10 times its concentration in breast milk, sulfanilamide (pK_a of 10.4, a weak base) is found in equal concentrations in both plasma and breast milk.¹⁷⁶

The net effect of these physiologic processes is expressed in the milk-to-plasma (M/P) ratio. Xenobiotics with higher M/P ratios have relatively greater concentrations in breast milk. The M/P ratio does not, however, reflect the absolute concentration of a xenobiotic in the breast milk, and a xenobiotic with a high M/P ratio is not necessarily found at a high concentration in the breast milk. For example, morphine has an M/P ratio of 2.46 (is concentrated in breast milk), but only 0.4% of a maternal dose is excreted into the breast milk.²¹ In general, for most pharmaceuticals, approximately 1% to 2% of the maternally administered dose is presented to the infant in breast milk.¹⁷⁶

The M/P ratio has several limitations. It does not account for differences in xenobiotic concentration that may result from (1) repeat or chronic dosing, (2) breastfeeding at different times relative to maternal xenobiotic dosing, (3) differences in milk production during the day or even during a particular breastfeeding session, (4) the time postpartum (days, weeks, or months) when the measurement is made, and (5) maternal disease.

While being cognizant of the limitations, a spot breast milk xenobiotic concentration or a concentration estimate based

on the M/P ratio allows a simplistic estimation of the quantity of xenobiotic to which an infant is exposed, assuming a constant breast milk concentration:

$$\text{Infant dose} = \text{Breast milk concentration} \times \text{Amount consumed}$$

The effect of this dose on the infant depends on the bioavailability of the xenobiotic in breast milk, the pharmacokinetic parameters that determine xenobiotic concentrations in the infant, and the infant's receptor sensitivity to the xenobiotic. These parameters are often different in neonates than in adults and may lead to xenobiotic accumulation; generally, absorption is greater, but metabolism and clearance are reduced.²⁰ These effects are exaggerated in premature infants.^{247,256} The amount of most xenobiotics delivered to infants in breast milk is usually adequately metabolized and eliminated.¹⁷⁶

Many of the above considerations are theoretical, and the number of specifically contraindicated xenobiotics is quite small.¹⁴ Published guidelines on the advisability of breastfeeding during periods of maternal therapy are generally based on the expected effects of full doses in the infant or on case reports of adverse occurrences. Interestingly, when the reports of adverse effects were reviewed, 37% of cases were in infants younger than 2 weeks old, 63% were in infants younger than 1 month old, and 78% were in infants younger than 2 months old; 18% were in infants 2 to 6 months old; and only 4% were in infants older than 6 months.¹⁶ It seems, therefore, that adverse effects are most likely to be observed in the first few weeks of life, when an infant's metabolic capacity is significantly less than that of an older infant, child, or adult.^{9,79}

For most xenobiotics, a risk-to-benefit analysis must be made. For example, lithium is transferred in breast milk and may lead to measurable, although subtherapeutic, serum concentrations in a breastfed infant. Although the effects of such exposure to lithium are unknown, many practitioners believe that the benefit of treating a mother's bipolar illness outweighs the potential risk to the infant.^{176,277} There may also be a small increased risk of carcinogenicity associated with exposure to some environmental xenobiotics through breast milk.²⁵⁹

Similarly, the breastfed infant of a woman who smokes is exposed to nicotine and other tobacco constituents, both by inhalation and via breast milk. Although this child may be at increased risk for respiratory illness as a result of exposure to tobacco smoke, some of the risk may be reduced by breastfeeding.^{14,254}

In most cases, women do not need to stop breastfeeding while using pharmaceuticals, such as most common antibiotics. However, "compatibility" with breastfeeding is generally based on a lack of reported adverse effects, which may reflect limited clinical experience with a particular xenobiotic in breastfeeding patients. Therefore, in the setting of limited information, exposure to a xenobiotic through breast milk should be regarded as a small potential risk, and the infant should receive appropriate medical follow-up. Not all "compatible" medications are safe in all situations. For instance, phenobarbital can produce CNS depression in an infant if the mother's serum concentration is in the high therapeutic or supratherapeutic range, which often occurs while dosage adjustments are being made. Such a concentration may or may not produce CNS depression in the mother. Nalidixic acid, nitrofurantoin, sulfapyridine, and sulfisoxazole, although generally safe, can cause hemolysis in a breastfed infant with glucose-6-phosphate dehydrogenase deficiency.

When women use substances postpartum, there is delivery of some xenobiotic to the infant via breast milk, and there are rare cases reports of infants experiencing adverse effects.⁵⁹ Because of these possible direct effects on the baby, as well as the detrimental effects on the physical and emotional health of the mother and on the caregiving environment, the use of substances such as cocaine, methamphetamine, and heroin during the breastfeeding period is discouraged, and women actively using substances are discouraged from breastfeeding.¹⁴ However, women who are or have been abstinent from substance use and are participating in a treatment program are generally encouraged to breastfeed their infants.^{6,176}

Although ethanol is not specifically contraindicated for breastfeeding mothers, decreased milk production and adverse effects in infants are noted with maternal consumption of large amounts of ethanol.

Questions sometimes arise regarding possible lead exposure during breastfeeding. Lead crosses into breast milk from blood and is the most likely source of lead exposure for most breastfeeding infants.¹⁸⁹ Approximately 1% of US women between the ages of 15 and 49 years have blood lead concentrations greater than 5 µg/dL.⁹⁴ Some estimates suggest that breast milk concentrations are less than 3% of the maternal blood lead; therefore, if the maternal lead concentration is 5 µg/dL, then the amount of lead delivered to the infant could be 1.5 µg/L of breast milk.^{118,164} This represents a relatively small exposure. In a sample of breastfed babies from one US city, the mean infant lead concentration was less than 3 µg/dL, the highest concentration was 8 µg/dL, and only 7.8% of values were greater than 5 µg/dL.¹⁸⁹ The current consensus is that the benefits of breastfeeding outweigh the relatively small exposure to lead in breast milk.³²⁹ Blood lead screening for most women is not recommended.

There are, however, some subpopulations of pregnant women at increased risk of elevated environmental lead exposure for whom blood lead screening is recommended. Risk factors for significant lead exposure in pregnant women include recent immigration, pica practices, occupational exposure, poor nutritional status, culturally specific practices such as the use of traditional remedies or imported cosmetics, and the use of traditional lead-glazed pottery for cooking and storing as well as those involved with renovation or remodeling in older homes.⁹⁴

All women should have an assessment of risk for environmental lead exposure. Women at increased risk should have blood lead screening. When possible, pregnant and postpartum women with blood lead concentrations of 5 µg/dL or higher should be removed from occupational or environmental lead sources and discouraged from practices or activities that result in increased exposure.⁹⁴ In addition, some evidence suggests that dietary supplementation of calcium can reduce the mobilization of lead in postpartum women.¹²⁶ In cases of elevated maternal lead concentrations, decisions regarding breastfeeding should be made on an individual basis.

In 2007, after the death of a breastfeeding 13 day-old infant whose mother was using codeine, the US FDA issued a public health advisory regarding the use of codeine by breastfeeding women.³¹⁵ In the initial case, the mother was found to be compound heterozygous for a CYP2D6*2A allele and a CYP2D6*2x2 gene duplication and therefore an “ultrametabolizer” of codeine.¹⁵⁹ In other words, codeine was metabolized to morphine at an exaggerated rate, and the infant ingested a high dose of morphine via the breast milk. The ultrametabolizer phenotype is present in up to 10% of whites and up to 30% of Ethiopians, North Africans, and Saudi Arabians.³¹⁵ In addition, both the mother and the infant were homozygous for the UGT2B7*2 allele, which leads to elevated concentrations of morphine-6-glucuronide, an active metabolite.

Another decreased-function gene variant of ABCB1 may also have a role in this codeine toxicity. ABCB1 codes for a P-glycoprotein involved in transporting morphine out of the CNS. Decreased gene function would lead to increased accumulation of morphine in the CNS and potentially increased toxicity.²⁹⁰

Decisions on breastfeeding should be made with the informed involvement of the woman; her physicians; and when necessary, a consultant with special expertise in this field. Guidelines are available from several sources.^{45,176}

TOXICOLOGIC PROBLEMS IN NEONATES

Physiologic differences between adults and newborn infants affect xenobiotic absorption, distribution, and metabolism.^{20,154,321} Appropriate administration of xenobiotics to newborn infants therefore requires an understanding of the appropriate developmental state for medication dosing and pharmacokinetics. Even so, approximately 8% of all medication doses administered in neonatal intensive care units (NICUs) may be up to 10 times greater or lesser than the dose ordered,⁶⁷ and as many as 30% of newborns in NICUs may sustain adverse drug effects, some of which may be life threatening or fatal.²¹ Pharmacokinetic differences between adults and newborns may account for some cases of unanticipated xenobiotic toxicity that occur in newborn infants.

Gastrointestinal absorption of xenobiotics in neonates is generally slower than in adults.^{20,154,321} This delay may be related to decreased gastric acid secretion, decreased gastric emptying and transit time, and decreased pancreatic enzyme activity. The GI environment of newborns and young infants may allow the growth of *Clostridium botulinum* and the subsequent development of infantile botulism (Chap. 41). Infantile botulism has been reported in infants several weeks of age.^{139,308}

Although it is uncommon, cutaneous absorption of xenobiotics may be a route of toxic exposure in a newborn.^{92,268} Aniline dyes used for marking diapers are absorbed, causing methemoglobinemia,²⁶⁸ and contaminated diapers were responsible for one epidemic of mercury poisoning.²⁵ The absorption of hexachlorophene antiseptic wash has led to neurotoxicity with marked vacuolization of myelin seen microscopically.^{172,204,288} The dermal application of antiseptic ethanol has caused hemorrhagic necrosis of the skin of some premature infants. Iodine antiseptics have led to hypothyroidism in mature newborns.⁵³ An increased potential for absorption and toxicity has followed the application of corticosteroids^{109,266} and boric acid⁹⁰ to the skin of children with cutaneous disorders.

Other routes of exposure have led to clinical poisoning. Several children aspirated talcum powder and died.^{46,220} Inhalation of mercury from incubator thermometers may be a potential risk.¹³ One child died after the ophthalmic instillation of cyclopentolate hydrochloride.²⁷

Because of differences in total body water and fat compared with adults, the distribution of absorbed xenobiotics may differ in neonates.^{20,154,321} Water represents 80% of body weight in a full-term baby compared with 60% in an adult. Approximately 20% of a term baby's body weight is fat compared with only 3% in a premature baby. The increased volume of water means that the volume of distribution for some water-soluble xenobiotics, such as theophylline and phenobarbital, is increased.

Protein binding of xenobiotics is reduced in newborns compared with adults: the serum concentration of proteins is lower, there are fewer receptor sites that become saturated at lower xenobiotic concentrations, and binding sites have decreased binding affinity.^{20,154,321} Protein binding has potential relevance with respect to bilirubin, an endogenous metabolite that at very high concentrations can cause kernicterus; bilirubin competes with exogenously administered xenobiotics for protein binding sites. In vitro, certain xenobiotics, such as sulfonamides and ceftriaxone, displace bilirubin from protein receptor sites, which might increase the risk of kernicterus, although this has not been clinically demonstrated.

Conversely, bilirubin may itself displace other xenobiotics, such as phenobarbital or phenytoin, leading to increased plasma xenobiotic concentrations.

Newborn infants have decreased hepatic metabolic capacity compared with adults, which may lead to xenobiotic toxicity.^{20,154} For example, caffeine, used in the treatment of neonatal apnea, has an extremely prolonged half-life in newborns because CYP1A2 has only 5% of the normal adult activity.²⁰ Except for CYP1A2, most of the CYP isoenzymes reach approximately 25% of adult activity in newborns by about 1 month of age.

Two syndromes related to immature metabolic function are described. The “gasping baby syndrome,” characterized by gasping respirations, metabolic acidosis, hypotension, CNS depression, convulsions, kidney failure, and occasionally death, is attributed to high concentrations of benzyl alcohol and benzoic acid in the plasma of affected infants.^{12,48,110} Benzyl alcohol, a bacteriostatic, was added to IV flush solutions and accumulated in newborns after repetitive doses. The high concentrations of benzoic acid could not be further metabolized to hippuric acid by the immature liver. Immature glucuronidation in neonates is responsible for the “gray-baby syndrome” after high doses of chloramphenicol (Chaps. 32, 55, and 57).¹³⁰

The umbilical vessels are a common site of vascular access in sick neonates. Because blood drains into the portal vein, it is possible that IV medications experience a “first-pass” effect, although whether this route of xenobiotic administration affects metabolism or clearance has not been well studied. Most functions of the kidney, including glomerular filtration rate (GFR) and tubular secretion, are relatively immature at birth²⁰; the GFR of a newborn is approximately 30% of that of an adult. Xenobiotics such as aminoglycosides and digoxin are excreted unchanged by the kidney and therefore depend on glomerular filtration for clearance. Dosing of these xenobiotics in a newborn must account for these differences.

An interesting association has been made periodically over the years between the use of erythromycin, particularly in the first 2 weeks of life, and idiopathic hypertrophic pyloric stenosis.^{66,132,196,271,297} Although erythromycin is known to interact with motilin receptors in the antrum of the stomach, no specific etiology has been defined.¹²⁴

Very little information is available to guide clinicians in the management of xenobiotic poisoning in newborn infants. Cutaneous absorption is probably already complete by the time toxicity is noted, although further exposure may be prevented. GI decontamination is not generally performed in neonates, and neonates may be at increased risk of fluid, electrolyte, and thermoregulatory problems after gastric lavage or the use of cathartic agents. Multiple-dose activated charcoal was used in a 1.4-kg, 2 week-old premature infant to treat iatrogenic theophylline toxicity.²⁸⁴ Hemodialysis, hemoperfusion, and exchange transfusion can be used in neonates to treat xenobiotic toxicity (Chaps. 10 and 32).

SUMMARY

- Human embryos and fetuses are exposed to xenobiotics through the placenta of the pregnant woman; the neonates are exposed to xenobiotics via breast milk.
- Xenobiotic effects on developing humans include both congenital malformations as well as neurobehavioral abnormalities, which may manifest later in a child’s or adult’s life.
- The use of xenobiotics in a pregnant or breastfeeding woman is a complex area of medical practice and presents clinicians with potentially difficult management decisions regarding the benefit of therapy to the mother and the risk to the mother or fetus of xenobiotic exposure. In general, the goal is to optimize benefit to the mother while minimizing the risk to the fetus. In almost all cases, the primary approach is to fully and appropriately treat the mother.
- Appropriate management of many of the potential problems is facilitated by the coordinated efforts of obstetricians, perinatologists, neonatologists, pediatricians, and toxicologists.

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32 PEDIATRIC PRINCIPLES

Jeffrey S. Fine

Phone calls to poison centers regarding childhood exposures to xenobiotics are more frequent than those regarding any other age group. Because of this and the frequent role of poisoning as a cause of pediatric injury, pediatricians have been active for many years in helping to establish and promote the study of medical toxicology, as well as in establishing and supporting the use of regional poison centers. Although the basic approaches to the medical management of toxicologic problems outlined in Chaps. 3 and 4 are generally applicable to both children and adults, issues such as child abuse by poisoning are of particular concern. This chapter provides a perspective on the application of generally accepted toxicologic principles for children.

EPIDEMIOLOGY

To analyze the problem of pediatric poisoning, it is necessary to understand the magnitude of the problem. When assessing the impact of a particular type of injury such as poisoning, epidemiologists examine multiple parameters, such as exposure, morbidity, mortality, and cost, to measure the effect of the injury; however, these parameters are difficult to measure accurately. An important source for information on the extent and effects of poisoning exposures in the United States is the American Association of Poison Control Centers (AAPCC). Every year, the AAPCC compiles standardized data collected from poison centers throughout the United States; the 2012 annual review includes information submitted by 57 poison centers. In the following discussion, comments on AAPCC data refer to cumulative information from the previous five published reports covering the years 2007 to 2011 ([Chap. 136](#)).

Each year, the AAPCC reports approximately 1.2 million potentially toxic exposures in children and adolescents from birth to 19 years, which account for 66% of all reported exposures. In fact, children younger than age 6 years account for 53% of all reported exposures. Of the reported exposures in children and adolescents, children younger than age 6 years account for 79%, children between 6 and 12 years of age account for 10%, and adolescents between 13 and 19 years of age account for 11%. Girls represent 47% of the reported poisoning exposures in young children and 54% of the reported exposures among adolescents.

Among the AAPCC reported xenobiotic exposures in children younger than age 6 years, 99% are labeled unintentional. In contrast, only 44% of the reported adolescent exposures are unintentional; 50% of exposures in adolescents are labeled intentional, mostly resulting from substance use or suicide attempts. The high frequency of intentional poisoning in adolescents has been reported by others.^{34,183,184} The remaining 6% of adolescent exposures include adverse drug events and other miscellaneous or unknown causes. Differences in the reasons for exposure between young children and adolescents account for differences in the outcomes of these exposures.

Approximately 125,000 xenobiotic exposures each year are classified by the AAPCC as therapeutic errors, accounting for approximately 6% of exposures in children younger than 6 years of age, 24% in children 6 to 12 years of age, and 11% in adolescents. An additional 4700 exposures each year are classified as adverse drug reactions, which account for approximately 0.4% of exposures in children younger than 6 years of age, 2% in children 6 to 12 years of age, and 3% in adolescents.

[Table 32–1](#) shows the leading causes of reported exposures in children and adolescents. According to the AAPCC, approximately 54% of childhood exposures are to xenobiotics that are commonly found around the house, such as cleaning products, cosmetics, plants, hydrocarbons, and insecticides; approximately 46% are to pharmaceuticals. In older children and adolescents, approximately 49% of exposures are to nonpharmaceutical xenobiotics, and approximately 51% are to pharmaceuticals. Most hospitalizations and deaths in both groups are caused by pharmaceuticals.

TABLE 32–1. Average Annual Xenobiotic Exposures Reported to the American Association of Poison Control Centers (2007–2011)^{a,b}

<i>Age Younger Than 6 Years</i>	
<i>Category</i>	<i>Number of Exposures</i>
Cosmetics and personal care products	166,950
Cleaning substances	115,268
Analgesics	110,325
Topical preparations	84,882
Vitamins	47,080
Cough and cold preparations	42,426
Insecticides, pesticides, and rodenticides	40,793
Antihistamines	39,926
Plants	36,789
Gastrointestinal preparation	33,697
<i>Ages 6–19 Years</i>	
<i>Category</i>	<i>Number of Exposures</i>
Analgesics	32,953
Cosmetics and personal care products	16,011
Cough and cold preparations	13,662
Cleaning substances	13,483
Bites and envenomations	13,196
Antihistamines	11,142
Sedative–hypnotics	11,126
Stimulants and street drugs	10,295
Antidepressants	9014
Pesticides	7448

^aSee Chap. 136 for references and discussion. ^bDoes not include the American Association of Poison Control Centers' category "foreign bodies."

Table 32–1 lists the most common reported exposures, but not all of these exposures lead to serious morbidity and mortality (Table 32–2). For example, children frequently ingest cosmetic products, so the number of reported exposures is large, but most cosmetics manufactured in the United States are nontoxic. Clinically significant poisoning is unusual in children younger than age 6 months but may result from the inadvertent administration of an incorrect drug or drug dose by a parent,^{60,123} intentional administration of a drug by a parent or sibling,^{43,74} or passive exposure (eg, to the smoke of “crack” cocaine or phencyclidine).^{16,73,124,158,192} Any poisoning in a child younger than one year of age should be carefully evaluated for possible child abuse or neglect (see later discussion).⁷⁴

TABLE 32–2. Xenobiotics Responsible for Significant Pediatric Poisoning Morbidity and Mortality

Category	Younger Than 6 Years Old						13–19 Years Old	
	Reported Major Effects ^a		Reported Deaths ^b		Reported Deaths 2007–2011 ^b		Reported Deaths 2007–2011 ^b	
	Number	%	Number	%	Number	%	Number	%
Alcohol	53	2	9	7	7	5	17	5
Analgesics	119	5	8	7	31	22	130	41
Anticonvulsants	106	5	4	3	1	1	1	<1
Antidepressants and antipsychotics	182	8	9	7	6	4	37	12
Antihistamines and cough and cold medications	92	4	8	7	8	6	11	3
Batteries	7	<1	0	0	6	5	0	0
Bites and envenomations	100	4	0	0	3	2	1	<1
Carbon monoxide	42	2	18	15	25	17	16	5
Cardiovascular agents	182	8	7	6	6	4	13	4
Cleaning agents and chemicals	297	13	10	8	9	6	3	1
Hydrocarbons	168	7	5	4	16	11	13	4
Insecticides, pesticides, and rodenticides	123	5	7	6	5	3	2	<1
Iron	52	2	7	6	0	0	0	0
Sedative-hypnotics	151	7	0	0	0	0	11	3
Stimulants and street drugs	84	4	1	1	5	3	40	13
Theophylline	38	2	3	2	0	0	0	0
Other or unknown	474	21	26	21	15	10	20	6
Totals	2270		122		143		315	

^aData from Litovitz T, Manoguerra A: Comparison of pediatric poisoning hazards: an analysis of 3.8 million exposure incidents. *Pediatrics*. 1992;89:999–1106. ^bData from American Association of Poison Control Centers (AAPCC), 2007 to 2011. ^cMajor effect is defined as life-threatening signs and symptoms, or significant residual disability or disfigurement. ^dThe AAPCC does not report specific outcomes, other than death, by age, for individual xenobiotics; consequently, the number of major effects cannot be calculated from annual reports.

Several typical characteristics associated with ingestions by toddlers differentiate them from ingestions by adolescents or adults: (1) they are without suicidal intent; (2) there is usually only one xenobiotic involved; (3) the xenobiotics are usually nontoxic; (4) the amount is usually small; and (5) toddlers usually present for evaluation relatively soon after the ingestion is discovered, generally within 1 to 2 hours. As many as 30% of children who experience one ingestion will experience a repeat ingestion; adolescents may be particularly prone to recidivism.^{61,81} Children who ingest poisons may also be at a greater risk for other types of injuries.^{14,51}

The peak age for childhood poisoning is between 1 and 3 years.²⁹ Unintentional ingestion is unusual after age 5 years, although when it occurs, it can sometimes be the result of mistaken consumption of a xenobiotic from a mislabeled container.²⁶ Between the ages of 5 and 9 years, poisoning may result from intrafamilial stress or suicidal intent. After age 9 years and through adolescence, overdose or poisoning frequently results from either suicidal gestures and attempts or from the adverse effects of alcohol or substance use. Unintentional poisonings are largely preventable (Chap. 136).

Because many children are exposed to nontoxic xenobiotics or to only small amounts of potentially toxic xenobiotics, the proportion of children and adolescents who experience significant morbidity is small (Table 32–3). However, because there are millions of such exposures each year, the number of children and adolescents who experience at least moderate effects is large.

TABLE 32–3. Outcome of Reported Pediatric Xenobiotic Exposures (2007–2011)^a

Age (years)	Effects (% of Reported Exposures) ^{b,c}			
	Minor or None	Moderate	Major	Death
0–5	99	0.86	0.07	0.004
6–12	97	3	0.15	0.007
13–19	86	13	1.3	0.05
All children and adolescents 0–19	98	2	0.20	0.009

^aSee Chapter 136 for references and discussion. ^bApproximate percentage. ^cMinor is minimal signs and symptoms, often not requiring therapy or had no follow-up; moderate is more pronounced, prolonged, or systemic signs and symptoms, often requiring therapy; and major is life-threatening signs and symptoms.

Another source of data related to poisoning morbidity is the National Injury Surveillance database maintained by the US Centers for Disease Control and Prevention (CDC), which provides information on emergency department (ED) visits and hospitalizations.³⁰ For the period 2001 to 2011, the CDC estimates approximately 59,000 ED visits (246 per 100,000) and 3900 hospitalizations (~7%) per year for children 0 to 5 years who are exposed to a xenobiotic. Children 6 to 12 years account for approximately 11,000 ED visits (40 per 100,000) and 1000 hospitalizations (9%) per year, and adolescents 13 to 19 years old account for approximately 100,000 ED visits (349 per 100,000) and 21,000 hospitalizations (21%) per year. Overall, approximately 80% of the patients hospitalized are adolescents, and approximately 75% of those cases are the result of intentional poisonings.

These numbers are consistent with estimates of 100,000 to 170,000 ED visits for poisoning and overdose per year, or approximately 300 to 840 visits per 100,000 for children younger than 5 years of age and 290 to 360 per 100,000 visits for adolescents. Hospitalization rates are 10% to 20%.^{28,29,52,59,114,180}

As mentioned, adolescents are more frequently hospitalized than children after exposure to xenobiotics.⁶¹ This may be a result of the need for either medical management or psychiatric hospitalization. The peak age for hospitalizing young children exposed to xenobiotics is between 1 and 3 years, reflecting the peak age of exposure. Whereas among hospitalized children younger than age 2 years, exposure to nonpharmaceutical xenobiotics is more common, children older than age 2 years and adolescents are more commonly exposed to pharmaceuticals.^{52,61,183}

Although the AAPCC reports overall outcome related to age, it does not generally stratify outcome of exposure to individual xenobiotics by age. In a multiyear review published in 1992, the AAPCC reported the xenobiotics that caused the greatest number of major and fatal effects in children younger than 6 years old.¹⁰⁵ Table 32–2 lists the xenobiotics causing significant morbidity and mortality. Other reports of hospitalized patients include a similar distribution of xenobiotics that cause significant morbidity.^{8,31,45,197} However, in rural areas of many developing countries, kerosene and pesticides are the leading causes of xenobiotic-related hospitalizations, and the spectrum of pharmaceutical exposures is often different^{1,2,110,122,128} (Chap. 137).

Poisoning accounts for approximately 2% of childhood and 7% of adolescent injury-related deaths in the United States.³⁰ Based on information from death certificates filed in state vital statistics offices as well as demographic information provided by funeral directors, the CDC reports 1123 poisoning deaths in children younger than 6 years of age from 1999 to 2010 for an average of about 94 per year. These deaths represent approximately 10% of the reported poisoning fatalities for all children and adolescents for those years and a 79% decrease from the 456 deaths reported by the CDC in 1959.²⁹ There may be several factors responsible for this decrease. Some of the difference may be related to improved poisoning prevention strategies such as child-resistant closures or to improved medical care. In addition, some industrial or pharmaceutical products that were previously found around the home may have been replaced with less toxic products or been reformulated at safer concentrations. It is also possible that there may have been a decrease in reporting (Chap. 136).

Forty-seven percent of the AAPCC-reported childhood fatalities result from unintentional ingestions; 20% are from environmental exposures, mostly carbon monoxide poisoning; 12% are caused by therapeutic errors and adverse reactions; and 10% are malicious. The remaining 11% have miscellaneous causes or are unknown. In contrast, 50% of AAPCC-reported adolescent fatalities are the result of suicide, and 30% follow abuse or misuse of substances; only 2% are related to environmental exposures, and only 2% are caused by medication errors and adverse reactions; the remaining 16% have miscellaneous or unknown causes.

Although the AAPCC data provide a remarkable amount of epidemiologic information, there are questions about the accuracy of the data.^{71,72,190} For example, as mentioned earlier, whereas the CDC reported 1123 poisoning-related deaths in children younger than 6 years of age from 1999 to 2010, the AAPCC reported 409 for those same years based on voluntary calls. Some of the differences may be related to methods of ascertainment. Nonetheless, there is recognition that many significant poisonings are not reported to poison centers. Physicians managing “common” toxicologic problems may

not feel the need for the assistance of a local or regional poison center and may not feel compelled to participate in the reporting process. Therapeutic misadventures may also go unreported. In Rhode Island, only 45 of 369 poisoning deaths were reported to the regional poison center¹⁰³ (Chap. 136).

The most notable difference between the xenobiotics listed in Table 32–2 and studies from the 1960s and 1970s is that salicylates are no longer a leading cause of reported poisoning morbidity and mortality.^{37,42} This change may be related to federal regulations requiring child-resistant closures as well as to the decreased use of aspirin for use in children after a now unproven association between Reye syndrome and aspirin was reported (Chap. 39).^{19,36,79,125,144}

There are some significant etiologic differences between children and adolescents (Table 32–1), particularly with regard to the lethality of xenobiotics. For 2007 to 2011, the xenobiotics causing the greatest number of childhood deaths were analgesics, carbon monoxide, cleaning agents and chemicals, and antihistamines and cough and cold preparations, which together account for 51% of all reported poisoning deaths. The xenobiotics causing the greatest number of adolescent deaths were analgesics, stimulants and street drugs, and antidepressants, which together account for 66% of reported poisoning deaths.

With respect to AAPCC-reported analgesic-related deaths, there are significant differences between children and adolescents for this population of exposed individuals. For children younger than 6 years, opioids accounted for 94% of the analgesic-related deaths (methadone, 52%; oxycodone or hydrocodone, 26%; fentanyl, 10%; and morphine, 10%). The high frequency of childhood exposures to these xenobiotics has been identified as a significant consequence of both the therapeutic and illicit use of prescription opioid analgesics.¹¹ These fatalities were related to unintentional exposures in 48% of the children, malicious exposures or intentional misuse in 23%, and therapeutic errors in 6%; the reasons in the rest of the cases were unknown.

In adolescents, opioids accounted for 55% of the analgesic-related deaths (methadone, 22%; oxycodone or hydrocodone, 16%), and acetaminophen (APAP)-opioid combination products accounted for 13% of the deaths. Forty-one percent of the fatalities were the result of abuse or misuse, and 47% were suicides.

Hydrocarbon-related fatalities occur in both children and adolescents; whereas the hydrocarbon deaths of young children generally result from unintentional aspiration after ingestion, almost all of the hydrocarbon-related deaths in adolescents are related to inhalational abuse of hydrocarbons such as trichloroethanes or chlorofluorocarbons.

Poisoning also has an economic cost. Charges for hospitalized patients range from \$2000 to \$10,000, depending on the length of stay and outcome.^{89,176,197} In a large-scale economic analysis of the cost of injury in the United States in 1985, the estimated average lifetime cost was \$495 per child and \$10,839 per adolescent or young adult injured or killed by poisoning for a total lifetime cost of approximately \$140 million for children and \$1.5 billion for adolescents and young adults.¹³⁷ According to the CDC, for 2005, the average combined medical and work loss cost for children and adolescents treated and released from the ED after an unintentional injury is approximately \$714 and approximately \$1390 after an intentional injury for a total cost of approximately \$88 million. The average cost for a hospitalized patient is approximately \$9000 for a total cost of approximately \$358 million. For fatal injuries, the average medical cost is approximately \$4800, but the average work loss cost is \$1.5 million for a total cost of \$1.5 billion.³⁰

BEHAVIORAL, ENVIRONMENTAL, AND PHYSICAL ISSUES

An oversimplification of the etiology of childhood poisonings would be the formulation that unobserved toddlers exploring their environment inadvertently ingest xenobiotics. However, this approach ignores the complex interplay of factors that may contribute to some ingestions in children.

One approach to understanding injury causation that can be applied to poisoning uses an infectious diseaselike model.⁷⁰ According to this model, there are three interacting factors: host, agent, and environment. These factors interact during three phases: preinjury, injury, and postinjury. The factors themselves contribute to the likelihood, nature, magnitude of, and host response to an injury.

During the preinjury phase, there is an interaction of the host, agent, and environment. Under the proper circumstances, an injury may occur. Modification of these factors may help to prevent an injury. For example, if a 2 year-old child finds two pills on a bedside table, there is a fair chance the child will ingest the tablets. However, storing the pills out of reach of the child can prevent the ingestion.

The injury phase covers both the ingestion and the initial pathophysiologic host response. Again, particular factors determine the nature and extent of injury. Continuing the example, if the two pills are 325-mg APAP tablets, the ingestion will not lead to injury. However, if the pills are 0.2-mg clonidine tablets, there is a high likelihood of toxicity.

The postinjury phase is concerned both with the ongoing host response and the medical management of the patient who has been poisoned. In this phase, it would be determined whether the 2 year-old child with a clonidine ingestion manifests signs of toxicity, such as coma or hypotension; whether the child requires treatment with activated charcoal (AC), intravenous (IV) fluid, or naloxone; and whether the child requires hospital admission.

This paradigm is only a model; in reality, it is often difficult to examine any individual factor independently, and the

relative contributions of these factors are not well defined. Nonetheless, consideration of the individual factors of host, agent, and environment allows us to focus on several relevant aspects of poisoning in children.

Childhood and adolescence are times of tremendous growth and development.²⁰³ Some of these physical and social changes place children and teenagers at increased risk for poisonings. By 7 months of age, an infant sitting up can pivot to grab an object; by 9 to 10 months of age, most infants can creep and crawl; by 15 months of age, most toddlers are walking quite competently and eagerly exploring. Between 9 and 12 months of age, a skillful pincer grasp with the thumb and forefinger develops that allows the child to pick up small objects. Throughout this period, one of the child's primary sensory experiences is sucking on or gumming objects that are placed in the mouth. Thus, the combination of three developmental skills—the ability to move around the home and go beyond the immediate view of a guardian, the ability to pick up and manipulate small objects, and the tendency of children to put things in their mouths—places them at risk for poisoning.

As children develop socially, they desire to become more similar to their parents, and they tend to imitate behaviors, such as taking medicine or using mouthwash. Children are taught that medicine is good for them when they are sick. Many children's medicines are sweetened and flavored to make them more palatable, and many parents inappropriately encourage their children to take medicines by telling them "it tastes like candy." Children have been observed "making tea" from plants or "making pizza" with mushrooms from the yard.²⁶

As children become more mobile, agile, and curious, xenobiotics that were previously outside their reach become accessible even when stored in some difficult-to-reach places. Some evidence suggests that parents underestimate the developmental skills of their children.⁵¹ The meaning of the term unintentional with respect to childhood poisoning should also be reconsidered—a toddler quite purposefully intends to get to a pill and eat it, but the child does not intend to injure him- or herself.

Some of the reasons why a child wants to ingest a pill are because it is there, it looks and maybe tastes like candy or food, or the child is mimicking the behavior of a parent who ingests medicines or vitamins to cure illness and improve health. However, these reasons may not be sufficient to explain why xenobiotic exposures occur. Another aspect of poisoning that must be considered is the interaction between the child's temperament and the social environment.

Many authors have tried to identify psychosocial predictors for childhood poisoning in general and for repeat poisoning in particular.^{22,53,83,169,185} As many as 30% of children repeatedly ingest xenobiotics, frequently the same xenobiotic. Certain risk factors have been identified for single and repeat episodes of childhood poisoning, such as hyperactivity, impulsive risk-taking behavior, rebelliousness, and negativistic attitude. Other factors seem to be associated more with the quality of supervision by parents or guardians, who themselves are experiencing medical illnesses, depression, or social isolation.¹⁸⁵ Finally, a stressful environment or a major social problem may also contribute.^{166,170} It is not difficult to imagine a situation of a parent who is depressed, uses antidepressant medication that is kept at the bedside, and cannot give adequate attention to a demanding child. In a bid for attention or as an expression of anger or frustration, the child ingests some of the parent's medication.

With regard to the agent, a number of issues affect the preinjury and injury phases, and modification of any one of the interacting factors of host, agent, or environment may potentially prevent or reduce the severity of injury. When household products of lower toxicity are available around the house, the likelihood of injury is reduced if one of these products is ingested. For example, less toxic rodenticides such as warfarin have replaced more toxic ones such as thallium or sodium monofluoroacetate, and relatively nontoxic paradichlorobenzene mothballs have largely replaced the relatively more toxic camphor-containing mothballs.

It may also be possible to reduce the likelihood of ingestion by making a xenobiotic unpalatable. Denatonium benzoate is an aversive, bitter xenobiotic that is added to some liquids such as windshield washer fluid and antifreeze to prevent unintentional poisoning.⁸⁰ However, some trials show that whereas older children may respond negatively to these xenobiotics with the first taste, younger children may ingest 1 to 2 teaspoonfuls before being deterred by the bitter flavor.^{20,165} This is an important consideration because even a small amount of a xenobiotic such as methanol can be toxic (see later discussion). The actual usefulness of denatonium benzoate in poison prevention is largely unstudied.¹⁴⁵

The problem of unintentional ingestions is compounded by poison "look-alikes," that is, xenobiotics that resemble candy or food products.⁵⁴ Some common examples are ferrous sulfate tablets and vitamins that look like common candies and fuel oils that come in cans resembling soft drink containers. Many shampoos and dishwashing detergents are given lemon or strawberry scents and have pictures of fruits on the labels. Children are not always able to distinguish poison "look-alikes" from real candies, fruits, and sodas, and they may be attracted to bright colors, pleasant smells, and appealing packages. Eliminating these "look-alikes" might prevent some unintentional ingestions.

Probably the most significant changes have occurred in the physical characteristics with regard to packaging and dispensing of pharmaceuticals and some other xenobiotics with child-resistant closures mandated by the Poison Prevention Packaging Act of 1972 ([Chap. 1](#)). This legislation is credited with causing a significant reduction in morbidity and mortality caused by poisoning from aspirin and other regulated products, although this analysis has been challenged.^{36,143,187} Child-resistant closures have also been credited with reducing the number of toxic exposures to kerosene.⁹⁷

Nonetheless, problems with child-resistant closures include the dispensing of pharmaceuticals in nonresistant containers, not properly closing child-resistant containers, and leaving pharmaceuticals out of the child-resistant container.^{28,168} Seventy percent of potentially toxic pharmaceuticals may be in non-child-resistant or in improperly functioning child-resistant containers. Several studies have identified poor functioning of the closures when there is sticky liquid or pill residue around the top or in the screw threads of the child-resistant container.^{81,89,196}

Although child-resistant containers are a significant deterrent to unintentional ingestions in toddlers, they are not completely effective, and even without the problems noted, some children can open them. A false sense of security associated with these closures may lead some parents to be less compulsive regarding safe storage of the containers. A double barrier, such as a unit-dose dispenser within a child-resistant container or a blister pack, has been recommended for a few pharmaceuticals associated with a large number of significant poisonings such as iron and antidepressants.⁸⁹

In fact, in 1997, the Food and Drug Administration (FDA) issued a regulation to package products with 30 mg or more of elemental iron per tablet in unit-dose packages such as blister packs.³⁰ The intent of this regulation was to reduce the likelihood of iron poisoning in children. Even before this regulation was instituted, the number of fatal childhood iron ingestions had declined significantly; therefore, it is not known how much if any of the decrease is related to the mandated packaging changes. In any case, the rule was overturned in 2003, when it was determined that the FDA did not have the statutory authority to regulate a drug for the purpose of poison prevention.¹¹ As yet there is no evidence of a resurgence of iron-related fatalities.

A discussion of containers and storage naturally leads to a consideration of the third factor in the injury-causation model discussed earlier, the environment, which is particularly important in the preinjury and the injury phases. Approximately 80% of childhood pharmaceutical ingestions occur at home; the remainder occurs at the homes of grandparents, other relatives, and friends. At home, the medicine usually belongs either to the child or to a parent, although a significant number of medications, both at home and away from home, belong to a grandparent.^{81,104} Grandparents, other relatives, and family friends without children at home may not obtain or retain medications in child-resistant containers and may not be as attentive to safe storage practices. Poison prevention education directed to these groups may be particularly helpful.¹¹⁷

Medications are frequently kept in the kitchen or bedroom while they are being used.^{81,196} In the kitchen, medications are stored in the refrigerator, on the table, or on the counter; in the bedroom, medications are left on a dresser or bedside table. A mother's or grandmother's purse is another location where medications are commonly found. Interestingly, there are no significant differences in the storage practices in the homes of children who ingest and those who do not ingest medicines, so storage practices alone cannot predict the likelihood of childhood poisoning.^{169,196}

One important caveat relates to the storage of nonpharmaceutical xenobiotics, particularly those in liquid form. These types of xenobiotics should never be transferred for storage to familiar household containers, such as food jars or wine or soda bottles; stored in areas low to the ground such as beneath sinks; or kept in cabinets that do not have child-resistant locks. Both children and adults have been unintentionally exposed to xenobiotics, such as sodium hydroxide, pesticides, hydrocarbons, and potassium cyanide, that was stored in bottles in the refrigerator.¹⁸¹ Many of the kerosene exposures reported from developing countries occur because the kerosene is stored in water bottles, jugs, or other containers in easily accessible locations. When the weather is hot, children may mistake the clear liquid kerosene for water.^{1,40,101}

HISTORY OF THE INGESTION

The appropriate management of any poisoned patient is influenced by the history of the exposure. Except in rare cases of child abuse-related poisoning, parents or guardians generally provide information to the fullest extent possible. As a rule, in the case of children, the xenobiotic and time of ingestion are known. However, the reported number of pills or volume of liquid ingested may not be as accurate. Clues to the amount ingested are the number of pills or volume of liquid in a bottle before and after an ingestion, the number of pills set out on the night table, or the area of a spot of liquid after a spill. When symptoms are suggestive of poisoning but the history is inadequate, information about possible exposure outside of the home, such as with a babysitter, grandparent, friend, or other relative, should be obtained because approximately 15% of childhood poisonings occur outside the home.^{81,132}

In contrast, adolescents may not be forthcoming when relating the history of an intentional ingestion, especially when they are depressed, suicidal, or concerned about the response of their guardian or parent. When caring for these patients, the clinician must use the history provided but should remain skeptical about the reported type and number of xenobiotics ingested, as well as the time of ingestion.

When a child may be the victim of abuse or intentionally poisoned by a parent or guardian, the health care provider must ensure that (1) the history of the poisoning remains consistent over time and among people providing the details of the event, (2) the child's clinical presentation is consistent with the history of the poisoning, and (3) the reported actions are consistent with the child's developmental level.

GASTROINTESTINAL DECONTAMINATION

Chapter 8 is devoted to a complete discussion of gastrointestinal (GI) decontamination. This section reiterates and emphasizes only a few important points.

As described earlier, children generally ingest small quantities of a single xenobiotic. For most of these ingestions, gastric emptying is unnecessary. Some examples of nontoxic ingestions are eating a crayon or the leaf of a jade plant, licking the cap of a household bleach container, or swallowing two adult-strength APAP tablets.

Orogastric lavage is the preferred method of gastric emptying when indicated for most serious ingestions. Small children can generally tolerate orogastric lavage with a large-bore 28- or 34-French tube; however, the smaller “large-bore” tubes may not be effective for removing large pills or fragments from the stomach of a small child. Placement of an orogastric tube is an unpleasant and frightening procedure for an infant or small child to undergo. Some local trauma may result from tube placement, and rarely, there may be more serious injury, such as esophageal perforation. Also, many children vomit during placement of an orogastric tube. Therefore, the use of orogastric lavage should be limited to cases in which the risk of significant morbidity or mortality is high, the likelihood of benefit is at least moderate, and the likely risk of injury to the child from the procedure is small. Orogastric lavage should never be used as a form of punishment. The patient should be intubated to protect the airway before orogastric lavage is used in a child with a diminished gag reflex or a depressed level of consciousness.

Previously, administration of syrup of ipecac to poisoned patients was considered a primary emergency intervention, and the availability of syrup of ipecac in the home was a primary tenet of pediatric anticipatory guidance. The AAPCC reports that the use of syrup of ipecac for case management declined from 13% in 1983 to 0.1% by 2005. This is not surprising because syrup of ipecac is contraindicated in cases associated with hemodynamic instability, seizures, or a depressed level of consciousness. Although syrup of ipecac is highly effective at making children vomit, the efficacy of preventing morbidity after an ingestion is questionable.

Even before the use of syrup of ipecac was abandoned, it had been used only infrequently in the ED management of poisonings, with lavage favored when evacuation of the stomach was considered important. However, it was only 10 years ago that it was still advocated for use at home at the direction of a poison center to avoid an unnecessary evaluation in an ED. However, in 2003, the American Academy of Pediatrics (AAP) recommended against the use of syrup of ipecac at home, and in 2004, the American Academy of Clinical Toxicology and the European Association of Poison Control Centres and Clinical Toxicologists recommended against the general use of syrup of ipecac for the management of poisoning.^{4,6} The reasons for the new recommendations include its unproven benefit, its adverse effects, its interference with and complication of subsequent ED evaluation, its abuse potential, and its administration in cases in which there is no indication or there is a contraindication because of lack of consultation with a poison center.

Activated charcoal (AC) is a current mainstay of poison treatment in EDs.^{3,35} Children generally will not drink AC willingly, although some children can be coaxed to do so if the AC is disguised in a baby bottle or soft drink container or sweetened with juice or sorbitol.¹⁹³ A nasogastric or orogastric tube may have to be inserted to administer AC. This can be a small-bore tube because it is not intended for lavage, although the smaller the bore, the more difficult it is to administer the thick slurry of AC. Placement of the tube, the presence of AC in the stomach, the effects of the xenobiotic, or the previous use of an emetic all may make the child vomit, making aspiration of AC or stomach contents a risk. For AC to be used safely in a patient who is comatose and who does not have a gag reflex, the patient should be intubated and the airway protected. Because of this risk, AC alone is unnecessary for a nontoxic or minimally toxic ingestion.

AC is available for home use.^{98,174} Administration of AC at home or by prehospital personnel allows for administration significantly earlier than can be achieved after arrival and evaluation in the ED.^{38,174} Although it would seem to have potential benefit as home therapy, AC is unpalatable, quite messy, and not always available; as a result, it has not achieved widespread use in the home.^{127,142} It is also unclear how well parents can administer AC at home.^{154,155,175} Whether the earlier administration of AC would affect outcome is unknown. If AC is to become a standard to replace syrup of ipecac for home therapy, it will require a substantial reeducation effort on the part of pediatricians, toxicologists, and pharmacists.

METHODS OF ENHANCED ELIMINATION

For consequential poisoning with xenobiotics such as methanol, ethylene glycol, salicylates, lithium, and theophylline, either hemodialysis or charcoal hemoperfusion is the optimal technique to enhance elimination, depending on the particular xenobiotic. These extracorporeal techniques can be performed on newborns or small infants in specially equipped centers with dedicated personnel. The primary limiting factor is the ability to obtain vascular access.^{18,48,50,182} However, even large centers that routinely do hemodialysis in children may not be able to manage very small infants. There has been a report of the use of peritoneal dialysis for the treatment of alcohol intoxication in a child,⁶⁹ but this technique is not generally recommended.

Exchange transfusion is occasionally used to enhance xenobiotic elimination. This technique might be useful when multiple-dose AC cannot be administered, the xenobiotic is poorly adsorbed to AC, or access to specialized hemodialysis

or hemoperfusion is not readily available. Exchange transfusion has been used successfully for poisoning by salicylates^{49,113} and theophylline.^{15,129,161} Another xenobiotic for which exchange transfusion may be a therapeutic alternative is chloral hydrate.⁹

XENOBIOTICS THAT MAY BE TOXIC OR FATAL IN SMALL QUANTITIES

When children ingest even small quantities of toxic xenobiotics, they are potentially ingesting large relative doses because of their small size. There are a number of xenobiotics that may cause significant toxicity or even death with as little as one pill or one teaspoonful.^{13,102} Table 32–4 lists these xenobiotics.

TABLE 32–4. Xenobiotics That May Cause Severe Toxicity to an Infant after a Small Adult Dose, a Single Pill, or a Small Volume

β-Adrenergic antagonists (sustained release)

Benzocaine

Bupropion

Calcium channel blockers (sustained release)

Camphor

Clonidine

Cyclic antidepressants

Diphenoxylate and atropine (Lomotil)

Methanol or ethylene glycol

Methylsalicylate

Opioids (buprenorphine, codeine, methadone, oxycodone)

Pesticides/Herbicides/Rodenticides

Phenothiazines

Quinine or chloroquine

Sulfonylureas

Theophylline

XENOBIOTICS THAT MAY CAUSE DELAYED TOXICITY IN CHILDREN

Several xenobiotics warrant particular concern because their effects may be significantly delayed. Classic examples are atropine–diphenoxylate (Lomotil)^{23,39,115} and sulfonylureas such as glipizide.^{67,134,178} Both of these xenobiotics may cause serious morbidity with initial symptoms or recurrence of symptoms delayed by as much as 24 hours after ingestion.

Children with real or possible ingestions of Lomotil or a sulfonylurea should be admitted for observation and monitoring even if they are asymptomatic because effects may not become apparent for 24 hours (Chaps. 38 and 53).

With the advent of new modified-release formulations of calcium channel blockers and β-adrenergic antagonists, concern for delayed toxicity and possibly death has become even greater.¹²³

XENOBIOTICS THAT CAUSE UNUSUAL OR IDIOSYNCRATIC REACTIONS IN CHILDREN

Benzyl Alcohol: Gaspings Syndrome

Benzyl alcohol is a preservative added to liquid pharmaceutical preparations; for small-volume medications administered to adults, the benzyl alcohol additive is quite safe (Chap. 55). However, at toxic doses, benzyl alcohol may cause respiratory failure, vasodilation, hypotension, convulsions, and paralysis. IV flush solutions containing benzyl alcohol were implicated as the cause of the “gasping syndrome” in sick newborns; the syndrome includes severe metabolic acidosis, encephalopathy, respiratory depression, and gasping.⁵ The association was made when infants with this syndrome were found to have elevated concentrations of benzoic acid and hippuric acid, metabolites of benzyl alcohol.^{27,63} Benzyl alcohol is metabolized by the conjugation of benzoic acid with glycine to form hippuric acid; this pathway may not be functional in premature infants. Benzyl alcohol administration has also been associated with kernicterus and intraventricular hemorrhage in premature infants.^{76,82} Although benzyl alcohol has been removed from many of the medications used for neonates, some preparations may still contain this agent.¹⁹¹

Imidazolines and Clonidine: Central Nervous System Effects

Imidazolines such as tetrahydrozoline, oxymetazoline, xylometazoline, and naphazoline are nonprescription sympathomimetics used as nasal decongestants and conjunctival vasoconstrictors (Chap. 49). Clonidine is an imidazoline derivative used as an antihypertensive (Chap. 63). In small children, these xenobiotics can cause central nervous system (CNS) depression, respiratory depression, bradycardia, miosis, and hypotension.^{12,112,194} The presumed mechanism of action is by stimulation of central α_2 -adrenergic and imidazole receptors. Although naloxone has been reported to reverse some of the CNS effects of clonidine, there are no reports of its successful use with the other imidazolines (Chap. 63).

Ethanol: Hypoglycemia

Ethanol is the primary component of alcoholic beverages, as well as a major constituent of many liquid preparations, such as mouthwash, vanilla flavoring, and perfume. Besides its well-known sedative–hypnotic effects, ethanol poisoning in children is associated with hypoglycemia because of reduced hepatic glycogen stores in children. Ethanol-induced hypoglycemia may cause seizures and may exacerbate the other CNS effects induced by ethanol poisoning. Hypoglycemia results from the inhibition of gluconeogenesis in the setting of alcohol poisoning. There does not seem to be a blood alcohol concentration threshold for the development of hypoglycemia, which has been reported with blood alcohol concentrations as low as 20 mg/dL⁴² (Chap. 80).

Chloramphenicol: Gray Baby Syndrome

Chloramphenicol is a broad-spectrum antibiotic that has been used in children because of its activity against *Haemophilus influenzae*. It has largely been replaced by other antibiotics in the United States because of its association with aplastic anemia. When administered at high doses, chloramphenicol can produce the “gray baby syndrome,” which includes abdominal distension, vomiting, metabolic acidosis, progressive pallid cyanosis, irregular respirations, hypothermia, hypotension, and vasomotor collapse. Although these effects occur primarily in premature newborn infants, they may also occur in older children and adults (Chap. 57).

Gray baby syndrome is associated with serum concentrations greater than 100 mg/L. Increased chloramphenicol concentrations may result from (1) inadequate conjugation of chloramphenicol with glucuronic acid because of inadequate activity of glucuronyl transferase in the newborn liver and (2) decreased renal elimination of unconjugated chloramphenicol. The exact mechanism of toxicity is unknown; there is speculation that free radicals produced during the metabolism of chloramphenicol may interfere with mitochondrial function.⁷⁸

MEDICATION ERRORS

Ever since the publication of the Institute of Medicine’s report titled *To Err is Human* in 1999, increasing attention has been paid to the issue of medical errors in medicine.⁹⁰ Although most of the research regarding medication errors has focused on adults (Chap. 140), this problem also affects children. Remarks in this section are generally limited to the pediatric literature.

Approximately 125,000 exposures each year are classified by the AAPCC as therapeutic errors, accounting for approximately 6% of exposures in children younger than 6 years of age, 24% in children 6 to 12 years of age, and 11% in adolescents. For 2007 to 2011, there were a total of 26 deaths attributed to therapeutic errors, representing 3% of all reported deaths in children and adolescents. Eight percent of the AAPCC-reported fatalities in young children were related to therapeutic errors, but only 1% of the adolescent fatalities were related to therapeutic errors. Of children younger than the age of 6 years, approximately 40% of the errors resulting in severe injury or death occur in children younger than the age of 1 year.¹⁸⁴

Medication errors may occur at any phase of a process that includes ordering, order transcription, pharmacy dispensing, preparation and administration of the medication, and monitoring of medication effects. In fact, the same types of errors can

occur at different points in the process. [Table 32–5](#) lists the types of errors that can occur, and [Table 32–6](#) provides some examples of errors.

TABLE 32–5. Medication Errors

1. Wrong patient—someone else’s drug
2. Wrong drug
 - a. Wrong individual drug
 - b. Wrong formulation
 - c. Known allergy
 - d. Known drug–drug interactions
 - e. Wrong indication
 - f. Contraindication
 - g. Expired
 - h. Deteriorated
3. Wrong dose
 - a. Miscalculation
 - i. Decimal point error
 - ii. Wrong formula
 - iii. Right formula using wrong dose, frequency, units, weight
 - iv. Pound–kilogram confusion
 - v. Mg–g units confusion
 - vi. Dilution error
 - b. Appropriate individual dose divided into multiple doses
 - c. Total daily dose for an individual dose
 - d. Wrong intravenous infusion rate
 - e. Measuring error
4. Wrong route
5. Wrong frequency
 - a. Increased or decreased dosing interval
 - b. Omitted, delayed, or added dose
 - c. Delay or failure to supply
6. Transcription errors
7. Documentation (order, prescription, transcription, logs)
 - a. Illegible
 - b. Incomplete or missing information (weight, signature, maximum daily dose, stop date)
8. Monitoring
9. Miscellaneous
 - a. Wrong label
 - b. Wrong information or advice
 - c. Failure to detect error
 - d. Breast milk exposure

Data based on Kaushal R, Bates DW, Landrigan C, et al: Medication errors and adverse drug events in pediatric inpatients. *JAMA*. 2001;285:2114–2120; Lesar TS: Errors in the use of medication dosage equations. *Arch Pediatr Adolesc Med*. 1998;152:340–344; and Wilson DG, McArtney RG, Newcombe RG, et al: Medication errors in paediatric practice: insights from a continuous quality improvement approach. *Eur J Pediatr*. 1998;157:769–774.

TABLE 32–6. Examples of Medication Errors

1. **Wrong drug.** In one nursery, an epidemic mimicking neonatal sepsis was caused when racemic epinephrine was inadvertently administered instead of vitamin E because both drugs were manufactured by the same company, distributed in nearly identical bottles, and stored near each other inside the nursery refrigerator.¹⁷³
2. **Wrong drug formulation.** APAP suppositories (120 mg) were ordered for a toddler, but adult-strength suppositories (650 mg) were distributed and administered every 4 hours. The child developed hepatotoxicity requiring hospitalization and therapy (Chap. 35).
3. **Wrong dose.** A 1 kg premature infant required sedation for a diagnostic study. A high dose of chloral hydrate, 100 mg/kg, was miscalculated to be 1 g (1000 mg) instead of 100 mg. The child had a cardiopulmonary arrest and died. When drugs require milligram per kilogram dosing, it is easy to make decimal mistakes in the calculation or in the transcription.
4. **Wrong route.** A 17 month-old girl with a central venous line (CVL) and a gastrostomy tube required an upper gastrointestinal series. Barium sulfate was inadvertently injected into the CVL instead of the gastrostomy tube. The patient had several episodes of vomiting and developed fever and rigors but ultimately recovered.¹⁷²
5. **Wrong dose.** A patient had the dose of cyclosporine changed from 10 mg to 7 mg twice daily. The child received 70 mg (0.7 mL of solution) instead of 7 mg (0.07 mL). When the prescription was refilled, the parents received a 5 mL syringe to use instead of a 1 mL syringe they had used previously.⁴⁴

Most of the analyses of medication errors have occurred in inpatient settings. The reported frequencies of medication errors vary widely—from 0.47% to 5.7% of written orders and from 0.51 to 157 per 1000 patient-days.^{55,62,77,84,87,151} The variance largely depends on whether the definition of “error” does or does not include prescribing errors, regardless of whether or not they are corrected, and whether potential, or only actual, adverse drug events are included. The reported frequencies also vary depending on whether there is active case finding or whether there is only voluntary reporting.

In a 2001 study of pediatric inpatients in which orders were actively monitored for a 6-week period, 5.7% of 10,778 prescriptions had errors in the order for the medication, transcription of the order, dispensing or administration of the medication, or monitoring of medication effects (56 per 100 admissions, 157 per 1000 patient-days);⁸⁷ 1.1% could have potentially caused an adverse effect (10 per 100 admissions, 29 per 1000 patient-days). Eighty-four percent of the errors occurred during the ordering or transcription phase, so most of the errors were intercepted and corrected before drug administration. There were 26 true adverse drug events, but only five were considered preventable errors (0.05%, 0.52 per 100 admissions, 1.8 per 1000 patient-days). Although the overall error rate was similar to that reported by the same group in a study of adults, the rate of errors that could potentially have caused harm was three times greater; 41% of the potentially harmful errors were not intercepted. However, one review suggests that the prescription error rate is higher in adults than in children.¹⁰¹

Generally, error rates are higher in intensive care units, where the sickest patients are cared for; such patients often receive multiple medications with complex administration regimens.^{55,77,87,135,151,186,195} Results similar to those from inpatient settings have been reported in pediatric EDs.^{62,95,153,159,164}

The studies cited suggest that the frequency of significant errors leading to significant adverse drug events is low; however, even a low frequency applied to a large population of patients could result in a large number of patients being harmed. The most important outcome of the analysis would be to try to reduce the overall number of errors to reduce the number of potential and actual adverse drug events.

The causes of medication errors are numerous, varied, and complex; they are organizational, environmental, and personal, which includes factors such as the level of training, knowledge and competence, the time of day, workload, staff interactions, communications, number of distractions or interruptions, ambient noise, and drug formulation and drug packaging.^{41,57,65,90,189} (Chap. 140).

Children may be placed at increased risk of a medication error for several reasons: (1) someone other than the child administers the medication, so there is little opportunity to prevent or limit drug administration; (2) a young child cannot warn practitioners about possible problems such as allergies; (3) a young child cannot inform practitioners when he or she is experiencing an adverse event; (4) medication ordering and administration in children frequently requires dose calculations; (5) inexperienced practitioners may be uncomfortable with pediatric dosing or related calculations; and (6) incorrect measurement or dilution of concentrated stock solutions may yield a small volume, which is not perceived as containing a relatively large dose of medication.^{32,44,65}

One of the most common errors is prescription, preparation, or administration of an incorrect dose, particularly in children, for whom almost every prescription requires knowledge of the patient’s weight and a calculation of a weight-based dose.^{87,96,100} In addition, even the milligram per kilogram dose may vary depending on the age of the patient or the diagnosis. Although pediatric doses are generally determined on a milligram per kilogram basis, if the weight is recorded in pounds and this weight is used in the calculation, there will be a built-in twofold error. Calculation errors also occur when drug preparation requires dilution of a concentrated stock solution or special compounding.¹⁸⁴ Further confusion can

arise when mg is written as or misinterpreted as mL or μg in a calculation or vice versa.⁴⁰

When an extra zero is added or a required zero is omitted from calculations, written or verbal prescriptions, or in dispensed and administered medications, a 10-fold error occurs. These large errors are common and result in significant under- or overdosing; 10-fold errors have been reported in testing scenarios, case series, and case reports.^{47,92,93,96,139,147,151,184} These errors are of particular concern because the risk of toxicity generally increases with significant overdose.

Because the causes of medication error are numerous and complex, the solutions must be multifaceted and interdisciplinary. The approach to the problem is contained within the field of human factors research and potentially requires changes in individual factors such as knowledge; environmental factors such as interruptions; and system problems such as how medications are ordered, stocked, and dispensed^{90,177,189} (Chap. 140).

The most commonly recommended solutions to reduce the frequency of medication errors are computerized physician order entry (CPOE) with clinical decision support systems^{85,185}; ward-based clinical pharmacists; and improved communication among and between all levels of medical, nursing, and pharmacy staff.^{86,99,141,177} In one of the studies cited earlier, it was estimated that these three solutions together could have prevented more than 90% of the potential errors,⁵⁶ although the effect of interventions other than CPOE has generally not been studied.

In its simplest form, CPOE eliminates errors related to legibility. Decision support adds the ability to check a prescription against age, weight, dose, allergies, and drug–drug interactions, but it may not prevent ordering the wrong drug or dose, so there is still a need for education and human oversight in addition to other safeguards. The implementation of CPOE is generally associated with at least some reduction in errors related to medication ordering, although an effect on morbidity or mortality has not yet been demonstrated.^{1,185} Sometimes there are unanticipated consequences associated with computerized systems.^{91,116,188}

In the future, all inpatient medication orders and outpatient prescriptions may be transmitted electronically, but until that time, it will be necessary to ensure that prescriptions are written legibly and correctly. The Joint Commission and many other groups have issued recommendations to reduce errors in medication ordering (Chap. 140).

Standardized tests of the math skills necessary to calculate doses and administer medications have demonstrated deficiencies in both nursing and physician groups.^{17,21,126,130,133,146,152} Tests of this nature may be a means of identifying practitioners at risk for making calculation errors, highlighting areas in need of remediation, and serving as ongoing educational tools.

As described earlier, there may be an increased risk of medication errors in critical care areas because of severity of illness and intensity of medication therapy. In many cases, such as during resuscitations, critically ill patients require immediate therapy, verbal orders are common, and there is often insufficient time to carefully review all of the particulars related to medication ordering and administration.^{45,62,96,108,131}

Critical care areas, including the ED, benefit from having precalculated dosing charts available for resuscitation medications and for other commonly prescribed medications; this is a recommendation of the American Heart Association.⁷ Many clinical units have developed their own dosing schemes. Commercial products, such as the Broselow-Luten system, are also available and have been shown to reduce the number of medication errors in simulated^{2,107,109,160} and actual resuscitations.¹⁵⁰ There has been some controversy related to the ability of these length-based commercial products to accurately predict the weights of children from diverse domestic and international populations for the purpose of medication dose calculation.^{110,122}

The previous discussion has been almost exclusively related to hospital-based medication use, but significant errors also may occur in outpatient settings. Antipyretics are among the most frequently recommended medications for children. Although significant toxicity after unintentional ingestions in toddlers is now rare, administration of multiple supratherapeutic doses of APAP is common and can cause significant hepatotoxicity.⁹⁴

In fact, many parents have difficulty calculating the appropriate dose of APAP and measuring out the appropriate amount after it is calculated despite having received instructions and graduated cups or oral-dosing syringes.^{68,111,119,167,171} Relevant factors related to these errors include the characteristics of the instructions regarding medication measurement and administration, the health literacy of caregivers, and the accuracy of different measuring devices.

Two of the most commonly used measuring devices are also the most inaccurate—the teaspoon and the graduated cup.^{153,199} The household teaspoon is not standardized for volume and can easily be confused with a household tablespoon.¹¹¹ APAP and ibuprofen elixirs are typically packaged with a graduated cup for administration even though graduated syringes are considered the most accurate of the measuring instruments available and are recommended by the AAP for young children. In addition, the instructions and measuring devices distributed with these products, as well as other nonprescription medications, are highly variable and inconsistent.²⁰⁰

Health literacy and health numeracy are becoming increasingly understood factors with regard to the safe and effective delivery of health care in general and the reduction of the rate of medical errors in particular. Health literacy plays a key

role in a caregiver's ability to read and understand instructions about and labels on prescriptions and nonprescription medications.¹⁶⁴ The labels on medication containers are not standardized with respect to the layout and placement of information or the use of abbreviations or units of measure, may be printed in small fonts that are physically difficult to read, and may be difficult to understand by people with lower health literacy or limited English proficiency.^{106,200,202} Instructions for medication administration have the same problems. Visual cues using pictograms in the instructions or color-coded or premarked syringes are practical ways to improve the accuracy of parental medication dosing.^{58,198,201}

INTENTIONAL POISONING AND CHILD ABUSE

Intentional poisoning of children is an unusual, but significant, form of child abuse. Most cases are related to pathologic characteristics of the parent or guardian and have been categorized as (1) undifferentiated child abuse, neglect, or impulsive acts under stress; (2) factitious illness (Munchausen syndrome by proxy {MSBP}); (3) overt parental psychosis; and (4) the Medea complex, or the vengeful killing of a child out of spite for one's spouse.^{74,149,179} Rare cases of intentional poisoning may be related to bizarre childrearing practices.

Intentional poisoning is rarely suspected unless the patient dies and an autopsy is performed, a wide-ranging drug screen is ordered, or the history is bizarre enough to raise suspicions. In many cases in which children are later found to be poisoned, the initial diagnoses were sepsis, meningitis, seizures, intracranial hemorrhage, gastroenteritis, apnea, apparent life-threatening events, or metabolic derangements.⁷⁴ In addition to many pharmaceuticals, salt, pepper, water, caffeine, ethylene glycol, herbs, plants, and traditional remedies have been used to poison children.^{46,74} Although the death rate from unintentional poisoning in children is much less than 1%, the death rate from "malicious" intentional poisoning may be as high as 20% to 30%.^{46,74,179}

Intentional poisoning may be associated with other forms of abuse; approximately 20% of poisoned children may have evidence of physical abuse.^{46,74} Of children presenting to EDs after presumed unintentional poisoning, 36% had previous ED visits for trauma, 7% for poisoning, 6% for both trauma and poisoning, and 1.4% for failure to thrive. At the time of the visit, only 7% were evaluated for possible abuse, and 2.7% were considered neglected.⁷⁴ These data do not prove an association between poisoning and physical trauma; however, in some children, repeat episodes of trauma or poisoning may be a manifestation of significant intrafamilial stress. Health care providers must remain vigilant to the possibility that a presumed unintentional poisoning may have been "malicious" intentional, especially in the setting of a repeat ingestion or when there have been previous evaluations for trauma.

Substance abuse by a parent or guardian may play a role in unintentional or intentional poisoning of children. Children have been poisoned with cocaine or phencyclidine by passive inhalation of side smoke,^{16,73,124,157,192} unintentional ingestion,^{88,140} and rectal administration,¹³⁶ as well as through breast milk.³³ Children have been given doses of alcohol, methadone, and other xenobiotics to quiet them or to prevent withdrawal.^{42,75,138} There are reports of babysitters blowing marijuana smoke into babies' faces to "get them high" or to quiet them.¹⁵⁸

In 1977, the term Munchausen syndrome by proxy was first used to describe a condition in which a parent or guardian, typically the mother, fabricates a history of nonexistent disease(s) in a child or creates the signs and symptoms of disease in a child (factitious illness).^{120,121,149} This is usually a manifestation of the parent's complex psychiatric illness, which may include Munchausen syndrome itself.^{24,66,156} There may be only a fine line separating MSBP from an intentional poisoning with intent to harm or kill a child. However, regardless of the specific intent, this condition is considered a form of child abuse.

Over the years, child protection experts have tried to develop more specific terminology than MSBP. In light of the fact that this entity involves two individuals—the child victim and the adult perpetrator—the American Professional Society on the Abuse of Children recommends that the child victim be diagnosed with "pediatric condition falsification" and that the psychiatric diagnosis of "factitious disorder by proxy" be applied to the adult perpetrator. The diagnosis of MSBP requires that both criteria be met.^{10,156}

A child's fabricated illness may lead to multiple medical evaluations by several different physicians, frequent hospitalizations, unnecessary surgeries and diagnostic testing, unneeded prescribing and administration of medication, and at times even the death of the child. Administration of medications to the child by the adult perpetrator is frequently how a particular set of signs and symptoms is created. Xenobiotics used to create factitious illness have included analgesics, antidepressants, insulin, syrup of ipecac, Lomotil, phenothiazines, sedative-hypnotics, warfarin, phenolphthalein, and hydrocarbons.¹⁴⁸ Several warning signals may suggest a diagnosis of MSBP (Table 32–7).

TABLE 32–7. Factitious Illness (Munchausen Syndrome by Proxy): Suggestive Characteristics in Clinical Situations

1. The child has a persistent or recurrent illness that cannot be explained.
2. The history of disease or results of diagnostic tests are inconsistent with the general health and appearance of the child.

3. The signs and symptoms cause the clinician to remark, “I’ve never seen anything like this before!”
4. The signs and symptoms do not occur when the child is separated from the parent.
5. The parent is particularly attentive and refuses to leave the child’s bedside even for a few minutes.
6. The parent develops particularly close relations with hospital staff.
7. The parent seems less worried than the physician about the child’s condition.
8. Treatments are not tolerated (eg, intravenous lines fall out frequently, prescribed medications lead to vomiting).
9. The proposed diagnosis is a rare disease.
10. “Seizures” are unwitnessed by medical staff and reportedly do not respond to any treatment.
11. The parent has a complicated medical or psychiatric history.
12. The parent is or was associated with the health care field.

Data from Meadow R: Munchausen syndrome by proxy. *Arch Dis Child*. 1982;57:92–98.

In one illustrative case of MSBP, a 29 month-old boy who had undergone a previous appendectomy was hospitalized multiple times for vomiting, diarrhea, and dehydration.⁶⁴ Evaluation included multiple blood and stool analyses, a gastric pH probe, endoscopy, upper GI series, computed tomography, and magnetic resonance imaging. On the fourth admission, a small bowel obstruction was identified, and the child had lysis of adhesions. Nonetheless, symptoms recurred every 2 to 4 months, necessitating hospitalization. The child failed to thrive and required a nasoduodenal tube for feeding, which frequently became dislodged. The child went on to have a jejunostomy tube and a permanent central venous catheter placed. Eighteen months after his initial presentation, the child presented in congestive heart failure with evidence of cardiomyopathy. A urine screen identified emetine and cephaline, components of syrup of ipecac. The child was removed from his home to protective custody after which he recovered and remained asymptomatic on a regular diet.

Siblings of children evaluated and treated for poisoning may also have suffered from factitious illness. In addition, significant psychiatric problems may be manifested by the victim, parents, and siblings.^{25,118,156,162}

Child abuse or neglect must be part of the differential diagnosis of any case of childhood poisoning. Intentional poisoning should be considered for,^{74,75}

- An “ingestion” in a child younger than one year of age
- A case with a confusing history or presentation
- A child with a previous poisoning or a child whose siblings have previously been evaluated for poisoning
- A child with a previous presentation for a rare or unexplained medical condition
- A child with apnea, unexplained seizures, or an apparent life-threatening event
- A massive ingestion by a small child
- An ingestion of multiple xenobiotics by a small child
- An exposure to substances of abuse
- An intoxication with a xenobiotic to which a child could or would not typically have access
- “Accidental ingestions” in a school-age child
- A history of previous trauma, child abuse, or neglect
- Sudden infant death syndrome or an unexplained death

These considerations of child abuse notwithstanding, rare diseases do occur. One child’s rare, inherited metabolic disorder, methyl malonic acidemia, was misdiagnosed as ethylene glycol poisoning because of the chromatographic appearance of the metabolite propionic acid, which was similar to that of ethylene glycol.¹⁶³

SUMMARY

- Children are frequently exposed to potentially toxic xenobiotics; fortunately, most childhood exposures are ingestions of nonpoisonous xenobiotics or small nontoxic quantities of potentially toxic xenobiotics.
- When a child sustains a significant toxic exposure, management follows general toxicologic principles.
- Although most childhood exposures are unintentional, the clinician should be alert to the possibility of intentional poisoning of a child with pharmaceutical or household products.
- The normal development of children places them at risk for unintentional ingestions. A chaotic home environment or a disorganized social structure may compound these risks.
- Small size puts children at increased risks for medication dosing and dispensing errors, and their immature metabolic processes may lead to unexpected toxicity from pharmaceuticals.
- Toxicologists should encourage parents to provide as safe a home environment as possible to prevent unintentional ingestions and must encourage practitioners to exercise special vigilance when administering medications to children.

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33 GERIATRIC PRINCIPLES

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PREVALENCE, LETHALITY, AND UNDERRECOGNITION OF TOXIC EXPOSURE

The population is aging steadily across the world. In the United States, people older than 65 years of age comprise not only an increasing proportion of the population at large (13%) but also an increasing proportion of patients seen in medical practices. Compared with all other age groups, patients older than 65 years of age account for one-fourth of emergency department (ED) ambulance arrivals with the highest proportion of patients in EDs triaged as emergent¹⁰² and the highest number of hospital and intensive care unit admissions.¹¹⁷

Although the elderly account for only a small minority of toxicologic exposures, when exposed, they have a high mortality rate. Among exposures reported to the American Association of Poison Control Centers (AAPCC), the fatality ratio for adults (ie, number of cases divided by number of deaths) exhibits a bimodal pattern, declining after age 30 until age 60, when it again rises (Chap. 136). The factors associated with the increased fatality ratio after age 60 are complex but are likely due in part to physiologic vulnerability.

In a separate study, seven specific pharmaceuticals were selected from the AAPCC database for analysis based on their prevalent use and potential toxicity from 1995 through 2002. These pharmaceuticals were theophylline, digoxin, benzodiazepines, tricyclic antidepressants (TCAs), calcium channel blockers, acetaminophen (APAP), and salicylates.¹¹⁴ The death rate from intentional or unintentional exposure to these pharmaceuticals was found to increase by 35% for each decade of life after age 19 years.¹¹⁴ Although prescribing for some of these drugs has dramatically decreased over time, specific categories continue to pose problems for patients in the latest decades of life.^{14,62}

Exposures reported to the AAPCC may underestimate the serious consequences for elderly people exposed to xenobiotics that are toxic or potentially toxic. Data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES) indicate that patients aged 65 years and older accounted for 25% of estimated visits related to adverse drug events (ADEs) and almost 50% of such visits requiring hospitalization or prolonged monitoring in the ED during 2004–2005.¹⁵ Furthermore, the incidence of ADEs increases steeply from age 65 years through the tenth decade of life.¹⁵ More recent NEISS-CADES data indicate that almost 50% of elders who required emergency hospitalization as a result of ADEs are people 80 years of age or older.¹⁴ The problem may be even greater than the NEISS-CADES study suggests, because their data did not capture ADEs in patients treated or dying outside of EDs, ADEs that could only have been recognized after admission, or ADEs that might be erroneously diagnosed as non-drug-related problems.

Toxic exposures in the elderly may be underrecognized for several reasons. First, because of pharmacokinetic and pharmacodynamic changes that occur with aging,³³ which a “standard” therapeutic dose may produce as an unexpected serious effect. Second, the presentation of disease, including drug toxicity, is often atypical in the elderly.⁷¹ For example, falls may be a presenting sign of toxicity in the elderly, with prescribed sedative–hypnotics, opioids, antipsychotics, antidepressants, and certain cardiovascular xenobiotics among the most often associated with an increased risk of falling.^{46,107,115,133}

If the patient is cognitively impaired and the fall is unwitnessed, the immediate consequences of the fall may be adequately addressed, but the xenobiotic and primary etiology causing it may not.⁸⁰ Another important syndrome in older patients is delirium, which may be caused by many factors but is a common presentation of xenobiotic toxicity.⁵⁹ A large variety of xenobiotics may cause mental status changes, which may mistakenly be attributed to non-xenobiotic-related causes in the elderly.¹²⁸ Conversely, altered mental status may be unrecognized^{67,89} or misdiagnosed—for example, as Alzheimer’s disease or psychiatric illness.¹¹¹ A striking case of drug-induced mental status changes is represented by a previously normal 66 year-old man who developed psychosis and attempted suicide after taking increasing doses of dextromethorphan-containing cough syrup for a respiratory infection. The patient was treated with psychiatric medications, and several months elapsed before providers realized that his behavior was xenobiotic-induced rather than due to a primary psychiatric condition.⁹³

Finally, the presentation of drug toxicity may be delayed in elderly individuals. Drugs with long half-lives may not reach a steady state and hence not achieve peak effects until days after the drug therapy is initiated. In some older patients, the active metabolite of flurazepam, desalkylflurazepam, has a half-life of up to 100 hours or longer, which requires days to achieve a steady state.⁵³ When peak effects are delayed in this way, drug toxicities may easily be mistaken for non-xenobiotic-related illnesses.

Table 33–1 lists xenobiotics commonly responsible for toxicity in the elderly.

TABLE 33–1. Xenobiotics That Pose an Increased Risk of Toxicity in the Elderly^a

Anticholinergics
Anticoagulants
Antidepressants
Antipsychotics
Cardiovascular medications
β-Adrenergic antagonists
Calcium channel blockers
Digoxin
Ethanol
Insulin secretagogues
Magnesium and phosphate containing laxatives
Nonsteroidal antiinflammatory drugs
Opioids
Salicylates
Sedative–hypnotics

^aIn addition, polypharmacy may lead to toxicity as a result of diverse drug–drug interactions.

SUICIDE AND INTENTIONAL POISONINGS

The risk of suicide in men increases with age in a bimodal distribution, rising steadily after age 70. Although data for individual ethnic groups are limited, white men have a substantially higher risk of suicide than age-matched cohorts among the African American population.²⁵ Another high-risk group appears to be Native American and Alaskan Native men, although the number of deaths from all causes in elderly men and certain other groups is too low to make meaningful comparisons.²⁵ Among people 65 years of age and older in the United States, white men have the highest rate of suicide of all groups, with almost 32 suicides per 100,000. The rate in the next highest risk group, Asian/Pacific Islander men, is almost 15 suicides per 100,000.²⁵ In women, the suicide rate peaks in midlife and then declines. However, for all age groups, women have a much lower rate of suicide than men; in 2010, for all races combined, the rate for men was 29 suicides per 100,000 and for women was 4.2 suicides per 100,000.²⁵

In the United States, firearms account for far more suicide-related deaths than do poisonings or other methods, particularly in men. The proportion of deaths due to firearm increases steadily after age 50, among men; by age 70 more than 75% of male suicides are by firearms, when all races are combined.²⁵ Suicides by poisoning are much less common in men than women at all ages. In women, poisonings account for similar or greater proportions of suicide than firearms.

Xenobiotic overdose is an important factor in suicide attempts by the elderly of both sexes.⁴⁷ Although less likely than men to complete suicide, women are more likely to attempt it.²⁶ The male-to-female ratio of suicide attempts narrows with increasing age, and in the oldest age groups, men attempt suicide slightly more often than women, when all methods of

attempted suicide are considered (Chap. 27).^{26,124}

Geographic and cultural factors also determine the method of suicide. In countries other than the United States, firearms are much less frequently used to commit suicide at any age, with suicide by oral overdose, toxic inhalation, or hanging comprising a much greater proportion.^{2,130} Among the elderly, the pattern of xenobiotics responsible for suicidal deaths may be changing because selective serotonin reuptake inhibitors are increasingly prescribed for depression instead of TCAs.²⁰ In the United States, higher suicide rates are associated with greater use of TCAs than non-TCA antidepressants,⁵¹ which could be related to greater lethality of TCAs in overdose or poorer tolerability of TCAs leading to nonadherence and enhanced suicide risk. In a Swedish study examining autopsy-confirmed suicides that included analysis of legal xenobiotics, the incidence of suicidal fatalities attributed to benzodiazepines was reported to be increasing despite a marked decrease in benzodiazepine prescriptions.²⁰ Overdose of benzodiazepines is rarely fatal unless it is accompanied by alcohol or another toxin or occurs in the presence of serious medical conditions.⁴⁰ However, the likelihood of fatality from an overdose of benzodiazepine taken alone increases markedly with each decade of life,¹¹⁴ perhaps because benzodiazepines in frail elderly people commonly lead to secondary morbidity and mortality from aspiration pneumonia, falls including hip fracture, and other medical complications that may be the proximate cause of death in the case of overdose.

Notably, flunitrazepam and nitrazepam, the two most frequently implicated in single benzodiazepine suicides in Sweden,²¹ are not available in the United States. However, single-drug suicides have been reported with other benzodiazepines that are available, such as flurazepam, triazolam, diazepam, and oxazepam.^{21,92,94}

SUBSTANCE ABUSE IN THE ELDERLY

Substance abuse declines with age⁴² but is important to consider in older adults under relevant clinical circumstances. Alcohol is the most common substance of abuse in people older than age 65 years. However, in recent years, an increase in the use of illicit xenobiotics and prescription drug misuse has been documented among older adults.¹⁴⁷

Currently, this change is largely noted in adults 50 to 64 years of age, as opposed to those 65 and older;¹²⁷ however, with increasing numbers of people entering the seventh decade of life (including those with past history of abuse disorders), illicit and nonmedical use is expected to increase substantially in older age groups. Unfortunately, a strong case can be made that middle-aged substance abusers have an “accelerated rate of biologic aging” than their nonabusing peers⁷³ and may be less likely to survive into the seventh decade, or, if they do, may be frailer than their same-age peers. However, approximately 22% of people 65 years of age and older use one or more prescription medications with abuse potential, including opioids and other central nervous system depressants.¹²¹

Analgesics are among the most commonly prescribed group of drugs among elderly people, second only to cardiovascular drugs. In one survey of community residing elderly, 23%, 21%, and 52% of those aged 65 to 74, 75 to 84, and 85 and older, respectively, had some exposure to opioids.⁹⁹ Although only a small proportion of people who take opioids are likely to abuse them, concern exists that long-term use could ensue once a prescription is written. In a recent study of elderly opioid-naïve patients undergoing low-risk surgery, those who received a prescription within a week of surgery were 44% more likely to become long-term users within the first year than those who were not given an opioid.³ Although the surgeries themselves were largely for conditions not associated with chronic pain, one cannot conclude that opioid use constituted “misuse,” because the study did not report specific reasons for the ongoing analgesic use. Notably, new users of nonsteroidal antiinflammatory drugs (NSAIDs) were far more likely than opioid users to continue analgesic use in this elderly group of patients,³ who would have been likely to experience chronic pain from a variety of causes.²⁸

Abuse of alcohol or other xenobiotics may be a continuation of long-term habits, but some individuals may first begin later in life.⁷⁵ Substance abuse in late life is probably underrecognized and underreported.¹¹² In one Illinois study of patients presenting to a trauma facility, only 5% of those aged 65 years and older were tested for alcohol or other substances, but among those younger than age 65, 22% were tested for alcohol and 29% for other xenobiotics.¹⁴⁹ Among elderly patients presenting to trauma facilities a large majority have a blood alcohol concentration (BAC) of 80 mg/dL or above.^{118,149} Such results, while similarly found in nonelderly trauma patients,¹⁴⁹ have different implications in the older adult, reflecting a smaller amount of alcohol ingested,^{134,138} owing to changes in body composition, and a greater impact on cognitive and motor function, owing to a diminished tolerance for alcohol (Table 33–2).

TABLE 33–2. Pharmacokinetic Considerations in the Elderly

	Young	Elderly	Effect on Kinetics
Fat (% of body weight)	15	↑30	↑Vd for xenobiotics distributing to fat (amitriptyline, diazepam)
Intracellular water (% of body weight)	42	↓30	↓Vd for water soluble xenobiotics
Muscle (% of body weight)	17	↓12	↓Vd for xenobiotics distributing into lean tissue (APAP, caffeine, digoxin, ethanol)
Albumin (g/dL)	4	↓With acute or chronic illness	↑Free concentrations of xenobiotics if > 90% bound to albumin, especially in overdose; interpretation of serum concentration altered
Liver	Normal	↓Size ↓Hepatic blood flow	Liver enzymes not predictive of compromise; concentrations of xenobiotics with high extraction (propranolol, triazolam) may increase; ↓hepatic oxidation (diazepam, chlordiazepoxide)
Kidney	Normal	↓Renal blood flow ↓GFR ↓Tubular secretion	↑Accumulation (lithium, aminoglycosides, N-acetyl procainamide, ACE inhibitors, cimetidine, digoxin, opioid metabolites)

ACE = angiotensin converting enzyme; APAP = acetaminophen; GFR = glomerular filtration rate; Vd = volume of distribution.

Elderly patients who are tested for BAC may also have positive urine toxicology screening results, although this occurs less often than in younger adults.¹⁴⁹ In one study, the most common xenobiotics detected in the elderly were benzodiazepines, opioids, and barbiturates,¹⁴⁹ which, like alcohol, are more likely to impair older than younger adults. The failure to consider use of these xenobiotics, whether illicit, nonprescription, or prescription, may have serious consequences. When admitted to hospitals, if a careful history is not elicited, withdrawal from these xenobiotics may be missed or misdiagnosed and be inappropriately managed as a result. Given the ongoing “graying” of the “baby boom” generation, greater vigilance will be needed and screening used appropriately.

Some caveats are in order when it comes to the older alcoholic at risk for withdrawal. Studies suggesting a longer duration or greater severity of the syndrome in the elderly have been criticized for their small size, retrospective nature, and absence of middle-aged comparison groups.⁷⁹ However, vigilance is called for because delayed assessment could lead to greater morbidity.⁴⁵ “Hypoactive” delirium, as opposed to typical delirium tremens, may occur, but this could be related to benzodiazepine use, because age-related enhanced sensitivity to these xenobiotics could lead to greater sedation and delirium in elderly who are being treated for withdrawal. Some clinicians may recommend shorter acting benzodiazepines, such as lorazepam rather than chlordiazepoxide,¹¹³ because the latter and its metabolites may be particularly long acting in the elderly and may cause progressive and excessive sedation as the drug and metabolites accumulate. Long-acting benzodiazepines, moreover, are more often associated with injury, including fractures, than short-acting benzodiazepines.¹³¹ Regardless of which benzodiazepine is used for alcohol withdrawal, careful monitoring with symptom-triggered dosing is generally preferable to a fixed-dose schedule in elderly patients, as in all other patients being treated for alcohol withdrawal.

PHARMACOKINETICS

Age-related pharmacokinetic changes have important clinical implications for elderly patients. The most consistent pharmacokinetic change that occurs with aging is a decrease in kidney function. Glomerular filtration rate (GFR) declines, on the average, by 50% between the ages of 30 and 80 years^{37,116} and cannot be accurately predicted by serum creatinine, which does not increase significantly with age,¹¹⁶ because muscle mass, the source of serum creatinine, declines with age.^{81,103}

Because it is impractical and often difficult to measure 24-hour creatinine clearance before instituting therapy with a renally excreted xenobiotic, clinicians commonly estimate creatinine clearance using age-adjusted formulas or nomograms. Frequently applied formulas are fairly predictive of GFR when kidney function is stable.¹⁰¹ However, age-related declines in GFR are not universal, and limited data from longitudinal studies suggest that as many as 33% of elderly individuals do not experience this age-related decline.⁹¹ Conversely, predictive formulas could significantly overestimate actual creatinine clearance in chronically ill, debilitated elderly people, especially those with chronic kidney disease (CKD).⁸⁴ Modifications to the Cockcroft-Gault equation to correct for body surface area^{69,119} and obesity¹⁴⁴ are proposed to better reflect kidney function (Table 28–7). However, anthropomorphic measurements are unreliable in the elderly,^{78,122} and physiologic variability is great. Alternative measurements, such as the Modification of Diet in Renal Disease (MDRD) Study Group equation, serum cystatin C, and others are also proposed, but no current method of estimating kidney function in the elderly appears to be superior for use in the clinical setting.^{125,136} For all of these reasons, it is difficult to accurately predict the renal elimination of xenobiotics or their metabolites in the elderly. A practical solution is to assume that kidney

function has declined significantly and to exercise caution when prescribing maintenance doses of drugs with a narrow therapeutic-to-toxic ratio (Table 33–3). Failure to do so is an important cause of toxicity.⁸⁷

TABLE 33–3. Xenobiotics with Narrow Therapeutic-to-Toxic Ratios and Potential for Accumulation in the Presence of Diminished Kidney Function

Antimicrobials
Aminoglycosides
Imipenem
Pyrazinamide
Vancomycin
Opioids with active metabolites that may cause toxicity
Morphine (morphine 6-glucuronide): respiratory depression; (morphine 3 glucuronide): neuroexcitation
Codeine (morphine)
Hydromorphone (hydromorphone 3-glucuronide): potential for neuroexcitation
Meperidine (normeperidine: neuroexcitation, seizures)
Dabigatran
Digoxin
Glyburide
Heparins (low-molecular-weight)
Lithium
Metformin
Nonsteroidal antiinflammatory drugs
Procainamide (N-acetyl procainamide)
Salicylates

The nature and degree of impact of age-related hepatic changes on drug elimination is controversial. Liver mass decreases with an associated decrease in hepatic blood flow,¹⁴⁶ which results in decreased efficiency of hepatic extraction. Enzymatic processes are often unpredictable,⁷⁷ and although hepatic oxidation appears to decline with age, this change is difficult to demonstrate. There is substantial genetic variability among cytochrome P450 isoenzymes, making it difficult to interpret studies of age-related alterations in oxidative metabolism. Some studies that consider cofactors that could affect hepatic enzymes, such as concurrent xenobiotics or cigarette smoking, or that determine isoenzyme genotype may demonstrate that there is no age-related change in hepatic oxidative enzyme function.¹⁰

Hepatic conjugation does not decline significantly with age, so xenobiotics such as temazepam and oxazepam that are metabolized by these processes do not have prolonged elimination half-lives. In contrast, xenobiotics such as diazepam and flurazepam, which are metabolized by hepatic oxidative enzymes, are eliminated more slowly with age.⁵³ Similar to many oxidized xenobiotics, metabolites of diazepam and flurazepam are active, undergo further metabolism, and remain in circulation after the parent xenobiotic has been metabolized. The active metabolites of some xenobiotics, such as opioids, are renally eliminated, and excretion may be prolonged because of an age-related decline in kidney function (Table 33–3).

Other changes in enzyme systems may occur late in life. For example, a decline in gastric alcohol dehydrogenase activity increases the bioavailability of ingested ethanol in the elderly.¹⁰⁸ The decline in this enzyme is attributed to the increased incidence of gastric atrophy with age. The etiology of the age-related gastric mucosal changes is uncertain, with the relative contributions of underlying *Helicobacter pylori* infection^{7,38} and antiparietal cell antibodies the subjects of research.¹⁵⁰ Whether age-related changes occur in metabolic enzymes that are present in the intestines, brain, kidneys, and

other organ systems and what impact such changes have on drug disposition and drug interactions are also likely to become active areas of research. Studies to date have not demonstrated a substantial effect of age on P-glycoprotein, a transmembrane transport protein involved in xenobiotic interactions in the kidneys, intestines, and other organs.¹¹

Age-related alterations in body composition may affect xenobiotic disposition in later life (Table 33–2). For example, lean muscle mass and total body water decline, and the fat-to-lean ratio increases with advancing age.^{81,103} Thus, highly lipid-soluble xenobiotics tend to have an increased volume of distribution (Vd). As a result, there may be a delay before steady state is reached, and peak effect and toxicity may occur later than expected as demonstrated with amiodarone and certain benzodiazepines. In contrast, xenobiotics that distribute in water, such as ethanol, have a smaller Vd, leading to higher peak concentrations, accounting at least in part for the more pronounced peak effect of ethanol in the elderly. This may also account for the increased BAC attained in an older adult who drinks an equivalent amount of alcohol as a younger person, as noted above.^{134,138}

Protein reserve diminishes with age as a consequence of decreased muscle mass and decreased protein synthesis.¹¹⁰ Although serum albumin concentration remains in the normal range in healthy elderly individuals,¹⁹ elderly people are more likely to experience a rapid decrease in albumin concentrations when experiencing acute or chronic illness or when their protein intake diminishes.^{34,148} A decline in serum protein concentration increases the free or active fraction of xenobiotics that are otherwise highly protein bound. Free xenobiotic is able to travel more readily to the liver and kidney for metabolism or excretion, so a gradual change in the serum protein concentration is unlikely to lead to a change in the patient's response to the xenobiotic. However, these changes may be clinically important for interpreting serum concentrations of highly protein-bound xenobiotics. Clinical laboratories typically measure total xenobiotic concentrations, which include both free and bound xenobiotic. Because most xenobiotic is bound, the reported value reflects mostly bound xenobiotic; therefore, the total xenobiotic concentration may be in the therapeutic range even though the active unbound fraction is actually elevated. Phenytoin, which is highly bound to albumin, serves as an illustrative example. If the serum concentration of phenytoin is reported as subtherapeutic, the physician might order a dose increase even though the free fraction of phenytoin actually is in the therapeutic range. With a dose increase, the free or active fraction may increase to toxic concentrations. Basic xenobiotics are not bound to albumin but to α -1-acid glycoprotein, an acute-phase reactant that tends to increase, rather than decrease, with age.¹ However, the increase attributed to age is most likely related to underlying disease. These unpredictable changes would be expected to have the reverse effect on the ratio of bound to unbound xenobiotic in any laboratory report. However, the correlation between clinical effect and free xenobiotic concentrations requires further study because there may be complex factors involved—for example, alterations in Vd, tissue-specific xenobiotic concentrations, and the contribution of other serum proteins to xenobiotic binding.

The precise contributions of age-related changes in the gastric and intestinal tract to toxicity have not been adequately determined. Changes in gastric absorption are not substantial enough to have an important clinical impact, and if anything, there is a modest decline, partly because of delayed gastric emptying, which could cause a delay in absorption of certain xenobiotics. However, age-associated changes in the gastric mucosa may account for enzymatic changes, as demonstrated in the case of alcohol dehydrogenase, noted above.

PHARMACODYNAMICS

Pharmacodynamic factors may also affect a patient's response to a particular xenobiotic. In general, age-related physiologic changes in target or non-target organs lead to increased sensitivity to most xenobiotics, although sensitivity to some xenobiotics may also be decreased. For example, there is evidence that the sensitivity of the β -adrenergic receptor declines with aging, leading to a diminished response to both β -adrenergic agonists and antagonists.^{31,43,139} However, these experimental findings may not necessarily be demonstrated clinically.^{5,6} Observed enhanced sensitivity to xenobiotics is probably due to altered pharmacokinetics in many, if not most, cases.⁵⁶ Proving that enhanced sensitivity is related to altered pharmacodynamics would require demonstrating that the concentration of drug at the tissue site was not increased as the result of diminished elimination. Regardless of the mechanism, it is important to recognize that the response to a given xenobiotic might be altered in specific ways among the elderly. These altered responses are probably caused less by chronologic aging and more by an increased prevalence of disease.^{28,56} Table 33–4 provides examples of pathologic or physiologic changes that frequently occur in the elderly and disorders that are worsened or unmasked by xenobiotics.

TABLE 33–4. Pathophysiologic Disorders Exacerbated or Unmasked by Xenobiotics in the Elderly^a

Disorder or Alteration	Drug	Possible Outcome
ADH secretion (increased)	Antipsychotics, SSRIs	Hyponatremia
Androgenic hormones (decreased in men)	Digoxin, spironolactone	Gynecomastia
Baroreceptor dysfunction, venous insufficiency	Antipsychotics, diuretics, TCAs, α_1 -adrenergic antagonists	Orthostatic hypotension
Bladder dysfunction	Diuretics, α_1 -adrenergic antagonists	Incontinence
Cardiac disease	Thiazolidinediones	Congestive heart failure
Dementia	Sedatives, anticholinergics, many others	Confusion
Gastritis (atrophic)	NSAIDs, salicylates	Gastric hemorrhage
Immobility, cathartic bowel	Anticholinergics, opioids, CCBs	Constipation; fecal impaction
Nodal disease (sinus or AV)	β -Adrenergic antagonists, digoxin, CCBs	Bradycardia
Parkinson disease; Lewy body dementia	Antipsychotics, metoprolol	Parkinsonism
Prostatic hyperplasia	Anticholinergics, TCAs, doxapramide	Urinary retention
Thermoregulation, disordered	Antipsychotics	Hypo- or hyperthermia
Venous insufficiency	CCBs, gabapentin	Edema

*Disorder may be preclinical.

ADH = antidiuretic hormone; AV = atrioventricular; CCB = calcium channel blocker; NSAID = nonsteroidal antiinflammatory drug; SSRI = serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

UNINTENTIONAL POISONING, ADVERSE DRUG EVENTS, AND THERAPEUTIC ERRORS

Although the elderly account for numerically far fewer poisoning exposures overall, the exposure rate per 100,000 population remains substantial. The contribution of ADEs and therapeutic errors may pose a particular problem for older patients and have become an important part of poisoning exposure analysis in recent years.

The incidence of ADEs among adults increases steadily with age.¹⁵ An ADE is defined as “one that occurs with normal, prescribed, labeled or recommended use of the drug.”¹³ ADEs are more likely to be serious in the elderly than in younger adults. Serious ADEs are those resulting in death, hospitalization, life-threatening outcome, disability, or other serious outcome²³ and are most prevalent among people 85 years of age and older.¹⁸

Likewise, exposures in persons older than age 60 years are often the result of therapeutic errors.^{29,36,62} A therapeutic error is defined as “an unintentional deviation from a proper therapeutic regimen [of a medication or product used as a medication]⁶² that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance;” therapeutic errors also include “unintentional administration of drugs or foods which are known to interact.”¹³ In the NEISS-CADES study, unintentional overdoses (defined as “excessive doses or supratherapeutic drug effects”) accounted for 65.7% of ADE-related hospitalizations in older adults.¹⁴ Risk factors for this age-related vulnerability include physiologic changes that affect xenobiotic disposition or effect, patient errors caused by cognitive or visual impairment, or lack of provider proficiency in geriatric prescribing principles.

In contrast to serious consequences of therapeutic errors or unintentional overdoses, serious reactions can occur with appropriate doses of certain medications. An important example is the neuroleptic malignant syndrome (NMS), which is potentially life threatening.²² Although one might predict it would be more common to occur in late life when abnormalities in thermoregulation are more common,¹² the risk of developing NMS has not been linked to advanced age per se.²² However, antipsychotic drugs are often prescribed to frail elderly, especially those with dementia, and NMS can be overlooked in a patient with comorbidities that could obscure a precise diagnosis. For example, NMS must be distinguished from such geriatric syndromes as cerebrovascular events, heat stroke, or neuroleptic sensitivity syndrome that occurs in Lewy body dementia.²²

Syndromes such as NMS are unpredictable and relatively rare at any age. Among elderly patients, serious or life-threatening ADEs are more typically caused by commonly prescribed drugs, such as anticoagulants, insulin, cardiovascular and insulin secretagogues and drugs that cause delirium, such as sedative-hypnotics, opioids, and anticholinergics (Table 33-1).

As many as 42% of serious ADEs reported in elderly patients are potentially preventable.^{8,57,58} NEISS-CADES data reveal that drugs requiring careful outpatient monitoring are disproportionately represented among ED visits attributed to unintentional drug overdose.^{14,16} Data from 2007 to 2009 indicate that warfarin, insulins, antiplatelet agents, and insulin secretagogues accounted for an estimated 67% of ADE-related hospitalizations in people 65 years of age and older, with digoxin and anticonvulsants contributing another 5.2%.¹⁶ The previously mentioned medications can be supervised with therapeutic as well as clinical monitoring. For certain other medications, ADEs are often best prevented by not prescribing them to vulnerable patients or by cautioning against their use if they are available without prescription. Criteria have been developed to guide clinicians regarding these “potentially inappropriate medications” (PIMs) in elderly patients.⁴ Xenobiotics deemed potentially inappropriate in the elderly have caused numerically fewer ADEs than more frequently prescribed xenobiotics,^{14,16,100} but consensus as well as evidence exist that they are strongly associated with adverse outcomes in elderly patients, including hospitalization and mortality.^{4,48,85} PIMs are also linked to enhanced risk of specific ADEs. For example, the elderly are at enhanced risk of severe upper gastrointestinal (GI) bleeding from NSAIDs.¹⁴⁵ Although this could be partly explained by increased exposure to and regular use of these drugs for chronic conditions, older adults may be more vulnerable to their effects because of underlying atrophic gastritis. The elderly are also at greater risk of prolonged hypoglycemia from certain sulfonylureas, particularly glyburide (glibenclamide).¹²⁰ Age-related mechanisms to explain this vulnerability to glyburide may include a decreased counterregulatory hormonal response to xenobiotic-induced hypoglycemia,⁹⁷ inappropriate stimulation of insulin if hypoglycemia is present,¹²⁹ or reduced excretion of a renally eliminated active metabolite of glyburide.⁷² Finally, as noted earlier, data gleaned from ED visits do not capture problems that occur and may or may not be managed in other settings. Other age-related factors involved in enhanced susceptibility to ADEs are given in [Tables 33–2 and 33–4](#).

ADVERSE DRUG EVENTS: RECOGNIZING RISK AND AVOIDING PITFALLS

A complicated medication regimen reduces adherence,⁹⁸ increases errors, and increases the risk of clinically important xenobiotic interactions. Geriatric patients take more prescription and nonprescription xenobiotics than any other patient group.⁷⁴ The likelihood of experiencing an ADE increases with the increasing number of xenobiotics taken.⁶⁵ The problem can be amplified by the common practice of pharmacies to fill an ongoing prescription of a particular medication with different brands over time; this diversity is expected but often problematic, and it is not necessarily accompanied by an adequate discussion with the patient or caregiver, or in the case of a mail order pharmacy, without highlighting the change. The new drug will differ in size, shape, or color from the medication previously dispensed, sometimes also appearing similar or identical to a different medication on the regimen, and medication errors can occur. The same problem can occur when a generic version of the prescribed medication replaces the drug with the “brand” name.

Concurrent disease in target or nontarget organs may alter the patient’s sensitivity to a xenobiotic, resulting in a serious ADE even when the patient is given a standard or previously used dose. Coexistent disease is often subclinical, and the patient’s enhanced sensitivity may not be anticipated. For example, a patient with subclinical Alzheimer disease whose cognitive function is overtly normal may acutely develop delirium or symptoms of dementia when given standard doses of drugs such as sedative–hypnotics or TCAs. Delirium is a medical emergency and an important cause of ED visits by the elderly.⁶⁷

Another factor contributing to ADEs is physician’s lack of knowledge with regard to the principles of geriatric prescribing.^{41,60,105} In addition to prescribing inappropriate doses or increasing the dose too rapidly, clinicians may prescribe drugs considered potentially inappropriate for the elderly at any dose, such as TCAs, anticholinergics, and long-acting benzodiazepines.⁴ At a minimum, and particularly in the case of potentially inappropriate medications, it is reasonable to attend to specific risk factors outlined here and elsewhere in an effort to prevent ADEs.

Another problem is that clinicians may be unduly ready to prescribe drugs recently on the market, despite availability of acceptable and often less expensive alternatives. Recently approved medications are sometimes promoted as being safer than older ones, but problems often become apparent only after marketing and use by large numbers of patients. For example, the hypnotic agent zolpidem was marketed as a safe alternative to benzodiazepines for the elderly. However, like benzodiazepines, zolpidem may cause confusion, global amnesia, memory loss, and falls.^{140,142} Low-molecular-weight heparins (LMWHs), such as enoxaparin and dalteparin, are other examples. LMWHs have more predictable pharmacokinetics than unfractionated heparin and are associated with a lower rate of overall bleeding. However, because therapeutic monitoring requires measurement of anti-factor Xa activity, which is not as readily available as standard tests such as activated partial thromboplastin time (aPTT), monitoring is usually not performed.⁶⁴ LMWHs such as enoxaparin and dalteparin are eliminated by the kidneys, and repeated doses lead to progressive increases in antifactor Xa activity when GFR is 30 mL/min or below,^{27,90} a degree of CKD that is common in frail elderly patients. Less severe levels of CKD may also result in reduced enoxaparin clearance that might be avoided with lowered doses.⁶⁶ Most reported cases of

serious, unexpected enoxaparin-induced bleeding occur in elderly patients who are receiving “standard,” not age-appropriate, dosing.^{96,135,137} Similar problems should be anticipated with other new anticoagulants. For example, the release of dabigatran, a renally eliminated direct thrombin inhibitor approved in 2010 for management of atrial fibrillation, was soon followed by many reports of severe GI bleeding and hemorrhagic stroke in the United States⁴⁴ and internationally.⁶³ The latter source specifically noted the preponderance of elderly patients in the reports. This finding is consistent with its use in atrial fibrillation, which is most prevalent among the elderly. Whether the risk of dabigatran is greater than that of warfarin is not known, because direct reports to the Food and Drug Administration (FDA) and others in the postmarketing period are not subject to comparison with other xenobiotics.¹²³ Likewise, it is premature to conclude that lack of monitoring or failure to adjust for occult CKD is a cause; however, the clinical trial supporting approval of dabigatran, which randomized subjects with mean age of 71 years, specifically excluded those with estimated GFR \leq 30 mL/min.³² Importantly, anticoagulants in general remain among the most important causes of ADEs, therapeutic errors, and hospitalizations.^{14,62} For elderly patients in particular, it is essential for clinicians to be mindful of the possible presence of occult CKD and lesions with the potential to bleed in order to reduce untoward bleeding in this high-risk group of patients.

It is not surprising that ADEs are first noted following drug approval in the postmarketing period when actual patients (as opposed to carefully selected research subjects) are exposed to the drug, because drugs and their effects are often inadequately studied in the elderly (Chap. 139).^{17,86} Reactions occurring in a small percentage of patients in a special subgroup can easily be missed during the initial drug evaluations. Even when a substantial number of subjects older than age 60 years are studied, a much smaller proportion of patients older than age 70 years may be included in clinical trials.⁸⁶ Thus, the adults at highest risk for many forms of toxicity are in a population that is often the least studied. Xenobiotic testing is typically carried out in subjects who are young adults and disease free, so pharmacokinetic profiles do not reflect patterns of xenobiotic disposition characteristic of geriatric patients. Pharmacokinetic testing may be limited to a one-time dose, and frequently the evaluation takes place over a short period of time. On average, approximately five half-lives of a xenobiotic are necessary to achieve steady-state xenobiotic concentrations (Chap. 9). Thus, a xenobiotic with a half-life of 24 hours might not reach a steady state for 5 days, and in the presence of prolonged elimination associated with age-related factors, a steady state might not be reached for substantially longer. As a result, even if elderly subjects are included in a drug trial, the ultimate effect might not be appreciated during testing intervals designed for younger patients.

Another factor is the nature of pharmaceutical research itself. Morbidity and mortality in elderly patients as a result of specific drugs might be avoided if the responsible drugs were studied under the predictably high-risk conditions typically present in the elderly. For example, xenobiotics eliminated by the kidney need to be evaluated after repeated dosing in elderly subjects. Gatifloxacin was removed from the market only after several years of use when it was finally linked to both hypoglycemia and hyperglycemia in large numbers of elderly subjects.^{55,106} Adverse events from xenobiotics that are studied in the elderly or others with chronic illness may be less obvious in the presence of comorbidity in the population at risk. The cyclooxygenase-2 (COX-2) inhibitor rofecoxib (Vioxx) was withdrawn from the market in 2004 after it was shown to increase the risk of myocardial infarction and stroke, especially in older adults.³⁹ Based on the complex actions of COX-1 and COX-2 in many tissues, the possibility existed that COX-2 inhibition might increase cardiovascular morbidity, for example, by leaving COX-1-mediated platelet aggregation unopposed while inhibiting prostacyclin-induced vasodilation or by leading to fluid retention and increased blood pressure via renal mechanisms.^{61,109} Because the elderly typically have one or more chronic illnesses²⁸ as well as occult disease, extra vigilance is required when new xenobiotics are given, and clinicians and clinical investigators must be very mindful of the theoretical possibilities of adverse outcomes. In view of the vulnerability of older patients to many medications, the FDA now requires that sponsors of new drug applications present effectiveness and safety data for important demographic subgroups, including the elderly, in their FDA submission data.²⁴ However, exceptions to the rule are allowed. For example, when studies have included insufficient numbers of subjects older than age 65 years to determine whether the elderly respond differently to the drug, the labeling must state this, but the statement is a poor substitute for providing actual efficacy and safety data.³⁰ Unfortunately, geriatric recommendations in the package insert may thus be insufficiently specific to provide guidance for drugs commonly used in this population.¹²⁶

Drugs, such as digoxin, warfarin, and diuretics, commonly prescribed in the elderly, are frequently involved in serious drug interactions. This situation is complicated by the frequency with which elderly patients, who often have multisystem disease, visit multiple physicians, who prescribe medications without specific knowledge of, or attention to, the remainder of the patient’s drug regimen, thereby increasing the risk of inappropriate combinations.^{52,132} Problems can also arise when patients obtain prescriptions from more than one pharmacy or mail order service. Warfarin is a particular problem, owing to its narrow therapeutic index and numerous pharmacokinetic as well as pharmacodynamic interactions, the potential for which (eg, with certain antibiotics) may often be ignored at the point of care.⁵⁰

Herbal preparations used by the elderly also may interact with prescription medications.⁷⁰ The use of herbal preparations has increased substantially in recent years, particularly in patients with illnesses such as cancer, dementia, and depression, which commonly affect the elderly. Very few patients voluntarily report use of these or other nonprescribed therapies to their physicians, and too often the physician fails to inquire specifically about such “alternative” or

“complementary” therapies. Poisonings, herb–drug interactions, and other problems related to herbal preparations are discussed further in [Chap. 45](#).

The use of nonprescription pharmaceuticals may also cause serious adverse effects. For example, excessive use of magnesium-containing preparations frequently causes severe toxicity in older individuals. Impaired GFR, decreased GI motility, and other medical comorbidities are just three risk factors that potentiate magnesium toxicity in the elderly. The source of magnesium in these cases may include the cathartics that contain magnesium hydroxide (Milk of Magnesia) and magnesium citrate, antacid preparations, and magnesium sulfate (Epsom salts).⁴⁹ Magnesium-containing laxatives are still sometimes used in hospital settings with serious outcomes.¹⁰⁴ Likewise, sodium phosphate formulations may harm kidney function in certain elderly patients despite normal baseline creatinine.⁷⁶ Virtually all of the most popular nonprescription medications⁷⁴ are more likely to produce problems in the elderly than in younger patients, including GI bleeding (aspirin and other NSAIDs), enhanced warfarin sensitivity (cimetidine), confusion and urinary retention (anticholinergic antihistamines), and cardiovascular symptoms (pseudoephedrine).

Outdated and discontinued xenobiotics are an additional problem for the elderly, who often retain unused or partially used products in their homes for decades or may continue to request prescription renewals when safer or more effective alternatives are available. Patients may be unwilling to change or physicians may continue to renew the prescription without sufficiently reevaluating the patient. Potential examples include digoxin and theophylline, which have been responsible for large numbers of adverse events diagnosed in EDs,^{14,15} as well as sedating antihistamines, other anticholinergics, and diazepam.

Other age-related factors may increase the risk of unintentional poisonings in geriatric patients; impaired vision, hearing, and memory may lead to misunderstanding or an inability to follow directions concerning the use of prescription and nonprescription drugs. Dementia is another important risk factor in unintentional poisonings. In addition to cognitive impairment, patients with dementia sometimes exhibit abnormal feeding behaviors, which may lead to ingestion of toxic xenobiotics.¹⁴³

MANAGEMENT

Management decisions must be made with the foregoing principles in mind. GI decontamination should proceed as in younger patients. However, because constipation is a more frequent problem in the elderly, when multiple-dose activated charcoal is used, particular attention must be paid to GI function and motility. The specific precautions and contraindications in the basic management and GI decontamination detailed in [Chap. 8](#) are particularly pertinent for the geriatric population.

The presence of clinical or preclinical congestive heart failure or CKD may increase the risk of fluid overload when sodium bicarbonate is used. In the elderly, extracorporeal removal may be indicated earlier in cases of salicylate, lithium, or metformin poisoning, in which elimination may be hampered by a decreased GFR.

A situation that may go unrecognized in geriatric patients is the problem of alcohol or other substance withdrawal syndromes. Because elderly patients are typically not perceived as substance abusers, or because a physician evaluating an unfamiliar patient may not be aware of the patient’s chronic use of prescribed benzodiazepines or opioids, the possibility of substance withdrawal may not be considered when unanticipated complications occur during hospitalization.

Strategies to limit unintentional toxic exposures in elderly patients with cognitive or sensory impairment should be similar to those used in young children, who are also at high risk of ingesting toxic substances or pharmaceuticals prescribed for others in the household. The strategies should include the removal of potentially dangerous and unnecessary xenobiotics from the patient’s environment. The physician should request that the patient or caregiver bring all medications to the office in the original bottles. The physician should then make an effort to limit the number of medications prescribed or to seek alternative medications with a safer therapeutic index or appropriate geriatric safety profile. Administration and control of the medications by directly observed therapy may, of necessity, become the responsibility of the caregiver rather than the patient.

CRITERIA FOR ADMISSION AND TIMING OF DISCHARGE

When geriatric patients are evaluated in the ED for poisonings or serious ADEs, the need for hospital admission should be weighed carefully against the known hazards of hospitalization for the elderly.³⁵ The physician should be particularly alert to certain situations that might mandate admission, including unexplained mental status changes, overdose of a prescribed medication with a prolonged duration of action, or evidence of inadequate home care or elder abuse/neglect, such as poor hygiene or unexplained injury.

When there is concern that the established caregivers at home may be abusing or neglecting the patient, the patient requires further observation, removal from the environment, and possibly hospitalization. Signs of actual physical abuse may be more obvious than signs of neglect.⁸² Vulnerable elderly who are physically disabled or cognitively impaired may

be brought to the hospital because of presumed illness, but the source of the problem may actually be the caregiver. The caregiver, frequently but not necessarily a family member, may be depleting the patient's funds for personal use. Patients may become ill because funds were diverted from the purchase of food or because the patient's prescription drugs were sold on the street. More direct abuse may take the form of intentional poisoning or oversedation of the patient by overdose of the patient's own prescription drugs, or selling the patient's medications (diversion), resulting in clinical deterioration. Provision for follow-up care, such as an alternative place to live and guardian appointment, is essential because abuse and neglect are associated with serious outcomes.⁸³

Unresolved mental status changes may require close observation and hospitalization. Elderly patients who are confused or unable to walk are sometimes mistakenly assumed to be chronically impaired. However, incomplete explanation of an altered mental status or physical impairment should prompt careful inquiry into the patient's baseline functional status. Poor function should never be assumed to be "normal aging." Many very elderly patients are cognitively normal, physically robust, and independent in all activities of daily living.

A patient whose problem has been attributed to overdose with or accumulation of a long-acting medication requires careful monitoring. Because the durations of action may be markedly prolonged among geriatric patients, a higher degree of vigilance is required. An important example is chlordiazepoxide, which is commonly used for alcohol withdrawal and exhibits very long half-life in older patients, especially after repeated dosing. The ultra-long-acting sulfonylurea chlorpropamide is rarely used today, but glyburide may cause relatively prolonged hypoglycemia compared with other insulin secretagogues, as noted above.

SUMMARY

- Older patients may account for only a small fraction of total poisoning victims, but when poisoned, they have a high mortality rate.
- The elderly are much more likely to experience serious ADEs as a consequence of both appropriate and inappropriate use of medications.
- Attention to risk factors is essential in this vulnerable population.
- Important risk factors include pharmacokinetic and pharmacodynamic changes; the presence of overt or subclinical disease, including dementia; patient and provider error; suicide risk; complex therapeutic drug regimens; and a general lack of knowledge about the principles of prescribing for the geriatric population.

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34 POSTMORTEM TOXICOLOGY

Rama B. Rao and Mark A. Flomenbaum

Postmortem toxicology is the study of the identification, distribution, and quantification of xenobiotics after death. This information is used to account for physiologic effects of a xenobiotic at the time of death through its quantification and possible redistribution in the body at the time of autopsy. Several variables may cause changes in xenobiotic concentrations during the interval between (1) the time of death and subsequent autopsy and (2) the storage interval between the time of sampling and the time of testing. Toxicologists and forensic pathologists are frequently asked to interpret postmortem xenobiotic concentrations and decide whether the reported values are meaningful and whether these xenobiotics were incidental or contributory to the cause of death.

The development of the field of forensic toxicology and the improvement of laboratory technology now permit more refined identification and quantification of xenobiotics. The interpretation of postmortem xenobiotic concentrations and their significance, however, continues to evolve.

This chapter reviews factors that affect xenobiotic concentrations identified at autopsy and discusses an approach for interpreting postmortem toxicologic reports as they relate to the cause and manner of death.^{38,41,43,49–51,59,69,79,97}

HISTORY AND ROLE OF MEDICAL EXAMINERS

The relationship between antemortem xenobiotic exposures and death has been a subject of investigation for centuries. In 12th-century England, an appointee of the royal court, eventually named the coroner, was designated to record and identify causes of death.⁷³ In suspicious circumstances, coroners investigated poisonings, but scientific methods were primitive, and conclusions regarding such deaths were conjecture at best.

By the mid-19th century, however, techniques for detecting certain xenobiotics in postmortem tissue were developed and focused generally on identifying heavy metals as a cause of death in homicides.^{44,73,77,94,99} At that time, coroners were still elected or appointed individuals with little or no medical training. However, with better laboratory techniques and autopsies being performed by trained pathologists, the specialty of forensic medicine continued to develop. In late 19th-century Massachusetts, trained pathologists, referred to as medical examiners, ultimately replaced the coroner system and were eventually empowered by the state to investigate certain types of unusual or suspicious deaths (medicolegal autopsies).⁷³ Currently in the United States, legal jurisdiction of death investigations is the responsibility of either a coroner or a medical examiner depending upon the state or county, with 19 states using medical examiner systems almost exclusively.⁴⁸

The medicolegal autopsy, ideally, is performed by a forensic pathologist who attempts to establish the cause and manner of death (Table 34–1). The cause of death is the etiology ultimately responsible for death to occur. For example, the presence of cyanide in the toxicologic evaluation may be sufficient to establish cardiorespiratory arrest from cyanide poisoning. The manner of death is an explanation of how the death occurred, or the circumstances surrounding the terminal events. It broadly distinguishes natural from nonnatural (or violent) deaths. Nonnatural deaths, depending on the jurisdiction, may be divided into several categories (Table 34–2). With the identification of cyanide, the manner of death cannot be considered natural because a poisoning is a “chemically traumatic” (violent) event. The medical examiner must make the best determination of the manner of death based on the available evidence.^{99,106} An unintentional exposure may be classified as an accident (a legal term for some unintentional nonnatural deaths), and intentional self-injury may be classified as a suicide. If the circumstances indicate an exposure due to the acts of another person, the manner of death is classified as a homicide.

TABLE 34–1. Information Used by Forensic Pathologists

Autopsy

Evidence from the crime scene

Laboratory investigations

- Medical consultants
- Available history
- Medical records
- Police reports
- Interviews with contacts

TABLE 34–2. Categories of Manner of Death

- Natural
- Nonnatural
- Homicide
- Suicide
- Accident
- Therapeutic complication^a
- Undetermined

^aNot all jurisdictions recognize therapeutic complication as a manner of death.

Determination of the manner of death has important consequences. Homicide necessitates involvement of law enforcement officials for further investigation. Cases deemed suicide not only impact survivors psychologically but also may nullify some life insurance payments. Conversely, a case deemed an “accident” may have a double-indemnity insurance clause. Assignment of financial responsibility for workplace deaths may be similarly affected when xenobiotics are identified in the postmortem specimens of involved workers.

Recognition of xenobiotic-related deaths also has significant public health consequences. The forensic pathologist may be the first to identify and report critical information regarding fatal drug reactions, medication errors, rapidly fatal epidemics associated with illicit xenobiotic use or malicious intent activities. In cases of occupational and environmental xenobiotic-related fatalities, interventions can be implemented to prevent subsequent morbidity and mortality. In addition, the pathologist describes gross and microscopic autopsy findings that may elucidate mechanisms of xenobiotic toxicity.

Postmortem toxicologic techniques may be used in other types of investigations as well. For example, when carboxyhemoglobin is identified in burned human remains from an airplane crash, a cabin fire before descent is more probable than deaths due to a fire on impact. This type of postmortem analysis is useful in the reconstruction of events leading to the crash.^{8,55,64,98}

THE TOXICOLOGIC INVESTIGATION

Ordinarily, toxicologic samples are collected as part of a complete autopsy. In the hospital, when a death is assumed to be from natural causes, the hospital pathologist may perform an autopsy with the consent of the family. In a medicolegal investigation, however, the forensic pathologist determines the need for a complete or partial autopsy and has statutory authority to act on that determination independent of familial consent. Occasionally, only fluid samples may need to be obtained along with an external inspection of the body if a complete autopsy is either unnecessary or the family has legal or religious grounds for objection. The precise list of xenobiotics screened in postmortem samples varies greatly by jurisdiction. Investigations in large cities may routinely screen for hundreds of illicit, therapeutic, and environmental xenobiotics. Occasionally, the suspicions of the medical examiner or death scene investigator warrant special assays that are performed only upon request.

The sampling of fluid and tissue may be obtained minutes to years after death. The postmortem interval, defined by the time between death and autopsy, is important, but many other factors will define the extent of bodily decomposition. This is dependent on environmental conditions such as ambient temperature, humidity, aerobic versus anaerobic surroundings, and immersion in water.⁶⁵ Samples may be collected from a body during advanced stages of decomposition, after exhumation from graves, or even after embalming.^{8,37,38,45,62,78} Knowing the condition of the body at the time of sampling assists in interpreting the toxicologic findings. These postmortem changes are reviewed below.

DECOMPOSITION AND POSTMORTEM BIOCHEMICAL CHANGES

The first stage of decomposition is autolysis, during which endogenous enzymes are released and normal mechanisms maintaining cellular integrity fail.⁵⁸ Chemicals move across compromised and leaky cellular membranes down relative concentration gradients. Glycolysis continues in the red blood cells until intracellular glucose is depleted, and then lactate is produced. Ultimately, intracellular ions and proteins are released into the blood, and tissue and blood acidemia develops leading to the biochemical changes described in Table 34–3.⁹⁹

TABLE 34–3. Postmortem Biochemical Changes over the First 3 Days^a

Increased	Decreased	Stable	Variable
Amino acids	Cl ⁻	BUN/Cr (vitreous)	Lipids
Ammonia	Glucose	Cholinesterases	T ₃
Ca ²⁺ , K ⁺ , Mg ²⁺	Na ⁺	Cortisol (serum)	
Epinephrine	pH	Proteins (serum)	
Hepatic enzymes	T ₄	Sulfates	
Insulin (especially right heart blood)			

^aIn refrigerated bodies.

BUN = blood urea nitrogen; Cr = creatinine; T₃ = triiodothyronine; T₄ = thyroxine.

The next stage of decomposition in most normal environments is putrefaction. This stage involves digestion of tissue by bacterial organisms, which typically colonize the bowel or respiratory system. Later, additional organisms may be introduced by insects or other external sources. As the putrefactive process advances, the colors of the skin and organs change; epithelial blebs may form and separate from the underlying dermis; and gases may accumulate, resulting in foul odors and bloating.⁹⁹

If death occurs in a very warm, dry climate, such as a desert or comparably arid environment, the body may desiccate so rapidly that putrefactive changes may not occur. This results in mummification and produces a lightweight cadaver with a tight, dry skin enveloping a prominent bony skeleton.⁹⁹

If the environment is very cold and devoid of oxygen, such as at great depths under water, putrefaction will be slowed. Anoxic decomposition of fatty tissues occurs, forming a white, cheesy material known as adipocere.

Another phase of decomposition, anthropophagia, occurs in unprotected environments where insects or other animals feed on the remains.⁹⁹

Because most postmortem changes are derived by chemical reactions and are temperature dependent, with increased temperatures accelerating the process and cooler temperatures retarding it. In general, morgue refrigerators achieve low enough temperatures (40°F {4°C}) to prevent further gross decomposition and many associated postmortem changes.

Another process that alters natural decomposition is embalming, a process of chemically preserving tissues that may be performed in a variety of ways.^{46,47} Typically, blood is drained through large vessel pumps, and an embalming fluid is injected intravascularly to perfuse and preserve the face or other tissues. Intracavitary spaces may be injected with the preserving substances, and solid organs may or may not be removed.

SAMPLES USED FOR TOXICOLOGIC ANALYSIS

Unless the medical examiner is suspicious about a death, only standard autopsy samples will be available in an otherwise intact body.^{24,38,53,60,82,97} These typically include samples of blood, gastric contents, bile, urine, and occasionally solid organs such as the liver or brain. Less commonly, vitreous humor is obtained for analysis (Table 34–4). If the decedent was hospitalized before death, antemortem specimens may also be available for evaluation and comparison. These specimen analyses are reviewed in greater detail below.

TABLE 34–4. Sampling Sites^{16,21,25,37,51,92}

<i>Routine</i>	<i>Infrequent</i>	<i>Uncommon</i>
Bile	Antemortem blood	Casket fluid
Blood	Cerebrospinal fluid	Extravasated fluid
Brain	Fat	Extravasated blood
Gastric contents	Hair	Insect larvae
Liver	Kidneys	Pupae casings
Vitreous humor	Muscle	
	Nails, skin	

Blood

Postmortem cell lysis limits the concept of plasma concentrations, and “blood” concentrations are reported instead. Most commonly a single site such as femoral or subclavian blood is usually sampled unless an unusual xenobiotic with nonuniform distribution is suspected of causing the death. In patients with a prolonged postmortem interval and in cases where intravascular blood is coagulated, right heart blood may serve as an alternative sample site.

Other sources of blood may sometimes be available to the forensic pathologist. These frequently include antemortem samples and occasionally extravasated blood, which is unlikely to undergo extensive metabolism. Intracranial clots, in particular, serve as useful comparative samples in patients with a prolonged survival period after exposure to a xenobiotic.⁶⁶

In advanced states of decomposition, blood from the abdominal or thoracic cavities is less useful because it may be contaminated by bacteria or other substances that may affect xenobiotic recovery or analysis.

Vitreous Humor

Because of the relatively avascular and acellular nature of the fluid, the vitreous humor is well protected from the early decompositional changes that typically occur in blood.^{16,19–21,25} When bodies are immediately refrigerated, creatinine, blood urea nitrogen, and sodium can be reliably approximated from vitreous humor samples for up to 3 or 4 days. Potassium concentrations are less reliable because cell lysis causes intracellular release. When vitreous glucose is elevated, hyperglycemia at the time of death can be assumed. A low vitreous glucose concentration, however, is a less reliable indicator of the antemortem serum glucose concentration, because a low vitreous glucose concentration may be attributable to either antemortem hypoglycemia or postmortem glycolysis even in the relatively avascular vitreous.

The aqueous content of the vitreous is normally higher than that of blood and may affect the partitioning of certain water-soluble xenobiotics, such as ethanol.

Urine

Urine may be available during the autopsy and may reveal renally eliminated substances or their metabolites. Because the bladder serves as a reservoir in which metabolism is unlikely to occur, the concentrations of xenobiotics obtained during the autopsy reflect antemortem urine concentrations. An isolated urine sample is of limited quantitative value but may be useful when compared with other sample sites.

Gastric Contents

The gross contents of the stomach are inspected for color, odor, and the presence or absence of pill fragments, food particles, activated charcoal, and other foreign materials.⁹⁷ Typically, gastric concentrations of xenobiotics are reported as milligrams of substance per gram of total gastric contents. Xenobiotic-induced pylorospasm, diminished intestinal motility, or decreased splanchnic blood flow may all decrease gastric emptying and affect the quantitative values obtained from sampling different parts of the gastrointestinal tract.

Solid Organs and Other Sources

Xenobiotic concentrations in solid organs, such as the liver and brain, are usually reported as milligrams of substance per kilogram of tissue. Other tissue samples, including hair and nails, are used for thiol-avid xenobiotics such as metals. Rarely, tracheal aspirates of gases may be analyzed to confirm inhalational exposures. Pleural fluid analysis of postmortem xenobiotics typically yields qualitative results in decomposed bodies because redistribution of xenobiotics from the stomach and intestines may occur.^{32,89}

OTHER SAMPLING SOURCES

In an embalmed body, either the organs or tissues that remain relatively unembalmed, such as deep leg muscle,⁶⁸ or the embalming fluid itself may be used for analysis. Some authorities regulate the contents of embalming fluid specifically to avoid confounding postmortem analysis. Most embalming fluid in the United States consists of formaldehyde, sodium borate, sodium nitrate, glycerin, and water. When a body is disinterred, soil samples are usually obtained from above and below the coffin to permit identification of xenobiotics that may have leached into or out from the body.⁷⁸

On rare occasions, cremated remains, often referred to as cremains, are the only source of sampling available. Most metallic implants, such as pacemakers, are removed before cremation, and only dental remains, particulate matter, and occasionally calcified blood vessels are available for analysis.^{3,105} In most cremations performed in the United States, the incineration process is followed by mechanical grinding to yield a fine particulate matter.¹⁰⁵ The ability to extract xenobiotics from cremains is markedly limited at best, and little published data are available on the subject. A new technique to identify heavy metals such as lead from cremains has been described, but is not routinely used at present.^{3,105}

ENTOMOTOXICOLOGY

A variety of other anthropophagic insect species may demonstrate the presence of xenobiotics.^{1,42,62,63} This process of analysis is termed entomotoxicology. In putrefied bodies or bodies that have undergone anthropophagy, fluids and even insect parts can be analyzed. Forensic entomologists can collect samples of these insects from the remains. After taking into account the stage of insect life, environmental conditions, and the season, the approximate time of death can be extrapolated. The species Calliphoridae, or the bluebottle fly, is attracted to unprotected remains by a very fine scent that develops in the cadaver within hours of death. The adult fly lays eggs on mucosal surfaces or in open wounds. After the eggs hatch, the larvae feed on the decomposing tissue. Larval samples can then be examined for the presence of xenobiotics. To achieve accurate analysis, these samples must be preserved immediately after collection because living larvae can continue to metabolize certain xenobiotics. In another phase of their life cycle, the larvae undergo pupation, secreting a substance that encloses them into pupal casings until they hatch as adults. These pupal casings are often found in the soil beneath the body. Some xenobiotics have been identified in the casings long after the adult fly has emerged⁸⁴ (Table 34–5).

TABLE 34–5. Xenobiotics Reported from Larvae and Pupae Casings

Benzoyllecgonine

Cocaine

Heroin

Malathion

Mercury

Methamphetamine

Morphine

Nortriptyline

Oxazepam

Phenobarbital

Triazolam

INTERPRETATION OF POSTMORTEM TOXICOLOGY RESULTS

After fluid and tissue samples have been collected and analyzed for the presence of xenobiotics, the process of interpreting these results begins. This complex task attempts to account for the clinical effects of a xenobiotic at the time of death by integrating medical history, autopsy, death-scene findings, and toxicologic reports. Multiple confounding variables may affect the sample concentrations of xenobiotics from the time of death to the time of testing after the autopsy. Variables include the nature, metabolism, and distribution of the xenobiotic; the state of health of the decedent prior to death; physical

and environmental variables during the postmortem interval; the techniques of analysis; and other findings of the autopsy (Tables 34–6 and 34–7).

TABLE 34–6. Considerations in Interpreting Postmortem Xenobiotic Concentrations

<i>Xenobiotic Dependent</i>	<i>Decedent Dependent</i>	<i>Autopsy Dependent</i>	<i>Other</i>
Pharmacokinetic considerations	Comorbid conditions	Handling and preservation	Laboratory techniques
State of absorption or distribution at time of death	Tolerance	Postmortem interval: State of preservation or decomposition	Evidence at scene
Postmortem redistribution	Pharmacogenetic variability	Sample sites	Previously published tissue concentrations
Postmortem metabolism		Specimens sampled	
Pharmacodynamic considerations			
Expected clinical effects			
Synergistic interactions			
Postmortem xenobiotic stability during			
Putrefaction			
Preservation			

TABLE 34–7. Xenobiotic Stability and Laboratory Recovery^{10,12,23,28,74,80,81,88}

Quantitative recovery affected by preservatives

As, Ag, Cu, Hg, Pb
Carbon monoxide
Cyanide
Ethchlorvynol
Nortriptyline (converted to amitriptyline in fixatives)

Chemical stability in formalin

Stable

Diazepam
Phenobarbital
Phenytoin (30 days)
Succinylcholine

Labile

Desipramine

Chemical stability in putrefying liver

Stable

Acetaminophen
Amitriptyline
Barbiturates
Chloroform
Clemastine
Dextropropoxyphene
Diazepam
Doxepin
Flurazepam
Glutethimide
Hydrochlorothiazide
Imipramine
Lorazepam
Methaqualone
Morphine
Nicotine
Paraquat
Pentachlorophenol
Plant alkaloids
Quinine
Strychnine

Labile

o,p-Aminophenols
Chlordiazepoxide
Chlorpromazine
Clonazepam
Malathion
Metronidazole
Nitrofurazone
Nitrazepam
p-Nitrophenol
Obidoxime
Perphenazine
Trifluoperazine

Variables Relating to the Xenobiotic

Postmortem Redistribution. The xenobiotic concentration in blood may be higher during the time of sampling at autopsy than at the actual time death occurred if significant postmortem redistribution occurs.^{54,81,104–111} Redistribution typically occurs with xenobiotics that have large volumes of distribution and when decomposition results in release of intracellular xenobiotic into the extracellular compartment.⁸⁶ For example, amitriptyline may be released from tissue stores into the blood as autolysis progresses, resulting in a significantly higher blood concentration during the autopsy than at the time of death. If postmortem redistribution is not considered, xenobiotic concentrations obtained during the autopsy may be misinterpreted as being supratherapeutic or even toxic, and the cause of death may be inappropriately attributed to this xenobiotic.

Postmortem Metabolism. Less commonly, xenobiotic concentration may decrease secondary to postmortem metabolism. For example, cocaine continues to be degraded after death by endogenous enzymes such as cholinesterases in the blood, which continue to function in postmortem tissue and in vitro. Unless blood is collected immediately after death and placed in tubes containing enzyme inhibitors such as sodium fluoride, the concentration of cocaine will continue to decrease, and the analysis will not accurately reflect the concentration of the drug at the time of death.^{59,71,98,102} All available information regarding postmortem redistribution or metabolism of a specific xenobiotic must be considered for the proper interpretation

of the toxicologic results.

State of Absorption and Distribution. Both in the living and deceased, the state of absorption, distribution, and other toxicokinetic principles affect the apparent concentration of a sampled xenobiotic. For a xenobiotic with minimal postmortem metabolism or redistribution, the phase of absorption is suggested by the relative quantity of the xenobiotic in different fluids and solid organs. For example, a high concentration of xenobiotic in the gastric contents, with progressively lower concentrations in the liver, blood, vitreous, and brain, suggests an early phase of absorption at the time of death. When a xenobiotic is orally administered and the tissue concentration is highest in the liver, the relationship suggests a postabsorption phase but a predistribution concentration. A concentration found to be highest in the urine suggests that the xenobiotic was in an elimination phase at the time of death. Although this approach has limitations, it may be important for correlating the state of absorption and the expected clinical course of the xenobiotic. Unfortunately, multiple samples may not always be available at the time of autopsy or the interpretation of reports, and opportunities for subsequent sampling are often limited.

Xenobiotic Stability. Xenobiotic stability refers to the ability of a xenobiotic to maintain its molecular integrity despite postmortem changes such as decomposition of the body, adverse storage conditions, or the lack of preservatives.^{5,13,15,56,57,62,92,100,107,109,110} Postmortem xenobiotic stability was assessed in homogenized liver tissue infused with various concentrations of xenobiotics.¹⁰⁰ The samples were allowed to putrefy outdoors, and sequential sampling of xenobiotic concentrations was performed. The xenobiotics that decreased in concentration as putrefaction progressed were considered labile, and samples with a constant concentration were considered stable. The authors proposed that the chemical characteristics of a xenobiotic determine its stability. For example, labile xenobiotics share the molecular configuration of an oxygen–nitrogen bond, thiono groups, or aminophenols. Conversely, chemical structures that enhance stability include single-bonded sulfur groups, carbon–oxygen and carbon–nitrogen bonds, and sulfur–oxygen and hydrogen–nitrogen bonds. Although not explicitly studied in otherwise intact but putrefying bodies, logically, a less stable xenobiotic may be recovered in a lower concentration than the actual concentration at the time of death. This must be considered when information regarding stability is available and the body of a decedent is in an advanced stage of decomposition.

Xenobiotic Chemical Interactions. An artifact may result from a chemical interaction with a xenobiotic added during the postmortem interval, such as embalming fluid.³⁹ In a study of xenobiotic-spiked blood and formalin in test tubes, amitriptyline was formed by the methylation of nortriptyline.^{27,110} Identification of amitriptyline, which was not present at the time of death, could confuse the interpretation of toxicologic analyses.

Expected Clinical Effects of the Xenobiotic. For a fatality to be attributed to a xenobiotic, the expected clinical course from the exposure should be consistent with the autopsy findings. For example, what are the implications of a person found dead minutes after having been seen ingesting pills, if a large concentration of acetaminophen (APAP) is identified in both the gastric contents and blood but not in other tissues at autopsy?⁹¹ Although suicidal intent may be supported by this finding, the onset of death within minutes is inconsistent with a fatality due to an APAP overdose. Thus, another cause of death must be sought. Interpretation of postmortem toxicology must also incorporate clinically relevant consequences of xenobiotic interactions. For example, the combined ingestion of phenobarbital and ethanol can cause fatal respiratory depression. Although neither may be fatal alone, their additive effects must be acknowledged during toxicological interpretation.

Variables Related to the Decedent

Comorbid Conditions. The clinical response to a xenobiotic may be affected by acquired and inherited physiologic conditions that are not always identified or identifiable on autopsy. A thorough medical history is important and may assist in interpreting the clinical effects of a xenobiotic exposure. Similarly, certain clinical conditions may produce substances that interfere with postmortem laboratory assays. For example, an individual with a critical illness may produce digoxinlike immunoreactive substances (DLIS), which may cross-react with the postmortem digoxin assay.⁶ Without knowledge of DLIS production, the results may confound toxicologic analysis ([Chap. 65](#)).

Tolerance. Tolerance is an acquired condition in which increasingly higher xenobiotic concentrations are required to produce a given clinical effect. It is an important consideration for deaths in the presence of opioids, ethanol, and sedative–hypnotics. For example, respiratory depression and death from methadone may be easily diagnosed in an opioid-naïve individual with a history of methadone exposure and methadone-positive postmortem samples. However, the same methadone concentrations in a patient on chronic methadone maintenance therapy will not produce the same outcome. Unfortunately, no autopsy markers are available to indicate tolerance, and no biochemical or histologic markers are available during autopsy that may be used to predict clinically dangerous xenobiotic concentrations in a tolerant individual.²⁸ Complex postmortem assays analyzing opioid receptors are not routinely used.³⁶ Postmortem assessment of tolerance ultimately depends on knowledge of the patient, pharmacokinetics of the xenobiotic, and the best judgment of the investigator.

Pharmacogenetics. There is genetic variability in the expression of certain metabolic enzymes. For example, pharmacogenetic differences in metabolic enzymes, such as CYP2D6, predispose some individuals to fatal hypotension

from an inability to metabolize debrisoquine.

Similarly, deaths in young children have been reported from the use of therapeutic codeine. Postmortem blood analysis may reveal an elevated concentration of morphine, the codeine metabolite, and raise suspicion for a malicious overdose. Postmortem genotyping may provide an alternate explanation. Individuals with duplicate alleles for CYP2D6 may be ultrarapid metabolizers of codeine, rendering them susceptible to morphine toxicity despite generally acceptable dosing of codeine. Such distinctions are not routinely identifiable on autopsy.^{17,29,30}

Variables Relating to the Autopsy

State of Decomposition. In decedents in advanced stages of decomposition, xenobiotics may diffuse from depot compartments such as the stomach or bladder into adjacent tissues and blood vessels and secondarily affect their sample concentrations.^{23,38,66,76–78,85–87}

During putrefaction, bacteria cause fermentation of endogenous carbohydrates, resulting in ethanol formation. In decedents without gross evidence of putrefaction, especially those in cool, dry environments, endogenous ethanol production is minimal.^{18,22} With a longer postmortem interval or in an environment that is more conducive to ethanol production, the distinction between endogenous and exogenous sources of ethanol becomes more difficult. Sampling from multiple sites is often useful in making the distinction.¹⁰¹ A comprehensive review of interpreting postmortem ethanol concentrations is available elsewhere.⁶⁶

Handling of the Body or Samples. Inappropriate handling of the body may result in artifacts.^{91,93} In one reported case, methanol was detected in the vitreous humor of a decedent after embalming.¹² The methanol was subsequently traced to a spray cleanser that likely settled on the surface of open eyes during washing of the body.

In addition, inappropriate handling of samples may affect xenobiotic concentrations. In one study, autopsy blood was obtained from a diabetic man who died of bronchopneumonia. The samples were stored at 40°F (4°C) and tested at 2 and 5 days postmortem. The blood ethanol increased from 0.4 to 3.5 g/L because of an inadequate addition of fluoride preservative to the samples. The combination of inadequate preservation, hyperglycemia (vitreous glucose of 996 mg/dL), and bacterial sepsis created an ideal environment for ethanol production via fermentation.⁶⁶

In the United States, preservatives containing metals are currently banned for use in embalming because they may contaminate subsequent evaluation for metal poisoning. Formalin may also affect stability or quantitative identification of some xenobiotics. When necessary, an analysis of embalming fluid used by the mortician or soil sampling around disinterred bodies may facilitate the toxicologic investigation.^{19,34,107,109,110}

Autopsy Findings. In many xenobiotic-related deaths, the anatomic findings are nonspecific.¹⁰⁸ In some cases, the autopsy reveals confirmatory or supportive findings. A large quantity of undigested pills in the stomach is consistent with an intentional overdose, and suicide should be considered. Centrilobular hepatic necrosis may be found in decedents with a history of APAP overdose. The autopsy may also reveal other findings such as coronary artery narrowing, chronic hypertension, renal abnormalities, or a clinically silent myocardial injury. Such information may be useful to assess the potential effects of a xenobiotic in a patient with previously undiagnosed conditions. In other cases, the absence of a chronic condition may be strongly suggestive of a xenobiotic-related death. For example, a decedent with an autopsy finding of aortic dissection in the absence of chronic hypertensive findings or other predisposing conditions may suggest a xenobiotic-induced hypertensive crisis as may occur from use of cocaine or other sympathomimetics.

Artifacts Related to Sampling Sites. Site-specific differences in postmortem xenobiotic blood concentrations are common.³⁵ For example, blood obtained from femoral vessels may have low glucose concentrations because of postmortem glycolysis, but the blood glucose concentration removed from the right heart chambers may be high as a result of perimortem release of liver glycogen stores. As noted above, hyperglycemic conditions are more reliably assessed from sampling the vitreous humor as vitreous is a relatively protected environment in the early postmortem interval. An elevated vitreous glucose concentration suggests antemortem hyperglycemia. The individual interpreting the toxicologic report must know the exact site from which the sample was taken.^{20,60}

Ideally, samples from more than one site would be available for comparison; unfortunately, multiple blood samples are not often routinely obtained. Comparison of concentrations from different sites may reveal important information regarding the extent of xenobiotic absorption at the time of death and acute versus chronic exposure.^{9–11,20,26,30,52,67,72,80,82,85,88–90,95,96,101,103}

Other Considerations. Published therapeutic, toxic, and fatal postmortem xenobiotic concentrations are available to aid in the interpretation of postmortem specimens.^{4,70} However, the conditions associated with reported concentrations do not necessarily permit comparisons with the concentrations of the particular case under investigation. Thus, these resources are valuable but should be used mainly as representative of prior attempts at rigorous analysis and not accepted as absolute values that define either toxic or therapeutic concentrations. Similarly, formulas available for assessing xenobiotic doses or concentrations in the living are not usually applicable when analyzing postmortem samples.

Other Limitations

Although there are generalized standards of practice in forensic investigations, specimen collection and laboratory methodologies may vary.^{2,4} Some xenobiotic concentrations may be falsely elevated or depressed depending on the chosen methodology.^{32,72} Descriptions of specific toxicology laboratory techniques are beyond the scope of this chapter, but these variables must also be given consideration in the interpretations of results. Other limitations may include a lack of information relating to the circumstances of death and possible compromises in specimen handling because of the required protocols for the maintenance of proper chain of custody often of paramount importance in forensic autopsies.^{37,38}

SUMMARY

- Accurate interpretation of postmortem toxicologic reports requires an understanding of potential biochemical changes and other artifacts that affect postmortem testing.
- It is exceptionally difficult to absolutely correlate postmortem xenobiotic blood and tissue concentrations to those at the actual time of death.
- Postmortem toxicology is an evolving discipline that may permit only the most likely cause and manner of xenobiotic-related death to be identified.
- Progress in this field will depend on the continued collaboration between the treating physicians, medical and forensic toxicologists, and forensic pathologists.

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SC2 SPECIAL CONSIDERATIONS

Organ Procurement from Poisoned Patients

Rama B. Rao

Xenobiotics can cause brain death due to the unique vulnerabilities of the central nervous system. With supportive care, however, such patients may be suitable candidates for organ donation.^{9,10,31,38} Early identification of potential donors is critical because the viability of transplantable tissue diminishes as duration from the time of brain or cardiac death prolongs.^{26,38} Timely identification may be further complicated by the presence of xenobiotics that mimic brain death.^{4,10,36}

A variety of protocols to establish brain death are reviewed elsewhere.^{4,10,36} Once brain death is established, organ procurement personnel assist in obtaining familial consent, deciding which organs are most suitable for transplant, and maximizing physiological support and perfusion until organ procurement occurs.³⁸ The protocols following controlled or uncontrolled donation after cardiac arrest are socially complicated and practiced extensively in Europe.³⁵

Successful transplantation of organs is reported from poisoned donors associated with a variety of xenobiotics^{1,2,5,7,9,10,12,16,25,29,30-34,37} (Tables SC2–1 and SC2–2). Although some xenobiotics are highly toxic, such as cyanide and carbon monoxide (CO), transfer of clinical poisoning to the organ recipient is not reported. This is likely caused by several factors, including xenobiotic metabolism, tissue redistribution or binding prior to procurement, as well as the means of handling organs during the transplantation process. For example, some xenobiotic clearance may occur in the myocardium during organ rinsing and cardiopulmonary bypass.²⁹ Furthermore, individual organs may not uniformly manifest toxicity in response to xenobiotic insults. For example, the heart of a CO poisoned donor was examined after a transplantation failed for technical reasons. The myocardium did not demonstrate histological signs of CO poisoning.³⁴ A comprehensive review with organ-specific procurement recommendations post–carbon monoxide poisoning is presented elsewhere.³

TABLE SC2–1. Organs Transplanted after Donor Poisonings

<i>Organ</i>	<i>Xenobiotics Identified in Donors</i>
Cornea ^{a,1,23,25,26,29}	Brodifacoum, cyanide
Heart ^{8,14,25,28,30}	Acetaminophen, β -adrenergic antagonists, alkylphosphate, benzodiazepines, brodifacoum, carbamazepine, carbon monoxide, chlormethiazole, cyanide, digitalis, digoxin, ethanol, glibenclamide, insulin, meprobamate, methanol, propoxyphene, thiocyanate
Kidney ^{a,2,4,6,10,25,26,29}	Acetaminophen, brodifacoum, carbon monoxide, <i>Conium maculatum</i> , cyanide, ethylene glycol, insulin, malathion, methanol, tricyclic antidepressants
Liver ^{4,6,7,10,14}	Brodifacoum, carbon monoxide, <i>Conium maculatum</i> , cyanide, ethylene glycol, insulin, malathion, methanol, methaqualone, tricyclic antidepressants
Lung ^{5,7,14,25,27,29}	Brodifacoum, carbon monoxide, methanol
Pancreas ^{6,7,10,25}	Acetaminophen, brodifacoum, carbon monoxide, <i>Conium maculatum</i> , cyanide, ethylene glycol, methanol, tricyclic antidepressants
Skin ^{7,27}	Cyanide, methanol

^aCan be cadaveric procurement.

TABLE SC2–2. Xenobiotic Related Deaths Resulting in Successful Organ Donation

- β -Adrenergic antagonists
- Alkylphosphate
- Barbiturates
- Benzodiazepines
- Brodifacoum
- Carbamazepine

Carbon monoxide
Cardioactive steroids
Chlormethiazole
Conium maculatum
Cyanide
Ethanol
Ethylene glycol
Glibenclamide
Ibuprofen
Insulin
Malathion
Methaqualone
Meprobamate
Methanol
Propoxyphene
Tricyclic antidepressants

Probably more critical to transplantation success is adequate tissue perfusion and well-maintained cellular morphology. For example, patients suffering brain death from acetaminophen poisoning are not suitable liver donors given the hepatotoxicity. Alternatively, xenobiotics considered toxic to organ function by impairing enzymes have resulted in successful transplantation if the cellular structure is otherwise maintained. For example, a death from cardioactive steroid poisoning did not preclude successful heart transplantation even when the donor had a bradydysrhythmia, an elevated serum digoxin concentration, and required cardiopulmonary resuscitation.³⁴ Similarly, the liver of a patient poisoned with brodifacoum was transplanted after administration of fresh frozen plasma and vitamin K₁. The recipient's international normalized ratio (INR) post-transplant was 2 and corrected rapidly with supportive care. Recipient concentrations of brodifacoum were not reported and not clearly causative of the elevated INR.²⁹ In both examples, the target of toxicity was enzymatic and the tissue morphology was otherwise minimally affected. Organs from a patient who suffered hypoxic brain death after malathion poisoning were procured 2 weeks after the exposure at which time no further evidence of acute cholinergic toxicity was present and successfully transplanted.⁵ Most transplant failures from poisoned donors are due to rejection, sepsis, or technical reasons. The one year survival in recipients from poisoned donors approximates that from nonpoisoned donors; one series reported at 75% survival.¹² In another review, 5-year survival rates were between 33% and 100%, with heart transplant recipients the lowest.⁹

Ideally, a comprehensive international registry of transplants from poisoned donors will be established to improve understanding of transplants from such patients. It appears that patients who suffer brain death from poisoning are potentially suitable donors when cellular infrastructure is preserved.^{22,24,26,38} Consideration for organ procurement should not be limited by the xenobiotic.

SUMMARY

- Organ procurement from poisoned donors may reach success rates similar to non-poisoned donors when carefully selected.
- Clinically significant xenobiotic concentrations have not been reported in organ recipients.
- Adequate tissue perfusion is important for the viability of a transplanted organ, regardless of the primary toxicological insult.

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PART C

**THE CLINICAL BASIS OF MEDICAL
TOXICOLOGY**

CASE STUDY 1

History A 22 year-old man was brought to the emergency department after being found unconscious at a movie theater. In the field the paramedics inserted an intravenous (IV) line, performed a rapid reagent glucose test that was recorded as 88 mg/dL, and placed the patient on oxygen via nasal cannula at 4 L/min when his room air pulse oximetry was determined to be 91%. The patient had no medical records at the receiving hospital, and no useful information was found among his belongings.

Physical Examination On arrival to the hospital he was deeply unconscious with no response to sternal rub. Vital signs were: BP, 92/56 mm Hg; P, 52 beats/min; RR, 10 breaths/min; T, 97.4°F (36.3°C); oxygen saturation, 98% on 4 L O₂/min; a repeat rapid reagent glucose was unchanged. Examination was notable for 2 to 3 mm pupils that responded to light, normal oculoccephalic testing, nearly flaccid muscle tone, and downgoing toes bilaterally. His head was without signs of trauma and his neck was supple. Examination of the chest revealed scattered coarse breath sounds and a regular heart rhythm with normal heart sounds and no murmurs. The abdomen was soft with quiet bowel sounds and no abnormalities were noted on the skin or extremities. When oxygen was removed, his saturation fell to 92%, and a continuous end-tidal CO₂ monitor measured 48 mm Hg.

Immediate Management Given the patient's hypoventilation and small pupils graded doses of naloxone were given (0.04, 0.1, and 2 mg IV) without response (Antidotes in Depth: A4). On further examination, the patient's gag reflex was absent prompting endotracheal intubation, which was performed without medications, and the patient was attached to a mechanical ventilator. A postintubation arterial blood gas, a complete blood count, electrolytes, and ethanol and acetaminophen (APAP) concentrations were obtained. Electrocardiography (ECG) showed sinus bradycardia with normal axis and intervals, and no ST segment or T-wave abnormalities were observed. A total of 1 L of 0.9% sodium chloride was infused and his blood pressure increased to 102/60 mm Hg, with no change in his pulse. A nasogastric tube was inserted through which 60 g of activated charcoal was instilled into the stomach.

What Is the Differential Diagnosis? This patient has deep coma, with relatively unremarkable vital signs (mild hypotension, bradycardia, and hypoventilation) and an unremarkable physical examination. The differential diagnosis is extensive and includes many xenobiotics from diverse chemical classes. The most common causes are listed in [Table CS1–1](#). In many cases it is not necessary to establish the correct diagnosis, but rather to exclude diagnoses that require specialized care or are amenable to specific interventions.

TABLE CS1–1. Common Causes of Coma with Relatively Normal Vital Signs and Unremarkable Physical Examination

Anticonvulsants	Ethanol
Antidepressants	Gabapentin and pregabalin
Antipsychotics	γ-Hydroxybutyric acid
Baclofen	Inhalants
Clonidine and other centrally acting α-adrenergic agonists	Insulin secretagogues
	Sedative-hypnotics

What Clinical and Laboratory Analyses Help Exclude Life-Threatening Causes of This Patient's Presentation?

Either a rapid reagent glucose determination should be obtained or hypertonic dextrose should be administered in every comatose patient ([Chap. 4](#) and Antidotes in Depth: A12). A normal blood glucose concentration or failure to respond to an appropriate dose of hypertonic dextrose essentially excludes hypoglycemia. When hypoventilation is present, a trial of naloxone is indicated, because recognizing that patients who have overdosed on clonidine and similarly acting antihypertensives may respond (Antidotes in Depth: A4). A screening ECG is essential and may guide diagnosis and management ([Chap. 16](#)). Prolongation of the QRS complex occurs with some antidepressants, antipsychotics, and anticonvulsants, and it may indicate the need to administer hypertonic sodium bicarbonate (Antidotes in Depth: A5). In addition, prolongation of the QT interval is commonly recognized with many antipsychotic and antidepressant overdoses. Although metabolic acidosis with an elevated anion gap is not typical of the xenobiotics listed, it might be indicative of a serious co-ingestant. Similarly, deep coma is not expected following a typical APAP overdose, but APAP is commonly ingested and co-formulated with sedatives and opioids.

When a patient presents with coma, relatively normal vital signs, and an unremarkable examination, and if ECG results and [glucose], oxygenation, [anion gap], and [acetaminophen] are normal or can be corrected, then the patient will likely do well with supportive care.

Further Diagnosis and Treatment The arterial blood gas and electrolytes showed no evidence of acidosis or anion

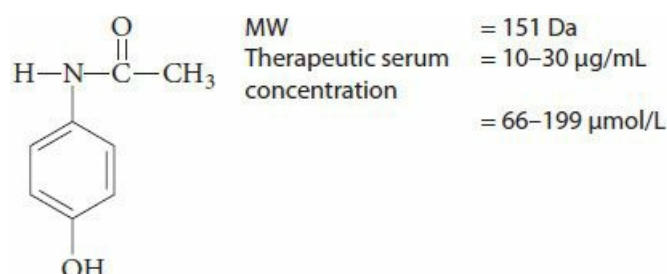
gap. Other than bradycardia, the ECG was normal. A serum [APAP] was 162 µg/mL. Because the time of ingestion was unknown IV, N-acetylcysteine (NAC) was initiated (Antidotes in Depth: A3). After some time a family member was contacted who disclosed that the patient had several previous suicide attempts and was known to be taking phenobarbital. A serum phenobarbital concentration was obtained on original blood in the laboratory and was reported to be 132 µg/mL. A bicarbonate infusion was started to alkalinize the urine of the patient (Antidotes in Depth: A5). A 21 hour NAC regimen was completed at which time the patient's [APAP] was not detectable and the aminotransferases were within normal limits. Over the next 48 hours the patient regained consciousness and was extubated. A consultation with a psychiatrist determined the need for involuntary hospitalization and the patient was transferred to the psychiatric service.

SECTION I

A. ANALGESICS AND ANTIINFLAMMATORY MEDICATIONS

35 ACETAMINOPHEN

Robert G. Hendrickson



HISTORY AND EPIDEMIOLOGY

By the late 1800s, both phenacetin and acetanilide were used as analgesics and antipyretics, but their acceptance was limited by significant side effects including methemoglobinemia. N-acetyl-p-aminophenol (APAP) is a major metabolite of phenacetin and acetanilide, and is responsible for, both analgesia and antipyresis. APAP was synthesized in 1878 and has a low risk of causing methemoglobinemia. N-acetyl-p-aminophenol is referred to as acetaminophen (N-**acetyl**-para**aminophenol**) in the United States, Canada, Japan, and several other countries and as paracetamol (para-acetylaminophenol) in most other areas of the globe. Both terms are abbreviations of the chemical name. APAP was first used clinically in the United States and the United Kingdom in the mid 1950s, but its widespread acceptance was delayed until the 1970s because of concerns of the toxicities of its precursors. APAP has since proved to be a remarkably safe xenobiotic at appropriate dosage, which has led to its popularity. APAP is available in a myriad of single-agent dose formulations and delivery systems, and in a variety of combinations with opioids, other analgesics, sedatives, decongestants, expectorants, and antihistamines.¹⁸⁴ The diversity and wide availability of APAP products dictate that APAP toxicity be considered not only after identified ingestions but also after exposure to unknown or multiple xenobiotics in settings of intentional overdose, abuse, and therapeutic misadventures.

Despite enormous experience with APAP toxicity, many controversies and challenges remain unresolved. New formulations and new analogs are being introduced, that will require reassessments of the available knowledge.^{57,113,326} To best understand the continuing evolution in the approach to APAP toxicity, it is critical to start with certain fundamental principles and then to apply these principles to both typical and atypical presentations in which APAP toxicity must be considered.

PHARMACOLOGY

APAP is an analgesic and antipyretic with weak peripheral antiinflammatory and antiplatelet properties. Analgesic activity is reported at a serum [APAP] of 10 µg/mL and antipyretic activity at 4 to 18 µg/mL.³⁴⁵

APAP has a unique mechanism of action among the analgesic antipyretics. Most of the nonsteroidal antiinflammatory drugs (NSAIDs) occupy the cyclooxygenase (COX) binding site on the enzyme prostaglandin H₂ synthase (PGH₂) and prevent arachidonic acid from physically entering the site and being converted to prostaglandin H₂. APAP also inhibits prostaglandin H₂ production but does so indirectly by reducing a heme on the peroxidase (POX) portion of the PGH₂,¹⁹⁹ and indirectly inhibiting COX activation.^{13,154,195} In this way, APAP function is highly dependent on cellular location and intracellular conditions.^{12,111,231} APAP strongly inhibits prostaglandin synthesis where concentrations of POX and arachidonic acid (“peroxide tone”) are low such as in the brain.^{90,101} In conditions of high peroxide tone, such as inflammatory cells (macrophages) and platelets, prostaglandin synthesis is less affected by APAP,^{13,39,111,125,195,221,231} although this is not universal.¹⁵ This dissociation explains the strong central antipyretic and analgesic effect of APAP but weak peripheral antiinflammatory and antiplatelet effects. Functionally, APAP predominantly acts as a central indirect inhibitor of COX-2 enzymes,^{136,219,221} with some mild peripheral COX-2 inhibition¹⁸⁶ and minimal COX-1 inhibition (Chap. 37).⁵⁴

Antipyresis and analgesia are predominantly mediated by this central indirect COX-2 inhibition and the resulting decrease in prostaglandin E₂ (PGE₂) synthesis.^{98,111,169,189,221} Additional analgesic effects may be mediated by indirect stimulation by APAP of serotonergic and opioid descending pathways or activation of the cannabinoid system. Stimulation of descending serotonergic pathways is demonstrated in rats³⁶ and humans,^{111,236} and the analgesic effect of APAP may be inhibited by several serotonin antagonists or serotonin depletion.^{6,236,237,238,268} In rats, the analgesic effect of APAP is attenuated by opioid receptor antagonists.^{49,269} However, APAP binds poorly to opioid receptors,^{248,249,250} and the exact mechanism of opioid stimulation remains unexplained.²⁷⁰ Finally, activation of the central or peripheral endogenous cannabinoid system, potentially from an APAP metabolite,¹³⁸ has been theorized but remains controversial.^{27,73,124,230}

PHARMACOKINETICS

After ingestion of a therapeutic dose, immediate-release APAP is rapidly absorbed from the small intestine with a time to peak [APAP] of approximately 30 minutes for liquid formulations and 45 minutes for tablet formulations.^{7,83,104} Extended-release APAP has a time to peak of 1 to 2 hours but is almost entirely absorbed by 4 hours.⁸⁵ The time to peak may be delayed by food⁸³ and co-ingestion of opioids or anticholinergics.¹²³ The oral bioavailability is 60% to 98%,²⁵² and the volume of distribution (Vd) is 1 L/kg.^{7,9,104} Peak [APAP] after recommended doses typically ranges from 8 to 20 µg/mL.^{7,104} After administration of 20 to 25 mg/kg rectal suppositories, the peak [APAP] ranges from 4.1 to 13.6 µg/mL, the time to peak [APAP] is 2 to 4 hours (range, 0.4–8 hours), and the bioavailability is 30% to 40%.^{18,33,122} APAP is available in the intravenous form as an APAP solution in the United States, United Kingdom, Australia, New Zealand, and many other countries as well as a prodrug (eg, propacetamol) in the United Kingdom. The time to peak of the intravenous formulations are immediate (< 15 minutes), and peak [APAP] after a 1 g infusion is approximately 30 µg/mL, and after a 2 g infusion is approximately 75 µg/mL with a large range of 31 to 161 µg/mL.^{102,116,235} The Vd is higher in both pregnant women and neonates, while clearance rates are higher in pregnant women and lower in neonates.^{5,174} APAP has total protein binding of 10% to 30% that does not change in overdose.²⁰⁸ APAP crosses the placenta, the blood–brain barrier, and in small amounts (< 2% of ingested dose), into breast milk.^{108,188,225}

After absorption, approximately 90% of APAP normally undergoes hepatic conjugation with glucuronide (40%–67%), mostly via UGT1A6, and sulfate (20%–46%), mostly via SULT1A1, to form inactive metabolites, which are eliminated in the urine. A small fraction of unchanged APAP (< 5%) and other minor metabolites reach the urine.²¹³ The remaining fraction, approximately 5% in therapeutic doses, is oxidized by CYP2E1 (and, to a lesser extent, CYP3A4, CYP2A6, and CYP1A2),^{130,198} resulting in the formation of N-acetyl-p-benzoquinoneimine (NAPQI).⁶⁵ Glutathione (GSH) quickly combines with NAPQI,²¹² and the resulting complex is converted to nontoxic cysteine or mercaptate conjugates, which are eliminated in the urine (Fig. 35–1).^{207,213} The elimination half-life of APAP is approximately 2 to 3 hours after a nontoxic dose^{4,246} but may become prolonged in patients who develop hepatotoxicity.

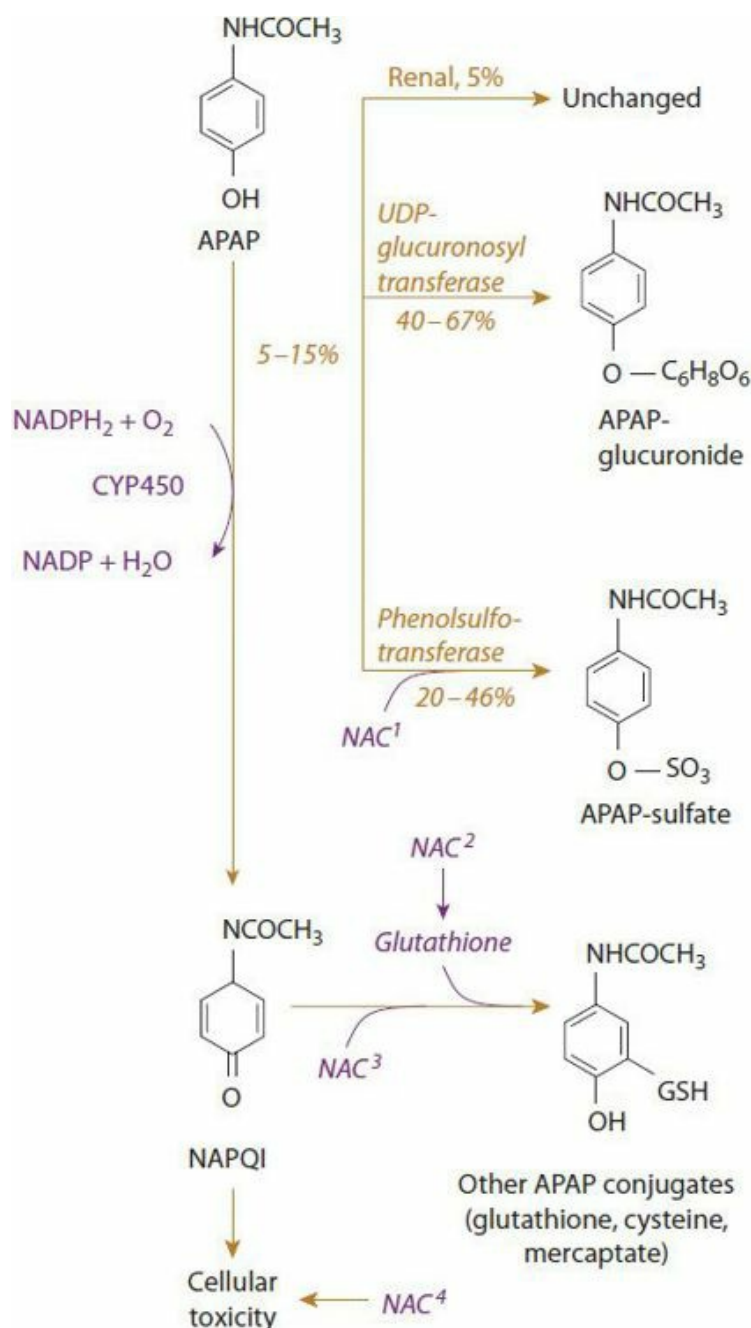


FIGURE 35–1. Important routes of APAP metabolism in humans and mechanisms of N-acetylcysteine (NAC) hepatoprotection. NAC¹ augments sulfation, NAC² is a glutathione (GSH) precursor, NAC³ is a GSH substitute, and NAC⁴ improves multiorgan function during hepatic failure and possibly limits the extent of hepatocyte injury. APAP = N-acetyl-p-aminophenol = acetaminophen.

TOXICOKINETICS

After most oral overdoses, the majority of APAP absorption occurs within 2 hours and peak plasma concentrations generally occur within 4 hours. Later peaks or double peaks are rarely documented in overdoses and have generally occurred after large ingestions (> 50 g) with or without co-ingested antimuscarinics.^{31,134,303,332} Evidence suggests that NAPQI production is largely the result of activity of the CYP2E1 enzyme after both therapeutic and supratherapeutic doses of APAP.^{91,130} Contributions of CYP1A2, CYP3A4, and CYP2A6 to the production of NAPQI in humans are small and insignificant in most cases, but they may be variable, depending on individual host factors and dosage.^{130,233,251,320} After clinically significant overdose, nontoxic sulfation metabolism of APAP may become saturated.¹⁶⁶ The amount of NAPQI formed is increased out of proportion to the APAP dose and may account for up to 20% to 50% of metabolism in patients with hepatotoxicity.²⁴⁴ Glucuronidation rates are likely not saturatable in humans (Fig. 35–1).^{80,166,242}

The toxicokinetics of intravenous APAP are largely unknown. Doses of 75 mg/kg and 146 mg/kg have produced 4 hour [APAP] of 35 µg/mL and 117 µg/mL, respectively, with half-lives ranging from 2 to 6 hours. One patient who received a 75 mg/kg intravenous APAP dose had a 1 hour [APAP] of 72 µg/mL.

PATHOPHYSIOLOGY

The safety of appropriate APAP dosing results from the availability of electron donors such as reduced GSH and other thiol (S-H)-containing compounds. After therapeutic APAP dosing, GSH supply and turnover far exceed that required to detoxify NAPQI. With ample GSH supply, NAPQI is largely bound by GSH, and no toxicity occurs, although NAPQI-cysteine protein adducts do form within the liver and some are released into the serum.^{133,206} After overdose, the rate and quantity of NAPQI formation outstrip supply and turnover of GSH, resulting in the release of NAPQI within the cell. NAPQI then rapidly binds to hepatocyte constituents, including the cysteine portion of proteins, producing protein adducts within the liver. In animal experiments, hepatotoxicity becomes evident only when hepatic [GSH] decreases to 30% of baseline or below.²¹¹

When NAPQI formation overwhelms the supply of thiol-containing compounds, it covalently binds^{92,240} and arylates proteins throughout the cell,^{63,149,153} inducing a series of events that result in cell death.¹⁵¹ Covalent binding and arylation occur rapidly after GSH depletion.^{32,149,151,254} Both covalent binding and GSH deficiency are necessary for hepatotoxicity; however, the selective arylation of specific cellular proteins is more predictive of toxicity than total covalent binding.^{63,143}

Protein binding of NAPQI and the formation of protein adducts does not imply toxicity as adducts are formed at therapeutic [APAP]. However, highly elevated concentrations of protein adducts in the serum may be indicative of cellular necrosis and hepatotoxicity. After covalent protein binding and GSH depletion occur, a cascade of events follows that alters normal cell function and impairs cell defenses against endogenous reactive oxygen species.^{153,254,323} This cascade can be ameliorated with N-acetylcysteine (NAC) even after covalent binding occurs.^{45,81,106,149,254} These events include mitochondrial dysfunction,^{50,84} an increase in mitochondrial permeability,²⁵⁴ mitochondrial oxidant stress or peroxynitrite formation,^{66,135,164} hepatocellular hypoxia,²⁶⁴ DNA fragmentation,⁶⁶ which results from interactions with topoisomerase 2- α ,^{20,287} calcium dyshomeostasis,^{216,323,324} lipid peroxidation,^{118,337} nitric oxide release,²⁶⁵ inflammatory cell mobilization and activation,^{140,177,191} inflammatory cytokine release,^{148,149,177,191} and up- or downregulation of protein expression.^{30,143,144,264} Which specific events are critical and irreversibly commit the cell to death is not known.

The final pathway of hepatic cell death is predominantly cellular necrosis.¹²¹ Cellular injury leads to release of intracellular molecules, which further activate the immune system. Some of these intracellular components that are released from necrotic cells may be used as biomarkers of hepatic injury and include aspartate aminotransferase (AST), alanine aminotransferase (ALT), microRNA 122 (miRNA-122), high-mobility group box-1 protein (HMGB-1), keratin-18 protein (K-18), and protein adducts.^{10,11,310} Apoptosis may occur after activation of the immune system in response to this cellular necrosis,^{1,11} although there is evidence that apoptosis may occur early in APAP toxicity as well.^{197,253} Macrophages, neutrophils, and inflammatory cells infiltrate after necrosis^{140, 142,185,191} followed by a cascade of inflammatory cytokines such as interleukin (IL) 1, IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1).^{140,148,149,191} Hepatocellular destruction caused by secondary inflammation, impairment of microcirculation,²¹⁰ and hepatic nitric oxide release^{149,264} are all demonstrated, although none appear to be necessary for hepatic injury.^{66,144,145,181}

Hepatotoxicity initially and most profoundly occurs in hepatic zone III (centrilobular) because this zone is the area with the largest concentration of oxidative metabolism (CYP2E1; Fig. 23–1). In more severe hepatotoxicity, necrosis may extend into zones II and I, destroying the entire hepatic parenchyma.

Kidney injury after acute overdose is typically acute tubular necrosis (ATN) that may be caused by local production of NAPQI by renal CYP2E1 enzymes.^{42,90,139} However, several other nephrotoxic mechanisms have been proposed.¹²⁸ Conversion of APAP and hepatically derived APAP–GSH²¹⁵ to nephrotoxic p-aminophenol⁵³ are both demonstrated in selected animal models.^{103,202} NAPQI formation via renal prostaglandin H synthase³²⁹ and prostaglandin-mediated renal medullary ischemia²⁴⁵ are also suspected of contributing to chronic analgesic nephropathy from APAP alone or in combination with other analgesics.^{103,267} In patients with hepatic failure, volume depletion and hepatorenal syndrome may be the most important contributory cofactors because the rate of acute kidney injury is similar regardless of the cause of hepatic failure.³⁴⁴ Dose-related renal potassium wasting^{107,232,337} after acute APAP overdose may be related to APAP-induced renal vasoconstriction due to COX inhibition or a NAC effect, or both.²³²

Direct injury to organs other than the liver and kidney is rarely reported. The mechanism of early central nervous system (CNS) depression after APAP ingestion is undefined, but theoretical mechanisms include serotonin and opioid effects as well as APAP-induced CNS GSH depletion.⁵⁶ Metabolic acidosis and elevated lactate early after massive APAP ingestion may be the result of alterations in mitochondrial respiratory function, but the exact mechanism is unknown.^{48,95,101,168,313} Rare cases of metabolic acidosis with 5-oxoprolinemia and 5-oxoprolinuria are reported and appear to be more likely in women with chronic APAP use and chronic kidney disease.^{44,99,137,180} In this rare condition, it is theorized that chronic APAP use combined with acute oxidative stress and inflammatory mediators may lead to an alteration of the γ -glutamyl cycle and elevations of γ -glutamylcysteine and 5-oxoproline.^{44,87,137}

The remaining sequelae of severe toxicity are secondary effects of fulminant hepatic failure rather than direct APAP effects, and the pathophysiology of these complex multisystem problems is well described.¹⁸⁵ For example, myocardial

injury and pancreatitis are both reported in patients with APAP-induced fulminant hepatic failure. The ability of NAC to ameliorate secondary multiorgan failure via extrahepatic mechanisms suggests that the oxidation of vital thiols and the loss of normal microvascular function are important components of secondary organ failure.^{127,157}

CLINICAL MANIFESTATIONS

Early recognition and treatment of patients with APAP poisoning are essential to minimize morbidity and mortality. This task is made difficult by the lack of early predictive clinical findings. The first symptoms after APAP overdose may be those of hepatic injury, which develop many hours after the ingestion, when antidotal therapy will have diminished efficacy.

The clinical course of acute APAP toxicity can be divided into four stages.²⁶² During stage I, hepatic injury has not yet occurred, and even patients who ultimately develop severe hepatotoxicity may be asymptomatic. Clinical findings, when present, are nonspecific and may include nausea, vomiting, malaise, pallor, and diaphoresis. Laboratory indices of hepatic function are normal. In rare cases of massive overdose, a decreased level of consciousness,^{88,114,168,258,311} metabolic acidosis and elevated lactate,^{114,168,205,258,284,341,354} due to inhibition of electron transport by APAP, NAPQI, or both,^{94,95,114} and even death^{37,291} may occur during this stage in the absence of signs or symptoms of hepatotoxicity.^{37,100,168,258,284,311,355} These clinical findings should never be attributed to APAP alone without thorough evaluation of other possible causes.

Stage II represents the onset of hepatic injury, which occurs in fewer than 5% of those who overdose.²⁹⁹ AST is the most sensitive, widely available measure to detect the onset of hepatotoxicity, and AST abnormalities always precede evidence of actual hepatic dysfunction (prolonged prothrombin time {PT}, international normalized ratio {INR}, elevated bilirubin concentration, hypoglycemia, encephalopathy, and metabolic acidosis). When stage II occurs, onset of AST elevation is most common within 24 hours after ingestion but is nearly universal by 36 hours.^{117,289} In the most severely poisoned patients, AST concentrations may increase as early as 12 hours after ingestion.^{117,289} Symptoms and signs during stage II vary with the severity of hepatic injury. By convention, acetaminophen-induced hepatotoxicity is defined as a peak ALT concentration above 1000 IU/L. Although lower peak concentrations of AST or ALT represent some injury to hepatic tissue, they rarely have any clinical relevance.

Stage III, defined as the time of maximal hepatotoxicity, most commonly occurs between 72 and 96 hours after ingestion. The clinical manifestations of stage III include fulminant hepatic failure with encephalopathy and coma, and, rarely, hemorrhage. Results of laboratory studies are variable; AST and ALT concentrations above 10,000 IU/L are common, even in patients without other evidence of hepatic failure. Much more important than the degree of aminotransferase concentration elevation, abnormalities of PT and INR, glucose, lactate, creatinine, and pH are essential determinants of prognosis and treatment.

Renal function abnormalities are rare (< 1%) overall,^{243,334} but they can occur in as many as 25% of patients with significant hepatotoxicity²⁴³ and in 50% to 80% of those with hepatic failure.^{176,228,344} Renal abnormalities may be more common after sustained, repeated excessive dosing¹⁷⁶ and in adolescents and young adults.^{40,201,217} After acute ingestions, elevations of serum creatinine typically occur between 2 and 5 days after ingestion, peak on days 5 to 7 (range, 3–16 days),³³⁴ and normalize over 1 month.²⁰¹ When severe acute kidney injury necessitating hemodialysis occurs, it nearly always occurs in patients with marked hepatic injury. Patients with hepatorenal syndrome are commonly treated with continuous renal replacement therapy, and among those who survive, kidney failure generally resolves within one month.^{190,228} Infrequently, mild acute kidney injury occurs without elevations in aminotransferase concentrations.^{3,40,62,89}

Fatalities from fulminant hepatic failure generally occur between 3 and 5 days after an acute overdose. Death results from either single or combined complications of multiorgan failure, including acute respiratory distress syndrome, sepsis, cerebral edema, or, rarely, hemorrhage. Patients who survive this period reach stage IV, defined as the recovery phase. Survivors have complete hepatic regeneration, and no cases of chronic hepatic dysfunction have ever been reported. The rate of recovery varies; in most cases, AST, pH, PT, and INR, and lactate are normal by 7 days in survivors of acute overdoses. ALT may remain elevated longer than AST, and creatinine may be elevated for more than one month. The recovery time is much longer in severely poisoned patients, and histologic abnormalities may persist for months.^{187,200,239}

DIAGNOSTIC TESTING

Assessing the Risk of Toxicity

Principles Guiding the Diagnostic Approach. Most APAP exposures result in no toxicity, and the overall mortality rate after acute APAP ingestion is less than 0.5%.²⁹⁹ However, APAP is now the leading cause of acute hepatic failure in the United States and much of the developed world.¹⁷⁶ To maintain the seemingly divergent goals of avoiding the enormous cost of over-treatment while minimizing patient risk, clinicians must understand the basis for and sensitivity of current toxicity screening methods. A discussion of the diagnostic approach follows.

When considering risk determination, it is useful to separate different categories of APAP exposure. There is an extensive body of experience and literature on acute overdose in typical circumstances, permitting a more systematic approach with demonstrated efficacy. For issues related to repeated supratherapeutic APAP dosing, uncertain circumstances, new APAP formulations, and many other permutations, there is an important conceptual framework for decision-making but little in the way of validated strategies. For these challenges, the central concepts and one approach are presented here, with the understanding that the challenges continue to evolve and that more than one approach may have validity.

The ideal model for determining risk after APAP overdose would assess the individual's metabolic enzyme activity (CYP2E1, UDP-glucuronosyl transferase, and sulfotransferase activity), the amount and rate of NAPQI formation, the availability of hepatic GSH, and the balance of NAPQI formation and hepatic GSH turnover. At present, none of these measures is available to clinicians.

Plasma GSH concentration can be measured or approximated using the plasma γ -glutamyl transferase (GGT) concentration but have an uncertain relationship to hepatic GSH availability.^{283,302}

Protein adducts indicate intracellular binding of NAPQI to hepatocyte proteins^{78,147,247,339} and can be determined experimentally, but have been inadequately studied to be useful in risk assessment or the assignment of causality of hepatic failure. After over-exposure to APAP, NAPQI is not immediately bound to GSH and is released within the cell to bind with the cysteine components on proteins. One of these protein-APAP adducts is 3-(cysteinyl-S-yl)-APAP, for which there is a research assay. However, hepatic toxicity from APAP requires not only protein binding, and therefore protein adducts, but an inflammatory cascade to produce cell necrosis.³⁸ Therefore, protein adducts are signs of NAPQI binding, but not necessarily of toxicity. Animals exposed to APAP overdose develop elevated concentrations of serum protein adducts. However, those who are rescued with NAC have protein adducts within the liver, but little is spilled into the blood because hepatic cellular necrosis does not occur.^{34,133,149}

In humans with therapeutic dosing of APAP, protein adducts are usually detected in small quantities in the blood (< 0.5 nmol/mL), likely from intrahepatic protein binding followed by hepatic cellular turnover. However, concentrations of up to 1.0 nmol/mL have also been detected in patients with therapeutic dosing.¹³³ In humans after overdose, protein adducts are released into the serum and largely parallel the aminotransferases in their time-course. Peak concentrations are detected in 2 to 3 days and decrease with an elimination half-life of 1.7 days. Protein adducts remain detectable for up to 2 weeks.¹⁴⁶ A protein adduct concentration above 1.0 nmol/mL has been suggested as being consistent with an acute APAP overdose, but this recommendation will require further validation.¹³³

Other hepatic cellular components may be detected in serum during APAP toxicity and are being analyzed as biomarkers of hepatotoxicity. miRNA are small, noncoding RNA that regulate cell proteins by repressing mRNA.³¹⁰ miRNA-122 is the most abundant hepatic microRNA and is specific to the liver.³¹⁰ In human studies, miRNA-122 increases prior to other markers, such as ALT, and may be actively released from hepatocytes prior to cell lysis.³⁰⁹ [miRNA-122] correlates with peak ALT¹⁰ and peak INR.¹⁰ In patients with acute APAP overdose whose initial ALT is normal and in patients who are treated within 8 hours, [miRNA-122] is higher in those who develop hepatic injury,¹⁰ suggesting that it may be useful in differentiating low risk patients from high risk patients earlier than other markers.

Another biomarker, HMGB-1, is passively released by hepatocytes during necrosis. HMGB-1 is elevated in patients with APAP hepatotoxicity but not in those without hepatotoxicity and correlates with both peak ALT and INR. An acetylated form of HMGB-1 is secreted as an inflammatory mediator by macrophages and monocytes and increases only in patients with APAP toxicity who later either meet transplant criteria (King's College Criteria), die, or receive a hepatic transplant. This biomarker requires further study, but has promise as an earlier marker for more intensive treatment or for transplant.¹¹

Risk Determination Following Acute Overdose. Determining risk in a patient with acute overdose consists of determining the initial risk based on dosing history and then potentially further risk stratifying with serum [APAP].

Acute overdose usually is considered a single ingestion, although many patients actually overdose incrementally over a brief period of time. For purposes of this discussion, an acute overdose is arbitrarily defined as one in which the entire ingestion occurs within a single 8-hour period.⁷⁵ Doses of 7.5 g in an adult or 150 mg/kg in a child are widely disseminated as the lowest acute dose capable of causing toxicity.²⁴⁴ These standards are likely quite conservative but have stood the test of time as sensitive markers and have been corroborated with some data in humans.^{335,357} However, it is more likely that doses of at least 12 g in an adult or 200 mg/kg in a child are necessary to cause hepatotoxicity in most patients.^{214,335}

The adult standard may be considered less controversial than that for children because massive ingestions, unreliable histories, and factors that might predispose to toxicity occur primarily in adults, justifying continued use of 7.5 g as a screening amount to avoid missing serious toxicity. In patients younger than 6 years of age, with unintentional ingestions, use of a higher 200-mg/kg cutoff has been suggested^{52,214,315} and is likely appropriate but has been incompletely studied.

The dose history should be used in the assessment of risk only if there is reliable corroboration or direct evidence of validity. Although the amount ingested by history roughly correlates with risk of toxicity and an [APAP] over the treatment

line,^{21,335,357} historic information is not sufficiently reliable in all patients to exclude significant ingestion, particularly in patients with the intent of self-harm or drug abuse.³⁵⁷ In fact, suicidal patients with ingestions who do not confirm an ingestion of APAP may have a measurable concentration in 1.4% to 8.4% of cases^{14,194} and a concentration over the treatment line in up to 0.2% to 2.2%.^{14,194} Therefore, when the history suggests possible risk, the patient should be further assessed an [APAP].

Interpretation of [APAP] after acute exposures is based on adaptation of the Rumack-Matthew nomogram (Fig. 35–2).²⁵⁹ The original nomogram was based on the observation that untreated patients who subsequently developed AST or ALT concentrations above 1000 IU/L could be separated from those who did not on the basis of their initial [APAP]. A nomogram was constructed that plotted the initial concentration versus time since ingestion, and a discriminatory line was drawn to separate patients who developed hepatotoxicity from those who did not. The initial discriminatory line stretched from [APAP] of 300 µg/mL at 4 hours to 50 µg/mL at 12 hours but was lowered to between 200 µg/mL at 4 hours and 50 µg/mL at 12 hours after evaluation of additional patients.²⁵⁹ The half-life of APAP was not a factor in the development of the nomogram, and the slope of the treatment line is based on empirical clinical data and does not reflect any discriminatory APAP half-life or APAP kinetics.²⁵⁹ The nomogram is designed and validated using a single value obtained at or greater than 4 hours after ingestion to allow for complete APAP absorption. Although patients who develop hepatotoxicity may have APAP half-lives greater than 4 hours,^{246,292} plotting multiple points on the nomogram or using an APAP half-life to determine risk has not been adequately studied and has significant limitations.^{165,301} The nomogram was later extrapolated to 24 hours using the same slope of the original nomogram line.²⁵⁹

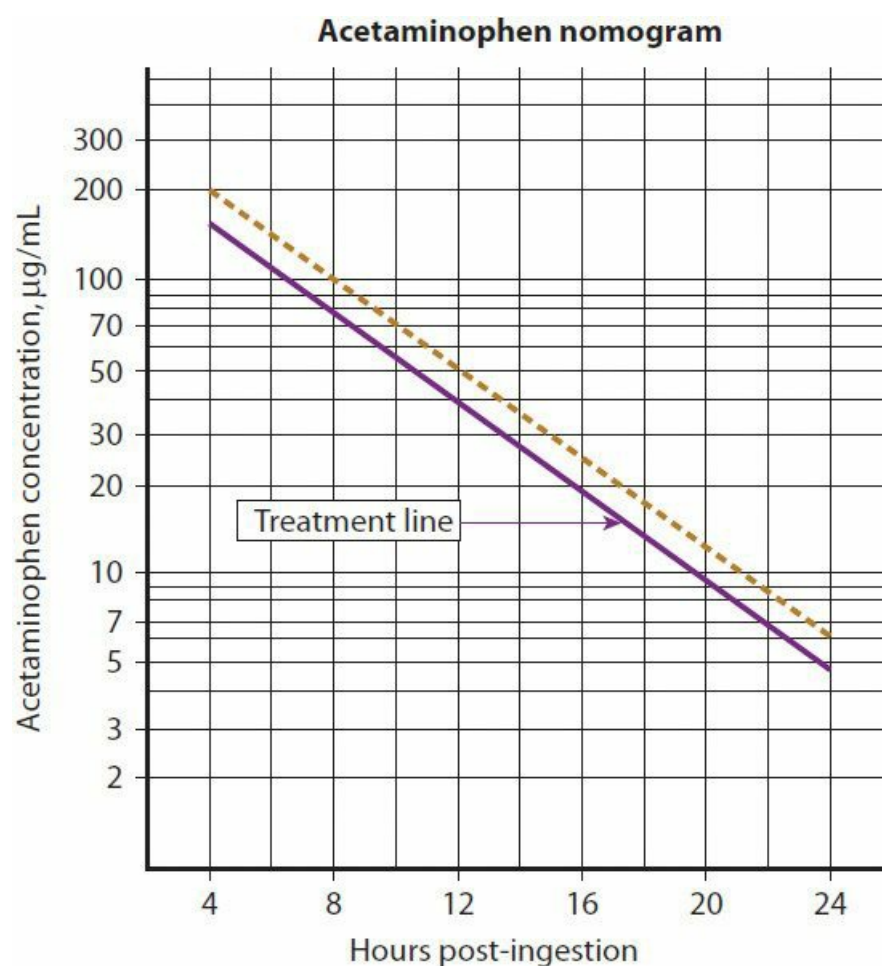


FIGURE 35–2. Rumack-Matthew nomogram (reconstructed) for determining the risk of APAP induced hepatotoxicity after a single acute ingestion. Serum concentrations above the treatment line on the nomogram indicate the need for N-acetylcysteine therapy.

It is important to realize that the line was based on aminotransferase concentration elevation rather than on hepatic failure or death, and it was chosen to be very sensitive, with little regard to specificity. Without antidotal therapy, only 60% of those with an initial [APAP] above this original line will develop hepatotoxicity as defined by aminotransferase concentrations above 1000 IU/L, but the risk of hepatotoxicity is not the same for all such patients. Elevated aminotransferase concentration develops in virtually all untreated patients with [APAP] far above the line, and serious hepatic dysfunction occurs frequently; the incidence of hepatotoxicity among untreated people with [APAP] immediately above the line is very low, and the risk of hepatic failure or death is far less.^{243,293}

The line used in the United States runs parallel to the original but was arbitrarily lowered by 25% to add even greater

sensitivity.^{259,262} The lower line, subsequently referred to as the treatment line or 150-line, starts at a concentration of 150 µg/mL at 4 hours following ingestion; declines with a 4 hour half-life, and ends at 4.7 µg/mL 24 hours following the overdose. The treatment line is one of the most sensitive screening tools used in medicine. The incidence of nomogram failures in the United States using this line is only 1% to 3% (depending on time to treatment).²⁵⁹ These infrequent “failures” may result from inaccurate ingestion histories, or may include patients with currently undefined risk factors for toxicity, including unique GSH handling or CYP enzyme activities.^{204,259}

In September 2012, the United Kingdom adopted a single nomogram line starting at 100 µg/mL at 4 hours (“100-line”) for all acute APAP ingestions.¹⁰⁹ This single 100-line replaced a two-tiered treatment protocol that treated low risk patients if either [APAP] exceeded the “200-line” and high risk patients if their [APAP] exceeded the “100-line”.³³³ The change was motivated by concern with regard to a small number of patients with [APAP] between the 100- and 200-lines who developed hepatic toxicity^{19,43,79,259,297,333} and a desire to simplify the treatment protocol. Why a 100-line was chosen by the UK Medicines and Healthcare Regulatory Agency and not a 150-line is not clear and has been questioned by several authors.^{109,204}

Based on these observations and more than 25 years of use, the 150-line should be considered adequate in nearly all cases and is reliable when rigorously followed. When using the APAP nomogram, it is essential to precisely define the time window during which APAP exposure occurred and, if the time is unknown, to use the earliest possible time as the time of ingestion. Using this approach, patients with [APAP] below the treatment line, even if only slightly so, do not require further evaluation or treatment for acute APAP overdose. This also applies to most patients with factors that may predispose them to APAP-induced hepatotoxicity. There appears to be adequate experience with acute APAP overdose in the settings of potentially predisposing factors such as chronic heavy ethanol use, chronic medication with CYP-inducing xenobiotics, and inadequate nutrition to recommend that no special approach is required in such cases. Further study is needed to determine if rare events, such as acute APAP ingestion in the setting of chronic isoniazid (INH) use,^{93,220,353} may uniquely predispose patients to toxicity and require alteration of this approach.

The goal should be to determine [APAP] at the earliest point at which it will be meaningful in decision-making. Therefore, measurement of [APAP] 4 hours after ingestion or as soon as possible thereafter is used to confirm the patient’s risk of toxicity and, thus, the need to initiate NAC. No established guidelines are available for the use of determinations made less than 4 hours after ingestion, and because of variability in absorption, such values have less predictive value. Although it is optimal to start NAC therapy as soon as possible after confirmation of risk, NAC is nearly 100% effective if started prior to 6 to 8 hours after ingestion.^{293,299} This allows clinicians some leeway to wait for the laboratory results before starting therapy in patients in whom the history of ingestion suggests that the 4h [APAP] will fall below the treatment line. However, it should be noted that delaying NAC therapy longer than 6 to 8 hours after ingestion may increase the patient’s risk. If there is any concern about the availability of an [APAP] before this time, then treatment with NAC should be initiated. In such cases, [APAP] still should be determined as soon as possible. The results, when they become available, should be interpreted according to the treatment line on the APAP nomogram and NAC either continued or discontinued on the basis of this result. In the unusual circumstance in which no determination of [APAP] can ever be obtained, evidence of possible risk by history alone is sufficient to initiate and complete a course of NAC therapy post ingestion.

Early Measurement of [APAP]. Measurement of [APAP] between 1 and 4 hours after ingestion may be helpful only to exclude ingestion of APAP. If [APAP] is undetectable in this time frame, significant APAP overdose can likely be excluded. However, an [APAP] that is detectable between 1 and 4 hours cannot be definitively interpreted and, unless undetectable, mandates repeat testing at 4 hours.

Determination of Risk When the Acetaminophen Nomogram Is Not Applicable

Risk Determination When Time of Ingestion Is Unknown. With careful questioning of the patient, family, and others, it is almost always possible to establish a time window during which the APAP ingestion must have occurred. The earliest possible time of ingestion (“worst-case scenario”) is used for risk-determination purposes. If this time window cannot be established or is so broad that it encompasses a span of more than 24 hours, then the following approach is suggested. Determine both [APAP] and AST concentrations. If the AST concentration is elevated, regardless of [APAP], treat the patient with NAC. If the time of ingestion is completely unknown and [APAP] is detectable, it is prudent to assume that the patient is at risk and to initiate treatment with NAC. If [APAP] is undetectable and the AST concentration is normal, there is little evidence that subsequent consequential hepatic injury is possible²⁹¹ and NAC is unnecessary.

Risk Assessment Following Extended-Release Acetaminophen. Extended-release formulations of APAP exist in the United States, Australia, New Zealand, and other countries worldwide. The pills available in the United States consists of a 325 mg immediate-release APAP dose and an additional 325 mg dose designed for delayed dissolution.⁷⁶ The pills found in Australia and New Zealand (all three have identical contents) consist of a 665 mg bilayer tablet with 206 mg in the immediate release form and 459 mg in a sustained-release gel matrix.^{112,113} Both products result in the immediate release of APAP with delayed release of an additional dose. Pharmacokinetic analysis of the US product reveals that the majority of

APAP is absorbed within 4 hours,^{85,327} the peak [APAP] is within 4 hours,^{58,85,312} and a small number of patients may have an initial [APAP] below the treatment line, but then have a subsequent [APAP] above the treatment line (“nomogram crossing”).^{58,327} “Nomogram crossing” has been described with the Australian and New Zealand products as well.¹¹² This “nomogram crossing” is not unique to the extended-release products and occurs in up to 10% of acute ingestions of immediate-release APAP.⁴⁶ There is little evidence that nomogram crossing affects outcome⁷⁶ and no evidence that an alternate approach to extended-release products should be used. In a 9 year review of 2596 extended-release APAP overdoses in the United States, one death was reported from acute overdose and there was no increased risk over immediate-release APAP.⁷⁶ In Australia and New Zealand, five cases of overdose have been described. Three patients had an [APAP] over the treatment line at 4 hours or later, were treated with NAC and did not develop hepatotoxicity.¹¹² One patient ingested 79 g of extended-release APAP, developed a double-hump [APAP] and a peak [APAP] of about 470 µg/mL at 10 to 15 hours, was treated with early NAC and developed mild aminotransferase elevations.¹¹³ The final patient had an [APAP] that was just below the treatment line at 4 hours, just above the line at 6 hours, was treated with NAC, and also did not develop hepatotoxicity.^{112,113} Certainly, a single [APAP] can reliably be plotted on the treatment nomogram after ingestion of the US APAP extended-release ingestion. Whether an alternative approach will be necessary for the Australian and New Zealand products, or any other new formulation, will require additional study.

Acute Overdose of Intravenous Acetaminophen. Several intravenous APAP and prodrug APAP products exist worldwide and the US Food and Drug Administration (FDA) approved an intravenous APAP product in 2010 (intravenous APAP, 1 g in 100 mL).¹¹⁵ Experience with intravenous APAP overdoses is limited, but 23 intravenous APAP overdoses have been described, as well as one case of hepatic toxicity with coagulopathy.^{22,115,224} Errors commonly occur in young children and include 10-fold dosing errors, confusion between mg and mL, and incorrect route (oral product given intravenously).^{23,115}

The approach described here is likely conservative and unstudied and is based on limited information including a well-documented case in which a dose of 90 mg/kg intravenously produced a 6h [APAP] of 38 µg/mL with hepatic toxicity and coagulopathy.²² This approach is reasonable based on current data, but should be modified as more information emerges. If a single dose error occurs that is in excess of 60 mg/kg, then immediate treatment with NAC is recommended.^{22,115} If a single dose is given but the exact dose is unknown, then an [APAP] should be drawn and plotted on the nomogram using a new, lower line starting at 50 µg/mL at 4 hours and decreasing with a 4 hour half-life. If the concentration is above this “50-line,” then treatment with NAC is indicated.²² There are few data on which to base a treatment decision prior to 4 hours if the dose is unknown. However, in this circumstance, there is likely no harm in waiting for a 4 hour [APAP] prior to initiating therapy. Finally, patients receiving multiple supratherapeutic doses of intravenous APAP should be treated with NAC if there is evidence of hepatic toxicity (eg, elevated aminotransferase concentrations or evidence of hepatic failure) or if there is evidence of APAP accumulation (eg, [APAP] is above therapeutic concentrations that are expected for the last dose).¹¹⁵

Risk Determination Following Repeated Supratherapeutic Ingestions (or Chronic Overdose). No well-established guidelines are available for determining risk after chronic exposure to APAP. Conceptually, several factors must be considered before assessing and determining an individual’s risk of toxicity. It has been well established that therapeutic dosing of APAP is safe; however, some risk factors may put individual patients at risk for toxicity at supratherapeutic doses.

The chronic ingestion of “maximal therapeutic” doses (4 g/day) in normal adults without special circumstances appears to be safe. Several randomized, controlled trials have used maximal therapeutic doses of APAP (4 g/day) in thousands of patients over periods from 4 weeks to 2 years with no reported increase in adverse events or hepatic injury. A transient increase in aminotransferases of one to three times normal, but rarely up to 10 times normal is detected in some patients taking therapeutic doses,^{2,338} but these abnormalities resolve spontaneously despite continued use and have not led to hepatic dysfunction.^{172,338} Finally, several studies have evaluated abstaining chronic alcoholics administered APAP 4 g/day for up to 10 days with no evidence of hepatic damage, although elevations in aminotransferases were detected in both APAP and control groups.^{72,173}

In 2009, an FDA advisory committee recommended to the FDA to decrease the daily dose of APAP to 3250 mg/day and in 2011 McNeil Pharmaceuticals limited its recommended daily dose for the 500 mg tablet to 3000 mg/day. This recommendation and the change in dosing was neither evidence based nor based on any safety data. The recommended daily dose for the 325 mg tablet and 650 mg extended-relief tablet remains at 3900 mg/day. The FDA did not mandate this reduction of daily dosing.¹⁷⁰

Although therapeutic dosing appears to be safe, repeated supratherapeutic ingestions (RSTIs) may lead to toxicity. Given the amount of APAP use, the incidence of serious APAP toxicity after repeated doses is small, and hepatotoxicity appears to occur only after massive dosing¹⁸⁸ or prolonged excessive dosing. The risk of hepatotoxicity is likely proportional to both the total amount of APAP ingested and the duration of the exposure; however, exact cutoffs for safe dosing are difficult to determine and are likely subject to factors related to the individual.

Although short-term prospective studies of supratherapeutic dosing (6–8 g/day) have not identified alterations in APAP kinetics or hepatotoxicity,¹⁰⁵ several series and case reports have identified patients with hepatotoxicity who retrospectively report therapeutic or slightly supratherapeutic doses. Retrospective dosage reporting is prone to significant errors and issues in which those giving the history may be unable or unwilling to report or estimate ingestions accurately. Cases describing hepatic toxicity after in-hospital therapeutic doses exist, but are exceedingly rare, involve unusual risk factors, and demonstrate multifactorial hepatic injury.^{55,61} Furthermore, because APAP is commonly used in patients with chronic heavy ethanol use and viral infections, it is unclear in which cases APAP was causative, contributory, or unrelated to hepatotoxicity.

Conceptually, the groups that are at “high risk” for hepatotoxicity after RSTI of APAP have either potentially increased activity of CYP2E1 and therefore proportionally increased NAPQI formation or have decreased GSH stores and turnover rate. Many reported cases of APAP toxicity from RSTI involve patients who have factor(s) that influence their GSH supply or turnover, NAPQI production, or both, including infants with febrile illness who have received excessive dosing, chronic heavy ethanol users, and patients chronically taking CYP-inducing medications. The interplay of NAPQI and GSH may also be an important factor. For example, malnutrition is theorized to increase the risk of APAP toxicity³⁴²; however, both CYP2E1 activity⁵⁹ and GSH supply¹⁶³ are decreased in malnourished patients, and their relative impact on risk is unknown.

When there is concern about risk of toxicity after RSTI dosing, several approaches are suggested. The goal should be to select patients at risk based on dosing history and other risk factors and to then use limited laboratory testing to determine the need for NAC. A logical screening laboratory evaluation consists of determination of [APAP] and AST concentrations, with additional testing as indicated by these results and other clinical features. The objective is to identify the two conditions that warrant NAC therapy—remaining APAP yet to be metabolized and potentially serious hepatic injury.

Role of History and Physical Examination in Repeated Supratherapeutic Ingestions. The first consideration when evaluating a patient with a history of repeated supratherapeutic APAP dosing is the presence or absence of signs or symptoms of hepatotoxicity. Regardless of risk factors or dosing history, such findings should prompt treatment with NAC and laboratory evaluation. This is particularly important because most reported cases of serious toxicity after repeated dosing are symptomatic for more than 24 hours before diagnosis, and earlier treatment may improve outcome.

In asymptomatic patients, a reasonable approach is to perform laboratory evaluation for those who have ingested more than 200 mg/kg/day (or 10 g/day, whichever is less) in a 24 hours period or more than 150 mg/kg/day (or 6 g/day, whichever is less) in a 48 hours period.^{72,75,196} In children younger than 6 years of age, laboratory evaluation should be performed if the reported ingestion is more than 100 mg/kg/day during a 72 hours period or longer.

Several factors or characteristics place patients at higher risk for chronic APAP toxicity. High-risk factors that have been theorized include chronic heavy ethanol use; chronic ingestion of INH; febrile illnesses in infants and young children; and malnutrition, AIDS, or anorexia. In some cases, animal or basic science studies show evidence of increased risk, and in most cases, there have been multiple anecdotal reports of toxicity at therapeutic or slightly supratherapeutic doses. Whether these patients require a lower threshold for laboratory screening is unknown.

Role of Laboratory Evaluation in Repeated Supratherapeutic Ingestions. After a patient is determined to be at risk, an [APAP] and [AST] should be determined. These should be interpreted using the concept that a patient may be at risk of hepatotoxicity if there is evidence of hepatic injury (elevation of AST) or there remains enough APAP to produce further hepatic damage.

Using the strategy described here, patients with elevated [AST] are considered at risk, regardless of [APAP]. An [APAP] is useful in patients with normal [AST] as a tool to determine only whether sufficient APAP remains to lead to subsequent NAPQI formation and delayed hepatotoxicity. In many cases, [AST] is normal and [APAP] is below 10 µg/mL, obviating the need for NAC. If the [AST] is normal, then the patient should be considered at risk if [APAP] is 10 µg/mL or above. Higher thresholds for non-treatment, such as APAP below 30 µg/mL or AST twice as high as normal, have been suggested, but have not been studied and their sensitivity is unknown.

Patients who develop highly elevated [AST] after chronic APAP overdose should be treated and further evaluated with laboratory tests to assess hepatotoxicity and prognosis (creatinine, PT, INR, pH, phosphate, and lactate). Initial elevations of INR or creatinine may be markers of poor prognosis in APAP RSTI.⁴

The measurement of APAP protein adducts in urine has been described and theoretically could quantify NAPQI production in the liver. It has been suggested that adduct concentrations may identify APAP-induced hepatotoxicity in undifferentiated patients with elevated [AST]; however, adducts are elevated after both therapeutic and RSTI APAP ingestions and a clear defining value has not been determined.¹³³ In addition, the test remains largely unavailable and has been insufficiently studied.^{78,149,218} Several other biomarkers, including miRNA-122 and acetylated HMGB-1, have been tested in acute overdoses, but their utility in RSTI is unclear.

Patients who are identified as at risk, with either an elevated [AST] or an elevated [APAP], should be treated with NAC.

Risk Determination Following Acetaminophen Exposure in Children

Serious hepatotoxicity or death after acute APAP overdose is extremely rare in children.^{261,315} Predominant theories⁵ for resistance to toxicity include a relative hepatoprotection in children because of increased sulfation capacity²⁰⁷ or differences in the characteristics of children poisonings, including smaller ingested doses, overestimation of liquid doses, and unique formulations (pediatric elixirs that contain propylene glycol may result in decreased toxicity due to inhibition of CYP2E1).^{158,317} This has led some to suggest higher screening values and a higher nomogram line for children.³⁵ However, no significant change in NAPQI production has been demonstrated in children, and a more liberal approach to children's acute APAP ingestions has been inadequately studied and is not recommended. After repeated supratherapeutic APAP dosing, there is no evidence that children are relatively protected. Hepatic injury after therapeutic APAP is likely exceedingly rare in children.¹⁷⁹ However, infants and children with acute febrile illnesses comprise one of the few groups in which toxicity after repeated excessive dosing is well described.²⁴⁶ Common sources of dosing errors include substitution of adult for pediatric preparations; overzealous dosing by amount or frequency in attempts to maximize effect, and failure to read the label and dose carefully.^{8,246} Age younger than 2 years is an independent risk factor for development of toxicity.¹⁵⁶ These rare cases of toxicity in febrile children with repeated supratherapeutic dosing may simply reflect that these children constitute the most common setting for pediatric APAP use and that children are at greater relative risk for excessive dosing because of their size. Although logically one can argue that inflammatory oxidant stress and short-term fasting during febrile infectious illnesses affect oxidative drug metabolism and decrease GSH supply, these relationships are complex and not well defined. Of the reported cases of repeated supratherapeutic APAP dosing in children with hepatic injury, the cause was likely an isolated infectious illness in some, APAP in others, and a combination of the two in still others.

Risk Determination Following Acetaminophen Exposure in Pregnancy

The initial risk of toxicity in a pregnant woman is similar to that of a nonpregnant patient with a few exceptions. Little evidence suggests that any alteration of the treatment line is necessary. In fact, there are no reported cases of fetal or maternal toxicity in women with [APAP] below the treatment line²⁰³ or in those treated with NAC within 10 hours of an acute ingestion.²⁵⁵ However, there is controversy in assessing the risk of fetal toxicity after the mother has been determined to be at risk. To better understand the issues, a review of maternal–fetal physiology and pharmacokinetics related to APAP and NAC is necessary.

APAP is capable of crossing the human placenta,^{188,223,256} and APAP may be present in concentrations similar to maternal serum concentrations within hours after ingestion.^{223,256} Fetal metabolism of APAP probably is inefficient but is not completely understood. Fetal sulfation and oxidative metabolism of APAP are slower than in adults, and glucuronidation is undetectable until 23 weeks of gestation.²⁵⁷ CYP enzymes that are capable of oxidizing APAP are present in the fetus as early as 18 weeks gestation.²⁵⁷ However, the activity of these enzymes is less than 10% that of adult enzymes at 18 weeks gestation and increases to only 20% activity at 23 weeks.²⁵⁷ How the opposing forces of decreased overall metabolism of APAP and decreased NAPQI formation impact fetal risk is unclear.

The mechanism of fetal risk in women with APAP toxicity remains controversial. The degree of fetal toxicity that is attributable to fetal metabolism of APAP or to maternal illness is unclear. In clinical case series, the majority of pregnant women who overdose on APAP have uneventful pregnancies.^{203,255} Pregnant women who develop APAP toxicity in the first trimester have an increased risk of spontaneous abortion,²⁵⁵ fetal demise is described in the second trimester,³¹⁸ and those who develop APAP toxicity in the third trimester have a potential risk of fetal hepatotoxicity because of fetal metabolism. However, reports of third-trimester fetal hepatotoxicity are rare^{203,255} and are only associated with severe maternal toxicity.^{255,331} The factors associated with poor fetal outcome after a large APAP overdose are delayed treatment with NAC and young gestational age.

The decision to treat a pregnant woman with NAC requires consideration of what is known about the efficacy and beneficial effects as well as the adverse events of NAC for both the fetus and the mother. Every indication suggests that NAC is both safe and effective in treating the mother,²⁵⁵ but there are inadequate data to evaluate efficacy in the fetus, although fetal outcome has generally been excellent after maternal treatment with NAC.²⁵⁵ Given that NAC has been safely used in many pregnancies^{203,255} and fetal mortality is linked to delays to treatment, NAC should be initiated in pregnant women who meet the same criteria as nonpregnant patients. The necessary length of NAC therapy is difficult to determine. The 20 hour intravenous protocol probably is the most commonly recommended NAC protocol used for pregnant women worldwide; however, there is a paucity of published experience supporting NAC treatment courses shorter than the oral 72 hour protocol (Chap. 31).^{203,255}

Ethanol and Risk Determination

The effects of ethanol on APAP toxicity are complex and are best described by clearly separating experimental animal data

from actual human overdose experience, acute ethanol use from chronic heavy ethanol use or alcoholism, and single from repeated supratherapeutic APAP dosing. Ethanol use itself is difficult to define and many studies used different definitions. For the purpose of this section, the term chronic heavy ethanol use is defined as a person who ingests a mean of greater than two to three standard ethanol-containing drinks per day.²⁷⁶ Moderate ethanol use is defined as a mean of one to two standard ethanol-containing beverages per day. The term alcoholic will be used to define people whom either self-define as alcoholics or are identified as an alcoholic by the CAGE questionnaire, the Michigan Alcohol Screening Test, or similar screen.^{77,171,173}

Although not entirely consistent, both animal and human data suggest that acute ethanol coingestion with APAP may be hepatoprotective. Ethanol coingestion decreases NAPQI formation presumably by inhibiting CYP2E1 in both humans^{321,322} and animals.^{271,322} In large retrospective evaluations of overdoses, acute ethanol ingestion independently decreases the risk of severe hepatotoxicity in chronic heavy ethanol users²⁷⁶ and in nonchronic heavy ethanol users,²⁹³ but did not significantly decrease the risk of hepatotoxicity (ALT > 1000 IU/L) in a smaller prospective study.³³⁶

However, chronic ethanol administration increases the risk of hepatotoxicity from APAP dosing in animals.^{325,356} This may be a consequence of increased NAPQI formation due to induction of CYP2E1 metabolism once the ethanol is metabolized³¹⁹ or decreased mitochondrial GSH supply or regeneration.³⁵⁶

After acute APAP overdose, chronic heavy alcohol users who have not coingested ethanol may be at a slightly increased risk; however, this elevated risk appears to be of little clinical importance given the sensitivity of the treatment line.²⁹⁸ There is no credible evidence that chronic heavy alcohol use should alter the approach after an acute APAP overdose using the treatment line. In fact, the treatment line was developed with clinical data that included chronic heavy ethanol users.^{246,262} Given the paucity of data linking chronic heavy ethanol use to nomogram failures, it appears that the treatment line is adequately sensitive for screening after an acute APAP overdose, regardless of the patient's history of chronic heavy ethanol use.

The relationship between chronic heavy ethanol use and chronic APAP use is complex. Hepatotoxicity has been sporadically reported in patients with chronic heavy ethanol use after repeated supratherapeutic APAP dosing. Complicating these reports are the clinical challenges of obtaining accurate histories in chronic heavy ethanol users, failure to exclude non-APAP causes of hepatotoxicity, and other factors. Alcoholics are at higher risk of both using supratherapeutic doses of APAP and using combinations of multiple APAP-containing products.²⁸³ In contrast, prospective evidence demonstrates minimal risk of hepatotoxicity in alcoholic patients who ingest therapeutic doses of APAP.^{17,132,171,173} In prospective trials of ingestion of 4 g/day of APAP or placebo in chronic moderate to heavy ethanol users for up to 10 days, no clinically relevant increases in AST versus placebo have been identified.^{17,77,132,171,173} However, it should be noted that, in studies involving persons who abuse alcohol, mild AST elevations (< 120 IU/L) were noted in 40% of both study and controls, and more significant increases (> 120 IU/L, or three times normal) were noted in 4% to 6% of participants.^{171,173} In addition, in all studies, a small group of patients developed significant increases in aminotransferases, but most were unchanged. Patients who develop elevated aminotransferases after therapeutic dosing who are then rechallenged with additional APAP develop similar [AST] increases,¹³² implying that individual factors are likely more important than the chronic heavy ethanol use itself.

CYP Inducers and Risk Determination

Inducers of the CYP enzymes have long been theorized to increase the risk of toxicity from APAP because of a proportionally increased production of NAPQI. It is now clear that APAP is metabolized to NAPQI largely by CYP2E1^{130,198} and that only induction of this specific enzyme is likely to increase the risk of hepatotoxicity.

Although ethanol and INH are known inducers of CYP2E1, there is no evidence that the clinical approach to these patients should be altered. Similarly, several other medications, including phenytoin, carbamazepine, and phenobarbital, are theorized to increase APAP toxicity because of nonspecific CYP induction activity. None of these anticonvulsants induces CYP2E1, although there is some evidence that they increase NAPQI formation in cultured human hepatocyte and animal models, possibly through inhibition of glucuronidation.^{87,211} However, clinical experience suggests that there is no need to change the approach to these patients.

Assessing Actual Toxicity: Critical Components of the Diagnostic Approach

Initial Testing. The [APAP] should be measured in patients with acute APAP overdose and no evident hepatotoxicity, but no other initial laboratory assessment is required. AST concentration should be measured in patients who are considered to be at risk for APAP toxicity according to the nomogram or history (in the case of repeated supratherapeutic dosing) or in those suspected of already having mild hepatotoxicity by history and physical examination.

Unless evidence of serious hepatotoxicity is present, [AST] is a sufficient indication of hepatic conditions, and no additional testing is initially needed. Death of hepatocytes, resulting in release of measurable hepatic enzymes, precedes all

cases of serious hepatic dysfunction. Mild renal toxicity may rarely occur without hepatotoxicity⁴⁰; however, at least minimal elevation of [AST] generally precedes evidence of clinically significant nephrotoxicity.^{3,51} Exceptions are rare,^{40,161} and routine screening of renal function in the absence of elevated [AST] is probably unnecessary.

APAP overdose may lead to minor prolongation of PT even without causing hepatotoxicity.³⁴³ This most commonly occurs between 4 and 24 hours following ingestion and may be a result of NAPQI-related inhibition of vitamin K–dependent γ -carboxylation of factors II, VII, IX, and X.^{316,343} These minor prolongations (resulting PT usually is less than twice control) are rarely clinically relevant, are not evidence of hepatotoxicity, and should not be used as prognostic factors or indications for NAC treatment. In fact, treatment with NAC may also prolong PT^{150,167} by interfering with the PT assay, by reversing an APAP/NAPQI effect,³¹⁶ or by direct NAC effects.³¹⁶

Ongoing Monitoring and Testing. If no initial elevation of [AST] is noted, then repeated determination of [AST] alone—without other biochemical testing—is sufficient to exclude the development of hepatotoxicity. [AST] should be determined at the end of the protocol (eg, at 21 hours if using the standard intravenous protocol) or every 24 hours if using a longer protocol. If an elevated [AST] is noted, then PT and INR and creatinine should be measured and repeated every 24 hours or more frequently if clinically indicated. Results of other hepatic tests, such as GGT, alkaline phosphatase, lactate dehydrogenase, and bilirubin, which are useful when determining the cause of hepatic abnormalities, will be abnormal in cases of serious APAP-induced hepatotoxicity but provide little additional useful information if the cause is certain ([Chap. 23](#)).

If evidence of hepatic failure is noted, then careful monitoring of blood glucose, pH, PT, INR, creatinine, lactate, and phosphate concentrations are important in assessing extrahepatic organ toxicity and are vital in assessing hepatic function and the patient's potential need for hepatic transplant (see Assessing Prognosis). In addition, meticulous bedside evaluation is necessary to determine and document vital signs, neurologic status, and evidence of bleeding. Many additional tests may be useful in the setting of hepatic failure based on clinical condition and local protocols. Testing for other rare APAP-associated conditions by electrocardiography, lipase determination, or other studies should be performed on a case-by-case basis only.

MANAGEMENT

Gastrointestinal Decontamination

In cases of very early presentation or coingestion of xenobiotics that delay gastrointestinal (GI) absorption, gastric emptying may be appropriate for some patients. In general, however, gastric emptying is not appropriate for patients with isolated APAP overdose because of the very rapid GI absorption of APAP and the availability of an effective and safe antidote.

Administration of activated charcoal (AC) shortly following APAP ingestion may decrease the number of patients who have an [APAP] above the treatment line.⁴⁷ Although AC is most effective when given within the first 1 to 2 hours following APAP ingestion, it may be reasonable to consider AC at later times provided there are no contraindications.^{306,307}

Interactions between AC and orally administered NAC are likely clinically unimportant. In the majority of cases, there should be no interaction because GI absorption of APAP, and therefore the necessity to give AC, is complete by 4 hours following ingestion, and NAC typically is administered between 4 and 8 hours following ingestion. As a result, there is generally no difficulty separating the doses. If delayed or repeated AC dosing is indicated because of suspected delayed absorption or coingestants, then a strategy using an intravenous NAC protocol should be considered. Alternatively, oral NAC and AC doses may be separated by 1 to 2 hours, with NAC given the priority for the first dose because time to administration of NAC correlates with risk of hepatotoxicity.^{293,299} NAC is absorbed high in the GI tract and is not likely to interact with AC if they are not administered simultaneously.

Supportive Care

General supportive care consists primarily of controlling nausea and vomiting and managing the hepatic injury, acute kidney injury, and other manifestations. Treatment of these problems is based on general principles and is not APAP dependent. Discussion of the management of hepatic failure is clearly beyond the scope of this chapter, but certain aspects deserve mention. Monitoring for and treatment of hypoglycemia are critical because hypoglycemia is one of the most readily treatable of the life-threatening effects of hepatic failure. If adequate viable hepatocytes are present, vitamin K may produce some improvement in coagulopathy; thus, trial dosing is logical as hepatic injury develops and as it resolves. Administration of fresh-frozen plasma (FFP) and prothrombin complex concentrates (PCCs) should be based on specific indications rather than PT and INR alone. Hemorrhage is rare in APAP-induced hepatic failure and correction of coagulopathy should only be necessary for procedures and life-threatening bleeding. Supportive therapy for cerebral edema, including cooling, hypertonic saline, elevation of the head, and support of the cerebral perfusion pressure, are all

indicated.

Antidotal Therapy with N-Acetylcysteine. Mechanism of action of N-acetylcysteine. Conceptually, it is helpful to think of NAC as serving three distinct roles. During the metabolism of APAP to NAPQI, NAC prevents toxicity by limiting the formation of NAPQI. More importantly, it increases the capacity to detoxify NAPQI that is formed (Fig. 35–1). In fulminant hepatic failure, NAC treats toxicity through nonspecific mechanisms that preserve multiorgan function. A complete discussion of NAC can be found in Antidotes in Depth: A3. A brief review follows.

NAC prevents toxicity mostly by serving as a GSH precursor¹⁷⁸ and also as a GSH substitute,²⁸⁶ combining with NAPQI and being converted to cysteine and mercaptate conjugates.⁴⁸ NAC may also lead to increased substrate for nontoxic sulfation, allowing less metabolism by oxidation to NAPQI.²⁹⁴ Each of these preventive mechanisms must be in place early, and none is of benefit after NAPQI has initiated cell injury. Time is required to saturate nontoxic metabolism, form excessive NAPQI, deplete GSH, and overcome GSH production; thus there is a window of opportunity after exposure to an APAP overdose during which NAC can be initiated before the onset of hepatic injury without any loss of efficacy. Based on large clinical trials, it appears that NAC efficacy is nearly complete as long as it is initiated within 6 to 8 hours of an acute overdose.^{159,293,299,300} However, the relationship between the time to administration of NAC and the risk of hepatotoxicity should be considered a continuous variable. The risk of hepatotoxicity begins to increase at 6 hours for patients with very high [APAP] and is closer to 8 hours for patients with [APAP] just over the treatment line.^{293,308} For this reason, NAC therapy should not be unnecessarily delayed past 6 hours if it can be safely administered earlier.

Several observations illustrate the effectiveness of NAC by other mechanisms of action even after NAPQI formation and binding. NAC actually reverses NAPQI oxidation in both a mouse model⁶⁵ and an in vitro human hepatocyte model,¹⁹⁷ and even after cell injury is initiated, NAC may diminish hepatocyte injury.⁴⁴ Most significantly, a prospective, randomized trial found that even after fulminant hepatic failure was evident, intravenous NAC diminished the need for vasopressors and the incidences of cerebral edema and death.¹⁵⁷ In this study, despite improved organ function and survival in the NAC-treated group, there was no apparent difference in the degree of hepatic injury, implying that much of the benefit of NAC in this setting may not be derived from hepatic effects. Whether based on its nonspecific antioxidant effects, its increase in oxygen delivery and utilization, its ability to enhance GSH supply and mitochondrial ATP production, or its role in mediating microvascular tone,^{82,127,152,263,305,330,331} NAC improves function in several organs affected by multisystem failure.^{82,328} In fact, NAC may preserve cerebral blood flow and perfusion in the setting of cerebral edema³⁴⁰ more effectively than traditional therapies such as mannitol and hyperventilation, which may actually be detrimental.

Although NAC has a defined role in preventing and treating APAP-induced hepatic injury, its role in treating APAP-induced acute kidney injury is less clear. When used early after ingestion in animals, NAC produces a small reduction in kidney injury.^{215,295} In retrospective reviews of human data, NAC has had little effect on kidney injury⁸⁰ but does not appear to be harmful.²¹⁷ However, few data are available to recommend NAC therapy in treating isolated acute kidney injury or acute kidney injury after resolution of hepatic injury.

N-acetylcysteine administration. NAC may be administered via the oral or intravenous routes and in protocols that have historically varied in length. The two most common regimens are a 21 hour intravenous infusion and a 72 hour oral dosing protocol. However, the concept of a set-length protocol is obsolete. Conceptually, practitioners should start NAC when the patient is at risk of toxicity, continue NAC while the patient remains at risk or has hepatotoxicity, and stop NAC when that risk or toxicity is gone. Most institutions now use either oral or intravenous NAC in a variable length protocol, using indicators of patient toxicity rather than a set protocol length.¹³¹ These are described at length in Antidotes in Depth: A3.

With the exception of established hepatic failure, for which only the intravenous route has been investigated,¹⁵⁷ the intravenous and oral routes of NAC are equally efficacious in preventing or treating APAP toxicity.^{46,241} The decision to treat with intravenous or oral dosing is complex and is described in Antidotes in Depth: A3. In brief, whereas intravenous NAC has been associated with rare but severe anaphylactoid reactions and medication errors,¹²⁹ oral NAC is associated with a greater than 20% risk of vomiting. There are three scenarios in which intravenous NAC is generally recommended: (1) APAP toxicity in pregnant women, (2) APAP-induced hepatic failure, and (3) intractable vomiting preventing oral treatment.

Duration of N-acetylcysteine treatment. Known mechanisms of action and the observation that all studied durations of NAC are effective when started within 8 hours⁴⁶ suggest that all courses of treatment currently published are effective when NAC is used for its early preventive actions. There is some suggestion that there may be a slightly decreased risk of hepatotoxicity if intravenous NAC, as opposed to oral NAC, is used before 10 hours after the ingestion, but this remains controversial.³⁵⁰ Results from use of the traditional 21 hour intravenous NAC protocol, the 48 hour and 36 hour intravenous NAC protocols studied in the United States,²⁹⁶ one 20 hour protocol,³⁵¹ and other “short-course” dosing protocols^{29,28,347} indicate that those therapies are likely safe and effective in these low-risk scenarios.^{314,352}

It is important to realize that even in low-risk patients (those treated within 8 hours), regardless of the protocol length (21, 36, 48, or 72 hours) or route of delivery, NAC therapy should be continued until APAP metabolism is complete (the [APAP] is below detection) and there are no signs of hepatotoxicity. With this concept in mind, it may seem reasonable to

shorten a set course of NAC if the patient is low risk and the above criteria are met ([APAP] undetectable, [AST] normal, PT/INR less than twice normal, and no encephalopathy).^{29,74,293} This approach is conceptually reasonable and is aimed at decreasing unnecessary therapy as there is no evidence that prolonged NAC is helpful and there is one animal study that suggests that prolonged NAC may inhibit hepatic recovery,³⁴⁹ however, adequate studies have not definitively confirmed its safety.^{285,293}

NAC therapy should be continued beyond the prescribed “protocol length” if there is evidence of hepatic injury ([AST] significantly above normal or PT/INR > twice normal or encephalopathy is present) or APAP metabolism is incomplete ([APAP] detectable). This likely will not be an issue in the vast majority of cases because the aminotransferases of approximately one-half of all NAC-treated patients with [APAP] above the treatment line will remain below 100 IU/L.³⁰⁰ The intravenous NAC dosing protocol that has proved beneficial in patients with hepatic failure is the same initial dosing as the traditional intravenous protocol but with the third intravenous infusion continued until there is resolution of hepatic failure. These observations suggest that rather than a single duration of therapy for all patients, it is appropriate to extend treatment protocols based on the clinical course of the patient.⁷⁴

After NAC therapy is extended beyond a set-length protocol, the decision to discontinue therapy should be entirely based on the patient’s condition. For patients who develop hepatic failure, intravenous NAC is continued until the PT or INR is below twice the rate of normal and encephalopathy, if present, is resolved.¹⁹⁶ For patients without hepatic failure but with elevated [AST], NAC is often continued until all hepatic abnormalities resolve (eg, [AST] is decreasing and < 1000 IU/L).

Assessing Risk of Hepatotoxicity. Most patients who are treated with NAC do not develop hepatotoxicity and have short hospital stays, whereas a small percentage develop hepatotoxicity and an even smaller group develop hepatic failure. It may be helpful to predict the risk of hepatotoxicity based on initial findings to direct the intensity of monitoring and therapy (see Dose Adjustment) and patient disposition.

In general, both the time from ingestion to the initiation of NAC and [APAP] are directly proportional to the patient’s risk of developing hepatotoxicity and hepatic failure.^{274,293,299} Even in patients treated early after their ingestion, their risk of hepatotoxicity is significant if their [APAP] is highly elevated.²⁵⁹ Using these principles, a nomogram has been produced that may be used to determine the risk of hepatotoxicity on patient arrival. Unfortunately, this only predicts the risk of a peak aminotransferase concentration above 1000 IU/L and has not been studied to determine the risk of death or need for transplantation. In addition, the multiplicative sum of [AST] (or [ALT]) and [APAP] has also been studied to predict hepatotoxicity, but requires validation.²⁹² Acetylated HMGB-1 is a promising biomarker for detecting patients who will go on to have severe hepatic failure and may be useful for early prognostication.¹¹ Initial human studies, [acet-HMGB-1] increased only in patients who later met the King’s College Criteria for hepatic transplant, received a transplant, or died.¹¹ These results are promising and require validation and further study.

Dose Adjustment. In rare cases, patients with massive ingestions with or without antimuscarinic co-ingestants may have highly elevated [APAP] for prolonged periods or secondary elevations of the [APAP].^{86,88,134,282,332} Several of these patients have developed hepatotoxicity despite early (< 6 hours) intravenous NAC therapy,^{88,134,282,332} raising the question of whether the traditional intravenous NAC infusion (6.25 mg/kg/h) provides enough NAC for these rare patients with late elevated [APAP] or massive ingestions. Several theoretical solutions have been noted, but none are tested and a consensus opinion on optimal therapy does not exist. In these rare patients, consideration should be given to treating with greater amounts of NAC once prolonged, massive [APAP] are evident.^{282,303} No data exist to determine which, if any, alternative NAC dosing strategy is superior. For a detailed description of increased dosing for massive ingestions, highly elevated [APAP], and prolonged elevations of [APAP], see Antidotes in Depth: A3. A brief synopsis is described below and is based on calculations that use logical inferences, but none of these concepts has been studied and should not be considered standard therapy. The described dosing protocol has little risk, but has unproven benefit, and should be used with caution in extreme clinical cases:²⁶⁰

1. If the ingestion is between 16 and 32 g or the initial [APAP] is between the “300-line” and the “500-line,” then consider using 12.5 mg/kg/h as the 16 hour infusion rate.
2. If the ingestion is between 32 and 48 g or the initial [APAP] is above the “500-line,” then consider using 18.75 mg/kg/h as the 16 hour infusion rate.
3. If the ingestion is greater than 48 g, then consider using 25 mg/kg/h as the 16 hour infusion rate.
4. If the [APAP] at 20 hours or later is 25 to 50 µg/mL, then use 12.5 mg/kg/h as the continuous infusion. If the [APAP] at 20 hours or later is > 50 µg/mL, then use 18.75 mg/kg/h as the continuous infusion.

An alternative approach equally logical, but also unstudied, is to combine both the oral NAC protocol with the intravenous NAC protocol. This method provides both an additional bolus dose (290 mg/kg), as well as 23.75 mg/kg/h as the continuous infusion.

Hepatic Transplantation. Hepatic transplantation may increase survival for a select group of severely ill patients who have APAP-induced fulminant hepatic failure.^{196,226} Tremendous improvements in transplantation and supportive hepatic

care have increased immediate survival rates after hepatic transplantation to 69% to 78% with 3- to 5-year survival rates of 54% to 66%,^{26,64,160,196,288} respectively, which is similar to transplant survival for other causes of acute hepatic failure. Patients who meet criteria for transplant but do not receive an organ have had survival rates ranging from 5% to 17%,^{24,25,176,196,209,227} but higher survival rates have recently been reported.²⁷⁵

Concerns that patients who receive transplants for APAP-induced fulminant hepatic failure will have lower survival rates and be unable to maintain post-transplant medication regimens have resulted in the majority of patients not being listed for transplant.²⁶ However, those who meet psychosocial criteria for transplantation have high rates of survival,^{26,64,196} and 12% later die from intentional rejection or suicide attempts.²⁶ Techniques that allow subtotal hepatectomy with transplantation and eventual weaning of immunosuppressants are promising and may allow for higher rates of transplantation.¹⁹³

Assessing Prognosis. Determining a patient's prognosis and predicting patients who require transplantation early in the course of the disease is an important area of current research.

The most commonly used indicator of the need for immediate transplantation is the King's College Criteria (KCC; [Table 35–1](#)), which was developed and validated on patients with APAP-induced fulminant hepatic failure. The criteria include a serum pH below 7.30 after fluid resuscitation or the combination of creatinine above 3.3 mg/dL, PT above 100 sec (INR > 6.5 is commonly used), and grade III or IV encephalopathy. The survival rate of patients who meet the KCC but do not receive an organ remains below 20% in most centers.^{16,26,60,67,68,227} Significantly higher survival rates in patients meeting transplant criteria have recently been reported and may be due to the utilization of prolonged NAC therapy and improved supportive care for patients with acute hepatic failure.^{110,275}

TABLE 35–1. King's College Criteria for Predicting Need for Hepatic Transplant

Either of the following predicts a survival rate < 20% and the need for immediate transplantation, if available and appropriate:

1. Arterial pH < 7.3 or lactate > 3.0 mmol/L after fluid resuscitation

OR

2. All of the following:

- a. Creatinine > 3.3 mg/dL
- b. Prothrombin time > 100 sec (or international normalized ratio > 6.5)
- c. Grade III or IV encephalopathy (somnolence to stupor; responsive to verbal stimuli; confusion; gross disorientation)

When determining the KCC, interpretation of PT and INR must include awareness of concurrent NAC therapy as well as therapy with vitamin K, PCCs, factor VII, and FFP. The use of vitamin K, if effective, implies that transplant may be unnecessary because viable liver remains. If vitamin K is ineffective, then PT and INR can be used, as discussed in the previous paragraph. Transfusion of exogenous clotting factors, such as FFP or PCCs, alters interpretation because improvement in PT and INR may not indicate improvement in hepatic function. The prognostic importance of monitoring PT and INR in this setting suggests that FFP should be given only with evidence of bleeding, with risk of bleeding from known concomitant trauma, or before invasive procedures and not based merely on the PT and INR.

A lactate concentration above 3.5 mmol/L at a median of 55 hours after APAP ingestion or lactate concentration above 3.0 mmol/L after fluid resuscitation is shown to be both sensitive and a specific predictor of patient death without transplant.^{25,71} Additional studies confirmed lactate as an independent predictor of prognosis but suggest that it does not add significantly to the KCC.^{60,279} Others have confirmed a lower specificity than initially reported.^{110,279} Using a higher cutoff (> 4.7 mmol/L) has a high sensitivity (98%) and NPV (95%), but moderate specificity (58%) for determining death or transplant.^{60,279}

Unfortunately, patients often meet the KCC and lactate criteria quite late in their course of disease, so these criteria are not useful as early predictors or as standards for transfer to a facility that performs hepatic transplant. General factors that are associated with increased mortality include unintentional overdose, repeated supratherapeutic dosing, and delays to receiving NAC therapy.^{69,70} Additional predictors of severity of hepatic toxicity in patients treated with NAC include a rapid doubling of [AST] or [ALT] (doubling < 8 hours)¹¹⁷ and [AST] or [ALT] reaching 1000 IU/L within 20 hours of NAC treatment.¹¹⁷ Several attempts at determining early predictors of death or the need for transplant have proven to be no more effective than the KCC, including serum phosphate (day 2),^{24,277} Model for Endstage Liver Disease (MELD) score of 32 or above,^{60,192,278} serum Gc-globulin,^{183,273} factor V concentration,^{141,234} factor VIII:V ratio,^{41,234} worsening day 4 PT and INR,¹²⁶ and PT (in seconds) larger than the number of hours since ingestion.²²²

An Acute Physiology and Chronic Health Evaluation (APACHE) II score above 15 in isolated APAP ingestions may be as specific as the above KCC criteria and slightly more sensitive.^{60,209} These criteria may be beneficial in determining whether to transfer a patient to a transplant center because the score is easily calculated, is sensitive, and is available within the first day of admission; however, confounders such as coingestants may decrease its utility. Furthermore, an APACHE III score above 60 may be helpful in identifying additional patients with multiorgan dysfunction who may require transplantation.²⁶

Several measurements of organ failure have been postulated as indications for transfer to a regional transplant center from a non-transplant facility. The Sequential Organ Failure Assessment (SOFA) score higher than 7 within the first 96 hours after acute overdose and evidence of the systemic inflammatory response syndrome both predict increased mortality (a 100% sensitivity and a 74% to 77% specificity).⁶⁷ Conversely, a patient with a SOFA score of 7 or less during the first 96 hours after acute overdose has a low mortality (< 2%), low risk of requiring renal replacement therapy (< 4%), and low risk of requiring intracranial pressure monitoring (< 2%).⁶⁷ Additionally, SOFA score below 6 after repeated supratherapeutic ingestion of APAP predicts survival and a low risk of the need for renal replacement therapy or intracranial pressure monitoring (< 10%).⁶⁸

The KCC, APACHE II, SOFA, and MELD scores, as well as serum lactate 12 hours after admission, have been recently compared and may all be helpful in making patient decisions.⁶⁰ The MELD score (> 32) and lactate concentration (> 4.7 mmol/L) are the most sensitive to determine death or transplant in APAP-induced hepatic failure. These scores may be helpful in predicting death or the need for a higher level of care (Table 35–2), whereas, the most specific scores are the KCC, APACHE II (> 11), and SOFA (> 12). These may be most helpful in determining patients who need transplant (Table 35–2).

TABLE 35–2. Prediction of Death or Transplant in 125 Patients with APAP Induced Liver Failure⁶⁰

Score	Sensitivity (%)	Specificity (%)	PPV	NPV
King's College Criteria	47	83	0.70	0.65
Acute Physiology and Chronic Health Evaluation II (> 12)	67	76	0.69	0.75
Sequential Organ Failure Assessment (> 12)	67	80	0.74	0.74
Model for Endstage Liver Disease (> 32)	89	25	0.49	0.77
Lactate (> 3.3 mmol/L)	91	52	0.69	0.83

NPV = negative predictive value; PPV = positive predictive value.

Acetylated HMGB-1 is a biomarker that is released as a proinflammatory mediator from monocytes and macrophages and in one small study was highly correlated with patients that met transplantation criteria or died.¹¹ These studies are promising, but will require validation before clinical use is postulated.

Additional Elimination Techniques

Several clinical scenarios may benefit from increasing clearance of APAP from the body. Indications early after APAP overdose may include patients with exceedingly high [APAP] who are at high risk of hepatotoxicity despite NAC therapy as well as those with hyperlactatemia and metabolic acidosis. Later in the course of APAP toxicity, elimination techniques may be used to remove elevated [APAP] in patients who are imminently receiving a hepatic transplant or for removal of toxins related to hepatic failure (Table 35–3).

TABLE 35–3. Management of Patients at Risk for APAP Toxicity

1. Start NAC on patients at risk of hepatotoxicity:
 - a. In acute overdose, plot a single [APAP] on the nomogram using the earliest possible time of ingestion. If the plot is over the treatment line, initiate NAC
 - i. If patient is at risk for massive and prolonged exposure to [APAP] (eg, ingestion > 30 g and/or co-ingested antimuscarinics), consider higher-dose NAC therapy
 - b. In RSTI, if [AST] is elevated, initiate NAC

- c. If AST is normal and [APAP] > 10 µg/mL, initiate NAC
- d. If patient has evidence of liver failure (encephalopathy, INR/prothrombin time elevation), consider transfer to liver transplant center
2. Initiate IV NAC or rarely oral NAC.
3. Laboratory evaluation at 20 to 24 hours (20 hours if IV NAC is used, 20–24 hours if PO NAC is used). Continue NAC on patients who remain at risk of toxicity or have developed toxicity.
 - a. If patient remains at risk of toxicity ([APAP] detectable) or if toxicity is evident ([AST] elevated), then continue NAC for 16–24 hours more
 - b. If [APAP] at 20 to 24 hours is very elevated, consider higher dose NAC therapy
4. Continue laboratory evaluation every 16–24 hours.
5. Stop NAC when the patient is no longer at risk of toxicity:
 - a. If liver failure was evident, continue NAC until INR < 2, encephalopathy resolves, and [APAP] is undetectable
 - b. If liver failure was not evident, but [AST] was elevated, then continue NAC until [AST] has decreased to < 1000 IU/L, no evidence of liver failure, and [APAP] is undetectable

AST = aspartate aminotransferase; INR = international normalized ratio; IV = intravenous; NAC = N-acetylcysteine; PO = oral; RSTI = repeated supratherapeutic ingestion.

Hemodialysis. Both intermittent hemodialysis (HD) and continuous venovenous hemodialysis (CVVHD) increase elimination of APAP. HD has been used early after overdose to eliminate highly elevated [APAP], typically above 500 µg/mL,^{96,119,341} and in patients with slow clearance of [APAP] late after overdose.³⁴⁸ Clearance averages about 150 mL/min^{96,119,348} with blood flow of approximately 300 mL/min. In one case, HD removed approximately 2 g of APAP when the initial [APAP] was 103 µg/mL, and the amount that HD removes varies directly with the initial [APAP].^{96,348} HD reduces the APAP elimination half-life by approximately 50%^{119,229,348} and has an extraction ratio of 50% to 80%.^{119,346,348} HD also removes NAC and NAC infusion rates should be increased to 12.5 mg/kg/h (from 6.25 mg/kg/h) during HD.¹¹⁹

CVVHD has been described in one case³⁴¹ in which the continuous modality was used due to concerns of hypotension on intermittent HD. In 16 hours, CVVHD had an average clearance of 42.1 mL/min and removed about 24 g of APAP; ([APAP] at initiation of CVVHD was 1212 µg/mL).³⁴¹

Plasmapheresis and Plasma Exchange. Plasmapheresis removes small amounts (5%) of APAP with therapeutic dosing, but few data exist with regard to overdose.⁹⁷ Plasmapheresis may be useful in patients with acute liver failure to correct coagulopathy, but it does not reliably correct encephalopathy.²⁹⁰

Exchange transfusion was used in one 1.22 kg neonate who had a [APAP] of 75 µg/mL after maternal oral overdose and subsequent delivery.¹⁸² Exchange transfusion eliminated a portion of total APAP as evidenced by reduced [APAP] and rebound [APAP] after transfusion. For example, in one exchange of 210 mL blood (1.22-kg patient), the serum [APAP] decreased from 32 µg/mL to zero, then rebounded to 30 µg/mL.¹⁸²

Liver Dialysis. Liver dialysis devices include extracorporeal albumin dialysis (eg, molecular adsorbent recirculation system [MARS]), fractionated plasma separation and adsorption and single pass albumin dialysis (SPAD). The MARS system may be used as a bridge to transplantation, for hemodynamic stabilization prior to hepatic transplant, or as a bridge to spontaneous recovery in patients with APAP-induced hepatic failure. Although MARS improves encephalopathy,²⁶⁶ cerebral blood flow,²⁸⁰ hemodynamics (increases in SVR, MAP, and decreases in cardiac index {CI} and pulse {HR}),^{175,281} and intracranial pressure,³⁰⁴ a meta-analysis concluded that MARS has no effect on mortality in multiple cause acute liver failure.¹⁶² One report notes complete removal of APAP from the blood ([APAP] decreased from 40 µg/mL to 0 µg/mL from inflow to outflow) during MARS with rebound [APAP], suggesting that MARS may improve APAP clearance.¹²⁰

Prometheus may also be used as a bridge to transplantation, but is relatively unstudied in APAP induced acute hepatic failure. Prometheus produces higher clearance of ammonia than MARS, but does not improve hemodynamics.¹⁷⁵

SPAD is venovenous hemodialysis with a dialysate containing 4.4% albumin. SPAD may more effectively clear ammonia than MARS,²⁷² but there were no changes in hemodynamics or encephalopathy after therapy with SPAD in one study of patients with acute hepatic failure.¹⁵⁵

SUMMARY

- The decision to treat an acute APAP overdose requires plotting a single [APAP] onto the modified Rumack-Matthew

nomogram and treating patients with NAC if their [APAP] plots above the treatment line, or the “150-line.”

- Patients should be treated with NAC after RSTIs of APAP if their [AST] is greater than normal or their [APAP] is detectable.
- The King’s College Criteria identifies patients with high mortality and is an indication for evaluation for hepatic transplantation:
 - a. Arterial pH < 7.3 or lactate > 3.0 mmol/L after fluid resuscitation OR
 - b. All of the following:
 - i. Creatinine > 3.3 mg/dL
 - ii. PT > 100 sec (or INR > 6.5)
 - iii. Grade III or IV encephalopathy (somnolence to stupor; responsive to verbal stimuli; confusion; gross disorientation)
- NAC therapy should no longer be given as a set length protocol. Once NAC therapy is started, an informed decision should be made when to stop NAC, which requires an assessment of [AST] and [APAP], that the risk of developing toxicity is low ([APAP] is undetectable and [AST] is normal), and any toxicity that occurred has now resolved ([AST] has decreased and is near normal and there is no evidence of hepatic failure).

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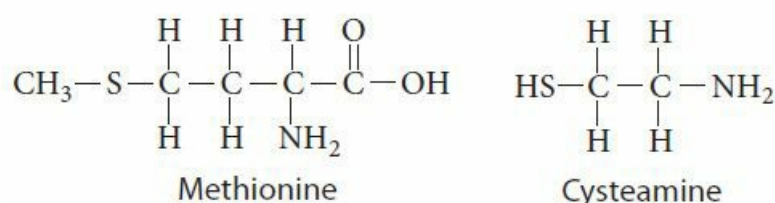
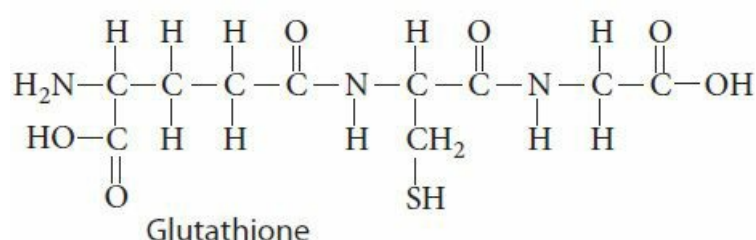
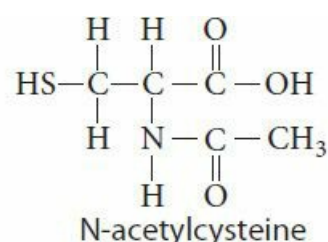
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A3 ANTIDOTES IN DEPTH

N-Acetylcysteine

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INTRODUCTION

N-acetylcysteine (NAC) is the cornerstone of therapy for patients with potentially lethal acetaminophen (APAP) overdoses. If administered early, NAC can then prevent APAP induced hepatotoxicity. If administered after the onset of hepatotoxicity, NAC improves outcomes and decreases mortality. NAC may also limit hepatotoxicity from other xenobiotics that result in glutathione depletion and free radical formation, such as cyclopeptide-containing mushrooms, carbon tetrachloride, chloroform, pennyroyal oil, clove oil, and possibly liver failure from chronic valproic acid use.³¹ Finally, NAC may be useful in the management of adults with fulminant hepatic failure caused by nontoxicologic etiologies.^{20,75,81,84,149}

HISTORY

Shortly after the first case of APAP hepatotoxicity was reported, Mitchell described the protective effect of glutathione.^{97,127} Prescott¹¹³ first suggested NAC for APAP poisoning in 1974. Early experiments demonstrated that NAC could prevent APAP-induced hepatotoxicity in mice and that the oral (PO) and intravenous (IV) routes were equally efficacious when treatment was initiated early after ingestion.¹⁰⁶ Several groups^{96,112,113,126} performed human research with oral and IV NAC in the 1970s. The US Food and Drug Administration (FDA) approved NAC for oral use in 1985 and for IV use in 2004.

PHARMACOLOGY

Chemistry

NAC is a thiol containing (R-SH) compound that is deacetylated to cysteine, an amino acid used intracellularly. The amino acids cysteine, glycine, and glutamate are used to synthesize glutathione.¹²³

Related Xenobiotics

Cysteamine, methionine, and NAC, which are all glutathione precursors or substitutes, have been used successfully to prevent hepatotoxicity, but cysteamine and methionine both produce more adverse effects than NAC, and methionine is less effective than NAC. Therefore, NAC has emerged as the preferred treatment.^{110,137,160,162}

Mechanism of Action

NAC has several distinct roles in the treatment of APAP poisoning. Early after ingestion when APAP is being metabolized to N-acetyl benzoquinoneimine (NAPQI), NAC prevents toxicity by rapidly detoxifying NAPQI. After hepatotoxicity is evident, NAC decreases toxicity through several nonspecific mechanisms, including free radical scavenging, increasing oxygen delivery, increased mitochondrial adenosine triphosphate (ATP) production, antioxidant effects, and alteration of microvascular tone.

NAC effectively prevents APAP induced hepatotoxicity if it is administered before glutathione stores are depleted to 30% of normal. This level of depletion occurs approximately 6 to 8 hours following toxic APAP ingestion.^{112,120} In this preventive role, NAC acts primarily as a precursor for the synthesis of glutathione.⁷⁷ The availability of cysteine is the rate-limiting step in the synthesis of glutathione, and NAC is effective in replenishing diminished supplies of both cysteine and glutathione. Additional minor mechanisms of NAC in preventing hepatotoxicity include acting as a substrate for sulfation,¹³⁹ as an intracellular glutathione substitute by directly binding to NAPQI,²⁹ and by enhancing the reduction of NAPQI to APAP.^{78,135}

After NAPQI covalently binds to hepatocytes and other tissues,¹²⁰ NAC modulates the subsequent cascade of inflammatory events in a variety of ways.⁵⁵ NAC may act directly as an antioxidant or as a precursor to glutathione. Glutathione protects cells against electrophilic compounds by acting as both a reducing agent and an antioxidant.¹²⁴ NAC improves oxygen delivery^{38,55,146,163,164} and utilization in extrahepatic organs such as the brain, heart, and kidney, probably by improving blood flow in the microvasculature, although the exact mechanism is unclear.^{83,133} In addition, NAC increases hepatic mitochondrial ATP production in mice¹²⁹ and demonstrates a suppressive action on macrophages, neutrophils, leukocyte endothelial cell adhesion, and cytokines.⁷⁵

Pharmacokinetics/Pharmacodynamics

Administered NAC is present in plasma in the reduced or oxidized state and is either free or bound to plasma proteins or with other thiols and SH groups to form mixed disulfides such as NAC–cysteine.¹¹¹ NAC has a relatively small volume of distribution (0.5 L/kg), and protein binding is 83%. NAC is metabolized to many sulfur containing compounds such as cysteine, glutathione, methionine, cystine, and disulfides, as well as conjugates of electrophilic compounds, that are not routinely measured.^{47,105,111} Thus, the pharmacodynamic study of NAC is complex. In addition, the pharmacokinetics of NAC are complicated based on whether total or free NAC is being measured.¹¹¹

Pharmacokinetics of Oral N-Acetylcysteine. Oral NAC is rapidly absorbed, but its bioavailability is low (10%–30%) because of significant first-pass metabolism.^{47,105,111} The mean time to peak serum concentration is 1.4 ± 0.7 hours. The mean elimination half-life is 2.5 ± 0.6 hours and is linear with increasing dose up to 3200 mg/m²/day given as a single daily dose. Inter-subject serum NAC concentrations vary tenfold.¹⁰⁵ Chronic administration leads to a decrease in plasma concentrations from a C_{\max} of 8.9 mg/L (55 μ mol/L) at the end of 1 month to 5.1 mg/L (31 μ mol/L) at the end of 6 months.¹⁰⁵

Conflicting in vitro^{30,73,127} and in vivo^{28,45,101,117} data regarding the concomitant use of PO NAC and activated charcoal suggest that the resultant bioavailability of NAC is either decreased or unchanged. This interaction is likely of limited clinical importance, and PO or IV NAC can be initiated without concern for activated charcoal interaction (**Chap. 35**).

Pharmacokinetics of IV N-Acetylcysteine. When only free NAC was analyzed, healthy volunteers given 600 mg IV NAC achieved peak serum NAC concentration of 49 mg/L (300 μ mol/L) with a half-life of 2.27 hours compared with a peak serum concentration of 2.6 mg/L (16 μ mol/L) after 600 mg PO.²⁴ Serum concentrations after IV administration of an initial loading dose of 150 mg/kg over 15 minutes reach approximately 500 mg/L (3075 μ mol/L).¹¹¹ A steady-state serum concentration of 35 mg/L (10–90 mg/L) is reached in approximately 12 hours with the standard IV protocol.¹¹¹ Approximately 30% is eliminated renally.

Once in the blood, IV and PO NAC have a similar half-life (2–2.5 hours). This half-life is increased in the setting of severe liver failure or end-stage kidney disease because of a reduction in clearance.^{67,100}

Intravenous vs. Oral Administration. As in the case of many issues related to APAP toxicity, the choice of PO versus IV NAC is complex. The available information suggests that each has advantages and disadvantages, and each may be more appropriate than the other in certain settings. Because no controlled studies have compared IV with PO NAC, conclusions about the relative benefit of each are largely speculative.

With the exception of fulminant hepatic failure, for which only the IV route has been investigated, IV and PO NAC administration are equally efficacious in treating patients with APAP toxicity.¹¹⁴ Some data suggest that IV NAC may be slightly more efficacious when given less than 12 hours after an overdose and that PO NAC is significantly more efficacious when given after 16 hours after overdose; however, this study compared patient groups that differed by decade of treatment and by country. It remains unclear if these differences are true or clinically relevant.^{114,172,173} In addition, any difference in outcome for patients who are treated after 16 hours almost certainly is related to the duration and total dose of NAC therapy rather than the route itself. The decision of which route to use should depend on the rate of adverse events, safety, availability, and ease of use. Efficacy should not be a consideration.

Safety is the best understood of these issues. Nausea and vomiting may occur in up to 20% of patients treated with PO NAC compared to 7% with IV NAC.⁵⁷ Diarrhea and headache are prevalent, but there is no credible evidence of more serious complications resulting from PO NAC. Reports of skin rash and unusual complications are rare.⁹⁷ In contrast, IV NAC is associated with a 14% to 18%⁷² rate of anaphylactoid reactions, although rates of 2% to 6% are reported in retrospective trials.^{63,68,168,175} Most of these reactions are mild and include rash, flushing, nausea, and vomiting.^{10,72,130,140,177} Anaphylactoid reactions may be severe in approximately 1% of cases^{72,94,176} and in rare instances may lead to hypotension and death.^{7,17,35,68,89,93,106,140,173,174} Anaphylactoid reactions are attributed to both the dose and concentration of NAC and are caused by a non IgE mediated release of histamine from mast cells and mononucleocytes.³² APAP inhibits mast cell histamine release; therefore, a higher APAP concentration at the time of NAC delivery decreases the risk of anaphylactoid reactions.^{32,166} The anaphylactoid reaction rate is decreased by using a more dilute NAC solution^{68,72,175} and by slowing NAC infusions in some studies.²⁸ In one prospective study, prolongation of the loading infusion from 15 to 60 minutes did not decrease the anaphylactoid rate significantly (from 18% to 14%).^{48,63,72,88}

Minor reactions, such as rash, generally do not require treatment, rarely recur, and do not preclude administration of subsequent NAC doses.^{11,140,175,178} Even when urticaria, angioedema, and respiratory symptoms develop, they usually are easily treated, and NAC can be subsequently restarted with a very low incidence of recurrence.^{11,108,130,178} Although proper dosing of IV NAC is very safe, it nevertheless must be considered less safe than PO NAC because of the possibility of severe anaphylactoid reactions, the risk of dosing errors,^{56,58,98} and the possibility of incomplete or delayed treatment because of anaphylactoid reactions.^{63,108}

IV NAC is dosed using a complex three-bag preparation system (see Dosing and Administration below) that has led to an up to 33% error rate including 19% of patients having a greater than 1 hour interruption of NAC.⁵⁶ Attempts at simplifying this system are described but have not been adequately studied for general use^{67,136} (Table A3–1).

TABLE A3–1. Three-Bag Method Dosage Guide ¹ for Patients Weighing ≥ 40 kg ^a				
Body Weight		Loading Dose (150 mg/kg in 200 mL D ₂ W over 60 minutes)	Second Dose (50 mg/kg in 500 mL D ₂ W over 4 hours)	Third Dose (100 mg/kg in 1000 mL D ₂ W over 16 hours)
(kg)	(lb)	Acetadote (mL) ^b	Acetadote (mL) ^b	Acetadote (mL) ^b
100	220	75	25	50
90	198	67.5	22.5	45
80	176	60	20	40
70	154	52.5	17.5	35
60	132	45	15	30
50	110	37.5	12.5	25
40	88	30	10	20

^aThe total volume administered should be adjusted for patients weighing less than 40 kg and for those requiring fluid restriction. ^bAcetadote is available in 30 mL (200-mg/mL) single-dose glass vials. D₂W = 5% dextrose in water.

Additional safety concerns have involved dosing for both small children and obese adults. The IV NAC dosing regimen

includes a milligrams per kilogram dose in a fixed water volume, leading to variability of IV NAC concentration.^{27,63} This leads to a large solute-free water administration in children, with the potential for hyponatremic seizures.¹⁴⁹ The NAC high concentration in obese adults potentially risks an increased rate of anaphylactoid reactions. Thus, alternative dosing strategies have been developed for children (constant 3% concentration)²⁷ and obese adults (ceiling weight of 100 kg; see Dosing).⁴²

The main disadvantage of the NAC PO formulation is the high rate of vomiting and the concern that vomiting may delay therapy.¹¹⁴ Delays in administration of NAC are correlated with an increased risk of hepatotoxicity.¹⁴¹ The IV route avoids an increased rate of vomiting in patients who typically are already nauseated and avoids the use of high-dose antiemetics that may alter mental status.⁹⁴ A potential disadvantage of PO NAC is that its absorption may be delayed up to one hour compared with IV NAC.⁶¹ Finally, PO NAC doses may be difficult to administer to patients with altered mental status because of aspiration risks; IV NAC offers a distinct advantage in these instances.

One theoretical, albeit unproven, advantage of PO NAC early in the course of toxicity is that direct delivery via the portal circulation yields a higher concentration of NAC in the target compartment of toxicity, the liver. Because of this first-pass clearance, PO NAC results in circulating NAC 20 to 30 fold lower than after IV dosing, suggesting that most PO NAC is taken up by the liver.^{24,61} However, an elevated serum NAC concentration may be an advantage of IV NAC administration when the liver is not the only target organ of NAC, such as liver failure accompanied by cerebral edema or in pregnancy.

Several economic analyses have concluded that IV NAC is less expensive than PO NAC,^{92,93} whereas others have concluded the opposite.⁷⁹ However, the majority of cost is associated with length of hospital stay and since none of these studies have taken into account that many patients treated with PO NAC now receive shorter courses than 72 hours,^{19,34} the studies do not represent current use.

Prior to the availability of the current IV formulation in the United States, the PO formulation was used intravenously with an excellent safety profile^{41,68,175} and without published evidence of infectious or febrile consequences.^{41,68} The IV use for this purpose is not generally recommended, but was historically effective and necessary in cases in which only the PO formulation was available and the patient had intractable vomiting or APAP induced fulminant hepatic failure.⁷⁹

Specific Indications for IV NAC. In addition to decisions based on cost, duration, safety, and ease of use, three situations exist for which the available information suggests IV NAC is preferable to PO NAC: (1) fulminant hepatic failure, (2) inability to tolerate PO NAC, and (3) APAP poisoning in pregnancy. Each of these requires further study for validation, but all three seem well supported by current information.

Fulminant hepatic failure is an important indication for IV NAC. IV is the only route that has been studied in liver failure.⁷¹ Although PO NAC may be effective, it has not been formally studied. Second, evidence that (some or all of) the benefit of NAC in liver failure is extrahepatic suggests that IV NAC is preferable.⁵⁶ IV NAC results in higher serum NAC concentrations, which presumably leads to more NAC delivery to critical organs. Finally, concomitant gastrointestinal bleeding, use of lactulose, and other factors make IV NAC more practical.

Common indications for IV NAC are for patients with very high APAP concentrations who are approaching or are more than 6 to 8 hours from the time of ingestion as well as those who are unable to tolerate PO NAC following a brief aggressive trial of antiemetic therapy. Use of IV NAC is logical to prevent further delays and resultant loss of NAC efficacy, even without proof that continued vomiting significantly limits NAC absorption.

The most controversial indication for IV NAC use is during pregnancy. Administration of IV NAC to the mother has the theoretical advantage of increased delivery to the fetus over PO NAC use. IV administration circumvents first-pass metabolism, presumably exposing the fetal circulation to higher maternal serum concentrations. Some studies have suggested that placental transfer of NAC to the fetus is limited.^{66,133} However, one case series found that the NAC concentration in cord or neonatal blood after PO maternal NAC administration equaled the NAC concentration that is achieved in patients treated with PO NAC.⁶⁴ Of course, an equivalent serum NAC concentration does not prove adequacy of therapy. Unlike the neonates studied, patients treated with PO NAC have extensive first-pass hepatic uptake before NAC entry into the serum, where NAC concentration was measured.^{24,61} Whether serum NAC concentration in the neonates studied reflects any significant hepatic NAC delivery is uncertain.

ROLE IN ACETAMINOPHEN TOXICITY

In acute overdose, treatment with NAC should be initiated if the serum APAP concentration is plotted on or above the treatment line on the Rumack-Matthew nomogram or the patient's history suggests an acute APAP ingestion of 150 mg/kg or greater and the results of blood tests will not be available within 8 hours of ingestion. In patients with chronic APAP ingestions, treatment with NAC should be initiated if either aspartate aminotransferase (AST) is above normal or the APAP concentration is above 10 µg/mL ([Chap. 35](#)).

IV NAC is approved by the FDA for treatment of potentially hepatotoxic quantity of APAP within 8 to 10 hours

following ingestion. The oral formulation is approved for use in a 72 hour protocol for APAP toxicity.

ROLE IN NONACETAMINOPHEN POISONING

Diverse investigations of NAC as a treatment for a number of xenobiotics associated with free radical or reactive metabolite toxicity are reported. Some of these xenobiotics include acrylonitrile, amatoxins, cadmium, chloroform, carbon tetrachloride, cyclophosphamide, 1,2-dichloropropane, doxorubicin, eugenol, pulegone, ricin, and zidovudine.^{31,44,47,154,155,157,162} NAC has not been studied well enough for any of these xenobiotics in humans to definitively recommend it as a therapeutic intervention. However, the best evidence supports the use of NAC in cases of acute exposures to cyclopeptide-containing mushrooms and carbon tetrachloride.^{31,47,162} NAC has also decreased cisplatin-induced nephrotoxicity in both rats and human cell cultures, although in vivo human data are sparse.^{7,122} NAC may be considered in cases of acute pennyroyal oil (ie, pulegone) or clove oil (eg, eugenol) ingestions based on their similarities to APAP-induced hepatotoxicity. Both pulegone and eugenol are converted to reactive metabolites that deplete glutathione, leading to centrilobular hepatic necrosis.^{153–156} NAC may be effective in treating patients with hepatotoxicity from chronic valproate use, given the evidence that the 2,4-diene valproic acid metabolite acts as an electrophile and reduces hepatic glutathione. However, there is no evidence that NAC is effective in treating patients with acute valproate toxicity and no evidence or theoretical efficacy in treating valproate-induced hyperammonemia. In animal studies NAC increases the excretion of several metals and other elements, including boron, cadmium, chromium, cobalt, gold, and methylmercury.^{13,15,31,59} The clinical usefulness of this effect remains unclear.

NAC has been studied as an oncological chemopreventive and antineoplastic^{3,36,84,123} as well as for lung injury,^{36,37} cardiac injury,^{143,144} multiorgan failure from trauma and sepsis,^{52,115,131,145} traumatic brain injury,^{14,153,174} chronic obstructive pulmonary disease,¹⁴⁸ ifosfamide-induced nephrotoxicity,⁵³ postcardiac surgery,⁸⁷ hepatorenal syndrome,⁶² H. pylori infections,⁸⁸ necrotizing enterocolitis,¹⁵¹ sickle cell disease,¹⁰² and bipolar disorder.¹⁸ NAC has extracellular antimutagenic effects, enhances repair of nuclear DNA damaged by carcinogens, and inhibits malignant cell invasion and metastases.^{36,104,116} Rescue NAC therapy has been studied with high-dose APAP (> 20 g/m²) used as chemotherapy in patients with select advanced malignancies.^{74,169}

NAC has been extensively studied to determine its effects on IV contrast-induced nephropathy. Pretreatment with either PO^{5,21,25,39,50,70,138,152} or IV^{12,43,91} formulations has been studied before angiography with mixed results. Absolute creatinine change in the positive studies remains quite small and is typically below 0.2 mg/dL.^{51,76} Recent large randomized trials found no reduction in the risk of nephrotoxicity after intravascular angiographic procedures² or in emergency department computed tomography,¹⁵⁹ and current knowledge suggests that NAC is ineffective for these indications.^{51,58,76,103,128}

NAC has been studied in the treatment of patients with non APAP-related acute liver failure with mixed results. In a randomized trial in adults, NAC improved transplant-free survival in early non-APAP-related acute liver failure (eg, mild encephalopathy), but had no effect in those with severe encephalopathy.⁸¹ However, although a study using historic controls suggests that NAC improves survival in children with non-APAP-related acute liver failure,⁷⁵ a randomized study showed no difference in 1 year survival rates and a lower 1 year transplant-free survival rate, particularly in children younger than 2 years of age.¹⁴⁷

NAC has been used for decades in cases of cyclopeptide-containing mushroom poisoning, particularly poisoning with *Amanita phalloides*. NAC therapy for amatoxin poisoning is largely based on the similarity of toxicity of amatoxin to APAP, specifically delayed onset of centrilobular hepatic necrosis. Decreases in intracellular glutathione stores were identified in isolated rat hepatocytes that were exposed by amanita extracts,⁶⁹ leading to the reasonable conclusion that supplying the tissue with thiols may decrease toxicity. In retrospective studies, patients treated with NAC had lower mortality rates than those treated with supportive care;⁴⁶ however, in animal studies, NAC has little effect on hepatotoxicity.¹⁵⁸

ADVERSE EVENTS AND SAFETY ISSUES

Oral NAC may cause nausea, vomiting, flatus, diarrhea, gastroesophageal reflux, and dysgeusia; generalized urticaria occurs rarely. Generalized anaphylactoid reactions described following IV NAC dosing^{6,17,23,35,49,60,86,90,111,118,161,165} are not noted after PO therapy and may be related to rate, concentration, or high serum NAC concentrations.^{16,111}

While the IV route ensures delivery, rate-related anaphylactoid reactions occur in up to 18% of patients.⁷² Most reactions are mild (6%) or moderate (10%) such as cutaneous reactions, nausea, and vomiting; severe reactions such as bronchospasm, hypotension, and angioedema are rare (1%).¹ Anaphylactoid reactions are more common in patients with lower [APAP] (25% if APAP < 150 µg/mL) than in those with high [APAP] (3% if APAP > 300 µg/mL),¹⁶⁶ because APAP decreases histamine release from mononucleocytes and mast cells in a dose-dependent manner.³²

If hypotension, dyspnea, wheezing, flushing, or erythema occurs, then NAC should be stopped and standard symptomatic therapy instituted. After the reaction resolves, NAC can be carefully restarted at a slower rate after one hour, assuming NAC is still indicated. If the reaction persists or worsens, IV NAC should be discontinued and a switch to PO NAC should be considered. Adverse reactions, confined to flushing and erythema, are usually transient, and NAC can be continued with meticulous monitoring for systemic symptoms that indicate the need to stop the NAC. Urticaria can be managed with diphenhydramine with the same precautions.¹¹ Iatrogenic overdoses with IV NAC have resulted in severe reactions, hypotension, cerebral edema, seizures, and death.^{1,11,58,90}

IV NAC decreases clotting factors and increases the prothrombin time in healthy volunteers and overdose patients without evidence of hepatic damage.^{65,85,99,107,167} This effect occurs within the first hour, stabilizes after 16 hours of continuous IV NAC, and rapidly returns to normal when the infusion is stopped.⁶⁵ International normalized ratio (INR) elevations are mild and are typically below 1.5 to 2.0. Because the INR is used as a marker of the severity of toxicity and is one of the criteria for transplantation, this adverse effect of NAC should always be considered when evaluating the patient's condition. An elevated INR that remains below 2 without other indicators of hepatic damage is probably related to the NAC.

SAFETY IN PREGNANCY AND NEONATES

Untreated APAP toxicity is a far greater threat to fetuses than is NAC treatment.^{33,119} NAC traverses the human placenta and produces cord blood concentrations comparable to maternal blood concentrations.⁶⁴ For treatment of the pregnant patient with APAP toxicity, IV NAC (not PO NAC) has the advantage of assuring fetal delivery of NAC due to reduction of the first pass metabolism. NAC is FDA Pregnancy Category B.

Limited data exist with regard to the management of neonatal APAP toxicity,^{9,80,121,134} although IV and PO NAC have been used safely.^{1,9} No adverse events were observed when preterm newborns were treated with IV NAC^{1,4,109} (Chaps. 31 and 35). The elimination half-life of NAC in preterm neonates was 11 hours compared with 5.6 hours in adults.⁴ When treating neonates, IV administration has the advantage of assuring adequate antidotal delivery and has been administered without adverse effects.^{4,109}

DOSING AND ADMINISTRATION

The standard IV NAC protocol is a loading dose of 150 mg/kg up to a maximum of 15 g in 200 mL of 5% dextrose in water (D₅W) (for adults) infused over 60 minutes followed by a first maintenance dose of 50 mg/kg up to a maximum of 5 g in 500 mL D₅W (for adults) infused over 4 hours followed by a second maintenance dose of 100 mg/kg up to a maximum of 10 g in 1000 mL D₅W (for adults) infused over 16 hours (6.25 mg/kg/h).

When NAC is administered orally, the patient should receive a 140-mg/kg loading dose either orally or by enteral tube. Starting 4 hours after the loading dose, 70 mg/kg should be given every 4 hours, for an additional 17 doses, for a total dose of 1330 mg/kg. The solution should be diluted to 5% and can be mixed with a soft drink to enhance palatability. If any dose is vomited within one hour of administration, then the dose should be repeated⁸³ or IV delivery used. Antiemetics (eg, metoclopramide, or ondansetron) should be used to ensure absorption.

Several other regimens, including 48 hours IV, 36 hours IV, 36 hours PO, and 20 hours PO protocols, are described; however, none of these has been adequately studied for general use^{34,140,170,176} (Chap. 35).

Conceptually, NAC therapy should be started if the patient is at risk of toxicity, continued as long as is necessary, and it should be stopped when the patient is no longer at risk of toxicity.¹⁷¹ For a detailed description of the indications for treating APAP toxicity with NAC, see Chap. 35. Briefly, in acute overdoses (from 4–24 hours after ingestion), NAC therapy should be initiated if the initial APAP concentration falls above the treatment line of the Rumack-Matthew nomogram. In acute overdoses where the patient arrives more than 24 hours following ingestion, then NAC should be started if the APAP concentration is detectable or if the AST is elevated. In repeated supratherapeutic ingestions, NAC therapy should be initiated if either the APAP concentration is detectable or the AST is elevated. For other scenarios, see Chap. 35.

Once the protocol is initiated, an APAP concentration and AST are evaluated prior to the end of the NAC infusion (20 hours for IV NAC) or at 24 hours (for oral NAC). If the APAP concentration is undetectable and the AST is normal, then NAC can safely be discontinued. NAC should be continued beyond the “protocol length” if the APAP concentration remains detectable or the AST is significantly elevated. There are no data to support what degree of AST elevation should be used as a cutoff for treatment. The NAC protocol should be continued until the APAP concentration is undetectable, there is no evidence of hepatic failure, and the AST, if it were elevated, is decreasing. If hepatic failure intervenes, then IV NAC should be administered at the dose of the “third bag” (16 hour infusion of 6.25 mg/kg/h) and continued until the patient has a normal mental status (or recovery from hepatic encephalopathy)⁵⁵ and the patient's INR decreases below 2.0¹¹⁹ or

until the patient receives a liver transplant.^{26,54,71}

For the rare patient who ingests exceptionally large doses of APAP, or who has prolonged and significantly elevated APAP concentrations, consideration should be given to treating with greater amounts of NAC once prolonged, massive APAP concentrations are evident.^{40,133,143} The rationale for increasing NAC dosing include that the IV infusion rate (6.25 mg/kg/h) was derived to treat a 16 g ingestion of APAP.¹²⁴ While it is effective for most patients who ingest APAP, an ingestion that is several times larger than 16 g may require additional NAC. In addition, published cases of patients who have developed hepatotoxicity despite early NAC therapy have ingested more than 16 g of APAP and been treated with the IV (6.25 mg/kg/h) infusion.^{40,132,142} There are no reported early NAC failures with the PO protocol.

No data exist to determine which, if any, alternative NAC dosing strategy is effective; however, it seems reasonable to increase NAC dosing if the hepatic exposure to APAP (and therefore NAPQI) is prolonged and massive. Several strategies have been theorized, but none have been studied. Potential strategies include:

1. Using the oral protocol for high-risk patients who can tolerate oral NAC
2. Administer both oral NAC and IV NAC simultaneously, an approach that increases initial loading and total doses
3. Base the IV NAC dosing on the ingestion size or [APAP]:¹²¹
 - a. If the ingestion is between 16 and 32 g, or the initial [APAP] is between the “300 line” and the “500 line,” then consider using 12.5 mg/kg/h as the 16 hour infusion rate.
 - b. If the ingestion is between 32 and 48 g, or the initial [APAP] is above the “500 line,” then consider using 18.75 mg/kg/h as the 16 hour infusion rate.
 - c. If the ingestion is greater than 48 g, then consider using 25 mg/kg/h as the 16 hour infusion rate.

Your poison control center can help with the most current information (1-800-222-1222).

There are no specific dosing guidelines for patients who are obese. However, it may be reasonable to limit PO and IV NAC dosing using a maximum weight of 100 kg. This maximum limit is not based on experimental evidence; however, patients who are larger than 100 kg have an equivalent hepatic volume and similar ingestion amounts as patients who weight less than 100 kg. Although dosing with a maximum weight is logical, it has not yet been adequately studied in obese humans.

Previously dosing information for IV NAC was unavailable for patients weighing less than 40 kg, and problems with osmolarity, sodium concentrations, and fluid requirements became apparent when improper dilutions were used. The package insert now gives specific information for dosing in these patients (Table A3–2).

TABLE A3–2. Three-Bag Method Dosage Guide by Weight for Patients Weighing < 40 kg^a

Body Weight		Loading Dose (150 mg/kg over 60 minutes)		Second Dose (50 mg/kg over 4 hours)		Third Dose (100 mg/kg over 16 hours)	
(kg)	(lb)	Acetadote (mL)	D ₁ W (mL) ^b	Acetadote (mL) ^b	D ₁ W (mL)	Acetadote (mL) ^b	D ₁ W (mL)
30	66	22.5	100	7.5	250	15	500
25	55	18.75	100	6.25	250	12.5	500
20	44	15	60	5	140	10	280
15	33	11.25	45	3.75	105	7.5	210
10	22	7.5	30	2.5	70	5	140

^aAcetadote is hypersmolar (2600 mOsm/L) and is compatible with D₁W, one-half normal saline (0.45% sodium chloride injection), and water for injection. ^bAcetadote is available in 30 mL (200-mg/mL) single-dose glass vials. D₁W = 5% dextrose in water.

The IV dosing of NAC is complicated because three different preparations must be prepared with each based on weight. A retrospective study estimated that there was a 33% medication error rate in the preparation and delivery of IV NAC.⁵⁶ To limit these errors, Tables A3–1 and A3–2 from the package insert, which give the appropriate doses and dilutions for adults and patients weigh less than 40 kg.¹ In addition, the following web site has a dosage calculator: <http://acetadote.com/dosecalc.php>.

FORMULATION

NAC is available as a 20% concentration in 30 mL single-dose vials designed for dilution before IV administration and

should also be diluted before administration.

SUMMARY

- NAC is the primary antidote for APAP toxicity.
- Limited evidence also supports NAC use in cyclopeptide containing mushroom toxicity (eg, *Amanita phalloides*), carbon tetrachloride, and pulegone toxicity (pennyroyal oil).
- NAC should be started if there is significant risk of toxicity and stopped when the risk of toxicity is gone and any toxicity that had occurred is resolving.
- Oral and IV NAC have essentially equivalent efficacy.
- IV NAC has approximately an 18% risk of anaphylactoid reactions, most of which are mild, and oral NAC has a 20% risk of vomiting.
- Higher doses of NAC should be considered for cases of massive ingestion or cases in which a prolonged high concentration of APAP is present.

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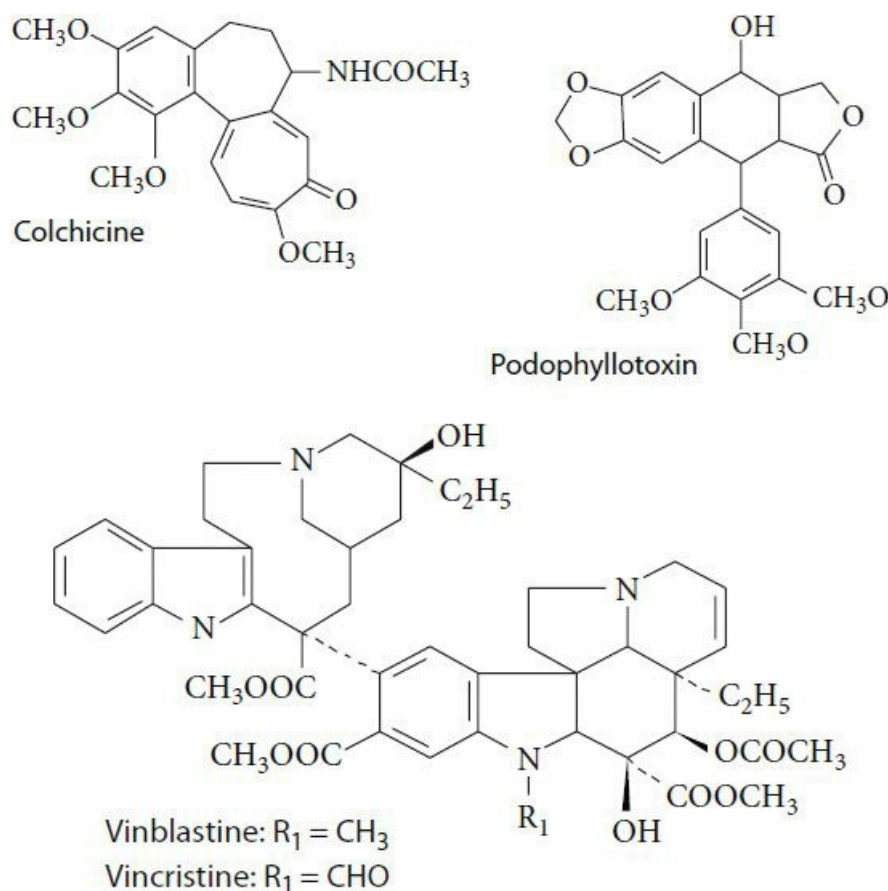
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36 COLCHICINE, PODOPHYLLIN, AND THE VINCA ALKALOIDS

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COLCHICINE

History

The origins of colchicine and its history in poisoning can be traced to Greek mythology. Medea was the evil daughter (and a known poisoner) of the king of Colchis, a country that lay east of the Black Sea in Asia Minor. After being betrayed by her husband Jason (of Jason and the Argonauts), she killed their children and her husband's lover. Medea is often used plants of the Liliaceae family to poison her victims, one of which is *Colchicum autumnale*.^{25,144,192} The use of colchicum for medicinal purposes is reported in Pedanius Dioscorides *De Materia Medica*, an ancient medical text, written in the 1st century A.D.^{25,144,192} and subsequently in the 6th century A.D. by Alexander of Trallis, who recommended it for arthritic conditions.^{25,40,181,192,176} However, colchicum fell out of favor, perhaps because of its pronounced gastrointestinal (GI) effects, until it was reintroduced for dropsy and various other nonrheumatic conditions in 1763.^{25,192} In the late 18th century, a colchicum containing product known as Eau Medicinale reportedly had strong antigout effects.¹⁹² Colchicine, the active alkaloidal component in colchicum, was isolated in 1820 and rapidly became popular as an antigout medication.^{144,192} Benjamin Franklin reportedly had gout and is credited with introducing colchicine in the United States.¹⁴⁴ Colchicine is still used in the treatment of gout and has been used in a multitude of other disorders, including amyloidosis, Behçet syndrome, familial Mediterranean fever, chronic pericarditis, arthritis, pulmonary fibrosis, vasculitis, biliary cirrhosis, microcrystalline arthritis, certain spondyloarthropathies, calcinosis, and scleroderma.^{12,25,133,137} Unfortunately, systematic data supporting the efficacy of colchicine therapy in many of these other diseases are lacking.

Colchicine is derived from two plants of the Liliaceae family, *C. autumnale* (autumn crocus, meadow saffron, wild saffron, naked lady, son-before-the-father) and *Gloriosa superba* (glory lily).¹⁹² Colchicine is not distributed evenly in the

autumn crocus with the highest concentrations found in the bulb and seeds (0.8%) followed by the corm or underground stem (0.6%) and the flowers (0.1%).^{144,169,181} Colchicine concentrations within the plant peak during the summer months.¹⁴⁴ The leaves of *C. autumnale* closely resemble those of the *Allium ursinum* or wild garlic and have been mistaken for them.^{44,45,110} The tubers of *G. superba* may be confused with *Ipomoea batatas* (sweet potatoes).¹⁹²

There is a dearth of epidemiologic data on colchicine poisoning. The American Association of Poison Control Centers records several hundred overall exposures annually (Chap. 136). Most of these exposures are in adults and are categorized as unintentional. Approximately 10% of the cases with a recorded outcome typically have evidence of moderate or major toxicity or resulted in death.⁴¹ Although a limited number of cases are due to intentional suicidal ingestions, recent work suggests that therapeutic colchicine administration contributes to adverse health effects and in some cases death among hospitalized patients (probably related to failure to adjust dosing for renal impairment).¹⁶⁵ At least 50 adverse events (23 of which were fatalities) are linked to the use of intravenous (IV) colchicine.⁴ The US Food and Drug Administration announced its intent to stop the marketing of unapproved injectable drug compounds containing colchicine in 2009.⁴ Although all approved IV formulations in the United States were subsequently withdrawn, it may in theory be obtainable from compounding pharmacies and from other countries. Serious questions remain about the safety of colchicine in light of its extremely narrow therapeutic index.

Pharmacology

Colchicine is a potent inhibitor of microtubule formation and function, and thereby interferes with cellular mitosis, intracellular transport mechanisms, and maintenance of cell structure and shape.^{137,192} The ubiquitous presence of microtubules in cells throughout the body presents a wide variety of targets for colchicine poisoning.^{137,192} Colchicine accumulates in leukocytes and has inhibitory effects on leukocyte adhesiveness, amoeboid motility, mobilization, lysosome degranulation, and chemotaxis.^{25,51,61,88,95,186–188} At doses used clinically, colchicine inhibits neutrophil and synovial cell release of chemotactic glycoproteins.^{195,218} Colchicine also inhibits microtubule polymerization, which disrupts inflammatory cell-mediated chemotaxis and phagocytosis.¹⁹⁹ It reduces expression of adhesion molecules on endothelial and white blood cells and affects polymorphonuclear cell cytokine production.^{10,26,161} Colchicine also acts as a competitive antagonist at GABA_A receptors in a human ex-vivo model.²⁴³

Pharmacokinetics and Toxicokinetics

Oral colchicine is rapidly absorbed in the jejunum and ileum and has a bioavailability generally between 25% and 50%.^{25,203} It is highly lipid soluble^{19,25,192} with a volume of distribution that ranges from 2.2 to 12 L/kg, which may increase to 21 L/kg in overdose.^{168,196,197,230} Colchicine binding to plasma proteins approaches 50%.^{25,137,160,192} Protein binding is principally to albumin, although some binding to α_1 -glycoprotein acid and other lipoproteins is reported.²⁰³ During the first several hours after acute overdose, colchicine is sequestered in white and red blood cells in concentrations five to 10 times higher than in serum.²⁰³ Peak serum concentrations after ingestion occur between 1 to 3 hours.¹³⁷ Toxic effects usually do not occur with concentrations less than 3 ng/mL.^{89,160,239}

Colchicine is primarily metabolized through the liver with up to 20% of the ingested dose excreted unchanged in the urine.²³⁰ Colchicine undergoes demethylation by CYP3A4.^{120,229} Detoxification mainly occurs through deacetylation, demethylation, biliary secretion, and excretion in the stool.^{201,203} Enterohepatic recirculation of colchicine occurs.^{3,192}

Serum elimination half-lives ranging from 9 to 108 minutes are reported.^{17,107,192,203,240} However, upon closer examination, these times probably more accurately reflect a rapid initial distribution phase. The drug undergoes a more delayed terminal elimination phase, which ranges from 1.7 to 30 hours, depending on the individual compartment model used to estimate elimination and the amount of colchicine absorbed.^{3,93,192,197,201,203,230} These values are on the same order as, and probably reflect the tubulin–colchicine complex disassociation time.¹⁷⁶ Individuals with stage 5 chronic kidney disease (CKD) and liver cirrhosis may have elimination half-lives that are prolonged up to tenfold.¹³⁷ Colchicine can remain in measurable tissue quantities for a long time, as evidenced by its detection in white blood cells after 10 days and in urine 7 to 10 days after exposure.^{88,192} Colchicine can cross the placenta and is secreted in breast milk, but it is not dialyzable.¹³⁷ Postmortem examination of colchicine-poisoned patients reveals high concentrations within the bone marrow, testicles, spleen, kidney, lung, brain, and heart.¹⁹⁶

Drug Interactions. Colchicine metabolism is susceptible to drug interactions. Because colchicine is metabolized through CYP3A4, serum concentrations are susceptible to xenobiotics that alter the function of this enzyme, such as erythromycin, clarithromycin, and grapefruit juice.^{53,80,99,137} In particular, coadministration of clarithromycin and colchicine, especially in patients with CKD, increases the risk of fatal interaction.^{5,119} P-glycoprotein (PGP) expels and clears colchicine; therefore, PGP inhibitors directly affect the amount of colchicine eliminated and hence, toxicity.¹⁷⁶ For example, cyclosporine increases colchicine toxicity.^{85,137,216,217} Coadministration of colchicine with statin or fibrate drugs, nephrotoxins such as

nonsteroidal antiinflammatory drugs and angiotensinogen-converting enzyme inhibitors, and fluindione (antivitamin K anticoagulant) can result in colchicine poisoning.²³³

Pathophysiology

Microtubules play a vital role in cellular mitosis and demonstrates significant dynamic instability.^{22,87,127,210} Microtubules are made up of tubulin protein subunits, of which three are known to exist: α , β , and γ .^{127,154,210} These structures are highly dynamic with α - β -tubulin heterodimers, constantly being added at one end and removed at the other.^{127,128} Microtubules undergo two forms of dynamic behavior: dynamic instability, in which microtubule ends switch between growth and shortening phases, and tread milling, in which there is a net growth (addition of heterodimers) at one end and a shortening (loss) at the other.³⁰ Assembly and polymerization dynamics are regulated by additional proteins known as stabilizing microtubule-associated proteins (MAPs) and destabilizing MAPs.³⁰ These dynamic behaviors and a resultant equilibrium are needed for multiple cell functions, including cell support, transport, and mitotic spindle formation for cell replication.¹²⁷ Xenobiotics that bind to specific regions on tubulin can interfere with microtubule structure and function, thereby causing mitotic dysfunction and arrest.^{154,210} This leads to cellular dysfunction and death.²¹⁰ Xenobiotics that target microtubules can be generally divided into two categories: polymerization inhibitors (ie, vinca alkaloids, colchicine) and polymerization promoters (ie, taxanes, laulimalides).³⁰

Colchicine binds to a tubulin dimer at a specific region known as the colchicine-binding domain, which is located at the interphase of the α and β subunits of the tubulin heterodimer.^{30,111,127,182,210,234} This binding is relatively slow, temperature dependent, and generally irreversible, resulting in an alteration of the secondary structure of the protein.^{111,127,143,182,204} Colchicine binds at a second reversible but lower-affinity site on tubulin.^{127,143} The colchicine-tubulin complex binds to the microtubule ends and prevents further growth by sterically blocking further addition of dimers.³⁰ Conformational changes in the tubulin and colchicine complex also result as colchicine concentrations increase, which weakens the lateral bonds at the microtubule end.^{30,154,196,210} Lateral and longitudinal interactions between dimers within a microtubule help stabilize the structure. The number of tubulin-colchicine dimers incorporated into the microtubule determines the stability of the microtubule ends.³⁰ All of these processes may prevent adequate binding of the next tubulin subunit and result in cessation of microtubule growth.^{154,210} At low concentrations, colchicine arrests microtubule growth, whereas at high concentrations, colchicine can actually cause microtubule depolymerization through disassociation of tubulin dimers.³⁰

These conformational changes ultimately result in disassembly of the microtubule spindle in metaphase of cellular mitosis, cellular dysfunction, and death.^{91,111,127,182,204,210} Colchicine also inhibits microtubule-mediated intracellular granule transport.^{25,137} Some in vitro animal studies also show that colchicine might inhibit DNA synthesis by changing cell regulatory events at a critical time during the mitotic cycle.^{86,92,113,140}

Toxic Dose

The toxic dose for colchicine is not well established. An early case series suggested that patients who ingested greater than 0.8 mg/kg uniformly died and those who ingested above 0.5 mg/kg but less than 0.8 mg/kg would survive if given supportive care.³³ This information was based on a limited series of patients and is not generalizable.¹⁶⁶ More recent literature suggests that severe toxicity and even death may occur with doses smaller than 0.5 mg/kg, and patients can survive ingestions reported to be in excess of 0.8 mg/kg.^{16,81,100,163,166,220} This inability to accurately quantify the toxic dose in humans is likely due in great part to difficulty in dose estimation from the patient's history and significant advances in supportive care. Furthermore, many comorbid conditions (eg, CKD, liver disease) and other pharmaceuticals, which, when coadministered, can enhance the adverse effects of colchicine, complicating the determination of a minimal toxic dose.

Clinical Presentation

The clinical findings in patients poisoned with colchicine are commonly described as triphasic (Table 36–1).^{115,150,168,220} GI irritant effects, such as nausea, vomiting, abdominal distress, and diarrhea, occurring within several hours of an overdose^{8,43,45,71,79,129,150,155,236} and may lead to severe volume depletion.^{99,118,146,166,168,170,220,242} This first stage usually persists for the first 12 to 24 hours following ingestion.^{118,150} The second stage is characterized by widespread organ system dysfunction, particularly the bone marrow, and lasts for several days.^{45,81,166,168,220} The final phase is characterized by recovery or death, and the progression can usually be defined within one week.^{115,118,150,220}

TABLE 36–1. Colchicine Poisoning: Common Clinical Findings, Timing of Onset, and Treatment

Phase	Time ^a	Signs and Symptoms	Therapy/Follow-Up
I	0–24 hours	Nausea, vomiting, diarrhea Salt and water depletion Leukocytosis	Antiemetics Consider GI decontamination IV fluids Close observation for leukopenia
II	1–7 days	Risk of sudden cardiac death (24–48 hours) Pancytopenia Acute kidney injury Sepsis Acute respiratory distress syndrome Electrolyte imbalances Rhabdomyolysis	ICU admission and appropriate resuscitation G-CSF Hemodialysis Antibiotics Oxygen, mechanical ventilation Repletion as needed IV fluids, hemodialysis
III	> 7 days	Alopecia (may not develop for 2–3 weeks) Myopathy, neuropathy, or myoneuropathy	Follow-up within 1–2 months EMG testing, biopsy and neurologic follow-up as needed

^aThe interval time course is not absolute, and overlap of symptom presentation may occur.

EMG = electromyography; G-CSF = granulocyte-colony stimulating factor; GI = gastrointestinal; ICU = intensive care unit; IV = intravenous.

After overdose, the hematopoietic effects of colchicine are characterized by an initial leukocytosis, which may be as high as 30,000/mm³. This is followed by a profound leukopenia, which may be lower than 1000/mm³ and is commonly accompanied by pancytopenia, usually beginning 48 to 72 hours after overdose.^{25,43,93,99,114,150,172} The hematopoietic manifestations occur as a result of the effects of colchicine on bone marrow cell division.^{40,118,153,196,242} A rebound leukocytosis and recovery of all cell lines occur if the patient survives.

Colchicine toxicity is associated with the development of dysrhythmias and cardiac arrest.^{40,115,118,150,168} Sudden cardiovascular collapse from colchicine typically occurs between 24 to 36 hours after ingestion.^{40,52,150,153,166} Profound hypovolemia and shock may contribute to this collapse,^{25,99,166,168,220} but colchicine also has direct toxic effects on skeletal and cardiac muscle.^{36,62,148,156,167,237,242}

Myopathy,^{46,47,209,247} neuropathy,^{13,140} and combined myoneuropathy^{11,64,72,84,135,136,193,215,253} result from both long-term therapy and acute poisoning.¹⁴⁰ Combined myoneuropathy is reported more often, with myopathy dominating the clinical picture.^{11,64,72,135,136,193,215,253} Myoneuropathy is often initially misdiagnosed as polymyositis or uremic neuropathy (caused by coexistent kidney failure).^{13,136} Myoneuropathy usually develops in the context of chronic, therapeutic dosing in patients with some baseline CKD,^{11,64,72,84,134,136,193,215,253} although it may also occur in the presence of normal kidney function.¹⁹⁰ Patients may present with proximal limb weakness, distal sensory abnormalities, distal areflexia, and nerve conduction problems consistent with an axonal neuropathy.^{136,185} A small amount of myelin degeneration is reported on autopsy, which suggests a myelinopathic component.⁴² The myopathy is characterized by vacuolar changes on biopsy and accompanied by lysosome accumulation.^{11,84,136,253} An elevated serum creatine kinase concentration is present concurrently with symptoms.^{136,168} Weakness usually resolves within several weeks of drug discontinuation.¹³⁶ Myopathy may also occur when hydroxymethylglutaryl-coenzyme A reductase inhibitors are concomitantly used in patients with renal insufficiency.⁶ Myopathy symptoms typically resolve within 4 to 6 weeks, although it may take up to 6 to 8 months in some patients.²⁴⁷

Acute respiratory distress syndrome occurs with colchicine toxicity.^{18,71,114,158,208,211} The etiology is not well understood but may result from several factors, including respiratory muscle weakness, multisystem organ failure, and possibly direct pulmonary toxicity.^{71,150,158,208,228} Other indirect effects of colchicine include acute kidney injury (AKI) and various electrolyte abnormalities resulting from fluid loss and impaired glomerular filtration rate.^{25,81,99,140,168}

Alopecia, which is usually reversible, is a well-described complication that occurs 2 to 3 weeks after poisoning.^{12,25,93,99,100,118,143,227} Dermatologic complications range in severity from epithelial cell atypia to toxic epidermal necrolysis.^{9,15,91,98,200} Neurologic effects, including delirium, stupor, coma, and seizures, might be at least partly

attributable to the multisystem disease caused by poisoning and not necessarily a direct effect of colchicine.^{46,172,192,211} The cause of seizures is unclear but it might be partly attributable to antagonism of GABA_A receptors.²⁴³ Other reported complications of colchicine poisoning include bilateral adrenal hemorrhage,^{66,224} disseminated intravascular coagulation,^{118,192,211} pancreatitis,^{172,232} and liver dysfunction.^{46,168,192}

Although uncommon, poisoning from IV colchicine administration has occurred. Clinical and laboratory manifestations are similar to those that occur after oral exposure including multisystem organ dysfunction and cytopenias.⁵⁵

Colchicine does not appear to be a significant human teratogen but the limited work on this subject is not definitive.⁷⁶

Diagnostic Testing

Colchicine concentrations in body fluids are not available in a clinically relevant time frame and have no well-established correlation with severity of illness. However, effective steady-state serum concentrations for treatment of patients with various illnesses are reported as 0.5 to 3.0 µg/L.¹⁶⁰ Concentrations > 3.0 µg/L can be associated with toxicity depending on the clinical situation and concentrations > 24 µg/L are definitely associated with toxicity.^{89,160,239,249} Serum concentrations do not correlate well with ingested dose in massive oral overdose settings.⁷⁵ Initial laboratory monitoring should include a complete blood count (CBC), serum electrolytes, renal and liver function tests, creatine kinase, phosphate, calcium, and magnesium. A prothrombin time, activated partial thromboplastin time, urinalysis, and other focused testing can be considered depending on clinical suspicion for different end-organ injury. The need for other laboratory studies, such as a troponin, arterial or venous blood gas, lactate, fibrinogen, and fibrin split products, should be considered, depending on the clinical situation. Following significant overdose or in any case if cardiac toxicity is present or suspected, serial troponins (every 6–12 hours) should be performed because increasing concentrations may be predictive of cardiovascular collapse.^{96,237} Electrocardiography and chest radiography should also be obtained. Serial CBCs are indicated (at least every 12 hours) to evaluate for the development of depression in cell lines. Bile appears to be the biologic matrix of choice for postmortem testing, probably due to normal postmortem biologic processes that can increase blood colchicine concentration.^{28,171} One colchicine-associated fatality who had a premortem blood colchicine concentration of 50 µg/L, also had a postmortem femoral blood concentration of 137 µg/L and a bile concentration above 600 µg/L.²⁴⁹ Another reported a postmortem blood concentration of 60 µg/L.² Two IV colchicine-associated fatalities had postmortem blood colchicine concentrations of 32 µg/L and 44 µg/L.⁵⁵

Management

Treatment for patients with colchicine toxicity is mainly supportive, which includes IV fluid replacement, vasopressor use, hemodialysis (as indicated for acute kidney injury), antibiotics for suspected secondary infection, colony-stimulating factors, and adjunctive respiratory therapy (endotracheal intubation, positive end-expiratory pressure), as necessary. Consultation with nephrologists and hematologists may be useful. In severe poisoning, intraaortic balloon pump therapy and extracorporeal membrane oxygenation therapy may be of help but there is no proof of clinical benefit.¹⁷⁹

Because most patients with an acute oral colchicine overdose present several hours after their ingestion, vomiting has already begun, and the utility of GI decontamination is inadequately defined. However, given the extensive morbidity and mortality associated with colchicine overdose, orogastric lavage should be considered in patients who present within 1 to 2 hours of ingestion and are not already vomiting.^{1,35,235} A dose of activated charcoal (AC) should be administered after lavage, or in its place if lavage is not appropriate or possible in the judgment of the physician. Since limited evidence suggests that colchicine undergoes some enterohepatic recirculation, administration of a single dose of AC to a patient presenting to a health care facility beyond 2 hours following ingestion can be considered if no contraindications exist. Multiple-dose AC (MDAC) can also be considered in these patients for the same reason.^{3,192} The delay in presentation to a health care facility coupled with the fact that patients often have GI symptoms such as vomiting limits the potential benefit of using MDAC. However, antiemetic medications can be given to control emesis and facilitate AC administration (Antidotes in Depth: A1).

Experimentally, colchicine-specific antibodies can restore colchicine-affected tubulin activity in vitro and were successfully used in a single case of severe colchicine poisoning.²¹ The administration of Fab fragments was temporally associated with a dramatic improvement in clinical and hemodynamic status. This improvement was also associated with a significant increase in serum colchicine concentrations, which suggests a redistribution of drug into the intravascular space.²¹ Unfortunately, this therapy is not commercially available.

Granulocyte-colony stimulating factor (G-CSF) is useful in the treatment of patients with colchicine-induced leukopenia and thrombocytopenia.^{69,109,131,252} The dose of G-CSF, the dosing frequency, and the route of administration were variable in the reported cases.^{69,109,131,252} G-CSF should be started if the patient develops leukopenia. Dosing should be in accordance with the manufacturer's instructions.

Hemodialysis and hemoperfusion are not viable options to enhance colchicine clearance based on its large volume of

distribution, but hemodialysis may be required if AKI is severe.^{24,31,32,196,197,230,242} Whole blood and plasma exchange have been suggested for cases presenting with lethal-dose colchicine exposures, but evidence of efficacy is lacking, and therefore these procedures are not recommended at this time.¹⁷⁹

Because of the significant morbidity and mortality associated with colchicine toxicity, all symptomatic patients with suspected or known overdoses should be admitted to the hospital for observation. Because these patients have a risk of sudden cardiovascular collapse within the first 24 to 48 hours¹⁶⁶ intensive care unit monitoring is recommended for at least this initial time period. Troponin should be checked every 6 to 12 hours during this period because increasing results may suggest an increased risk of cardiotoxicity and cardiovascular collapse.^{96,237} CBCs should be followed at least daily to evaluate for cytopenias. Poisoned patients manifest GI signs and symptoms within several hours of ingestion and should be observed for at least 8 to 12 hours. Patients who do not manifest GI signs and symptoms within that time period after ingestion are unlikely to be significantly poisoned.

PODOPHYLLUM RESIN OR PODOPHYLLIN

History

Podophyllin is the name often used to refer to a resin extract from the rhizomes and roots of certain plants of the genus *Podophyllum*.^{74,103} Examples include the North American perennial *Podophyllum peltatum* (May apple or mandrake), the related Indian species *Podophyllum emodi*, and the Taiwanese *Podophyllum pleianthum*.⁷⁴ It is more descriptive to refer to it as podophyllum resin.^{74,103} Podophyllum resin, or podophyllin, contains at least 16 active compounds.^{57,74,103} These include a variety of lignins and flavonols, including podophyllotoxin, picropodophyllin, α - and β -pellatins, desoxypodophyllotoxin, and quercetin.^{54,57,74,103} Podophyllotoxin, a component of podophyllin, is a potent microtubular poison, similar to colchicine, and causes similar effects in overdose.⁷⁴

The first reported modern era medicinal use of podophyllin preparations was as a laxative in the 19th century.^{54,57,188} Its cathartic properties, and its potential toxicity, were noted as early as 1890, when the first fatality from podophyllin was recorded.^{212,246} Podophyllin was used to treat individuals with a variety of other health issues, including liver disease, scrofula, syphilis, warts, and cancer.⁷⁴ Etoposide and teniposide are semisynthetic derivatives of podophyllotoxin used as chemotherapeutics.⁷⁴

Poisoning usually is caused by systemic absorption after topical application, after ingestion of the resin or plant, and after consumption of a commercial preparation of the extract. Systemic toxicity is described after unintentional dispensing of the incorrect herb, and after ingestion of herbal preparations containing podophyllin.^{58,59,78}

Pharmacology

Podophyllin is primarily used in modern pharmacopeia as a topical treatment for patients with verruca vulgaris and condyloma acuminatum.^{54,90,139} The active ingredient is believed to be podophyllotoxin.^{19,74,130,212,226,238,248} Podophyllotoxin exists in the plant as a β -D-glucoside.^{90,130,212} Numerous synthetic and semisynthetic derivatives of podophyllotoxin exist; however, the most important are probably the chemotherapeutics etoposide and teniposide.⁷⁴ The antitumor effect of etoposide and teniposide results from their interaction with topoisomerase II and free radical production, leading to DNA strand breakage, an effect not shared by podophyllin and colchicine.^{50,74} Etoposide and teniposide also arrest cell growth in the late S or early G2 phase of the cell cycle.^{50,74,97} Further discussion of these xenobiotics can be found in [Chap. 52](#).

Pharmacokinetics and Toxicokinetics

Very limited information exists regarding the pharmacokinetics of podophyllin as a preparation or for its major active ingredient, podophyllotoxin. Podophyllotoxin is highly lipid soluble and can easily cross cell membranes.^{90,101,175,212} It can be eliminated through the bile with a half-life of 48 hours.^{54,65} However, review of the referenced articles failed to adequately support this elimination half-life and may have been based solely on observed clinical course.⁶⁵

Absorption of podophyllotoxin was measured in seven men after application of various amounts of a 0.5% ethanol podophyllotoxin preparation for condylomata acuminata.²³⁸ Peak serum concentrations of 1 to 17 $\mu\text{g/L}$ were achieved within 1 to 2 hours after administration of doses ranging from 0.1 to 1.5 mL (0.5–7.5 mg).²³⁸ Patients treated with 0.05 mL or less had no detectable podophyllotoxin in their serum. Administration of 0.1 mL yielded peak serum concentrations up to 5 $\mu\text{g/L}$ within 1 to 2 hours and up to 3 $\mu\text{g/L}$ at 4 hours. Administration of 1.5 mL yielded peak serum concentrations ranging from 5 to 9 $\mu\text{g/L}$ within 1 to 2 hours; 5 to 7 $\mu\text{g/L}$ at 4 hours; 3 to 4.5 $\mu\text{g/L}$ at 8 hours; and 3.5 $\mu\text{g/L}$ at 12 hours.²³⁸

Pathophysiology

The components of podophyllin have numerous actions within the cell, including inhibition of purine synthesis, inhibition of purine incorporation into RNA, reduction of cytochrome oxidase and succinoxidase activity, and inhibition of microtubule structure and function.^{54,97,241} Podophyllotoxin causes toxicity similar to colchicine^{74,248} because of binding to tubulin subunits and interference with subsequent microtubule structure and function.^{74,248} Radiolabeled podophyllotoxin inhibits colchicine binding to tubulin, suggesting that their binding sites overlap.⁷⁴ Podophyllotoxin binds more rapidly than colchicine, and in contrast to colchicine, binding is reversible.⁷⁴ Podophyllotoxin also inhibits fast axoplasmic transport similar to colchicine by interference with microtubule structure and function.^{185,233} Many other compounds, such as the vinca alkaloids, cryptophycins, and halichondrins, also inhibit microtubule polymerization in a similar manner.¹²⁸

Toxic Dose

The minimum toxic dose associated with podophyllin ingestion is unknown. Limited information on the situations surrounding the few case reports of podophyllin poisoning that do exist does not provide sufficient detail from which to estimate it.

Clinical Presentation

Podophyllin poisoning is described after both ingestion,^{49,60,78,94,116,151,202,245} and absorption following cutaneous application.^{152,159,162,183,194,221,223} Toxicity also is reported following IV administration of podophyllotoxin¹⁰⁶ and ingestion of mandrake root or herbal remedies containing podophyllin.^{78,94,246} Nausea, vomiting, abdominal pain, and diarrhea usually begin within several hours after ingestion.^{65,101,106,116,152,157,159,194,202,212,221,245,246} Symptoms of poisoning might be delayed for 12 hours or more after cutaneous exposure to podophyllin and are often caused by improper usage (excessive cutaneous exposure, interruption in skin integrity, or failure to remove the preparation after a short time period).^{152,157,162,212} Initial clinical findings are not necessarily determined by the route of exposure.¹⁵²

Alterations in central and peripheral nervous system function tend to predominate in podophyllin toxicity. Some patients present with, or rapidly progress to, confusion, obtundation, and coma.^{49,65,78,151,157,159,162,194,202,221,223,226,245}

Delirium and both auditory and visual hallucinations occur during the initial presentation.^{67,90,223} Patients develop paresthesias, lose deep tendon reflexes, and might develop plantar extension.^{49,57,60,65,78,151,159,162,177,212,223,233} Cranial nerve involvement, including diplopia,⁵⁷ nystagmus,⁶⁵ dysmetria,⁶⁰ dysconjugate gaze,²²³ and facial nerve paralysis,⁶⁷ are all reported. Patients who recover from the initial event are at risk of developing a peripheral sensorimotor axonopathy.^{60,65,78,90,151,159,175,177,194,212,223} The reported duration for recovery from podophyllin-induced axonopathy is variable but can take several months.^{65,78,159,175} Dorsal radiculopathy¹⁰¹ and autonomic neuropathy are also reported.¹³⁹ There may be a mild myelopathic component in the neuropathy.⁵⁹

Hematologic toxicity from podophyllin most likely results from its antimitotic effects. A review of the limited literature suggests that it is similar to colchicine but is not nearly as consistent in its pattern, severity, and frequency. An initial leukocytosis^{159,162,194,212} may occur after poisoning, which can be followed by leukopenia, thrombocytopenia, or generalized pancytopenia.^{116,139,157,159,212,221} In patients who recover, cell lines tend to reach their nadir within 4 to 7 days after exposure.^{90,116,159,194,221}

Other complications of poisoning include fever,¹⁵⁷ ileus,^{90,157,223} elevated liver function tests,^{78,116,159,221,245} and hyperbilirubinemia,¹¹⁶ coagulopathy,¹¹⁶ seizures,^{67,202} and AKI.^{157,245} Teratogenic effects resulting from exposure during pregnancy may also occur.^{57,130}

Diagnostic Testing

Podophyllin or podophyllotoxin concentrations are not readily available. Routine testing for suspected or known podophyllin poisoning should include routine laboratory tests and other targeted testing, as needed. Serial CBCs should be obtained in cases of poisoning to evaluate for pancytopenia.

Management

Management primarily consists of supportive and symptomatic care. Orogastric lavage may be considered following recent ingestion based on its high toxicity profile.^{35,235} If the patient presents within the first several hours of ingestion, then a dose of AC should be given. Any cutaneously applied podophyllin should be removed and the area thoroughly cleansed. Supportive and symptomatic care should be instituted as needed. Patients either progress to multisystem organ dysfunction and death or recover. CBCs should be monitored similarly to colchicine poisoning (at least daily).

A few case reports of treatment with extracorporeal elimination techniques exist. These reports include resin

hemoperfusion¹¹² and charcoal hemoperfusion.^{159,212} The role these procedures played in the clinical courses is unclear. As a result, firm recommendations regarding the use of these techniques cannot be made at this time.

Patients with significant ingestions of podophyllin develop GI symptoms within a few hours,^{60,94,116,177,245,246} but patients may also present with primarily neurologic symptoms, such as confusion or obtundation.^{49,54,90,152} An isolated number of cases suggest the onset of toxicity can be delayed for as long as 12 hours.^{49,54,65,78} Cutaneous exposure might result in even further delayed toxicity because systemic absorption is delayed and symptom onset is more insidious.^{90,139,162,194,212,221,223} Patients probably should be observed for toxicity for at least 12 hours after ingestion and perhaps even longer after dermal exposures. Asymptomatic patients with unintentional exposures and good follow up that are discharged after 12 to 24 hours should have scheduled follow up with their primary care physician and a repeat CBC obtained within 24 hours.

VINCRIStINE AND VINBLASTINE

History

More than 150 different alkaloidal compounds can be isolated from the periwinkle plant (*Catharanthus roseus*), most of which have been used to manage illness from a variety of medical disorders including cancer, scurvy, diabetes, toothache, and hypertension.²⁵⁰ Among these 150 are about 20 different compounds that have antineoplastic activity. Vincristine and vinblastine are pharmaceuticals derived from compounds in the periwinkle plant and are probably among the most commonly used vinca alkaloid derivatives in medicine.¹⁹¹ They are typically used as part of a chemotherapy regimen for various cancers. Both are administered intravenously and should never be administered intrathecally. Intrathecal administration of vinblastine or vincristine is always the result of an error, is a neurosurgical emergency, and is associated with life-threatening complications⁷ (Special Considerations: SC3). There are a few case reports of intramuscular administration of these chemotherapeutics but they will not be discussed since there are so few and the reader is referred to the primary literature for further information.^{20,184} Although other vinca derivatives exist, and sharing similar modes of action (causing microtubule dysfunction); this section will focus primarily on vincristine and vinblastine. Regardless, the pathophysiology of disease, clinical manifestations of illness and management of poisoning from similar compounds and the plant itself is similar to vincristine and vinblastine.²⁵⁰

Pathophysiology

Vincristine and vinblastine are used specifically for the treatment of patients with leukemias, lymphomas, and certain solid tumors. Their mechanism of activity is similar to that of colchicine, podophyllotoxin, and the taxoids (eg, paclitaxel, docetaxel).^{73,180} These chemotherapeutics disrupt microtubule assembly from tubulin subunits by either preventing their formation or depolymerization, both of which are necessary for routine cell maintenance. Vinblastine binds to the β -subunit of the tubulin heterodimer at a specific region known as the vinblastine-binding site.¹⁸² Mitotic metaphase arrest is commonly observed because of the inability to form spindle fibers from the microtubules. Cell death quickly ensues because of the interruption of these homeostatic functions, accounting for the clinical manifestations.

The mechanism of neurotoxicity is not well understood but is probably related to inhibition of microtubular synthesis, which leads to axonal degeneration in the peripheral nervous system.^{102,178} Brain biopsy of a patient who experienced a vincristine-related death showed neurotubular dissociation, which is characteristic of vincristine damage in experimental animals.^{38,63}

Pharmacokinetics

After IV administration, vincristine is rapidly distributed to tissue stores and highly bound to proteins and red blood cells.⁴⁸ Plasma protein binding ranges from 50% to 80%.¹⁸⁹ In more than 50% of children given IV vincristine, serum concentrations were not detected 4 hours after administration.¹⁶⁴ Elimination of vincristine occurs via the hepatobiliary system,⁴⁸ and it has a terminal half-life of about 24 hours.¹⁷⁴ Patients with hepatic dysfunction are susceptible to toxicity. Vincristine overdose is the most frequently reported antineoplastic overdose in the literature. This is because there are at least four different potential inappropriate ways to dose and administer vincristine, including confusing it with vinblastine, misinterpreting the dose, administering it by the wrong route, and confusing two different-strength vials. The normal dose of vincristine is 0.06 mg/kg, and a single dose should not exceed 2 mg for either an adult or child.

Drug Interactions. Administration of itraconazole with therapeutic doses of intravenously administered vincristine can cause toxicity probably for two reasons: (1) itraconazole-induced inhibition of certain cytochrome P450 enzymes (most likely the CYP3A subfamily) delays vincristine metabolism in vivo, and (2) inhibition of PGP mediated efflux of vincristine from inside cells, where it then accumulates.¹⁴ Coadministration of other azole antifungals, cyclosporine, isoniazid, erythromycin, mitomycin C, phenytoin, and nifedipine are also implicated in vincristine toxicity for the same

aforementioned reasons.^{77,206,207}

Toxic Dose

The minimum toxic doses associated with adverse health effects from a single dose of vincristine and vinblastine are not well established. However, chemotherapeutic regimens tend to keep single doses at or below 2 mg to decrease the likelihood of peripheral neuropathy. Unfortunately, toxicity occurs with cumulative dosing over time, as which typically occurs with chemotherapeutic regimens. Peripheral neuropathy tends to begin after a cumulative dose (administered over multiple sessions, not all at once) of 30 to 40 mg.²⁹

Clinical Presentation

Despite their similarity in structure, vincristine and vinblastine differ in their clinical toxicity. Vincristine produces less bone marrow suppression and more neurotoxicity than does vinblastine. During the therapeutic use of vincristine, myelosuppression occurs in only 5% to 10% of patients.¹¹⁷ However, this effect is common in the overdose setting, and when it occurs, the need for blood products and concern for overwhelming infection is apparent.¹⁴² The decrease in cell counts begins within the first week and may last for up to 3 weeks. Other manifestations of acute vincristine toxicity are mucositis, central nervous system disorders, and syndrome of inappropriate antidiuretic hormone secretion (SIADH; Chap. 19).

Central nervous system disorders are varied and unusual during therapeutic vincristine therapy because of its poor penetrance of the blood–brain barrier. However, they are more common when there is delayed elimination, damage to the blood–brain barrier, overdose, or inadvertent intrathecal administration. Generalized seizures may occur from 1 to 7 days following exposure.^{121,126,132,222} Other manifestations are depression, agitation, insomnia, and hallucinations. Vincristine stimulation of the hypothalamus may be responsible for the fevers and SIADH noted in overdosed patients.¹⁹⁸ The fevers begin 24 hours after exposure and last 6 to 96 hours. Serum electrolytes must be monitored, typically for 10 days.

Autonomic dysfunction may occur, and it commonly includes ileus, constipation, and abdominal pain. Paraparesis, paraplegia, atony of the bladder, cranial nerve palsies (specifically ptosis), hypertension, and hypotension may also occur.^{77,83,132,254}

Ascending peripheral neuropathies can occur following inadvertent large ingestions and during routine chemotherapy. The risk can be limited somewhat by keeping the total for a single dose below 2 mg.²¹³ Neuropathy may appear after an overdose, starting at about 2 weeks and lasting for 6 to 7 weeks. Paresthesias, neuritic pain, ataxia, bone pain, wrist drop, foot drop, involvement of cranial nerves III to VII and X, and diminished reflexes may be observed.²⁴⁴ The incidence of paresthesia increases with dose and is reported to be 56% in patients treated at doses between 12.5 and 25 µg/kg.¹¹⁷ At a dose of 75 µg/kg, the incidence of patients with a sensory disorder increased by sixfold. The loss of reflexes, the earliest and most consistent sign of vincristine neuropathy, is maximal at 17 days after a single massive dose. Muscular weakness is a limiting point in therapy and typically involves the distal dorsiflexors of the extremities, although laryngeal involvement is also reported.^{138,205} These severe neurologic symptoms may be reversed by either withholding therapy or reducing dosage upon manifestation of these findings.¹³⁸ Unlike the vinca alkaloids, taxol-induced peripheral neuropathy is predominantly sensory and resolves faster with discontinuation.¹⁴¹ This is because of the different effects on microtubule assembly by these chemotherapeutics.

Vincristine-associated myocardial infarctions are reported, but their cause is not understood.^{147,214,225,251} They may be related to vinca alkaloid–induced platelet aggregation, coronary artery spasm, or increased sensitivity of myocardium to hypoxia.

Although rare, IV vincristine administration may be associated with an allergic-type cutaneous reaction.¹⁷³

Diagnostic Testing

Determination of vincristine and vinblastine concentrations is not readily available at most hospitals (Table 36–2). Routinely available laboratory tests such as electrolyte panels, kidney function tests, and others can be used as needed to assess the patient as indicated.

TABLE 36–2. Comparison of Antimitotic Overdose

	Colchicine	<i>Podophyllum Resin</i>	Vincristine	Vinblastine
Route of exposure	PO	PO and cutaneous	IV	IV
Initial symptoms	GI*	GI* and/or neurologic effects (obtundation, confusion, delirium)	GI effects,* fever, neurologic effects	GI effects,* fever, myalgias, neurologic effects
Initial symptom onset	Several hours after ingestion; delayed onset beyond 12 hours very unlikely	Several hours after ingestion; delayed presentation (past 12 hours) is possible, especially in those with a cutaneous route of exposure	Usually within 24–48 hours	Usually within 24–48 hours
Hematotoxic effects	Leukocytosis (24–48 hours after ingestion); pancytopenia (beginning 48–72 hours after ingestion)	Similar to colchicine; however, not well characterized and reported less frequently	Hematotoxicity may occur; less toxicity compared with vinblastine	Hematotoxicity may occur; more toxicity compared with vincristine
CNS effects	Late (48–72 hours after ingestion); obtundation, confusion, and lethargy secondary to progression of MSD	Can be early (< 12 hours after ingestion); CNS toxicity may occur later or secondary to progression of MSD	Variable; cranial neuropathies; seizures; obtundation, confusion, and lethargy may occur because of progression of MSD	Variable; cranial neuropathies; obtundation, confusion, and lethargy may occur because of progression of MSD
Delayed PNS effects	Myoneuropathy most common; reported most often in chronic colchicine users with renal insufficiency	Peripheral sensorimotor axonopathy	Autonomic and ascending peripheral neuropathy; increased severity compared with vinblastine	Can see autonomic and peripheral neuropathy; decreased severity compared with vincristine
Clinical course	Recovery or MSD and death	Recovery or MSD and death	Recovery or MSD and death; May develop SIADH	Recovery or MSD and death; may develop SIADH
Management	Supportive; GI decontamination; G-CSF for neutropenia	Supportive; consider GI decontamination for oral exposures and skin decontamination for cutaneous exposures	Primarily supportive; G-CSF for neutropenia For treatment of intrathecal overdoses see Special Considerations: SCI	Primarily supportive; G-CSF for neutropenia; consider exchange transfusion, plasmapheresis or plasma exchange For treatment of intrathecal overdoses see Special Considerations: SCI

*Nausea, vomiting, diarrhea, abdominal discomfort.

CNS = central nervous system; G-CSF = granulocyte colony-stimulating factor; GI = gastrointestinal; IV = intravenous; MSD = multisystem organ dysfunction; PNS = peripheral nervous system; PO = oral; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Management

Generalized seizures can be a life-threatening complication of vincristine or vinblastine overdose (Table 36–2). Treatment with benzodiazepines or phenobarbital is usually successful; phenytoin was used successfully in a patient with known barbiturate hypersensitivity.¹³² Prophylactic phenobarbital and benzodiazepines were used to prevent seizures in two patients.^{56,134} Dysrhythmias and alterations in blood pressure may also be expectantly managed. Calcium channel blockers (nifedipine and amlodipine) were used to control hypertension in a patient with vincristine overdose.⁵⁶ Blood counts must be monitored daily, and G-CSF may be used to treat neutropenia.^{56,142,222} However, the red blood cell response from the use of erythropoietin may be limited because of the induction of metaphase arrest in the erythroblasts.¹⁴⁹

The symptoms of acute toxicity usually last for 3 to 7 days, and the neurologic sequelae may last for months before some resolution is observed. Nerve conduction studies are helpful in assessing the extent of any clinical signs and symptoms of peripheral neuropathy.

Clinical findings of a peripheral neuropathy may appear following an excessive dose or after multiple small doses in which the cumulative dose exceeds 30 to 40 mg.²⁹ Treatment for this condition is variable and includes pain and paresthesia management with various medications, including opioids, nonsteroidal antiinflammatory drugs, cyclic antidepressants, vitamin E, and other drugs such as gabapentin and lamotrigine.²⁹ In a controlled clinical trial for vincristine-induced peripheral neuropathy, glutamic acid therapy had some efficacy. Patients receiving vincristine therapy were given glutamic acid as 500 mg orally three times a day.¹²⁴ There was a decreased incidence in loss of the Achilles tendon reflex and a delayed onset of paresthesias in the glutamic acid–treated group. No reported adverse events with glutamic acid were observed in this investigation. Animal studies involving the administration of glutamic and aspartic acid to mice poisoned with either vinblastine or vincristine demonstrate increased survival and decreased sensorimotor peripheral neuropathy.^{37,70,123} Although the exact mechanisms of these observed effects with glutamic acid remain unclear, several authors have suggested the ability of glutamic acid to competitively inhibit a common cellular transport mechanism

for vincristine.^{34,68} It may assist in the stabilization of tubulin and promote its polymerization into microtubules.^{39,108} Finally, glutamic acid may improve cellular metabolism by overcoming vinca alkaloid-associated inhibition in the Krebs cycle.^{82,125} Although the role of glutamic acid in acute toxicity needs further study, it is likely not harmful and should be considered. Glutamic acid may be initiated as 500 mg orally three times a day and should be continued for at least 5 days following exposure (approximately 95% of the drug should be eliminated after five half-lives) and possibly longer in very large exposures.^{124,174} L-Glutamic acid is the preferred stereoisomer because it is biologically active, and this product is available as a powder from various distributors in the United States.

Leucovorin may shorten the course of vincristine-induced peripheral neuropathy¹⁰⁴ and myelosuppression.¹³⁴ The mechanism is attributed to the ability of leucovorin to overcome the vincristine-mediated block of dihydrofolate reductase and thymidine synthetase.¹⁰⁴ However, neither leucovorin^{23,122,231} nor pyridoxine¹²² has been definitely shown to be effective. An initial experimental investigation evaluating the efficacy of antibody therapy to limit vinca alkaloid toxicity shows promise.¹⁰⁵ Unfortunately, vinca alkaloid specific antibodies for human poisoning are not commercially available.

The rapid distribution and high protein binding characteristics of vincristine favor early intervention with methods other than hemodialysis. Double-volume exchange transfusion was performed at 6 hours post-exposure in three children who were overdosed with 7.5 mg/m² of IV vincristine.¹³⁴ Of the two survivors, their respective postexchange serum vincristine concentrations were 57% and 71% lower than their preexchange concentrations. The amount of vincristine removed was not determined. Although these patients developed peripheral neuropathies, myelosuppression, and autonomic instability, the author noted that the duration of illness was shorter than previously reported. Thus, based on the pharmacokinetic profile of vincristine and these two reports, exchange transfusion in children is the preferred method of enhanced elimination when the patient presents soon after the administration of the drug, and plasmapheresis is the preferred method in adults.

Plasmapheresis was attempted with vinca alkaloid overdoses.^{142,189} In an 18 year-old patient who received two 8 mg IV doses of vincristine at 12 hour intervals, the procedure was performed 6 hours after the second dose, and 1.5 times the plasma volume was plasmapheresed.¹⁸⁹ Postplasmapheresis serum vincristine concentration was 23% lower than the starting concentration. The patient survived with myelosuppression, neurotoxicity, and SIADH.

One case of IV vinblastine overdose was reported to be successfully managed with plasma exchange procedures performed at 4 hours and 18 hours after vinblastine administration resulting in markedly less toxicity than what was expected.²¹⁹

Patients receiving an overdose of vincristine intravenously should be admitted to a cardiac-monitored bed and observed for 24 to 72 hours.¹⁴⁵ If patients remain asymptomatic during the observation period, then they can be discharged with follow-up for bone marrow suppression and SIADH; otherwise, depending on the patient's clinical condition, continual observation for progression of neurologic symptoms is warranted.²⁷

SUMMARY

- Colchicine toxicity manifests within several hours after ingestion and consists of severe nausea, vomiting, diarrhea, and abdominal pain followed by pancytopenia several days later.
- Colchicine poisoned patients are at risk of sudden cardiac death, especially during the period between 24 and 36 hours after ingestion; increasing serial troponin concentrations may be predictive of that risk.
- Podophyllum toxicity is less pronounced than colchicine toxicity but may occur after dermal application.
- When excessive doses of intravenously administered vincristine or vinblastine are likely to cause severe toxicity exchange transfusion, plasmapheresis and plasma exchange should be considered.
- Intrathecal administration of vincristine or vinblastine constitutes a life-threatening neurosurgical emergency.
- Management of patients with toxicity from ingested colchicine, podophyllotoxin, and vinca alkaloid derivatives is similar. Early GI decontamination and supportive treatment are the mainstays of therapy. G-CSF may be of benefit in patients who develop neutropenia.

Disclaimer

The findings and conclusions in this chapter are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.

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37 NONSTEROIDAL ANTIINFLAMMATORY DRUGS

William J. Holubek

HISTORY AND EPIDEMIOLOGY

In the late 1800s, acetylsalicylic acid, aspirin, was shown to have antiinflammatory properties similar to those of corticosteroids when used in high doses in patients with rheumatoid arthritis. In a quest to develop a compound with antiinflammatory properties equivalent to corticosteroids but chemically nonsteroidal, Dr. Stewart Adams discovered and developed 2-(4-isobutylphenyl) propionic acid, now known as ibuprofen, and in the process created a new class of drugs designated as nonsteroidal antiinflammatory drugs (NSAIDs).³⁵ Ibuprofen was initially marketed in the United Kingdom in 1969 and was introduced to the US market in 1974. Ibuprofen became available without a prescription in the United States in 1984.

In addition to the numerous benefits of NSAIDs, some deleterious and life-threatening effects are associated with both their therapeutic use and overdose. In an attempt to circumvent some of these adverse effects, selective cyclooxygenase-2 (COX-2) inhibitors were developed, and in 1999, the first selective COX-2 inhibitor, rofecoxib, was approved by the US Food and Drug Administration (FDA), but it was withdrawn from the market in 2004 after postmarketing surveillance concluded an increase in myocardial infarctions and cerebrovascular accidents were associated with its use.

NSAIDs are considered among the most commonly used and prescribed medications in the world.^{10,72} An estimated one in seven patients with rheumatologic diseases is given a prescription for NSAIDs, and another one in five people in the United States use NSAIDs for acute common complaints.⁹⁴

Ibuprofen, naproxen, and ketoprofen are currently the only nonprescription NSAIDs in the United States. NSAIDs are also contained in cough and cold preparations and in prescription combination drugs (eg, ibuprofen with hydrocodone) and have occasionally been found as adulterants in herbal preparations.⁶²

The American Association of Poison Control Centers (AAPCC) compiles data regarding potentially toxic exposures called into participating poison centers throughout the United States using the National Poison Data System (NPDS) (Chap. 136). Beginning in 2006, a list of substances associated with the largest number of fatalities was reported annually, and since then NSAIDs have consistently been included in the top 25 substances.

The term NSAID used in this chapter does not refer to salicylates, which are unique members of the NSAID class and are covered in Chap. 39.

PHARMACOLOGY

These chemically heterogeneous compounds can be divided into carboxylic acid and enolic acid derivatives and COX-2 selective inhibitors (Table 37–1). They all share the ability to inhibit prostaglandin (PG) synthesis. PG synthesis begins with the activation of phospholipases (commonly, phospholipase A₂) that cleave phospholipids in the cell membrane to form arachidonic acid (AA). AA is metabolized by PG endoperoxide G/H synthase, otherwise known as COX, to form many eicosanoids, including PGs and the prostanoids, prostacyclin (PGI₂) and thromboxane A₂ (TXA₂). AA can also be metabolized by lipoxygenase (LOX) to form hydroperoxy eicosatetraenoic acid (HPETE), which is converted to many different leuko-trienes (LTs) that are involved in creating a proinflammatory environment (Fig. 37–1).

TABLE 37–1. Classes and Pharmacology of Selected Nonsteroidal Antiinflammatory Drugs^{8,17,18,29,56,64}

	<i>Time to Peak Plasma Concentration (hours)</i>	<i>Half-Life (hours)</i>	<i>Pharmacokinetics</i>	<i>Unique Features</i>
CARBOXYLIC ACIDS				
Acetic Acids				
Diclofenac ^{††}	2–3	1–2	First-pass effect; hepatic metabolism (CYP2C9)	Decreases leukocyte arachidonic acid concentration; topical activity; hepatotoxic
Etoricoxib	1	7	Hepatic metabolism	Inhibits leukocyte motility; coronary vasoconstrictor effect
Indomethacin	1–2	2.5	Demethylation (50%)	Poor antiinflammatory effect; topical activity
Ketorolac	<1	4–6	Urinary excretion	For parenteral use also
Sulindac	1–2	7	Active metabolite with a half-life of 18 hours	Prodrug; hepatotoxic
Tolmetin	<1	5	Hepatic metabolism	Accumulates in synovia
Fenamates				
Meclofenamate	0.5–2.0	2–3		Seizures; gastrointestinal inflammation
Mefenamic acid	2–4	3–4	Urinary excretion (50%)	Seizures; prostaglandin antagonist
Propionic Acids				
Fenoprofen	2	2–3	Decreased oral absorption (~85%)	Increased cerebrospinal fluid concentration
Flurbiprofen	1–2	6		Increased cerebrospinal fluid concentration
Ibuprofen ^{††}	<0.5	2–4	Hepatic metabolism; urinary excretion	Also formulated for parenteral use
Indobufen [†]	2	6–7	Urinary excretion (70%–80%)	In Europe, used as prophylaxis for thrombus formation
Ketoprofen [†]	1–2	2	Hepatic metabolism; urinary excretion	Bradykinin antagonist; stabilizes lysosomal membranes
Naproxen [†]	1	14	Increased half-life with kidney dysfunction	Inhibitory effect on leukocytes; prolonged platelet inhibition
Oxaprozin	3–6	40–60		Once-daily administration
Salicylates (Chap. 39)				
ENOLIC ACIDS				
Oxicams				
Meloxicam [†]	5–10	15–20		High Cyclooxygenase-2 selectivity
Nabumetone	3–6	24	Hepatic metabolism; active metabolites	Prodrug
Piroxicam	3–5	45–50	Hepatic metabolism (CYP2C9)	Inhibits neutrophil activation
Pyrazolone				
Phenylbutazone [†]	2	54–99	Hepatic metabolism; active metabolites	Irreversible agranulocytosis; aplastic anemia
CYCLOOXYGENASE-2 SELECTIVE INHIBITORS[†]				
Celecoxib	2–4	6–12	Hepatic metabolism (CYP2C9)	Inhibits CYP2D6
Limeciclib [†]	1–3	2–5	Urinary excretion (60%); active metabolites	Inhibits neutrophil activation

[†]COX-2 preferential. ^{††}Nonprescription. ^{†††}Not available in the United States for humans. ^{††††}Robicoxib (Vion) and valdecoxib (Dextra) are no longer available. ^{†††††}Available in combination with misoprostol. Available in combination with acetaminophen and hydrocodone.

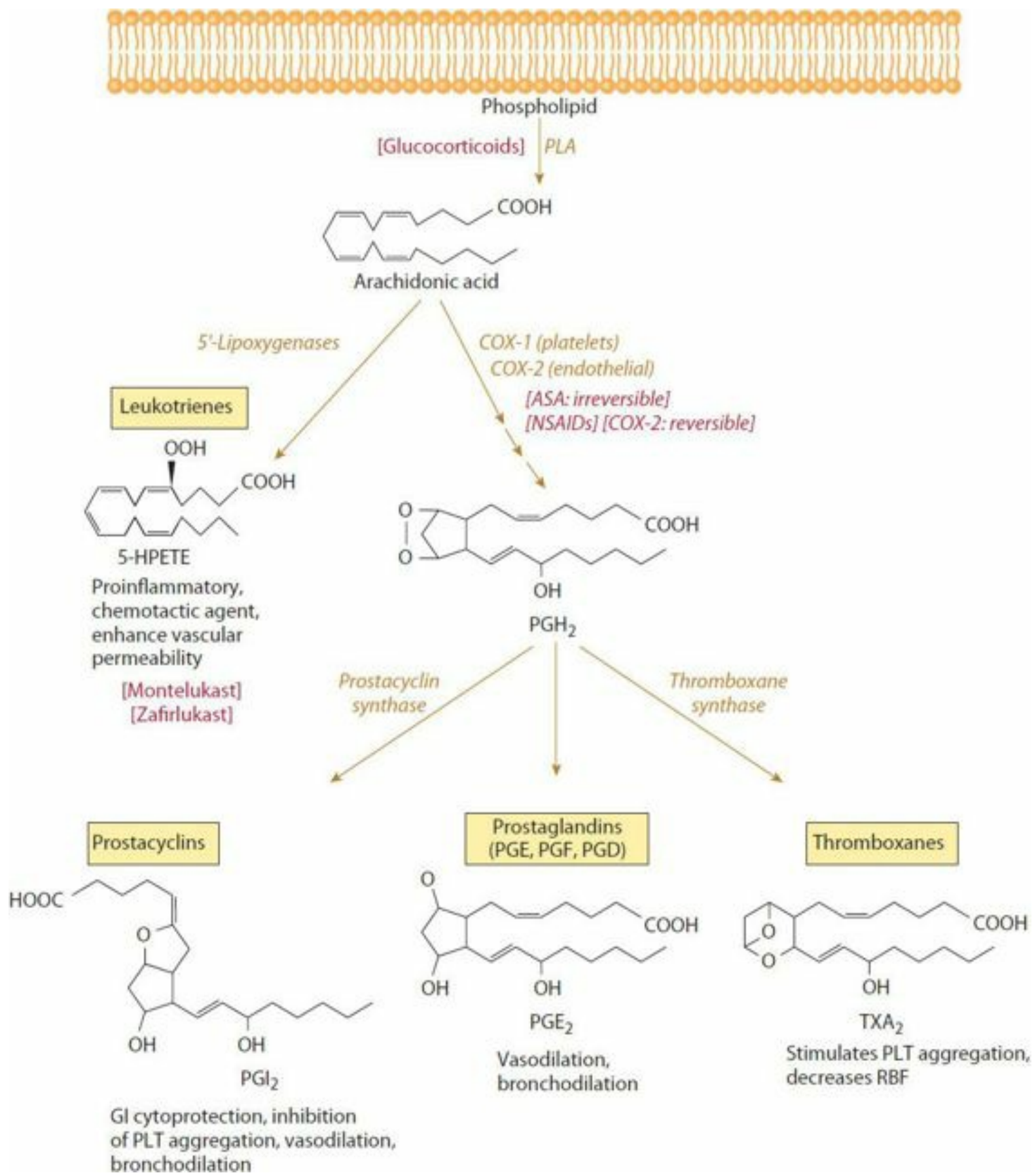


FIGURE 37–1. Arachidonic acid (AA) metabolism. This figure also illustrates some of the major differences between cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Phospholipase A (PCA) is stimulated by physical, chemical, inflammatory, and mitogenic stimuli and releases AA from cell membranes. The COX-1 enzyme synthesizes prostaglandins (PGs) that maintain cellular and vascular homeostasis. The COX-2 enzyme produces PGs within activated macrophages and endothelial cells that accompany inflammation. Whereas nonsteroidal antiinflammatory drugs (NSAIDs) reversibly inhibit both COX isoforms, selective COX-2 inhibitors inhibit the COX-2 isoform. Some authors suggest that inhibiting the COX enzymes shunts AA metabolism toward the production of chemotactic-vasoactive leukotrienes. Glucocorticoids inhibit PLA and down regulate induced expression of COX-2. ASA = acetylsalicylic acid; 5-HPETE, hydroperoxy eicosatetraenoic acid; GI = gastrointestinal; PGI₂ = prostacyclin; PGD = prostaglandin D; PGE₂ = prostaglandin E₂; PGF = prostaglandin F; PLT = platelet; RBF = renal blood flow; TXA₂ = thromboxane.

The COX enzyme responsible for PG production exists in two isoforms termed COX-1 and COX-2. COX-1 is constitutively expressed by virtually all cells throughout the body but is the only isoform found within platelets. This enzyme produces eicosanoids that govern “housekeeping” functions, including vascular homeostasis and hemostasis, gastric cytoprotection, and renal blood flow (RBF) and function.^{11,75} COX-2, on the other hand, is rapidly induced (within 1–3 hours) in inflammatory tissue by laminar shear (or mechanical) forces and cytokines, producing PGs involved in the inflammatory response. COX-2 is also upregulated by several cytokines, growth factors, and tumor promoters involved with cellular differentiation and mitogenesis, suggesting a role in cancer development.^{11,30,80}

Glucocorticoids can inhibit phospholipase A (PLA) and downregulate the induced expression of COX-2, which decreases the production of eicosanoids and PGs, respectively, but oral steroids are clinically not the first choice for an antiinflammatory drug regimen given their extensive adverse side effect profile, which includes osteoporosis, hyperglycemia, hypertension, glaucoma, muscle weakness, fluid retention, and mood swings. Most NSAIDs nonselectively inhibit the COX enzymes in a competitive or time-dependent, reversible manner, unlike salicylates, which irreversibly acetylate COX (Chap. 39). Inhibiting COX-1 can interrupt tissue homeostasis, leading to deleterious clinical effects. In what may seem advantageous, some NSAIDs (eg, etodolac, meloxicam, and nimesulide) preferentially inhibit COX-2 over COX-1, while others were specifically designed to selectively inhibit COX-2 (eg, celecoxib).⁹² As will be discussed later in this chapter, many of the selective COX-2 inhibitors (sometimes referred to as coxibs) were removed from the market in the United States because of their increased risk of adverse cardiovascular events.

NSAIDs do not directly affect LOX enzyme or the production of LTs; however, some data suggest that blocking the COX enzymes allows AA to be shunted toward the LOX pathway, increasing the production of proinflammatory and chemotactic-vasoactive LTs.^{54,94}

PHARMACOKINETICS AND TOXICOKINETICS

Most NSAIDs are organic acids with extensive protein binding (>90%) and small volumes of distribution of approximately 0.1 to 0.2 L/kg. Oral absorption of most NSAIDs occurs rapidly and near completely, resulting in bioavailabilities above 80%. Time to achieve peak plasma concentrations can vary widely (Table 37–1).¹⁶

Some NSAIDs possess unique characteristics regarding their sites of action and accumulation within the body. For example, whereas indomethacin, tolmetin, diclofenac, ibuprofen, and piroxicam achieve significant synovial concentrations, fenamates and indomethacin have both peripheral and central effects.¹⁶ NSAIDs have the ability to cross the blood–brain barrier, but the specific pharmacologic and physicochemical properties facilitating this ability are not well defined.^{3,55} Ketorolac and diclofenac have topical activity and are both used in ophthalmologic solutions, and diclofenac is also used in dermal preparations.¹⁶

Plasma half-lives in therapeutic dosing vary from as short as 1 to 2 hours for diclofenac and ibuprofen, to 50 to 60 hours for oxaprozin and piroxicam (Table 37–1). Most NSAIDs undergo hepatic metabolism with renal excretion of metabolites. Diclofenac undergoes extensive first-pass metabolism, only 10% to 20% of indomethacin and ketorolac are excreted unchanged in the urine. Variable amounts of NSAIDs are recovered in the feces.¹⁶

The kinetics of NSAIDs may change in overdose, depending on the particular xenobiotic. Therapeutic and supratherapeutic doses of naproxen (250 mg–4 g) result in the same half-life and time to peak plasma concentration, but the clearance and volume of distribution increase proportionately.^{65,74} When plasma protein binding of naproxen becomes saturated, the free drug concentration increases more rapidly than the total drug concentration, resulting in increased urinary excretion.⁷⁴ Overdoses of oral ibuprofen do not appear to prolong its elimination half-life.^{36,56,95}

PATHOPHYSIOLOGY

Gastrointestinal (GI) toxicity is the most common adverse effect from NSAID use (Table 37–2). Normally, the COX-1 enzyme expressed in the gastric epithelial cells leads to the production of PGs (PGE₂ and PGI₂), which are responsible for maintaining GI mucosal integrity by increasing mucous production and decreasing acid production. NSAIDs not only inhibit the production of these cytoprotective PGs and platelet aggregatory TXA₂ but also have a direct cytotoxic effect, increasing the risk of gastric and duodenal ulcers, perforations, and hemorrhage.^{23,68,72} Esophageal and small intestinal ulcers and strictures are also associated with NSAID use. Small intestinal diaphragms (or webs) are concentric weblike septa arising from submucosal fibrosis that can eventually cause a small bowel obstruction. These diaphragms rarely occur but are considered pathognomonic for NSAID use.²³

TABLE 37–2. Selected Adverse Effects of Nonsteroidal Antiinflammatory Drugs

Gastrointestinal

Chronic: dyspepsia, ulceration, perforation, hemorrhage, elevated hepatic aminotransferases, hepatocellular injury (rare)

Acute: same as above

Renal

Chronic: acute kidney failure, fluid and electrolyte retention, hyperkalemia, interstitial nephritis, nephrotic syndrome, papillary necrosis, azotemia

Acute: same as above

Hypersensitivity or Pulmonary

Chronic: angioedema, drug-induced lupus

Acute: asthma exacerbation, anaphylactoid and anaphylactic reactions, urticaria, angioedema, acute respiratory distress syndrome, drug-induced lupus

Hematologic

Chronic: increased bleeding time, agranulocytosis, aplastic anemia, thrombocytopenia, neutropenia, hemolytic anemia

Acute: same as above

Central Nervous System

Chronic: headache, dizziness, lethargy, coma, aseptic meningitis, delirium, cognitive dysfunction, hallucinations, psychosis

Acute: same as above

Drug Interactions

Aminoglycosides: increased risk of aminoglycoside toxicity⁷⁷

Anticoagulants (eg, warfarin, salicylates, heparins, direct thrombin inhibitors and Xa

inhibitors): increased risk of gastrointestinal bleeding^{11,76}

Antihypertensives (especially diuretics, β -adrenergic antagonists, and angiotensin-converting

enzyme inhibitors): reduced antihypertensive effects⁹⁵

Digoxin: increased risk of digoxin toxicity⁸⁵

Ethanol: increased bleeding time⁷⁶

Lithium: increased risk of lithium toxicity⁶⁸

Methotrexate: increased risk of methotrexate toxicity⁶⁸

Sulfonylureas: increased hypoglycemic effect⁸³

Selective COX-2 inhibitors decrease the incidence of significant GI toxicity compared with some nonselective NSAIDs, a benefit that is lost in patients concomitantly taking warfarin or low-dose aspirin.^{4,12,30,93} Although *Helicobacter pylori* and NSAID use both individually increase the risk of gastroduodenal ulcers, there are conflicting data regarding the relationship between the two, given the wide array of study designs, individual responses to infection and treatments, and different gastric acid suppressants. Current evidence suggests that the risk of GI toxicity may be decreased by eradicating *H. pylori* before initiating NSAID therapy in NSAID-naïve patients.^{10,18,23,72}

The kidney produces locally homeostatic PGs largely via COX-1, including PGI₂, PGE₂, and PGD₂, that maintain adequate glomerular filtration rate (GFR) and RBF and function by augmenting renal vasodilation, inhibiting sodium chloride absorption, and antagonizing the action of antidiuretic hormone (vasopressin). NSAIDs oppose this homeostatic

renal vasodilation and augment sodium reabsorption, blunting the antihypertensive effect of thiazide and loop diuretics. NSAIDs also decrease renin synthesis, a mechanism shared by β -adrenergic antagonists, rendering this antihypertensive therapy less effective.^{30,94} Patients with volume contraction (salt and water depletion) or poor cardiac output (congestive heart failure) have elevated concentrations of renal vasoconstrictor substances from stimulation of both the renin–angiotensin–aldosterone axis and the sympathetic nervous system, so NSAID use in these patients inhibits the synthesis of compensatory vasodilatory PGs, resulting in unopposed renal vasoconstriction and causing decreased RBF and GFR. This effect may lead to medullary ischemia and possibly acute kidney injury, particularly in elderly adults.⁷⁰ This vasoconstrictive effect is also associated with COX-2 selective inhibitors and appears to be reversible upon discontinuation of therapy.^{61,70,94}

Normal platelet function depends partly on endothelial-derived PGI₂ (largely via constitutively expressed COX-1), which blocks platelet activation and causes vasodilation, allowing blood to flow freely within vessels. At the site of vascular injury, platelets are activated by binding to collagen-bound von Willebrand factor and synthesize and release TXA₂, a potent platelet stimulator and vasoconstrictor. The antiplatelet activity of NSAIDs stems from their ability to inhibit COX-1, thereby inhibiting platelet-stimulating TXA₂ synthesis. Selective COX-2 inhibitors also decrease PGI₂ and TXA₂ synthesis but affect TXA₂ synthesis to a lesser degree, creating a more prothrombotic environment, which is the predominant theory of how selective COX-2 inhibitors increase the risk of adverse cardiovascular events (see below for further discussion).⁷⁵

Prostaglandins play a major role during the initiation of parturition. Administration of exogenous PGF_{2 α} and PGE₂ is used to induce uterine activity, and indomethacin has been used successfully as a tocolytic agent by blunting PG-mediated uterine stimulation. However, a major clinical drawback in using NSAIDs as tocolytics is their potential to cause premature constriction or closure of the ductus arteriosus in utero. Vasodilatory PGs are required to keep the fetal ductus arteriosus patent, and inhibiting these PGs causes fetal ductal constriction, leading to pulmonary hypertension and persistent fetal circulation after birth.⁵⁹

CARDIOVASCULAR RISK OF SELECTIVE CYCLOOXYGENASE-2 INHIBITORS AND NONSELECTIVE NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Atherosclerosis is a dynamic process of thrombus formation and inflammation involving numerous tissue factors and inflammatory mediators.³¹ Given the ability to inhibit synthesis of proinflammatory PGs, selective COX-2 inhibitors would be expected to be antithrombotic; however, their ability to inhibit endothelial-derived PGI₂ combined with their relative inability to inhibit platelet-activating TXA₂ (a predominantly COX-1 effect) may shift the balance toward thrombus formation.⁶⁰

In 2000, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study reported a slightly higher incidence of myocardial infarction in patients taking rofecoxib compared with those taking naproxen (0.4% vs. 0.1%). This was thought to be because of a substantial number of patients who were not taking daily aspirin but should have been (based on FDA criteria) and that naproxen may have had a cardioprotective effect.^{12,57,60}

In 2004, Merck pharmaceutical company withdrew rofecoxib from the worldwide market given the prepublication results of a study demonstrating an undisputed elevated cardiovascular risk.¹⁴ Results from a meta-analysis⁴⁴ spawned controversy within the medical literature regarding the extent of delay before the withdrawal of rofecoxib from the market.^{26,42,48,86} Several other studies addressing selective COX-2 inhibitors had similarly increased risk of adverse cardiovascular events, suggesting this to be a class effect.^{26,66,81} Valdecoxib has subsequently been removed from the market, leaving celecoxib as the only selective COX-2 inhibitor available; however, it carries an FDA alert on a possible increased cardiovascular risk.⁸¹

The data on nonselective NSAID use and cardiovascular risk remain controversial. Many of the currently published studies and meta-analyses use large databases and are unable to exclude significant confounding factors, including smoking, body mass index, chronic disease, concurrent aspirin use, and socioeconomic status.⁹¹ Some of the nonselective NSAIDs that show a trend toward elevated cardiovascular risk include diclofenac, meloxicam, indomethacin, and, to a lesser extent, ibuprofen.^{33,57,77,91} In 2005, the FDA asked manufacturers of all nonprescription NSAIDs to revise their package inserts to provide more information on the potential cardiovascular risks pending further investigation.

CLINICAL MANIFESTATIONS

NSAIDs are a heterogeneous class of drugs, some carrying a unique toxicity profile. Fortunately, most nonselective

NSAIDs behave similarly in overdose, although much of the medical literature specifically describes ibuprofen. Regardless of the particular NSAID ingested, symptoms typically manifest within 4 hours after ingestion.^{36,37,38,53,56,90}

Initial clinical manifestations are usually mild and predominantly include GI symptoms, such as nausea, vomiting, or abdominal pain, or neurologic symptoms, such as drowsiness, headache, tinnitus, blurred vision, diplopia, and dizziness. More moderate and severe findings are rare and include coma, seizures, central nervous system (CNS) depression, metabolic acidosis, hypotension, hypothermia, rhabdomyolysis, electrolyte imbalances, cardiac dysrhythmias, and acute kidney injury.^{19,36,37,53,56,58,90} Massive NSAID ingestions may lead to multisystem organ failure and death.^{21,41,79,88,95}

Neurologic Effects

The neurologic effects of NSAID use vary from the mild drowsiness, headache, and dizziness with therapeutic dosing to the more life-threatening CNS depression, coma, and seizures in overdose. The mechanism associated with the decreased level of consciousness is unknown; however, several animal studies suggest a relationship with opioid receptors, and a human case report documents a dramatic return of consciousness in a child after intravenous (IV) administration of high-dose naloxone.²⁷ Other reported neurologic manifestations of toxicity include optic neuritis, amblyopia, color blindness, transient diplopia, other visual disturbances, transient loss of hearing, acute psychosis, and cognitive dysfunction.^{39,67}

Drug-induced aseptic meningitis is reported with several NSAIDs, including tolmetin, rofecoxib, naproxen, sulindac, piroxicam, and diclofenac, but ibuprofen is more commonly implicated, perhaps because of its widespread use.⁶⁴ Clinical findings include fever and chills, headache, meningeal signs, nausea, vomiting, and altered mental status; cerebrospinal fluid findings include pleocytosis, elevated protein, and normal glucose.⁶⁴ Studies suggest an immunologic mechanism behind NSAID-induced aseptic meningitis because it appears to be more common in patients with systemic lupus erythematosus (SLE) or mixed connective tissue disease.^{39,64,67}

Muscle twitching and generalized tonic-clonic seizures are described with mefenamic acid overdose and usually occur within 7 hours after ingestion.² Seizures are also associated with ibuprofen overdose,⁶⁹ although the specific mechanism for NSAID-induced seizures is unknown.

Renal and Electrolyte Effects

Both acute overdose and chronic therapeutic dosing of NSAIDs may have deleterious effects on kidney function, most of which are reversible. These include sodium retention and edema, hyperkalemia, acute kidney injury (AKI), membranous nephropathy, nephrotic syndrome, interstitial nephritis, and both acute and chronic renal papillary necrosis.^{39,71,94} General risk factors for NSAID-induced AKI include congestive heart failure, volume depletion, diabetes mellitus, underlying kidney disease, SLE, cirrhosis, diuretic therapy, and advanced age.⁵⁴ There is also growing concern over the potential development of AKI with NSAID use in patients who are concurrently taking multiple antihypertensive medications, such as diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.⁵⁰

Acute tubulointerstitial nephritis (ATIN) is one of the more common forms of NSAID-induced renal impairment, and it may occur with short-term therapeutic dosing.^{24,54} Many cases of ATIN probably go undiagnosed because clinical symptoms usually do not appear until significant renal impairment occurs.^{24,73} Significant elevations in blood urea nitrogen (azotemia) may occur in elderly patients within 5 to 7 days of initiating NSAID therapy and usually return to baseline within 2 weeks of discontinuation.³⁴

Analgesic abuse nephropathy is a condition whose pathogenesis is not well defined, but it develops from excessive, chronic therapeutic consumption of NSAIDs. This results in AKI manifested by renal papillary necrosis, often requiring hemodialysis.^{78,94} Analgesic abuse nephropathy was originally described with the use of analgesic combinations including phenacetin and aspirin in addition to caffeine and has decreased in prevalence after the removal of phenacetin from many world markets.

Anion gap metabolic acidosis, with and without AKI, complicates many acute, massive ibuprofen ingestions and may be profound.^{25,41,95,96} The cause of the acidosis in this setting is most likely multifactorial, involving profound hypotension and tissue hypoperfusion with elevated lactate concentrations and the accumulation of ibuprofen and its two major metabolites, all weak acids.⁵³ An elevated anion gap metabolic acidosis with elevated lactate concentrations is also described after naproxen overdose, suggesting this to be a class effect given that all NSAIDs are acid derivatives.¹³

Use of NSAIDs by pregnant women is associated with reversible oligohydramnios and is used therapeutically as a treatment modality for polyhydramnios. Decreased fetal urine output and neonatal acute and chronic kidney failure, including transient oligoanuria, are associated with gestational NSAID use, commonly indomethacin.^{5,29,45}

Gastrointestinal Effects

Although the most common adverse GI effect of therapeutic NSAID use is dyspepsia, most patients with dyspepsia do not

have ulcers.²³ To help prevent the development of ulcers associated with NSAID therapy, concomitant use of misoprostol (a PGE₁ analog), an H₂-blocker, or a proton pump inhibitor (PPI) is often used; however, PPIs may be superior for both preventing and healing gastroduodenal ulcers resulting from chronic NSAID therapy.⁷² The most serious adverse GI effect is ulcer formation, which has the potential for life-threatening perforation and hemorrhage, and numerous studies reported an increased risk of these effects with therapeutic use of NSAIDs.^{32,51,68} The relative risk of developing gastroduodenal perforation, ulcer, or hemorrhage during chronic, therapeutic NSAID therapy ranges from 2.7 to 5.4, with ketorolac posing the greatest risk.^{68,87} Acute NSAID overdoses cause bloody emesis, fecal occult blood loss, and severe, life-threatening GI hemorrhage.

NSAID-induced hepatotoxicity is a well-known adverse effect that has prompted the removal of several NSAIDs from the market. Hepatotoxicity occurs with an incidence of less than 0.1% and can be quite difficult to diagnose because many patients on chronic NSAID therapy have underlying conditions, such as SLE or rheumatoid arthritis, which may cause hepatotoxicity. NSAID-induced hepatotoxicity is an idiosyncratic reaction primarily causing hepatocellular injury and does not depend on the chemical class. Diclofenac and sulindac are most commonly implicated.⁸⁵

Immunologic and Dermatologic Effects

The nonimmunologic anaphylactoid and the IgE-mediated anaphylactic reactions that are reported with the use of NSAIDs are clinically indistinguishable from one another, producing flushing, urticaria, bronchospasm, edema, and hypotension.⁷ Evidence for anaphylactic reactions includes the presence of NSAID-specific IgE antibodies, positive wheal-and-flare skin reactions, and lack of cross-reactivity with oral challenges of aspirin and other NSAIDs.⁷ The proposed mechanism of NSAID-induced anaphylactoid reactions involves the inhibition of COX-1, which not only inhibits the production of PGE₂ (which causes bronchodilation and inhibits the release of histamine from mast cells and basophils) but also shunts the AA metabolism to increased production of bronchoconstricting LTs.

The term aspirin-sensitive asthmatic is a bit of a misnomer because it refers to anaphylactoid reactions that may occur with any COX-1 inhibiting NSAID, not only aspirin.^{7,83} Selective COX-2 inhibitors cause similar clinical reactions but with an unclear mechanism. There appears to be very little cross-reactivity between NSAIDs and selective COX-2 inhibitors, and reports of reactions to one COX-2 inhibitor and not another suggest a predominant IgE-mediated mechanism.^{7,47,83}

The most common skin reactions include angioedema and facial swelling, urticaria and pruritus, bullous eruptions, and photosensitivity.³⁹ Although rare, toxic epidermal necrolysis and Stevens-Johnson syndrome are reported.³⁹

Hematologic Effects

As a class, NSAIDs are frequently implicated in the development of drug-induced thrombocytopenia and cause adverse effects on most other cell lines and function, including agranulocytosis, aplastic anemia, hemolytic anemia, methemoglobinemia, and pancytopenia.^{22,39,46,63,89} Specifically, phenylbutazone in chronic, therapeutic doses was associated with agranulocytosis and aplastic anemia,⁷⁹ prompting its removal from the US market in the 1970s. The inhibitory effect of NSAIDs on granulocyte adherence, activation, and phagocytosis, along with the potential for masking signs and symptoms, has been suggested as the mechanism responsible for the association between NSAID use and necrotizing fasciitis.⁴⁰

The ability of a particular type of NSAID to inhibit platelet aggregation and affect bleeding time depends on the dose and half-life because NSAIDs reversibly inhibit COX. One dose of ibuprofen prolongs the bleeding time within 2 hours and persists for up to 12 hours; however, this increase in bleeding time usually remains within the upper limit of normal range. This is in contrast to aspirin, which irreversibly inhibits COX, and typically doubles the bleeding time within 12 hours, returning to normal within 24 to 48 hours.⁷⁵ Compared with placebo, flurbiprofen and indobufen clinically inhibit platelet function, thereby decreasing vascular reocclusion after angioplasty and preventing thromboembolic complications.^{9,15} The concern over whether ketorolac has clinically significant effects on postoperative bleeding remains controversial.^{1,20}

NSAID use may also potentiate bleeding in patients already at higher risk. These patients include those with thrombocytopenia, coagulation factor deficiencies, or von Willebrand disease and those ingesting alcohol or on warfarin therapy.⁷⁵

Cardiovascular Effects

Although no evidence supports a direct cardiotoxic effect of NSAIDs or their metabolites, acute and massive NSAID overdoses may be complicated by persistent and severe hypotension; myocardial ischemia; and cardiac conduction abnormalities and dysrhythmias, including bradycardia, ventricular tachycardia or fibrillation, and prolonged QT

interval.^{25,41,95} The cause of these findings is yet to be elucidated, although these effects are reported only in severely ill patients with acid–base abnormalities and multisystem organ involvement (see Cardiovascular Risk earlier).

Pulmonary Effects

Although there is no evidence of direct pulmonary toxicity, some case reports describe the development of acute respiratory distress syndrome similar to the clinical manifestations of salicylate toxicity, suggesting an NSAID class mechanism based process.^{25,41,52,58} Although chest radiographic findings such as bilateral pulmonary infiltrates appear to resolve rapidly, one study reported persistent clinical abnormalities associated with exertional dyspnea one month later (see Immunologic Effects earlier).⁵⁸

Diagnostic Testing

Serum concentrations of most NSAIDs can be determined but usually only by a specialty laboratory requiring several days to report results. Although ibuprofen nomograms were constructed in an attempt to correlate serum concentrations with clinical toxicity,^{36,43} the utility of these nomograms proved limited.^{38,56}

Laboratory measurements, including complete blood count, serum electrolytes, blood urea nitrogen, and creatinine, should be obtained for all symptomatic patients, patients with intentional ingestions, ibuprofen ingestion of greater than 400 mg/kg in a child, or ibuprofen ingestion of greater than 6 g in an adult.³⁸ For patients presenting with significant neurologic effects, such as CNS depression, further evaluation of acid–base and ventilatory status by blood gas, hepatic aminotransferases, and prothrombin time should be obtained. A computed tomography scan of the head and a lumbar puncture may be clinically indicated in cases of suspected aseptic meningitis or when structural or infectious etiologies are suspected. An acetaminophen (APAP) concentration should always be determined in patients with intentional ingestions and in patients presenting with an unclear history because many people mistake APAP for NSAIDs because of confusing labeling and packaging or unawareness that they are completely different types of analgesics. For similar reasons, obtaining a salicylate concentration may also be considered.

MANAGEMENT

Management of a patient with an NSAID overdose is largely supportive and guided by the clinical signs and symptoms. Most asymptomatic patients with intentional overdose and those with normal vital signs require observation for 4 to 6 hours and a serum APAP concentration before being medically cleared. Children with ibuprofen ingestions of less than 100 mg/kg can be observed at home, but those who ingest greater than 400 mg/kg are at high risk for toxicity and require medical evaluation.³⁸ GI decontamination with activated charcoal (AC) should be considered for an asymptomatic patient with the potential for a large ingestion, symptomatic patients, and children with a history of ibuprofen ingestion greater than 400 mg/kg.^{38,49} Serum concentrations of ibuprofen continue to increase even after the time of emergency department arrival, so gastric lavage for massive overdose followed by AC should be considered, and multiple-dose AC may be useful for patients with massive overdoses of sustained-release preparations.⁹⁵

Patients who develop severe, life-threatening manifestations usually present with lethargy or unresponsiveness.^{25,41,58,69,95} Aggressive, supportive care is indicated in these patients, including stabilization of the airway and IV fluid therapy. An early electrocardiogram is essential to detect any significant electrolyte abnormalities or conduction disturbances. Electrolyte imbalances should be corrected and sodium bicarbonate therapy considered for life-threatening metabolic acidosis. Hypotension should be treated initially with IV fluid therapy followed by direct-acting vasopressors if necessary. Electrocardiograms should be monitored for the development of any life-threatening electrolyte imbalances or cardiac conduction abnormalities.

Given their high protein binding, NSAIDs do not appear to be amenable to extracorporeal removal methods; however, in cases of refractory metabolic acidosis or kidney failure, hemodialysis or continuous renal replacement therapies may be useful to correct the acid–base status.^{6,52} Patients with seizures, which are characteristic of mefenamic acid overdose,² should be treated with IV benzodiazepines.

SUMMARY

- NSAIDs are among the most commonly used drugs in the world.
- Most patients with NSAID overdoses develop nonspecific symptoms, including nausea and abdominal discomfort, requiring little clinical management other than psychiatric assessment.
- Patients with large ingestions may require GI decontamination and treatment of metabolic acidosis and kidney failure.
- In all cases of intentional NSAID ingestion, APAP coingestion should be excluded.

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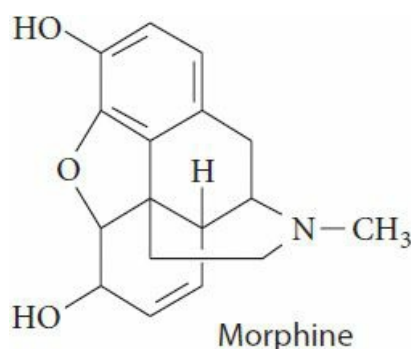
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38 OPIOIDS

Lewis S. Nelson and Dean Olsen



Opioids are among the oldest therapies in our armamentarium, and clinicians recognize their universal utility to limit human distress from pain. Opioids enjoy widespread use as potent analgesics, even though they are abused because of their psychoactive properties. Although the therapeutic and toxic doses are difficult to predict because of the development of tolerance with chronic use, the primary adverse event from excessive dosing is respiratory depression.

HISTORY AND EPIDEMIOLOGY

The medicinal value of opium, the dried extract of the poppy plant *Papaver somniferum*, was first recorded around 1500 B.C. in the Ebers papyrus. Raw opium is typically composed of at least 10% morphine, but extensive variability exists depending on the environment in which the poppy is grown.⁸⁹ Although reformulated as laudanum (deodorized tincture of opium; 10 mg morphine/mL) by Paracelsus, paregoric (camphorated tincture of opium; 0.4 mg morphine/mL), Dover's powder (pulvis Doveri), and Godfrey's cordial in later centuries, the contents remained largely the same: phenanthrene poppy derivatives, such as morphine and codeine. Over the centuries since the Ebers papyrus, opium and its components have been exploited in two distinct manners: medically to produce profound analgesia and nonmedically to produce psychoactive effects.

Currently, the widest clinical application of opioids is for acute or chronic pain relief. Opioids are available in various formulations that allow administration by virtually any route: epidural, inhalational, intranasal, intrathecal, oral, parenteral (ie, subcutaneous {SC}, intravenous {IV}, intramuscular {IM}), rectal, transdermal, and transmucosal. Patients also may benefit from several of the nonanalgesic effects engendered by certain opioids. For example, codeine and hydrocodone are widely used as antitussives, and diphenoxylate is used as an antidiarrheal.

Unfortunately, the history of opium and its derivatives is marred by humankind's endless quest for xenobiotics that produce pleasurable effects. Opium smoking was so problematic in China by the 1830s that the Chinese government attempted to prohibit the importation of opium by the British East India Company. This act led to the Opium Wars between China and Britain. China eventually accepted the importation and sale of the drug and was forced to turn over Hong Kong to British rule. The euphoric and addictive potential of the opioids is immortalized in the works of several famous writers, such as Thomas de Quincey (*Confessions of an English Opium Eater*, 1821), Samuel Coleridge (*The Rime of the Ancient Mariner*, 1798), and Elizabeth Barrett Browning (*Aurora Leigh*, 1856).

Because of mounting concerns of addiction and toxicity in the United States, the Harrison Narcotic Act, enacted in 1914, made nonmedicinal use of opioids illegal. Since that time, recreational and habitual use of heroin and other opioids have remained epidemic in the United States and worldwide despite extensive and diverse attempts to curb their availability.

Morphine was isolated from opium by Armand Séguin in 1804. Charles Alder Wright synthesized heroin from morphine in 1874. Ironically, the development and marketing of heroin as an antitussive agent by Bayer, the German pharmaceutical company, in 1898 legitimized the medicinal role of heroin.¹⁶⁵ Subsequently, various xenobiotics with opioidlike effects were marketed, each promoted for its presumed advantages over morphine. This assertion proved true for fentanyl because of its pharmacokinetic profile. However, in general, the advantages of such medications have fallen short of expectations, particularly with regard to their potential for abuse.

Prescription drug abuse (use for psychoactive effects) and misuse (eg, use of someone else's medication) is among the leading causes of death in the United States, and the opioid analgesics account for approximately 80% of these outcomes. Although media reports highlight the abuse of prescription opioids by sports figures and other personalities, such use has reached epidemic levels in regions of the country where heroin is difficult to obtain (thus the term "hillbilly heroin"). In 2009, deaths from prescription drugs, mainly opioids, first exceeded those from motor vehicle crashes.²¹ The abuse liabilities of these semisynthetic opioids, based on their subjective profile, are similar.¹⁸⁷ Although many users initially receive oxycodone or hydrocodone as analgesics, the majority of abusers obtain the drugs illicitly or from friends.^{14,67} Regulatory agencies (such as the Food and Drug Administration {FDA} through Risk Evaluation and Mitigation Strategies or REMS)¹²⁶ and individual states through prescription drug monitoring programs,¹³³ law enforcement, and the drug manufacturer have made tremendous efforts to control drug diversion to illicit use.^{64,182} Physicians and pharmacists have been charged criminally with complicity for inappropriate prescribing and dispensing, respectively, for patients with the intent to sell or abuse these drugs.⁶⁴ As supplies of the prescription opioids fall, some abusers are turning to heroin, which is easily available and less expensive, as a substitute, but carries distinct risk.²⁵

Over the past decade and along with the realization that opioid analgesics are subject to abuse and misuse, newer formulations of existing opioids have attempted to be recognized for their reduced abuse potential.²⁵ In general, this has been through the use of tamper resistant formulations that reduce the abuser's ability to crush or dissolve the tablet for insufflation or injection, respectively.¹⁴⁹ However, the true benefit of such formulations is not known, and the majority of abusers ingest their medications whole, suggesting that the overall benefit will be limited.

The terminology used in this chapter recognizes the broad range of xenobiotics commonly considered to be opiumlike. The term opiate specifically refers to the relevant alkaloids naturally derived directly from the opium poppy: morphine; codeine; and, to some extent, thebaine and noscapine. Opioids are a much broader class of xenobiotics that are capable of either producing opiumlike effects or binding to opioid receptors. A semisynthetic opioid, such as heroin or oxycodone, is created by chemical modification of an opiate. A synthetic opioid is a chemical, that is not derived from an opiate, and is capable of binding to an opioid receptor and producing opioid effects clinically. Synthetic opioids, such as methadone and meperidine, bear little structural similarity to the opiates. Opioids also include the naturally occurring animal derived opioid peptides such as endorphin and nociceptin/orphanin FQ. The term narcotic refers to sleep-inducing xenobiotics and initially was used to connote the opioids. However, law enforcement and the public currently use the term to indicate any illicit psychoactive substance. The term opioid as used hereafter encompasses the opioids and the opiates.

PHARMACOLOGY

Opioid Receptor Subtypes

Despite nearly a century of opioid studies, the existence of specific opioid receptors was not proposed until the mid-20th century. Beckett and Casy noted a pronounced stereospecificity of existing opioids (only the L-isomer is active) and postulated that the drug needed to "fit" into a receptor.⁸ In 1963, after studies on the clinical interactions of nalorphine and morphine, the theory of receptor dualism¹⁶⁷ postulated the existence of two classes of opioid receptors. Such opioid binding sites were not demonstrated experimentally until 1973.¹³⁴ Intensive experimental scrutiny using selective agonists and antagonists continues to permit refinement of receptor classification. The current, widely accepted schema postulates the coexistence of three major classes of opioid receptors, each with multiple subtypes, and several poorly defined minor classes.

Initially, the reason such an elaborate system of receptors existed was unclear because no endogenous ligand could be identified. However, evidence for the existence of such endogenous ligands was uncovered in 1975 with the discovery of met-enkephalin and leu-enkephalin¹⁰⁸ and the subsequent identification of β -endorphin and dynorphin. As a group, these endogenous ligands for the opioid receptors are called endorphins (endogenous morphine). Each is a five amino acid peptide cleaved from a larger precursor peptide: pro-enkephalin, pro-opiomelanocortin, and prodynorphin, respectively. More recently, a minor related endogenous opioid (nociceptin/orphanin FQ) and its receptor ORL have been described.

All three major opioid receptors have been cloned and sequenced. Each consists of seven transmembrane segments, an amino terminus, and a carboxy terminus. Significant sequence homology exists between the transmembrane regions of opioid receptors and those of other members of the guanosine triphosphate (GTP)-binding protein (G-protein)-binding receptor superfamily. However, the extracellular and intracellular segments differ from one another. These nonhomologous segments probably represent the ligand binding and signal transduction regions, respectively, which would be expected to differ among the three classes of receptors. The individual receptors have distinct distribution patterns within the central nervous system (CNS) and peripherally on nerve endings within various tissues, mediating unique but not entirely understood clinical effects. Until recently, researchers used varying combinations of agonists and antagonists to pharmacologically distinguish between the different receptor subtypes. However, knockout mice (ie, mutant mice lacking the genes for an individual opioid receptor) promise new insights into this complex subject.⁵⁷

Because multiple opioid receptors exist and each elicits a different effect, determining the receptor to which an opioid preferentially binds should allow prediction of the clinical effect of the opioid. However, binding typically is not limited to one receptor type, and the relative affinity of an opioid for differing receptors accounts for the clinical effects (Table 38–1). Even the endogenous opioid peptides exhibit substantial crossover among the receptors.

TABLE 38–1. Clinical Effects Related to Opioid Receptors

<i>1996 Conventional Name</i>	<i>Proposed IUPHAR Name</i>	<i>IUPHAR Name</i>	<i>Important Clinical Effects of Receptor Agonists</i>
μ_1	OP _{3a}	MOP	Supraspinal analgesia Peripheral analgesia Sedation Euphoria Prolactin release
μ_2	OP _{3b}		Spinal analgesia Respiratory depression Physical dependence Gastrointestinal dysmotility Pruritus Bradycardia Growth hormone release
κ_1	OP _{2a}	KOP	Spinal analgesia Miosis Diuresis
κ_2	OP _{2b}		Psychotomimesis Dysphoria
κ_3	OP _{2b}		Supraspinal analgesia
δ	OP ₁	DOP	Spinal and supraspinal analgesia Modulation of μ -receptor function Inhibit release of dopamine
Nociceptin/ orphanin FQ	OP ₄	NOP	Anxiolysis Analgesia

IUPHAR = International Union of Pharmacology Committee on Receptor Nomenclature.

Although the familiar pharmacologic nomenclature derived from the Greek alphabet is used throughout this textbook, the International Union of Pharmacology (IUPHAR) Committee on Receptor Nomenclature has twice recommended a nomenclature change from the original Greek symbol system to make opioid receptor names more consistent with those of other neurotransmitter systems.¹⁸⁵ In the first new schema, the receptors were denoted by their endogenous ligand (opioid peptide {OP}), with a subscript identifying their chronologic order of discovery.⁴² The δ receptor was renamed OP₁, the δ receptor was renamed OP₂, and the μ receptor was renamed OP₃. However, adoption of this nomenclature met with significant resistance, presumably because of problems that would arise when merging previously published work that had used the Greek symbol nomenclature. The currently proposed nomenclature suggests the addition of a single letter in front of the OP designation and the elimination of the number. In this schema, the μ receptor is identified as MOP. In addition, the latest iteration formally recognizes the nociceptin/orphanin FQ or NOP receptor as a fourth receptor family.

Mu Receptor (μ , MOP, OP₃). The early identification of the μ receptor as the morphine binding site gave this receptor its designation.¹¹³ Although many exogenous xenobiotics produce supraspinal analgesia via μ receptors, the endogenous ligand is elusive. Nearly all of the recognized endogenous opioids have some affinity for the μ receptor, although none is selective for the receptor. Endomorphin-1 and –2 are nonpeptide ligands present in brain that may represent the endogenous ligand.

Experimentally, two subtypes (μ_1 and μ_2) are well defined, although currently no xenobiotics have sufficient selectivity to make this dichotomy clinically relevant. Experiments with knockout mice suggest that both subtypes derive from the same gene and that either posttranslational changes or local cellular effects subsequently differentiate them. The μ_1 subtype appears to be responsible for supraspinal (brain) analgesia and for the euphoria engendered by these xenobiotics. Although stimulation of the μ_2 subtype produces spinal-level analgesia, it also produces respiratory depression. All of the currently available μ agonists have some activity at the μ_2 receptor and therefore produce some degree of respiratory compromise. Localization of μ receptors to regions of the brain involved in analgesia (periaqueductal gray, nucleus raphe magnus, medial thalamus), euphoria and reward (mesolimbic system), and respiratory function (medulla) is not unexpected.⁷³ Predictably, μ receptors are found in the medullary cough center; peripherally in the gastrointestinal (GI) tract; and on various sensory nerve endings, including the articular surfaces (see analgesia under Clinical Manifestations below).

Kappa Receptor (κ , KOP, OP_2). Although dynorphins now are known to be the endogenous ligands for these receptors, originally they were identified by their ability to bind ketocyclazocine and thus were labeled δ .¹¹³ Receptors exist predominantly in the spinal cords of higher animals, but they also are found in the antinociceptive regions of the brain and the substantia nigra. Stimulation is responsible for spinal analgesia, miosis, and diuresis (via inhibition of antidiuretic hormone release). Unlike μ -receptor stimulation, δ -receptor stimulation is not associated with significant respiratory depression or constipation. The receptor currently is subclassified into three subtypes. The δ_1 receptor subtype is responsible for spinal analgesia. This analgesia is not reversed by μ -selective antagonists,¹²⁰ supporting the role of δ receptors as independent mediators of analgesia. Although the function of the δ_2 receptor subtype is largely unknown, stimulation of cerebral δ_2 receptors by xenobiotics such as pentazocine and salvinorin A produces psychotomimesis in distinction to the euphoria evoked by μ agonists.¹⁵⁸ The δ_3 receptor subtype is found throughout the brain and participates in supraspinal analgesia. This receptor is primarily responsible for the action of nalorphine, an agonist–antagonist opioid. Nalbuphine, another agonist–antagonist, exerts its analgesic effect via both δ_1 and δ_3 agonism, although both nalorphine and nalbuphine are antagonists to morphine at the μ receptor.¹³⁶

Delta Receptor (δ , DOP, OP_1). Little is known about δ receptors, although the enkephalins are known to be their endogenous ligands. Opioid peptides identified in the skin and brain of *Phyllomedusa* frogs, termed dermorphin and deltorphin, respectively, are potent agonists at the δ receptor. δ Receptors may be important in spinal and supraspinal analgesia (probably via a noncompetitive interaction with the μ receptor) and in cough suppression. δ Receptors may mediate dopamine release from the nigro-striatal pathway, where they modulate the motor activity associated with amphetamine.⁷⁴ δ Receptors do not modulate dopamine in the mesolimbic tracts and have only a slight behavioral reinforcing role. Subpopulations, specifically δ_1 and δ_2 , are postulated based on in vitro studies but presently are not confirmed in vivo.¹⁸⁵

Nociceptin/Orphanin FQ Receptor (ORL_1 , NOP, OP_4). The ORL_1 receptor was identified in 1994 based on sequence homology during screening for opioid-receptor genes with DNA libraries. It has a similar distribution pattern in the brain and uses similar transduction mechanisms as the other opioid-receptor subtypes. It binds many different opioid agonists and antagonists. Its insensitivity to antagonism by naloxone, often considered the sine qua non of opioid character, delayed its acceptance as an opioid-receptor subtype. Simultaneous identification of an endogenous ligand, called nociceptin by the French discoverers and orphanin FQ by the Swiss investigators, allowed the designation OP_4 . A clinical role has not yet been defined, but anxiolytic and analgesic properties are described.²⁹

Opioid-Receptor Signal Transduction Mechanisms

Figure 38–1 illustrates opioid-receptor signal transduction mechanisms. Continuing research on the mechanisms by which an opioid receptor induces an effect has produced confusing and often contradictory results. Despite the initial theory that each receptor subtype is linked to a specific transduction mechanism, individual receptor subtypes may use one or more mechanisms, depending on several factors, including receptor localization (eg, presynaptic vs postsynaptic). As noted, all opioid-receptor subtypes are members of a superfamily of membrane-bound receptors that are coupled to G proteins.¹⁸⁵ The G proteins are responsible for signaling the cell that the receptor is activated and for initiating the desired cellular effects. The G proteins are generally of the pertussis toxin-sensitive, inhibitory subtype known as G_i or G_o , although coupling to a cholera toxin-sensitive, excitatory G_s subtype has been described. Regardless of subsequent effect, the G proteins consist of three conjoined subunits, α , β , and γ . The $\beta\gamma$ subunit is liberated upon GTP binding to the subunit. When the α subunit dissociates from the $\beta\gamma$ subunit, it modifies specific effector systems, such as phospholipase C or adenylate cyclase, or it may directly affect a channel or transport protein. GTP subsequently is hydrolyzed by a GTPase intrinsic to the α subunit, which prompts its reassociation with the $\beta\gamma$ subunit and termination of the receptor-mediated effect.

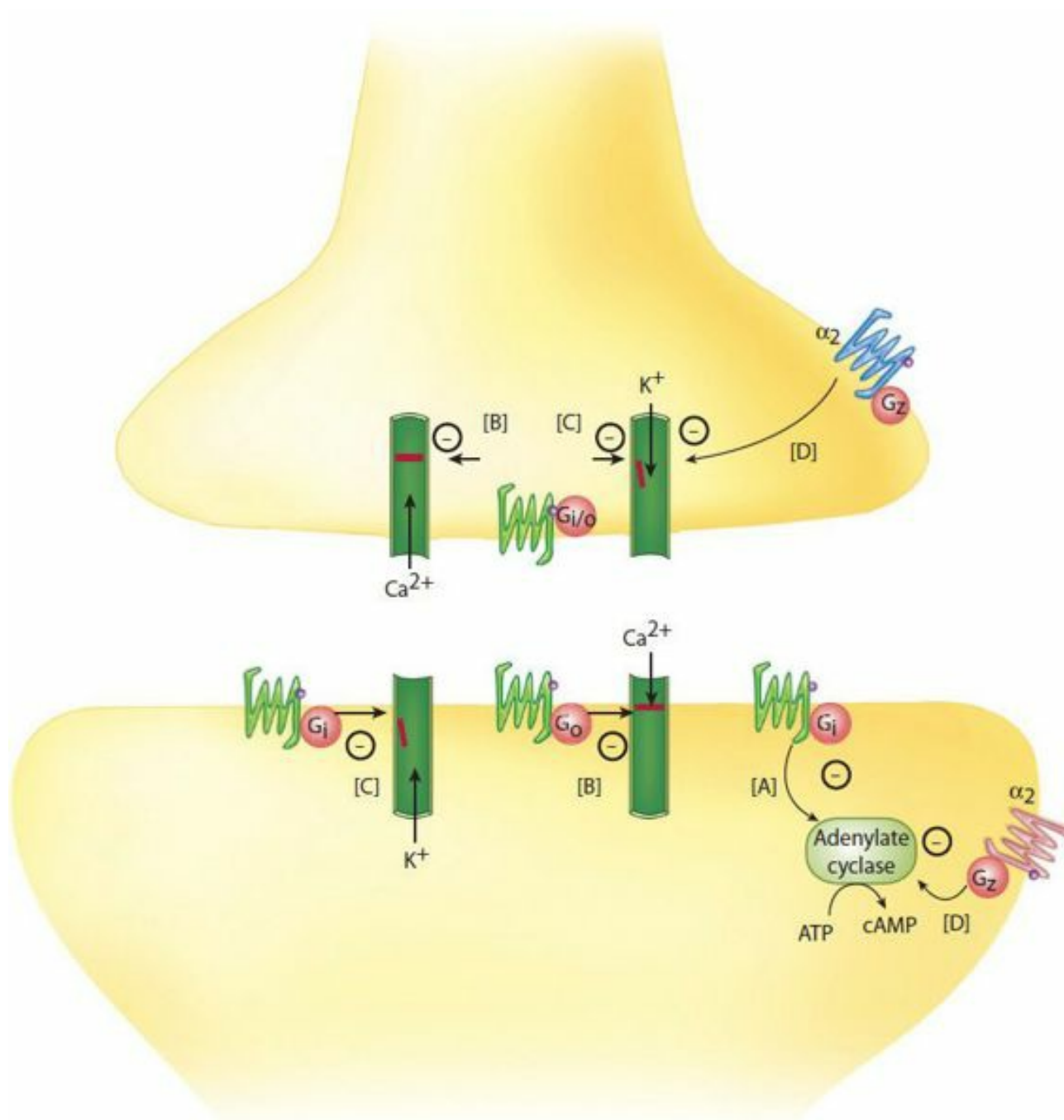


FIGURE 38–1. Opioid-receptor signal transduction mechanisms. Upon binding of an opioid agonist to an opioid receptor, the respective G protein is activated. G proteins may reduce the capacity of adenylate cyclase to produce cyclic adenosine monophosphate (cAMP) (A); close calcium channels that reduce the signal to release neurotransmitters (B); or open potassium channels and hyperpolarize the cell, which indirectly reduces cell activity (C). Each mechanism has been found coupled to each receptor subtype, depending on the location of the receptor (pre- or postsynaptic), and the neuron within the brain (see text). Note that α_2 receptors (D) mediate similar effects, using a different G protein (G_z).

(A) Adenylate cyclase/cAMP. Inhibition of adenylate cyclase activity by G_i or G_o is the classic mechanism for postsynaptic signal transduction invoked by the inhibitory μ receptors. However, this same mechanism also has been identified in cells bearing either δ or δ receptors. Activation of cAMP production by adenylate cyclase, with subsequent activation of protein kinase A, occurs after exposure to very-low-dose opioid agonists and produces excitatory, antianalgesic effects.⁴⁴

(B) Calcium (Ca^{2+}) channels. Presynaptic μ receptors inhibit norepinephrine release from the nerve terminals of cells of the rat cerebral cortex. Adenylate cyclase does not appear to be the modulator for these receptors because inhibition of norepinephrine release is not enhanced by increasing intracellular cAMP levels by various methods. Opioid-induced blockade is, however, prevented by increased intracellular calcium levels that are induced either by calcium ionophores, which increase membrane permeability to calcium, or by increasing the extracellular calcium concentration. This implies a role for opioid-induced closure of N-type calcium channels, presumably via a G_o protein. Reduced intraterminal concentrations of calcium prevent the neurotransmitter-laden vesicles from binding to the terminal membrane and releasing their contents. Nerve terminals containing dopamine appear to have an analogous relationship with inhibitory δ receptors, as do acetylcholine-bearing neurons with opioid receptors.

(C) Potassium (K^+) channels. Increased conductance through a potassium channel, generally mediated by G_i or G_o , results

in membrane hyperpolarization with reduced neuronal excitability. Alternatively, protein kinase A mediated reduction in membrane potassium conductance enhances neuronal excitability. ATP = adenosine triphosphate.

CLINICAL MANIFESTATIONS

Table 38–2 outlines the clinical effects of opioids.

TABLE 38–2. Clinical Effects of Opioids

Cardiovascular	Bradycardia Orthostatic hypotension Peripheral vasodilation
Dermatologic	Flushing (histamine) Pruritus
Endocrinologic	Reduced antidiuretic hormone release Increased prolactin release Reduced gonadotrophin release
Gastrointestinal	Increased anal sphincter tone Increased biliary tract pressure Reduced gastric acid secretion Reduced motility
Neurologic	Analgesia Antitussive Euphoria Sedation, coma Seizures (meperidine, propoxyphene)
Ophthalmic	Miosis
Pulmonary	Acute respiratory distress syndrome Bronchospasm (histamine) Respiratory depression

Therapeutic Effects

Analgesia. Although classic teaching attributes opioid analgesia solely to the brain, opioids actually appear to modulate cerebral cortical pain perception at supraspinal, spinal, and peripheral levels. The regional distribution of the opioid receptors confirms that μ receptors are responsible for most of the analgesic effects of morphine within the brain. They are found in highest concentration within areas of the brain classically associated with analgesia—the periaqueductal gray, nucleus raphe magnus, locus ceruleus, and medial thalamus. Microelectrode-induced electrical stimulation of these areas¹⁴¹ or iontophoretic application of agonists into these regions results in profound analgesia.¹⁰ Specifically, enhancement of inhibitory outflow from these supraspinal areas to the sensory nuclei of the spinal cord (dorsal roots) dampens nociceptive neurotransmission. Additionally, inactivation of the μ opioid receptor gene in embryonic mouse cells results in offspring that are insensitive to morphine analgesia.¹¹⁴

Interestingly, blockade of the N-methyl-D-aspartate (NMDA) receptor, a mediator of excitatory neurotransmission, enhances the analgesic effects of μ opioid agonists and may reduce the development of tolerance (see dextromethorphan later).¹ Even more intriguing is the finding that low dose naloxone (0.25 $\mu\text{g/kg/h}$) actually improves the efficacy of morphine analgesia.⁵⁴ Administration of higher dose, but still low dose, naloxone (1 $\mu\text{g/kg/h}$) obliterated its opioid-sparing effect. Although undefined, the mechanism may be related to selective inhibition of G_s -coupled excitatory opioid receptors by extremely low concentrations of opioid receptor antagonist.^{31,32}

Xenobiotics with strong binding affinity for δ receptors in humans produce significantly more analgesia than morphine administered intrathecally. Indeed, the use of spinal and epidural opioid analgesia is predicated on the direct administration of opioid near the δ and δ receptors in the spinal cord. Agonist–antagonist opioids, with agonist affinity for the δ receptor and antagonist effects at the μ receptor, maintain analgesic efficacy.

Interestingly, communication between the immune system and the peripheral sensory nerves occurs in areas of tissue inflammation. In response to inflammatory mediators, such as interleukin-1, immune cells locally release opioid peptides, which bind and activate peripheral opioid receptors on sensory nerve terminals.¹⁸⁶ Agonism at these receptors reduces afferent pain neurotransmission and may inhibit the release of other proinflammatory compounds, such as substance P.¹⁶⁸ Of note, intraarticular morphine (1 mg) administered to patients after arthroscopic knee surgery produces significant, long lasting analgesia that can be prevented with intraarticular naloxone.¹⁶⁹ The clinical analgesic effect of 5 mg of intraarticular morphine is equivalent to 5 mg of morphine given IM.²⁴ Intraarticular analgesia is locally mediated by μ receptors.⁵⁰

The data to support the safety and efficacy of opioids for the management of chronic pain are limited. Addiction and dependence, which share a complicated relationship and often overlap with pain and depression, occur in at least 5% of patients using classical definitions, but other studies suggest it may be as high as 30%.¹²³ The pleasurable effects of many xenobiotics used by humans are mediated by the release of dopamine in the mesolimbic system. This final common pathway is shared by all opioids that activate the μ - δ receptor complex in the ventral tegmental area, which, in turn, indirectly promotes dopamine release in the mesolimbic region. Opioids also may have a direct reinforcing effect on their self administration through μ receptors within the mesolimbic system.⁷²

The sense of well being and euphoria associated with strenuous exercise appears to be mediated by endogenous opioid peptides and μ receptors. This so-called “runner’s high” is reversible with naloxone.¹⁵⁶ Naloxone may also reverse euphoria or even produce dysphoria in nonexercising, highly trained athletes. Even in normal individuals, high dose naloxone (4 mg/kg) may produce dysphoria.²⁶

Exogenous opioids do not induce uniform psychological effects. Some of the exogenous opioids, particularly those that are highly lipophilic such as heroin, are euphorogenic, but morphine is largely devoid of such pleasurable effects.¹⁶³ However, morphine administration results in analgesia, anxiolysis, and sedation. Because heroin has little affinity for opioid receptors and must be deacetylated to morphine for effect, these seemingly incompatible properties likely are related to pharmacokinetic differences in blood–brain barrier penetration.¹³⁰ Chronic users note that fentanyl produces effects that are subjectively similar to those of heroin.¹⁰² This effect may explain the higher prevalence of fentanyl, as opposed to other accessible opioids, as an abused drug by anesthesiologists.^{12,189} In distinction, certain opioids, such as pentazocine, produce dysphoria, an effect that is related to their affinity for δ or σ receptors.

Chronic use of opioid analgesics is associated with hyperalgesia, or a heightened sensitivity to pain.²⁷ This effect was described decades ago in methadone maintenance patients⁷⁶ and has been revisited as the use of chronic opioid therapy for pain has increased.¹⁸ Hyperalgesia may be part of the development of tolerance or the need for increasing amount of opioid to maintain a stable level of analgesia, but the treatment for hyperalgesia should include attempts at alternative modalities of pain relief.

Antitussive. Codeine and dextromethorphan are two opioids with cough suppressant activity. Cough suppression is not likely mediated via the μ_1 opioid receptor because the ability of other opioids to suppress the medullary cough centers is not correlated with their analgesic effect. Various models suggest that cough suppression occurs via agonism of the μ_2 or δ opioid receptors or antagonism of the δ opioid receptor and that the σ or NMDA receptors also are involved.¹⁷⁵

Toxic Effects

When used appropriately for medical purposes, opioids are generally safe and effective. However, excessive dosing for any reason may result in serious toxicity. Most adverse or toxic effects are predictable based on opioid pharmacodynamics (eg, respiratory depression), although several xenobiotics produce unexpected “nonopioid” or xenobiotic-specific responses. Determining that a patient has an opioid toxicity is generally more important than identifying the specific opioid involved. Notwithstanding some minor variations, patients poisoned by all available opioids predictably develop a constellation of signs, known as the opioid syndrome (**Chap. 3**). Mental status depression, hypoventilation, miosis, and hypoperistalsis are the classic elements.

Respiratory Depression. Experimental use of various opioid agonists and antagonists consistently implicates μ_2 receptors in the respiratory depressant effects of morphine.¹⁵⁸ Through these receptors, opioid agonists reduce ventilation by diminishing the sensitivity of the medullary chemoreceptors to hypercapnea.¹⁹² In addition to loss of hypercarbic stimulation, opioids depress the ventilatory response to hypoxia.¹⁰³ The combined loss of hypercarbic and hypoxic drive leaves virtually no stimulus to breathe, and apnea ensues. Equianalgesic doses of the available opioid agonists produce approximately the same degree of respiratory depression.^{47,159} This reasoning is supported by experiments in MOR deficient knockout mice.¹⁴⁵ Patients chronically exposed to opioid agonists, such as those on methadone maintenance, experience chronic hypoventilation, although tolerance to loss of hypercarbic drive may develop over several months.¹¹¹ However, such patients never develop complete tolerance to loss of hypoxic stimulation.¹⁴⁷ Although some opioids, notably the agonist–antagonists and partial agonists, typically demonstrate a ceiling effect on respiratory depression, such sparing generally occurs at the expense of analgesic potency and is incomplete. The different activity profiles likely are a

result of differential activities at the opioid-receptor subtypes; that is, agonist–antagonists are predominantly δ -receptor agonists and either partial agonists or antagonists at μ sites.

It is important to recognize that ventilatory depression may be secondary to a reduction in either respiratory rate or tidal volume. Thus, although respiratory rate is more accessible for clinical measurement, it is not an ideal index of ventilatory depression. In fact, morphine-induced respiratory depression in humans initially is related more closely to changes in tidal volume.¹⁵⁹ Large doses of opioids also result in a reduction of respiratory rate.

Respiratory depression is the primary cause of death after therapeutic use or misuse. Common reasons for iatrogenic overdose include not appreciating the importance of genetic polymorphisms (see Codeine), sleep apnea, drug interactions, active metabolites (see Morphine), or the complicated pharmacokinetics of the long-acting and sustained-release opioids.¹²⁸

Acute Respiratory Distress Syndrome (ARDS). Reports linking opioids with the development of acute pulmonary abnormalities became common in the 1960s, although the first report was made by William Osler in 1880.¹³² Almost all opioids are implicated, and opioid-related acute respiratory distress syndrome is reported in diverse clinical situations. Typically, the patient regains normal ventilation after a period of profound respiratory depression, either spontaneously or after the administration of an opioid antagonist, and over the subsequent several minutes to hours develops hypoxemia and pulmonary crackles. Occasionally, classic frothy, pink sputum is present in the patient's airway or in the endotracheal tube of an intubated patient. Decedents often have what is described as a "foam cone" of frothy material extruding from their noses and mouths. Acute lung injury (ALI) was described in 71 (48%) of 149 hospitalized heroin overdose patients in New York City,⁴⁵ although the current incidence in this patient group appears to be lower. The outcome generally depends on comorbid conditions and the delay to adequate care. ALI may be an isolated finding or may occur in the setting of multisystem organ damage.

No single mechanism can be consistently invoked in the genesis of opioid associated ARDS. However, several prominent theories are each well supported by experimental data. Rather than causing ARDS, naloxone likely "uncovered" the clinical findings of ARDS that were not evident because an adequate examination could not be performed until breathing is restored. Other evidentiary cases involve surgical patients given naloxone postoperatively who subsequently awoke with clinical signs of pulmonary edema. In addition to presumably receiving the naloxone for ventilatory compromise or hypoxia, these patients received multiple intraoperative medications, further obscuring the etiology.¹³⁷ Although naloxone ordinarily is safe when appropriately administered to nonopioid tolerant individuals, the production of acute opioid withdrawal may be responsible for "naloxone-induced" ARDS. In this situation, as in patients with "neurogenic" pulmonary edema, massive sympathetic discharge from the CNS occurs and produces "cardiogenic" pulmonary edema from the acute effects of catecholamines on the myocardium. In an interesting series of experiments, precipitated opioid withdrawal in nontolerant dogs was associated with dramatic cardiovascular changes and abrupt elevation of serum catecholamine concentrations.^{121,122} The effects were more dramatic in dogs with an elevated PCO₂ than in those with a normal or low PCO₂, suggesting the potential benefit of adequately ventilating patients before opioid reversal with naloxone. Similar effects occur in humans undergoing ultrarapid opioid detoxification (UROD; see later discussion).⁴⁹

Even though abrupt precipitation of withdrawal by naloxone may contribute to the development of ARDS, it cannot be the sole etiology. Alveolar filling was noted in 50% to 90% of the postmortem examinations performed on heroin overdose patients, many of whom were declared dead before arrival to medical care and thus never received naloxone.^{71,75} In addition, neither naloxone nor any other opioid antagonist was available when Osler and others described their initial cases of "pulmonary edema." Alternatively, the negative intrathoracic pressure generated by attempted inspiration against a closed glottis creates a large pressure gradient across the alveolar membrane and draws fluid into the alveolar space. This mechanical effect, also known as the Müller maneuver, was invoked as the cause of ventilator-associated ARDS before the advent of demand ventilators and neuromuscular blockers. In the setting of opioid poisoning, glottic laxity may prevent adequate air entry during inspiration. This effect may be especially prominent at the time of naloxone administration, in which case breathing may be reinstituted before the return of adequate upper airway function.

Cardiovascular. Arteriolar and venous dilation secondary to opioid use may result in a mild reduction in blood pressure.¹⁹⁰ This effect is clinically useful for treatment of patients with acute cardiogenic pulmonary edema. However, although patients typically do not develop significant supine hypotension, orthostatic changes in blood pressure and pulse routinely occur. A reduction in heart rate is common as a result of the associated reduction in CNS stimulation. Opioid induced hypotension appears to be mediated by histamine release, although induction of histamine release does not appear to occur through interaction with an opioid receptor. It may be related to the nonspecific ability of certain xenobiotics to activate mast cell G-proteins,⁷ which induce degranulation of histamine containing vesicles. Many opioids share this ability, which seems to be conferred by the presence of a positive charge on a hydrophobic molecule. Accordingly, not all opioids are equivalent in their ability to release histamine.⁷ After administration of one of four different opioids to 60 healthy patients, meperidine produced the most hypotension and elevation of serum histamine concentrations; fentanyl produced the least.⁵³ The combination of H₁ and H₂ antagonists is effective in ameliorating the hemodynamic effects of

opioids in humans.¹³⁵

Adulterants or coingestants may produce significant cardiovascular toxicity. For example, quinine adulterated heroin is associated with dysrhythmias. Cocaine, surreptitiously added to heroin, may cause significant myocardial ischemia or infarction. Similarly, concern that naloxone administration may “unmask” cocaine toxicity in patients simultaneously using cocaine and heroin (“speedball”) probably is warranted but rarely is demonstrated unequivocally.

Certain opioids at therapeutic concentrations, particularly methadone, may interfere with normal cardiac repolarization and produce QT interval prolongation, an effect that predisposes to the development of torsade de pointes.^{99,127} Many patients who receive methadone experience minor increases in QT interval, although a small percentage of patients experience a substantial increase to more than 500 msec.⁹⁹ Methadone and levo- α -acetylmethadol (LAAM) both prolong the QT interval via interactions with cardiac K⁺ channels.⁹³ Additionally, certain opioids, primarily propoxyphene (which was recently removed from the US market), may alter the function of myocardial Na⁺ channels in a manner similar to that of the antidysrhythmics (Chap. 64).

Miosis. Stimulation of parasympathetic pupilloconstrictor neurons in the Edinger-Westphal nucleus of the oculomotor nerve by morphine produces miosis. Additionally, morphine increases firing of pupilloconstrictor neurons to light,¹⁰⁶ which increases the sensitivity of the light reflex through central reinforcement.¹⁹³ Although sectioning of the optic nerve may blunt morphine-induced miosis, the consensual reflex in the denervated eye is enhanced by morphine. Because opioids classically mediate inhibitory neurotransmission, hyperpolarization of sympathetic nerves or of inhibitory neurons to the parasympathetic neurons (removal of inhibition) ultimately may be found to mediate the classic “pinpoint pupil” associated with opioid use.

Not all patients using opioids present with miosis. Meperidine has a lesser miotic effect than other conventional opioids, and propoxyphene use does not result in miosis.⁵⁹ Use of opioids with predominantly δ -agonist effects, such as pentazocine, may not result in miosis. Mydriasis may occur in severely poisoned patients secondary to hypoxic brain insult. Additionally, concomitant drug abuse or the presence of adulterants may alter pupillary findings. For example, the combination of heroin and cocaine (“speedball”) may produce virtually any size pupil, depending on the relative contribution by each xenobiotic. Similarly, patients ingesting diphenoxylate and atropine (Lomotil) or those using scopolamine adulterated heroin typically develop mydriasis.⁶⁸

Seizures. Seizures are a rare complication of therapeutic use of most opioids. In patients with acute opioid overdose, seizures most likely are caused by hypoxia. However, experimental models demonstrate a proconvulsant effect of morphine in that it potentiates the convulsant effect of other xenobiotics.¹⁹⁸ These effects are variably inhibited by naloxone, suggesting the involvement of a mechanism other than opioid receptor binding. In humans, morphine-induced seizures are reported in neonates and are reversed by naloxone,³⁴ although opioid withdrawal seizures in neonates are more common.

Seizures should be anticipated in patients with meperidine, propoxyphene, tapentadol, or tramadol toxicity. Naloxone antagonizes the convulsant effects of propoxyphene in mice, although it is only moderately effective in preventing seizures resulting from meperidine or its metabolite normeperidine.⁶⁰ Interestingly, naloxone potentiates the anticonvulsant effects of benzodiazepines and barbiturates, but in a single study, it antagonized the effects of phenytoin.⁸⁵ The ability of fentanyl and its analogs to induce seizures is controversial. They are used to activate epileptiform activity for localization in patients with temporal lobe epilepsy who are undergoing surgical exploration.¹¹⁷ However, electroencephalography (EEG) performed on patients undergoing fentanyl anesthesia did not identify seizure activity even though the clinical assessment suggested that approximately one-third of them had seizures.¹⁶⁴ It appears likely that the rigidity and myoclonus associated with fentanyl use are readily misinterpreted as a seizure.

Movement Disorders. Patients may experience acute muscular rigidity with rapid IV injection of certain high potency opioids, especially fentanyl and its derivatives.¹⁷³ This condition is particularly prominent during induction of anesthesia and in neonates.⁵² The rigidity primarily involves the trunk and may impair chest wall movement sufficiently to exacerbate hypoventilation. Chest wall rigidity may have contributed to the lethality associated with epidemics of fentanyl adulterated or fentanyl substituted heroin. Although the mechanism of muscle rigidity is unclear, it may be related to blockade of dopamine receptors in the basal ganglia. Other postulated mechanisms include γ -aminobutyric acid (GABA) antagonism and NMDA agonism. Opioid antagonists generally are therapeutic but may produce adverse hemodynamic effects, withdrawal phenomena, or uncontrollable pain, depending on the situation.⁵² Although not a problem for patients taking stable doses of methadone, rapid escalation of methadone doses may produce choreoathetoid movements.¹¹

Gastrointestinal Effects. Historically, the morphine analog apomorphine was used as a rapidly acting emetic whose clinical use was limited by its tendency to depress the patient’s level of consciousness. Emesis induced by apomorphine is mediated through agonism at D₂ receptor subtypes within the chemoreceptor trigger zone of the medulla. Many opioids, particularly morphine, produce significant nausea and vomiting when used therapeutically.²³ Whether these effects are inhibited by naloxone is not clearly established, but they likely are not.

Although diphenoxylate and loperamide are widely used therapeutically to manage diarrhea, opioid-induced constipation is most frequently a bothersome side effect of both medical and nonmedical use of opioids. Constipation,

mediated by μ_2 receptors within the smooth muscle of the intestinal wall,⁸⁰ is ameliorated by oral naloxone. Provided the first pass hepatic glucuronidative capacity is not exceeded (at doses of ~6 mg), enteral naloxone is poorly bioavailable and thus induces few, if any, opioid withdrawal symptoms.¹¹⁹ Methylnaltrexone and alvimopan are bioavailable, “peripherally restricted” opioids that cannot cross the blood brain barrier. Although they antagonize the effects of opioids on the GI tract opioid receptor,^{17,200} opioid withdrawal does not occur¹¹⁸ (Antidotes in Depth: A4).

Endocrine Effects. Chronic use of opioids is associated with hypofunction of the hypothalamic pituitary gonadal axis by binding to hypothalamic opioid receptors and decreasing the secretion of gonadotropin releasing hormone.¹⁵ Clinical findings include reduced libido, erectile dysfunction, hot flashes, and depression, as well as anemia, hair loss, and osteopenia.¹⁵⁴ Additionally, both men and women may have infertility. Furthermore, opioids reduce the release of corticotropin-releasing hormone from the hypothalamus, leading to a reduction of adrenocorticotrophic hormone (ACTH) release from the pituitary. This reduces adrenal function, and clinically relevant adrenal insufficiency may occur.¹⁵ In addition, prolactin concentrations commonly rise and may lead to gynecomastia.¹⁴⁰

Hearing Loss. Although relatively rare, rapidly progressive sensorineural hearing loss may occur in heavy users of opioid analgesics.⁷⁷ This effect has been associated with most opioids, including hydrocodone, oxycodone, and methadone. The mechanism remains unknown, and suggested causes include ischemia, genetic predisposition, direct cochlear toxicity, and hypersensitization that manifests upon re-exposure after a period of opioid abstinence.¹⁵⁷ Most patients recover after abstinence, although some are only successfully treated with cochlear implants (Chap. 26).⁷⁷

DIAGNOSTIC TESTING

Laboratory Considerations

Opioid-poisoned patients are particularly appropriate for a rapid clinical diagnosis because of the unique characteristics of the opioid toxic syndrome. Additionally, even in situations in which the assay results are available rapidly, the fact that several distinct classes of opioids and nonopioids can produce similar opioid effects limits the use of laboratory tests, such as immunoassays, that rely on structural features to identify xenobiotics. Furthermore, because opioids may be chemically detectable long after their clinical effects have dissipated, assay results cannot be considered in isolation but rather viewed in the clinical context. Several well-described problems with laboratory testing of opioids are described here and in Chap. 6.

Cross-Reactivity. Many opioids share significant structural similarities, such as morphine and oxycodone or methadone and propoxyphene, but they do not necessarily share the same clinical characteristics (Fig. 38–2). Because most clinical assays depend on structural features for identification, structurally similar xenobiotics may be detected in lieu of the desired one. Whether a similar xenobiotic is noted by the assay depends on the sensitivity and specificity of the assay and the serum concentration of the xenobiotic. Some cross-reactivities are predictable, such as that of oxycodone with morphine, on a variety of screening tests. Other cross-reactivities are less predictable, as in the case of the cross-reaction of dextromethorphan and the phencyclidine (PCP) component of the fluorescence polarization immunoassay (Abbott TDx),¹⁵⁰ a widely used drug abuse screening test (Chap. 6).¹⁷⁰

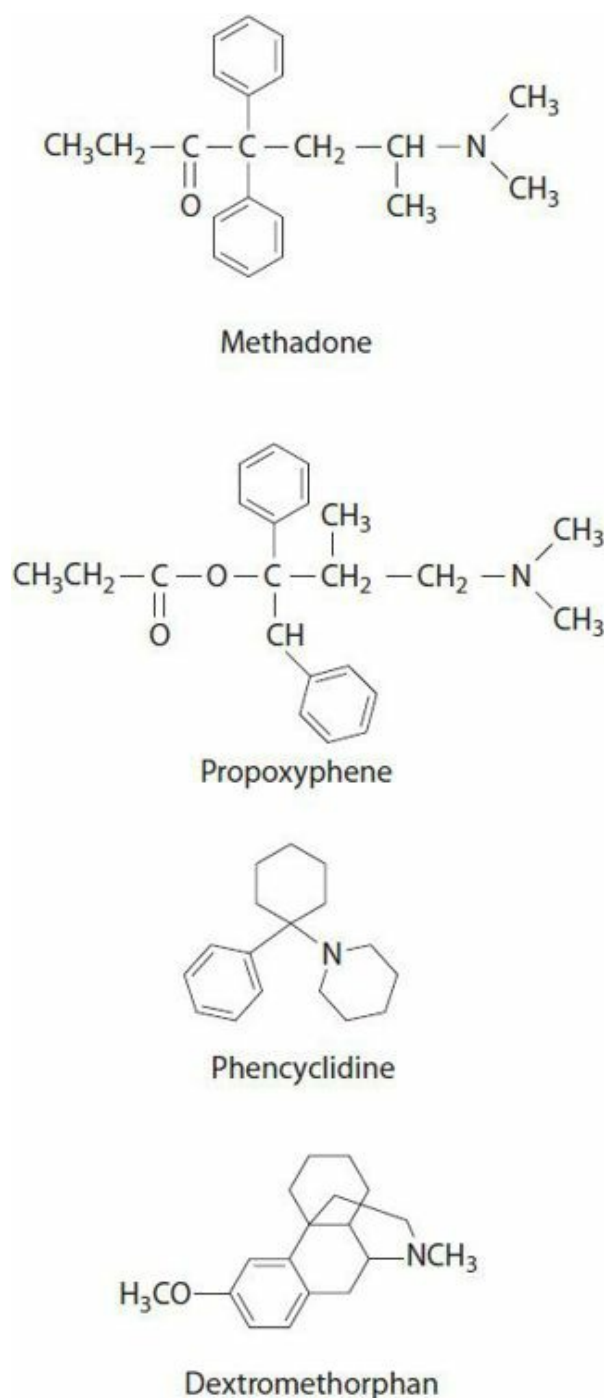


FIGURE 38–2. The figure demonstrates the structural similarities between methadone and propoxyphene and between phencyclidine and dextromethorphan.

Congeners and Adulterants. Commercial opioid assays, which are specific for morphine, will not readily detect most of the semisynthetic and synthetic opioids. In some cases, epidemic fatalities involving fentanyl derivatives remained unexplained despite obvious opioid toxicity until the ultrapotent fentanyl derivative α -methylfentanyl (although initially misidentified as 3-methylfentanyl) was identified by more sophisticated testing.^{98,113} Oxycodone, hydrocodone, and other common morphine derivatives have variable detectability by different opioid screens and generally only when in high concentrations.¹¹⁰

Drug Metabolism. A fascinating dilemma may arise in patients who ingest moderate to large amounts of poppy seeds.⁹⁶ These seeds, which are widely used for culinary purposes, are derived from poppy plants and contain both morphine and codeine. After ingestion of a single poppy seed bagel, patients may develop elevated serum morphine and codeine concentrations and test positive for morphine.^{124,144} Because the presence of morphine on a drug abuse screen may suggest illicit heroin use, the implications are substantial. Federal workplace testing regulations thus require corroboration of a positive morphine assay with assessment of another heroin metabolite, 6-monoacetylmorphine, before reporting a positive result.^{125,184} Humans cannot acetylate morphine and therefore cannot synthesize 6-monoacetylmorphine, but humans can readily deacetylate heroin, which is diacetylmorphine.

A similar problem may occur in patients taking therapeutic doses of codeine. Because codeine is demethylated to morphine by CYP2D6, a morphine screen may be positive as a result of metabolism and not structural cross-reactivity.⁵⁶ Thus, determination of the serum codeine or 6-monoacetylmorphine concentration is necessary in these patients.

Determination of the serum codeine concentration is not foolproof, however, because codeine is present in the opium preparation used to synthesize heroin.

Forensic Testing. Decision making regarding the cause of death in the presence of systemic opioids often is complex.³⁶ Variables that often are incompletely defined contribute substantially to the difficulty in attributing or not attributing the cause of death to the opioid. These variables include the specifics regarding the timing of exposure, the preexisting degree of sensitivity or tolerance, the role of cointoxicants (including parent opioid metabolites), and postmortem redistribution and metabolism.^{44,92} Interesting techniques to help further elucidate the likely cause of death that have been studied include the application of postmortem pharmacogenetic principles⁸⁶ and the use of alternative specimens ([Chap. 34](#)).

MANAGEMENT

The consequential effects of acute opioid poisoning are CNS and respiratory depression. Although early support of ventilation and oxygenation is generally sufficient to prevent death, prolonged use of bag-valve-mask ventilation and endotracheal intubation may be avoided by cautious administration of an opioid antagonist. Opioid antagonists, such as naloxone, competitively inhibit binding of opioid agonists to opioid receptors, allowing the patient to resume spontaneous respiration. Naloxone competes at all receptor subtypes, although not equally, and is effective at reversing almost all adverse effects mediated through opioid receptors (Antidotes in Depth: A4).

Because many clinical findings associated with opioid poisoning are nonspecific, the diagnosis requires clinical acumen. Differentiating acute opioid poisoning from other etiologies with similar clinical presentations may be challenging. Patients manifesting opioid toxicity, those found in an appropriate environment, or those with characteristic physical clues such as fresh needle marks require little corroborating evidence. However, subtle presentations of opioid poisoning may be encountered, and other entities superficially resembling opioid poisoning may occur. Hypoglycemia, hypoxia, and hypothermia may result in clinical manifestations that share features with opioid poisoning and may exist concomitantly. Each can be rapidly diagnosed with routinely available, point-of-care testing, but their existence does not exclude opioid toxicity. Other xenobiotics responsible for similar clinical presentations include clonidine, PCP, phenothiazines, and sedative-hypnotics (primarily benzodiazepines). In such patients, clinical evidence usually is available to assist in diagnosis. For example, nystagmus nearly always is noted in PCP toxic patients, hypotension or electrocardiographic (ECG) abnormalities in phenothiazine-poisoned patients, and coma with virtually normal vital signs in patients poisoned by benzodiazepines. Most difficult to differentiate on clinical grounds may be toxicity produced by the centrally acting antihypertensive agents such as clonidine (see Clonidine later and [Chap. 63](#)). Additionally, myriad traumatic, metabolic, and infectious etiologies may occur simultaneously and must always be considered and evaluated appropriately.

Antidote Administration

The goal of naloxone therapy is not necessarily complete arousal; rather, the goal is reinstitution of adequate spontaneous ventilation. Because precipitation of withdrawal is potentially detrimental and often unpredictable, the lowest practical naloxone dose should be administered initially, with rapid escalation as warranted by the clinical situation. Most patients respond to 0.04 to 0.05 mg of naloxone administered IV, although the requirement for ventilatory assistance may be slightly prolonged because the onset may be slower than with larger doses. Administration in this fashion effectively avoids endotracheal intubation and allows timely identification of patients with nonopioid causes of their clinical condition yet diminishes the risk of precipitation of acute opioid withdrawal. SC administration may allow for smoother arousal than the high-dose IV route but is unpredictable in onset and likely prolonged in offset.¹⁸⁸ Prolonged effectiveness of naloxone by the SC route can be a considerable disadvantage if the therapeutic goal is exceeded and the withdrawal syndrome develops.

In the absence of a confirmatory history or diagnostic clinical findings, the cautious empiric administration of naloxone may be both diagnostic and therapeutic. Naloxone, even at extremely high doses, has an excellent safety profile in opioid-naïve patients receiving the medication for nonopioid-related indications, such as spinal cord injury or acute ischemic stroke. However, administration of naloxone to opioid-dependent patients may result in adverse effects; specifically, precipitation of an acute withdrawal syndrome should be anticipated. The resultant agitation, hypertension, and tachycardia may produce significant distress for the patient and complicate management for the clinical staff and occasionally may be life threatening. Additionally, emesis, a common feature of acute opioid withdrawal, may be particularly hazardous in patients who do not rapidly regain consciousness after naloxone administration. For example, patients with concomitant ethanol or sedative-hypnotic exposure and those with head trauma are at substantial risk for pulmonary aspiration of vomitus if their airways are unprotected.

Identification of patients likely to respond to naloxone conceivably would reduce the unnecessary and potentially dangerous precipitation of withdrawal in opioid-dependent patients. Routine prehospital administration of naloxone to all patients with subjectively assessed altered mental status or respiratory depression was not beneficial in 92% of patients.¹⁹⁹ Alternatively, although not perfectly sensitive, a respiratory rate of 12 breaths/min or less in an unconscious patient

presenting via emergency medical services best predicted a response to naloxone.⁷⁸ Interestingly, neither respiratory rate below 8 breaths/min nor coma was able to predict a response to naloxone in hospitalized patients.¹⁹⁵ It is unclear whether the discrepancy between the latter two studies is a result of the demographics of the patient groups or whether patients with prehospital opioid overdose present differently than patients with iatrogenic poisoning. Regardless, relying on the respiratory rate to assess the need for ventilatory support or naloxone administration is not ideal because hypoventilation secondary to hypopnea may precede that caused by bradypnea.^{142,161}

The decision to discharge a patient who awakens appropriately after naloxone administration is based on practical considerations. Patients presenting with profound hypoventilation or hypoxia are at risk for development of ARDS or posthypoxic encephalopathy. Thus, it seems prudent to observe these patients for at least 24 hours in a medical setting. Patients manifesting only moderate signs of poisoning who remain normal for at least several hours after parenteral naloxone likely are safe to discharge. However, the need for psychosocial intervention in patients with uncontrolled drug use or after a suicide attempt may prevent discharge from the emergency department (ED).

Patients with recurrent or profound poisoning by long acting opioids, such as methadone, or patients with large GI burdens (eg, “body packers” or those taking sustained release preparations) may require continuous infusion of naloxone to ensure continued adequate ventilation (Table 38–3). An hourly infusion rate of two thirds of the initial reversal dose of naloxone is sufficient to prevent recurrence.⁶² Titration of the dose may be necessary as indicated by the clinical situation. Although repetitive bolus dosing of naloxone may be effective, it is labor intensive and subject to error.

TABLE 38–3. How to Use Naloxone

1. If a naloxone bolus (start with 0.04 mg IV and titrate) is successful, administer two-thirds of the effective bolus dose per hour by IV infusion; frequently reassess the patient’s respiratory status.
2. If respiratory depression is not reversed after the initial bolus dose: Administer up to 10 mg of naloxone as an IV bolus. If the patient does not respond, do not initiate an infusion.

OR

Intubate the patient, as clinically indicated.

3. If the patient develops withdrawal after the bolus dose: Allow the effects of the bolus to abate. If respiratory depression recurs, administer half of the initial bolus dose and begin an IV infusion at two-thirds of the new bolus dose per hour. Frequently reassess the patient’s respiratory status.
4. If the patient develops withdrawal signs or symptoms during the infusion: Stop the infusion until the withdrawal symptoms abate. Restart the infusion at half the initial rate; frequently reassess the patient’s respiratory status. Exclude withdrawal from other xenobiotics.
5. If the patient develops respiratory depression during the infusion: Readminister half of the initial bolus and repeat until reversal occurs. Increase the infusion by half of the initial rate; frequently reassess the patient’s respiratory status. Exclude continued absorption, readministration of opioid, and other etiologies as the cause of the respiratory depression.

IV = intravenous.

Despite the availability of long-acting opioid antagonists (eg, naltrexone) that theoretically permit single-dose reversal of methadone poisoning, the attendant risk of precipitating an unrelenting withdrawal syndrome hinders their use as antidotes for initial opioid reversal. However, these long acting opioid antagonists may have a clinical role in the maintenance of consciousness and ventilation in opioid-poisoned patients already awakened by naloxone. Prolonged observation and perhaps antidote readministration may be required to match the pharmacokinetic parameters of the two antagonists. Otherwise well children who ingest short-acting opioids may be given a long-acting opioid antagonist initially because they are not expected to develop a prolonged, potentially hazardous withdrawal. However, the same caveats remain regarding the need for extended hospital observation periods if ingestion of methadone or other long-acting opioids is suspected.

Rapid and Ultrarapid Opioid Detoxification

The concept of antagonist-precipitated opioid withdrawal is promoted extensively as a “cure” for opioid dependency, particularly heroin and oxycodone, but has fallen out of favor in recent years. Rather than slow, deliberate withdrawal or detoxification from opioids over several weeks, antagonist-precipitated withdrawal occurs over several hours or days.⁶⁵ The purported advantage of this technique is a reduced risk of relapse to opioid use because the duration of discomfort is reduced and a more rapid transition to naltrexone maintenance can be achieved. Although most studies find some beneficial short-term results, relapse to drug use is very common.¹¹⁶ Rapid opioid detoxification techniques are usually offered by outpatient clinics and typically consist of naloxone- or naltrexone-precipitated opioid withdrawal tempered with varying

amounts of clonidine, benzodiazepines, antiemetics, or other drugs. UROD uses a similar concept but involves the use of deep sedation or general anesthesia for greater patient control and comfort. The risks of these techniques are not fully defined but are of substantial concern. Massive catecholamine release, ARDS, kidney injury, and thyroid hormone suppression have been reported after UROD, and many patients still manifest opioid withdrawal 48 hours after the procedure. As with other forms of opioid detoxification, the loss of tolerance after successful completion of the program paradoxically increases the likelihood of death from heroin overdose if these individuals relapse. That is, recrudescence of opioid use in predetoxification quantities is likely to result in overdose.¹⁷² Both techniques are costly; UROD under anesthesia commonly costs thousands of dollars. Professional medical organizations involved in addiction management have publicly expressed concern for this form of detoxification.²

SPECIFIC OPIOIDS

The vast majority of opioid-poisoned patients follow predictable clinical courses that can be anticipated based on our understanding of opioid receptor pharmacology. However, certain opioids taken in overdose may produce atypical manifestations. Therefore, careful clinical assessment and institution of empiric therapy usually are necessary to ensure proper management (Table 38–4).

TABLE 38–4. Classification, Potency, and Characteristics of Opioids and Opioid Antagonists

Opioid (Representative Trade Name)	Type ^a	Derivation	Analgesic Dose (mg) (via route, equivalent to 10 mg of morphine SC ^b)	Comments ^{c,d}
Alvimopan (Entereg)	Ant	Synthetic	Nonanalgesic (12 PO)	Peripherally acting antagonist; reverses opioid constipation
Buprenorphine (Suboxone)	PA	Semisynthetic	0.4 IM	Opioid substitution therapy requires 6–16 mg/day (contains naloxone)
Butorphanol (Stadol)	AA	Semisynthetic	2 IM	
Codeine	Ag	Natural	120 PO	Often combined with acetaminophen; requires demethylation to morphine by CYP2D6
Dextromethorphan (Robitussin DM)	NEC	Semisynthetic	Nonanalgesic (10–30 PO)	Antitussive; psychotomimetic via NMDA receptor
Difenoxylate (Lomotil)	Ag	Synthetic	Nonanalgesic (2.5 PO)	Antidiarrheal, combined with atropine; difenoxin is potent metabolite
Fentanyl (Sublimaze)	Ag	Synthetic	0.125 IM	Very short acting (<1 hour)
Heroin (Diamorph)	Ag	Semisynthetic	5 SC	Diacetylmorphine, used therapeutically in some countries; schedule I medication in the United States
Hydrocodone (Vicodin, Hycodan)	Ag	Semisynthetic	10 PO	
Hydromorphone (Dilaudid)	Ag	Semisynthetic	1.3 SC	
LAAM (Orlaam)	Ag	Synthetic	(Flexible oral dosing ^e)	Long acting, potent metabolites; no longer distributed in United States because of QT interval prolongation
Levorphanol (Levodromoran)	Ag	Semisynthetic	2 SC/IM	
Loperamide (Imodium)	Ag	Synthetic	Nonanalgesic (2 PO)	Antidiarrheal
Meperidine, pethidine (Demerol)	Ag	Synthetic	75 SC/IM	Seizures caused by metabolite accumulation
Methadone (Dolophine)	Ag	Synthetic	10 IM	Very long acting (24 hours)
Methylnaltrexone (Relistor)	Ant	Synthetic	Nonanalgesic (8–12 SC)	Peripherally acting antagonist; reverses opioid induced constipation
Morphine	Ag	Natural	10 SC/IM	
Nalbuphine (Nubain)	AA	Semisynthetic	10 IM	
Nalorphine	AA	Semisynthetic	15 IM	Historically used as an opioid antagonist ^f
Naloxone (Narcan)	Ant	Semisynthetic	Nonanalgesic (0.04 IV/IM)	Short-acting antagonist (0.5 hours)
Naltrexone (Trexan, Revia)	Ant	Semisynthetic	Nonanalgesic (50 PO)	Very long-acting antagonist (24 hours)
Oxycodone (Percocet, OxyContin)	Ag	Semisynthetic	10 PO	Often combined with acetaminophen; OxyContin is sustained release
Oxymorphone (Numorphan, Opuna)	Ag	Semisynthetic	1 SC	
Paragoric (Parapectolin)	Ag	Natural	25 mL PO	Tincture of opium (0.4 mg/mL)
Pentazocine (Talwin)	AA	Semisynthetic	50 SC	Psychotomimetic via receptor
Propoxyphene (Darvon)	Ag	Synthetic	65 PO	Seizures, dysrhythmias
Tapentadol (Nucynta)	Ag	Synthetic	50–100 PO	Seizures
Tramadol (Ultram)	Ag	Synthetic	50–100 PO	Seizures possible with therapeutic dosing

^aAgonist-antagonists, partial agonists, and antagonists may cause withdrawal in tolerant individuals. ^bTypical dose (mg) for analgesics without analgesic effects is given in parentheses. ^cDuration of therapeutic clinical effect 3–4 hours unless noted, likely to be exaggerated in overdose. ^dAlthough approximately equivalent with methadone, LAAM is not used as an analgesic.

AA = agonist-antagonist (α-agonist, β-antagonist); Ag = full agonist (μ, κ, δ); Ant = full antagonist (μ, κ, δ-antagonist); IM = intramuscular; IV = intravenous; NEC = not easily classified; NMDA = N-methyl-D-aspartate; PA = partial agonist (μ, κ, agonist, α-antagonist); PO = oral; SC = subcutaneous.

Morphine and Codeine

Morphine is poorly bioavailable by the oral route because of extensive first-pass elimination. Morphine is hepatically metabolized primarily to morphine-3-glucuronide (M3G) and, to a lesser extent, to morphine-6-glucuronide (M6G), both of which are cleared renally. Unlike M3G, which is essentially devoid of activity, M6G has μ -agonist effects in the CNS.²³ However, M6G administered peripherally is significantly less potent as an analgesic than is morphine.¹⁶⁰ The polar glucuronide has a limited ability to cross the blood–brain barrier, and P-glycoprotein is capable of expelling M6G from the cerebrospinal fluid. The relative potency of morphine and M6G in the brain is incompletely defined, but the metabolite is generally considered to be several-fold more potent.³

Codeine itself is an inactive opioid agonist, and it requires metabolic activation by O-demethylation to morphine by CYP2D6 (Fig. 38–3). This typically represents a minor metabolic pathway for codeine metabolism. N-Demethylation into norcodeine by CYP3A4 and glucuronidation are more prevalent but produce inactive metabolites. The need for conversion to morphine explains why approximately 5% to 7% of white patients, who are devoid of CYP2D6 function, cannot derive an analgesic response from codeine.^{83,101} An increasingly recognized phenomenon is that ultrarapid CYP2D6 metabolizers produce unexpectedly large amounts of morphine from codeine, with resulting life-threatening opioid toxicity.^{55,138}

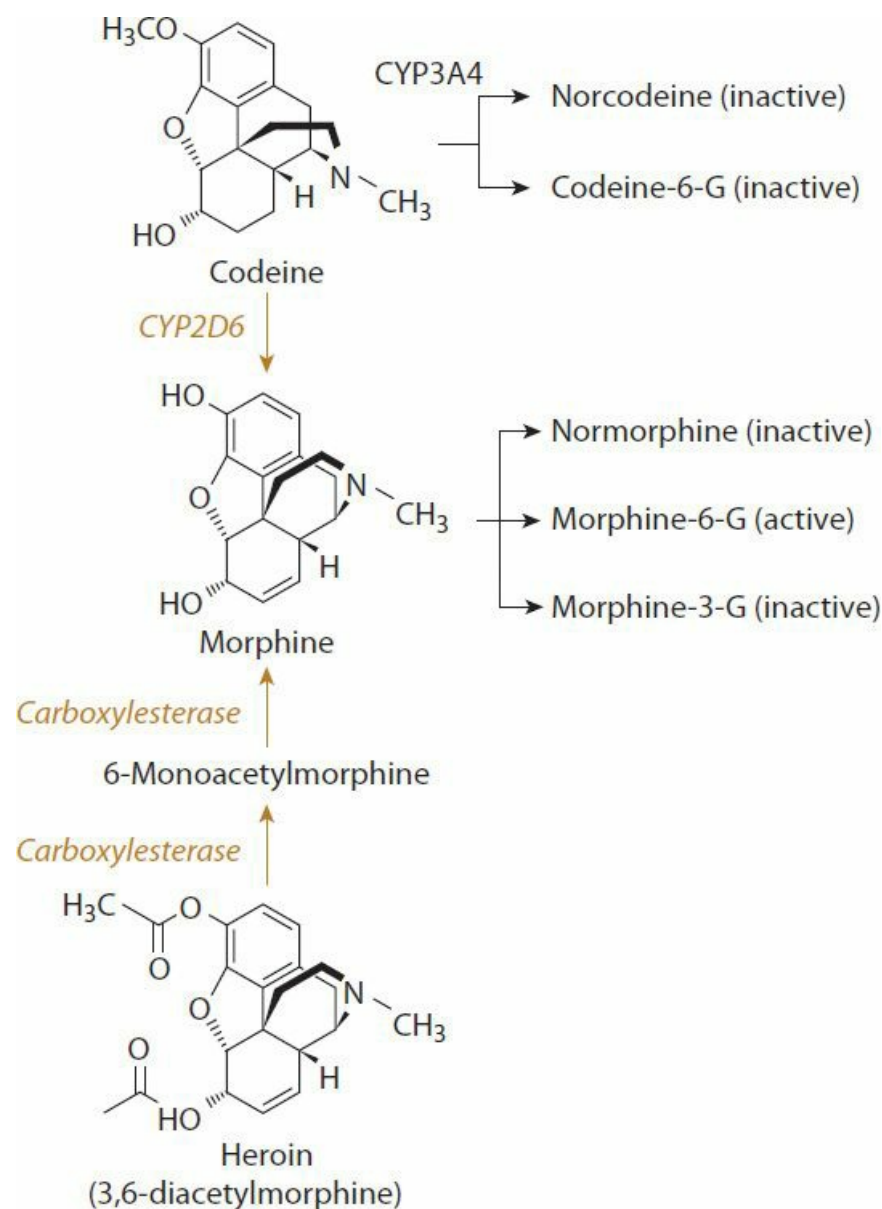


FIGURE 38–3. Opiate and opioid metabolism. Codeine can be O-methylated to morphine, N-demethylated to norcodeine, or glucuronidated to codeine-6-glucuronide (codeine-6-G). Morphine can be N-demethylated to normorphine or glucuronidated to either morphine-3-glucuronide (morphine-3-G) or morphine-6-glucuronide (morphine-6-G). Heroin is converted to morphine by a two-step process involving plasma cholinesterase and two human liver carboxylesterases known as human carboxylesterase-1 and human carboxylesterase-2.

Heroin

Heroin is 3,6-diacetylmorphine, and its exogenous synthesis is performed relatively easily from morphine and acetic anhydride. Heroin has a lower affinity for the receptor than does morphine, but it is rapidly metabolized by plasma

cholinesterase and liver human carboxylesterase (hCE)-2 to 6-monoacetylmorphine, a more potent μ agonist than morphine (Fig. 38–3).¹⁵⁵ Users claim that heroin has an enhanced euphorogenic effect, often described as a “rush.” This effect likely is related to the enhanced blood–brain barrier penetration occasioned by the additional organic functional groups of heroin and its subsequent metabolic activation within the CNS. Interestingly, cocaine and heroin compete for metabolism by plasma cholinesterase and the two human liver carboxylesterases hCE-1 and hCE-2. This interaction may have pharmacokinetic and clinical consequences in patients who “speedball.”^{9,90}

Heroin can be obtained in two distinct chemical forms: base or salt. The hydrochloride salt form typically is a white or beige powder and was the common form of heroin available before the 1980s.⁸⁸ Its high water solubility allows simple IV administration. Heroin base, on the other hand, now is the more prevalent form of heroin in most regions of the world. It often is brown or black. “Black tar heroin” is one appellation referring to an impure South American import available in the United States. Because heroin base is virtually insoluble in water, IV administration requires either heating the heroin until it liquefies or mixing it with acid. Alternatively, because the alkaloidal form is heat stable, smoking or “chasing the dragon” is sometimes used as an alternative route. Street-level heroin base frequently contains caffeine or barbiturates,⁸⁸ which improves the sublimation of heroin and enhances the yield.⁸¹

Widespread IV use has led to many significant direct and indirect medical complications, particularly endocarditis and AIDS, in addition to fatal and nonfatal overdose. Nearly two-thirds of all long-term (>10 years) heroin users in Australia had overdosed on heroin.⁴⁰ Among recent-onset heroin users, 23% had overdosed on heroin, and 48% had been present when someone else overdosed.⁶³ Risk factors for fatality after heroin use include the concomitant use of other drugs of abuse, particularly ethanol; recent abstinence, as occurs during incarceration¹⁵³; and perhaps unanticipated fluctuations in the purity of available heroin.^{37,143} Because most overdoses occur in seasoned heroin users and about half occur in the company of other users,⁴⁰ the prescribing of naloxone to heroin users for companion administration has become increasingly available but remains poorly studied.²⁰ Although earlier administration of antidote could be beneficial, certain issues make this approach controversial. For example, despite the acknowledged injection skills of the other users in the “shooting gallery,” their judgment likely is impaired. In one survey, summoning an ambulance was the initial response to overdose of a companion in only 14% of cases.³⁹ A survey of heroin users suggested they lacked an understanding of the pharmacology of naloxone, which might lead to inappropriate behaviors regarding both heroin and naloxone administration.¹⁵²

Recognition of the efficacy of intranasal heroin administration, or snorting, has fostered a resurgence of heroin use, particularly in suburban communities. The reasons for this trend are unclear, although it is widely suggested that the increasing purity of the available heroin has rendered it more suitable for intranasal use. However, because intranasal administration of a mixture of 3% heroin in lactose produces clinical and pharmacokinetic effects similar to an equivalent dose administered IM, the relationship between heroin purity and price and intranasal use is uncertain.^{28,146} Needle avoidance certainly is important, reducing the risk of transmission of various infectious diseases, including HIV. Heroin smoking has also increased in popularity in the United States, albeit not to the extent in other countries (see Chasing the Dragon later). In addition, users of prescription drugs such as oxycodone or hydrocodone may change to heroin as the supplies of prescription opioids tighten and prices rise.⁸⁷ Celebrities and blogs have popularized intranasal heroin use as a “safe” alternative to IV use. This usage is occurring despite a concomitantly reported rise in heroin deaths in regions of the country where its use is prevalent. Although intranasal use may be less dangerous than IV use from an infectious disease perspective, it is clear that both fatal overdose and drug dependency remain common.¹⁷⁸

Adulterants, Contaminants, and “Heroin” Substitutes. The history of heroin adulteration and contamination has been extensively described. Retail (street-level) heroin almost always contains adulterants or contaminants. What differentiates the two is the intent of their admixture. Adulterants typically are benign because inflicting harm on the consumer with their addition would be economically and socially unwise, although adulterants occasionally are responsible for epidemic deaths. Interestingly, most heroin overdose fatalities do not have serum morphine concentrations that substantially differ from those of living users, raising the unlikely possibility that the individual death is related to an adulterant or contaminant.³⁸

Historically, alkaloids, such as quinine and strychnine, were used to adulterate heroin to mimic the bitter taste of heroin and to mislead clients. Quinine may have first been added in a poorly reasoned attempt to quell an epidemic of malaria among IV heroin users in New York City in the 1930s.⁷¹ That quinine adulteration was common is demonstrated by the common practice of urine screening for quinine as a surrogate marker for heroin use. However, quinine was implicated as a causative factor in an epidemic of heroin-related deaths in the District of Columbia between 1979 and 1982. Toxicity attributed to quinine in heroin users includes cardiac dysrhythmias (Chap. 16), amblyopia, and thrombocytopenia. Quinine adulteration currently is much less common than it was in the past. Trend analysis of illicit wholesale and street-level heroin adulteration over a 12-year period in Denmark revealed that although caffeine, acetaminophen (APAP), methaqualone, and phenobarbital all were prevalent adulterants, quinine was not found.⁸⁸ Recent data on adulteration in the United States are unavailable. Many other adulterants or contaminants, including thallium, lead, cocaine, and amphetamines, are reported.

Poisoning by scopolamine-tainted heroin reached epidemic levels in the northeastern United States in 1995.⁶⁸ Exposed patients presented with acute psychosis and anticholinergic signs. Several patients were treated with physostigmine, with excellent therapeutic results.

Clenbuterol, a β_2 -adrenergic agonist with a rapid onset and long duration of action, was found to be a contaminant in street heroin in the Eastern United States in early 2005. Users rapidly developed nausea, chest pain, palpitations, dyspnea, and tremor. Physical findings included significant tachycardia and hypotension, as well as hyperglycemia, hypokalemia, and increased lactate concentrations on laboratory evaluation, and a few fatalities occurred.^{79,197} The initial patients were thought to be cyanide poisoned. Several patients were treated with β -adrenergic antagonists or calcium channel blockers and potassium supplementation with good results.

“Chasing the Dragon.” IV injection and insufflation are the preferred means of heroin self-administration in the United States. In other countries, including the Netherlands, the United Kingdom, and Spain, a prevalent method is “chasing the dragon” whereby users inhale the white pyrolysate that is generated by heating heroin base on aluminum foil using a handheld flame. This means of administration produces heroin pharmacokinetics similar to those observed after IV administration.⁷³ Chasing the dragon is not a new phenomenon, but it has gained acceptance recently among both IV heroin users and drug-naïve individuals. The reasons for this shift are diverse but probably are related to the avoidance of injection drug use with its concomitant infectious risks.

In the early 1980s, a group of individuals who smoked and inhaled heroin in the Netherlands developed spongiform leukoencephalopathy. Other causes of this rare clinicopathologic entity include prion-related infections such as bovine spongiform leukoencephalopathy, hexachlorophene, pentachlorophenol, and metal poisoning, although none appeared responsible for this phenomenon. Since the initial report, similar cases have been reported in other parts of Europe and in the United States.^{100,109} Initial findings may occur within 2 weeks of use and include bradykinesia, ataxia, abulia, and speech abnormalities. Of those whose symptoms do not progress, half may recover. However, in others, progression to spastic paraparesis, pseudobulbar palsy, or hypotonia may occur over several weeks. Approximately half of individuals in this group do not develop further deficits or improve, but death occurs in approximately 25% of reported cases. The prominent symmetric cerebellar and cerebral white matter destruction noted on brain computed tomography and magnetic resonance imaging corresponds to that noted at necropsy.^{95,129}

The syndrome has the characteristics of a point-source toxic exposure, but no culpable contaminants have been identified, although aluminum concentrations may be elevated.⁵¹ A component or pyrolysis product unique to certain batches of “heroin” is possible.¹⁶ Treatment is largely supportive. Based on the finding of regional mitochondrial dysfunction on functional brain imaging and an elevated brain lactate concentration, supplementation with 300 mg four times a day of coenzyme Q has purported benefit but has not undergone controlled study.¹⁰⁰

Other Opioids

Fentanyl and Its Analogs. Fentanyl is a short-acting opioid agonist that has approximately 50 to 100 times the potency of morphine. It is well absorbed by the transmucosal route, accounting for its use in the form of a “lozenge.” Fentanyl is widely abused as a heroin substitute (intentionally or because of adulteration) and is the controlled substance most often abused by anesthesiologists.¹²

Transdermal fentanyl in the form of a patch (Duragesic) was approved in 1991 and is widely used by patients with chronic pain syndromes. Fentanyl has adequate solubility in both lipid and water for transdermal delivery (Special Considerations: SC1).⁹⁷ A single patch contains an amount of drug to provide a transdermal gradient sufficient to maintain a steady-state plasma concentration for approximately 3 days (eg, a 50 $\mu\text{g}/\text{h}$ patch contains 5 mg). However, even after the patch is considered exhausted, approximately 50% of the total initial fentanyl dose remains. Interindividual variation in dermal drug penetration and errors in proper use, such as use of excessive patches or warming of the skin, may lead to an iatrogenic fentanyl overdose. Fentanyl patch misuse and abuse occur either by application of one or more patches to the skin or by withdrawal or extraction of the fentanyl from the reservoir for subsequent administration.¹⁷⁷

Regional epidemics of heroin substitutes with “superpotent” activity occasionally produce a dramatic increase in “heroin-related” fatalities. Epidemic deaths among heroin users first appeared in Orange County, California, in 1979 and were traced to α -methylfentanyl sold under the brand name China White.⁹⁸ Similar epidemics of China White poisoning occurred in Pittsburgh in 1988 and in Philadelphia in 1992, although the adulterant in these cases was 3-methylfentanyl, another potent analog. A later epidemic in New York City marked the reappearance of 3-methylfentanyl under the brand name Tango and Cash. Typically, patients present comatose and apneic, with no opioids detected on routine blood and urine analysis. In such cases, unsuspecting users had administered their usual “dose of heroin,” measured in 25-mg “bags” that contained variable amounts of the fentanyl analog. Because of the exceptional potency of this fentanyl analog (as much as 6000 times greater than that of morphine), users rapidly developed apnea.

The largest epidemic of more than 1000 fentanyl-related deaths occurred between 2005 and 2007 primarily in the Philadelphia, Chicago, and Detroit regions because of surreptitiously adulterated or substituted heroin. Fentanyl use was

identified by postmortem urine and blood testing or through analysis of unused drug found on either the decedent or persons with whom the decedent shared drugs. In response to this large epidemic, drug users and others were counseled in overdose prevention and cardiopulmonary resuscitation and provided with “take-home” parenteral or intranasal naloxone.²²

Sufentanil and alfentanil are anesthetic opioids with increased potency compared with fentanyl. In some regions of the country, fentanyl and both licit and illicit fentanyl analogs (eg, 3-methylfentanyl and para-fluorofentanyl) are common drugs of abuse. Experienced heroin users could not easily differentiate fentanyl from heroin, although in one study, heroin was noted to provide a more intense “rush.”¹⁰² Although unconfirmed, the xenobiotic used by Russian authorities to overcome terrorists and subdue a hostage situation in Moscow in October 2002 may have been carfentanil,¹⁹¹ a potent μ -receptor agonist that is commonly used as a positron emission tomography scan radioligand.

Although fentanyl is a more potent opioid agonist than heroin, the dose of naloxone required to reverse respiratory depression appears to be similar to that of other common opioids.¹⁷⁶ This is because the binding affinity (K_d) of fentanyl at the μ opioid receptor is similar to that of both morphine and naloxone.^{107,183} In a typical overdose, the quantity of fentanyl is likely to be equipotent to typical heroin. However, if large quantities of fentanyl are involved in the poisoning, higher than normal doses of naloxone may be required for reversal. Use of other opioids, such as sufentanil and buprenorphine, which have higher affinity for opioid receptors (lower K_d), may lead to the need for larger doses of naloxone to reverse the patient’s respiratory depression¹⁰⁷ (Antidotes in Depth: A4).

Oxycodone and Hydrocodone. Both oxycodone and hydrocodone are sold in fixed combination with APAP (eg, Percocet [oxycodone], Vicodin [hydrocodone]), raising concerns about the complications of APAP hepatotoxicity as the dose of opioid is escalated. Several opioids, including oxycodone and oxymorphone, can be obtained in a controlled-release form that contains a large quantity of opioid intended to be released over many hours. Up until recently, abusers were able to crush the tablet, which destroys the sustained-release matrix and liberates large amounts of insufflatable or injectable opioid. New tamper-resistant formulations, required of most extended release opioids, make physical or chemical release of the opioid difficult limiting this practice.¹⁴⁹ Users can still ingest intact large dose pills. The psychoactive effects of these opioids are similar to each other and to other μ receptor agonists^{196,202} and often are used as a substitute for heroin. Opioid dependence, overdose, and death are common sequelae of oxycodone abuse.

Body Packers. In an attempt to transport illicit drugs from one country to another, “mules,” or body packers, ingest large numbers of multiple-wrapped packages of concentrated cocaine or heroin. When the authorities discover such individuals or when individuals in custody become ill, they may be brought to a hospital for evaluation and management. Although these patients generally are asymptomatic on arrival, they are at risk for delayed, prolonged, or lethal poisoning as a consequence of packet rupture.¹⁸⁰ In the past, determining the country of origin of the current journey was nearly diagnostic of packet content. However, because most of the heroin imported into the United States now originates from South America, which is also the major source of imported cocaine, the discernment from cocaine on this basis is impossible. Given the current greater revenue potential of heroin, the majority of body packers carry heroin.⁶¹ Details of diagnosis and management are discussed in Special Considerations: SC5.

Agonist–Antagonists. The opioid agonists in common clinical use tend to have specific binding affinity toward the μ opioid receptor subtype. The agonist–antagonists differ in that they interact with multiple receptor types and may have different effects at each receptor. Thus, although most opioids typically produce either agonist or antagonist effects, the agonist–antagonists generally have agonist effects at the δ -receptor subtype and antagonistic effects at the μ receptor subtype. Therefore, opioids such as pentazocine (Talwin) may elicit a withdrawal syndrome in a μ -opioid–tolerant individual because of antagonist effects at the μ receptor. This effect forms the basis of the claim offered by many methadone-dependent patients that they are “allergic to Talwin.” However, this same drug may act as an analgesic in nonopioid-using patients through its agonist effects at the δ_1 -receptor subtype. Although the clinical effects of agonist–antagonists after overdose resemble those of the other opioids, including lethal respiratory depression,¹³¹ they are less likely than the full agonists to produce severe morbidity or mortality (see Respiratory Depression above).

Pentazocine. Historically, patients abusing pentazocine (Talwin) administered it with tripeleminamine, a blue capsule, accounting for the appellation “T’s and Blues.” Although this mixture has largely fallen out of favor, pentazocine abuse occurs occasionally. The psychotomimetic effects noted with high doses of pentazocine likely are mediated by δ_2 or perhaps σ receptors. Because pentazocine can be readily dissolved, IV injection was a preferred route for its abuse until the commercial formulation was altered to include 0.5 mg naloxone (Talwin NX), which is not orally bioavailable but fully active parenterally.

Xenobiotics Used in Opioid Substitution Therapy: Methadone and Buprenorphine

Two contrasting approaches to the management of patients with chronic opioid use exist, detoxification and maintenance therapy. Detoxification probably is most appropriate for patients motivated or compelled to discontinue opioid use. It can

be performed either by tapered withdrawal of an opioid agonist or with the assistance of opioid antagonists. Maintenance therapy may include use of a long-acting opioid antagonist, such as naltrexone, to pharmacologically block the effects of additional opioid use. Alternatively, and more commonly, maintenance therapy involves opioid substitution therapy.¹⁹

Methadone. Methadone is a synthetic μ opioid receptor agonist used both for treatment of chronic pain and as a maintenance substitute for opioid dependence. Methadone has been available for the latter use for more than 40 years through methadone maintenance treatment programs (MMTPs).⁴³ In MMTPs, the opioid in use is replaced by methadone, which is legal, oral, and long acting. This opioid allows patients to abstain from activities associated with procurement and administration of the abused opioid and eliminates much of the morbidity and mortality associated with illicit drug use. Although often successful in achieving opioid abstinence, some methadone users continue to use heroin, other opioids, and other xenobiotics.⁹²

Methadone is administered as a chiral mixture of (R,S)-methadone. In humans, methadone metabolism is mediated by several cytochrome P450 (CYP) isozymes, mainly CYP3A4 and CYP2B6, and to a lesser extent CYP2D6. CYP2B6 demonstrates stereoselectivity toward (S)-methadone,⁵⁸ and in vivo data show that CYP2B6 slow metabolizer status is associated with high (S)- but not serum (R)-methadone concentrations.³³ In clinical trials, QT prolongation was exacerbated in individuals who were CYP2B6 slow metabolizers, and this population had higher (S)-methadone concentrations.⁴⁶ (R)-methadone is used in Germany and is both more effective and safer than the chiral mixture or the (S) enantiomer, but it is not available in the United States at the present time.

Methadone predictably produces QT interval prolongation because of blockade of the hERG (human ether-a-gogo related gene) channel. In the human heart, the hERG voltage-gated potassium channel mediates the rapidly activating delayed rectifier current ([Chap. 16](#)). Blocking potassium efflux from the cardiac myocyte prolongs cellular repolarization, prolonging the QT interval. Syncope and sudden death caused by ventricular dysrhythmias (eg, torsade de pointes) are the result. Initially described in case reports of patients on high doses of methadone, clinical trials now reveal that methadone can prolong the QT interval in a concentration-dependent fashion.¹¹² Genetic factors in the metabolism of methadone⁴⁶ and probably baseline QT status at the initiation of methadone therapy may underlie and potentially predict adverse effects. (S)-methadone binding to hERG is greater than twofold than that of (R)-methadone and accounts for the cardiotoxicity.⁸⁴

A major difficulty is identification of individuals who are at risk for life-threatening dysrhythmias from methadone-induced QT interval prolongation. Expert-derived guidelines recommend questioning patients about intrinsic heart disease or dysrhythmias, counseling patients initiating methadone therapy, and obtaining a pretreatment ECG and a follow-up ECG at 30 days and yearly.⁹⁹ Patients who receive methadone doses of greater than 100 mg/day might warrant more frequent ECGs, particularly after dose escalation or change in comorbid disease status.⁹⁹ Although these guidelines are disputed by some and limited data exist on the utility of the ECG as a screening test for persons at risk for torsade de pointes from methadone, given its low cost, easy availability, and minimal invasiveness, the guideline recommendations seem practical and appropriate.⁹¹ Although therapeutic methadone is generally safe, rapid dose escalation during induction of therapy may unintentionally produce toxicity and, rarely, fatal respiratory depression.¹⁹ This adverse effect is generally the result of the combination of variable pharmacokinetics (unpredictable but generally long half-life) and the time lag for the development of tolerance.

After a successful therapeutic response to the administration of naloxone, recurrence should be expected because the duration of effect of naloxone is only approximately 30 to 60 minutes. In many cases, continuous infusion of naloxone or possibly administration of a long-acting opioid antagonist is indicated to maintain adequate ventilation ([Table 38–3](#)).

Unintentional methadone overdose may be related to the manner in which MMTPs dispense the drug. Most patients attending MMTPs are given doses of methadone greater than needed to simply prevent withdrawal and in order to prevent surreptitious heroin or other opioid use.¹⁷¹ Additionally, many MMTPs provide their established patients with sufficient methadone to last through a weekend or holiday without the need to revisit the program. This combination of dose and quantity may allow diversion of portions of the dose without the attendant risk of opioid withdrawal. Furthermore, home storage of this surplus drug in inappropriate containers, such as juice containers or baby bottles,⁶⁹ is a cause of unintentional methadone ingestion by children. Such events can be anticipated because methadone is frequently formulated as a palatable liquid and may not be distributed in child-resistant containers. The primary reason for distribution as a liquid, as opposed to the pill form given to patients with chronic pain syndromes, is to ensure dosing compliance at the MMTP. Unfortunately, death is frequent in children who overdose.¹⁰⁸

Buprenorphine. Because prescription of methadone for maintenance therapy is restricted to federally licensed programs, it is inaccessible and inconvenient for many patients. Buprenorphine was approved in 2000 as a schedule III medication for office-based prescription, administered three times weekly, providing an attractive alternative for patients with substantially broader potential for obtaining outpatient therapy. However, because of the initial limitations on patient volume (subsequently expanded), the requirement for physician certification, and possibly the hesitation on the part of community physicians to welcome patients with substance use problems into their practices, many of the perceived benefits of buprenorphine therapy over methadone have not been realized.

Buprenorphine, a partial μ -opioid agonist, in doses of 8 to 16 mg sublingually, is effective at suppressing both opioid withdrawal symptoms and the covert use of illicit drugs. Buprenorphine, although still abused and misused, has a substantially better safety profile than methadone. That is, buprenorphine overdose is associated with markedly less respiratory depression than full agonists such as methadone, and there is no reported effect on the QT interval.

Buprenorphine competes with the extant opioid for the μ receptor; thus, administration of initial doses of buprenorphine in patients taking methadone for opioid substitution therapy can be complicated by opioid withdrawal, particularly in patients on higher doses of methadone. For this reason, the initial dose of buprenorphine is administered in the presence of a physician and when the patient is in mild withdrawal. Buprenorphine cessation results in a mild withdrawal syndrome and for this reason may prove efficacious in opioid detoxification programs.⁴ After the initial doses of buprenorphine, sublingual film containing both buprenorphine and naloxone (Suboxone) are prescribed to prevent their IV use.

At therapeutic doses, buprenorphine produces nearly complete occupancy of the μ opioid receptors, and its receptor affinity is sufficiently strong that it prevents other opioids from binding.⁶⁶ Interestingly, naloxone may prevent the clinical effects of buprenorphine, but the reversal of respiratory effects by naloxone appears to be related in a nonlinear fashion. Relatively low bolus doses of IV naloxone have no effect on the respiratory depression induced by buprenorphine, but high doses (5–10 mg) caused only partial reversal of the respiratory effects of buprenorphine. More recently, data in healthy volunteers suggest a bell-shaped dose response to naloxone.^{148,181} Although doses that would reverse other opioids were ineffective (0.2–0.4 mg), increasing the dose of naloxone to 2 to 4 mg caused full reversal of buprenorphine respiratory depression. However, the onset of reversal is usually slower than occurs when antagonizing other opioids.¹⁸¹ Further increasing the naloxone dose to 5 to 7 mg caused a decline in reversal activity and actually increased the degree of respiratory depression. The reasons for this are unclear. Therefore, reversal of respiratory depression should be treated with a starting dose that is slightly higher than that used to reverse other opioids and increased slowly and titrated to reversal of respiratory depression. For example, a starting dose of naloxone of 0.02 mg/kg, or between 1 and 2 mg, is reasonable, and upward titration should not provide doses in excess of about 5 mg without careful consideration and monitoring. Furthermore, because respiratory depression from buprenorphine may outlast the reversal effects of naloxone boluses or short infusions, a continuous infusion of naloxone may be required to maintain respiratory function.

As a partial agonist, buprenorphine has a ceiling effect on respiratory depression in healthy volunteers, with minimal plateau in analgesic effect.³⁵ However, in some patients, despite the ceiling effect, clinically consequential respiratory depression may occur.¹⁷⁹ Data from multiple case series indicate that most buprenorphine-related deaths are associated with concomitant use of other drugs, most often benzodiazepines, or to the IV injection of crushed tablets.¹⁷⁹

The higher affinity (lower K_d) and partial agonism of buprenorphine should allow it to function as an antagonist to the respiratory depressant effects of heroin and improve spontaneous respiration. Although administration of sublingual buprenorphine for opioid overdose is reportedly successful in some case reports,¹⁹⁴ this practice is largely unstudied and not recommended at this time. Interestingly, some reported deaths involved patients given buprenorphine tablets intravenously by fellow drug users for the treatment of heroin-induced respiratory depression.¹³

Unique Opioids

Meperidine. Meperidine, called pethidine outside of the United States, was previously widely used for treatment of chronic and acute pain syndromes. Meperidine produces clinical manifestations typical of the other opioids and may lead to greater euphoria.²⁰¹ Pupillary constriction is less pronounced and, if it occurs, is less persistent than that associated with morphine.⁵⁹ However, normeperidine, a toxic, renally eliminated hepatic metabolite, accumulates in patients receiving chronic high-dose meperidine therapy, such as those with sickle cell disease or cancer. A similar accumulation occurs in patients with kidney disease, in whom the elimination half-life increases from a normal of 14 to 21 hours to 35 hours.¹⁷⁴ Normeperidine causes excitatory neurotoxicity, which manifests as delirium, tremor, myoclonus, or seizures. Based on animal studies, the seizures should not be expected to respond to naloxone.⁶⁰ In fact, experimental evidence suggests that naloxone may potentiate normeperidine-induced seizures, presumably by inhibiting an anticonvulsant effect of meperidine.³⁰ Hemodialysis using a high-efficiency membrane may be of limited clinical benefit but rarely, if ever, is indicated because the toxicity generally is self-limited.

Although primarily an opioid, meperidine is capable of exerting effects at other types of receptors. The most consequential nonopioid-receptor effects occur through the serotonin receptor. Blockade of the presynaptic reuptake of released serotonin may produce serotonin toxicity, which is characterized by muscle rigidity, hyperthermia, and altered mental status, particularly in patients using monoamine oxidase inhibitors (MAOIs) ([Chap. 73](#)). However, dextromethorphan (see Dextromethorphan later) also may produce toxicity. Conversely, the simultaneous use of MAOIs and morphine, fentanyl, or methadone is not expected to produce serotonin toxicity based on the currently appreciated pharmacology of these drugs. Despite its purported (and likely overstated) beneficial effects on biliary tract physiology, meperidine offers little to support its clinical use and has significant disadvantages. Meperidine use has been dramatically reduced or is closely monitored in many institutions and has been eliminated in other centers because of its adverse risk–

benefit profile.

MPTP. In 1982, several cases of acute, severe parkinsonian symptoms were identified in IV drug users.¹⁰⁴ The patients were labeled “frozen addicts” because of the severe bradykinesia, and extensive investigations into the etiology of the problem ensued. This ultimately led to the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an inadvertent product of presumed errors in the attempted synthesis of the illicit meperidine analog MPPP (1-methyl-4-phenyl-4-propionoxy-piperidine). MPTP is metabolized to the ultimate toxicant MPP⁺ by monoamine oxidase-B in glial cells. Toxicity is inhibited by pretreatment with deprenyl, a monoamine oxidase-B inhibitor. MPP⁺ is a paraquatlike xenobiotic capable of selectively destroying the dopamine-containing cells of the substantia nigra by inhibiting mitochondrial oxidative phosphorylation.¹⁵¹ The index cases initially responded to standard antiparkinsonian therapy, but none improved substantially, and the effects of the medications waned.⁶ Although calamitous for exposed patients, MPTP has proved to be invaluable in the development of experimental models for the study of Parkinson disease. Several of the original “frozen” patients subsequently underwent stereotactic implantation of fetal adrenal tissue grafts into their basal ganglia, with significant clinical improvement.¹⁰⁵

Dextromethorphan. Dextromethorphan is devoid of analgesic properties altogether even though it is the optical isomer of levorphanol, a potent opioid analgesic. Based on this structural relationship, dextromethorphan is commonly considered an opioid, although its receptor pharmacology is much more complex and diversified. At high doses, dextromethorphan does bind to opioid receptors to produce miosis, respiratory depression, and CNS depression. Reversal of these opioid effects by naloxone is reported. Binding to the PCP site on the NMDA receptor and subsequent inhibition of calcium influx through this receptor-linked ion channel causes sedation. This same activity may account for its antiepileptic properties and for its neuroprotective effects in ischemic brain injury. Because NMDA receptor blockade also enhances the analgesic effects of μ -opioid agonists, combination therapy with morphine and dextromethorphan (MorphiDex) has been introduced.

Blockade of presynaptic serotonin reuptake by dextromethorphan may elicit serotonin toxicity in patients receiving MAOIs.¹⁶⁶ Movement disorders, described as choreoathetoid or dystonialike, occasionally occur and presumably result from alteration of dopaminergic neurotransmission. Dextrophan, the active O-demethylation metabolite of dextromethorphan, is produced by CYP2D6, an enzyme with a well-described genetic polymorphism.⁵ Whereas patients with the “extensive metabolizer” polymorphism appear to experience more drug-related psychoactive effects, poor metabolizers experience more adverse effects related to the parent compound.²⁰³

Dextromethorphan is available without prescription in cold preparations, primarily because of its presumed lack of significant addictive potential. However, abuse of dextromethorphan is increasing, particularly among high school students.⁹ This increase in use likely is related to the easy availability of dextromethorphan and its perceived limited toxicity. Common street names include “DXM,” “dex,” and “roboshots.” Users often have expectations of euphoria and hallucinations, but a dysphoria comparable to that of PCP commonly ensues. Reports of substantial cold medicine consumption raise several concerns, including APAP poisoning, opioid dependency, and bromide toxicity.⁸² This last concern relates to the common formulation of dextromethorphan as the hydrobromide salt. At times, the first clue may be an elevated serum chloride concentration when measured on certain autoanalyzers (Chaps. 6 and 19).

Tramadol and Tapentadol. Tramadol (Ultram) and tapentadol (Nucynta) are novel synthetic analgesics with both opioid and nonopioid mechanisms responsible for their clinical effects. Tramadol is a reuptake inhibitor of norepinephrine and 5-HT, and it has an active metabolite, formed via CYP2D6, that is a weak μ opioid receptor agonist.¹³⁹ Tapentadol, which does not require activation, has relatively strong μ -opioid receptor agonism and inhibits the reuptake of norepinephrine but not serotonin.⁷⁰ Both are available in immediate-release and extended-release formulations.

A large number of spontaneous reports to the FDA suggest that therapeutic use of tramadol may cause seizures, particularly on the first day of therapy. However, epidemiologic studies have not confirmed this association.⁵⁶ Tramadol-related seizures are not responsive to naloxone but are suppressed with benzodiazepines. In fact, the package insert cautions against using naloxone in patients with tramadol overdoses because in animals treated with naloxone, the risk of seizure is increased. Correspondingly, one patient in a prospective series had a seizure that was temporally related to naloxone administration.¹⁶⁷ Acute overdose of tramadol is generally considered non-life threatening, and most fatalities were associated with polysubstance overdose. Ultrarapid metabolizers at CYP2D6 may experience complications at conventional doses.⁴⁸ Patients using MAOIs may be at risk for development of serotonin toxicity after taking tramadol.

Tramadol abuse is reported, but its extent is undefined. In a review of physician drug abuse in several states, tramadol was the second most frequent opioid reported.¹⁶² Opioid users recognized tramadol as an opioid only when given in an amount that was six times the therapeutic dose, but at this dose, the users did not develop opioidlike clinical effects such as miosis. Patients may develop typical opioid manifestations after a large overdose. Significant respiratory depression is uncommon and should respond to naloxone.¹⁶⁷ Generally, urine drug screening for drugs of abuse is negative for opioids in tramadol-exposed patients. Tapentadol is relatively new to the market, and although its abuse potential remains concerning and case reports exist,⁹⁴ there are insufficient epidemiologic data to identify diversion or abuse.⁴¹

Propoxyphene. Propoxyphene is a weak analgesic with limited efficacy data and serious safety concerns. Similar to its

structural analog methadone, propoxyphene binds μ -opioid receptors and produces the expected opioid clinical findings. However, unanticipated properties of propoxyphene manifest after overdose. Propoxyphene and its hepatic metabolite, norpropoxyphene, produce myocardial sodium channel blockade identical to the type IA antidysrhythmics. This process results in QRS complex widening and negative inotropy (Chap. 64).

Diphenoxylate and Loperamide. Although diphenoxylate is structurally similar to meperidine, its extreme insolubility limits absorption from the GI tract. This factor may enhance its use as an antidiarrheal agent, which presumably occurs via a local opioid effect at the GI μ receptor. However, the standard adult formulation may result in significant systemic absorption and toxicity in children, and all such ingestions should be deemed consequential. Diphenoxylate is formulated with a small dose (0.025 mg) of atropine (as Lomotil), both to enhance its antidiarrheal effect and to discourage illicit use.

Because both components of Lomotil may be absorbed and their pharmacokinetic profiles differ somewhat, a biphasic clinical syndrome is occasionally noted.¹¹⁵ Patients may manifest atropine poisoning (anticholinergic syndrome), either independently or concomitantly with the opioid effects of diphenoxylate. Delayed, prolonged, or recurrent toxicity is common and is classically related to the delayed gastric emptying effects inherent to both opioids and anticholinergics. However, these effects are more likely explained by the accumulation of the hepatic metabolite difenoxin, which is a significantly more potent opioid than diphenoxylate and possesses a longer serum half-life. Still, the relevance of gastroparesis is highlighted by the retrieval of Lomotil pills by gastric lavage as late as 27 hours after ingestion.

A review of 36 pediatric reports of Lomotil overdoses found that although naloxone was effective in reversing the opioid toxicity, recurrence of CNS and respiratory depression was common.¹¹⁵ This series included a patient with an asymptomatic presentation 8 hours after ingestion who was observed for several hours and then discharged. This patient returned to the ED 18 hours after ingestion with marked signs of atropinism. In this same series, children with delayed onset of respiratory depression and other opioid effects were reported, and others describe cardiopulmonary arrest 12 hours after ingestion. Naloxone infusion may be appropriate for patients with recurrent signs of opioid toxicity. Because of the delayed and possibly severe consequences, all children and all adult patients with potentially significant ingestions should be admitted for monitored observation in the hospital.

Loperamide (Imodium) is another insoluble meperidine analog that is used to treat diarrhea. This medication is available without a prescription, and the paucity of adverse patient outcomes reported in the medical literature suggests that the safety profile of this agent is good.

SUMMARY

- Opioid overdose and toxicity remain major causes of drug-related morbidity and mortality.
- Although the therapeutic and toxic doses of opioids are difficult to predict because of the development of tolerance with chronic use, the primary adverse event from excessive dosing is respiratory depression.
- Thus ventilatory support, or administration of a short-acting opioid antagonist such as naloxone, should be adequate initial therapy.
- An appreciation of the pharmacologic differences between the various opioids allows for the identification and appropriate management of patients poisoned or otherwise adversely affected by these xenobiotics.

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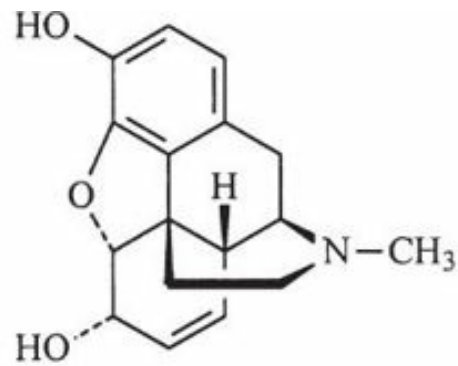
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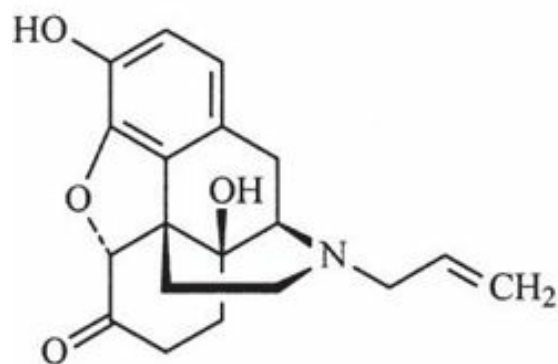
A4 ANTIDOTES IN DEPTH

Opioid Antagonists

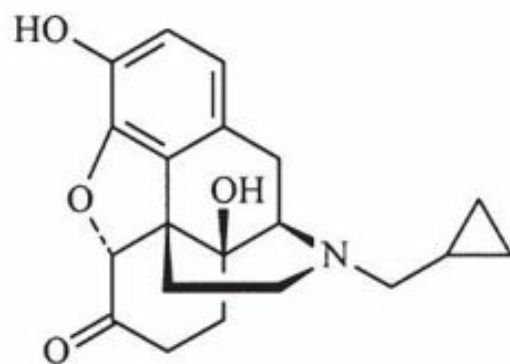
Lewis S. Nelson and Mary Ann Howland



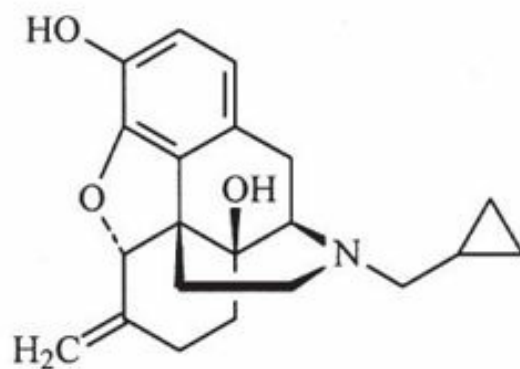
Morphine



Naloxone



Naltrexone



Nalmefene

INTRODUCTION

Naloxone, nalmefene, naltrexone, and methylnaltrexone are pure competitive opioid antagonists at the mu (μ), kappa (δ), and delta (δ) receptors. Opioid antagonists prevent the actions of opioid agonists, reverse the effects of both endogenous and exogenous opioids, and cause opioid withdrawal in opioid-dependent patients. Naloxone is the primary opioid antagonist used to reverse respiratory depression in patients manifesting opioid toxicity. The parenteral dose should be titrated to maintain adequate airway reflexes and ventilation. By titrating the dose, beginning with 0.04 mg and increasing as indicated to 0.4 mg, 2 mg, and finally 10 mg, abrupt opioid withdrawal can be prevented. This titrated low dose method of administration limits withdrawal induced adverse effects, such as vomiting and the potential for aspiration pneumonitis, and a surge in catecholamines with the potential for cardiac dysrhythmias and acute respiratory distress syndrome (ARDS). Because of its poor oral bioavailability, oral naloxone may be used to treat patients with opioid induced constipation. Methylnaltrexone, a parenteral medication, and alvimopan, an oral capsule, are effective in reversing opioid-induced constipation without inducing opioid withdrawal. This is because neither is able to enter the central nervous system (CNS). Naltrexone is used orally for patients after opioid detoxification to maintain opioid abstinence and as an adjunct to achieve ethanol abstinence. Nalmefene, no longer available in the United States, has a duration of action between those of naloxone and naltrexone.

HISTORY

The understanding of structure–activity relationships led to the synthesis of many new molecules in the hope of producing potent opioid agonists free of abuse potential. Although this goal has not yet been achieved, opioid antagonists and partial agonists resulted from these investigations. N-Allyl norcodeine was the first opioid antagonist synthesized (in 1915), and N-allylnormorphine (nalorphine) was synthesized in the 1940s.^{37,66} Nalorphine was recognized as having both agonist and antagonist effects in 1954. Naloxone was synthesized in 1960, and naltrexone was synthesized in 1963. The synthesis of opioid antagonists that are unable to cross the blood–brain barrier (sometimes called peripherally restricted) allowed patients receiving long-term opioid analgesics to avoid opioid induced constipation, one of the most uncomfortable side effects associated with this therapy. Since the mid 1990s, there has been a steady increase in the use of naloxone that has been prescribed or directly dispensed to heroin users for administration by bystanders in case of overdose.¹⁰

PHARMACOLOGY

Chemistry

Minor alterations can convert an agonist into an antagonist. The substitution of the N-methyl group on morphine by a larger functional group led to nalorphine and converted the agonist levorphanol to the antagonist levallorphan.³⁵ Naloxone, naltrexone, and nalmefene are derivatives of oxymorphone with antagonist properties resulting from addition of organic or other functional groups.^{35,39} Relatedly, nalmefene is a 6-methylene derivative of naltrexone.

Mechanism of Action

The μ receptors are responsible for analgesia, sedation, miosis, euphoria, respiratory depression, and decreased gastrointestinal (GI) motility. The δ receptors are responsible for spinal analgesia, miosis, dysphoria, anxiety, nightmares, and hallucinations. The δ receptors are responsible for analgesia and hunger. The currently available opioid receptor antagonists are most potent at the μ receptor, with higher doses required to affect the δ and δ receptors. They all bind to the opioid receptor in a competitive fashion, preventing the binding of agonists, partial agonists, or mixed agonist–antagonists without producing any independent action.

Pharmacokinetics

Naloxone, naltrexone, and nalmefene are similar in their antagonistic mechanism but differ primarily in their pharmacokinetics. Both nalmefene and naltrexone have longer durations of action than naloxone, and both have adequate oral bioavailability to produce systemic effects. Methylnaltrexone can be given orally or parenterally but is excluded from the CNS and only produces peripheral effects. Selective antagonists for μ , δ , and δ are available experimentally and are undergoing investigation.

The bioavailability of sublingual naloxone is only 10%.⁵ In contrast, naloxone is well absorbed by all parenteral routes of administration, including the intramuscular (IM), subcutaneous (SC), endotracheal, intranasal, intralingual, and inhalational (nebulized) routes. The onset of action with the various routes of administration are as follows: intravenous (IV), 1 to 2 minutes; SC, approximately 5.5 minutes; intralingual, 30 seconds; intranasal, 3.4 minutes; inhalational, 5 minutes; endotracheal, 60 seconds; and IM, 6 minutes.^{23,41,53,73} The distribution half-life is rapid (~5 minutes) because of its high lipid solubility. The volume of distribution (Vd) is 0.8 to 2.64 L/kg.³¹

A naloxone dose of 13 µg/kg in an adult occupies approximately 50% of the available opioid receptors.⁵⁴ The duration of action of naloxone is approximately 20 to 90 minutes and depends on the dose of the agonist, the dose and route of administration of naloxone, and the rates of elimination of the agonist and naloxone.^{5,25,68} Naloxone is metabolized by the liver to several compounds, including a glucuronide. The elimination half-life is 60 to 90 minutes in adults and approximately two to three times longer in neonates.

Naltrexone is rapidly absorbed with an oral bioavailability of 5% to 60%, and peak serum concentrations occur at 1 hour.³⁴ Distribution is rapid, with a Vd of approximately 15 L/kg and low protein binding.⁴⁵ Naltrexone is metabolized in the liver to β-naltrexol (with 2%–8% activity) and 2-hydroxy, 3-methoxy-β-naltrexol and undergoes an enterohepatic cycle.⁷² The plasma elimination half-life is 10 hours for β-naltrexone and 13 hours for β-naltrexol, with terminal phases of elimination of 96 hours and 18 hours, respectively.⁷⁰

Nalmefene has an oral bioavailability of 40%, with peak serum concentrations usually reached within 1 to 2 hours.²¹ After SC administration, peak concentrations do not occur for more than 2 hours, although therapeutic concentrations are reached within 5 to 15 minutes. A 1 mg parenteral dose blocks more than 80% of opioid receptors within 5 minutes. The apparent Vd is 3.9 L/kg for the central compartment and 8.6 L/kg at steady state. Protein binding is approximately 45%.²⁰ Nalmefene has a redistribution half-life of 41 ± 34 minutes and a terminal half-life of 10.8 ± 5 hours after a 1 mg IV dose. It is metabolized in the liver to an inactive glucuronide conjugate that probably undergoes enterohepatic recycling, accounting for approximately 17% of drug elimination in the feces. Less than 5% is excreted unchanged in the urine.

Methylnaltrexone is a quaternary amine methylated derivative of naltrexone that is peripherally restricted because of its poor lipid solubility and inability to cross the blood–brain barrier.⁷⁹ After SC administration, peak serum concentrations occur in about 30 minutes. The drug has a Vd of 1.1 L/kg and is minimally protein bound (11%–15%). Although there are several metabolites, 85% of the drug is eliminated unchanged in the urine.⁷⁹

Pharmacodynamics

In the proper doses, pure opioid antagonists reverse all of the effects at the µ, δ, and δ receptors of endogenous and exogenous opioid agonists, except for those of buprenorphine, which has a very high affinity for and slow rate of dissociation from the µ receptor.⁵⁴ Actions of opioid agonists that are not mediated by interaction with opioid receptors, such as direct mast cell liberation of histamine or the potassium channel blocking effects of methadone, are not reversed by these antagonists.² Chest wall rigidity from rapid fentanyl infusion is usually reversed with naloxone.¹⁴ Opioid-induced seizures in animals, such as from propoxyphene, tend to be antagonized by opioid antagonists, although seizures caused by meperidine (normeperidine) and tramadol are exceptions.³⁰ The benefit in humans is less clear. A report of two newborns who developed seizures associated with fentanyl and morphine infusion demonstrated abrupt clinical and electroencephalographic resolution after administration of naloxone.¹⁷

Opioids operate bimodally on opioid receptors.¹⁵ At very low concentrations, µ opioid receptor agonism is excitatory at this receptor and actually may increase pain. This antianalgesic effect is modulated through a G_s protein and usually is less important clinically than the well-known inhibitory actions that result from coupling to a G_o protein at usual analgesic doses. For this reason, extremely low doses of opioid antagonists (ie, 0.25 µg/kg/h of naloxone) enhance the analgesic potency of opioids, including morphine, methadone, and buprenorphine.^{16,29} Naloxone also attenuates or prevents the development of tolerance and dependence.²⁹ Coadministration of these very low doses of antagonists with the opioid also limits opioid-induced adverse effects such as nausea, vomiting, constipation, and pruritus.⁷⁹

The opioid antagonists may reverse the effects of endogenous opioid peptides, including endorphins, dynorphins, and enkephalins. Endogenous opioids are found in tissues throughout the body and may work in concert with other neurotransmitter systems to modulate many physiologic effects.^{26,67} For instance, during shock, the release of circulating endorphins produces an inhibition of central sympathetic tone by stimulating δ receptors within the locus coeruleus, resulting in vasodilation. Vagal tone is also enhanced through stimulation of opioid receptors in the nucleus ambiguus.

Research investigating the cardioprotective effects of opioid agonists through their action at the sarcolemmal and mitochondrial K⁺-ATP (adenosine triphosphate) channels is ongoing.²⁷ Nonselective opioid antagonists may negate these protective effects.

ROLE IN OPIOID TOXICITY

Naloxone has been used for decades by medical personnel for the management of patients with opioid toxicity. Initial studies found the use of naloxone to be relatively safe and highly effective in awakening opioid-toxic patients.^{40,76} Although recommended to be administered empirically to nearly every patient with a depressed level of consciousness and respiratory depression,³⁸ as complications of precipitated opioid withdrawal became more apparent, aggressive use of naloxone has been scaled back.⁶ Currently, the empiric dose that is considered safe for all opioid-dependent patients is

0.04 mg, although in nondependent patients, higher doses may be administered without concern for precipitating withdrawal. The goal of reversal of opioid poisoning is to improve the patient's ventilation while avoiding withdrawal, which is associated with significant complications (see later discussion).

Take-home naloxone programs are developing around the world. In these programs, opioid abusers and their families are supplied naloxone to be administered to others after opioid overdose, generally by the SC (by needle and syringe) or intranasal (by atomizer) route.^{1,42,76} An autoinjector containing 0.4 mg naloxone was approved for IM use in 2014. These bystander programs are credited with saving numerous lives, although the absolute number and rate are unknown.^{10,13} However, concerns exist regarding proper dosing, relative safety, use in mixed overdose (eg, cocaine or benzodiazepine for distinct reasons), attempts to overcome precipitated withdrawal with larger doses of agonist, comfort pushing the opioid dose because of the availability of rescue therapy, risk of arrest with drug paraphernalia (covered in most jurisdictions with Good Samaritan clauses), and refusal of emergency medical services involvement (with subsequent recrudescence of opioid toxicity after naloxone effect wanes). (See Adverse Effects and Safety Issues.)

ROLE IN MAINTENANCE OF OPIOID ABSTINENCE

Opioid dependence is managed by substitution of the abused opioid, typically heroin or a prescription opioid, with methadone or buprenorphine or by detoxification and subsequent abstinence. Maintenance of abstinence is often assisted by naltrexone, although any pure opioid antagonist could be used.⁶² Typically, naltrexone is chosen because of its oral absorption and long duration of action compared with those of naloxone.^{48,62}

Before naltrexone can be administered for abstinence maintenance, the patient must be weaned from opioid dependence and be a willing participant. Naloxone should be administered IV to confirm that the patient is no longer opioid dependent and safe for naltrexone. With naloxone, opioid withdrawal, if it occurs, will be short lived instead of prolonged after use of naltrexone. Naltrexone does not produce tolerance, although prolonged treatment with naltrexone produces up regulation of opioid receptors.⁷⁷

ROLE IN ETHANOL ABSTINENCE

Naltrexone, particularly the IM depot form (Vivitrol), is used as adjunctive therapy in ethanol dependence based on the theory that the endogenous opioid system modulates ethanol intake.⁶⁵ Naltrexone reduces ethanol craving, the number of drinking days, and relapse rates.^{46,57} Naltrexone induces moderate to severe nausea in 15% of patients, possibly as a result of alterations in endogenous opioid tone induced by prolonged ethanol ingestion.

OTHER USES

Poorly orally bioavailable opioid antagonists (eg, naloxone) and peripherally restricted opioid antagonists (eg, methylnaltrexone) are used to prevent or treat the constipation that occurs as a side effect of opioid use, whether for pain management or drug abuse maintenance therapy.⁸ Methylnaltrexone administered SC results in evacuation within 4 hours in nearly half of those who receive the drug for this indication.⁶⁴

Opioid antagonists are sometimes used in the management of overdoses with nonopioids such as ethanol,²² clonidine,⁶¹ captopril,⁶⁹ and valproic acid.⁶³ In none of these instances is the reported improvement as dramatic or consistent as in the reversal of an opioid. The mechanisms for each of these, although undefined, may relate to reversal of endogenous opioid peptides at opioid receptors.

Naloxone has been used to reverse the effects of endogenous opioid peptides in patients with septic shock, although the results are variable.¹⁹ Treatment is often ineffective and may result in adverse effects, particularly in patients who are opioid tolerant. Naloxone may have a temporizing effect via elevation of mean arterial pressure.

Opioid antagonists at low doses are used for treatment of morphine-induced pruritus resulting from systemic or epidural opioids and for treatment of pruritus associated with cholestasis.^{52,55}

ADVERSE EFFECTS AND SAFETY ISSUES

Pure opioid antagonists produce no clinical effects in opioid-naïve or nondependent patients even when administered in massive doses.⁷

When patients dependent on opioid agonists are exposed to opioid antagonists or agonist-antagonists such as pentazocine, they exhibit opioid withdrawal, including yawning, lacrimation, diaphoresis, rhinorrhea, piloerection, mydriasis, vomiting, diarrhea, myalgias, mild elevations in heart rate and blood pressure, and insomnia. Antagonist-precipitated withdrawal may result in an "overshoot" phenomenon, from an increase in circulating catecholamines,

resulting in hyperventilation, tachycardia, and hypertension.⁴⁴ Under these circumstances, there is a potential for related complications such as myocardial ischemia, heart failure, and CNS injury.⁴³ Delirium, although rarely reported in patients withdrawing by opioid abstinence, may occur when an opioid antagonist is used to reverse effects in patients dependent on high doses of opioids or during rapid opioid detoxification.³² These severe manifestations of precipitated opioid withdrawal may occur with ultrarapid opioid detoxification and are associated with fatalities occurring in the postadministration period.³⁶ This rapid form of deliberate detoxification differs significantly from the opioid withdrawal associated with volitional opioid abstinence ([Chap. 15](#)).

Case reports describe ARDS, hypertension, and cardiac dysrhythmias in association with naloxone administration almost uniformly in opioid-dependent patients.^{56,60} The clinical complexities of the setting make it difficult to analyze and attribute these adverse effects solely to naloxone.⁹ ARDS occurs after heroin overdose in the absence of naloxone,²⁴ making the exact contribution of naloxone to the problem unclear. Rather, in certain patients, naloxone may unmask ARDS previously induced by the opioid but unrecognized because of the patient's concomitant opioid-induced respiratory depression.

If the patient's airway is unprotected during withdrawal and vomiting occurs, aspiration pneumonitis may complicate the recovery.¹² Given the frequency of polysubstance abuse and overdose associated with altered consciousness, the risk of precipitating withdrawal associated vomiting should always be a concern.

Resedation is a function of the relatively short duration of action of the opioid antagonist compared with the opioid agonist. Most opioid agonists have durations of action longer than that of naloxone and shorter than that of naltrexone. A long duration of action is advantageous when the antagonist is used to promote abstinence (naltrexone) but is undesired when inappropriately administered to an opioid-dependent patient.

Unmasking underlying cocaine or other stimulant toxicity may explain some of the cardiac dysrhythmias that develop after naloxone-induced opioid reversal in a patient simultaneously using both opioids and stimulants ([Chaps. 76 and 78](#)).⁵⁰

Antagonists stimulate the release of hormones from the pituitary, resulting in increased concentrations of luteinizing hormone, follicle-stimulating hormone, and adrenocorticotrophic hormone and stimulate the release of prolactin in women.⁵⁸

Management of Iatrogenic Withdrawal

Excessive administration of an opioid antagonist to an opioid-dependent patient will predictably result in opioid withdrawal. When induced by naloxone, all that is generally required is protecting the patient from harm and reassuring the patient that the effects will be short lived. Symptomatic care may be necessary on occasion. After inadvertent administration of naltrexone, the expected duration of the withdrawal syndrome generally mandates the use of pharmacologic intervention.^{28,47} Overcoming the opioid receptor antagonism is difficult, but if used in titrated doses, morphine or fentanyl may be successful. Adverse effects from histamine release from morphine and chest wall rigidity from fentanyl should be anticipated. If more moderate withdrawal is present, the administration of metoclopramide, clonidine, or a benzodiazepine is usually adequate.⁴³

What constitutes an appropriate observation period after antagonist administration depends on many factors. After IV bolus naloxone, observation for two hours should be adequate to determine whether sedation and respiratory depression will return. Although no fatalities were identified in medical examiner records after the rapid prehospital release of patients who had presumably overdosed with heroin and were administered naloxone, the true safety of this practice remains questionable.¹¹ Although the matched pharmacokinetics of heroin and naloxone suggests potential utility for such a practice, the high frequency of methadone or sustained-release prescription opioids use in many communities raises concerns. That is, the pharmacokinetic mismatch between naloxone and both methadone and sustained-release oxycodone results in recurrent opioid toxicity and prevents widespread implementation of this program.⁷¹ Similarly, patients on continuous naloxone infusion must be observed for 2 hours or more after its discontinuation to ensure that respiratory depression does not recur.

PREGNANCY AND LACTATION

Naloxone is a pregnancy Category C drug. A risk to benefit analysis must be considered in pregnant women, particularly those who are opioid tolerant, and their newborns. Inducing opioid withdrawal in the mother probably will induce withdrawal in the fetus and should be avoided. Likewise, administering naloxone to newborns of opioid-tolerant mothers may induce neonatal withdrawal and should be used cautiously ([Chaps. 31, 32, and 38](#)).⁵¹

DOSING AND ADMINISTRATION

The initial dose of antagonist depends on the dose of agonist and the relative binding affinity of the agonist and antagonist at the opioid receptors. The presently available antagonists have a greater affinity for the μ receptor than for the δ or κ

receptors. Some opioids, such as buprenorphine, require greater than expected doses of antagonist to reverse the effects at the μ receptor.^{68,75,85,95} The duration of action of the antagonist depends on many drug and patient variables, such as the dose and the clearance of both the antagonist and agonist.

A dose of 0.4 mg of IV naloxone will reverse the respiratory depressant effects of most opioids and is an appropriate starting dose in non opioid-dependent patients. However, this dose in an opioid-dependent patient usually produces withdrawal, which should be avoided if possible. The goal is to produce a spontaneously and adequately ventilating patient without precipitating significant or abrupt opioid withdrawal. Therefore, 0.04 mg IV is a practical starting dose in most patients, increasing to 0.4 mg, 2 mg, and finally 10 mg if the patient has no response at lower doses.⁶ If the patient has no response to 8 to 10 mg, then an opioid is not likely to be responsible for the respiratory depression. The dose in children without opioid dependence is essentially the same as for adults. However, for those with the possibility of withdrawal or recrudescence of severe underlying pain, more gentle reversal with 0.001 mg/kg, with concomitant supportive care, is warranted. Although both the adult and pediatric doses recommended here are lower than those conventionally suggested in other references, the availability of safe and effective interim ventilatory therapy permits these lower doses and lowers the acceptable risk of precipitating withdrawal.

When 1 mg of naloxone is administered IV, it prevents the action of 25 mg of IV heroin for 1 hour, but 50 mg of oral naltrexone antagonizes this dose of heroin for 24 hours; 100 mg of oral naltrexone has a blocking effect for 48 hours, and 150 mg of oral naltrexone is effective for 72 hours.

The use of low doses of IV naloxone to reverse opioid overdose may prolong the time to improvement of ventilation, and during this period, assisted ventilation may be required. The same limitation exists with SC naloxone administration, and the absorbed dose is more difficult to titrate than when administered IV.⁷³ Naloxone can also be administered intranasally, although this route results in the delivery of unpredictable doses. In the prehospital setting, the time to onset of clinical effect of intranasal naloxone is comparable to that of IV or IM naloxone, largely because of the delay in obtaining IV access and slow absorption, respectively.^{3,41} Intranasal naloxone is not recommended as first-line treatment by health care providers.⁴² Nebulized naloxone (2 mg is mixed with 3 mL of 0.9% sodium chloride solution) has similar limitations in dose accuracy and is further limited in patients with severe ventilatory depression, the group most in need of naloxone. Although reports suggest successful use of nebulized naloxone, these patients are not optimal candidates for inhalation therapy because of the likelihood of over- or underdosing of naloxone.⁷⁴ Although needleless delivery is a clear prehospital advantage,⁴⁹ there appears to be little role for hospital use of intranasal or nebulized naloxone by health professionals.

Evaluation for the redevelopment of respiratory depression requires nearly continuous monitoring. Resedation should be treated with either repeated dosing of the antagonist or, in some cases, such as after a long-acting opioid agonist, with another bolus followed by a continuous infusion of naloxone. Two-thirds of the bolus dose of naloxone that resulted in reversal, when given hourly, usually maintains the desired effect.³³ This dose can be prepared for an adult by multiplying the effective bolus dose by 6.6, adding that quantity to 1000 mL, and administering the solution IV at an infusion rate of 100 mL/h. It must be emphasized that if resedation occurs rebolus with the dose of naloxone that provided reversal and titrate the infusion upward. Titration upward or downward is easily accomplished as necessary to both maintain adequate ventilation and avoid withdrawal. A continuous infusion of naloxone is not a substitute for continued vigilance. A period of 12 to 24 hours often is chosen for observation based on the presumed opioid, the route of administration, and the dosage form (sustained release). Body packers are a unique subset of patients who, because the reservoir of drug in the GI tract, require individualized antagonist management strategies (Special Considerations: SC5).

Use of longer acting opioid antagonists, such as naltrexone, places the patient at substantial risk for protracted withdrawal syndromes. The use of a long-acting opioid antagonist in acute care situations should be reserved for carefully considered special indications together with extended periods of observation or careful follow-up. For example, the unintentional ingestion of long acting opioid agonists in naive patients. An oral dose of 150 mg of naltrexone generally lasts 48 to 72 hours and should be adequate as an antidote for the majority of opioid-intoxicated patients. Discharge of opioid-toxic patients after successful administration of a long-acting opioid antagonist, although theoretically attractive, is not well studied. There are concerns about attempts by patients to overcome opioid antagonism by administering high doses of opioid agonist, with subsequent respiratory depression as the effect of the antagonist wanes.

Naltrexone is administered orally in a variety of dosage schedules for treatment of opioid dependence. A common dosing regimen is 50 mg/day Monday through Friday and 100 mg on Saturdays. Alternatively, 100 mg every other day or 150 mg every third day can be administered. The IM extended-release suspension is injected monthly at a recommended dose of 380 mg.

Methylnaltrexone SC dosing for opioid-induced constipation is weight based.⁷⁸ The dose is 0.15 mg/kg for patients who weigh less than 38 kg and more than 114 kg. For patients who weigh between 38 and less than 62 kg, 8 mg is administered, and for those between 62 and 114 kg, 12 mg is provided. Patients with stage 4 or 5 chronic kidney disease should receive half the recommended dose.

Alvimopan (Entereg) is approved by the Food and Drug Administration for the management of postoperative ileus or

constipation in the hospital setting. The dose is 12 mg orally 0.5 to 5 hours before surgery. The day after surgery, the maintenance dosage is 12 mg twice a day. The total maximum number of doses is 15 during hospitalization.

Buprenorphine

Naloxone reverses the respiratory depressant effects of buprenorphine in a bell-shaped dose–response curve.^{18,59,68,75}

Bolus doses of naloxone of 2 to 3 mg followed by a continuous infusion of 4 mg/h in adults were able to fully reverse the respiratory depression associated with IV buprenorphine administered in a total dose of 0.2 and 0.4 mg over 1 hour.⁶⁸

Reversal was not apparent until about 45 to 60 minutes after the infusion. A reappearance of respiratory depression occurred when the naloxone infusion was stopped because the distribution of naloxone out of the brain and its subsequent elimination from the body are much faster than those of buprenorphine. Consistent with a bell-shaped response curve, doses of naloxone greater than 4 mg/h actually led to the recurrence of respiratory depression. It is postulated that buprenorphine has differential effects on the μ opioid receptor subtypes (Chap. 38), with agonist activity at low doses and antagonist action at high doses. Therefore, excess naloxone antagonizes the antagonistic effects of buprenorphine, worsening respiratory depression.

FORMULATION AND ACQUISITION

Naloxone (Narcan) for IV, IM, or SC administration is available in concentrations of 0.4 and 1.0 mg/mL with and without parabens in 1 and 2 mL ampoules, vials, and syringes and in 10 mL multidose vials with parabens. Naloxone can be diluted in 0.9% sodium chloride solution or 5% dextrose to facilitate continuous IV infusion. Naloxone is stable in 0.9% sodium chloride solution at a variety of concentrations for up to 24 hours.

Naltrexone (Revia, Trexan) is available as a 50-mg capsule-shaped tablet. It is also available as a 380 mg vial for reconstitution with a carboxymethylcellulose and polysorbate diluent to form an injectable suspension intended for monthly IM administration (Vivitrol).

Methylnaltrexone (Relistor) is available as a 12-mg/0.6 mL solution for SC injection.⁶⁷ Alvimopan is available as a 12-mg capsule.

SUMMARY

- Naloxone, naltrexone, and methylnaltrexone are pure competitive opioid antagonists at the μ , δ , and δ receptors. Methylnaltrexone does not enter the CNS.
- Naloxone is the primary opioid antagonist used to reverse respiratory depression in patients manifesting opioid toxicity.
- This titrated low dose method of administration, starting at 0.04 mg in an adult, limits withdrawal-induced adverse effects, such as vomiting and the potential for aspiration pneumonitis, and a surge in catecholamines with the potential for cardiac dysrhythmias and ARDS.
- Naltrexone is used orally for patients after opioid detoxification to maintain opioid abstinence and as an adjunct to achieve ethanol abstinence.

Acknowledgment

Richard S. Weisman, PharmD, contributed to this Antidote in Depth in previous editions.

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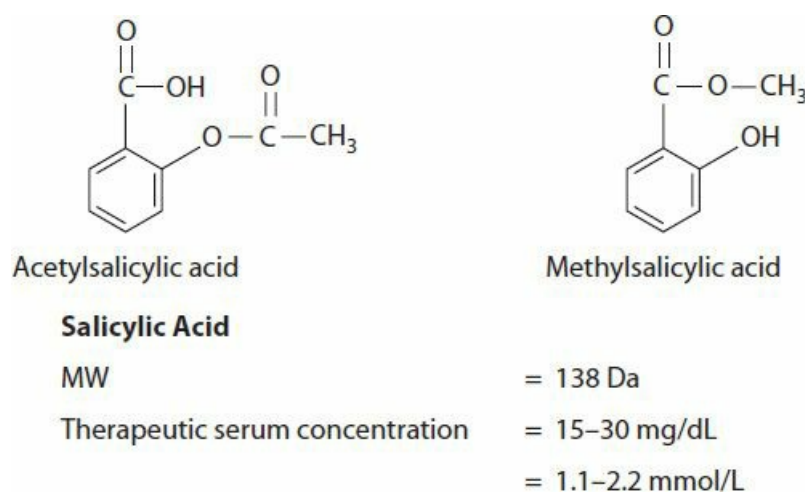
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39 SALICYLATES

Daniel M. Lugassy



HISTORY AND EPIDEMIOLOGY

The Ancient Egyptians recognized the pain-relieving effects of concoctions made from myrtle and willow leaves. Hippocrates may have been among the first to use willow bark and leaves from the *Salix* species to relieve fever, but it was not until 1829 that the glycoside salicin was extracted from the willow bark and used as an antipyretic. Seven years later, salicylic acid was isolated, and by the late 1800s, it was being used to treat gout, rheumatic fever, and elevated temperatures. The less irritating acetylated salicylate compound was first synthesized in 1833, and in 1899 acetylsalicylic acid was commercially introduced as aspirin by Bayer. With that, the modern era of aspirin therapy and salicylate toxicity began.

The American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) collects and reports annual exposure data in the United States. Analgesics, which include both aspirin and acetaminophen (APAP), continue to rank first among pharmaceuticals most frequently reported in human exposures ([Chap. 136](#)). Salicylate toxicity and fatalities have long been a major toxicological “concern.” From the 1950s to 1970s, salicylate was the leading cause of fatal childhood poisoning. The association with Reye syndrome; safer packaging; and the increased use of nonsteroidal antiinflammatory drugs (NSAIDs), APAP, and other alternatives to aspirin has decreased the incidence of unintentional salicylate poisoning. In the last 5 years of data available (2008–2012), there were 20 to 30 deaths per year reported ([Chap. 136](#)). Despite this decline in reported deaths and general use, it is still imperative that clinicians are adept at early recognition and swift management of patients with salicylate overdose.

Aspirin and other salicylate containing products continue to be some of the most common prescription and nonprescription xenobiotics used by the general public. Since landmark trials demonstrated the inhibition of platelet function by aspirin in the 1970s, its use became the standard of care for cardiovascular disease prevention and treatment. Subsequent investigations have demonstrated that aspirin can decrease the incidence of myocardial infarction, colon cancer, and transient ischemic attack. Its antiinflammatory properties have also continued to make it an active investigational xenobiotic for cancer.¹

Bayer, a company once associated exclusively with aspirin, several years ago turned to making products containing ibuprofen or APAP. But in a very recent move of re-branding, Bayer is now marketing a return of aspirin for pain relief with three new products containing aspirin alone; aspirin with caffeine; and aspirin, caffeine, and APAP. Salicylates continue to be readily available and will continue to lead to significant morbidity and mortality in overdose.

PHARMACOLOGY

Aspirin and other salicylates have analgesic, antiinflammatory, and antipyretic properties, a combination of traits shared by all of the NSAIDs ([Chap. 37](#)). Most of the beneficial effects of NSAIDs result from their inhibition of cyclooxygenase (COX). This enzyme enables the synthesis of prostaglandins, which in turn mediate inflammation and fever.^{116,136}

Contributing to the antiinflammatory effects and independent of the effects on prostaglandins, salicylates and other NSAIDs may also directly inhibit neutrophils.⁹ There are two types of salicylic acid esters, phenolic esters such as aspirin and carboxylic acid esters, including methyl salicylate, phenyl salicylate, and glycosalicylate.²⁶ Most of the studies of salicylate metabolism involve aspirin.²⁶ There is an implicit assumption that all members of the salicylate class have similar properties after being converted to salicylic acid.

Salicylates and NSAIDs are purportedly most effective in treating the pain accompanying inflammation and tissue injury. Such pain is elicited by prostaglandins liberated by bradykinin and other cytokines. Fever is also mediated by cytokines such as interleukin (IL)-1 β , IL-6, α and β interferons, and tumor necrosis factor- α , all of which increase synthesis of prostaglandin E₂. In turn, this inflammatory mediator increases cyclic adenosine monophosphate (cAMP), which triggers the hypothalamus to elevate the body temperature set point, resulting in increased heat generation and decreased heat loss.¹⁰⁸

Because platelets cannot regenerate COX-1, a daily dose of as little as 30 mg of aspirin inhibits COX-1 for the 8- to 12-day lifespan of the platelet.¹⁰⁸ Adverse effects of aspirin and some NSAIDs related to alteration of COX include gastrointestinal (GI) ulcerations and bleeding, interference with platelet adherence,¹⁰⁹ and a variety of metabolic and organ-specific effects described later.

To achieve an antiinflammatory effect for patients with chronic conditions such as rheumatoid arthritis, salicylates are primarily prescribed in doses sufficient to achieve a serum salicylate concentration between 15 and 30 mg/dL, which is considered the therapeutic range. Concentrations higher than 30 mg/dL are typically associated with signs and symptoms of toxicity.

PHARMACOKINETICS

Aspirin is rapidly absorbed from the stomach. The pK_a of aspirin is 3.5, and the majority is nonionized (ie, acetylsalicylic acid) in the strongly acidic stomach (pH 1–2).^{26,56} Although absorption of acetylsalicylate may be less efficient in the small bowel because of its higher pH, it is substantial and rapid because of the large surface area and the fact that the increase in pH increases the solubility of acetylsalicylate.^{84,85} After ingestion of therapeutic doses of immediate release acetylsalicylate, significant serum concentrations are achieved in 30 minutes, and maximum concentrations are often attained in less than 1 hour.²⁶

The plasma half-life of aspirin is about 15 minutes, because it is rapidly hydrolyzed to salicylate. The apparent half-life for salicylate is about 2 to 3 hours at antiplatelet doses and increases to 12 hours at antiinflammatory doses demonstrates dose dependent elimination.⁸⁸ Aspirin undergoes biotransformation in the liver and is then eliminated by the kidneys. The apparent volume of distribution (Vd) increases from 0.2 L/kg at low concentrations to 0.3 to 0.5 L/kg at higher concentrations.^{73,74,117}

TOXICOKINETICS

In overdose, several factors contribute to significantly altered pharmacokinetics that can present very challenging obstacles to effectively managing patients poisoned with salicylates. The dose obviously is critical in contributing to the magnitude and duration of toxicity, but other important factors include the formulation, rate of gastric emptying, bezoar formation, hepatic and renal function, and both the serum and urine pH.

There is a decrease in protein (albumin) binding from 90% at therapeutic concentrations to less than 75% at toxic concentrations caused by saturation of protein binding sites.^{2,11,33} Salicylates have substantially longer apparent half-lives at toxic concentrations than at therapeutic concentrations, varying from 2 to 4 hours at therapeutic concentrations to as long as 20 hours at toxic concentrations.^{28,73} The dosage form of salicylates (eg, effervescent, enteric coated) influences the absorption rate.^{107,110,131} Therapeutic doses of enteric-coated tablets may not produce peak serum concentrations until 4 to 6 hours after ingestion, and in overdose the peak may not be reached until 24 hours after ingestion.^{34,131} Delayed absorption of aspirin may result from salicylate induced pylorospasm or pharmacobezoar formation.^{11,107,113}

Salicylates are conjugated with glycine and glucuronides in the liver and are eliminated by the kidneys. Approximately 10% of salicylates are excreted in the urine as free salicylic acid, 75% as salicyluric acid, 10% as salicylic phenolic glucuronides, 5% as acylglucuronides, and 1% as gentisic acid¹⁰⁸ (Fig. 39–1). As the concentration of salicylates increases, two of the five pathways of elimination—those for salicyluric acid and the salicylic phenolic glucuronide—become saturated and exhibit zero-order kinetics. As a result of this saturation, overall salicylate elimination changes from first-order kinetics to zero-order kinetics^{73,74} (Chap. 9). In a healthy adult, these altered saturation kinetics may occur after as little as 1 to 2 g of acute aspirin ingestion.⁷³

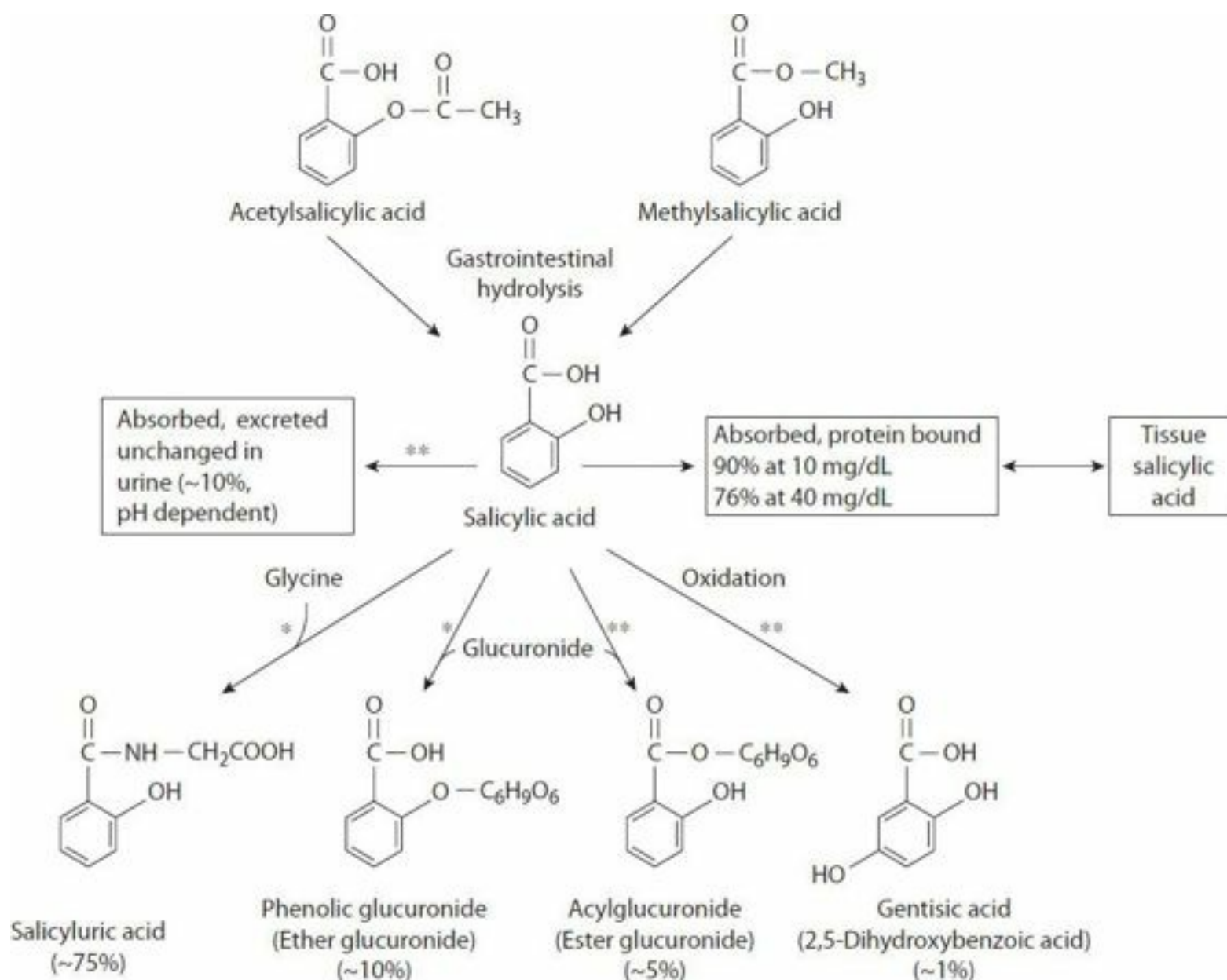


FIGURE 39–1. Salicylic acid metabolism. At excessive doses, the four mechanisms of salicylic acid metabolism are overloaded, leading to increased tissue binding, decreased protein binding, and increased excretion of unconjugated salicylic acid. Asterisk indicates Michaelis-Menten kinetics; double asterisk indicates first-order kinetics.

When administered chronically, a small increase in dosage or a small decrease in metabolism or elimination may result in substantial increases in serum salicylate concentrations and the risk of toxicity.⁶⁵ At very high serum concentrations, salicylate elimination may again resemble first-order elimination as an increasing fraction undergoes renal clearance.

Free salicylic acid is filtered through the glomerulus and is both passively reabsorbed and actively secreted from the proximal tubules. More than 30% of an ingested salicylate dose may be eliminated in alkaline urine and as little as 2% in acidic urine.¹²⁷ Salicylate conjugates (glycine and glucuronides) are filtered and secreted by the proximal tubules; salicylate conjugates are not reabsorbed across renal tubular cells because of limited lipid solubility, and the amount eliminated depends on the glomerular filtration rate and proximal tubule secretion but not urine pH. Protein-binding abnormalities, urine and plasma pH variations, and delayed absorption all influence both the maximum salicylate concentration and the rate of decline.^{85,107}

Other Forms of Salicylate

Topical Salicylate, Methyl Salicylate (Oil of Wintergreen), and Salicylic Acid. Topical salicylates, which are used as keratolytics (salicylic acid) or as rubefacients ($\leq 30\%$ methyl salicylate), are rarely responsible for salicylate poisoning when used in their intended manner because absorption through normal skin is very slow. However, particularly in children, extensive application of topical preparations containing methyl salicylate may result in poisoning.^{14,129} After 30 minutes of contact time, only 1.5% to 2.0% of a dose is absorbed, and even after 10 hours of contact with the methyl salicylate, only 12% to 20% of the salicylate is systemically absorbed.¹⁴ Heat, occlusive dressings, young age, inflammation, and psoriasis all increase topical salicylate absorption.^{16,17} In a study of healthy volunteers, a profound effect of transdermal absorption of methyl salicylate was demonstrated from exercise and heat exposure, with a threefold increase

in the systemic availability of salicylate.²⁵

Ingestion of methyl salicylate may be disastrous because 1 mL of 98% oil of wintergreen contains an equivalent quantity of salicylate as 1.4 g of aspirin. The minimum toxic salicylate dose of approximately 150 mg/kg body weight can almost be achieved with 1 mL of oil of wintergreen, which represents 140 mg/kg of salicylates for a 10-kg child. In Hong Kong, medicated oils containing methyl salicylate accounted for 48% of acute salicylate poisoning cases treated in one hospital.¹⁶ Methyl salicylate is rapidly absorbed from the GI tract, and much, but not all, of the ester is rapidly hydrolyzed to free salicylates. Despite rapid and complete absorption, serum concentrations of salicylates are much less than predicted after ingestion of methyl salicylate containing liniment compared with oil of wintergreen.¹²⁹ Vomiting is common, along with abdominal discomfort. The onset of symptoms usually occurs within 2 hours of ingestion.¹⁷ Patients with methyl salicylate exposure have died in less than 6 hours, emphasizing the need for early determinations of salicylate concentrations in addition to frequent testing after such exposures.

Bismuth Subsalicylate. Bismuth subsalicylate, which is available in several nonprescription formulations, releases the salicylate moiety in the GI tract, where it is subsequently absorbed. Each milliliter of common liquid preparations of bismuth subsalicylate contains 8.7 mg of salicylic acid.³⁹ After a large therapeutic dose (60 mL), peak salicylate concentrations may reach 4 mg/dL at 1.8 hours after ingestion.³⁹ Patients with diarrhea and infants with colic using large quantities of bismuth subsalicylate may develop salicylate toxicity.¹²⁵ Chronic use should also raise concerns for bismuth toxicity (Chap. 90).

PATHOPHYSIOLOGY

Because salicylic acid is a weak acid, at physiologic pH, it exists predominantly in a charged (ionized) state (Chap. 12). But in overdose as the serum pH falls, more salicylate shifts toward a nonionized (uncharged) salicylic acid form that is highly permeable, allowing swift movement across lipid bilayers and cell membranes. This is an important effect in that it allows salicylic acid to enter cells exerting its toxic effects across a wide variety of organs and is discussed later as a target for management.

Acid–Base and Metabolic Effects

Salicylate interferes with the Krebs cycle, which limits production of adenosine triphosphate (ATP).⁶³ It also uncouples oxidative phosphorylation, causing accumulation of pyruvic and lactic acids and releasing energy as heat⁶⁸ (Chaps. 12 and 13). Salicylate-induced increases in fatty acid metabolism generates ketone bodies, including β -hydroxybutyric acid, acetoacetic acid, and acetone. Toxic concentrations of salicylate impair renal hemodynamics, leading to the accumulation of inorganic acids. The net result of all of these metabolic processes is an anion gap metabolic acidosis (Chap. 19) in which the unmeasured anions include salicylate and its metabolites, lactate, ketoacids, and inorganic acids.

The salicylate effect on glucose metabolism is variable and may depend on the severity and phase of toxicity. Salicylate administration in mice increases glycogenolysis and can result in hyperglycemia.¹¹⁵ Early adrenergic effects of acute salicylate toxicity may stimulate epinephrine and glucagon release, enhancing glycogenolysis as well as gluconeogenesis. But salicylate can inhibit alanine and aspartate aminotransferase, and both enzymes provide key amino acid substrates for gluconeogenesis. Hypoglycemia may also occur because of the combined effect of increased energy demands, depletion of glycogen stores, and decreased gluconeogenesis.¹⁰⁴

Salicylate poisoned mice had dramatic increases in serum lactate concentration compared with control mice, likely because of increased glycogenolysis and anaerobic glycolysis to compensate partly for the energy loss caused by uncoupling of oxidative phosphorylation.^{53,83} There was also a marked increase in oxygen consumption in mice even with low salicylate concentrations, highlighting the importance of salicylate induced uncoupling of oxidative phosphorylation.⁵⁴ Several investigations using intact or fragmented mitochondria demonstrate that increasing concentrations of salicylate result in decreased phosphate uptake and a concomitant decrease in the phosphate/oxygen (P/O) ratio.^{83,94} The impaired P/O ratio demonstrates the inefficiency of ATP production by illustrating that the rate of phosphate incorporation into ATP per molecule falls despite oxygen consumed during oxidative phosphorylation. Salicylates reduce lipogenesis by blocking the incorporation of acetate into free fatty acids and increase peripheral fatty acid metabolism as an energy source, resulting in ketone formation. Salicylate-induced increased fatty acid metabolism generates ketone bodies, including β -hydroxybutyric acid, acetoacetic acid, and acetone.

NEUROLOGIC EFFECTS

The central nervous system (CNS) effects are the most visible and most consequential clinical effects in salicylate-poisoned patients. With increasing CNS salicylate concentrations, neuronal energy depletion likely develops as salicylate uncouples neuronal and glial oxidative phosphorylation.⁸³ Several other mechanisms also likely contribute to the neurotoxic

effects of salicylates. Salicylate also causes release of apoptosis inducing factor (AIF) or cytochrome C, triggers p38 mitogen, activated protein kinase, and activates glial caspase-3, which are responsible for programmed neuronal cell death.¹⁰⁵ It is likely that these effects in addition to severe cellular acidosis lead to neuronal dysfunction and ultimately cerebral edema.

Salicylate poisoning may produce a clinical discordance between serum and cerebrospinal fluid (CSF) glucose concentrations.¹⁰⁴ Despite normal serum glucose concentrations, CSF glucose concentration decreased 33% in salicylate-poisoned mice compared with control mice.¹²³ In other words, the rate of CSF glucose use exceeded the rate of supply even in the presence of a normal serum glucose concentration. This hypoglycorrhachia demonstrates that altered glucose metabolism and transport may also play a role in the deleterious neurologic effects of salicylate poisoning. Salicylate-poisoned mice have lower CSF glucose concentrations compared with control mice but can maintain similar concentrations of ATP by enhanced glycolysis. Administration of dextrose in these salicylate-poisoned mice suppressed clinical signs of toxicity underlying the importance of providing supplemental glucose despite normal serum concentrations as discussed later in the management of toxicity.¹²³

Hepatic Effects

Hepatic injury from either acute or chronic overdose of salicylate is rare. Although the hepatocyte is the location of its toxic effects on several metabolic pathways such as glycogenolysis and the Krebs cycle, other concurrent co-ingestants and causes should be considered if there is a clinically significant elevation of aminotransferases or bilirubin concentration or signs of acute liver failure.¹³⁴

An unavoidable historical link exists between the hepatic encephalopathy in Reye syndrome and aspirin. A buildup of fatty acids in the hepatocyte resulting in microvesicular steatosis is characteristic of Reye syndrome. This may occur through salicylate depletion of intrahepatocyte coenzyme A (Co-A), where fatty acids entering the hepatocyte cytoplasm cannot be transported into the mitochondria for β -oxidation. Although there is no mechanism to explain why aspirin has a causal relationship in Reye syndrome, it is clear from epidemiologic evidence that aspirin is an essential cofactor among others in the development of this syndrome.⁴⁶

Otolaryngologic Effects

The molecular mechanism of salicylate ototoxicity is not completely understood but appears to be multifactorial. Inhibition of cochlear COX by salicylate increases arachidonate, enabling calcium flux and neural excitatory effects of N-methyl-D-aspartic acid (NMDA) on cochlear spinal ganglion neurons.^{100,101,112} Also, the prevention of prostaglandin synthesis interferes with the Na^+ - K^+ -adenosine triphosphatase (ATPase) pump in the stria vascularis, and the vasoconstriction decreases cochlear blood flow.^{12,15,37,61} Membrane permeability changes cause a loss of outer hair cell turgor in the organ of Corti, which may impair otoacoustic emissions.^{100,102} A more complete description of the pathophysiology of salicylate-induced ototoxicity and sensorineural alterations as well as comparisons with the patterns of other ototoxic xenobiotics can be found in [Chap. 26](#).

Pulmonary Effects

Salicylates have very potent stimulatory effects on respiratory drive via several mechanisms. Direct stimulation of the medullary respiratory neurons produces hyperpnea and tachypnea even at therapeutic concentrations. In fact, in a human trial, salicylates decreased the number and duration of apneic events in patients with sleep apnea.⁹⁶ Increased sensitivity to PCO_2 and pH further increases ventilation. Carotid body and peripheral arterial chemoreceptor stimulation also contribute to salicylate-induced hyperventilation.⁸¹

Patients with either acute or chronic salicylism may develop acute respiratory distress syndrome (ARDS). It is often a sign of severe and advanced toxicity and can be lethal. One study¹⁰⁶ that summarized data from nearly 400 consecutive cases of salicylate toxicity reported in the literature^{4,51,122,128} concluded that ARDS occurred in approximately 7% of cases. The development of ARDS in salicylate poisoning is associated with a history of cigarette smoking, chronic overdose, metabolic acidosis, and neurologic symptoms at the time of arrival.⁹⁰

Although the exact etiology of salicylate-induced ARDS is unclear, as with other etiologies ARDS can result from increased pulmonary capillary permeability and subsequent exudation of high-protein edema fluid into the interstitial or alveolar spaces.⁵⁷ Adrenergic excess in salicylate poisoning may injure the hypothalamus, leading to a shift in blood from the systemic to the pulmonary circulation because of a loss of left ventricular compliance with left atrial and pulmonary capillary hypertension ([Chap. 17](#)). Additionally, the resulting hypoxia produces pulmonary arterial hypertension and a local release of vasoactive substances, worsening ARDS.⁵⁸ Unventilated salicylate-poisoned sheep were more likely to develop ARDS compared with a mechanically ventilated control group, suggesting that the mechanical stress of prolonged and severe hyperventilation is a significant contributing factor to this complication.⁷⁸

Gastrointestinal Effects

Salicylate disrupts the mucosal barrier that normally protects the gastric lining from the extremely acidic contents of the stomach. GI injury leading to ulcers or bleeding are among the most common adverse effects from therapeutic use of aspirin, but in acute overdose, the most common manifestations result from local gastric irritation presenting with nausea and vomiting. Emesis appears to be triggered both by local mucosal irritation and central stimulation of the chemoreceptor trigger zone.¹⁰ Hemorrhagic gastritis, decreased gastric motility, and pylorospasm result from the direct gastric irritant effects of salicylates.¹¹⁰

Renal Effects

The kidneys play a major role in the excretion of salicylate and its metabolites. Although some believe that salicylates are nephrotoxic, the majority of experimental evidence does not strongly support this notion.^{24,35,95} Most of the adverse renal effects historically associated with salicylates occurred with use of combination products such as aspirin–phenacetin–caffeine (APC) tablets and appear to have been mostly caused by the phenacetin.³⁵ Renal papillary necrosis and chronic interstitial nephritis, initially characterized by reduced tubular function and reduced concentrating ability, rarely occur in adults using salicylates unless they have chronic illnesses that already compromise renal function.

Volume losses in patients with salicylate toxicity that develop from hyperventilation and hyperthermia may also cause prerenal acute kidney injury (AKI). Rarely, salicylates may also induce a Fanconilike syndrome with generalized proximal tubular dysfunction characterized by glucosuria (despite normal serum glucose), proteinuria, aminoaciduria, and uric acid wasting.¹²⁴

Hematologic Effects

The hematologic effects of salicylate poisoning include hypoprothrombinemia and platelet dysfunction.⁹³ The platelet dysfunction, caused by irreversible acetylation of COX-1 and COX-2, prevents the formation of thromboxane A₂, which is normally responsible for platelet aggregation. Although the platelets are numerically and morphologically intact, they are unresponsive to thrombogenic stimulation. At supratherapeutic doses, salicylate decreases the plasma concentration of the γ -carboxyglutamate containing coagulation factors and an accumulation of microsomal substrates for vitamin K dependent carboxylase in the liver and in the lung.¹¹¹ The result of this interruption of vitamin K cycling is similar to that of warfarin,⁹² leading to hypoprothrombinemia (factor II) as well as decreases in factors VII, IX, and X (Chap. 60).

CLINICAL MANIFESTATIONS OF SALICYLATE POISONING

The following sections describe the typical clinical manifestations that follow toxic exposures to salicylates. The natural course of acute ingestions begins with nonspecific GI symptoms, early tachypnea caused by direct central respiratory stimulation, development of an anion gap metabolic acidosis, and several minor neurologic sequelae. As the acidosis worsens, symptoms progress and will invariably evolve to severe CNS toxicity. Hyperthermia, cerebral edema, coagulopathy, ARDS, and severe acidemia are the gravest clinical consequences and are often preterminal events. Cerebral edema is often seen at autopsy in those who succumb to salicylate toxicity.

The earliest signs and symptoms of salicylate toxicity, which include nausea, vomiting, diaphoresis, and tinnitus, typically develop within 1 to 2 hours of acute exposure.^{12,44} But the type of salicylate containing preparation, comorbidities, co-ingestants, and compromise in renal or hepatic function may alter the onset of symptoms that can be delayed up to 24 hours after exposure.¹¹⁰ Case reports of enteric-coated aspirin tablet ingestions have demonstrated delays in symptom onset and time to initial detectable salicylate concentration, with peak salicylate concentrations reported to occur 2 to 3 days after initial exposure.^{31,131}

Acute Salicylate Toxicity

Salicylates are extremely irritating to the GI lining; early vomiting after ingestion may be a warning sign of a clinically significant ingestion. Emesis occurs both by direct GI irritation and from salicylate-induced stimulation of the chemoreceptor trigger zone.¹⁰ Pylorospasm, delayed gastric emptying, and decreased GI motility can all be present, complicating toxicity by altering absorption kinetics. Hemorrhagic gastritis also occurs, likely as a consequence of severe emesis and alteration of protective GI barriers.

The initial evaluation of a patient suspected of salicylate poisoning must start at the bedside with a thorough assessment of the respiratory rate and depth. Subtle tachypnea or hyperpnea should not be overlooked because if missed, delays may occur in the initiation of appropriate laboratory analysis and management. Direct central stimulation of the respiratory center increases minute ventilation, determined by the product of respiratory rate and tidal volume. A primary respiratory alkalosis predominates initially, although an anion gap metabolic acidosis begins to develop early in the course of

salicylate toxicity. By the time a symptomatic adult patient presents to the hospital after a salicylate overdose, a mixed acid–base disturbance is often prominent.⁴⁴ This latter finding includes two primary processes, respiratory alkalosis and metabolic acidosis, and is discernible by arterial blood gas (ABG) or venous blood gas (VBG) and serum electrolyte analyses. In one study of 66 salicylate-poisoned adults, 22% had respiratory alkalosis, and 56% had mixed respiratory alkalosis and metabolic acidosis.⁴⁴

On presentation, salicylate poisoned adults who demonstrate respiratory acidosis should alert the clinician to the fact that systemic toxicity is severe. This patient may be late in the clinical course of poisoning and have salicylate induced ARDS, fatigue from hyperventilating for a prolonged period of time, or CNS depression (from either salicylate itself or co-ingestants). These broad variations of clinical toxicity can be divided into three general time frames based on rapidly available laboratory testing. Early, middle, and late salicylate poisoning are demonstrated in [Table 39–1](#).

TABLE 39–1. Acid-Base Stages of Salicylate Toxicity

Early: Respiratory alkalosis, alkalemia, and alkaluria

Middle: Respiratory alkalosis, metabolic acidosis, alkalemia, and aciduria

Late: Metabolic acidosis with either a respiratory alkalosis or respiratory acidosis, aciduria, and acidemia

Mixed overdoses are common; in one study, one-third of patients with a presumed primary salicylate overdose had taken other xenobiotics.⁴⁴ Benzodiazepines, barbiturates, alcohol, and cyclic antidepressants all blunt the centrally induced hyperventilatory response to salicylates, resulting in either actual respiratory acidosis ($\text{PCO}_2 > 40$ mm Hg) or metabolic acidosis without some respiratory compensation ($\text{PCO}_2 < 40$ mm Hg but inappropriately high for the concomitant degree of metabolic acidosis). In both adults and children, the development of respiratory acidosis may occur as salicylate poisoning progresses. The combination of metabolic and respiratory acidosis in a salicylate poisoning results in severe and worsening acidemia that is an exceedingly grave situation and almost invariably is a preterminal event.⁹⁸

When clinical and radiographic manifestations of ARDS are observed in the setting of salicylate toxicity, the following conditions should be considered: aspiration pneumonitis, viral and bacterial infections, neurogenic ARDS, and salicylate-induced ARDS^{58,64} ([Chap. 29](#)). In 111 consecutive patients with peak salicylate concentrations above 30 mg/dL, ARDS occurred in 35% of patients older than 30 years of age and none of the 55 patients younger than 16 years of age. Risk factors for developing ARDS included cigarette smoking, chronic salicylate ingestion, and the presence of neurologic symptoms on admission. The average arterial blood pH was 7.37 in the six adult patients with ARDS and 7.46 in the 30 adults without ARDS. There was no significant difference in salicylate concentrations, which were approximately 57 mg/dL in both groups.¹²⁸ In a 2-year review of all salicylate deaths in Ontario, Canada, 59% of 39 autopsies revealed pulmonary pathology, mostly “pulmonary edema” (ARDS).⁸⁰

Although hyperventilation is centrally mediated, patients may develop a spectrum of CNS abnormalities that includes confusion, agitation, and lethargy and then ultimately seizures and coma. Human and animal evidence suggests that hypoglycorrhachia despite euglycemia contributes to the neurotoxic effects. Stupor, coma, and delirium have been acutely reversed by the administration of dextrose in children and adults with salicylate toxicity and normal serum glucose concentrations. In one report, a child underwent lumbar puncture, and CSF analysis demonstrated no detectable glucose.²³ The most severe neurologic clinical findings are likely associated with the development of cerebral edema and portend a poor prognosis. Excluding effects on ventilation, signs of neurologic toxicity, even if mild, should be of great concern.

Tinnitus, a subjective sensation of ringing or hissing with or without hearing loss, loss of absolute acoustic sensitivity, and alterations of perceived sounds are the three effects resulting from exposure to large doses of salicylates.¹⁵ The pattern of salicylate-induced auditory sensorineural alterations is different than that of other ototoxic xenobiotics.¹⁵ Tinnitus should demonstrate to clinicians that CNS toxicity has occurred even without alterations in mental status. As CNS salicylate concentrations increase, tinnitus is rapidly followed by diminished auditory acuity that sometimes leads to deafness.¹² As acute toxicity progresses, other CNS effects may include vertigo, hyperactivity, agitation, delirium, hallucinations, lethargy, seizures, and stupor. Coma is rare and is generally a late finding occurring in severe acute poisoning or mixed overdoses.^{4,133}

Paratonia, extreme muscle rigidity, has been observed in severe salicylate poisoning pre- and postmortem, and in one case, it was even unresponsive to succinylcholine.^{80,103} Decreased ATP production, impaired glycolysis, increased lactate, and uncoupling of muscular oxidative phosphorylation likely contribute to this phenomenon. This excess neuromuscular activity may lead to rhabdomyolysis and most concerning hyperthermia that is typically a preterminal condition.^{72,83,84}

Chronic Salicylate Toxicity

Chronic salicylate poisoning most typically occurs in elderly individuals as a result of unintentional overdosing on salicylates used to treat chronic conditions such as rheumatoid arthritis and osteoarthritis^{5,29,65} (Table 39–2). Presenting signs and symptoms of chronic salicylate poisoning can be similar to those of acute toxicity and include nausea and vomiting, hearing loss and tinnitus, dyspnea and hyperventilation, tachycardia, hyperthermia, and neurologic manifestations such as confusion, delirium, agitation, hyperactivity, slurred speech, hallucinations, seizures, and coma.^{4,32,71} Although there is considerable overlap with acute salicylate poisoning, the slow, insidious onset of chronic poisoning in elderly individuals frequently causes delayed recognition of the true cause of the patient’s presentation.^{4,44,70}

TABLE 39–2. Differential Characteristics of Acute and Chronic Salicylate Poisoning

	<i>Acute</i>	<i>Chronic</i>
Age	Younger	Older
Etiology	Overdose usually intentional	Therapeutic misadventures; iatrogenic
Diagnosis	Easily recognized	Frequently unrecognized
Other diseases	None	Underlying disorders (especially chronic pain conditions)
Suicidal ideation	Typical	Atypical
Serum concentrations	Marked elevation	Intermediate elevation
Mortality	Uncommon when recognized and properly treated	More common due to delayed recognition

Typically, ill patients who have chronic salicylate poisoning may be misdiagnosed as having delirium, dementia, or encephalopathy of undetermined origin, or diseases such as sepsis (fever of unknown origin), alcoholic ketoacidosis, respiratory failure, or cardiopulmonary disease.^{4,6,20,36} Unfortunately, many of the signs and symptoms of chronic salicylate toxicity may be mistakenly attributed to the illness for which the salicylates were administered.^{20,119} Despite an extensive evaluation during a first hospitalization for ARDS, chronic salicylism was not diagnosed until a second hospitalization for the same respiratory symptoms.²² This case highlights the need to include chronic salicylism in the differential for ARDS with or without neurologic symptoms.

In a study of 73 consecutive adults hospitalized with salicylate poisoning, 27% were not correctly diagnosed for as long as 72 hours after admission.⁴ These patients manifested toxicity with standard or excessive therapeutic regimens and had significant associated diseases without a history of previous overdoses. In this group, 60% of the patients had a neurologic consultation before the diagnosis of salicylism was established. When diagnosis is delayed in elderly individuals, the morbidity and mortality associated with salicylate poisoning are high. The mortality rate was reported to be as high as 25% in the 1970s,⁴ and there are no data to suggest that survival after delayed diagnosis is substantially better today.

EVALUATION AND DIAGNOSTIC TESTING

The most commonly reported route of salicylate exposure is from the acute ingestion of aspirin, which, as mentioned earlier, has a very short serum half-life of about 15 minutes during which time it is rapidly converted to salicylate. The symptoms of toxicity are due to the systemic effects of salicylate and not the parent compound. Systemic toxicity is concerning after the following exposures: ingestions of 150 mg/kg or 6.5 g of aspirin, whichever is less; ingestion of greater than a lick or taste of oil of wintergreen (98% methyl salicylate) by children younger than 6 years of age; and more than 4 mL of oil of wintergreen by patients 6 years of age and older.²¹ These patients as well as those with significant topical exposures and signs of toxicity should be promptly evaluated for salicylate toxicity.

The initial approach to a patient suspected of salicylate toxicity should obviously include a serum salicylate concentration. But it is very important to recognize that other laboratory assays such as an ABG or VBG, electrolytes to determine anion gap, the presence of serum or urine ketones, and a lactate concentration can be critical in uncovering an unrecognized salicylate poisoning. It also may be important to evaluate renal and hepatic function because dysfunction in either will exacerbate toxicokinetic effects in patients with acute or chronic exposures.

As aspirin or other parent compounds are metabolized to salicylate, there should be a drop in serum bicarbonate,

leading to an increase in the anion gap. Elevated anion gaps are caused by increases in unmeasured anions that are primarily salicylate but also related to increases in lactic acid, ketoacids, and daily endogenous dietary acids. Volume loss from vomiting and excess metabolic energy can cause AKI, which will decrease the elimination of dietary acids.

Several studies have suggested that empiric serum salicylate concentrations are not required as part of a general toxicologic evaluation in patients with acute self-poisoning. Routine salicylate testing is likely unnecessary without a positive history of salicylate ingestion, an inability to obtain a valid history (altered mental status), or clinical features of salicylate poisoning.^{18,48,130} One retrospective study also suggested that screening for salicylism is not needed in the absence of an elevated anion gap.¹¹⁴ Although an anion gap metabolic acidosis is likely found in most cases of salicylate toxicity, severe salicylism may falsely elevate serum chloride, bringing the anion gap closer to a normal range.⁵⁹

Although it may be wise to curtail empiric testing, clinicians should likely err on the side of ordering a salicylate assay if there is any clinical concern because the morbidity and mortality are significantly increased with delays in recognition and management. Many of the signs and symptoms of salicylate toxicity are vague and may be mistakenly attributed to another illness with disastrous consequences. In the review of all salicylate deaths in Ontario, Canada, in 1983 and 1984, the author noted that in six of the 23 (26%) patients who arrived alert, no salicylate determination appears to have been made and that probably neither the diagnosis nor the severity of the salicylate poisoning was recognized.⁸⁰

Salicylate Analysis

Serum salicylate concentrations are relatively easy to obtain in most hospital laboratories today. Several methods are available for determining serum salicylate concentrations. The Trinder assay is the most popular method for the measurement of salicylate in serum by using spectrophotometric analysis. Trinder's reagent contains mercuric chloride and hydrochloric acid used to precipitate serum proteins. The measured absorbance at 540 nm of a ferric ion-salicylate complex allows for accurate determination of the serum salicylate concentration. Historically there have been several bedside urine qualitative tests (ie, mercuric chloride, ferric chloride) used to assess for the presence of salicylate. They have no clinical utility today because of poor specificity and chemical hazards and are no longer permissible under the federal Clinical Laboratory Improvement Amendments (CLIA) in the United States.

Serum salicylate concentrations are commonly reported in mg/dL in the United States, but confusion can arise because values can also be reported in mg/L and $\mu\text{g/mL}$. Analyzing and reporting salicylate concentrations as mg/L when the clinician is accustomed to receiving results as mg/dL or inadvertently reporting actual mg/L (before internal laboratory conversion) produces erroneous results.⁴⁹ These may suggest a toxic salicylate concentration in a patient whose serum salicylate concentration is actually within the therapeutic range (eg, "165 mg/L" instead of "16.5 mg/dL"). Most errors can be eliminated before initiation of aggressive therapy, such as hemodialysis (HD), by determining whether the reported salicylate concentration is consistent with the clinical presentation and ABG or VBG results and, when time permits, repeating the salicylate determination with appropriate consideration for methodology and conversion calculations.⁴⁹ Using the earlier example, a patient with a serum salicylate concentration of 165 mg/dL would undoubtedly show clinical signs of salicylate toxicity and have a profound acid-base abnormality, but a patient with a concentration of 165 mg/L would likely be asymptomatic.

It should also be noted that several clinical scenarios and xenobiotic exposures are recognized to cause false-positive or falsely elevated true salicylate concentrations. Medications that may interfere with the assay include thioridazine, promethazine, prochlorperazine, chlorpromazine, acetylcysteine, and cysteamine.⁸ Significantly falsely elevated serum salicylate concentrations are well recognized after diflunisal overdose.^{30,118} Hyperbilirubinemia can create clinically significant false-positive results in neonates and adults.^{8,13} Interestingly, hyperlipidemia can also cause significant interference and false elevation of serum salicylate concentrations.¹⁹ If there is concern for false salicylate concentrations, clinicians should contact laboratory personnel, who often have information regarding instrument-specific recognized interferences for each assay as published by the manufacturer. Several techniques may be used to determine a true salicylate concentration in the setting of a known interference. One of the most sensitive and specific assays now available is an automated immunoassay based on specific antisalicylate antiserum with fluorescence polarization immunoassay (FPIA) detection technology.⁸

Interpretation of Serum Salicylate Concentrations and Correlation with Toxicity

The recommended therapeutic concentration of salicylate is 10 to 30 mg/dL, but this varies by indication. Antiinflammatory dosing usually is advised to be on the higher end of this spectrum, but analgesic effects can be observed as low as 5 to 10 mg/dL. Values above 30 mg/dL are usually not found unless there is a supratherapeutic, acute, or chronic toxic exposure.

The correlation of serum salicylate concentrations and clinical toxicity is often poor and dependent on several factors. A concurrent arterial or venous blood pH should be determined when a serum salicylate concentration is obtained because in the presence of acidemia, more salicylic acid leaves the blood and enters the CSF and other tissues (Fig. 39-2), increasing the toxicity. A decreasing serum salicylate concentration may be difficult to interpret because it may reflect

either an increased tissue distribution with increasing toxicity or an increased clearance with decreasing toxicity. A decreasing serum salicylate concentration accompanied by a decreasing or low blood pH should be presumed to reflect a serious or worsening situation, not a benign or improving one. Patients with chronic toxicity demonstrate more significant clinical effects at lower concentrations compared with acute toxicity given the increased distribution over time into tissue compartments and specifically the CNS.

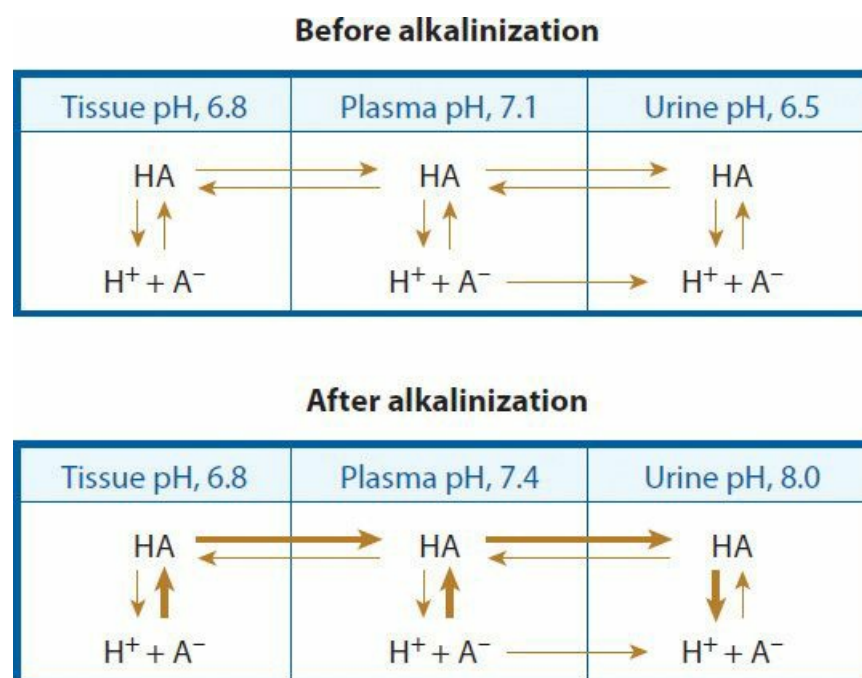


FIGURE 39–2. Rationale for alkalization. Alkalization of the plasma with respect to the tissues and alkalization of the urine with respect to plasma shifts the equilibrium to the plasma and urine and away from the tissues, including the brain. This equilibrium shift results in “ion trapping.”

Although impractical clinically, salicylate concentrations in the CSF are likely the most accurate measure of toxicity, directly correlating with death in a rat model.⁵⁴ Animals that were lethally poisoned with salicylate were comatose and died from seizures. The time to death after salicylate administration varied greatly as did the blood, muscle, and liver salicylate concentrations. However, regardless of the time of death and the concentrations in blood, muscle, or liver, all animals died with a consistent range of CSF salicylate concentrations.⁵⁴ Inhalation of CO₂ (lowering serum pH) in a rat resulted in a precipitous decrease in serum salicylate concentrations, which returned to baseline rapidly after the discontinuation of CO₂.⁵³ This suggests that the salicylate redistributed into tissue during the period of induced respiratory acidosis and reequilibrated after its correction. After administration of radiolabeled salicylate to cats, autoradiographs of the brain visually and objectively documented the profound effect that acidemia has on the distribution of salicylate into the brain.⁴⁷

Before serum assays were readily available, physicians who prescribed aspirin would advise patients to take repeated doses until tinnitus occurred and then “back off” a little to maintain this “steady state.” Tinnitus and the subsequent reversible hearing loss typically occur at serum salicylate concentrations of 20 to 45 mg/dL.^{12,15,87} This prompted investigations into whether salicylate-induced tinnitus could be used as an indicator of serum salicylate concentration and toxicity. Unfortunately, some patients with therapeutic concentrations of salicylates had tinnitus, and many with higher or toxic concentrations had no tinnitus. In a study of 94 patients with salicylate concentrations above 30 mg/dL on one or more occasions, tinnitus only correlated with serum salicylate concentrations in 30%; 55% had no tinnitus, although audiologic testing results were usually abnormal regardless of the patient’s perception of presence or absence of tinnitus.⁵⁰ Thus, although symptomatic ototoxicity may be a helpful warning sign of salicylate toxicity when present, it is too nonspecific and too insensitive to serve as an indicator of serum salicylate concentrations.

MANAGEMENT

The management of patients with salicylate toxicity is aimed at supporting vital signs and organ function, preventing or limiting ongoing exposure from the gut or skin, and enhancing elimination of salicylate that has already entered the systemic circulation. It is imperative to understand that there is no true antidote for salicylate toxicity; no xenobiotic can combat the clinical toxicity demonstrated in consequential exposures. HD, as discussed later, aims to remove salicylate from the tissues but may not correct severe organ toxicity such as ARDS or cerebral edema and can therefore not guarantee survival after severe toxicity occurs.^{40,82} Rather, all therapies are better at preventing tissue injury than treating it.

It is imperative to understand that the primary toxicity of salicylate is on the CNS, and the amount of salicylate in the brain is a function of pH with acidemia enhancing CNS penetration of the drug. Management strategies strive to create concentration gradients and pH conditions that favor exit of salicylate from the CNS and other tissues and enhanced renal elimination.

Gastrointestinal Decontamination and Use of Activated Charcoal and Catharsis

The use of orogastric lavage and activated charcoal (AC) is discussed in [Chap. 8](#) and Antidotes in Depth: A1. Their effects on the absorption and elimination of salicylates have been extensively studied. In vitro studies suggest that each gram of AC can adsorb approximately 550 mg of salicylic acid.^{75,89} In humans, AC reduces the absorption of therapeutic doses of aspirin by 50% to 80%, effectively adsorbing aspirin released from enteric-coated and sustained-release preparations in addition to immediate-release tablets.⁷⁵ Presumably, the sooner AC is given after salicylate ingestion, the more effective it will be in reducing absorption. A 10:1 ratio of AC to ingested salicylate appears to result in maximal efficacy but is often impractical given the fact that ingestions of salicylate often reach 20- to 30-g amounts or more. Although peak serum concentrations are markedly decreased from predicted concentrations, aspirin desorption from the aspirin-AC complex in the alkaline milieu of the small bowel may diminish the impact of AC on total absorption.^{42,79,89} The addition of a cathartic to the initial dose of AC has been questioned and largely abandoned for most xenobiotics, but a benefit of adding sorbitol to AC in preventing salicylate absorption was demonstrated in one study.⁶⁶ A single dose may still therefore be acceptable.

Repetitive or multiple-dose AC (MDAC) is necessary to achieve desired ratios of activated charcoal to salicylate (and probably limits desorption), which may reduce the concentration of initially absorbed salicylate to only 15% to 20%.⁴² MDAC appears to increase the elimination of unabsorbed salicylates over that achieved by single-dose AC.^{7,55} Thus, the use of MDAC to decrease GI absorption of salicylates is warranted, barring contraindications particularly if a pharmacobezoar or extended-release preparation is suspected (Antidotes in Depth: A1).

The value of MDAC in enhancing salicylate elimination through GI dialysis is controversial and is not generally warranted.^{3,60} In one volunteer study of a 2800-mg dose of aspirin followed by 25 g of AC at 4, 6, 8, and 10 hours after ingestion, the total amount of salicylate excreted from the body increased by 9% to 18% but was not considered statistically significant.⁶⁷ The efficacy is likely greater in an overdose situation, when more unbound salicylate is available because of decreased protein binding. However, in another study of the effects of MDAC on the clearance of high-dose intravenous (IV) aspirin in a porcine model, MDAC did not enhance the clearance of salicylates under conditions when the venous bicarbonate was kept at 15 mEq/L or less and urine pH kept at 7.5 or less.⁶⁰ In contrast to the findings of both of these studies, two children with salicylate overdoses were successfully treated with MDAC given every 4 hours for 36 hours.¹²⁶ Overall, extensive use of MDAC is currently discouraged, but the administration of two to four properly timed doses is reasonable. The administration of AC or MDAC must be balanced against risks of vomiting and aspiration, especially in patients with altered mental status and unprotected airways ([Chap. 8](#)).

Theoretical support may be found for the use of whole-bowel irrigation (WBI) with polyethylene glycol electrolyte lavage solution (PEG-ELS) in addition to AC to reduce absorption, particularly for enteric-coated aspirin preparations.¹²¹ However, because the addition of WBI to MDAC does not increase the clearance of absorbed salicylate in an experimental model,⁷⁹ it is not routinely recommended.

Fluid Replacement

There is a need to differentiate between restoration of fluid and electrolyte balance in salicylate-poisoned patients and increasing the fluid load presented to the kidneys in an attempt to achieve “forced diuresis.” Fluid losses in patients with salicylate poisoning are prominent, especially in children, and can be attributed to hyperventilation, vomiting, fever, a hypermetabolic state, cathartic administration, and perspiration.¹²⁰ The kidneys also respond to salicylate poisoning by excreting an increased solute load, including large quantities of bicarbonate, sodium, potassium, and organic acids.⁵ For all of these reasons, the patient’s volume status must be adequately assessed and corrected if necessary along with any glucose and electrolyte abnormalities. As in other cases, accurate management of volume status in poisoned patients may require invasive or noninvasive monitoring of central venous pressures, especially in patients with cardiac disease, ARDS, or AKI.

Increasing fluids beyond restoration of fluid balance to achieve forced diuresis is a practice that was inappropriately promoted in the past. Although forced diuresis theoretically increases renal tubular flow and reduces the urine tubular cell diffusion gradient for reabsorption, renal excretion of salicylate depends much more on urine pH than on flow rate, and use of forced diuresis alone is not effective regardless of whether diuretics, osmotic agents, or large fluid volumes are used to achieve the diuresis.⁹⁷ Although renal salicylate clearance varies in direct proportion to flow rate, its relation to pH is logarithmic.^{62,70} In summary, although fluid imbalance must be corrected, forced diuresis does little more than oral fluids to enhance elimination over a 24-hour period⁹⁷ and subjects the patient to the hazards of fluid overload.

Serum and Urine Alkalinization

The cornerstone of the management of patients with salicylate toxicity is to shift salicylate out of the brain and tissues into the serum, where elimination through the kidneys can then occur. Alkalinization of the serum with respect to the tissues and alkalinization of the urine with respect to the serum accomplishes this goal by facilitating the movement and “ion trapping” of salicylate into the serum and the urine (Fig. 39–2). Alkalinization of the serum by a substance that does not easily cross the blood–brain barrier such as intravenously administered sodium bicarbonate reduces the fraction of salicylate in the nonionized form and increases the pH gradient with the CSF. This both prevents entry and helps remove salicylate from the CNS.^{47,52–54,119}

Alkalinization with IV sodium bicarbonate should be considered for all symptomatic patients whose serum salicylate concentrations exceed the therapeutic range and for clinically suspected cases of salicylism until a salicylate concentration and simultaneously obtained blood pH are available to guide treatment. Patients on therapeutic regimens of salicylates who feel well with salicylate concentrations of 30 to 40 mg/dL and who do not manifest toxicity do not require intervention.

Alkalinization may be achieved with a bolus of 1 to 2 mEq/kg of sodium bicarbonate IV followed by an infusion of 3 ampules of sodium bicarbonate (132 mEq) in 1 L of 5% dextrose in water (D₅W), administered at 1.5 to 2.0 times the maintenance fluid range. Urine pH should be maintained at 7.5 to 8.0, and hypokalemia must be corrected (see later discussion) to achieve maximum urinary alkalinization. Volume load should remain modest while previous losses are replenished (Antidotes in Depth: A5).

Oral bicarbonate administration should never be substituted for IV bicarbonate to achieve alkalinization because the oral route may increase salicylate absorption from the GI tract by enhancing dissolution. Hyperventilation alone should not be relied upon, and intravenous sodium bicarbonate should be used for alkalinization.

Urine Alkalinization

Because salicylic acid is a weak acid (pK_a 3.0), it is ionized in an alkaline milieu and theoretically can be “trapped” there. This occurs because there is no specific uptake mechanism in the kidney for salicylate ion, and passive reabsorption of a charged molecule is very limited. Thus, alkalinization of the urine (defined as $pH \geq 7.5$) with sodium bicarbonate results in enhanced excretion of the ionized salicylate ion.

Alkalinization of the urine should be considered as a first-line treatment for patients with moderately severe salicylate poisoning who do not meet the criteria for HD.^{99,123} It should also be administered to salicylate-poisoned patients who require HD while preparations are being made to perform HD. Although salicylic acid is almost completely ionized within physiologic pH limits, small changes in pH obtained by alkalinization may have substantial changes in the relative amount of salicylate in the charged form.

Regardless of the reason for the change in serum pH, renal excretion of salicylate is very dependent on urinary pH.^{62,97,127} Alkalinization increases free salicylate secretion from the proximal tubule but does not affect renal elimination of salicylate conjugates. Alkalinizing the urine from a pH of 5 to 8 logarithmically increased renal salicylate clearance from 1.3 to 100 mL/min^{62,86} (Fig. 39–3). Assuming an overdose V_d of 0.5 L/kg, this increased clearance would decrease salicylate half-life from 310 to 4 hours. However, in reality alkalinizing the urine from a pH of 5 to 8 has a more modest effect on serum salicylate clearance.⁹⁷

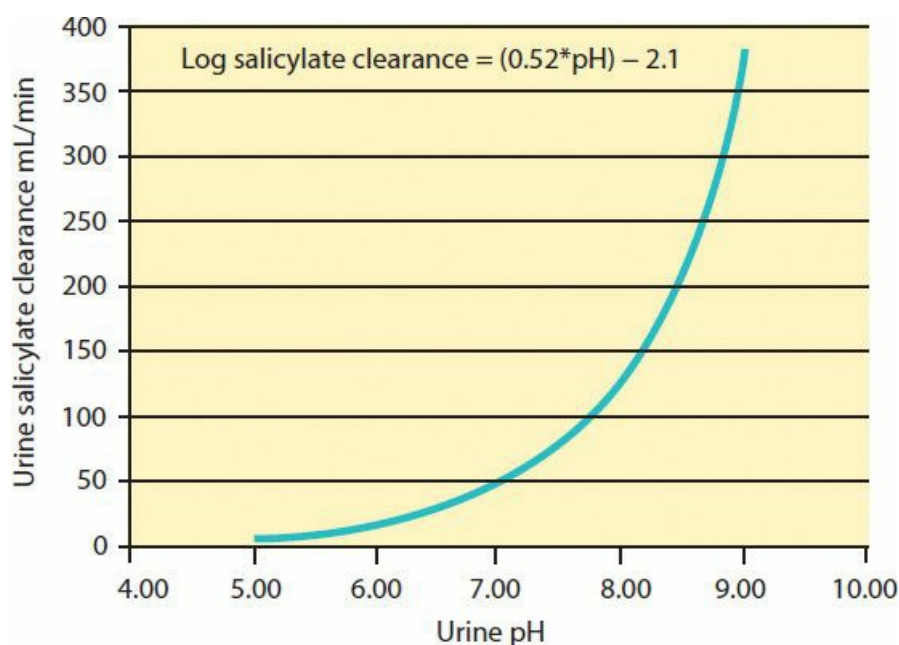


FIGURE 39–3. The relationship between urine pH and urine salicylate clearance. This curve was adapted from a

logarithmic relationship determined by Kallen in patients with salicylate poisoning. It illustrates the need to substantially increase urine pH above 7 to impact elimination.

Although the administration of acetazolamide, a noncompetitive carbonic anhydrase inhibitor, results in the formation of bicarbonate-rich alkaline urine, it also causes a metabolic acidosis and acidemia.^{41,52,53} This latter effect of acetazolamide is usually self-limited and mild but nevertheless increases the concentration of freely diffusible nonionized molecules of salicylic acid, thereby increasing the Vd and most probably enhancing the penetrance of salicylate into the CNS.^{53,73}

Hypokalemia is a common complication of salicylate poisoning and sodium bicarbonate therapy and can prevent urinary alkalization unless corrected. In the presence of hypokalemia, the renal tubules reabsorb potassium ions in exchange for hydrogen ions, preventing urinary alkalization. If urinary alkalization cannot be achieved easily, hypokalemia, excretion of organic acids, and salt and water depletion should be considered possible reasons. Calcium concentrations should be monitored because decreases in both ionized²⁹ and total serum calcium⁴³ are also complications of bicarbonate therapy.

Glucose Supplementation

As discussed earlier, salicylate poisoning may significantly alter glucose metabolism, transport, and relative requirements. Clinically, this is relevant in that the presence of a normal serum glucose concentration may not be reflective of a normal CSF glucose concentration. It is suggested that the neurotoxicity of salicylism may be partly caused by this hypoglycorrhachia. Dextrose administration alone has reversed acute delirium associated with salicylate toxicity.^{23,69} It is therefore wise to liberally administer dextrose to all patients with altered mental status in salicylate toxicity regardless of their serum glucose concentration. A bolus of 0.5 to 1 g/kg of dextrose with additional or even continuous infusion should be considered in patients being treated for severe salicylate toxicity.

Extracorporeal Removal

Extracorporeal measures are indicated if the patient has severe signs or symptoms, a very high serum salicylate concentration regardless of clinical findings, severe fluid or electrolyte disturbances, cerebral edema, or ARDS or is unable to eliminate the salicylates because of AKI (Table 39–3). It should also be considered when a patient cannot tolerate the increased solute load that results from alkalization or large-volume infusions necessary. Failure to tolerate such therapy can be anticipated if the patient has initial symptoms that are consistent with severe salicylate toxicity or has a history congestive heart failure or chronic kidney disease.

TABLE 39–3. Indications for Hemodialysis in Salicylate Poisoned Patients

Kidney failure
Congestive heart failure (relative)
Acute Respiratory Distress Syndrome
Persistent Central Nervous System disturbances
Progressive deterioration in vital signs
Severe acid–base or electrolyte imbalance despite appropriate treatment
Hepatic compromise with coagulopathy
Salicylate concentration (acute) >90 mg/dL (in the absence of the above)
Hemodialysis for patients with chronic poisoning is indicated for those with concerning symptoms regardless of salicylate concentrations

In most instances, HD is the extracorporeal technique of choice, not only to clear the salicylate but also to rapidly correct fluid, electrolyte, and acid–base disorders that will not be corrected by hemoperfusion (HP) alone. The combination of HD and HP in series is feasible and theoretically may be useful for treating patients with severe or mixed overdoses,²⁷ but it is rarely used. A rapid reduction of serum salicylate concentrations in severely poisoned patients has been described with the use of continuous renal replacement therapy, a technique that may be valuable for patients who are too unstable to undergo HD or when HD is unavailable¹³² (Chap. 10). There is only one published clinical experience with sustained low-efficiency dialysis (SLED) for salicylate toxicity, which demonstrated similar clearance rates to other

continuous extracorporeal therapies.⁷⁶ Its role still requires further investigation.⁷⁶

While the patient is awaiting HD, alkalization of serum and urine should be aggressively achieved with sodium bicarbonate therapy. During HD, it is unnecessary to continue bicarbonate therapy because it will be provided by HD. It is prudent to reinstitute bicarbonate therapy after HD has been completed, especially if patients are still symptomatic or serum salicylate concentrations are pending.

Nephrology consultation should be sought early and liberally to anticipate and prevent avoidable morbidity and mortality. Despite the well-recognized benefit of extracorporeal removal of salicylates in severe toxicity, delays in initiating HD remain a potentially preventable cause of death despite repeated calls over many years for prompt HD for patients with salicylate poisoning.⁴⁰ The initiation of HD should not be considered definitive treatment because patients may still have a significant GI burden of salicylate, resulting in continued absorption, and even with early and multiple runs of HD, patients may still succumb to this poisoning.⁸²

Chemical Sedation, Intubation, and Mechanical Ventilation Risks

Salicylate-poisoned patients have a significantly increased minute ventilation rate brought about by both tachypnea and hyperpnea, often exceeding 20 to 30 L/min. Any decrease in minute ventilation increases the PCO₂ and decreases the pH. This shifts salicylate into the CNS, exacerbating toxicity. Thus, extreme caution must be used when considering chemical sedation, intubation, and initiating mechanical ventilation.

Although induced hyperventilation may effectively increase the blood pH in certain patients, endotracheal intubation followed by assisted ventilation of a salicylate-poisoned patient poses particular risks if it is not meticulously performed. Although early endotracheal intubation to maintain hyperventilation may aid in the management of patients whose respiratory efforts are faltering, health care providers must maintain appropriate hypocarbia through hyperventilation. Ventilator settings that result in an increase in the patient's PCO₂ relative to premechanical ventilation will produce relative respiratory acidosis even if serum pH remains in the alkalemic range.

In a search of a poison center database of patients with salicylate poisoning between 2001 and 2007, seven patients were identified with salicylate concentrations above 50 mg/dL who had both premechanical ventilation and postmechanical ventilation data. All seven had postmechanical ventilation pH values below 7.4, and five of the six for whom recorded PCO₂ values were available had postmechanical ventilation PCO₂ values above 50 mm Hg, suggesting substantial underventilation. Two of the seven patients died after intubation, and one sustained neurologic injury. Inadequate mechanical ventilation of patients with salicylate poisoning was associated with respiratory acidosis, a decrease in the serum pH, and an abrupt clinical deterioration.¹¹⁶ Even when achieved, however, respiratory alkalosis sustained by hyperventilation (assisted or unassisted) alone should never be considered a substitute for use of either sodium bicarbonate (to achieve both alkalemia and alkaluria) or HD (when indicated).

If chemical sedation is required, although there is no clear choice of preferred sedative, the goals are to minimize respiratory depression and use the minimum amount required for desired sedation. If intubation is deemed necessary, which it often may be in situations of severe toxicity or multidrug ingestions, the following steps should be taken to optimize before, during, and after intubation conditions. The goal should be to maintain or exceed minute ventilation rates that were present before intubation. Before intubation, an attempt should be made to optimize serum alkalization by administering a 2-mEq/kg bolus of sodium bicarbonate. Preparations should be made to minimize the period of time the patient will spend with apnea or decreased ventilation by considering an awake intubation. The provider most experienced in intubation should be present as well as any adjunct materials to increase first-pass success. An intensivist, respiratory technician, or other mechanical ventilator expert should be consulted to help match preintubation minute ventilation. After mechanical ventilation has begun, frequent blood gas monitoring should be obtained and ventilator settings adjusted as needed. An emergent nephrology consult is indicated for HD if not previously obtained.¹¹⁶ One recent report suggested the use of ketamine for awake intubation, thereby minimizing the hypoventilation associated with rapid-sequence intubation.³⁸

Serum Salicylate Concentration and pH Monitoring

Careful observation of the patient, correlation of the serum salicylate concentrations with blood pH, and repeat determinations of serum salicylate concentrations every 2 to 4 hours are essential until the patient is clinically improving and has a low serum salicylate concentration in the presence of a normal or high blood pH. In all cases, after a presumed peak serum salicylate concentration has been reached, at least one additional serum concentration should be obtained several hours later. Analyses should be obtained more frequently in managing seriously ill patients to assess the efficacy of treatment and the possible need for HD.

Pediatric Considerations

The predominant primary respiratory alkalosis that initially characterizes salicylate poisoning in adults may not occur in young children.^{45,119} This likely results from the limited ventilatory reserve of small children that prevents the same degree

of sustained hyperpnea as occurs in adults. The typical acidemia noted in seriously poisoned children led some investigators in the past to incorrectly suggest that pediatric salicylate poisoning produces only metabolic acidosis. Although after a significant salicylate exposure, some children present with a mixed acid–base disturbance and a normal or high pH, most present with acidemia,⁴⁵ suggesting the need for more urgent intervention because the protective effect of alkalemia on CNS penetration of salicylate is already lost. Although not routinely recommended, exchange transfusion may effectively remove large quantities of salicylate in infants too small to undergo emergent HD without extensive delays.⁷⁷

Pregnancy

Considered a rare event, salicylate poisoning during pregnancy poses a particular hazard to fetuses because of the acid–base and hematologic characteristics of fetuses and placental circulation. Salicylates cross the placenta and are present in higher concentrations in a fetus than in the mother. The respiratory stimulation that occurs in the mother after toxic exposures does not occur in the fetus, which has a decreased capacity to buffer acid. The ability of a fetus to metabolize and excrete salicylates is also less than in the mother. In addition to its toxic effects on the mother, including coagulation abnormalities, acid–base disturbances, tachypnea, and hypoglycemia, repeated exposure to salicylates late in gestation displaces bilirubin from protein binding sites in the fetus, causing kernicterus.

A case report described fetal demise in a woman who claimed to ingest 50 aspirin tablets per day for several weeks during the third trimester of pregnancy. This raises concerns that a fetus is at greater risk from salicylate exposures than is the mother. Emergent delivery of near-term fetuses of salicylate-poisoned mothers should be considered on a case-by-case basis⁹¹ (Chap. 31).

SUMMARY

- The clinical presentation of a patient with a salicylate overdose may be characterized by an early onset of nausea, vomiting, abdominal pain, tinnitus, and lethargy.
- The combination of a primary respiratory alkalosis and a primary metabolic acidosis with net alkalemia constitutes the classic acid–base abnormality of salicylate poisoning in the adult.
- Initial efforts in managing patients with salicylate poisoning include restoration of intravascular volume, the use of AC to limit absorption, and urinary alkalization to enhance renal elimination of salicylate.
- HD is indicated in patients with significantly elevated salicylate concentrations, altered mental status, ARDS, and or AKI.
- It is essential to maintain alkalemia to prevent CNS penetration of salicylate. As such, sedation and mechanical ventilation can be rapidly lethal, if they impair minute ventilation, causing rises in PCO₂ and a fall in pH.

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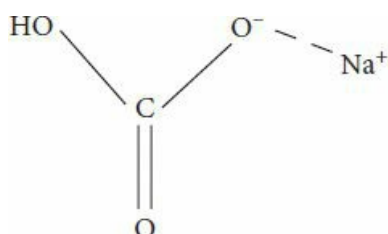
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A5 ANTIDOTES IN DEPTH

Sodium Bicarbonate

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INTRODUCTION

Sodium bicarbonate is a nonspecific antidote that is effective in the treatment of a variety of poisonings by means of a number of distinct mechanisms ([Table A5–1](#)). However, the support for its use in these settings is predominantly based on animal evidence, case reports, and consensus.¹¹ It is most commonly used to treat patients with cyclic antidepressant (CA) and salicylate poisonings. Sodium bicarbonate also has a role in the treatment of phenobarbital, chlorpropamide, and chlorophenoxy herbicide poisonings and wide-complex tachydysrhythmias induced by Na⁺ channel blocking xenobiotics such as type IA and IC antidysrhythmics and cocaine. Correcting the life-threatening acidemia induced by methanol and ethylene glycol metabolism and enhancing formate elimination are other important indications for sodium bicarbonate. The use of sodium bicarbonate in the treatment of rhabdomyolysis, metabolic acidosis with elevated lactate, cardiac resuscitation, and diabetic ketoacidosis is controversial and not addressed in this Antidote in Depth.^{3,6,17,57,113,114}

TABLE A5–1. Sodium Bicarbonate: Mechanisms, Site of Action, and Uses in Toxicology

<i>Mechanism</i>	<i>Site of Action</i>	<i>Uses</i>
Alters interaction between xenobiotic and Na ⁺ channel	Heart	β-Adrenergic antagonists with MSE Amantadine Carbamazepine Chloroquine Citalopram Cocaine Cyclic antidepressants Dimenhydrinate Diphenhydramine Disopyramide Encainide Flecainide Fluoxetine Hydroxychloroquine Lamotrigine Mesoridazine Orphenadrine Procainamide Propafenone Propoxyphene Quinidine Quinine Taxus containing species Thioridazine Venlafaxine
Alters xenobiotic ionization leads to altered tissue distribution	Brain	Formic acid Phenobarbital Salicylates
Alters xenobiotic ionization leading to enhanced xenobiotic elimination	Kidneys	Chlorophenoxy herbicides Chlorpropamide Diflunisal Fluoride Formic acid Methotrexate Phenobarbital Salicylates Uranium
Corrects life threatening acidemia	Metabolic	Cyanide Ethylene glycol Metformin Methanol
Increases xenobiotic solubility	Kidneys	DAMPA Methotrexate
Neutralization	Lungs	Chlorine gas, HCl
Maintenance of chelator effect	Kidneys	Dimercaprol (BAL)–metal
Reduces free radical formation	Kidneys	Contrast media

BAL = British anti-Lewisite; DAMPA = 4-amino-4-deoxy-10-methylpteroic acid; MSE = membrane-stabilizing effect: acebutolol, betaxolol, carvedilol, metoprolol, oxprenolol, propranolol.

PHARMACOLOGY

Sodium bicarbonate has a molecular weight of 84 Da. It is supplied in solution at approximately pH 8.0 (pH limits range from 7.0 to 8.5). The onset of action of intravenous (IV) sodium bicarbonate is within 15 minutes with a duration of action of 1 to 2 hours. Sodium bicarbonate increases plasma bicarbonate and buffers excess hydrogen ion.³² In normal individuals, the distribution volume for bicarbonate salts is approximately twice the extracellular fluid (ECF) volume.^{43,105} The apparent bicarbonate space (ABS) proportionally increases in severe acidemia, leading to higher bicarbonate requirements.³⁷ Canine studies demonstrated that this effect is not due to the acidemia per se, but due to the tight correlation of extracellular bicarbonate concentrations with the ABS.¹ Whether acidemic or alkalemic, low bicarbonate concentrations increase the apparent space of distribution in a highly dynamic manner.¹ Human studies, in which the ABS is described by the equation, $ABS = (0.36 + 2.44/[HCO_3^-]) \times \text{body weight (kg)}$, appear to support this concept.⁹²

ROLE IN MYOCARDIAL SODIUM CHANNEL TOXINS

The most important role of sodium bicarbonate in toxicology is the ability to reverse potentially fatal cardiotoxic effects of myocardial Na^+ channel blockers such as CAs and other type IA and IC antidysrhythmics.¹⁸ Its mechanism of action in these cases appears to result from both an increase in $[Na^+]$ and a change in the proportion of the Na^+ channel blocker ionized, resulting in an altered distribution away from its channel. Use of sodium bicarbonate for myocardial Na^+ channel blocker overdose developed as an extension of sodium lactate use in the treatment of patients with toxicity from type IA antidysrhythmics. Noting similarities in electrocardiographic (ECG) findings between hyperkalemia and quinidine toxicity (ie, QRS widening), investigators in the 1950s began to use sodium lactate (which is rapidly metabolized in the liver to sodium bicarbonate) to treat quinidine toxicity.^{5,10,117} In a canine model, quinidine-induced ECG changes and hypotension were consistently reversed by infusion of sodium lactate.⁹ Clinical experience confirmed this benefit.¹⁰ Similar efficacy in the treatment of patients with procainamide cardiotoxicity was also reported.¹¹⁷

The introduction of CAs during the 1960s also yielded reports of conduction disturbances, dysrhythmias, and hypotension occurring in overdose. Extending the use of sodium lactate for the type I antidysrhythmics to CA poisoning, uncontrolled observations in the 1970s showed a decrease in mortality rate from 15% to less than 3%.³⁸ In 1976, sodium bicarbonate was reported successful in a pediatric series of CA-induced dysrhythmias.²¹ In this series, nine of 12 children who had developed multifocal premature ventricular contractions (PVCs), ventricular tachycardia, or heart block reverted to normal sinus rhythm with sodium bicarbonate therapy alone. An early canine experiment of amitriptyline-poisoning demonstrated resolution of dysrhythmias upon blood alkalization to a pH above 7.40.²¹ Other methods of alkalization, including hyperventilation and administration of the nonsodium buffer tris (hydroxymethyl) aminomethane (THAM), were also effective in reversing the dysrhythmias.^{20,55}

An improved understanding of the mechanism and utility of sodium bicarbonate came from a series of animal experiments during the 1980s. In amitriptyline-poisoned dogs, sodium bicarbonate reversed conduction disturbances and ventricular dysrhythmias and suppressed ventricular ectopy.⁷⁵ When comparing sodium bicarbonate, respiratory alkalemia (hyperventilation), hypertonic sodium chloride, and lidocaine, sodium bicarbonate, and hyperventilation proved most efficacious in reversing ventricular dysrhythmias and narrowing QRS prolongation. Although lidocaine transiently antagonized dysrhythmias, this antagonism was demonstrable only at nearly toxic lidocaine concentrations and was associated with hypotension. Furthermore, prophylactic alkalization protected against the development of dysrhythmias in a pH-dependent manner.

In desipramine-poisoned rats, the isolated use of either sodium chloride or sodium bicarbonate was effective in decreasing QRS duration.⁸³ Both sodium bicarbonate and hypertonic sodium chloride also increased mean arterial pressure, but hyperventilation or direct intravascular volume repletion with mannitol did not. In further studies both in vivo and on isolated cardiac tissue, alkalization and increased sodium concentration improved CA effects on cardiac conduction.^{97,98} Although respiratory alkalemia and hypertonic sodium chloride each independently improved conduction velocity, this effect was greatest when sodium bicarbonate was administered.

Another study on amitriptyline-poisoned rats demonstrated that treatment with sodium bicarbonate was associated with shorter QRS interval, longer duration of sinus rhythm, and increased survival rates.⁵⁶ Sodium bicarbonate seems to work independently of initial blood pH. Animal studies show that cardiac conduction improves after treatment with sodium bicarbonate or sodium chloride in both normal and acidemic animals.⁸³ Clinically, CA-poisoned patients who were already alkalemic responded to repeat doses of sodium bicarbonate.⁷²

Although several authors suggest that the efficacy of sodium bicarbonate is modulated via a pH-dependent change in plasma protein binding that decreases the proportion of free drug,^{20,62} further study failed to support this hypothesis.⁸⁶ The administration of large doses of a binding protein α_1 -acid glycoprotein (AAG) (to which CAs show significant affinity) to desipramine poisoned rats only minimally decreased cardiotoxicity. Although the addition of AAG increased the

concentrations of total desipramine and protein-bound desipramine in the serum, the concentration of active free desipramine did not decline significantly. A redistribution of CA from peripheral sites may have prevented lowering of free desipramine concentration. The persistence of other CA-associated toxicities, antimuscarinic effects and seizures, also argues against changes in protein-binding modulating toxicity. In vitro studies performed in plasma protein-free bath further substantiate sodium bicarbonate's efficacy independent of plasma protein binding.⁹⁸

Sodium bicarbonate has a crucial antidotal role in myocardial Na^+ channel blocker poisoning by increasing the number of open Na^+ channels, thereby partially reversing fast Na^+ channel blockade. This decreases QRS prolongation and reduces life-threatening cardiovascular toxicity such as ventricular dysrhythmias and hypotension.^{75,83,98} The animal evidence supports two distinct and additive mechanisms for this effect: a pH-dependent effect and a sodium-dependent effect. The pH-dependent effect increases the fraction of the more freely diffusible nonionized xenobiotic. Both the ionized xenobiotic and the nonionized forms are able to bind to the Na^+ channel, but assuming myocardial Na^+ channel blockers act like local anesthetics, it is estimated that 90% of the block results from the ionized form. By increasing the nonionized fraction, less xenobiotic is available to bind to the Na^+ channel binding site (Fig. A5–1). The sodium-dependent effect increases the availability of Na^+ ions to pass through the open channels. Decreased ionization should not significantly decrease the rate of CA elimination because of the small contribution of renal pathways to overall CA elimination (<5%).

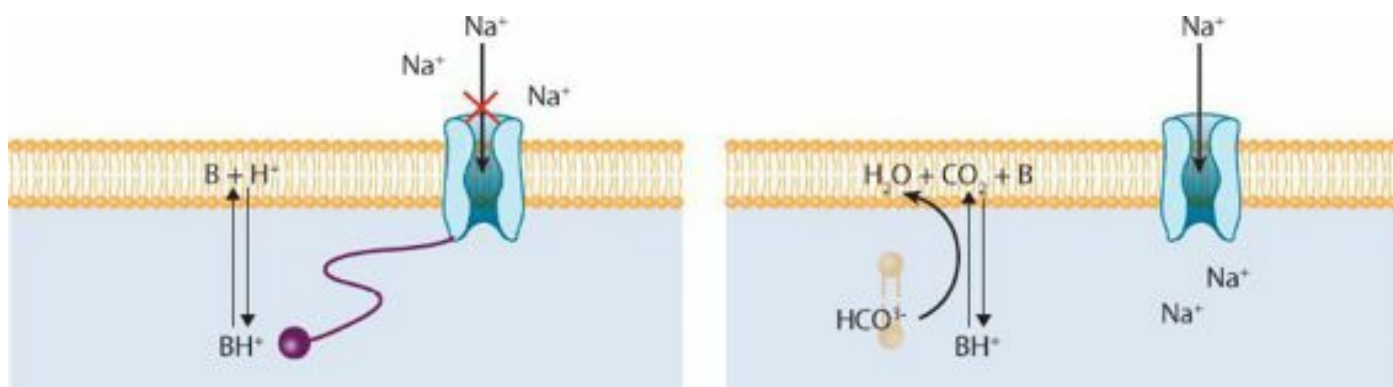


FIGURE A5–1. Blockade occurs by an ionized drug because the channel is a water (lipophobic) environment (left). As the drug becomes nonionized, it becomes more lipophilic and moves into the lipid bilayer of the membrane and away from the channel (right).

Although many anecdotal accounts support the efficacy of sodium bicarbonate in treating CA cardiotoxicity in humans,⁴⁷ these reports are uncontrolled observations; controlled studies are unavailable. In one of the largest retrospective observational studies involving 91 patients who received sodium bicarbonate after CA overdose, QRS prolongation corrected in 39 of 49 patients who had QRS durations above 120 msec, and hypotension corrected within 1 hour in 20 of 21 patients who had systolic blood pressures below 90 mm Hg.⁴⁸ Use of sodium bicarbonate was not associated with any complications in this study.

Prospective validation of treatment criteria for use of sodium bicarbonate after CA overdose has not been performed. Common indications are conduction delays (as manifested by QRS above 100 msec or right bundle branch block), wide-complex tachydysrhythmias, and hypotension.⁶³ Because studies demonstrate a critical threshold QRS duration (≥ 160 msec) at which ventricular dysrhythmias significantly increase in propensity,¹⁴ it seems reasonable that narrowing the QRS interval through use of sodium bicarbonate or hyperventilation may prophylactically prevent against development of dysrhythmias. Practice patterns vary considerably with regard to the use of sodium bicarbonate when the QRS interval is below 160 msec.¹⁰² Although sodium bicarbonate has no proven efficacy in either the treatment or prophylaxis of tricyclic antidepressant-induced seizures, seizures often produce acidemia, which rapidly increases the risks of conduction disturbances and ventricular dysrhythmias.¹¹¹ Administering sodium bicarbonate when the QRS duration is 100 msec or greater may establish a theoretical margin of safety in the event the patient suddenly deteriorates, without adding significant demonstrable risk. When the QRS duration is below 100 msec, given the minimal risk of seizures or dysrhythmias, prophylactic sodium bicarbonate administration is not indicated.¹⁰³ In patients exhibiting a Brugada ECG pattern (right bundle branch block with downsloping ST segment elevation in V1–V3) and QRS widening after CA ingestion, sodium bicarbonate administration may narrow the QRS without reversing the Brugada pattern⁷ (Chap. 16).

Because cardiotoxicity may worsen during the first few hours after ingestion, sodium bicarbonate therapy should be initiated immediately if the QRS interval is greater than 100 msec. Because CA-induced hypotension responds to sodium bicarbonate, hypotension should also prompt sodium bicarbonate therapy. However, no evidence supports a role for sodium bicarbonate in CA-poisoned patients who present with altered mental status or seizures without QRS widening or hypotension.

Because the potential benefits of alkalization in CA overdose usually outweigh the risks, sodium bicarbonate should

be administered regardless of whether the patient has an acidemic or normal pH.

The time to resolution of conduction abnormalities during continuous bicarbonate infusion varies significantly, ranging from several hours to several days.^{64,103} In a case of poisoning from modified-release amitriptyline, sodium bicarbonate was required on multiple occasions over 110 hours after the initial ingestion to reverse ongoing Na⁺ channel conduction disturbances.⁷⁷ Sodium bicarbonate infusion usually is discontinued upon hemodynamic improvement and resolution of cardiac conduction abnormalities and altered mental status, although controlled data supporting such an approach are lacking.

Sodium bicarbonate is useful in treating patients with cardiotoxicity from other myocardial Na⁺ channel blockers that present with widened QRS complexes, dysrhythmias, and hypotension. Isolated case reports provide the bulk of the evidence in these situations. The utility of sodium bicarbonate in treating patients with type IA and IC antidysrhythmics, diphenhydramine, propoxyphene, quinine, and others has been demonstrated.^{13,28,29,95,104,110,117}

Use of sodium bicarbonate in the treatment of patients with overdoses of amantadine, a xenobiotic with multiple myocardial channel effects has been suggested, but concurrent hypokalemia may limit its use.¹⁰⁰ Although the usefulness of sodium bicarbonate in reversing QRS prolongation, occasionally observed during fluoxetine and citalopram overdose has been reported,^{22,31,40} Na⁺ channel disturbances are uncommon in most cases of selective serotonin reuptake inhibitor (SSRI) overdose, and routine use of alkalization therapy in this setting is unwarranted and might risk worsening QT effects by promoting hypokalemia. Sodium bicarbonate may help in the management of patients with other ingestions associated with type IA-like cardiac conduction abnormalities and dysrhythmias, such as carbamazepine, lamotrigine, and the phenothiazines thioridazine and mesoridazine, but documentation of benefit is limited to case reports.⁴⁴ Although sodium bicarbonate efficacy in the treatment of *Taxus* spp induced wide-complex dysrhythmias is reported, an animal study failed to detect any benefit.^{87,94} Bupropion's reduction of cardiac intercellular coupling (ie, inhibition of gap junction communication), as opposed to Na⁺ channel blockade,²⁴ may explain the reported lack of efficacy of sodium bicarbonate in reversing QRS prolongation in bupropion poisoning.¹¹⁹

Cocaine, a local anesthetic with membrane-stabilizing properties resembling other type I antidysrhythmics, may cause similar conduction disturbances. In several canine models of cocaine toxicity, sodium bicarbonate successfully reversed cocaine-induced QRS prolongation^{8,81} and improved myocardial function.¹²⁰ Of interest, sodium loading by itself failed to produce a benefit. Similar findings were demonstrated in cocaine-treated guinea pig hearts.¹²¹ Patients with cocaine-induced cardiotoxicity responded to treatment with sodium bicarbonate.^{54,79,116} In many of these cases, simultaneous treatment with sedation, active cooling, and hyperventilation confounds the interpretation of sodium bicarbonate's benefit.

ROLE IN ALTERING DISTRIBUTION AND ENHANCING ELIMINATION

Salicylates

Although there is no known specific antidote, judicious use of sodium bicarbonate is an essential treatment for salicylate toxicity. Through its ability to alter the concentration gradient of the ionized and nonionized fractions of salicylates, sodium bicarbonate is useful in decreasing tissue (eg, brain) concentrations of salicylates and enhancing urinary elimination of salicylates.⁹⁰ This therapy may limit the need for more invasive treatment modalities, such as hemodialysis.

Salicylate is a weak acid with a pK_a of 3.0. As pH increases, the ionized proportion increases. Because of the presence of polar groups, ionized molecules penetrate lipid-soluble membranes less efficiently than do nonionized molecules. Consequently, when the ionized forms predominate, weak acids such as salicylates may accumulate in an alkaline milieu, such as an alkaline urine.^{69,107}

Although alkalinizing the urine to increase salicylate elimination is an important intervention in the treatment of patients with salicylate poisoning, increasing the serum pH in patients with severe salicylism may prove even more consequential by protecting the brain from a lethal central nervous system (CNS) salicylate burden. In these patients, using sodium bicarbonate to “trap” salicylate in the blood (ie, keeping it out of the brain) may prevent clinical deterioration of salicylate-poisoned patients. Salicylate lethality is directly related to primary CNS dysfunction, which, in turn, corresponds to a “critical brain salicylate concentration.”⁴⁶ At physiologic pH, at which a very small proportion of the salicylate is in the nonionized form, a small change in pH is associated with a significant change in amount of nonionized molecules. For example, whereas at a pH of 7.4, 0.004% of the salicylate molecules are in the nonionized form, at a pH of 7.2, 0.008%, of the salicylate is in the nonionized form. In experimental models, lowering the blood pH produces a shift of salicylate into the tissues.²³ Hence, acidemia in patients with significant salicylate poisonings can be devastating. In salicylate-poisoned rats, increasing the blood pH with sodium bicarbonate produced a shift in salicylate out of the tissues and into the blood.⁴⁵ This change in salicylate distribution did not result from enhanced urinary excretion because occlusion of the renal pedicles failed to alter these results.

Enhancing the elimination of salicylate by trapping ionized salicylate in the urine is also beneficial. Salicylate

elimination at therapeutic concentrations is predominantly first-order hepatic metabolism. At these low concentrations, without alkalization, only approximately 10% to 20% of salicylate is eliminated unchanged in the urine. With increasing concentrations, enzyme saturation occurs (Michaelis-Menten kinetics); thus, a larger percentage of elimination occurs as unchanged free salicylate. Under these conditions, in an alkaline urine, urinary excretion of free salicylate becomes even more significant, accounting for 60% to 85% of total elimination.^{41,91} The relationship between salicylate clearance and urine pH $\{\log(\text{salicylate clearance}) = [(0.52 \times \text{pH}) - 2.1]\}$ ⁵³ would suggest that increasing urine pH from 5.0 to 8.0 could increase the amount of salicylate cleared by almost 40-fold.

The exact mechanism of pH-dependent salicylate elimination has generated controversy. The pH-dependent increase in urinary elimination initially was ascribed to “ion trapping,” which is the filtering of both ionized and nonionized salicylate while reabsorbing only the nonionized salicylate.¹⁰¹ However, limiting reabsorption of the ionizable fraction of filtered salicylate cannot be the primary mechanism responsible for enhanced elimination produced by sodium bicarbonate.⁶⁵ Because the quantitative difference between the percentage of molecules trapped in the ionized form at a pH of 5.0 (99% ionized) and a pH of 8.0 (99.999% ionized) is small, decreases in tubular reabsorption cannot fully explain the rapid increase in urinary elimination seen at a pH above 7.0.

“Diffusion theory” offers a reasonable alternative explanation. Fick’s law of diffusion states that the rate of flow of a diffusing substance is proportional to its concentration gradient. A large concentration gradient between the nonionized salicylate in the peritubular fluid (and blood) and the tubular luminal fluid is found in alkaline urine. Because at a higher urinary pH, a greater proportion of secreted nonionized molecules quickly becomes ionized upon entering the alkaline environment, more salicylate (ie, nonionized salicylate) must pass from the peritubular fluid into the urine in an attempt to reach equilibrium with the nonionized fraction. In fact, as long as nonionized molecules are rapidly converted to ionized molecules in the urine, equilibrium in the alkaline milieu will never be achieved. The concentration gradient of peritubular nonionized salicylates to urinary nonionized salicylates continues to increase with increasing urinary pH. Hence, increased tubular diffusion, not decreased reabsorption, probably accounts for most of the increase in salicylate elimination observed in the alkaline urine.⁶⁵

Sodium bicarbonate is indicated in the treatment of salicylate poisoning for most patients with evidence of significant systemic toxicity. Although some authors have suggested alkali therapy for asymptomatic patients with concentrations above 30 mg/dL,¹¹⁸ limited data support this approach. For patients with chronic poisoning, salicylate concentrations are not as helpful and may be misleading; clinical criteria remain the best indicators for therapy. Patients with contraindications to sodium bicarbonate use, such as severe acute kidney injury (AKI) or chronic kidney disease (CKD) and acute respiratory distress syndrome (ARDS), should be considered candidates for intubation and subsequent hyperventilation, but extracorporeal removal is often required because of the difficulty and dangers of intubation.

Dosing recommendations depend on the acid–base considerations. For patients with hypobicarbonatemia, IV administration of 1 to 2 mEq of sodium bicarbonate per kilogram of body weight is recommended.¹¹² Alkalization can be maintained with a continuous sodium bicarbonate infusion of 150 mEq in 1 L of D₅W at 150 to 200 mL/h (or about twice the maintenance requirements in a child). Continued titration with sodium bicarbonate over 4 to 8 hours is recommended until the urinary pH reaches 7.5 to 8.0.^{109,112} The addition of the dextrose is important because salicylate toxicity may cause hypoglycemia.¹¹² Achieving a urinary pH of 8.0 is difficult but is the goal. Fastidious attention to the patient’s changing acid–base status is required. Systemic pH should not rise above 7.55 to prevent complications of alkalemia. Hypokalemia can make urinary alkalization particularly problematic.^{60,99} In hypokalemic patients, the kidneys preferentially reabsorb potassium in exchange for hydrogen ions. Urinary alkalization will be unsuccessful as long as hydrogen ions are excreted into the urine. Thus, appropriate potassium supplementation to achieve normokalemia may be required to alkalize the urine.¹²²

In the past, proper urinary alkalization was thought to require forced diuresis to maximize salicylate elimination.^{30,60} Suggestions included administering enough fluid (2 L/h) to produce a urine output of 500 mL/h. Because forced alkaline diuresis appears unnecessary and is potentially harmful as a result of its unnecessarily large fluid load, the goal is alkalization at a rate of approximately twice maintenance requirements to achieve a urine output of 3 to 5 mL/kg/h.

Phenobarbital

Although cardiopulmonary support is the most critical intervention in the treatment of patients with severe phenobarbital overdose, sodium bicarbonate may be a useful adjunct to general supportive care. The utility of sodium bicarbonate is particularly important considering the long plasma half-life (~100 hours) of phenobarbital. Phenobarbital is a weak acid (pK_a, 7.24) that undergoes significant renal elimination. As in the case of salicylates, alkalization of the blood and urine may reduce the severity and duration of toxicity. In a study of mice, the median anesthetic dose for mice receiving phenobarbital increased by 20% with the addition of sufficient sodium bicarbonate to increase the blood pH from 7.23 to 7.41, demonstrating decreased tissue concentrations associated with increased pH.¹¹⁵ The animal evidence has been extrapolated to humans to suggest that phenobarbital-poisoned patients in deep coma might develop a respiratory acidosis

secondary to hypoventilation, with the acidemia enhancing the phenobarbital transfer into the brain, thus worsening CNS and respiratory depression. Alternatively, increasing the pH with bicarbonate, ventilatory support, or both would enhance the phenobarbital efflux from brain, thus lessening toxicity. Given phenobarbital's relatively high pK_a , significant urinary phenobarbital accumulation is evident only when urinary pH is increased above 7.5.¹² As the pH approaches 8.0, a threefold increase in urinary elimination occurs. The urine-to-serum ratio of phenobarbital, although much higher in alkaline urine than in acidic urine, remains less than unity, thereby suggesting less of a role for tubular secretion than in salicylate poisoning.

Clinical studies examining the role of alkalization in phenobarbital poisoning have been inadequately designed. Many are poorly controlled and fail to examine the effects of alkalization, independent of coadministered diuretic therapy. In one uncontrolled study with phenobarbital overdoses, a 59% to 67% decrease in the duration of unconsciousness in patients occurred in patients administered alkali compared with nonrandomized control subjects.⁷¹ In other older studies, treatment with sodium lactate and urea reduced mortality and frequency of tracheotomy to 50% of control subjects, enhanced elimination, and shortened coma.^{59,74} In a later human volunteer study, urinary alkalization with sodium bicarbonate was associated with a decrease in phenobarbital elimination half-life from 148 to 47 hours.³⁵ However, this beneficial effect was less than the effect achieved by multiple-dose activated charcoal (MDAC), which reduced the half-life to 19 hours. In a nonrandomized study of phenobarbital-poisoned patients comparing urinary alkalization alone, MDAC alone, and both methods together, both the phenobarbital half-life decreased most rapidly and the clinical course improved most rapidly in the group of patients who received MDAC alone.⁷⁰ Interesting, the combination approach proved inferior to MDAC alone but was better than alkalization alone. The authors speculated that when both treatments were used together, the increased ionization of phenobarbital resulting from sodium bicarbonate infusion might have decreased the efficacy of MDAC. These studies suggest that MDAC is more efficacious than urinary alkalization in the treatment of phenobarbital-poisoned patients, although both approaches are beneficial and indicated.

Sodium bicarbonate therapy does not appear warranted in the treatment of patients with ingestions of other barbiturates, such as pentobarbital and secobarbital, which either have a pK_a above 8.0 or are predominantly eliminated hepatically.

Methotrexate

Urinary alkalization with sodium bicarbonate is routinely used during high-dose methotrexate cancer chemotherapy therapy.¹⁰⁸ Methotrexate is predominantly eliminated unchanged in the urine. Unfortunately, methotrexate, as well as its metabolites DAMPA (4-amino-4-deoxy-10-methylpteroic acid) and 7-hydroxymethotrexate, are poorly water soluble in acidic urine. Under these conditions, tubular precipitation of the methotrexate may occur, leading to AKI and decreased elimination, increasing the likelihood of methotrexate toxicity. Administration of sodium bicarbonate (as well as intensive hydration) during high-dose methotrexate infusions increases methotrexate solubility and the elimination of methotrexate and its metabolites.^{27,96}

Chlorophenoxy Herbicides

Alkalization is indicated in the treatment of patients with poisonings from weed killers that contain chlorophenoxy compounds, such as 2,4-dichlorophenoxyacetic acid (2,4-D) or 2-(4-chloro-2-methylphenoxy) propionic acid (MCP).⁸⁹ Poisoning results in muscle weakness, peripheral neuropathy, coma, hyperthermia, and acidemia. These compounds are weak acids (pK_a 2.6 and 3.8 for 2,4-D and MCP, respectively) that are excreted largely unchanged in the urine. In an uncontrolled case series of 41 patients poisoned with a variety of chlorophenoxy herbicides, 19 of whom received sodium bicarbonate, alkaline diuresis significantly reduced the half-life of each by enhancing renal elimination.³³ In one patient, resolution of hyperthermia and metabolic acidosis and improvement in mental status were associated with a transient elevation of serum concentration, perhaps reflecting chlorophenoxy compound redistribution from the tissues into the more alkalemic blood. The limited data suggest that the increased ionized fractions of the weak-acid chlorophenoxy compounds produced by alkalization is trapped in both the blood and the urine as demonstrated both with salicylates and phenobarbital; thus, its use ameliorates toxicity and shortens the duration of effect.

ROLE IN CORRECTING METABOLIC ACIDEMIA

Toxic Alcohols

Sodium bicarbonate has two important roles in treating patients with toxic alcohol ingestions. As an immediate temporizing measure, administration of sodium bicarbonate may reverse the life-threatening acidemia associated with methanol and ethylene glycol ingestions. In rats poisoned with ethylene glycol, the administration of sodium bicarbonate alone resulted in a fourfold increase in the median lethal dose.¹⁵ Clinically, titrating the endogenous acid with bicarbonate greatly assists in reversing the consequences of severe acidemia, such as hemodynamic instability and multiorgan dysfunction.

The second role of bicarbonate in the treatment of toxic alcohol poisoning involves its ability to favorably alter the distribution and elimination of certain toxic metabolites.⁹³ In cases of methanol poisoning, the proportion of ionized formic acid can be increased by administering bicarbonate, thereby trapping formate in the blood compartment.^{51,66} Consequently, decreased visual toxicity results from removal of the toxic metabolite from the eyes. In cases of formic acid (pK_a of 3.7) ingestion, sodium bicarbonate decreases tissue penetration of the formic acid and enhances urinary elimination.⁷³

Early treatment of acidemia with sodium bicarbonate is strongly recommended in cases of methanol and ethylene glycol poisoning.⁴³ Sodium bicarbonate should be administered to toxic alcohol-poisoned patients with an arterial pH below 7.30.⁵⁸ More than 400 to 600 mEq of sodium bicarbonate may be required in the first few hours.⁵⁰ In cases of ethylene glycol toxicity, sodium bicarbonate administration may worsen hypocalcemia, so the serum calcium concentration should be monitored. Combating the acidemia, however, is not the mainstay of therapy, and concurrent administration of IV fomepizole or ethanol and consideration for hemodialysis are almost always indicated.

Metformin

Metformin toxicity, either from overdose or therapeutic use in the setting of AKI or CKD, may cause severe, life-threatening metabolic acidemia with an elevated lactate concentration. The use of high-dose sodium bicarbonate to correct the metabolic acidemia, as well as extracorporeal removal of the metformin, is recommended in these cases.⁴²

ROLE IN NEUTRALIZATION

Chlorine Gas

Nebulized sodium bicarbonate serves as a useful adjunct in the treatment of patients with pulmonary injuries resulting from chlorine gas inhalation.^{4,25} Inhaled sodium bicarbonate neutralizes the hydrochloric acid that is formed when the chlorine gas reacts with the water in the respiratory tree. Although oral sodium bicarbonate is not recommended for neutralizing acid ingestions because of the problems associated with the exothermic reaction and production of carbon dioxide in the relatively closed gastrointestinal tract, the rapid exchange in the lungs of air with the environment facilitates heat dissipation. In a sheep model of chlorine inhalation, animals treated with 4% nebulized sodium bicarbonate solution demonstrated a higher PO_2 and lower PCO_2 than did the normal, saline-treated animals.²⁶ There was no difference, however, in 24-hour mortality or pulmonary histopathology. In a retrospective review, 86 patients with chlorine gas inhalation were treated with nebulized sodium bicarbonate.¹⁶ Sixty-nine patients were sent home from the emergency department, 53 of whom had clearly improved. In a more recent study, 44 patients who were diagnosed with reactive airway dysfunction syndrome after an acute exposure to chlorine gas were randomized to receive either nebulized sodium bicarbonate (4 mL of 4.2% sodium bicarbonate solution) or nebulized placebo.⁴ Both groups also received IV corticosteroids and inhaled β_2 -adrenergic agonists. Compared with the placebo group, the nebulized sodium bicarbonate group had significantly higher forced expiratory volume in 1 second (FEV_1) values at 120 and 240 minutes and scored significantly higher on a posttreatment quality of life questionnaire. Nebulized sodium bicarbonate failed to demonstrate a benefit in the treatment of chloramine gas exposure.⁸²

ROLE IN RENAL PROTECTION

Contrast Media

Although multiple meta-analyses suggest that hydration with sodium bicarbonate prevents contrast-induced nephropathy (CIN),^{49,52,76} other studies suggest no benefit.³⁹ A randomized trial of 119 patients compared an infusion of 154 mEq/L of either sodium bicarbonate or sodium chloride before (3 mL/kg for 1 hour) and after (1 mL/kg/h for 6 hours) iopamidol administration. CIN, defined as a 25% or greater increase in serum creatinine concentration within 2 days of contrast, occurred in eight patients in the sodium chloride group and one patient in the sodium bicarbonate group.⁶⁸ In another study comparing sodium bicarbonate with sodium chloride before emergency coronary angiography or intervention, the incidence of CIN was also significantly lower in the sodium bicarbonate group than in the sodium chloride group (7% vs. 35%).⁶⁷ However, in another recent study, an equal number of patients from the sodium bicarbonate and sodium chloride groups developed CIN.³⁹ It is suggested that increasing renal medullary pH with sodium bicarbonate infusion might protect the kidneys from oxidant injury by slowing free radical production. Although the addition of N-acetylcysteine to a sodium chloride hydration regimen to prevent CIN does not appear to offer any benefit compared with the use of only sodium chloride hydration,⁸⁰ the use of N-acetylcysteine and sodium bicarbonate together provides benefit compared with N-acetylcysteine and sodium chloride hydration.^{19,61} Whether N-acetylcysteine plus sodium bicarbonate is superior to sodium bicarbonate alone remains unproven.

Other Indications

Adverse effects and safety concerns may be associated with the dissociation of the dimercaprol (British anti-Lewisite {BAL}) metal binding that occurs in acid urine. Because dissociation of the BAL–metal chelate occurs in acidic urine, the urine of patients receiving BAL should be alkalinized with hypertonic sodium bicarbonate to a pH of 7.5 to 8.0 to prevent renal liberation of the metal.

Sodium bicarbonate may provide a renal protection benefit after exposure to depleted uranium. Animal studies suggest that sodium bicarbonate in conjunction with a chelator such as deferiprone may accelerate uranium excretion and reduce uranium nephrotoxicity.³⁶

ADVERSE EFFECTS AND SAFETY ISSUES

The use of sodium bicarbonate has associated risks. Concerns regarding excessive alkalemia, hypernatremia, fluid overload, hypokalemia, and hypocalcemia have all been raised.^{34,60,84,91,101} The package insert urges caution in patients with congestive heart failure, severe renal insufficiency, and preexisting edema with sodium retention.² Regarding its use to treat salicylism, early on, patients with pure respiratory alkalosis often have alkaluria and alkalemia and do not require urinary alkalization. Young children who rapidly develop metabolic acidosis often require alkalization but should be at less risk for complications of this therapy.⁷⁸ However, because hypertonic sodium bicarbonate has been reported to cause hypernatremia, decreased cerebrospinal fluid pressure, and possible intracranial hemorrhage in children younger than 2 years, the 4.2% solution may be preferred in these patients.² Extravasation has been reported to cause local tissue damage.² Dobutamine and norepinephrine are incompatible with sodium bicarbonate solutions, and calcium solutions may cause precipitation.

PREGNANCY AND LACTATION

According to the Food and Drug Administration (FDA), sodium bicarbonate is a Category C drug. The World Health Organization rates sodium bicarbonate as compatible with breastfeeding.

DOSING AND ADMINISTRATION

For the treatment of QRS prolongation in the setting of myocardial sodium channel poisoning, 1 to 2 mEq/kg of sodium bicarbonate should be initially administered IV as a bolus over a period of 1 to 2 minutes.⁸⁴ Greater amounts may be required to treat patients with unstable ventricular dysrhythmias.⁸⁸ Similar boluses can be repeated as needed to achieve a blood pH of 7.50 to 7.55.^{85,106} Because sodium bicarbonate has a brief duration of effect, a continuous infusion usually is required after the initial IV boluses. The treatment endpoint is the narrowing of the QRS interval. Excessive alkalemia (pH >7.55) and hypernatremia should be avoided. To prepare a sodium bicarbonate infusion three 50 mL ampules should be placed in 1 L of 5% dextrose in water (D₅W) and run at twice maintenance with frequent checks of QRS, potassium, and pH depending on the fluid requirements and blood pressure of the patient. Frequent evaluation of the fluid status should be performed to avoid precipitating pulmonary edema. An optimal duration of therapy has not been established.

For the treatment of salicylate poisoning, sodium bicarbonate can be administered by bolus or infusion using the dosing strategies described earlier until the urinary pH approaches 8. Careful and frequent monitoring of the urinary pH and serum potassium is critical to ensure optimal treatment. In salicylate-poisoned patients with altered mental status, aggressive administration of sodium bicarbonate may be required to ensure that the serum pH is greater than at least 7.40 to 7.45.

FORMULATIONS

The most commonly used sodium bicarbonate preparations are an 8.4% solution (1 M) containing 1 mEq each of sodium and bicarbonate ions per milliliter (calculated osmolarity of 2000 mOsm/L) and a 7.5% solution containing 0.892 mEq each of sodium and bicarbonate ions per milliliter (calculated osmolarity of 1786 mOsm/L). Fifty-milliliter ampules of the 8.4% and 7.5% solutions therefore contain 50 and 44.6 mEq of sodium bicarbonate, respectively. The common infant formulation is a 4.2% solution packaged as a 10 mL injectable ampule. This yields 5 mEq per container (0.5 mEq each of sodium and bicarbonate ions per mL). According to the package insert, the FDA approved indications for sodium bicarbonate include the “treatment of certain drug intoxications, including barbiturates (where dissociation of the barbiturate-protein complex is desired), in poisoning by salicylates or methyl alcohol, and in hemolytic reactions requiring alkalization of the urine to diminish nephrotoxicity of blood pigments. Urinary alkalization is also used in methotrexate therapy to prevent nephrotoxicity.”

SUMMARY

- Sodium bicarbonate remains an important antidote in the treatment of a wide variety of xenobiotic exposures.
- Sodium bicarbonate is effective in patients poisoned by myocardial sodium channel blockers by providing sodium through its effects on drug ionization and subsequent diffusion from the sodium channel binding site.
- Sodium bicarbonate is effective for salicylates, phenobarbital, methotrexate, and other weak acids because of its ability to “ion trap” in blood or urine compartments and mitigate target organ accumulation.
- Nebulized sodium bicarbonate may be effective in neutralizing inhaled acids such as chlorine gas.

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B. FOOD, DIET, AND NUTRITION

CASE STUDY 2

History Parents called 911 because they found their 5 year-old girl at home unresponsive. Shortly before emergency medical services (EMS) arrived, the girl had a witnessed self limited seizure that the parents described as the sudden onset of unresponsiveness with repetitive shaking and urinary incontinence. When EMS arrived, she was no longer shaking but could not be aroused. The paramedics recorded a respiratory rate of 30 breaths/min with a pulse of 150 beats/min and a point-of-care glucose of 122 mg/dL. They administered oxygen via nasal cannula and brought her to the emergency department.

On arrival at the hospital, the parents reported that the child had no significant past medical history, had a pediatrician, was current with all vaccinations, and was not taking any prescription medications. Although she had a mild cough and nasal congestion, she was able to attend kindergarten the previous day. As further history was being obtained, the child began to shake repetitively once again.

Immediate Assessment and Management The child was given an intramuscular injection of lorazepam (2 mg; 0.1 mg/kg for an estimated weight of 20 kg) while an intravenous (IV) line was being inserted. Within a few moments the shaking stopped. Blood samples were sent for a complete blood count and electrolytes and an electrocardiogram (ECG) was ordered. The child was attached to continuous cardiac monitoring and repeat vital signs were: blood pressure, 108/80 mm Hg; pulse, 155 beats/min; respiratory rate, 32 breaths/min; rectal temperature, 99.4°F (37.4°C); oxygen saturation, 100% on a 100% nonrebreather face mask; and glucose, 143 mg/dL. Physical examination revealed a normal head without signs of trauma, pupils that were 4 to 5 mm and reactive, a clear chest, normal heart sounds, a soft abdomen with normal bowel sounds, and skin that was without rashes or other abnormalities. The child was still not verbal but appeared to localize pain and moved all extremities, and she had normal muscle tone. Unfortunately, the patient began to seize again. IV lorazepam (2 mg) was given with nearly an immediate response. Repeat vital signs and physical examination was essentially unchanged.

What Is the Differential Diagnosis? In addition to idiopathic epilepsy, trauma, infections, and structural brain lesions, seizures can result from exposure to countless xenobiotics and even withdrawal. In most instances, seizures are usually single and either self-limited or respond easily to an appropriate dose of a benzodiazepine. This child had three seizures in a brief period of time without regaining consciousness, which meets criteria for status epilepticus. Although seizures are common, status epilepticus is rare, thereby narrowing the differential diagnosis to xenobiotics found in [Table CS2–1](#).

TABLE CS2–1. Xenobiotics Commonly Associated with Status Epilepticus

Bupropion	Insulin secretagogues
Camphor	Isoniazid
Carbon Monoxide	Theophylline
Hyponatremia	

Is There a Clinical Difference between Drug-Induced Seizures and Idiopathic Epilepsy? Several features distinguish toxic-metabolic seizures from idiopathic epilepsy. First and foremost is that with few exceptions, toxic-metabolic seizures often fail to respond to phenytoin. Although phenytoin is an excellent second line anticonvulsant after benzodiazepines, it either has no efficacy or is actually detrimental in diverse toxicological etiologies from alcohol withdrawal or seizures induced by dysrhythmias, theophylline, cyclic antidepressants, anticonvulsants, and or cocaine. Conceptually, phenytoin fails because its ability to prevent secondary generalization of a focal seizure in idiopathic epilepsy is lost in toxic-metabolic etiologies where many areas of the brain are likely coming to threshold simultaneously. Thus, when a toxic-metabolic cause is suspected, typically a barbiturate or propofol is added when benzodiazepines fail. In some cases, such as isoniazid, an antidote may be necessary ([Antidotes in Depth: A14](#)), and in others, such as theophylline, hemodialysis or hemoperfusion may be indicated ([Chap. 10](#)). Finally, it is important to recognize that the cessation of motor activity with toxic-metabolic seizures may be insufficient to prevent serious complications. For example, although it is likely that patients with hypoglycemia, hyponatremia, or carbon monoxide poisoning can have their seizures terminated with benzodiazepines, the failure to correct these underlying issues will likely prevent complete neurological recovery. The reader is referred to [Antidotes in Depth: A23](#) for information regarding the choice, dose, and route of commonly used benzodiazepines.

What Rapid Clinical and Laboratory Analyses Can Help Exclude Life Threatening Causes of This Patient's Presentation? Many rapidly reversible causes of seizures can be assessed by the history and physical examination.

Signs and symptoms of trauma, infection, and structural brain injury are often immediately evident. Bedside techniques can assess hypoxia, hypercarbia, and hypoglycemia, and a venous blood gas can confirm or exclude hyponatremia and dyshemoglobinemias ([Chaps. 19, 29, 53, and 125](#)). An ECG provides rapid information confirmation of sodium channel blockade, a frequent cause of seizures ([Chaps. 16 and 71](#)) and potassium channel blockade that might produce torsade de pointes ([Chaps. 16, 70, and 92](#)), which causes syncope that can be confused with seizures in unmonitored patients. Vomiting would be commonly expected following overdose, especially with isoniazid ([Chap. 58](#)) and theophylline ([Chap. 66](#)). In some patients, computed tomography (CT) of the head, lumbar puncture, and empiric antibiotics and antivirals may be indicated.

Further Diagnosis and Treatment Because of the child's continued depressed mental status, a clinical decision was made to protect her airway. During preparation for intubation, a unique odor was noted in the oropharynx. When the parents were questioned, they confirmed that they had bought camphor ([Chap. 105](#)) for use in a vaporizer in an attempt to help relieve the symptoms of an upper respiratory tract infection. The child had likely eaten some for unclear reasons. Intubation was not performed when this history was obtained, because the girl's mental status appeared to be improving. A head CT scan was obtained without contrast and was interpreted as normal. Over the next day, the girl awakened and was neurologically normal. She was discharged after her parents were counseled about chemical and medication safety.

40 ATHLETIC PERFORMANCE ENHANCERS

Susi U. Vassallo

HISTORY AND EPIDEMIOLOGY

Interest in extraordinary athletic achievement fuels the modern day science of performance enhancement in sports. The desire to improve athletic performance in a scientific manner is a relatively recent development. At one time, the focus on maximizing human physical and mental potential centered on the importance of manual work and military service. The role of sport was inconsequential, except for its potential in improving military preparedness.⁹² Today, “sports doping” refers to the use of a prohibited xenobiotic to enhance athletic performance. The word doping comes from the Dutch word *doop*, a viscous opium juice used by the ancient Greeks.²⁸

Controversy surrounding the systematic use of performance enhancing xenobiotics by the participating athletes has marred many sporting events. Since the International Olympic Committee (IOC) began testing during the 1968 Olympic games, prominent athletes have been sanctioned and stripped of their Olympic medals because they tested positive for banned xenobiotics. However, from a public health perspective, the use of performance-enhancing drugs among athletes of all ages and abilities is a far more serious concern than the highly publicized cases involving world class athletes. The majority of studies on the epidemiology of performance enhancing xenobiotics have investigated androgenic anabolic steroid use. Androgenic means masculinizing, and anabolic means tissue building. An anabolic process stimulates protein synthesis, promotes nitrogen deposition in lean body mass, and decreases protein breakdown. Studies of high school students document that 6.6% of male seniors have used anabolic steroids, and 35% of these individuals were not involved in organized athletics.³¹ Others find rates of androgenic steroid use in adolescent athletes range from 3% to 19%.^{101,114,170,226,231,232} Of the 243,193 samples analyzed by accredited laboratories for the presence of banned performance enhancing xenobiotics in Olympic and non-Olympic sports, 2% had positive findings. The majority of these findings are specific for anabolics and stimulants.

PRINCIPLES

Performance enhancers can be classified in several ways. Some categorize performance enhancers according to the expected effects. For example, some xenobiotics increase muscle mass, whereas others decrease recovery time, increase energy, or mask the presence of other xenobiotics. However, one xenobiotic may have several expected effects. For example, diuretics may be used to mask the presence of other xenobiotics by producing dilute urine, or they may be used to reduce weight. Clenbuterol is an anabolic xenobiotic, but it also is a stimulant because of its β_2 -adrenergic agonist effects. Depending on the xenobiotic, it is used either during training to improve future performance or during competition to improve immediate results.²⁸

According to the 2013 World Anti-Doping Agency (WADA) World Anti-Doping Code, a xenobiotic or method constitutes doping and can be added to the Prohibited List if it is a masking xenobiotic or if it meets two of the following three criteria: it enhances performance, its use presents a risk to the athlete’s health, and it is contrary to the spirit of sport²³⁰ (Table 40–1). Some of the prohibited substances and methods on the WADA 2013 Prohibited List are used to treat legitimate medical conditions of athletes.²³⁰ Athletes with documented medical conditions requiring the use of a prohibited substance or method may request a therapeutic use exemption (TUE). For example, the use of a β -adrenergic agonist other than albuterol, salbutamol, or formoterol in an athlete with documented asthma requires a TUE.

TABLE 40–1. Abbreviated Summary of World Anti-Doping Agency 2013 Prohibited List²³⁰

Substances (S) and Methods (M) Prohibited at All Times (In and Out of Competition)

S1. Anabolic Agents

- Anabolic Androgenic Steroids
- Other Anabolic Agents

Clenbuterol

Selective androgen receptor modulators

S2. Peptide Hormone, Growth Factors, and Related Agents

Erythropoiesis stimulation agents

Chorionic gonadotropin and luteinizing hormone

Corticotropins

Growth hormone

S3. β_2 -Adrenergic Agonists

Except inhaled salbutamol, formoterol, and salmeterol with urinary concentration limits

S4. Hormone Antagonists and Metabolic Modulators

Aromatase inhibitors

Selective estrogen receptor modulators

Antiestrogens

Myostatin modulators

Metabolic modulators

Insulins

Peroxisome proliferator activated receptor delta agonist and AMP activate protein kinase axis agonists

S5. Diuretics and Other Masking Agents

Prohibited Methods

M1. Manipulation of Blood and Blood Components

M2. Chemical and Physical Manipulation

Tampering with samples

Intravenous infusions

M3. Gene Doping

Substances (S) and Methods (M) Prohibited in Competition

In addition to the above, the following categories are prohibited only in competition:

S6. Stimulants

S7. Narcotics

S8. Cannabinoids

S9. Glucocorticosteroids

Substances Prohibited in Particular (P) Sports

P1. Alcohol

P2. β -Adrenergic Antagonists

Specified Substances^a

- Ephedrine
- Cannabinoids
- All inhaled β_2 -adrenergic agonists, except clenbuterol
- Probenecid
- All glucocorticosteroids
- All β -adrenergic antagonists
- Alcohol in competition only

^aIn certain circumstances, a doping violation involving specified substances may result in a reduced sanction, provided the athlete establishes that the use was not intended to enhance performance.

ANABOLIC XENOBIOTICS

Anabolic Androgenic Steroids

Anabolic-androgenic steroids (AASs) increase muscle mass and lean body weight, and cause nitrogen retention.¹⁴⁵ The androgenic effects of steroids are responsible for male appearance and secondary sexual characteristics such as increased growth of body hair and deepening of the voice. Testosterone is the prototypical androgen, and most AASs are synthetic testosterone derivatives. The WADA categorizes AASs into two groups: exogenous, referring to substances that are not ordinarily capable of being produced by the body naturally, and endogenous, referring to those capable of being produced by the body naturally. As such, there is sometimes discordance in categorization schemes with other governing entities. In this document, the term anabolic steroid means any xenobiotic, chemically and pharmacologically related to testosterone, other than estrogens, progestins, corticosteroids, and DHEA.

In the 1970s and 1980s, federal regulation of anabolic steroids was under the direction of the Food and Drug Administration (FDA). Because of increasing media reports on the use of AASs in sports, particularly by high school students and amateur athletes, Congress enacted the Anabolic Steroid Control Act of 1990, which amended the Controlled Substances Act and placed anabolic steroids in schedule III. Schedule III implies that a xenobiotic has a currently accepted medical use in the United States and has less potential for abuse than the drugs categorized as schedule I or II. The Anabolic Steroid Control Act of 2004 adds certain steroid precursors, such as androstenedione and dihydrotestosterone, to the list of controlled substances that are considered illegal without a prescription. However, DHEA is exempted. Possession of androstenedione or other metabolic precursors called prohormone drugs is considered a federal crime. Nevertheless, AASs are still available illicitly over the Internet from international marketers, veterinary pharmaceutical companies, and some legitimate US manufacturers (Table 40–2).

TABLE 40–2. Synthetic Testosterone Derivatives/Anabolic Androgenic Steroids: Generic Nomenclature

<i>17α-Alkyl Derivatives (Oral)</i>	<i>17β-Ester Derivatives (Parenteral)</i>	<i>Testosterone Preparations (Topical)</i>
Ethylestrenol	Boldenone	Buccal gel, sublingual
Fluoxymesterone	Nandrolone decanoate	Dermal gel, ointment
Methandrostenolone	Nandrolone	Transdermal reservoir
Methyltestosterone	phenpropionate	patch
Oxandrolone	Testosterone esters	
Oxymetholone	Testosterone cypionate	
Stanozolol	Testosterone enanthate	
	Testosterone ester	
	combination	
	Testosterone propionate	
	Trenbolone	

Antiestrogens and Antiandrogens

In male athletes using androgens, avoiding the unwanted side effects of feminization, such as gynecomastia, or in female athletes, avoiding masculinization and features such as facial hair and deepening voice, requires manipulation of the metabolic pathways of androgen metabolism. Creating a xenobiotic that completely dissociates the desired from the unwanted effects has not been possible. However, xenobiotics with properties capable of manipulating metabolic pathways associated with undesirable side effects are divided into four main groups, all on the Prohibited List.

1. Aromatase inhibitors such as anastrozole and aminoglutethimide prevent the conversion of androstenedione and testosterone into estrogen.
2. The antiestrogen clomiphene blocks estrogen receptors in the hypothalamus, opposing the negative feedback of estrogen, causing an increase in gonadotropin-releasing hormone, thereby increasing testosterone release.
3. Selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene bind to estrogen receptors and exhibit agonist or antagonist effects at the estrogen receptors. By indirectly increasing gonadotropin release, SERMs restore endogenous testosterone production upon discontinuation of AASs.¹⁷⁸
4. Selective androgen receptor modulators (SARMs) are nonsteroidal tissue selective anabolic xenobiotics. SARMs are neither aromatized and are not substrates for 5 α -reductase, nor do they undergo the same metabolic pathways as testosterone. Therefore, they have fewer unwanted androgenic side effects.^{73,209}

Administration

Approximately 50% of AASs are taken orally. The remainder are administered by intramuscular injection, with one-fourth of intramuscular users sharing needles.^{53,152} One third of the needles and syringes exchanged in a needle-exchange program in Wales were used for AAS injections.¹⁵⁹ Unlike therapeutically indicated regimens, which consist of fixed doses at regular intervals, athletes typically use AASs in cycles of 6 to 8 weeks.¹² For example, the athlete may use steroids for 2 months and then abstain for 2 months. Cycling is based on the athlete's individual preferences and not on any validated protocol. Stacking implies combining the use of several AASs at one time, often with both oral and intramuscular administration. To prevent plateauing, or developing tolerance, to any one xenobiotic, some athletes use an average of five different AASs simultaneously. The doses used are frequently hundreds of times in excess of scientifically based therapeutic recommendations.^{3,227} Pyramiding implies starting the AASs at a low dose, increasing the dose many times, and then tapering once again. Fat soluble steroids may require several months to be totally eliminated, whereas water soluble steroids may require only days to weeks to be cleared by the kidney. Water soluble testosterone esters are used for "bridging therapy." Bridging refers to the practice of halting the administration of long lasting alkylated testosterone formulations so that urine analyses at a specific time offer no evidence of use, whereas injections of shorter acting testosterone esters are used to replace the orally administered alkylated formulations. This strategy, which was used extensively in the German Democratic Republic, is documented in a review of the subject based on extensive research of previously classified records.⁶⁵ Clearance profiles for testosterone congeners were determined for each athlete. In general, the daily injection of testosterone esters was used when termination of the more readily detectable synthetic alkylated testosterone derivatives was necessary to avoid a positive doping test. These daily injections of testosterone propionate were halted 4 to 5 days before competition. Corrupt officials involved in doping were sure that the values would decrease to acceptable concentrations in time for the event, based on the science of athletes' clearance of testosterone esters.⁶⁵

Clinical Manifestations of Anabolic-Androgenic Steroid Use

Cancer. An association between AAS use and the development of cancer is observed in experimental animals.¹⁸⁰ Testicular and prostatic carcinomas are reported in more frequent users of anabolic-androgenic steroids.^{61,71,179} Hepatocellular carcinoma,^{100,153} cholangiocarcinoma,^{12,80} Wilms tumor, and renal cell carcinoma are also reported in young AAS users.^{30,169} The relationship between the dose of AASs and cancer is unknown.

Cardiovascular. Cardiac complications include acute myocardial infarction, venous thromboembolism, and sudden cardiac arrest.^{7,64,87,96,127,129,131,141} Autopsy examination of the heart may reveal biventricular hypertrophy, extensive myocardial fibrosis, and contraction-band necrosis. Myofibrillar disorganization as well as hypertrophy of the interventricular septum and left ventricle are present.¹²⁹ Intense training and use of AASs impair diastolic function by increasing left ventricular wall thickness. Animal models and in vitro myocardial cell studies show similar pathologic changes.^{45,113,142,208,216,217} Doppler echocardiography shows that several years after strength athletes discontinue using AASs, excessive concentric left ventricular hypertrophy remains. Growth hormone may potentiate the effects of AASs and further increase concentric remodeling of the left ventricle.¹⁰⁵ In addition to direct myocardial injury, vasospasm or thrombosis may occur.¹⁴² Alkylated androgens lower the concentration of high-density lipoprotein (HDL) cholesterol and may increase platelet aggregation.^{3,64} Thromboembolic complications include pulmonary embolus,^{50,72} stroke,^{109,110,196} carotid arterial occlusion,¹²⁰ cerebral sinus thrombosis,¹¹⁷ poststeroid balance disorder,²⁶ and popliteal artery

entrapment.¹²⁵

Dermatologic/Gingiva. Cutaneous side effects are common and include keloid formation, sebaceous cysts, comedones, seborrheic furunculosis, folliculitis, and striae.¹⁹² Acne is associated with steroid use and sometimes is referred to as “gymnasium acne.”^{39,162} A common triad of acne, striae, and gynecomastia occurs. The production of sebum is an androgen-dependent process, and dihydrotestosterone is active in sebaceous glands.¹² Gingival hyperplasia is reported.¹⁵⁴

Endocrine. Conversion of AASs to estradiol in peripheral tissues results in feminization of male athletes. Gynecomastia may be irreversible. AAS use causes negative feedback inhibition of gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone from the hypothalamus. This process results in testicular atrophy and decreased spermatogenesis, which may be reversible. In women, menstrual irregularities and breast atrophy may occur.²⁰⁶

Hepatic. Hepatic subcapsular hematoma with hemorrhage is reported.¹⁹¹ Peliosis hepatis, a condition of blood-filled sinuses in the liver that may result in fatal hepatic rupture, occurs most commonly with alkylated androgens and may not improve when androgen use is stopped.^{13,91,198,225} This condition is not associated with the dose or duration of treatment.^{12,99,201} Cyproterone acetate is a chlorinated progesterone derivative that inhibits 5 α -reductase and reportedly causes hepatotoxicity.^{12,70,75}

Infectious. Local complications from injection include infected joints,⁶⁰ cutaneous abscess,^{137,173} and *Candida albicans* endophthalmitis.²²⁶ Injection of AASs using contaminated needles has led to transmission of infectious diseases such as human immunodeficiency virus and hepatitis B and C.^{152,155,172,175,193,197} Severe varicella is reported in long-term AAS users.¹⁰¹

Musculoskeletal. Supraphysiologic doses of testosterone, when combined with strength training, increase muscle strength and size.²² The most common musculoskeletal complications of steroid use are tendon and ligament rupture.^{67,89,121,126}

Neuropsychiatric. Distractibility, depression or mania, delirium, irritability, insomnia, hostility, anxiety, mood lability, and aggressiveness (“roid rage”) may occur.^{17,68,166,167,207} These neuropsychiatric effects do not appear to correlate with serum AAS concentrations.^{196,207} Withdrawal symptoms from AAS include decreased libido, fatigue, and myalgias.^{108,232}

Specific Anabolic Xenobiotics

Dehydroepiandrosterone. DHEA is a precursor to testosterone (Fig. 40–1). Because it is produced endogenously, DHEA most commonly is not categorized as an AAS. However, DHEA is weakly anabolic and weakly androgenic. Although banned by the FDA in 1996, this xenobiotic subsequently was marketed as a nutritional supplement and is available for purchase without a prescription.²⁰⁶ DHEA is converted to androstenedione and then to testosterone by the enzyme 17 β -hydroxysteroid dehydrogenase.^{94,128,132} Administration of androstenedione in dosages of 300 mg/d increases testosterone and estradiol concentrations in some men and women.¹²⁴ Women with adrenal insufficiency given DHEA replacement at a dose of 50 mg/d orally for 4 months demonstrated increased serum concentrations of DHEA, androstenedione, testosterone, and dihydrotestosterone. Serum total and HDL cholesterol concentrations simultaneously decreased. Some women experienced androgenic side effects, including greasy skin, acne, and hirsutism.¹⁰ Sense of well-being and sexuality increased in men and women after 4 months of treatment.^{10,146,147} The neuropsychiatric effects of DHEA have been demonstrated in animals. Increased hypothalamic serotonin, anxiolytic effects, antagonism at the γ -aminobutyric acid type A (GABA_A) receptor, and agonism at the N-methyl-D-aspartate receptor (NMDA) are demonstrated.^{10,133,143}

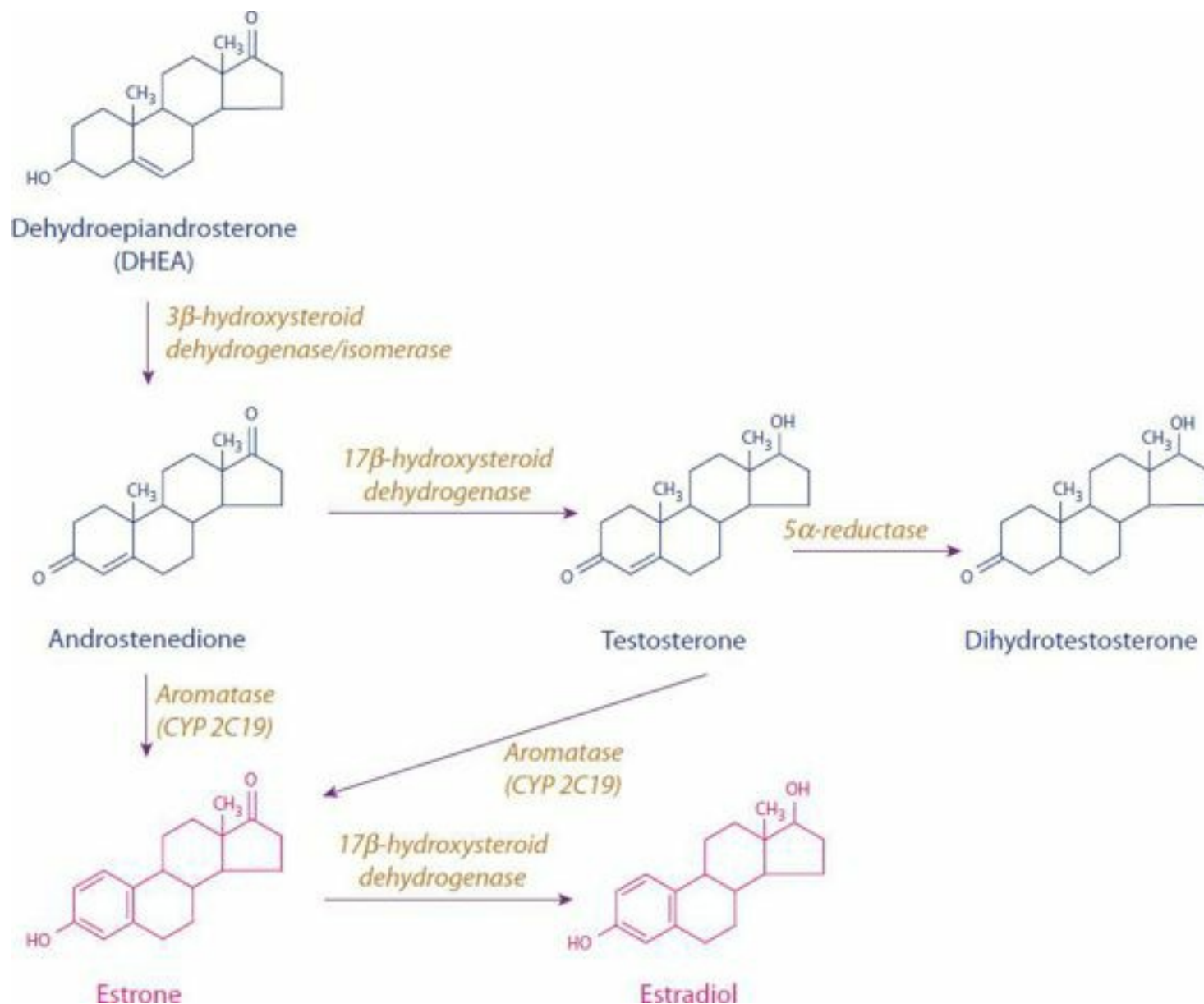


FIGURE 40–1. Metabolic pathway of dehydroepiandrosterone (DHEA).

Clenbuterol. Clenbuterol is a β_2 -adrenergic agonist that decreases fat deposition and prevents protein breakdown in animal models.^{6,38,90} Clenbuterol is also a potent nutrient partitioning agent, a term implying it can increase the amount of muscle and decrease the amount of fat produced per pound of feed given to cattle and other animals.^{68,177} Use of clenbuterol in cattle farming is illegal in many countries. Nevertheless, the consumption of veal liver contaminated with clenbuterol has resulted in sympathomimetic symptoms and positive urine tests in affected individuals.¹⁸³ Clenbuterol is composed of a racemic mixture of (+) and (–) stereoisomers, eliminated in urine in approximately equal amounts. As clenbuterol accumulates in animal meat, stereoisomer ratios change over time and (–) clenbuterol is depleted. By analyzing urinary ratios of clenbuterol stereoisomers, it is possible to differentiate administration of therapeutic clenbuterol preparations from inadvertent ingestion of clenbuterol in meat products.²¹¹ Clenbuterol increases the glycolytic capacity of muscle and causes hypertrophy, enhancing the growth of fast-twitch fibers^{134,234} (Chap. 66).

PEPTIDES AND GLYCOPROTEIN HORMONES

Creatine

Creatine is an amino acid formed by combining the amino acids methionine, arginine, and glycine. It is synthesized naturally by the liver, kidneys, and pancreas. Creatine is found in protein-containing foods such as meat and fish.¹⁵⁴ In its phosphorylated form, it is involved in the rapid resynthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) by acting as a substrate to donate phosphorus.²⁰⁵ Because ATP is the immediate source of energy for muscle contraction, creatine is used by athletes to increase energy during short, high-intensity exercise.²²⁰ More than 2.5 million kilograms of creatine are consumed annually in the United States.⁵⁶ Exceptional athletes have admitted to using creatine as part of their training nutritional regimen, leading to interest by athletes at all levels. Numerous studies demonstrate improved performance with creatine supplementation, particularly in sports requiring short, high-intensity

effort.^{25,31,84,116,140,220} Creatine is found in skeletal muscle and in the heart, brain, and kidney. Two-thirds of creatine is stored primarily as phosphorylated creatine and the remainder as free creatine.¹⁴ Consuming carbohydrates with creatine supplements increases total creatine and phosphorylated creatine stores in skeletal muscle.⁸³ This process explains why creatine is marketed in combination with carbohydrate. Human endogenous creatine production is 1 g/d, and normal diets containing meat and fish offer another 1 to 2 g/d as dietary intake. One to two grams of creatine is eliminated daily by irreversible conversion to creatinine.²²⁴

Creatine supplementation is most commonly accomplished with creatine monohydrate. A dose of 20 to 25 g/d can increase the skeletal muscle total creatine concentration by 20%.^{84,97} Creatine stores do not increase in some individuals despite creatine supplementation. Creatine uptake in skeletal muscle occurs via the creatine transporter proteins at the sarcolemma. Creatine transporter expression and activity, as well as exercise and training, influence the uptake of creatine and the effect of creatine loading on athletic performance.^{199,200,202}

One adverse effect of creatine supplementation is weight gain, which is thought to result primarily from water retention.^{84,140} However, evidence indicates that net protein increase is partially responsible for the weight gain associated with long-term creatine use.¹⁰⁴ Diarrhea was the most commonly reported side effect of creatine use in one study of 52 male college athletes. Other complaints were muscle cramping and dehydration, although many subjects had no complaints.¹⁰³

Creatine supplementation increases urinary creatine and creatinine excretion and may increase serum creatinine concentrations by 20%.^{84,104} Long- and short-term creatine supplementation does not appear to have an adverse effect on kidney function.^{164,165} One patient who had been taking creatine 5 g/d for 4 weeks developed interstitial nephritis that improved with cessation of creatine use. Whether ingestion of creatine caused the nephritis is unknown.¹¹⁵ A young man with focal segmental glomerular sclerosis developed an elevated creatinine concentration and decreased glomerular filtration rate when creatine supplementation was started. The values returned to baseline upon cessation of creatine supplementation.¹⁷¹ The possibility of developing decreased kidney function is a theoretical concern. Ingestion of large amounts of creatine may result in formation of the carcinogenic substance N-nitrososarcosine, which induces esophageal cancer in rats.^{8,9}

Human Growth Hormone

Human growth hormone (hGH) is an anabolic peptide hormone secreted by the anterior pituitary gland. It stimulates protein synthesis and increases growth and muscle mass in children. Recombinant hGH (rhGH) has been available since 1984. It is commonly used therapeutically for children with growth hormone deficiency in daily doses of 5 to 26 µg/kg body weight.²²¹

Growth hormone secretion is stimulated by growth hormone–releasing hormone and is inhibited by somatostatin. Growth hormone receptors are found in many tissues, including the liver. Binding of hGH to hepatic receptors causes secretion of insulinlike growth factor-1 (IGF-1), which has potent anabolic effects and is the mediator for many of the actions of hGH.

Release of hGH, which occurs mainly during sleep, occurs in a pulsatile manner. Exercise stimulates hGH release, and more intense exercise causes proportionately more hGH release.^{27,43,206} Amino acids such as ornithine, L-arginine, tryptophan, and L-lysine, increase hGH release through an unknown mechanism and often are ingested for this purpose.^{43,86}

By causing nitrogen retention and increased movement of amino acids into tissue, hGH stimulates protein synthesis and tissue growth. The effects on increasing muscle mass and size are demonstrated in growth hormone–deficient individuals. Some studies do not support an increase in strength secondary to the increase in muscle size in athletes,^{41,130} whereas others demonstrate lean body mass, strength, and power increases.⁸² Growth hormone improves muscle and cardiac function, increases red cell mass and oxygen-carrying capacity, stimulates lipolysis, normalizes serum lipid concentrations, and decreases subcutaneous fat. It also improves mood and sense of well-being.^{41,42,88,185,206,221}

Growth hormone is used by athletes for its anabolic potential. As a xenobiotic of abuse, it is particularly attractive because laboratory detection is difficult. In one survey, 12% of people in gyms used hGH for body building.⁵⁹ In another survey of adolescents, 5% of 10th-grade boys had used hGH.¹⁷⁶ It may be sold illicitly as recombinant hGH.

Administration of hGH may cause myalgias, arthralgias, carpal tunnel syndrome, and edema.⁹⁵ The effects of hGH on skeletal growth depend on the user's age. In preadolescents, excessive hGH may cause increased bony growth and gigantism. In adults, excessive hGH may cause acromegaly.^{217,219} Growth hormone may cause glucose intolerance and hyperglycemia. Skin changes, such as increased melanocytic nevi and altered skin texture, occur.¹⁶³ Lipid profiles may be adversely affected. HDL concentrations are decreased, a change associated with increased risk of coronary artery disease.²³⁵ Because hGH must be given parenterally, there is risk of transmission of infection.¹³⁰ The illicit sale of cadaveric human pituitary-derived growth hormone is associated with a risk of Creutzfeldt-Jakob disease.⁴⁹ Long-term users of hGH may be at increased risk for prostate cancer because of the complications associated with IGF-1⁷⁹ (see

below).

Testing for hGH is plagued by the difficulties inherent in testing for exogenous peptide doping in general—the identical amino acid sequences of both rhGH and hGH; the fluctuating, pulsatile secretion; short half-life; and variation in normal concentration depending on sleep as well as stress and exercise status. Unlike the ability to use the differing pattern of N-linked glycosylation in hEPO produced in the human kidney to distinguish it from rhEPO produced in the hamster, hGH has no N-linked glycosylation sites to facilitate differentiation.

There are currently two approaches to detection of hGH currently: the marker approach and the isoform approach.⁹³ The marker approach uses an immunoassay to measure hGH-dependent factors through which hGH exerts its effect, such as IGF-1 and insulinlike growth factor binding proteins, as well as other markers of bone growth and turnover, such as the N-terminal extension peptide of procollagen type III.^{23,168} The isoform approach refers to the measurement of the various forms of growth hormone. Whereas rhGH is primarily a 22-kDa monomeric form, pituitary hGH contains multiple isoforms. In athletes using rhGH, endogenous hGH with its multiple isoforms is suppressed through negative feedback on the pituitary. Therefore, the 22-kDa form characteristic of rhGH becomes predominant. The ratio of isoforms, as measured by immunoassay, changes.

Insulinlike Growth Factor-1

IGF-1 is a peptide chain structurally related to insulin. A recombinant form is available.¹⁷⁶ Parenteral administration of IGF-1 is approved for clinical treatment of dwarfism and insulin resistance. Children who develop antibodies to rhGH may respond to IGF-1.

The primary stimulus for release of IGF-1 is hGH, although insulin, DHEA, and nutrition play a role.^{146,182} The actions of IGF-1 can be classified as either anabolic or insulinlike.¹⁸² The effects of growth hormone are primarily mediated by IGF-1. IGF-1 is produced in the liver and many other cell types. IGF-1 binds principally to the type I IGF receptor, which has 40% homology with the insulin receptor and a similar tyrosine kinase subunit.²¹³ IGF-1 also binds to insulin receptors, but it has only 1% of insulin affinity for the insulin receptor. IGF-1 increases glucose utilization by causing the movement of glucose into cells, increasing amino acid uptake and stimulating protein synthesis.

Side effects are similar to those associated with use of growth hormone and include acromegaly. Other effects include headache, jaw pain, edema, and alterations in lipid profiles. A potentially serious side effect of IGF-1 is hypoglycemia. High endogenous plasma IGF-1 concentrations are associated with an increased risk for prostate cancer.³⁶

Few studies on the efficacy of IGF-1 in improving the conditioning of athletes are available. IGF-1 can be considered favorably by female athletes because it does not cause virilization.²⁰⁶

Insulin

Insulin is used by body builders for its anabolic properties. Of 20 self-identified AAS users in a single gym, 25% who had no medical reason to take insulin reported using it to increase muscle mass.¹⁷⁴ These individuals stated that they had injected insulin from 20 to 60 times over the 6 months prior to the study.¹⁷⁴ Their practice was to inject 10 units of regular insulin and then eat sugar-containing foods after injection. As expected, hypoglycemia is reported in body builders using insulin.^{56,98,171}

Insulin inhibits proteolysis and promotes growth by stimulating movement of glucose and amino acids into muscle and fat cells. It increases the synthesis of glycogen, fatty acids, and proteins⁴⁴ (Chap. 53).

Human Chorionic Gonadotropin (hCG)

In men, the glycoprotein hCG stimulates testicular steroidogenesis. In women, hCG is secreted by the placenta during pregnancy. It may be used by male athletes to prevent testicular atrophy during and after androgen administration.¹¹¹ Analysis of hCG in 740 urinary specimens of male athletes revealed abnormal concentrations in 21 individuals. This finding prompted the IOC ban on hCG use in 1987.^{30,43} Presently, distinguishing exogenous hCG administration from hCG production in early pregnancy is not possible, so the urine samples of women are not tested.¹¹¹

Very small amounts of hCG are normally present in men and nonpregnant women.¹²¹ Currently, measurement is made by immunoassay. The decision limit, the concentration at which the test is considered positive, is set at 5 IU/mL urine. Trophoblastic tumors and nontrophoblastic tumors can increase hCG concentrations, and this possibility must be considered in the evaluation of elevated urinary hCG concentration.⁴⁸ Administration of hCG causes an increase in the total testosterone and epitestosterone produced.

OXYGEN TRANSPORT

Erythropoietin (EPO)

Human erythropoietin (hEPO) is a hormone that, through a receptor-mediated mechanism, induces erythropoiesis by stimulating stem cells. EPO has been available since 1988 as recombinant human erythropoietin (rhEPO), and its use in international competition has been prohibited since 1990. While hEPO is produced primarily by the kidneys, rhEPO is produced in hamsters⁵²; this results in differing glycosylation patterns, an important piece in the laboratory detection of EPO in sports doping.

Because EPO increases exercise capacity and hemoglobin production, it is used by athletes, often with additional iron supplementation. The clinical effects of increased hemoglobin occur several days after administration.^{69,156} EPO increases maximal oxygen uptake by 6% to 7%, an effect that lasts approximately 2 weeks after rhEPO administration is completed.⁵⁵

Two EPO analogs exist. Darbepoetin, also known as new erythropoiesis-stimulating protein, differs from EPO by five amino acids. It has a much longer half-life and can be injected weekly.¹⁵⁷ Another protein, known as synthetic erythropoiesis protein, has a similar protein structure to EPO. The protein polymers created in this molecule have less immunogenicity, fewer biologic contaminants, and more predictable pharmacokinetics.¹⁵⁷

Human EPO is secreted primarily by the kidney, although some is produced by the liver. The mean apparent half-lives of rhEPO are 4.5 hours following intravenous administration and 25 hours after subcutaneous administration.¹⁸⁴

EPO enhances endothelial activation and platelet reactivity and increases systolic blood pressure during submaximal exercise.^{21,204} These effects, in addition to the increase in hemoglobin, increase the risk of thromboembolic events, hypertension, and hyperviscosity syndromes.^{21,139,156} Nineteen Belgian and Dutch cyclists died of uncertain causes between 1987 and 1990.⁵⁴ Increases in hematocrit subsequent to EPO use are believed to have contributed to these deaths. The 1998 Tour de France was marred by the discovery of widespread EPO use by members of several different cycling teams.

An EPO overdose occurred in a patient who self-administered 10,000 units/d for an unknown period of time as a result of a dosing error. The patient presented to the hospital with confusion, a plethoric appearance, blackened toes, decreased pulses, and a hematocrit of 72%. Emergent erythropheresis was performed and resulted in rapid reduction of hematocrit and improvement in the patient's condition.²³³ Another report of deliberate daily self-administration of an unknown dose of rhEPO resulted in a hematocrit of 70%. The patient was treated emergently with phlebotomy and intravenous hydration and improved.²⁹

Testing for Erythropoietin. EPO is directly measured by a monoclonal anti-EPO antibody test, which does not distinguish between endogenously produced and exogenously administered recombinant EPO. Therefore, indirect methods of EPO detection are used, such as measurement of hemoglobin or hematocrit.

Previously, some sports-governing bodies, such as the International Cycling Federation and the International Skiing Federation, selected a hematocrit of 50% in men and 47% in women as the action level above which an athlete may be disqualified for presumed EPO use. However, normal hematocrit values vary greatly among athletes. Several studies have shown that hematocrits above the action values of 50% in men and 47% in women are common in athletes. From 3% to 6% of athletes who did not use EPO had hematocrits greater than 50%.²²² Of those athletes living and training at altitudes between 2000 and 3000 meters above sea level, 20.5% had hematocrit values higher than 50%.²²² Other studies confirm the increased hematocrits of athletes training at altitudes of 1000 to 6000 meters.^{19,188,189,222}

Although many endurance athletes may have increased blood volume, the hematocrit may be lowered because of the increased plasma volume, which exceeds the RBC volume. This dilutional pseudoanemia is sometimes called sports anemia.¹⁹⁵ Additionally, hematocrit measurements are affected by hydration status, posture (upright versus supine), and nutrition, and they demonstrate an approximately 3% diurnal variation.¹⁸⁷ Because of natural variations among individuals, postural effects, and the ease of manipulation through saline infusion, indirect detection of EPO use by hematocrit measurement is fraught with potential for error.¹⁵⁶

Several methods have been studied to detect the use of rEPO by athletes. The ratio between serum soluble transferrin receptors (sTfr) and ferritin was used as an indirect method for detection of EPO use. The sTfr is released from RBC progenitors. EPO stimulates erythropoiesis and causes an increase in sTfr and a decrease in ferritin.⁷⁴ Individuals with other causes of polycythemia or accelerated erythropoiesis also can exhibit increased ratios and be falsely accused of EPO use. An increased hematocrit with sTfr greater than 10 µg/mL and sTfr-to-serum protein ratio greater than 153 has been proposed as an indirect measurement of EPO use.¹²

At the 2000 Olympics in Sydney, Australia, a combination of multiple indirect markers was developed for detection of altered erythropoiesis and rhEPO use.¹⁵⁶ Current EPO use, known as the "ON-model," and recent, but not current, use of EPO, known as the "OFF-model," were identified by measured laboratory values. For example, five variables predict current rhEPO use: reticulocyte count, serum EPO concentration, sTfr, hematocrit, and percentage of macrocytes. The three variables in combination, including hematocrit, reticulocyte count, and serum EPO concentration, were the best mechanism for detecting recent rhEPO use.¹⁵⁶ A major drawback to this method is the instability of these variables in whole blood, so that confirmatory testing of the split blood sample is impossible.¹⁵⁷

State-of-the-art detection of EPO doping is accomplished by two techniques: isoelectric focusing and immunoblotting performed on urine samples. The two isoforms of EPO, recombinant and endogenous, have different glycosylation patterns and glycan sizes, resulting in differing molecular charges.¹⁵⁷ An immunoblotting procedure takes advantage of these different net charges, and the proteins can be separated by their charges when they are placed in an electric field.¹²³ Subsequently, by isoelectric focusing, this method obtains an image of EPO patterns in the urine.¹²² WADA considers a positive urine test result by this method definitive, even without the blood testing of indirect markers.¹⁵⁷ Because of the structural similarity of darbepoetin to EPO, these detection techniques also are effective for darbepoetin.¹⁵⁷

Athlete's Biological Passport. A significant development in the detection of blood transfusion, known as blood doping, is the development of a longitudinal record of an athlete's red blood cell (RBC) parameters called the athlete's biological passport. The detection of plasticizer metabolites from blood storage and alteration of gene expression resulting from infusion of autologous blood are proposed adjuncts to detection of autologous blood transfusion.¹⁴⁸ The observation of physiological parameters over time has made it easier to detect use of performance enhancing agents.¹⁶

STIMULANTS

Caffeine

Caffeine is a central nervous system stimulant that causes a feeling of decreased fatigue and increases endurance performance^{58,158} (Chap. 66). These changes may occur through several different mechanisms, including increased calcium permeability in the sarcoplasmic reticulum and enhanced contractility of muscle, phosphodiesterase inhibition and subsequent increased cyclic nucleotides, adenosine blockade leading to blood vessel dilation, and inhibited lipolysis. Caffeine is no longer prohibited by World Anti-Doping Code 2005 Prohibited List. Caffeine and pseudoephedrine are included in a monitoring program that was implemented by the WADA to detect patterns of misuse for substances that are no longer on the Prohibited List.²¹⁵

Amphetamines

The beneficial effects of amphetamines in sports result from their ability to mask fatigue and pain.⁴⁶ Initial studies done in soldiers showed that they could march longer and ignore pain when taking amphetamines (Chap. 76).²¹⁴ In one study in college students, resting and maximal heart rate, strength, acceleration, and anaerobic capacity increased. However, although the perception of fatigue decreased, lactic acid continued to accumulate and maximal oxygen consumption was unchanged.³⁷ Other studies have shown no significant effects on exercise performance¹⁰⁷.

Sodium Bicarbonate

Sodium bicarbonate loading, known as "soda loading," has a long history of use in horse racing.¹⁵ Sodium bicarbonate may buffer the metabolic acidosis associated with an elevated lactate caused by exercise, thereby delaying fatigue and enhancing performance.⁷⁶

During high-intensity exercise, metabolism becomes anaerobic and lactic acid is produced. Intracellular acidosis is said to contribute to muscle fatigue by reducing the sensitivity of the muscle contractile apparatus to calcium.¹⁶⁰ Several studies demonstrated improved performance in running when sodium bicarbonate was ingested 2 to 3 hours before competition.^{40,181} The study dose was 0.2 to 0.3 g/kg body weight of sodium bicarbonate, approximately 160 mEq of sodium bicarbonate per day. The effects of sodium bicarbonate are greatest when periods of exercise last longer than 4 minutes because anaerobic metabolism contributes more to total energy production and energy from aerobic metabolism diminishes.^{76,77} Adverse effects of bicarbonate loading include diarrhea, abdominal pain, and the possibility of hypernatremia.⁷⁶

An animal model demonstrated that intracellular acidosis associated with lactate production reversed muscle fatigue.^{4,160} Previously, intracellular acidosis was thought to contribute to muscle fatigue by reducing the sensitivity of the muscle contractile apparatus to calcium, decreasing the force of muscle contraction. However, the mechanism of excitation-contraction is complex. Because it permeates membranes easily, chloride is an important ion in maintaining and stabilizing the muscle fiber resting membrane potential at normal pH. Because of this, a large sodium current is needed to overcome membrane stabilization and produce an action potential. In the case of intracellular acidosis, the permeability of the membrane to the chloride ion is reduced, the resting membrane potential is no longer stabilized, and less inward sodium influx is needed to produce an action potential. The excitability of the muscle T-tubule system is therefore increased by acidosis, protecting against muscle fatigue.¹⁶⁰

DIURETICS

The WADA bans nonmedical diuretic use.²²⁹ Diuretics are used in sports in which the athlete must achieve a certain weight to compete in discrete weight classes. In addition to weight loss, body builders find that diuretic use gives greater definition to the physique as the skin draws tightly around the muscles.² In one report, a professional body builder attempted to lose weight using diuretics including bumetanide and spironolactone as well as potassium supplements. He presented with hyperkalemia and hypotension² (Chap. 19). Diuretics also result in increased urine production, thereby diluting the urine and making the detection of other banned xenobiotics more difficult.^{32,47}

LABORATORY DETECTION

Enormous amounts of energy and money are expended to determine the presence or absence of performance-enhancing xenobiotics. Analysis of samples on the international level is performed by a limited number of accredited laboratories. The majority of tests are performed on urine, with careful procedural requirements regarding handling of samples. Attention must be paid to proper storage of specimens, because bacterial metabolism may increase urinary steroid concentrations.^{24,51} Upon arrival of a sample at the testing laboratory, the integrity of the sample is checked, including the code, seal, visual appearance, density, and pH. Registration of the sample is completed, and the sample is divided into two aliquots. All testing is done on the first aliquot, and any positive results are confirmed on the second aliquot. The aliquots are commonly referred to as sample A and sample B. Sample preparation is difficult and time consuming.

The complexity of the laboratory testing and continuous attempts to evade detection is illustrated in the discovery of an AAS previously undetectable by standard sport doping tests of urine. In the following situation, there was no preexisting reference data for the unknown xenobiotic. In the summer of 2003, a used syringe was provided anonymously to the US anti-doping authority. Through a painstaking process of analyses, a previously unrecognized chemical in the syringe was identified as a derivative of the AAS norbolethone, a known reference compound, leading to the discovery, synthesis, and detection of tetrahydrogestrinone (THG), a new chemical unknown as a pharmaceutical or veterinary compound.³⁴ Since the discovery of THG, the identity of another designer steroid, madol, or desoxymethyltestosterone, was similarly discovered and the structure synthesized.¹⁹⁴

Capillary Gas Chromatography–Mass Spectrometry

Capillary gas chromatography allows the determination of approximately 95% of all doping positive results. Gas chromatography typically is combined with mass spectrometry for detection of the majority of substances.¹⁵⁰ Analysis of the urine by gas chromatography–mass spectrophotometry (GCMS) is the current standard for detection of AASs.³² Such analysis relies on a large amount of previously derived reference data.³⁴

Testosterone-to-Epitestosterone Ratio

GCMS cannot distinguish endogenous testosterone from pharmaceutically derived exogenous testosterone. Therefore, other methods of detection are needed. One way of detecting the use of exogenous testosterone is to measure the testosterone-to-epitestosterone (T/E) ratio. Epitestosterone is not a metabolite of testosterone, but its a 17- α epimer, differing from testosterone only in the configuration of the hydroxyl group on C-17. Men produce 30 times more testosterone than epitestosterone; however, 1% of testosterone and 30% of epitestosterone is excreted unchanged in the urine. Therefore, the normal T/E ratio in the urine is about 1:1.²⁰³ A T/E ratio less than 4:1 is considered acceptable; a T/E ratio greater than 4:1 is considered evidence of doping using testosterone. In order to maintain a normal T/E ratio, an athlete may self-administer both testosterone and epitestosterone.³³

The overall pattern of the T/E ratio over time is important. Athletes subjected to testing will have previous measurements of their T/E ratios on record with antidoping authorities, or additional tests may be obtained to establish a pattern of T/E ratios. These results are plotted against time. The mean, standard deviation, and confidence values are calculated.³³ The confidence values of three or more samples taken over months will be less than 60% unless the athlete is using testosterone.³⁴ Sudden variations in an athlete's pattern of T/E ratios over time is a cause for further testing.

In one high-profile doping case where the T/E ratio was elevated, the athlete suggested that ethanol consumption the previous night caused the elevated T/E ratio. In this regard, there is evidence that at very high doses, for example, 2 g/kg, ethanol increases the T/E ratio, although the T/E ratio did not exceed 6:1.⁶² This effect of ethanol is more pronounced in women and is limited to 8 hours postingestion of ethanol. The mechanism of this effect of ethanol may be that it increases the NADH-to-NAD⁺ ratio and many steroid oxidation-reduction reactions are dependent on the relative abundance of NADH to NAD⁺.⁶² Ketoconazole inhibits testosterone synthesis and may cause a decrease in the T/E ratio within 6 hours of administration.¹¹²

Isotope Ratio Mass Spectrometry

Carbon is made up of six protons and six neutrons, giving it an atomic weight of 12 (^{12}C). Sometimes carbon has an extra neutron, giving it an atomic weight of 13 (^{13}C). Carbon is derived from carbon dioxide in the atmosphere. Warm climate plants, such as soy, process carbon dioxide differently than other plants, using different photosynthetic pathways for carbon dioxide fixation, causing the depletion of ^{13}C .¹⁸⁶ Pharmaceutical testosterone is made from plant sterols, primarily soy plants, and therefore has less ^{13}C isotope than endogenous testosterone, made in the body from a typical human diet based in corn and not soy. This difference in isotope ratios is measured by isotope ratio mass spectrometry. An athlete's natural carbon makeup is determined by analysis of an endogenous reference compound such as the testosterone precursor cholesterol. Cholesterol may be called an "autostandard" because it represents the athlete's $^{13}\text{C}/^{12}\text{C}$ ratio.²⁰ Finally, it is the difference between the ratio of the athlete's $^{13}\text{C}/^{12}\text{C}$ ratio and an international standard ratio that is measured and reported.¹ Values are negative because both endogenous and pharmaceutical testosterone contain less ^{13}C than the international standard.⁸⁵

Insulin

Laboratory detection methods for insulin are not yet standardized and accredited by WADA. Therefore, athletes are not currently tested for insulin use. The technology for testing for insulin uses immunoaffinity purification followed by liquid chromatography–tandem mass spectrometry to identify analytes including urinary metabolites of insulin.²¹² When insulin is modified to improve its receptor selectivity or give it other favorable properties, the change in molecular weight or amino acid profile from human insulin makes it detectable by GCMS.²¹²

Masking Xenobiotics

Any chemical or physical manipulation done with the purpose of altering the integrity of a urine or blood sample is prohibited by WADA.²²⁹ For example, use of intravenous fluids for dilution of the sample, or urine substitution, is prohibited. Some xenobiotics are added to the urine for the sole purpose of interfering with urine testing and are easily detected. Examples include "Klear," which is 90% methanol, and Golden Seal tea, which produces colored urine.²⁸ Other commercially available products include "Xxtra Clean," which contains pyridinium chlorochromate, and "Urine Luck," which contains glutaraldehyde.

Niacin has been used to alter urine test results, although there is no evidence it is effective for this purpose. There are reports of niacin toxicity, including skin reactions such as itching, flushing, and burning when niacin is used for this purpose.^{35,144} More serious symptoms, including nausea, elevated liver enzymes, hypoglycemia, and anion gap metabolic acidosis, are reported as a result of ingesting niacin in large amounts, in the 2.5 to 5.5 g range over 1 to 2 days.^{35,144}

A significant issue in the analysis of urine for the presence of prohibited peptides such as rEPO is the masking potential of proteases surreptitiously added to urine specimens slated for doping analysis. The proteases are packaged in "grains" known as protease granules or "rice grains" and placed in the urethra.²⁰⁹ Upon urination for the purpose of providing a specimen for doping analysis, the grain flows with urine into the specimen cup. The proteases, including trypsin, chymotrypsin, and papain, will quickly degrade renally excreted peptides, most notably EPO, making them undetectable. By the process of autolysis, proteases may themselves become undetectable over time. In one report, urine with elevated protease concentrations greater than 15 $\mu\text{g}/\text{mL}$ underwent further analysis to identify urinary proteins such as albumin.²⁰⁹ Normally, the presence of urinary proteins creates the image of a visible band by gel electrophoresis. However, the urine with elevated protease activity may demonstrate something called trace of burning, a term indicating an absence of proteins.²¹⁰ In this report, suspicious specimens were subjected to further testing using liquid chromatography–mass spectrometry. After further molecular sequencing of derived proteins, human proteases can be distinguished from nonhuman proteases, such as bovine chymotrypsin or papain. The addition of a protease inhibitor to urine samples immediately after collection may be a future strategy to control the effectiveness of protease addition as a masking method.²¹⁰

In approximately 15% of urine samples performed in anti-doping laboratories, there is no endogenous or rEPO detectable by immunoelectrophoresis.¹¹⁹ Undetectable EPO occurs more commonly in competition, the "competition effect." This is due in part to circumstances that may be unrelated to doping, such as physiological variation in EPO production, gender, and very low or very high urine specific gravity. However, doping with exogenous rEPO and inhibition of endogenous hEPO production or addition of proteases are other possible causes. Strenuous effort causes a shift in the isoforms of EPO yielding a more basic isoelectric point, a result known as "effort" urine.¹¹⁸ In any case, a urine deemed as suspicious may ultimately not result in a positive doping test result.^{119,209}

The list of prohibited masking xenobiotics includes diuretics, epitestosterone, probenecid, plasma expanders such as albumin, dextran, and hydroxymethyl starch, and α -reductase inhibitors such as finasteride and dutasteride.²²⁹ Probenecid blocks urinary excretion of the glucuronide conjugates of AAS.

Gene Doping

The discovery of the genetic codes for some diseases has made gene therapy of medical conditions, such as muscular dystrophy, a reality. It is now conceivable that this technology can be used to enhance athletic performance. Gene doping is included on the WADA 2013 Prohibited List.²³⁰ Gene doping is defined as “the non-therapeutic use of cells, genes, genetic elements, or of the modulation of gene expression, having the capacity to enhance athlete performance.”²²⁹ For example, insertion of a gene sequence could produce a desired effect, such as large muscles or increased body production of potentially advantageous substances such as testosterone or growth hormone. In animal models, genes for EPO lead to erythropoiesis and genes for IGF-1 produce increased muscle size and strength.¹⁸ Myostatin, which belongs to a family of proteins that control growth and differentiation of tissues in the body, inhibits skeletal muscle growth.^{102,190} Mutations of the myostatin gene may result in muscle hypertrophy. In dogs, the athletic performance of racing whippets is enhanced in those animals with a myostatin gene mutation.¹⁴⁹ In humans, a report of an extremely muscular baby born with a mutation in the myostatin gene illustrates the potential effect of gene alterations on athletic performance. The mother of this infant was a professional athlete, and other members of the family were known for their strength.¹⁹⁰ Transcription regulators such as AMP-activated protein kinase (AMPK) are exercise mimetics and increase muscle endurance when administered orally in animal models.^{81,151} Influencing the expression of the transcription factor peroxisome proliferator-activated receptor- δ (PPAR- δ), a nuclear hormone receptor hormone protein, leads to increased formation of slow twitch skeletal muscle. Angiotensin II receptor blockers such as telmisartan influence both the AMPK pathway and up-regulate PPAR- δ expression improving muscle performance.⁶³

PERFORMANCE ENHANCEMENT AND SUDDEN DEATH IN ATHLETES

Many unexpected deaths in certain groups of young competitors have occurred in the absence of obvious medical or traumatic causes. In some of these cases, the use of performance-enhancing drugs was linked to the deaths. The use of EPO, introduced in Europe in 1987, may have contributed to the large number of deaths in young European endurance athletes over the next several years.^{57,78,138,161,223} In young healthy athletes experiencing cerebrovascular events or myocardial infarction, the temporal link between the use of cocaine, ephedrine, or performance enhancers such as AASs suggests a role for these xenobiotics as precipitants of these adverse events.¹³⁵ Nevertheless, the leading cause of nontraumatic sudden death in young athletes is most often associated with cardiac anomalies.¹³³ In autopsy studies of athletes in the United States with sudden death, hypertrophic cardiomyopathy is the most common structural abnormality, accounting for more than one-third of the cardiac arrests, followed by coronary artery anomalies.¹³⁵ In Italy, dysrhythmic right ventricular cardiomyopathy is implicated in one fourth of these deaths.^{66,106,136,218} Medical causes of sudden death other than cardiac causes include heat stroke ([Chap. 30](#)), sickle cell trait, and asthma.

SUMMARY

- Although the press spotlights a few world-class athletes, the vast majority of individuals using performance-enhancing substances are not in the public view. Some individuals suffer adverse consequences. The knowledgeable clinician will identify these health effects when they occur and educate susceptible individuals on the health risks of using performance enhancing substances.
- Continuous development and refinement of anti-doping laboratory methods broadly benefits our understanding of the physiology of exercise.
- WADA is the international body responsible for coordinating anti-doping efforts nationally and internationally, and as such the WADA Prohibited List sets the standard for methods and substances barred in sport.

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41 BOTULISM

Howard L. Geyer

HISTORY AND EPIDEMIOLOGY

Botulism, a potentially fatal neuromuscular illness, results from exposure to botulinum neurotoxin (BoNT), which is produced by the bacterium *Clostridium botulinum* and other *Clostridium* species. The earliest cases of botulism were described in Europe in 1735 and were attributed to improperly preserved German sausage; the name of the disease alludes to this association, *botulus* being Latin for sausage. Emile van Ermengem identified the causative organism in 1897 and named it *Bacillus botulinum*; it was later renamed *Clostridium botulinum*.²² These Gram-positive, spore-forming bacteria produce seven serotypes of BoNT, denoted A through G.

In adults, most cases are due to contaminated food, resulting from ingestion of toxin, whereas in infants most cases result from ingestion of bacterial spores which proliferate and produce toxin in the gastrointestinal (GI) tract. Less common forms of botulism include wound botulism, in which spores are inoculated into a wound and locally produce toxin, and inhalational botulism due to aerosolized BoNT, potentially used as a weapon of bioterrorism.

Botulism outbreaks can occur anywhere in the world¹¹⁵ and have been reported from such diverse areas as Iran,¹⁰³ Japan,⁹⁷ Thailand,⁷⁰ France,¹ Portugal,⁷⁴ and Canada.⁹¹ In 2011, a total of 140 cases of botulism were reported to the US Centers for Disease Control and Prevention (CDC). Food-borne botulism constituted 14% of cases, infant botulism 73% of cases, and wound botulism 9%.³⁸ In this analysis, toxin type A accounted for the majority of cases of food-borne botulism (70%) and all cases of wound botulism, and infant botulism was due to toxin type A in 40% and to toxin type B in 59% of cases.³⁸ No deaths from food-borne botulism were reported in 2011. The case fatality rate has improved for all botulism toxin types, probably due to increasing awareness of the condition and consequent earlier diagnosis, appropriate and early use of antitoxin, and better and more accessible life support techniques.

In the past 50 years, home-processed food has accounted for 65% of outbreaks, with commercial food processing constituting only 7% of reported cases; in the remaining outbreaks, the origin is unknown.³⁴ Common home-canning errors responsible for botulism include failure to use a pressure cooker and allowing food to putrefy at room temperature. Minimally processed foods such as soft cheeses may lack sufficient quantities of intrinsic barriers to BoNT production, such as salt and acidifying agents.¹⁰⁹ These foods become high-risk sources of botulism when refrigeration standards are violated. The US Food and Drug Administration (FDA) continuously reviews recommendations for appropriate measures to process such foods.^{137,138}

Awareness of evolving trends and unusual presentations or locations of botulism permits the establishment of preventive education programs. Outbreaks of botulism have been associated with specialty foods consumed by different ethnic groups, such as chopped garlic in soy oil by Chinese in Vancouver, British Columbia^{91,132}; uneviscerated salted fish—called *kapchunka*—eaten by Russian immigrants in New York City^{37,136}; and the same fish—called *faseikh*—eaten in Egypt.¹⁴⁷ The incidence of botulism is high in Alaska where traditional foods include fermented fish and fish eggs, seal, beaver, and whale; between 1990 and 2000, 39% of cases of food-borne botulism in the United States occurred in Alaska.¹²⁹ Approximately 90% of toxin type E outbreaks have occurred in Alaska because of home-processed fish or meat from marine animals,^{39,76,146} while one incident occurred in New Jersey.⁴⁰ In the 1990s, three cases of botulism involved members of a Native American church after they ingested a ceremonial tea made from the buttons of dried, alkaline-ground peyote cactus that were prepared in a water-covered refrigerated jar. The resultant alkaline and anaerobic milieu presumably fostered the growth of toxin from naturally occurring spores.⁶³ In 1996, eight cases of food-borne botulism in Italy were linked to mascarpone cream cheese eaten either alone or in tiramisu contaminated with BoNT type A.¹⁴ In 2006, carrot juice was implicated in four cases in Georgia and Florida.³¹ Ten cases in California, Indiana, Ohio, and Texas were linked to commercially processed chili sauce in 2007.³¹ In October 2011, eight maximum security inmates at the Utah State Prison developed botulism from drinking “pruno,” an illicit alcoholic brew. A baked potato saved from a meal served weeks earlier was added to the “pruno” and was suspected as the source of *C. botulinum* spores.³³

Among cases attributed to commercial food processing, vegetables (peppers, beans, mushrooms, tomatoes, and beets, with or without meat) were thought to be the causative agents in approximately 70%, meat in 17%, and fish in 13% of cases.³⁴ Although only 4% of food-borne botulism is associated with food purchased in restaurants, restaurant-related

outbreaks usually affect large numbers of individuals.⁷⁶

Of 20 reported cases of food-borne intoxication in 2011, there were two multi-case outbreaks, involving three and eight cases, respectively.³⁸ Among hundreds of outbreaks from 1975 to 1988 totaling more than 400 persons, approximately 70% involved only one person, 20% involved two persons, and only 10% involved more than two persons, yielding a mean of 2.7 cases per outbreak.¹⁵¹ Single affected patients were more severely ill, with 85% requiring intubation compared to only 42% requiring intubation in multi-person outbreaks,¹⁵¹ presumably because diagnosis in the index case leads to more rapid therapeutic intervention for associated cases.

Infant botulism is more common in certain geographic areas, presumably due to higher concentrations of botulinum spores in soil. Raw honey is a potential source of spores.⁹² Most affected infants are younger than 6 months of age. Of 102 cases reported in 2011, most were from California (28%), Pennsylvania (13%), and New Jersey (11%). The median age was 17 weeks, and 77% were male. No US deaths from infant botulism were reported in 2011.³⁸ With appropriate support and treatment, a favorable outcome is achieved in the majority of cases.

In 2011, 13 cases of wound botulism were reported; 9 of those cases occurred in California. Ages ranged from 5 to 62 years, with a median of 38 years. One suffered a wound in a motorcycle crash and another sustained a facial wound that involved bark; all the others were injection drug users. No deaths from wound botulism were reported in the United States in 2011.³⁸

In recent years, concern about the use of inhalational BoNT as a biologic weapon has increased. In ways unimaginable when the first edition of this book was published, medical and public health realities associated with terrorism in the 21st century, unfortunately, have resulted in increased relevance of botulism to medical practitioners ([Chaps. 132 and 133](#)). The advent of therapeutic BoNT injections has raised other concerns regarding potential adverse consequences.¹¹

BACTERIOLOGY

The genus *Clostridium* comprises a group of four spore-forming anaerobic Gram-positive bacillary species that produce seven different neurotoxic proteins. *C. botulinum* produces all BoNT serotypes A through G, *Clostridium baratii* produces toxin type F, *Clostridium butyricum* produces toxin type E, and *Clostridium argentinense* produces toxin type G.^{64,121,126} Rare instances of both adult and infant botulism are attributed to *C. baratii* and *C. butyricum*.^{62,85,98,105} The reported incidence of cases due to BoNT type F may be underestimated because of the only recent capacity of most laboratories to determine the presence of *C. baratii* and other clostridial species producing toxin type F.⁶²

Clostridial species are ubiquitous, and the bacteria and spores are present in soil, seawater, and air.¹²⁸ Seven main toxin types, labeled A through G, are recognized, but genomic sequence analysis shows that multiple subtypes can exist within each category.⁶⁷ In the United States, toxin type A is found in soil west of the Mississippi⁷⁸; type B is found east of the Mississippi, particularly in the Allegheny range; and type E is found in the Pacific northwest and the Great Lakes states.^{35,128} Toxin types A and B typically are found in poorly processed meats and vegetables. Toxin type E is commonly found in raw or fermented marine fish and mammals. Toxin types C and D cause disease in birds and mammals. Toxin type G has not been associated with naturally occurring disease. Although the different botulinum toxins differ in the cellular molecules they target, their ultimate pathophysiology and clinical syndromes are identical.

All botulinum spores are dormant and highly resistant to damage. They can withstand boiling at 212°F (100°C) for hours, although they usually are destroyed by 30 minutes of moist heat at 248°F (120°C). Factors that promote germination of spores in food are pH greater than 4.5, sodium chloride content less than 3.5%, or a low nitrite concentration. Most viable organisms produce toxin in an anaerobic milieu with temperatures greater than 80.6°F (27°C), although some strains produce toxins even when conditions are not optimal. *C. botulinum* organisms can produce toxin type E at temperatures as low as 41°F (5°C). To prevent spore germination, acidifying agents such as phosphoric or citric acid are added to canned or bottled foods that have a low acid content, such as green beans, corn, beets, asparagus, chili peppers, mushrooms, spinach, figs, olives, and certain nonacidic tomatoes. Unlike the spores, the toxin itself is heat labile and can be destroyed by heating to 176°F (80°C) for 30 minutes or to 212°F (100°C) for 10 minutes. At high altitudes, where the boiling point of water may be as low as 202.5°F (94.7°C), boiling for a full 30 minutes is prudent in order to ensure that the toxin has been destroyed. Under high-altitude conditions, pressure cooking at 13 to 14 lb of pressure often is necessary to achieve appropriate temperatures to destroy the toxin in a timely fashion.

Food contaminated with *C. botulinum* toxin types A and B may look or smell putrefied because of the action of proteolytic enzymes.⁶¹ In contrast, because toxin type E organisms are saccharolytic and not proteolytic, food contaminated with toxin type E may look and taste normal.¹⁶

PHARMACOKINETICS AND TOXICOKINETICS

BoNT is the most potent toxin known. The LD₅₀ for mice is 3 million molecules injected intraperitoneally. The human oral

lethal dose is 1 µg/kg.¹¹⁴

Food-borne botulism results from ingestion of preformed BoNT from food contaminated with *Clostridium* spores. The toxin is complexed to associated proteins (hemagglutinins and a nontoxic nonhemagglutinin),¹²⁶ which protect it from the acidic and proteolytic environment in the stomach. In the intestine, the alkaline pH dissociates the toxin from the associated proteins, allowing for subsequent absorption into the bloodstream.⁸⁹ Because the toxin is often demonstrated only in the stool, determining the percentage of the toxin actually absorbed is difficult.^{49,51} The median incubation period for all patients is 1 day, but ranges from 0 to 7 days for toxin type A, 0 to 5 days for toxin type B, and 0 to 2 days for toxin type E.¹⁵¹

Infant botulism results not from ingestion of preformed BoNT but from ingestion of *C. botulinum* spores, which germinate in the GI tract and produce toxin. The immaturity of the bacterial flora in the infant GI tract facilitates colonization by the *Clostridia*. Adults with altered GI tracts (such as those who have undergone gastric bypass or are taking proton pump inhibitors or H₂ antagonists) can also develop botulism in the same way, with the onset of symptoms typically following ingestion by a month or two. A single case of food-borne botulism in a 6 month-old infant associated with home-canned baby food is reported.⁶

In wound botulism, spores proliferate in a wound or abscess and locally elaborate toxin. The incubation period is typically less than 2 weeks, but delays as long as 51 days are reported.⁶⁶

The duration of action of the BoNT types may vary, depending on the components of the neurotransmitter release apparatus that are disrupted (see Pathophysiology). The persistence of clinical effect may result from the individual cleavage target, the intraneuronal biological half-life of the toxin, or both. Current evidence indicating intraneuronal toxin metabolism or elimination is inadequate.¹²⁵

PATHOPHYSIOLOGY

BoNT is produced as a protein consisting of a single polypeptide chain with a molecular weight of 900 kDa, which includes a 750 kDa nontoxic protein and a 150 kDa neurotoxic component. To become fully active, the single-chain polypeptide 150 kDa neurotoxin must undergo proteolytic cleavage to generate a dichain structure consisting of a 100 kDa heavy chain linked by a disulfide bond to a 50 kDa light chain. The dichain form of the molecule is responsible for all clinical manifestations.^{26,64} Both the single polypeptide chain toxin and the dichain form are resistant to GI degradation.⁸⁰

The ingested toxin binds to serotype specific receptors on the mucosal surfaces of gastric and small intestinal epithelial cells, where endocytosis is followed by transcytosis, which permits release of the toxin on the serosal (basolateral) cell surface.^{72,79} The dichain form travels intravascularly to peripheral cholinergic nerve terminals, where it binds rapidly and irreversibly to the cell membrane and is taken up by endocytosis. The heavy chain is responsible for cell specific membrane binding to acetylcholine containing neurons (Fig. 41–1).¹⁰¹

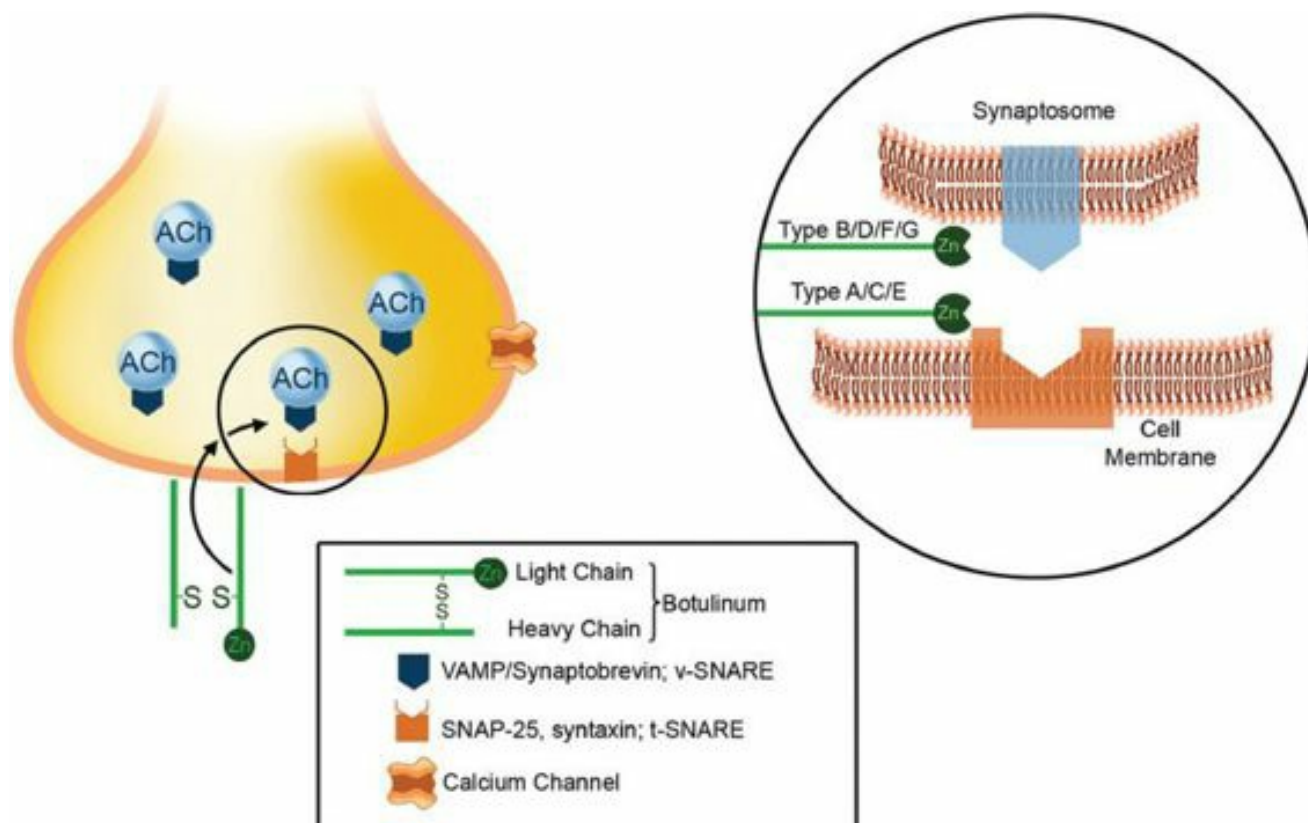


FIGURE 41–1. Botulinum toxins consist of two peptides linked by disulfide bonds. The heavy chain is responsible for specific binding to acetylcholine (ACh) containing neurons. Following binding to the cell surface, the entire complex undergoes endocytosis and subsequent translocation of the light chain into the nerve cell cytoplasm. The light chain contains a zinc-requiring endopeptidase that cleaves soluble N-ethylmaleimide sensitive factor (NSF) attachment protein receptor (SNARE) proteins belonging to the docking/fusion complex required for neuroexocytosis of ACh. These proteins may be associated with the synaptic vesicles (v-SNARE) or with their targets on the presynaptic membrane (t-SNARE). Botulinum toxin types A and E proteolyse the t-SNARE protein known as synaptosomal-associated protein (SNAP)-25, and BoNT type E cleaves both SNAP-25 and syntaxin, which is attached to SNAP-25 and to the presynaptic membrane. BoNT types B, D, F, and G target the v-SNARE protein synaptobrevin. As a result of cleavage of these components of the docking complex by the endopeptidase, ACh is not released and neuromuscular transmission is impaired.

Once inside the cell, the light chain acts as a zinc-dependent endopeptidase to cleave presynaptic membrane polypeptides that are essential components of the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) apparatus which subserves acetylcholine exocytosis, thereby inhibiting release.¹¹⁴ BoNT types specifically cleave different proteins belonging to the SNARE family, and these differences may be responsible for their variable toxicity.¹²³ SNARE proteins targeted by proteolysis include vesicle associated membrane protein (VAMP, also known as synaptobrevin) localized on synaptic vesicles, syntaxin found on the presynaptic membrane, and synaptosomal associated protein (SNAP)-25, which is attached to syntaxin and to the presynaptic membrane. Toxin types A and E cleave SNAP-25; types B, D, F, and G act on VAMP/synaptobrevin; and type C cleaves both syntaxin and SNAP-25 (Fig. 41–1).⁷² All BoNT types impair transmission at acetylcholine-dependent synapses in the peripheral nervous system, but cholinergic synapses in the central nervous system are not thought to be affected. Very high concentrations of BoNT can also impair release of other neurotransmitters including norepinephrine and serotonin.⁶⁰

CLINICAL MANIFESTATIONS

Food-Borne Botulism

Although botulism is the most dreaded of all food poisonings, the initial phase of the disease often is so subtle that it goes unnoticed. Botulism often is misdiagnosed on the first visit to a health care provider.^{27,152} When GI effects are striking and food poisoning is suspected, the differential diagnosis should include other acute poisonings, such as metals, plants, mushrooms, and the common bacterial, viral, and parasitic agents discussed in Chap. 44.

Onset of symptoms typically occurs the day following ingestion. Early GI signs and symptoms of botulism include nausea, vomiting, abdominal distension, and pain. A time lag (from 12 hours to several days, but typically not more than 24 hours) may be observed before neurologic signs and symptoms appear. Common findings include diplopia (often with lateral rectus palsy), blurred vision with impaired accommodation, and bilaterally symmetric flaccid paralysis that typically begins in cranial muscles and descends to the limbs. Constipation due to smooth muscle involvement is frequent, and urinary retention and ileus may also occur. Dry mouth, dysphagia, and dysarthria/dysphonia (manifested by a nasal quality to the voice) may be severe, and many patients exhibit fixed mydriatic pupils with ptosis. Deep tendon reflexes are usually reduced or absent. Hypotension and bradycardia sometimes develop, but temperature regulation is normal.

Weakness of respiratory muscles may necessitate intubation and mechanical ventilation. Approximately 67% of patients with toxin type A require intubation, compared to 52% of patients with toxin type B, and 39% with toxin type E botulism.¹⁵¹

Importantly, mental status and sensation remain normal. These negatives, along with the absence of tachycardia, distinguish botulism from the anticholinergic syndrome, which shares many features with botulism.

The differential diagnosis of botulism includes a variety of toxicologic and nontoxicologic conditions (Tables 41–1A and 41–1B). All of these disorders have weakness as a prominent feature, but many can be differentiated readily from botulism based on their more chronic time course. The most difficult and frequently encountered diagnostic challenge is differentiating between botulism and the Miller Fisher variant of the Guillain-Barré syndrome (Table 41–2). Because physicians so rarely encounter botulism (especially compared to other much more common disorders in the differential diagnosis), initiation of appropriate management often is seriously delayed. The index case of an epidemic or an isolated case often is misdiagnosed at a stage when the risk of morbidity and mortality still could be substantially diminished. This is particularly true of toxin type E botulism, which typically initially causes much more prominent GI signs than neurologic signs.¹⁶ The differences in the initial clinical symptoms associated with the various serotypes may be related to the presence of proteolytic enzymes in toxin types A and B and saccharolytic enzymes in toxin types E and C botulism.

TABLE 41–1A. Toxicologic Differential Diagnosis of Botulism

<i>Condition</i>	<i>Associated Findings</i>
Aminoglycosides	Postanesthetic paralysis
Anticholinergics	Mydriasis, vasodilation, fever, tachycardia, ileus, dry mucosa, urinary retention, altered mental status
Buckthorn (<i>Karwinskia humboldtiana</i>)	Rapidly progressive ascending paralytic neuropathy with quadriplegia
Carbon monoxide	Headache, nausea, altered mental status, tachypnea, elevated carboxyhemoglobin level
Diphtheria (demyelinating neuropathy)	Exudative pharyngitis, cranial polyneuropathy (late), cardiac manifestations, hypotension
Elapid (coral snake) envenomation	Euphoria, lightheadedness, fasciculations, tremor, weakness, salivation, nausea, vomiting followed by bulbar palsy and paralysis including slurred speech, diplopia, ptosis, dysphagia, dyspnea, respiratory compromise
Organic phosphorus pesticides	Salivation, lacrimation, urination, defecation, miosis, fasciculations, bronchorrhea, delayed neuropathy
Paralytic shellfish poisoning	Incubation <1 hour, dysesthesias, paresthesias, altered mental status, respiratory paralysis
Thallium	Alopecia, painful ascending sensory neuropathy, constipation, cranial neuropathy, Mees lines

TABLE 41–1B. Nontoxicologic Differential Diagnosis of Botulism

<i>Condition</i>	<i>Associated Findings</i>
Lambert-Eaton myasthenic syndrome	Neoplasm (especially small cell lung cancer), limb weakness exceeding ocular/bulbar weakness, increased strength following sustained contractions, postexercise facilitation on repetitive nerve stimulation, antibodies to voltage-gated calcium channels
Encephalitis	Fever, altered mental status, seizures, CSF showing elevated protein and pleocytosis
Food "poisoning" (other bacterial)	Rapid onset of disease, absence of cranial nerve findings
Guillain-Barré syndrome/acute inflammatory demyelinating polyneuropathy (and Miller Fisher variant)	Areflexia, paresthesias, ataxia, CSF showing elevated protein without pleocytosis, slowed nerve conduction velocity
Hypermagnesemia	Respiratory compromise, diffuse flushing, weakness, thirst
Inflammatory myelopathies	Complete (transverse) or incomplete spinal syndrome with paraparesis and/or sensory level, back pain, may be preceded by viral illness, CSF pleocytosis
Myasthenia gravis	Aggravation of fatigue with exercise, fluctuating weakness, positive edrophonium (Tensilon) test, acetylcholine receptor antibodies, decremental response on rapid repetitive nerve stimulation
Poliomyelitis	Fever, gastrointestinal symptoms, asymmetric neurologic findings; CSF showing elevated protein and pleocytosis
Polymyositis	Insidious onset, proximal limb weakness, dysphagia, muscle tenderness sometimes present, elevated creatine kinase, aldolase, c-reactive protein and erythrocyte sedimentation rate, fibrillations and sharp waves on electromyography
Stroke	Asymmetric paralysis, abnormal brain imaging
Tetanus	Rigidity, cranial nerves usually normal
Tick paralysis (<i>Dermacentor</i> species)	Rapidly evolving paralysis, ptosis, absence of paresthesias, normal CSF analysis, presence of an embedded tick with resolution upon removal

CSF = cerebrospinal fluid.

TABLE 41–2. Differentiating Botulism from Guillain-Barré Syndrome

	<i>Botulism</i>	<i>Guillain-Barré Syndrome</i>	<i>Miller Fisher Variant of Guillain-Barré Syndrome</i>
Fever	Absent (except in wound botulism)	Occasionally present	Occasionally present
Pupils	Dilated or unreactive (50%)	Normal	Normal
Ophthalmoplegia	Present (early)	May be present (late)	Present (early)
Paralysis	Descending	Ascending (classically, but not necessarily)	Descending
Deep tendon reflexes	Diminished	Absent	Absent
Ataxia	Absent	Often present	Present
Paresthesias	Absent	Present	Present
CSF protein	Normal	Elevated (late)	Elevated (late)

CSF = cerebrospinal fluid.

Infant Botulism

First described in California in 1976, several thousand cases of infant botulism have now been confirmed across the world.^{10,65,68} Interestingly, 95% of these cases are reported in the United States.^{46,98} Although infant botulism is reported from approximately half of the states in the United States and all inhabited continents except Africa,⁴⁶ 50% of reported cases originate from California, Utah, Pennsylvania, and New Mexico.¹⁵⁰ In California, aggressive surveillance and educational efforts have been practiced since 1976, which may help to explain the disproportionate distribution of reported cases.⁸

Infant botulism is the most common form of botulism in the United States, and virtually all cases are due to BoNT type A or B. Affected children are younger than 1 year (median of 15 weeks) and characteristically have normal gestation and birth. The first signs of infant botulism are constipation; difficulty with feeding, sucking, and swallowing; feeble cry; and diffusely decreased muscle tone (“floppy baby”).³⁶ The hypotonia is particularly apparent in the limbs and neck. Ophthalmoplegia, loss of facial grimacing, dysphagia, diminished gag reflex, poor anal sphincter tone, and respiratory failure are often present, but fever does not occur. Mydriasis is typical, and hypotension may occur. The differential diagnosis of infant botulism initially includes salt and water depletion, failure to thrive, sepsis, and a viral syndrome. Because the toxin in infant botulism is absorbed gradually as it is produced, the onset of clinical manifestations may be less abrupt than in severe cases of food-borne botulism, which are caused by large amounts of preformed toxin absorbed over a brief period of time.

Infant botulism may result from ingestion of *C. botulinum* organisms in food or following the inhalation or ingestion of organism-laden aerosolized dust. A number of factors determine a child’s susceptibility to development of botulism. Although bile acids and gastric acid in the GI tract may inhibit clostridial growth in older children and adults, gastric acidity is reduced in the infant during the first few months of life.⁸¹ Also, some infants may be deficient in immunologic mechanisms for spore control, resulting in a permissive environment for spore germination and toxin development within their GI tracts and subsequent gut absorption. Approximately 70% of infant botulism cases occur in breastfed infants, even though only 45% to 50% of all infants are breastfed. Formula-fed infants are rapidly colonized by *Coliforme* spp, *Enterococcus* spp, and *Bacteroides* spp, which may inhibit *C. botulinum* proliferation; conversely, the absence of these typical organisms in breastfed infants may facilitate *C. botulinum* multiplication.⁶⁵

Epidemiologic studies in Europe have found that ingestion of honey was associated with 59% of cases of infant botulism.¹⁵ When *C. botulinum* spores were isolated from honey implicated in cases of infant botulism, the same toxin type was isolated from the infant and, as expected, no preformed toxin was isolated from the honey.¹⁰ Honey is the only food generally considered likely to be a risk factor for infant botulism,¹⁰ although a 2001 report from the United Kingdom implicated a milk formula in the development of infant botulism.⁹⁴ It is possible that pollen and nectar carried by worker bees results in contamination of honey with spores of *Clostridia* found in soil.⁹² In addition, the oxidative metabolism of *Bacillus alvei*, another common contaminant of honey, may promote spore germination by creating an anaerobic microenvironment.⁸⁹

Previous studies suggested a correlation between the presence of both *C. botulinum* organisms and toxin and sudden infant death syndrome (SIDS).^{8,130} However, in a prospective study of 248 infants with SIDS, *C. botulinum* was not found on stool culture of any of the children.²⁸

Cases of infant botulism must be managed in the hospital, preferably in a pediatric intensive care unit for at least the first week, when the risk of respiratory arrest is greatest. In one study, approximately 80% of children with botulism

required intubation for reduced vital capacity, and 25% of these children had frank respiratory compromise.¹¹⁶ In a group of 57 affected infants, 18 days to 7 months of age, managed during the decade ending in the mid-1980s, 77% were intubated and 68% required mechanical ventilation. In the subsequent decade, investigators from the same institution found that 37 of 60 (62%) infants required endotracheal intubation (for a mean duration of 21 days).⁴ The apparent decrease in intubations and complications was ascribed to better understanding of disease progression and closer observation of patients. However, a similar study at another institution revealed that 13 of 24 (54%) infants admitted between 1985 and 1994 required ventilatory support, compared to 15 of 20 (75%) infants admitted in the subsequent decade.¹³⁹ All but one patient in this study required nasogastric feeding. Airway complications of intubation such as stridor, granuloma formation, and subglottic stenosis are common, yet tracheotomy is infrequently required.³ The survival rate in infant botulism is approximately 98%.¹¹⁷

Wound Botulism

Wound contamination previously was considered an uncommon cause of botulism. The first case of wound botulism was not reported until 1943. The classic presentation of wound botulism is that of a patient injured in a motor vehicle who sustains a deep muscle laceration, crush injury, or compound fracture treated with open reduction. The wound typically is dirty and associated with inadequate débridement, subsequent purulent drainage, and local tenderness, although in some cases the wound appears unremarkable. Four to 18 days later, cranial nerve palsies and other neurologic findings typical of botulism may appear.⁸⁷ Other manifestations characteristic of food-related botulism, such as GI symptoms, usually are absent.

In wound botulism, fever may be prominent and associated with abscess, sinusitis, or other tissue infection presumed to harbor the clostridial organisms. Although some patients may require management for wound-related problems, in other cases the wounds appear clean and uninfected. Recognition of botulism as a potential complication of wound infections is essential for appropriate early and aggressive therapy.

Between 2001 and 2009, the CDC identified between 22 and 30 cases of wound botulism each year, except in 2006 when 45 cases were identified.³⁸ In 2010, there were 17 cases reported, and in 2011, 13 cases. BoNT type A accounted for all cases of wound botulism in 2011.³⁸ Use of heroin, particularly subcutaneous injection (“skin-popping”) of black tar heroin, is associated with an increased number of wound botulism cases.^{42,100,112,148} This association appears to be related, at least in part, to the physical characteristics of black tar heroin such as its viscosity, its potential to facilitate anaerobic growth and spore germination, and its ability to devitalize tissue or inhibit wound resolution.¹⁹ Wound botulism is also reported in association with subcutaneous,¹⁰⁴ intravenous,¹³³ and intranasal^{71,107} cocaine use. The first case of wound botulism with BoNT type E was reported in 2007, affecting a drug user in Sweden.¹³

In a small series of parenteral drug-using patients with botulism in New York City, the most prominent symptoms were dysphagia, dysarthria, and dry mouth. BoNT type A toxin was detected in the serum of one patient, and in another patient *C. botulinum* was isolated from an abscess. In four other drug abusers with clinically comparable presentations, CDC investigators were not able to find any organism or toxin in serum, stool, or skin lesions.⁷⁷

Adult Intestinal Colonization Botulism

Although GI colonization is the typical pathogenetic mechanism responsible for infant botulism, it is rare in adults. Prior to 1997, only 15 cases were reported.^{59,85} Patients invariably have anatomic or functional GI abnormalities. Risk factors favoring organism persistence and *C. botulinum* colonization include achlorhydria (surgically or pharmacologically induced), previous intestinal surgery, and probably recent antibiotic therapy. These factors may compromise the gastric and bile acid barrier, gut flora, and motility, thus allowing spore germination, altered bacterial growth, and toxin development.

Cases of adult infectious botulism have occurred in patients after ileal bypass surgery and Crohn disease,⁵⁹ jejunoileal bypass for obesity,^{55,84} gastroduodenostomy,⁸⁴ vagotomy and pyloroplasty,⁸⁴ and necrotic volvulus.⁷⁶ In such hosts, botulism can result from the ingestion of food contaminated with *C. botulinum* organisms and no preformed toxin, with intraluminal elaboration of toxin occurring in vivo.⁴⁵

In one case of adult intestinal colonization botulism, a high concentration of endogenously produced antibody to toxin type A was identified.⁵⁹ This finding highlights a distinct characteristic of this form of botulism, because endogenous antitoxin immunity does not develop in patients with food-borne botulism.¹¹⁴

Iatrogenic Botulism

Botulinum toxins are used therapeutically in the treatment of a variety of disorders. Three preparations of BoNT type A are available in the United States: onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and incobotulinumtoxinA (Xeomin). BoNT type B is available as rimabotulinumtoxinB (Myobloc). All are approved by the FDA for treatment of cervical dystonia, and all three formulations of BoNT type A are approved for cosmetic purposes. OnabotulinumtoxinA and

incobotulinumtoxinA are also approved by the FDA for treatment of blepharospasm. Additionally, onabotulinumtoxinA is approved for treatment of strabismus, upper limb spasticity, chronic migraine, severe axillary hyperhidrosis inadequately managed by topicals, and detrusor overactivity associated with a neurologic condition. These xenobiotics are thought to exert their therapeutic effect in most cases by temporarily weakening those muscles whose overactivity results in the clinical condition. Doses range widely depending on the size of the muscles to be treated, the degree of overactivity, and the commercial preparation of the toxin. The injected toxin blocks the local neuromuscular junction by inhibiting release of acetylcholine. The “chemodenervated” muscles recover within 2 to 4 months as nerve transmission is restored through sprouting of new nerve endings and formation of functional connections at motor endplates,^{2,114} necessitating repeated injections of BoNT for prolonged clinical efficacy.

Doses of BoNT are measured in functional units corresponding to the median intraperitoneal lethal dose (LD₅₀) in female Swiss-Webster mice weighing 18 to 20 g.⁹⁹ The units of each marketed pharmaceutical are distinctly different and may lead to inadvertent overdosing.¹⁴³ The potential for confusion may be substantial when switching between products, because their relative potencies are quite different.^{95,110,119} Attempts to establish precise lethal doses of BoNT are complicated by the lack of human data, use of varying formulations of toxin by different investigators, changes in manufacturing processes, and factual errors in the published literature.²⁶ Arnon and coauthors estimated that “lethal amounts of crystalline type A toxin for a 70-kg human would be approximately 0.09 to 0.15 µg intravenously or intramuscularly, 0.70 to 0.90 µg inhalationally, and 07 µg orally,”¹¹ but it is unclear whether these values can be applied reliably to any currently available commercial product.

In a large series of 139 patients with cervical dystonia randomized to treatment with BoNT type A or BoNT type B, no difference in efficacy was found between serotypes; the groups were also equivalent in frequency of adverse effects such as neck pain and neck weakness, but dry mouth and dysphagia were more common in the group treated with BoNT type B.⁴⁷

Following repeated injections of therapeutic doses of BoNT, patients may develop neutralizing antibodies that subsequently may limit the efficacy of the toxins; this situation should prompt a clinician to switch to use of a different toxin type.²⁶ In Japan and the United Kingdom, a preparation of BoNT type F is available for use when antibodies to type A develop.¹²² Some studies suggest that animals receiving BoNT type F have more transient and reversible weakness than that associated with types A and B.²³ In 1998, the formulation of Botox was changed to reduce the amount of potentially antigenic protein (from 25 ng of neurotoxin complex protein per 100 units to 5 ng of complex protein per 100 units), and studies in patients with cervical dystonia demonstrate a sixfold lower rate of development of anti-BoNT antibodies with the newer formulation.^{67a} For Xeomin the protein content is 0.6 ng per 100 units, while Dysport contains 4.35 ng of protein per 500 unit-vial (ie, 0.87 ng per 100 units).

Although one early marketing assumption was that the neurotoxin does not diffuse from the injection site, BoNT does diffuse into adjacent tissues and produce local adverse effects.¹⁰⁸ Systemic manifestations are of concern when an inadvertent, excessive, or misdirected dose of toxin is administered, or in the setting of a neuromuscular disorder that may be previously undiagnosed, as in one case in which injection of BoNT type A unmasked Lambert-Eaton myasthenic syndrome (LEMS).⁵⁰ In addition, a number of studies demonstrate that even appropriately injected doses result in neuromuscular junction abnormalities throughout the body, occasionally producing autonomic dysfunction without muscle weakness.^{56,73,96} Several cases of iatrogenic botulismlike symptoms, including diplopia and severe generalized muscle weakness with widespread electromyographic abnormalities, have resulted from therapeutic doses of intramuscular BoNT injections.^{17,21,140} A 2008 report raised the possibility that BoNT type A may undergo retrograde axonal transport and transcytosis to afferent neurons,⁵ suggesting a potential mechanism for such generalized effects. However, the reproducibility and clinical significance of these findings have yet to be established.

In a well publicized case in late 2004, four patients in Florida developed paralysis after being injected with BoNT type A. An FDA investigation revealed that these patients were injected by an unlicensed physician who obtained raw toxin (not approved for medical purposes) and administered it at a dose 2000 to 100,000 times greater than that used in clinical practice.³ These events were not believed to be relevant to the use of approved pharmaceutical BoNT. In February 2008, the FDA issued an Early Communication stating that it was reviewing safety data on BoNT after receiving reports of hospitalization or death in patients injected with these agents, mostly in children treated for cerebral palsy–associated spasticity.¹⁴² In 2009, the FDA mandated changes to the prescribing information for the BoNT products, requiring a Boxed Warning highlighting the possibility of potentially life-threatening effects distant from the injection site; a Risk Evaluation and Mitigation Strategy, including a Medication Guide to help patients understand the risks and benefits of the botulinum toxins; and changes of the drug names to reinforce differences between the potencies of the individual products and the lack of interchangeability among them.¹⁴³

Inhalational Botulism

Inhaled BoNT is estimated to be 100 times more potent than orally ingested BoNT; a single gram of toxin, if disseminated evenly, could kill more than 1 million people.¹¹ A 1962 report from West Germany described three veterinary workers

who inhaled BoNT type A from the fur of animals they were handling; on the third day after exposure they developed mucus in the throat, dysphagia, and dizziness, and on the next day they developed ophthalmoparesis, mydriasis, dysarthria, gait dysfunction, and weakness.¹¹ Use of aerosolized BoNT as a bioweapon has been attempted by terrorists in Japan, and Iraq has developed BoNT (along with anthrax and aflatoxin) as part of a biological warfare program^{11,153} (Chap. 133).

Diagnostic Testing

The CDC case definition for food-borne botulism is established in a patient with a neurologic disorder manifested by diplopia, blurred vision, bulbar weakness, or symmetric paralysis in whom³⁵

- BoNT is detected in serum, stool, or implicated food samples; or
- *C. botulinum* is isolated from stool; or
- A clinically compatible case is epidemiologically linked to a laboratory-confirmed case of botulism.

Routine laboratory studies, including cerebrospinal fluid analysis, are normal in patients with botulism but are generally performed to exclude other etiologies. Specific tests that can be helpful in diagnosing botulism are discussed below.

Edrophonium Testing

Edrophonium (Tensilon) is a rapidly acting and short-acting cholinesterase inhibitor that can be useful in the diagnosis of myasthenia gravis. It is occasionally used to differentiate myasthenia gravis from botulism. This drug inhibits the metabolism of acetylcholine located in synapses, permitting continued binding with the reduced number of postsynaptic acetylcholine receptors in myasthenia gravis.

A syringe containing 10 mg of edrophonium is prepared, and then a test dose of 1 to 2 mg is administered intravenously. A positive result (ie, consistent with myasthenia gravis) consists of dramatic improvement in the strength of weak muscles within 30 to 60 seconds, lasting 3 to 5 minutes. If there is no effect, the remainder of the edrophonium is given and the same effect sought. Ideally, a second syringe is filled with saline and the test performed under double-blind conditions to ensure accurate assessment and remove the potential of a placebo effect.

Because release of acetylcholine is impaired in botulism, preventing its catabolism with anticholinesterase drugs typically has little clinical benefit, but an effect may be observed if some neurons maintain the ability to release acetylcholine. Thus, in rare cases, early in the course of botulism injection of edrophonium results in limited improvement in strength that is far less dramatic than occurs in patients with myasthenia gravis.¹⁰²

Electrophysiologic Testing

In all forms of botulism, sensory nerve action potentials are normal. Motor potentials are typically reduced in amplitude (although this reduction may not be appreciated unless severely affected muscles are studied), but conduction velocity is not affected. Repetitive nerve stimulation at high frequencies would be expected to result in an increment of the amplitude of the motor potential, given the presynaptic localization of the defect, but this finding is neither sensitive nor specific; it also may be more common in disease due to BoNT type B than with type A.^{44,82} A marked incremental response with high frequency repetitive stimulation is more likely to suggest LEMS than botulism. Likewise, a decremental response to low-frequency repetitive nerve stimulation is characteristic of LEMS but is not consistently present in botulism.⁸²

The needle electromyography (EMG) examination in botulism is characterized by low-amplitude, short-duration motor unit action potentials (MUAPs), due to blockade of neuromuscular transmission in many muscle fibers (Fig. 41–2). Polyphasic MUAPs are also common. Recruitment is usually normal but may be reduced in severely affected muscles if all muscle fibers of a motor unit are blocked. Spontaneous activity, including positive sharp waves and fibrillation potentials, is often seen.

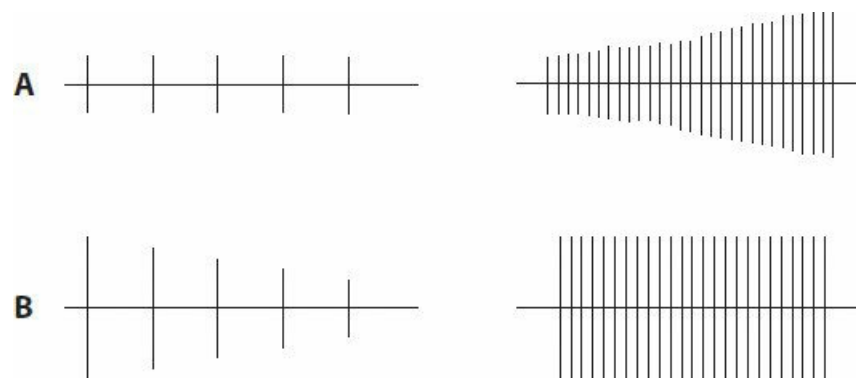


FIGURE 41–2. Schematic representations of repetitive nerve stimulation at low (5/sec) and high (50/sec) frequencies. In

botulism (**A**), repetitive stimulation produces a small-muscle action potential that facilitates (increases in amplitude) at higher frequencies. This effect (which, although classic, is not found in all cases of botulism) results from increased acetylcholine release with high-frequency stimulation because of intracellular calcium accumulation. In contrast, myasthenia gravis (**B**) is associated with a normal muscle action potential amplitude and a decremental response at low-frequency stimulation with a normal response at high-frequency stimulation. Myasthenia gravis, a disorder of the muscle end plate, produces this decremental response at low frequencies because the natural reduction in acetylcholine response with subsequent stimulation falls below threshold.^{105,148}

Although these electrodiagnostic abnormalities can support the diagnosis of botulism, they can be subtle. Nerve conduction studies and EMG are most useful in their ability to exclude differential diagnostic considerations, including Guillain-Barré syndrome and other neuropathies (both demyelinating and axonal), poliomyelitis, and myasthenia gravis. Moreover, there are no pathognomonic electrophysiologic findings in botulism; in particular, the findings can closely resemble those of a myopathic process, and muscle biopsy may be necessary to exclude such a condition.⁸²

Laboratory Testing

Samples of serum, stool, vomitus, gastric contents, and suspected foods should be subjected to anaerobic culture (for *C. botulinum*) and mouse bioassay (for BoNT) (Table 41–3). A list of the patient’s medications should accompany each sample to exclude other xenobiotics that might interfere with the assay (eg, pyridostigmine) or be toxic to the mice. The serum samples must be collected prior to initiation of antitoxin therapy. If wound botulism is suspected, serum, stool, exudate, débrided tissue, and swab samples should be collected. For infant botulism, feces and serum samples also should be obtained. Infants who are constipated may require an enema with nonbacteriostatic sterile water to facilitate collection. All enema fluid and stool should be sent for analysis. The specimens should be refrigerated (not frozen) and examined as soon as possible after collection. Detailed information on specimen collection and examination is available online from the CDC (<http://www.cdc.gov/ncidod/dbmd/diseaseinfo/files/botulism.pdf>).³⁴

TABLE 41–3. Epidemiologic and Laboratory Assessment of Botulism^a

Classification	Food Borne	Infant	Wound	Adult Intestinal Colonization
Toxin type	A, B, E, F, G in humans; C, D in animals	A, B, C, F	A, B	A
Route	Ingestion of toxin	Ingestion of bacteria and spores	Wound, abscess (sinusitis)	Ingestion of bacteria and spores
Specimens	Stool: positive for bacteria/spores and toxin	Stool: positive for bacteria/spores and toxin for up to 8 weeks after recovery	Wound site: Gram stain, aerobic and anaerobic cultures; positive for bacteria/spores	Stool: positive for bacteria/spores and toxin
Botulinum toxin in serum	Yes	Yes	Yes	Yes
Bacteria/spores in food	Yes	Yes	No	Yes
Botulinum toxin in food	Yes	No	No	No

^a“Toxin” refers to botulinum toxin. “Bacteria/spores” refers to *C. botulinum*.

In the mouse lethality assay, the standard test for detecting BoNT, the sample (serum, stool, or food) is injected intraperitoneally into mice, which are then observed for development of signs of botulism. Control mice are injected with the sample as well as antitoxin. This test is very sensitive, with a detection limit of 0.01 ng/mL of sample eluate. However, it is laborious, expensive, and a positive result may not appear for several days, reducing its usefulness in early diagnosis of botulism.⁷⁵ Alternative methods for detecting BoNT, including immunological methods (eg, enzyme-linked immunosorbent assay {ELISA}) and endopeptidase assays, are being explored.

C. botulinum can be cultured under strict anaerobic conditions. Stool specimens are incubated anaerobically and then subcultured on egg yolk agar to assess for lipase production, although this test is not specific as other clostridia also produce lipase. Numerous protocols using polymerase chain reaction and probe hybridization to detect and identify *C. botulinum* are described but these have not yet been applied widely in clinical practice.⁷⁵

MANAGEMENT

Supportive Care

Respiratory compromise is the usual cause of death from botulism. To prevent or treat this complication, hospital

admission of the patient and of all individuals with suspected exposure is mandatory. Careful continuous monitoring of respiratory status using parameters such as vital capacity, peak expiratory flow rate, negative inspiratory force (NIF), pulse oximetry, end-tidal CO₂, and the presence or absence of a gag reflex is essential to determine the need for intubation or tracheostomy, as the patient begins to manifest signs of bulbar paralysis.¹¹⁶ The most reliable, readily obtainable test is the NIF, which can be used in most institutions to determine the need for intubation. When suspicion of disease is high, and the vital capacity is less than 30% of predicted or the NIF is less than −30 cm H₂O, intubation should be strongly considered.^{86,135}

Reverse Trendelenburg positioning at 20° to 25° with cervical support has been suggested to be beneficial by enhancing diaphragmatic function, but the clinical application to seriously ill patients has not been validated.¹¹ This approach may reduce the risk of aspiration while decreasing the pressure of abdominal viscera on the diaphragm, with resultant improvement in ventilatory effort.

In addition to attention to respiratory issues, patients require nutrition (enteral or parenteral) and prompt recognition and treatment of secondary infections.

Gastric Decontamination

An attempt should be made to remove the spores and toxin from the gut. Although most patients present after a substantial time delay, the bacteria and/or BoNT may still be present hours or even days later. Activated charcoal should be a routine part of supportive care, because in vitro it adsorbs BoNT type A and probably also the other BoNT types.⁵⁷ Gastric lavage or emesis should be initiated only for an asymptomatic person who has very recently ingested a known contaminated food. If a cathartic is chosen, sorbitol is preferable because other cathartics such as magnesium salts may exacerbate neuromuscular blockade. Theoretically, whole-bowel irrigation may have a role in decontamination, particularly if there is concern about initiating emesis, but interventions other than activated charcoal have not been evaluated under these circumstances.

Wound Care

Thorough wound débridement is the most critical aspect in the management of wound botulism and should be performed promptly.^{66,76} Antibiotic therapy alone is inadequate, as evidenced by several case reports of disease despite antibiotic therapy. Penicillin G is one of many drugs with excellent in vitro antimicrobial efficacy against *C. botulinum* and is useful for wound management.¹³⁴ However, neither does penicillin play a role in the management of botulism caused by preformed toxin nor does it prevent gut spores from germinating. For these reasons, penicillin is not considered useful in infant and adult infectious botulism, and it is not by itself considered adequate for wound botulism. Medications that may interfere with neuromuscular transmission, such as aminoglycoside antibiotics¹¹³ and clindamycin,¹¹⁸ should not be used.

Guanidine, Dalfampridine (4-Aminopyridine), and 3,4-Diaminopyridine

Guanidine is no longer recommended for treatment of botulism, because its merits were not substantiated.^{52,69} (See previous editions of this text for a more extensive discussion.) Several studies¹¹¹ and case reports⁴⁸ have proposed that dalfampridine (4-aminopyridine) and 3,4-diaminopyridine are effective in improving neuromuscular transmission by enhancing acetylcholine release from the motor nerve terminal.¹¹¹ Dalfampridine (Ampyra) is FDA-approved to improve walking in patients with multiple sclerosis, but its potential to induce seizures at therapeutic doses limits its clinical usefulness. In a rat BoNT type A model of botulism, 3,4-diaminopyridine restored neuromuscular function and enhanced animal survival.¹²⁴ The therapeutic efforts for those with LEMS and the successful animal results all suggest that further investigative efforts are necessary. The fact that 3,4-diaminopyridine does not substantially cross the blood–brain barrier, resulting in limited CNS manifestations, makes this xenobiotic appropriate for further investigation.

Botulinum Antitoxin

Since the 1960s, passive immunization with antitoxin has been used to neutralize unbound BoNT. In the United States, the CDC supplies equine-derived antitoxin through state and local (except in California and Alaska) health departments. It is indicated for patients with food-borne or wound botulism. In 2010, an investigational heptavalent botulinum antitoxin (H-BAT) replaced the previously available bivalent antitoxin against BoNT types A and B and investigational antitoxin against type E. It contains equine-derived antibody to the seven known botulinum toxin types (A through G) and currently is the only botulinum antitoxin available in the United States for naturally occurring noninfant botulism.⁴¹ In a review of 132 cases of type A food-borne botulism, a lower fatality rate and a shorter course of illness were demonstrated for patients who received trivalent antitoxin, even after controlling for age and incubation period.¹³⁵ The earlier a patient received antitoxin, the shorter was the clinical course. In addition, no respiratory arrests occurred more than 5 hours after antitoxin was administered. Two studies on the use of antitoxin in the presence of wound botulism demonstrated that the longer the

delay to antitoxin administration, the more prolonged the requirement for ventilatory support and the poorer the outcome.⁴³ Consequently, antitoxin should be requested from the CDC at the time the diagnosis of botulism is first suspected.

Serum, stool, and gastric aspirate samples should be collected prior to administration of antitoxin. Because H-BAT is an investigational drug, informed consent must be obtained before giving it. The entire vial of antitoxin should be given intravenously as a 1:10 vol/vol dilution in 0.9% sodium chloride at rate of 0.5 mL/min for 30 minutes, optionally increasing to 1 mL/min for 30 minutes and then 2 mL/min if tolerated. Premedication with corticosteroids and antihistamines is recommended in children and in patients with a suspected history of reaction to equine-derived products. Although hypersensitivity skin testing for horse serum traditionally has been recommended prior to treatment with equine based antitoxins, it is not required for H-BAT; because H-BAT is despeciated, the risk of reaction may be lower than with previous products. Epinephrine and diphenhydramine should be readily available to treat anaphylaxis or hypersensitivity reactions.⁴¹ The overall rate of adverse reactions, including hypersensitivity and serum sickness,²⁴ to equine-derived botulinum antitoxins is reported as 9% to 17%, with an incidence of anaphylaxis as high as 1.9%.^{16,88} However, the risk is likely to be lower with the despeciated product.

The antitoxin neutralizes only unbound toxin, and consequently it can prevent paralysis but does not affect already paralyzed muscles.⁵⁴ Due to the high mortality rate associated with food-borne botulism, the antitoxin should be given to patients in whom the diagnosis is suspected; treatment should not be delayed while awaiting laboratory confirmation of the diagnosis. In the event of a potential outbreak of food-borne botulism, asymptomatic individuals should be closely monitored for early signs of illness so that antitoxin can be administered promptly¹²¹ (Antidotes in Depth: A6).

Treatment of Infant Botulism

Like adults, infants with botulism require intensive care, with meticulous monitoring for respiratory compromise. Autonomic dysfunction may also occur. Constipation may be severe.

Equine-derived antitoxin is not recommended in infant botulism because of doubtful efficacy as well as safety concerns.^{34,68,74,115} In October 2003, the FDA licensed human-derived botulism antitoxin antibodies as botulism immune globulin (BabyBIG) for treatment of infant botulism types A and B.⁷ A randomized trial of 122 cases of infant botulism showed that treatment with intravenous botulism immune globulin significantly reduced the length of hospital stay and intensive care, duration of mechanical ventilation and tube or intravenous feeding, and cost of hospitalization relative to placebo, without causing serious adverse effects.^{12,53} Similar results were seen in a 2007 retrospective chart review.¹⁴¹ BabyBIG is available from the California Department of Health Services Infant Botulism Treatment and Prevention Program (<http://www.infantbotulism.org>).²⁹

Prevention

Measures used to prevent infant botulism include limiting exposure to spores by thoroughly washing foods and objects that might be placed in a child's mouth. In addition, honey should not be given to infants younger than 6 months.

Numerous vaccination strategies are under investigation, including several recombinant vaccines that have shown promise in protecting against botulism in animal and human trials.^{18,127}

PROGNOSIS

The prolonged and variable period of recovery that occurs after exposure to BoNT is directly related to the extent of neuromuscular blockade and neurogenic atrophy as well as the regeneration rates of nerve endings and presynaptic membranes.⁸³ If the patient has excellent respiratory support during the acute phase and receives adequate parenteral nutrition, residual neurologic disability may not occur. Although the initial course may be protracted, near-total functional recovery can follow within several months to one year. Common long-term sequelae include dysgeusia, dry mouth, constipation, dyspepsia, arthralgia, exertional dyspnea, tachycardia, and easy fatigability.

The status of 13 patients who survived a toxin type B botulinum outbreak was characterized 2 years later by persistent dyspnea and fatigue, although surprisingly, pulmonary function tests had returned to normal in all patients.¹⁴⁸ Inspiratory muscle weakness persisted in 4 of 13 patients. Maximal oxygen consumption and maximal workload during exercise were diminished in all patients, and all had more rapid shallow breathing and a higher dyspnea score than controls. The reasons for premature exercise termination may be multifactorial. Although persistent respiratory muscle weakness may be an explanation, most dyspnea and fatigue appeared to be related to reduced cardiovascular fitness, leg fatigue, and diminished nutrition.¹⁴⁹

A 2007 case-control series reported long-term outcomes in 217 adults with food-borne botulism in the Republic of Georgia. Six patients died; the remaining 211 were interviewed a median of 4.3 years after onset of disease. They were significantly more likely than control subjects to report ongoing fatigue, dizziness, weakness, dry mouth, difficulty lifting

things, and difficulty breathing with moderate exertion.⁵⁸

PREGNANCY

At least three cases of botulism occurring during pregnancy are reported. One case occurred during the second trimester¹⁰⁶ and two cases occurred during the third trimester.¹³¹ Although in two cases BoNT or *C. botulinum* was isolated from the mother prior to administration of antitoxin therapy, no detectable toxin was isolated from the neonates in either of the third-trimester cases. The large molecular weight of the neurotoxin (150 kDa) makes passive diffusion through the placenta unlikely,⁶⁴ and, although theoretically possible, no active transport system has been identified.¹³¹ None of the three neonates had neurologic evidence of botulism. Appropriate care of the mother and preparation for maternal complications of delivery appear to ensure the best potential outcome for the infant.

A 2006 survey of physicians identified 16 women who were treated with BoNT type A during 19 pregnancies. One patient was injected while carrying twins, and another was treated during three separate singleton pregnancies. One patient who received a single session of 300 units of BoNT for cervical dystonia miscarried; she had a history of previous miscarriages. Another patient underwent a therapeutic abortion. No other complications occurred. Nevertheless, the authors “do not recommend injection of pregnant women ... until more data are available.”⁹⁰ All commercially available BoNT products are FDA pregnancy category C. It is unknown whether BoNT is excreted in breast milk.

EPIDEMIOLOGIC AND THERAPEUTIC ASSISTANCE

Whenever botulism is suspected or proven, the local health department should be contacted. The health department should report to the CDC Emergency Operations Center at 770-488-7100. The CDC can provide or facilitate diagnostic, consultative, and laboratory testing services, access to botulinum antitoxin, and assistance in epidemiologic investigations. All foods that are potentially responsible for the illness should be refrigerated and preserved for epidemiologic investigation. The merits of this surveillance and antitoxin release system were demonstrated in Argentina,¹⁴⁵ where the CDC assisted in establishing nation-specific principles, including local stocking of antitoxin and establishing mechanisms for distribution, emergency identification, response, and laboratory confirmation of suspected cases. Expansion of this system to other nations will enhance worldwide botulism surveillance for food-borne botulism and for potential terrorist dissemination of BoNT.¹²⁰

SUMMARY

- Most cases of botulism in the United States affect infants younger than 6 months of age. Because of an epidemiologic association, honey should not be given to babies younger than one year of age.
- Most cases of food-borne botulism relate to food processed at home under improper conditions.
- The diagnosis of botulism should be considered in patients presenting with diplopia, blurred vision, bulbar weakness, and/or symmetric paralysis.
- BabyBIG, a botulism immune globulin, is available for treatment of infant botulism types A and B, and there is a heptavalent botulinum antitoxin against serotypes A through G for noninfants. Treatment should not be delayed while laboratory diagnosis is pending.
- Botulinum toxins are injected therapeutically (both on-label and off-label) for numerous conditions, and they are safe and effective when used properly.

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A6 ANTIDOTES IN DEPTH

Botulinum Antitoxin

Silas W. Smith and Howard L. Geyer

INTRODUCTION

Antidotal therapies for adult and infant *Clostridium botulinum* infection are available as equine and human derived immunoglobulin antitoxins. Antitoxins may be beneficial for most clinical forms of botulism, although their utility is restricted to limiting disease progression rather than to reversing clinical manifestations.

HISTORY

Beginning in the 1930s, a formalin-inactivated toxoid against botulinum neurotoxin was first tested in humans, and in 1946 a bivalent (AB) formaldehyde-inactivated toxoid was deployed by the US Department of Defense as prophylaxis for at-risk individuals during the US Offensive Biological Warfare Program.^{48,56} By 1999, an equine trivalent antitoxin (ABE) was available to treat botulism.¹³ From 1999 to 2010, equine-derived, licensed bivalent botulinum antitoxin AB (BAT-AB) and investigational monovalent serotype E botulinum antitoxin (BAT-E) were available in the United States as immunoglobulin preparations. BAT-AB was used for patients with presumed wound botulism, and BAT-AB and BAT-E antitoxins were coadministered to patients with food-borne botulism. On March 13, 2010, equine heptavalent botulinum antitoxin (H-BAT, NP-018), the investigational new drug sponsored by the Centers for Disease Control and Prevention (CDC), replaced licensed bivalent BAT-AB and investigational botulinum antitoxin E.² Effective November 30, 2011, the CDC also stopped providing the investigational pentavalent (ABCDE) botulinum toxoid (PBT) for vaccination of workers at risk for occupational exposure.³ BabyBig, or Botulism Immune Globulin Intravenous (Human) (BIG-IV), was created by the California Department of Health Services (CDHS) in 1991 to treat infants afflicted by type A or type B botulism; it received Food and Drug Administration (FDA) approval in 2003.^{4,22} On March 22, 2013, the FDA approved H-BAT, equine Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) which is currently available.

PHARMACOLOGY

Chemistry/Preparation

A toxoid refers to an inactivated form of a bacterial toxin. An antitoxin is an antibody or antibody fragment capable of neutralizing a toxin. Multiple injections over months of formalin-inactivated toxoid are required to effectively immunize horses against botulinum toxin and to produce equine-derived antitoxins.³¹ The resultant antibotulinum immunoglobulin requires several purification and preparation steps.²⁵ H-BAT is produced by pooling plasma from horses immunized with specific botulinum toxoid subtypes (A–G), followed by pepsin digestion and blending of the seven serotype antitoxins into a heptavalent product.¹² H-BAT contains anti-type A, 4500 international units (IU); anti-type B, 3300 IU; anti-type C, 3000 IU; anti-type D, 600 IU; anti-type E, 5100 IU; anti-type F, 3000 IU; and anti-type G, 600 IU.²⁹ As the equine H-BAT is “despeciated” by pepsin enzymatic cleavage and removal of the Fc fragment portion, the result is a product composed of $\geq 90\%$ Fab and F(ab')₂ immunoglobulin fragments and less than 2% intact immunoglobulin G (IgG).² This decreases the risk of immediate hypersensitivity reactions and serum sickness.

Human whole IgG BIG-IV is derived from cold ethanol precipitation of pooled adult plasma collected from human donors immunized multiple times with PBT (A–E).^{37,52} The reconstituted product (50 ± 10 mg immunoglobulin/mL) contains greater than or equal to 15 IU/mL anti-type A toxin activity and greater than or equal to 4 IU/mL anti-type B toxin activity; antibody titers against botulinum neurotoxins C, D, and E remain undetermined.^{22,29}

Mechanism of Action

Current antitoxins (whether equine or human derived) bind to and neutralize free botulinum toxin.¹³ Thus, antitoxins are

ineffective against toxin bound to presynaptic acetylcholine release sites, toxin endocytosed by peripheral neuronal cells, and intracellular botulinum toxin light chain endopeptidase activity.¹⁰ Affected presynaptic end plates must regenerate in order to regain function.

Pharmacokinetics and Pharmacodynamics

Antidotal antibody fragments (eg, $F(ab')_2$, $F(ab')$, and single-chain variable fragments {scFv}) demonstrate shorter half-lives compared to whole immunoglobulins.³² Improved renal clearance and uptake by vascular endothelium and surrounding tissues may contribute to this effect.⁴² While linking fragments to polyethylene glycol can extend their half-life,¹⁶ this methodology remains investigational. Compared to the half-lives for antitoxin types A, B, and E of 6.5, 7.6, and 5.3 days measured in a patient provided whole immunoglobulin trivalent antitoxin, clinical trials following single vial administration determined shorter H-BAT antitoxin half-lives of anti-A (8.64 hours), anti-B (34.20 hours), anti-C (29.60 hours), anti-D (7.51 hours), anti-E (7.75 hours), anti-F (14.10 hours), and anti-G (11.70 hours).¹¹ These half-lives increased to 10.20 hours, 57.10 hours, 45.60 hours, 7.77 hours, 7.32 hours, 18.20 hours, and 14.70 hours, respectively, when two vials were administered.^{11,20,24} The volume of distribution ranges from 1465 mL (anti-D) to 14,172 mL (anti-E), depending on the number of vials.¹¹ The more rapid clearance of Fab and $F(ab')_2$ fragments compared to whole IgG may necessitate repeat H-BAT dosing in patients with wound or intestinal colonization or other cases in which in situ botulinum toxin production continues after antitoxin clearance.² Indeed, recurrence of paralysis was reported following H-BAT therapy in a patient with persistent type F intestinal colonization.²⁰

By convention, one IU of botulinum antitoxin neutralizes 10,000 mouse intraperitoneal median lethal doses (MIPLD₅₀) of toxin types A, B, C, D, and F, or 1000 MIPLD₅₀ of toxin type E (the IU for type G remains undefined).¹⁴ Thus, for example, in the doses found in H-BAT, the 4500 IU of anti-A, 3300 IU of anti-B, 3000 IU of anti-C, 600 IU of anti-D, 5100 IU of anti-E, and 3300 IU of anti-F would offset a total of 4.5×10^7 MIPLD₅₀ of botulinum A toxin, 3.3×10^7 MIPLD₅₀ of botulinum B toxin, 3.0×10^7 MIPLD₅₀ of botulinum C toxin, 6.0×10^6 MIPLD₅₀ of botulinum D toxin, 5.1×10^6 MIPLD₅₀ of botulinum E toxin, and 3.0×10^7 MIPLD₅₀ of botulinum F toxin, respectively.⁴⁶ These values would be anticipated to provide significant neutralization; patient serum botulinum toxin concentrations in food-borne botulism are usually less than 10 MIPLD₅₀/mL and rarely exceed 32 MIPLD₅₀/mL, using a plasma volume of 3000 mL reported previously.^{5,24,45} In isolated outbreaks, botulinum toxin concentrations in adult serum samples collected less than 18 hours after exposure are reported to be as high as 160 MIPLD₅₀/mL.⁷ Other recent cases have also yielded human serum botulinum toxin concentrations of type A of 1800 MIPLD₅₀/mL.⁴⁶ Following single vial administration, the reported H-BAT maximum concentration values¹² of 2.69 IU/mL for anti-A, 1.90 IU/mL for anti-B, 2.26 IU/mL for anti-C, 0.81 IU/mL for anti-D, 0.94 IU/mL for anti-E, and 2.37 IU/mL for anti-F would be anticipated to neutralize 2.69×10^4 MIPLD₅₀/mL of botulinum A toxin, 1.90×10^4 MIPLD₅₀/mL of botulinum B toxin, 2.26×10^4 MIPLD₅₀/mL of botulinum C toxin, 8.1×10^3 MIPLD₅₀/mL of botulinum D toxin, 9.4×10^2 MIPLD₅₀/mL of botulinum E toxin, and 2.37×10^4 MIPLD₅₀/mL of botulinum F toxin. One study that measured four patients' serum antitoxin concentrations following trivalent antitoxin (ABE) administration determined that those patients' measured antitoxin titers would retain the capability to neutralize 1500, 1000, and 12 times the anticipated toxin concentrations of types A, B, and E, respectively.²⁴ Complexity in anticipating or interpreting absolute neutralization efficacy is due to the fact that animal studies have revealed that the relationship between circulating neutralizing antibody concentrations and the amount of botulinum toxin neutralized is nonlinear, leading to a more efficacious, disproportional increase in botulinum toxin neutralization as antibody concentration is increased.⁴⁵

The half-life of BIG-IV is approximately 28 days.²⁹ BIG-IV anti-A titers were 0.5371 ± 0.2134 IU/mL on day one. Since one IU neutralizes 10,000 mouse intraperitoneal median lethal doses (MIPLD₅₀) of botulinum toxin A, this yields approximately titers of 5370 MIPLD₅₀/mL.^{14,29} Thus, a single infusion is anticipated to neutralize all botulinum toxin that might be absorbed from an infant's colon for several months.⁶

Related Agents

In order to properly interpret earlier botulism studies, it is important to recall that the previously available, equine BAT-AB antitoxin contained 7500 IU of anti-A antitoxin and 5500 IU of anti-B antitoxin.⁴¹ BAT-E contained 5000 IU of antitoxin. Trivalent antitoxin (ABE) contained 7500 IU of anti-A, 5500 IU of anti-B, and 8500 IU of anti-E antitoxins.²⁷ Investigational, whole, and fragment-derived monoclonal antibodies that have been raised in murine and equine species against types A and B are also being explored.^{31,32}

Investigational PBT vaccine, combining individual monovalent toxoids, was initially manufactured by Parke Davis more than 50 years ago and was subsequently produced by the Michigan Department of Public Health under contract from

the US Army.^{21,47} A replacement vaccine developed by US Army Medical Research Institute for Infectious Diseases (USAMRIID)—recombinant botulinum vaccine (rBV A/B)—is designed to protect adults 18 to 55 years of age against botulism type A (subtype A1) and type B (subtype B1).²³ It has been studied in animals and, completed human clinical trials await publication, although approval may be pursued under the FDA Animal Rule.^{17,23,44} Other recombinant subunit vaccines against C₁, D, E, and F have demonstrated efficacy in animals.⁴⁷ Humanized monoclonal antibodies, small peptides and peptide mimetics, receptor mimics, and small molecules targeting the endopeptidase activity are other avenues being explored for botulism treatment.¹⁰

ANTITOXIN ROLE IN ADULT BOTULISM

Rigorous adult morbidity and mortality studies are difficult to perform due to botulism's rarity, varied exposure and presentation, delayed recognition when bound toxin is no longer removable by antitoxin, and inconsistent clinical care. Given the delay involved in confirmatory testing by the CDC or public health laboratories and the lack of antitoxin reversal potential, the decision to administer H-BAT will often be made on the basis of empirical clinical and epidemiological grounds. Earlier disease recognition and an organized public health approach comprising surveillance, emergency notification, stocking, a release and distribution system, and laboratory confirmation appear to be responsible for decreasing morbidity and increasing survival after typical food-borne botulism.^{43,55} Simian experiments demonstrate reduced mortality with antitoxin administration.³⁵ Early antitoxin administration is a critical factor affecting clinical course and outcome. In a 1963 type E outbreak, all three patients who died failed to receive antitoxin, whereas three of five who received botulinum antitoxin survived.³⁰ Trivalent equine antitoxin decreased the fatality rate of botulinum A poisoning in a case series from 1973 to 1980.⁵¹ Patients who received antitoxin within the first 24 hours after symptom onset had a shorter disease course, although their mortality rate was equivalent to those who received antitoxin later. Age over 60 years and being an index patient conferred a greater mortality risk; a shorter incubation period of less than 36 hours (a surrogate measure of toxin dose) increased duration of hospitalization, mechanical ventilation, and time to sustained improvement.⁵¹ The case-fatality rate was 3.5% in patients with type E botulism who were provided antitoxin and 28.9% for untreated control subjects from previous years, although the utilization of supportive measures was uncontrolled.²⁸ In a retrospective review of 29 patients admitted from 1991 to 2005 with type A and a single case of type B wound botulism, a delay in antitoxin administration correlated with increased length of intensive care unit (ICU) stay.³⁶ In 20 patients with type A wound botulism treated from 1991 to 1998, those who received antitoxin within 12 hours of presentation required mechanical ventilation 57% of the time for a median duration of 11 days, compared to those who failed to receive antitoxin within 12 hours in whom 85% require mechanical ventilation for a median duration of 54 days.⁴⁰ Again, a shorter time to presentation heralded more severe disease (respiratory failure). A third wound botulism series (types A and B) with seven patients confirmed the importance of early therapy; those receiving antitoxin more than 8 days from symptom onset fared poorly compared to those receiving it within 4 days of symptom onset.¹⁵ Botulinum antitoxins are also beneficial in cases of iatrogenic botulism.⁴⁹ An earlier despeciated heptavalent botulism immune globulin (dBIG), which was prepared by the University of Minnesota under US Army contract, was deployed in the 1991 Egyptian type E botulism outbreak.²⁵ In a 2006 Thailand type A outbreak, heptavalent antitoxin was administered to 20 patients 5 days after toxin ingestion when respiratory failure was already present. Mechanical ventilation and hospital duration were shorter when compared to a historical study, and there were no deaths in those receiving antitoxin.⁵⁸

The absolute time frame for efficacy remains undetermined. In 109 patients treated under the CDC open-label protocol, H-BAT administration within 2 days after symptom onset (compared to >2 days) was associated with clinically significant, shorter mean durations of hospitalization (12.4 versus 26.1 days), ICU utilization (9.2 versus 15.8 days), and mechanical ventilation (11.6 versus 23.4 days).¹¹ However, circulating toxin can persist for long periods in patients with food-borne botulism. One study reported toxin detection in almost 20% of serum specimens taken greater than or equal to 10 days after toxin ingestion.⁵⁹ Furthermore, persistent, viable organisms or spores were present in stools 40% of the time at 10 days or more after toxin ingestion. A review of laboratory-confirmed botulism cases in Alaska from 1959 to 2007 demonstrated that toxin could be recovered in patients' sera up to 11 days after ingestion, while no serum specimens collected after antitoxin administration tested positive.¹⁹ In one case, toxin was detected in serum 12 days after the onset of descending paralysis.¹ Another patient in that multinational food-borne outbreak had toxin detected at 25 days after symptom onset.⁴⁶ Other isolated cases detail detectable circulating toxin as late as three and a half weeks after contaminated food consumption.¹⁸ Botulinum toxin-associated ileus might result in prolonged toxin exposure and continued absorption.

Collectively, these factors suggest that H-BAT might still prove clinically useful in patients with delayed presentations or disease recognition, in whom circulating toxins might present a persistent risk. Indeed, one report documented improvement when H-BAT was administered 48 hours after admission and many days after consumption of type-unspecified, botulism-contaminated canned corn.²⁶

A recently discovered, novel, eighth botulinum neurotoxin type H, recovered from an infant botulism patient, cannot be

neutralized by any of the currently available antitoxin therapies.^{7a,18a} Botulism poisoning does not appear to induce protective immunity or decrease subsequent morbidity or mortality associated with subsequent exposure in food or wound botulism.^{8,13,60} Thus, retreatment with antitoxin is required upon reexposure or in recurrent cases.

ANTITOXIN ROLE IN INFANT BOTULISM

BIG-IV is approved for treatment of patients younger than one year of age with infant botulism caused by toxin type A or B. BIG-IV does not treat rare serotype F disease, as human donors were vaccinated with PBT (A–E). In a double-blind and subsequent open-label trial, treatment with BIG-IV significantly reduced the overall length of hospital and ICU stay, the duration of mechanical ventilation, tube and intravenous feeding, and the cost of hospitalization.^{4,6} A retrospective review of 67 ICU patients with type A or B botulinum toxin from 1976 to 2005 found clinically significant decreases in length of hospital stay, ICU stay, and mechanical ventilation in patients who received BIG-IV versus those who did not.⁵³ Another retrospective review of patients with type A or B botulinum toxin from 1985 to 2005 reported a significant decrease in length of stay, a reduced need for nasogastric feeding, and duration of tracheal intubation in infants treated with botulism immune globulin.⁶⁰

BAT-AB and other equine derived products were rarely used in infants due to concern for anaphylaxis, life long hypersensitivity, and unclear efficacy.¹⁴ However, in situations where BIG-IV was unavailable due to lack of access or cost, BAT-AB treatment within 5 days of symptom onset significantly reduced overall hospital and ICU stays, duration of mechanical ventilation, tube feedings, and incidence of sepsis.⁵⁴

ADVERSE EFFECTS AND SAFETY ISSUES

Despite purification, inactivation, and filtration measures, potential transmission of blood-borne infectious agents from animal or human donors (pooled equine or human plasma) may still occur. Treatment with whole equine-derived antitoxins risks hypersensitivity reactions and serum sickness.⁴¹ Early rates of adverse reactions during the first decade during which botulinum antitoxin was available (1967–1977) ranged from 9% to 21%.^{9,34} The reported rates of anaphylaxis and serum sickness were 1.9% and 3.7%, respectively.⁹ However, the doses of antitoxin were larger than those subsequently used. H-BAT despeciation further decreases, but does not eliminate, this risk. Use of dBIG produced adverse reactions in 10 of 45 patients when used in one botulism type E outbreak.²⁵ These included nine “mild” reactions (local skin reactions, six; pruritus, one; urticaria, one; shivering, one) and one episode of “suggested serum sickness” without additional detail. The incidence of adverse effects of dBIG was similar to other internationally available antitoxins.²⁵ Healthy subjects administered H-BAT in clinical trials (56 total, of whom 20 received two vials) reported headache, pruritus, nausea, and urticaria at rates of 9%, 5%, 5%, and 5%, respectively.¹¹ Two moderate allergic reactions required treatment. Eleven subjects produced anti-BAT antibodies. The open-label CDC observation study revealed adverse reactions in 10% of 228 assessable patients; pyrexia, rash, chills, nausea, and edema occurred in 4%, 2%, 1%, 1%, and 1%, respectively.¹¹ There were no immediate hypersensitivity reactions, one cardiac arrest, and one episode of serum sickness. H-BAT contains maltose, which may interfere with certain non-glucose-specific blood glucose monitoring systems.

Hypersensitivity reactions might also occur to human BIG-IV, although this was not reported in clinical trials.²⁹ BIG-IV is contraindicated in patients with a prior history of severe reactions to other human immunoglobulin preparations and should be used cautiously in patients with or at risk for kidney dysfunction, because kidney dysfunction has been noted following treatment with other intravenous immunoglobulin products.²⁹ A mild, transient erythematous rash on the face or trunk was the most commonly reported adverse reaction. Potential but unreported adverse events include antibody development to immunoglobulin A (IgA) in patients with selective IgA deficiency and anaphylaxis upon subsequent exposure to blood products that contain IgA, aseptic meningitis syndrome, hemolytic anemia, thrombosis, transfusion-related acute lung injury, and hyperviscosity.²⁹ Administration of live virus vaccines (ie, measles, mumps, rubella, varicella) should be delayed for 5 months after infant BIG-IV treatment due to concerns of loss of immunization efficacy.

PREGNANCY AND LACTATION

Although there is limited information regarding H-BAT use in pregnancy, whole equine bivalent and trivalent antitoxins have been previously administered without apparent harm to the mother or the fetus.^{33,38,39,50} Pregnancy is not a contraindication to H-BAT. Given botulism’s life-threatening paralysis, treatment benefits would potentially exceed risks of harm, although all decisions are ultimately made on a case-by-case basis. H-BAT’s breast milk distribution is unknown. The labeled indication of BIG-IV for use in patients younger than one year of age does not address administration to pregnant women.²⁹

DOSING AND ADMINISTRATION

Close monitoring; medications including epinephrine, diphenhydramine, and corticosteroids, supportive airway modalities; and practitioners who are capable of diagnosing and treating anaphylactic or anaphylactoid reactions (including intubation competence) should be immediately available prior to and during antitoxin administration.

Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G)

Unlike prior equine derived products, H-BAT does not require routine sensitivity testing prior to administration, although it may be considered for those at risk of acute hypersensitivity reactions. If required, skin sensitivity testing with H-BAT is performed by administering 0.02 milliliters of 1:1000 saline-diluted BAT intradermally on the volar surface of the forearm (enough to raise a small wheal) with concurrent positive (histamine) and negative (saline) control tests.¹¹ Read after 15 to 20 minutes, a positive test is a wheal with surrounding erythema at least 3 millimeters larger than the negative control test. The histamine control must be positive for valid interpretation. A negative test is followed with repeat testing using a 1:100 dilution and then careful administration if no reaction occurs.

Three separate dosing strategies are recommended for adults, pediatric patients (1–17 years), and infants younger than 1 year. The adult dose is one vial. The vial is diluted 1:10 in 0.9% sodium chloride and administered intravenously via an optional 15-micron in-line filter. Barring any infusion-related safety concerns, the initial rate is 0.5 mL/min for the first 30 minutes, which is increased to 1 mL/min for the next 30 minutes, and then to 2 mL/min until completion of the infusion. For pediatric patients, the dose is a percentage of adult (one vial) dose calculated according to the dosing rule summarized in the package insert. For pediatric patients with a body weight ≤ 30 kg, the percentage of the adult dose to administer equals twice the body weight (in kg); for patients with a body weight >30 kg, the percentage of the adult dose to administer equals the weight (in kg) + 30. This rule yields the recommended percentages of the adult dose to administer according to the following pediatric weight intervals: 10 to 14 kg, 20%; 15 to 19 kg, 30%; 20 to 24 kg, 40%; 25 to 29 kg, 50%; 30 to 34 kg, 60%; 35 to 39 kg, 65%; 40 to 44 kg, 70%; 45 to 49 kg, 75%; 50 to 54 kg, 80%; and greater than or equal to 55 kg, 100%.¹¹ Without ever exceeding the adult rates, the infusion is initiated at a rate of 0.01 mL/kg/min for the first 30 minutes, which is increased 0.01 mL/kg/min every 30 minutes, to a maximum infusion rate of 0.03 mL/kg/min until completion. Infants (<1 year) receive 10% of the adult dose regardless of body weight. The infusion is initiated at a rate of 0.01 mL/kg/min for the first 30 minutes, which is increased 0.01 mL/kg/min every 30 minutes, to a maximum infusion rate of 0.03 mL/kg/min until completion.

Big-IV

The lyophilized product is reconstituted with 2 mL of sterile water for injection, to obtain a 50 mg/mL BIG-IV solution. The vial should not be shaken; this causes foaming. Infusion should begin within 2 hours of reconstitution. A dedicated intravenous line using low-volume tubing and a constant infusion pump are used to provide 75 mg/kg (1.5 mL/kg of reconstituted 50 mg/mL BIG-IV solution). The BIG-IV solution may be “piggybacked” into a preexisting line if it contains either 0.9% sodium chloride injection, 2.5% dextrose in water, 5% dextrose in water, 10% dextrose in water, or 20% dextrose in water (with or without added sodium chloride). If a preexisting line must be used, BIG-IV should not be diluted more than 1:2 with any of the solutions named above.²⁹ BIG-IV is administered at an initial rate of 25 mg/kg/h (0.5 mL/kg/h of reconstituted 50 mg/mL BIG-IV solution) for the first 15 minutes, which is then increased to 50 mg/kg/h (1 mL/kg/h of reconstituted 50 mg/mL BIG-IV solution), for a total infusion time of 97.5 minutes at the recommended dose.

Other Immunoglobins

In regions where whole, equine-derived antitoxins may still be available, it is important to note that these products required sensitivity testing and potential desensitization. The package inserts should be consulted for specific procedural details for dosing and administration, particularly as titers and volumes may differ by brand.⁴¹ For prophylaxis, the recommended dose of BAT-AB for an individual who had eaten food suspected of being infected with *C. botulinum* depended on the amount of food eaten and was 1500 to 7500 IU of anti-type A and 1100 to 5500 IU of anti-type B intramuscularly (20% to 100% of one vial). This initial therapy was followed in 12 to 24 hours by the injection of a second vial if any signs or symptoms of botulism developed.⁴¹ In addition, 1000 and 5000 IU (20% to 100% of one vial) of investigational anti-type E, based on the estimated ingested quantity of botulinum toxin, had been used for type E outbreaks.⁵⁷ The BAT-AB and BAT-E treatment doses were one vial of antitoxin diluted 1:10 (vol/vol) in 0.9% sodium chloride solution and administered slowly and intravenously over 30 to 60 minutes.^{27,41} Subsequent doses could be provided intravenously every 2 to 4 hours if progression of clinical findings occurred. BAT-AB and BAT-E were administered separately.

FORMULATION AND ACQUISITION

H-BAT is supplied in either 20 mL or 50 mL single-dose vials. Despite variable vial filling of 10 to 22 mL/vial, the

amount of A, B, C, D, E, F, and G antitoxin contained per vial is fixed: more than 4500 IU of anti-A, more than 3300 IU of anti-B, more than 3000 IU of anti-C, more than 600 IU of anti-D, more than 5100 IU of anti-E, more than 3000 IU of anti-F, and more than 600 IU of anti-G.¹¹ The bulk material contains approximately 30 to 70 mg/mL protein. H-BAT contains 10% maltose and 0.03% polysorbate 80. H-BAT is stored frozen at or below 5°F (−15°C) until used. Thawed H-BAT must be maintained at 36° to 46°F (2°–8°C) and used within 36 months, or until 48 months from the manufacture date, whichever occurs earliest. H-BAT should not be refrozen. Frozen H-BAT can be thawed in a refrigerator at 36° to 46°F (2°–8°C) over approximately 14 hours. Rapid thawing can be achieved by placing at room temperature for one hour, followed by a water bath at 98.6°F (37°C) until thawed. Reconstituted H-BAT may be stored refrigerated for use within 8 to 10 hours.

BIG-IV is formulated as a 6-mL, single-use, solvent-detergent-treated, sterile vial containing 100 ± 20 mg of lyophilized immunoglobulin (primarily IgG with trace amounts of IgA and IgM), stabilized with 5% sucrose and 1% albumin (human), without preservative.^{22,29}

BAT-AB, which may be available outside of the United States, must be maintained at 36° to 46°F (2°–8°C) and not frozen. It contains phenol 0.4% as a preservative.

Medical care providers who suspect botulism should immediately call their local or state health department's emergency 24-hour telephone service to request release of botulinum antitoxin and comply with legal reporting requirements. When local and state public health authorities are unavailable, the CDC Emergency Operations Center telephone contact is 770-488-7100. The CDC controls H-BAT distribution from stocks located throughout a national network of quarantine stations. The California Infant Botulism Treatment and Prevention Program (510-231-7600) maintains the supply of botulism immune globulin for infant botulism treatment. The Biomedical Advanced Research and Development Authority (BARDA) within the US Department of Health and Human Services has obtained approximately 120,000 H-BAT doses for the Strategic National Stockpile, with anticipated delivery of 80,000 additional doses.⁵⁶

SUMMARY

- In conjunction with frequent clinical assessments and aggressive supportive care of respiratory, gastric, and urinary function, provision of botulinum antitoxin appears to decrease morbidity and mortality after typical food borne or wound botulism.
- Preliminary data suggest that early administration of licensed H-BAT decreases the duration of hospitalization, ICU utilization, and mechanical ventilation.
- Current antitoxins cannot neutralize novel botulinum neurotoxin type H.
- Licensed BIG-IV provides effective treatment for infant botulism.
- Early consultation with local health departments, the CDC Emergency Operations Center, or a regional poison center (or other comparable agencies in other parts of the world) should occur to rapidly access effective therapeutic modalities and diagnostic tests for botulism.

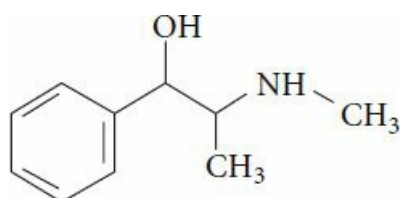
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42 DIETING XENOBIOTICS AND REGIMENS

Jeanna M. Marraffa



Ephedrine

INTRODUCTION AND HISTORY

Obesity is a worldwide epidemic, and the United States has the largest proportion of a national population of overweight and obese individuals.¹²⁵ Nearly 68% of Americans are overweight (body mass index {BMI}, 25–29.9) and 35% are obese (BMI >30 kg/m²).^{53,123} Even more alarming, the incidence of obesity in children between the ages of 6 and 19 years has tripled in the past 30 years.^{12,124} As many as 17% of children aged 2 to 19 years of age are obese, and 31% of children are overweight.^{12,123} There are conflicting data as to the exact number of deaths attributed to obesity annually; however, all of the studies agree that obesity results in excess mortality.^{53,54} In 2009, the Centers for Disease Control and Prevention reported greater than 110,000 deaths due to obesity in the United States. The cost of obesity is staggering and is reported to be upward of \$147 billion.²⁷ Obesity is linked to numerous health risks, including type 2 diabetes, hypertension, coronary heart disease,^{12,24} metabolic syndrome,¹⁷⁰ and low back pain.¹⁴⁸ Obesity is considered a leading preventable health risk, second only to cigarette smoking. Genetic links including particular gene polymorphisms have been identified and are being pursued.¹¹⁶

Americans spend upward of \$60 billion per year on weight loss therapies and modalities. Pharmacologic interventions typically result in a 5% to 10% weight loss, although a return to baseline upon drug cessation is common.⁴⁶ Surgical interventions consistently achieve substantial weight loss, causing up to a 30% reduction in weight, but they are not without complications.^{2,20}

One of the earliest accounts of weight loss therapy dates back to 10th century Spain. King Sancho I, who was obese, underwent successful treatment with a “theriaca” thought to contain plants and possibly opioids, administered with wine and oil. In addition, he was closely supervised and treated by a physician.⁷⁹

Currently, medicinal weight loss therapies (Table 42–1) are available as prescription medications (lorcaserin, phentermine, phentermine/topiramate), nonprescription dietary supplements (Citrus aurantium, chitosan, Garcinia cambogia, caffeine), and nonprescription diet aids (orlistat). Numerous other prescription medications, including thyroid medications and metformin, have been used on an off-label basis for weight loss. Numerous xenobiotics are promoted as weight loss aids, many with no proven efficacy and some with serious toxicity.

TABLE 42–1. Available Weight Loss Xenobiotics

<i>Drug or Supplement^a</i>	<i>Mechanism of Action</i>	<i>Regulatory Status</i>	<i>Adverse Effects/Contraindications^b</i>
Sympathomimetics			
Diethylpropion (Tenuate)	Increased release of norepinephrine and dopamine	Schedule IV prescription drug	Dry mouth, tremor, insomnia, headache, agitation, palpitations, hypertension, stroke, dysrhythmias
Mazindol (Mazanor, Sanorex)	Increased release of norepinephrine and dopamine	Schedule IV prescription drug	Contraindications: monoamine oxidase inhibitor use within 14 days, glaucoma, hyperthyroidism
Phentermine (Fastin, Adipex)	Increased release of norepinephrine and dopamine	Schedule IV prescription drug	Similar to diethylpropion
Phentermine/Topiramate (Qsymia)	Increased release of norepinephrine and dopamine (phentermine); exact mechanism of action for topiramate remains speculative	Schedule IV prescription drug	Phentermine: similar to diethylpropion Topiramate: central nervous system depression; ataxia; non-anion gap metabolic acidosis Contraindication: first trimester pregnancy
Bitter orange extract (<i>Citrus aurantium</i>)	Contains synephrine and octopamine; increases thermogenesis and lipolysis	Dietary supplement	Hypertension, cerebral ischemia, myocardial ischemia, prolonged QT interval
Guarana (<i>Paullinia cupana</i>)	Contains caffeine, which may increase thermogenesis	Dietary supplement	Nausea, vomiting, insomnia, diuresis, anxiety, palpitations
Raspberry ketones	Structurally similar to synephrine; increases thermogenesis and lipolysis	Dietary supplement	Nausea, vomiting, insomnia, hypertension, tachycardia, anxiety, palpitations
Serotonergics			
Lorcaserin (Belviq)	Selective agonist at 5-HT ₄	Schedule IV prescription drug	Dizziness, headache, nausea; serotonin toxicity possible after overdose
GI Agents			
Orlistat (Xenical/Alli)	Inhibits gastric and pancreatic lipases	Prescription and nonprescription drug	Abdominal pain, oily stool, fecal urgency or incontinence; fat-soluble vitamin loss Contraindications: cholestasis, chronic malabsorption
Chitosan	Insoluble marine fiber that binds dietary fat	Dietary supplement	Decreased absorption of fat soluble vitamins Contraindications: shellfish allergy
Fibers/Other Supplements			
Glucosulfate	Expands in stomach to increase satiety	Dietary supplement	Gastrointestinal (GI) obstruction with tablet form Contraindications: abnormal GI anatomy
Garcinia cambogia	Increases fat oxidation (unproven)	Dietary supplement	None reported
Chromium picolinate	Improves blood glucose and lipids; produces fat loss (unproven)	Dietary supplement	Dermatitis, hepatitis, possibly mutagenic in high doses

^aTrade names or botanical names are given in parentheses. ^bAll serotonergics are contraindicated during pregnancy and lactation.

The history of dieting xenobiotics is checkered. A number of weight loss therapies were withdrawn or banned by the Food and Drug Administration (FDA) because of serious adverse health effects (Table 42–2). Phenylpropanolamine,⁸⁷ fenfluramine-phentermine,³⁴ and sibutramine⁸² were withdrawn from the US market. The endocannabinoid receptor antagonists (rimonabant) never reached the US market. γ -Hydroxybutyric acid (GHB) and its congeners were initially sold as dietary supplements (Chap. 83) and promoted to body builders as a means to “convert fat into muscle” as a result of the effect of GHB on growth hormone. Because of toxicity and its association with drug-facilitated sexual assault, GHB is strictly controlled as a schedule I drug, with limited availability as a schedule III drug for narcolepsy (Xyrem). Clenbuterol is a long-acting β_2 -adrenergic agonist. Because of the stimulant properties and lipolytic effects, clenbuterol is abused by body builders as an energy source and anorectic agent.⁷⁶ It has been touted by celebrities to be an effective diet aid (Chap. 40).

TABLE 42–2. Unavailable and Withdrawn Weight Loss Xenobiotics

<i>Drug or Supplement*</i>	<i>Mechanism of Action</i>	<i>Adverse Effects</i>	<i>Regulation Status, DEA Schedule, or Withdrawal Date</i>
Amphetamine	Increased release of norepinephrine and dopamine	Sympathomimetic effects, psychosis, dependence	Schedule II
Benzphetamine (Didrex)	Increased release of norepinephrine and dopamine	Sympathomimetic effects, psychosis, dependence	Schedule III
Clenbuterol	β_2 -Adrenergic agonist activity	Tachycardia, headache, nausea, vomiting; may be prolonged	Never approved
Deferipraramine (Redux)	Promotes central serotonin release and inhibits its reuptake	Valvular heart disease, primary pulmonary hypertension	Withdrawn September 1997
Dieter's teas (senna, cascara, aloe, buckthorn)	Stimulant laxative herbs that promote colonic evacuation	Diarrhea, vomiting, nausea, abdominal cramps, electrolyte disorders, dependence	FDA required label warning, June 1995
Dinitrophenol	Alters metabolism by uncoupling oxidative phosphorylation	Hyperthermia, cataracts, hepatotoxicity	Never approved
Ma-huang (<i>Ephedra sinica</i>)	Increased release of NE and dopamine	Sympathomimetic effects, psychosis	Banned by FDA, April 2004
Fenfluramine (Fenfluramin)	Increased release and decreased reuptake of serotonin	Valvular heart disease, primary pulmonary hypertension	Withdrawn September 1997
Guar gum (Cai-Ban 3000)	Hygroscopic polysaccharide swells in stomach, producing early satiety	Esophageal and small bowel obstruction, fatalities	Banned by FDA, July 1990
Lipokinetix (sodium oxalate, norephedrine, 3,5-diiodothyronine, yohimbine, caffeine)	Unknown	Acute hepatitis	FDA warning, November 2001
Phendimetrazine (Adipost, Bontril)	Increased release of NE and dopamine	Sympathomimetic effects, psychosis	Schedule III
Phenylpropanolamine (Desatrim, Acatrim)	α_1 -Adrenergic agonist	Sympathomimetic effects, headache, hypertension, myocardial infarction, intracranial hemorrhage	Withdrawn November 2000
Rimonabant (Acomplia)	Endocannabinoid receptor antagonist	Anxiety, nausea, diarrhea, dizziness; increased suicidality and depression	Never approved in the United States; withdrawn from European market in 2011
Sibutramine (Meridia)	Inhibits reuptake of serotonin and norepinephrine	Increase in cardiovascular toxicity; increase in nonfatal myocardial infarction; increase in nonfatal stroke	Withdrawn October 2010

*Trade names or botanical names as appropriate are given in parentheses.

DEA = Drug Enforcement Administration; FDA = Food and Drug Administration.

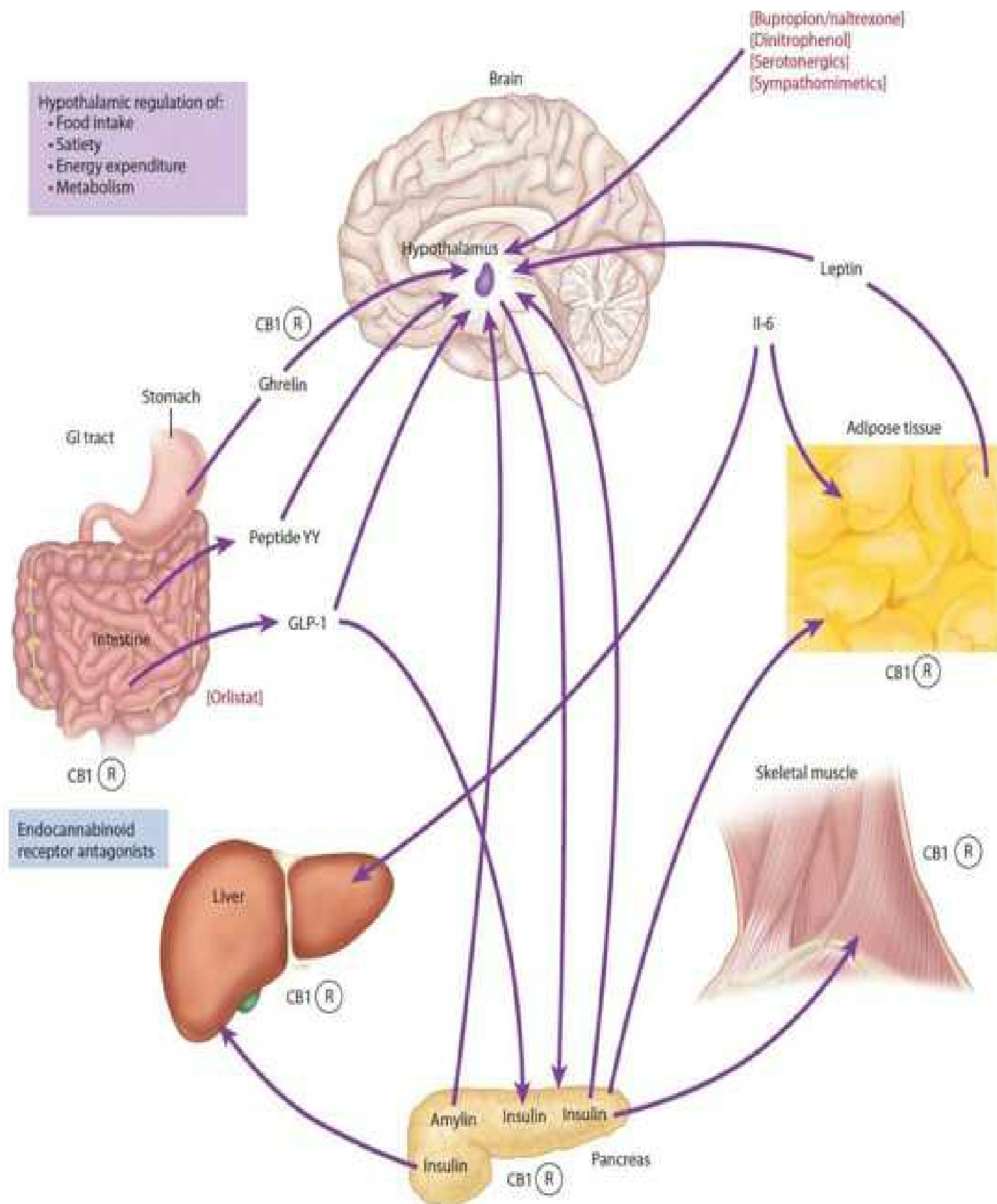
For the first time in many years, two new pharmaceutical preparations received FDA approval for weight loss in 2012. Phentermine/topiramate (Qsymia) and lorcaserin (Belviq) received FDA approval and became available late in 2012. Pharmacologically different, they show promise in the weight loss drug armamentarium. Other new pharmaceuticals are currently being investigated and likely to be presented to the FDA for consideration.

PATHOPHYSIOLOGY

Dieting xenobiotics can be divided into classes based on one or more of the following mechanisms of action: (1) appetite suppression (anorectics), (2) alteration of food absorption or elimination, or (3) increased energy expenditure. The hypothalamus is the key site in the brain that regulates food intake, energy expenditure, satiety, and metabolism. Sympathomimetics, serotonergics, dinitrophenol, and bupropion/naltrexone all work pharmacologically on the hypothalamus for weight loss. The endocannabinoid receptors, namely CB1, are located in the brain and in the intestines, liver, pancreas, adipose tissue, and skeletal muscle.

Endocannabinoid receptor antagonists bind to CB1 receptors and cause weight loss via different mechanisms. Neurohormonal approaches at targeting weight loss are under investigation, with specific focus on leptin, amylin, ghrelin, and glucagon-like peptide-1 (GLP-1). Leptin is secreted from fat proportionate to the amount of lipids contained in the

adipocyte, with women secreting more leptin than men. Leptin acts on the hypothalamus to decrease food intake, enhancing the metabolic rate and energy expenditure. Ghrelin is secreted by the stomach, and concentrations increase following fasting and just prior to meals. Ghrelin stimulates the hypothalamus and stimulates food intake. GLP-1 enhances glucose-induced insulin secretion while suppressing glucagon release (Fig. 42–1).^{47,57}



Sympathomimetics, serotonergics, dinitrophenol and bupropion/naltrexone work on the hypothalamus. Orlistat works in the stomach and decreases absorption. Endocannabinoid receptor antagonists work at various sites on central and peripheral CB1 receptors (CB1[®]). Ghrelin antagonists decrease appetite through the hypothalamus. Peptide YY inhibits appetite stimulation at the hypothalamus. Leptin increases metabolic rate and energy expenditure and decreases food intake.

FIGURE 42–1. Endocrine and neuroendocrine pathways of obesity and weight loss regimens. Systems regulating food ingestion and energy balance are interconnected and regulated. The hypothalamus regulates food intake, satiety, energy expenditure, and metabolism. Adipose tissue functions for glucose uptake and conversion; lipogenesis and lipolysis; β

oxidation of fatty acids; and release of leptin, adiponectin, and interleukin-6, all of which regulate energy balance.

Although there has been improvement and advancements in the understanding and treatment of obesity, significant challenges remain. The ideal xenobiotic for weight loss has yet to be identified.

SYMPATHOMIMETICS

Although controversial, certain sympathomimetic amines still carry official indications for short-term weight reduction (Table 42–1). Sympathomimetic amines share a β -phenylethylamine parent structure and include phentermine, diethylpropion, and mazindol, which are restricted as schedule IV drugs and carry warnings that advise prescribers to limit use to only a few weeks. Phentermine/topiramate extended release (Qsymia) was recently approved.^{6,11} Regardless of their source and legal status, sympathomimetics generally share a spectrum of toxicity and produce adverse effects similar to amphetamines (Chap. 76).

Pharmacology

Sympathomimetic amines that act at α - and β -adrenergic receptors are clinically effective in promoting weight loss but have numerous side effects that limit their clinical use. Soon after its introduction as a pharmaceutical for nasal congestion in the 1930s, the prototype sympathomimetic drug amphetamine (Fig. 42–2) was noted to cause weight loss (Chap. 76). The weight loss effect of amphetamine was also readily apparent in early animal studies, although tolerance to the anorectic effects was also noted.¹⁵⁸ The primary mechanism of action of the weight loss effects of sympathomimetic drugs is central nervous system (CNS) stimulation, resulting from increased release of norepinephrine and dopamine.¹⁵⁵ The effects include direct suppression of the appetite center in the hypothalamus and reduced taste and olfactory acuity, leading to decreased interest in food. Increased energy and euphoriant effects of the stimulants also contribute to weight loss. However, tachyphylaxis occurs, and the rate of weight loss diminishes within a few weeks of initiating therapy.⁴⁹ Significant side effects and abuse potential severely limit the therapeutic use of this class of drugs.

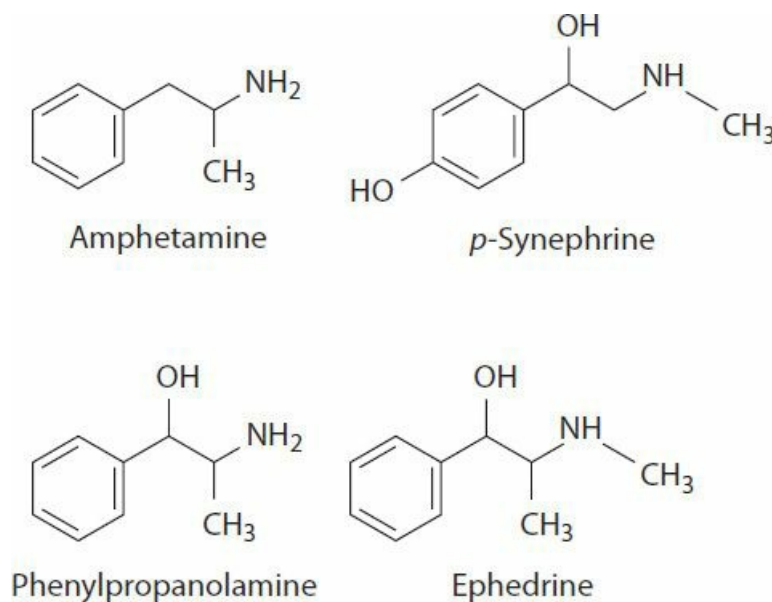


FIGURE 42–2. Sympathomimetic amines formerly and currently used for weight loss.

Adverse Effects

Absence of polar hydroxyl groups from a sympathomimetic amine increases its lipophilicity; therefore, unsubstituted or predominantly alkyl group substituted compounds (eg, amphetamine, ephedrine, phenylpropanolamine {PPA}) have greater CNS activity. Mild cardiovascular and CNS stimulant effects include headache, tremor, sweating, palpitations, and insomnia. More severe effects that may occur after overdose of sympathomimetic amines include anxiety, agitation, psychosis, seizures, palpitations, and chest pain.^{145,164}

Hypertension is common following overdose and occasionally following therapeutic use. Patients may present with confusion and altered mental status as a result of hypertensive encephalopathy. Reflex bradycardia after exposure to xenobiotics with predominantly α -adrenergic agonist effects may accompany the hypertension and provides a clue to the diagnosis. Children may be at especially high risk for hypertensive episodes because of the relatively significant dose per kilogram of body weight from even a single tablet. Other manifestations include chest pain, palpitations, tachycardia, syncope, hypertension, mania, psychosis, convulsions, and coronary vasospasm.^{129,180}

Clinically significant hypertension should be treated aggressively with either phentolamine, a rapidly acting α -adrenergic antagonist or nicardipine. Analogous to the management of cocaine toxicity, β -adrenergic antagonists should be avoided because the resultant unopposed α -adrenergic agonist effects may lead to greater vasoconstriction and hypertension.⁵ Agitation, tachycardia, and seizures should be treated initially with benzodiazepines.

Herbal Sympathomimetic Products

Since ephedra was banned, herbal weight loss supplements have been reformulated. Many now contain an extract of bitter orange (*C. aurantium*), a natural source of the sympathomimetic amine synephrine, often in combination with caffeine, theophylline, willow bark (containing salicylates), diuretics, and other constituents. The dried fruit peel of bitter orange is a traditional remedy for gastrointestinal ailments. The predominant constituents, p-synephrine (Fig. 42–2) and octopamine, are structurally similar to epinephrine and norepinephrine. The isomer m-synephrine (phenylephrine or Neo-Synephrine) is used extensively as a vasopressor and nasal decongestant. Although the physiologic actions of synephrine are not fully characterized, it appears to interact with amine receptors in the brain and acts at peripheral α_1 -adrenergic receptors, resulting in vasoconstriction and increased blood pressure.⁵⁸ Some evidence indicates that synephrine may also have β_2 -adrenergic agonist activity,¹³⁹ which could increase lipolysis. β_2 -Adrenergic agonists were found to have remarkable antiobesity effects in rodents; however, effects in human are not as profound. Octopamine stimulates lipolysis in rats, hamsters, and dogs, although this effect was not seen in human fat cells.^{24,58}

Nearly 2% of 4140 Californians surveyed had used a *C. aurantium*-containing product several times a week.⁹² Adverse effects associated with use of *C. aurantium*-containing weight loss products are reported, including tachydysrhythmias,⁵² cerebral ischemia in a 38 year-old man,¹⁶ exercise induced syncope, and QTc interval prolongation in a 22 year-old woman,¹¹⁹ and a possible case of myocardial infarction in a 55 year-old woman.¹²¹

Raspberry ketone, 4-(4-hydroxyphenyl)-2-butanone, is promoted to induce weight loss and is available as a supplement. Structurally similar to synephrine, its purported effects on weight loss are similar. The amount of raspberry ketone in a typical dose of a dietary supplement is equal to the amount derived from 40 kilograms of raspberries. Studies in rats show an increase in lipolysis and alteration in lipid metabolism.^{117,129} Toxicity is not yet described in the literature, although clinical effects would be expected to be similar to other sympathomimetics.

Phentermine/Topiramate

Phentermine is a sympathomimetic that still retains an FDA indication for short-term weight loss. It increases release of norepinephrine, which serves as an appetite suppressant via the effects on the hypothalamus. Topiramate has been on the US market for years for a variety of conditions including seizure disorder and migraine headaches. Weight loss is a demonstrated side effect of topiramate when used for these indications.⁸⁹ The mechanism of weight loss induced by topiramate remains speculative and is likely a combination of decreased caloric intake, increased energy expenditure, and decreased energy efficiency.^{6,59}

Phentermine/topiramate controlled release (Qsymia) is approved for long term management of weight loss. The FDA recommends discontinuation if 5% of body weight is not lost within 24 weeks of therapy initiation.^{32,33} The clinical trials evaluating the efficacy of phentermine/topiramate, were short term studies performed in approximately 4000 patients.^{6,11,59} In all of these trials, there was a substantial decline in body fat (upward of 10%) as well as improvement in other metabolic parameters, including lipid control and glucose regulation. In addition, blood pressure declined in all three trials. Adverse events appeared mild, although there were increases in heart rate and complaints of somnolence. There appears to be an increased risk of congenital malformations, particularly orofacial clefts, when taken during the first trimester of pregnancy.⁵⁷ Because topiramate is a carbonic anhydrase inhibitor, it can decrease serum bicarbonate resulting in a nonanion gap metabolic acidosis.¹⁴⁶

Although there have been no documented cases of overdose of this combination product, its toxicity can be extrapolated from the known toxicities of the individual components. Phentermine toxicity is described in detail above. Topiramate toxicity causes CNS depression, dizziness, ataxia, a nonanion gap metabolic acidosis, and hypokalemia^{17,106,146} (Chap. 48).

SEROTONERGICS

Xenobiotics that affect central release and reuptake of serotonin are approved for a number of indications, including depression, anxiety, nicotine addiction, migraine headache, and premenstrual dysphoric syndrome. Serotonin is believed to have a role in appetite suppression, which is due to the effect on the hypothalamic serotonin 5-HT_{2C} receptor, as well as the 5-HT_{1A}, 5-HT_{1B}, and 5-HT₆ receptors.^{67–69,71} Serotonin receptor effects may also enhance energy expenditure. The serotonin agonists have been associated with cardiac valvulopathy (5-HT_{2B} receptor), hallucinations (5-HT_{2A} receptor),

and pulmonary hypertension (5-HT_{1B}), as well as serotonin toxicity.

Lorcaserin (Belviq), approved by the FDA in 2012, is a novel selective agonist at the 5-HT_{2C} receptor.^{9,50,80,109} This novel selectivity for the 5-HT_{2C} receptor conceivably may permit weight loss with minimal risk of significant toxicity as recognized with other serotonergics.⁶⁸ Lorcaserin neither stimulates the release of norepinephrine, dopamine, or serotonin, nor does it inhibit the reuptake of these neurotransmitters.^{67,68}

Lorcaserin 10 mg twice daily showed a significant reduction in body fat (5.8 ± 0.2 kg) compared to placebo (2.2 ± 0.1 kg) after 52 weeks of therapy in 3182 subjects. In addition to the weight loss achieved in 1 year, the subjects maintained their body weight for 1 year.¹⁵³ No increase in the incidence of cardiac valvulopathy was demonstrated in the 2-year follow up in the subjects receiving lorcaserin.¹⁵³ In all of the clinical trials, the adverse events were minimal and included dizziness, headache, and nausea.^{50,75,84,136,153}

There have been no cases of overdose documented to date. Expected clinical toxicity includes nausea, vomiting, dizziness, and headache. In large overdoses, receptor selectivity is typically lost, suggesting that large overdoses of lorcaserin would cause effects from agonism at other serotonergic receptors. Serotonin toxicity may occur after overdose (Chap. 75).

Management of the toxic effects mediated by serotonin receptors should address the specific clinical effects. Benzodiazepines may be useful for tachycardia and hypertension. Rapid identification and management of serotonin toxicity is essential to prevent associated morbidity and mortality (Chap. 75).

XENOBIOTICS THAT ALTER FOOD ABSORPTION, METABOLISM, AND ELIMINATION

Fat Absorption Blockers

Orlistat (Xenical) was approved by the FDA in 1999 for treatment of obesity. In 2007, orlistat (Alli) became available as a nonprescription formulation. The availability may pose an abuse potential for patients with eating disorders, and abuse should be considered in patients presenting with related adverse events. Orlistat is the only FDA approved drug that alters the absorption, distribution, and metabolism of food. Orlistat is a potent inhibitor of gastric and pancreatic lipase, thus reducing lipolysis and increasing fecal fat excretion.²⁵ The drug is not systemically absorbed but exerts its effects locally in the gastrointestinal tract. It inhibits hydrolysis of dietary triglycerides and reduces absorption of the products of lipolysis, monoglycerides, and free fatty acids. Several clinical trials demonstrate that orlistat reduces gastrointestinal fat absorption by as much as 30%.¹⁷⁷ When taken in association with a calorie restricted diet, weight loss of approximately 10% body weight can be achieved in 1 year.¹⁵¹ Orlistat is associated with a modestly lower weight gain over a 3 year period when compared to placebo (4.6 kg versus 7 kg, respectively).¹³⁷

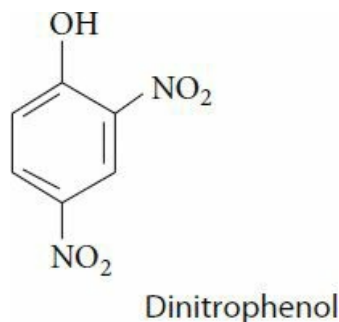
Orlistat should be taken only in conjunction with meals that have a high fat content; it should not be consumed in the absence of food intake. Adverse effects correlate with the amount of dietary fat consumption and include abdominal pain, oily stool, fecal incontinence, fecal urgency, flatus, and increased defecation. Systemic effects, which are rare due to the lack of systemic absorption,^{51,115,162} include cholestatic hepatitis and hepatocellular necrosis,^{115,162} but there is an inconsistent demonstration of a temporal relationship. In a cohort of nearly 16,000 patients in England, although there were no cases of serious hepatotoxicity, there were reports of aminotransferase elevations. Two of the cases were deemed as causally related to orlistat, and one had evidence of aminotransferase elevations and elevations on rechallenge.¹³² Concomitant use of natural fibers (6 g of psyllium mucilloid dissolved in water) may reduce the gastrointestinal side effects of orlistat.²⁶ Because orlistat reduces absorption of fat soluble food constituents, daily ingestion of a multivitamin supplement containing vitamins A, D, and K, and β -carotene is advised to prevent resultant deficiency. Pancreatitis⁴ and oxalate nephropathy¹⁴⁹ are rarely reported after orlistat use. Currently, there are no reported intentional overdoses of orlistat. There are limited data regarding unintentional pediatric exposure to orlistat, and the toxicity appears to be limited to mild gastrointestinal effects.¹²² In overdose and/or misuse, treatment should be responsive to clinical manifestations.

Chitosan is a weight loss dietary supplement derived from exoskeletons of marine crustaceans. It is thought to act similarly to orlistat by binding to dietary lipids in the gastrointestinal tract and reducing breakdown and absorption of fat. Animal models describe an increase in fecal fat excretion in rats administered chitosan when they are fed high-fat diets.⁴¹ The efficacy of chitosan in humans is disputed.^{60,112,113} Some evidence indicates that chitosan may decrease total serum cholesterol concentration in overweight people, but the majority of clinical studies indicate chitosan is ineffective for weight loss in the absence of dietary and lifestyle modifications.¹⁴⁷ It is estimated that in the presence of chitosan, it would take more than 7 months to lose 1 pound of body fat.⁶⁰ Chitosan is contraindicated in people with shellfish allergy.

Dietary Fibers

Glucomannan is a dietary fiber consisting of glucose and mannose, which is derived from konjac root, a traditional Japanese food. Edible forms of glucomannan include konjac jelly and konjac flour, which are mixed with liquid prior to ingestion. Purified glucomannan is available in capsule form and is found in various proprietary products marketed for weight loss. On contact with water, glucomannan swells to approximately 200 times its original dry volume, turning into a viscous liquid. It lowers blood cholesterol and glucose concentrations and decreases systolic blood pressure,^{7,167} but significant weight loss benefits are not demonstrated.⁹⁵ Following several reports of esophageal obstruction, glucomannan tablets were withdrawn from the market in Australia in 1985.⁷³ Serious adverse effects are not described with encapsulated glucomannan, presumably because slower dissolution allows for gastrointestinal transit prior to expansion. Glucomannan capsules are available as a nutritional supplement in the United States, although adequate safety and efficacy studies are not published.

Dinitrophenol



One of the earliest attempts at a pharmaceutical treatment for obesity was 2,4-dinitrophenol (DNP), which was popularized as a weight loss adjuvant in the 1930s.^{64,160} This chemical, which is used in dyes, wood preservatives, herbicides, and explosives, was never approved as a drug product. DNP was legally available as a dietary supplement prior to enactment of the US Federal Food, Drug, and Cosmetic Act of 1938 and thus remained legal. By increasing metabolic energy expenditure, it reportedly produces weight loss of 1 to 2 pounds per week in doses of 200 to 300 mg per day.^{31,64} DNP increases metabolic work by uncoupling oxidative phosphorylation in the mitochondria. Through this mechanism, the hydrogen ion gradient that allows ATP synthesis is destroyed and ATP production is stopped, though oxidative metabolism in the Krebs cycle continues (Chap. 13). This mechanism results in inefficient substrate utilization, and the resulting energy loss is dissipated as heat. This wastes calories but also elevates temperature and, occasionally, life-threatening hyperthermia can occur.¹⁵⁹ In fact, DNP was reportedly administered to Russian soldiers during World War II to keep them warm during winter battles.⁶⁴ Symptoms related to DNP toxicity include malaise, skin rash, headache, diaphoresis, thirst, and dyspnea. Severe toxic effects include hyperthermia, hepatotoxicity, agranulocytosis, respiratory failure, coma, and death.^{15,96,159} Delayed-onset cataracts were a frequent and serious complication of DNP use.¹⁵

Epidemic use of DNP occurred in Texas in the 1980s when industrial DNP was used at a physician's weight loss center. The physician distributed DNP under the trade name, Mitcal. The fatality of a wrestler following an intentional overdose in 1984 led a Texas court to stop the use of this practice.⁹⁶ DNP continues to reappear sporadically as a weight loss treatment, and cases of serious toxicity still are reported.^{64,127} Management should emphasize rapid cooling (Chap. 30). Benzodiazepines should also be used as an adjunct therapy for management of delirium and seizures.

Endocannabinoid Receptor Antagonists

In the past decade, the endocannabinoid system (ECS) and its involvement in weight loss sparked excitement and potential for novel xenobiotics. Endocannabinoids, which are the natural ligand for the cannabinoid receptor, have diverse effects on metabolic functions.⁷⁷ The ECS contributes to the regulation of food intake, body weight, and energy balance, and it may have a role in inflammation and neuropathic pain.^{83,141,169,174} It has long been known that tetrahydrocannabinol, the active principle in marijuana (*Cannabis sativa*), stimulates appetite and is an effective antiemetic (Chap. 77).^{29,131}

Several CB1 receptor antagonists showed promise in both animal and human studies of weight loss. Rimonabant was approved for therapeutic use in Europe and clinical trials in the United States were performed. Clinical studies note that these xenobiotics showed a significant and sustained reduction in body weight.¹³⁵ There was also improvement in insulin resistance with a decline in plasma leptin, insulin, and free fatty acid concentrations, presumably due to the upregulation of the peripheral ECS system in diabetes.^{74,140} In the clinical trials there was a significant increase in adverse events, including anxiety and depression in the rimonabant groups. This led to a delay in the FDA's approving this product for therapeutic use. Shortly after approval in Europe, it became evident that the effects of anxiety and depression were far greater than initially expected. Rimonabant was never approved by the FDA, and other Phase III studies, including those involving other endocannabinoid receptor antagonists (eg, tranabant), were terminated early. Rimonabant was removed

from the European market. Centrally acting CB1 antagonists proved to have an unfavorable risk–benefit relationship. However, peripherally acting CB1 antagonists have shown some promise for weight loss, and further research is currently underway.^{48,65}

Naltrexone/Bupropion

Naltrexone is an opioid receptor antagonist that is currently approved by the FDA for the treatment of alcohol and opioid dependence.¹⁶⁸ Bupropion is a norepinephrine and dopamine reuptake inhibitor that is approved for both depression and smoking cessation, and it is known to cause weight loss at therapeutic doses. The combination of naltrexone and bupropion is effective in inducing weight loss and is beneficial in other addictive disorders. The mechanisms by which naltrexone/bupropion cause weight loss is not completely understood.¹⁶⁸ Proopiomelanocortin (POMC)-producing neurons in the hypothalamus are stimulated with bupropion, and naltrexone inhibits the opioid mediated POMC autoinhibition. This combination of stimulation and inhibition of the negative feedback loop on POMC neurons is believed to facilitate ongoing weight loss. Additionally, it is believed that there is synergism with naltrexone and bupropion in midbrain dopamine areas resulting in decreased food intake, presumably through modulation of mesolimbic reward systems.^{63,86,168}

This potential synergistic effect has resulted in promising effects. A new drug application for the combination product of Naltrexone SR/Bupropion SR (Contrave/NB32) was submitted to the FDA in 2010.¹³ The Contrave Obesity Research Program consists of four 56-week, randomized, double-blind, placebo-controlled Phase III trials.^{63,168} The combination of naltrexone plus bupropion in these studies demonstrated a 5% to 15% weight reduction.¹⁶⁸ The naltrexone SR 32 mg/bupropion 360 mg/day per arm resulted in significantly greater weight loss and had improvements in markers of cardiovascular risk. The combination was generally well tolerated, with nausea and headache most frequently reported.^{63,168} There was no increased depression or suicidality in the treatment groups.

The FDA has mandated a clinical trial evaluating cardiovascular risk of naltrexone SR 32 mg/bupropion SR 360 mg in subjects with underlying cardiovascular risk factors. The status of the FDA approval of this combination therapy is pending the results of the current clinical trial. It is unclear if the combination drug will receive FDA approval despite its promising results on weight reduction.

Adverse events from this product result from the known toxicity of each individual xenobiotic. Naltrexone is generally expected to be safe and well tolerated in opioid naive patients; however, it will cause prolonged opioid withdrawal symptoms in opioid tolerant patients and will significantly reduce the efficacy of opioids if they are required. Bupropion toxicity is well described in the literature. Seizures may occur after bupropion at doses greater than 450 mg per day.^{38,145} The amount of bupropion available in this formulation is of particular concern as is the potential for misuse/overdose. Bupropion toxicity is discussed in detail in [Chap. 75](#).

Alternative Pharmaceutical Approaches

In an attempt to find the perfect therapeutic alternative for weight loss, there is an continuing approach to utilize currently approved xenobiotics for weight loss. Similar to topiramate, xenobiotics that are known to cause weight loss at therapeutic doses such as metformin, bupropion, and zonisamide, continue to be investigated for both label and off label use. Combination therapy aimed at multiple systems likely will prove most efficacious. Although these xenobiotics may provide a beneficial weight loss, each of them has their own inherent toxicities. Metformin can cause a metabolic acidosis with elevated lactate concentration, particularly in patients with underlying kidney dysfunction and after large intentional overdoses ([Chap. 53](#)). Zonisamide, an adjunct anticonvulsant that is not used commonly, is associated with adverse events including CNS depression and hypersensitivity^{120,175} ([Chap. 48](#)).

Future Targets for Xenobiotic Development

The desire to identify new biochemical pathways and pharmacologic approaches to weight loss began in antiquity. Research continues to evolve in an ongoing effort to determine the underlying etiology of obesity as well as develop new, more advanced pharmacologic interventions ([Table 42–3](#)).^{3,29,69} Gut peptides play an important physiologic role in normal gastrointestinal functions, including cessation of meals. Some gut peptides affect feeding control and show promise in the treatment of obesity.^{36,69,108,116}

TABLE 42–3. Potential Future of Xenobiotics for Obesity

Drug Name	Drug Class	FDA Approval Status	FDA Approved Indication	Route of Administration
Pramlintide	Synthetic analog of amylin	Approved	Type 1 diabetes	Subcutaneous
Metreleptin	Recombinant analog of leptin	Phase III	N/A	Subcutaneous
Exenatide (Byetta); extended-release exenatide (Bydureon)	Glucagonlike peptide-1 agonist	Approved	Type 2 diabetes	Subcutaneous
PYY 3-36	Peptide YY	Phase II	N/A	Intranasal
MOX-B11	Ghrelin antagonist	Phase I	N/A	Subcutaneous
GSK-598809	Dopamine antagonist	Phase I	N/A	Oral

FDA = Food and Drug Administration.

Leptin and the leptin gene are being explored as a basis for obesity and as a therapeutic strategy.^{28,78} Much of the enthusiasm about the potential role for leptin as an antiobesity therapy has subsided because leptin administration does not induce the expected response on weight control and is transient.^{134,142,161} In fact, obese people have elevated leptin concentrations, and obesity is believed to cause leptin resistance in the brain.⁴⁷ Amylin is cosecreted from the β islet cells in the pancreas and contributes to short-term energy regulation. The combination of leptin and amylin reduce food intake and body weight even in the setting of leptin resistance.¹⁶¹ Pramlintide acetate (a synthetic analog of amylin) and metreleptin (a recombinant analog of leptin) combination therapy has been studied in animals and humans for weight loss with promising results. The combination therapy was stalled in Phase II clinical trials because of safety concerns. It remains unclear if this potential combination therapy and novel approach will be continued in drug development.¹⁶¹ This suggests that combination therapy in the management of obesity is increasingly important.

Ghrelin antagonists are also suggested as a possible adjunct therapy for weight loss. Ghrelin is a growth hormone releasing agent produced by the stomach that stimulates appetite.^{93,94,163} Data suggest that ghrelin and leptin work together to stimulate food consumption.^{39,107} Ghrelin antagonists may decrease the increased appetite that often occurs with dietary modifications for weight loss and such agents are under investigation.¹¹⁶ Neuropeptide Y, a peptide found in the arcuate and paraventricular nucleus of the hypothalamus, is a potent central appetite stimulant.

GLP-1 is produced in the brain and distal intestine. During a meal, GLP-1 concentrations increase and remain elevated for several hours after. GLP-1 inhibits food intake, inhibits glucagon secretion, decreases gastric acid secretion, and delays gastric emptying. Exendin-4, extracted from the venom of the Gila monster, is a pharmaceutically available GLP-1 agonist, exenatide (Byetta), and is approved by the FDA for diabetes mellitus. It decreases food intake and produces a 2 to 5 kilogram sustained weight loss. Extended release exenatide (Bydureon) is available and has an FDA approved indication for type 2 diabetes. It is dosed every 7 days, and although it does not have an FDA approved indication for weight loss, it will likely be used off-label for weight loss. Acute overdoses of exenatide are rarely reported; however, the potential for hypoglycemia remains a significant concern, although it has not yet been reported.^{30,31}

Peptide YY is similar to GLP-1 and has been investigated for weight loss. Preliminary data suggest that intranasal peptide YY failed to induce a significant body weight reduction when compared to placebo and had a high incidence of nausea and vomiting.¹¹⁶

Because β_2 -adrenergic receptors mediate lipolysis in adipose tissue, β_2 -selective agonists also are under investigation to enhance weight loss.¹³⁹ Future drug therapy may target these genes, receptors, and proteins to modify metabolism. As obesity research proceeds and the biologic basis for obesity is defined, new approaches and mechanisms for therapy may be identified.¹⁹

Hypocaloric Diets and Cathartic/Emetic Abuse

Starvation, as well as abuse of laxatives, syrup of ipecac, diuretics, and anorectics, has led to morbidity and mortality, often in young patients.^{56,81} Fad diets and laxative abuse should be strongly considered in young people with unexplained salt and water depletion, syncope, hypokalemia, and metabolic alkalosis. A variety of extreme calorie-restricted diets resulting in profound weight loss were very popular in the late 1970s, but reports of a possible association between these diets and sudden death followed.¹⁵⁰ Myocardial atrophy was a consistent finding on autopsy. Torsade de pointes and other ventricular dysrhythmias may have occurred as a result of hypokalemia^{150,154} and protein-calorie malnutrition are proposed as causes of death.^{45,150, 154}

Following the negative reports and FDA warnings, the enthusiasm for liquid protein diets waned. Several current diets (Atkin's plan, South Beach diet) advocate intake of high protein, high fat, and low carbohydrates while allowing unlimited amounts of meat, fish, eggs, and cheese. Lack of carbohydrates induces ketosis, which results in salt and water depletion,

giving the user the appearance of rapid weight loss. With rehydration and resumption of a normal diet, weight gain generally occurs. In addition, salt and water depletion may cause orthostatic hypotension and ureterolithiasis. Atherosclerosis and hypercholesterolemia may occur as a result of substitution of high-calorie, high fat foods for carbohydrates. Despite the rapid weight loss early on with these diets, once carbohydrates are reintroduced, weight gain occurs rapidly and significantly.⁴⁶

Dieter's teas that contain combinations of herbal laxatives, including senna and Cascara sagrada, can produce profound diarrhea, salt and water depletion, and hypokalemia. They are associated with sudden death, presumably as a result of cardiac dysrhythmias. Despite FDA warnings of the dangers of these weight loss regimens, dieter's teas remain available in retail stores that sell nutritional supplements and are easily accessible to adolescents.

Chronic laxative use can result in an atonic colon ("cathartic bowel") and development of tolerance, with the subsequent need to increase dosing to achieve catharsis. Because cathartics do not decrease food absorption, they have limited effects on weight control.¹⁰ Various test methods can be used to detect laxative abuse.⁴⁰ Phenolphthalein can be detected as a pink or red coloration to stool or urine following alkalinization. Colonoscopy reveals the benign, pathognomonic "melanosis coli," the dark staining of the colonic mucosa secondary to anthraquinone laxative abuse. The combination of misuse/abuse of laxatives in conjunction with orlistat has the potential to cause severe diarrhea and subsequent fluid and electrolyte imbalances. Now that orlistat is readily available, there is a greater likelihood of these two xenobiotics being used together.³⁵

Chronic use of syrup of ipecac to induce emesis by patients with eating disorders, such as bulimia nervosa, leads to the development of cardiomyopathy, subsequent dysrhythmias, and death.^{56,128} Emetine, a component of syrup of ipecac, is the alkaloid responsible for the severe myopathy. Chronic administration of syrup of ipecac results in tolerance to the emetic effects and increased systemic absorption of emetine.¹²⁸ Emetine can be detected in serum by high pressure liquid chromatography or thin-layer chromatography. It persists for weeks to months after chronic ingestion. In 2003, an FDA advisory committee recommended that the nonprescription drug status of syrup of ipecac be rescinded because of its use by patients with bulimic disorders.

OTHER HERBAL REMEDIES

Several herbal remedies for weight loss have resulted in serious toxicity. In France, germander (*Teucrium chamaedrys*) supplements taken for weight loss resulted in seven cases of hepatotoxicity.⁹⁹ A "slimming regimen" first prescribed in a weight loss clinic in Belgium produced an epidemic of progressive kidney disease, known as Chinese herb nephropathy, when botanical misidentification led to the substitution of *Stephania tetrandra* with the nephrotoxic plant *Aristolochia fangji*.¹⁶⁵ The toxic constituent, identified as aristolochic acid, has been implicated in numerous cases of kidney failure and urothelial carcinoma.¹⁰⁴ A case of profound digitalis toxicity occurred with a laxative regimen contaminated with *Digitalis lanata*.¹⁵² Contamination of herbal products remains a concern today due to the lack of standardization of manufacturing processes. Until regulation of herbal products is improved and manufacturing practices worldwide are standardized, sporadic reports of herb-related toxicity likely will continue ([Chaps. 28 and 45](#)).

WITHDRAWN XENOBIOTICS

Sympathomimetics

PPA, a sympathomimetic amine ([Fig. 42–2](#)), was available until 2000 as a nonprescription diet aid (eg, Dexatrim, Acutrim). It is both a direct-acting xenobiotic, via stimulation of α -adrenergic receptors, and an indirect-acting xenobiotic, through release of norepinephrine. Both of these actions cause a net increase in blood pressure when given in high doses. PPA-induced anorexia is mediated via α -adrenergic receptors in the hypothalamus.¹⁷² PPA was voluntarily withdrawn after its use was linked to increased risk of hemorrhagic stroke in women.⁸²

Reported toxicity associated with PPA generally results from severe hypertension.¹³⁰ A comprehensive review of more than 100 case reports of adverse drug effects involving PPA revealed 24 intracranial hemorrhages, 8 seizures, and 8 fatalities between 1965 and 1990.^{62,97} Some adverse events occurred following ingestion of diet preparations that contained both PPA and caffeine, which have pharmacokinetic and pharmacodynamic interactions.^{90,98} Cardiac toxicity, although less common, was reported in two young patients who suffered myocardial injury following therapeutic daily dosing in one and acute overdose in the other.¹⁰¹

Ephedrine

Ephedra (*Ephedra sinica*), or Ma-huang, is a plant that contains six sympathomimetic amines, known collectively as ephedra alkaloids. The two primary alkaloids are ephedrine and pseudoephedrine ([Fig. 42–2](#)). Ephedra was popular as a

weight loss dietary supplement until the FDA banned ephedra-containing products in April 2004 because of cases of serious cardiovascular toxicity^{72,176} and acute hepatitis.¹¹⁸ In a review of 140 adverse events reported to MedWatch following use of ephedra, 31% of the cases were considered to be definitely or probably related to the use of ephedra supplements, including four strokes, five cardiac arrests, two myocardial infarctions, and three fatalities.⁷² In 2005, there was concern that the FDA ban would be overturned and ephedra would once again be available. But, in 2006, the US Court of Appeals upheld the FDA's final rule to ban ephedra. Despite this ban, ephedra still can be obtained from practitioners of complementary medicine as a traditional Chinese herbal medicine for short-term treatment of wheezing and nasal congestion associated with asthma, allergies, and colds. Synthetic ephedrine is still available, behind the pharmacy counter, as a nonprescription medication (eg, Primatene tablets) for asthma.

Serotonergics

Sibutramine blocks the reuptake of both serotonin and norepinephrine, but it does not promote neuronal release of serotonin. Its clinical effects include reduced appetite and increased satiety. Its effectiveness in producing weight loss was demonstrated in several randomized, double-blind studies.^{37,42,100,105} It also decreased binge-eating when compared to placebo.¹⁷³

Shortly after approval, reports of serious adverse events, including cardiovascular toxicity, emerged. Sibutramine use was associated with psychosis,^{14,103,157} hypertension, cardiac ischemia, dysrhythmias,¹³² and death.¹³² The increased risk of nonfatal myocardial infarction and nonfatal stroke in patients led to the withdrawal of sibutramine from the US market in the fall of 2010.⁸²

The serotonergics dexfenfluramine (Redux) and fenfluramine (Pondimin), used in the treatment of obesity, were withdrawn because of postmarketing reports of serious cardiac effects associated with their therapeutic use.^{18,21,34,44,171} The diet drug combination known as Fen-Phen (fenfluramine and phentermine {an amphetamine derivative}) was popular in the 1990s because of the presumed improved side-effect profile and efficacy achieved with lower doses of each drug. This drug combination was never approved by the FDA for treatment of obesity. Because of an unusual and serious cardiac valvulopathy in women taking Fen-Phen, fenfluramine was withdrawn from the market in 1997.³⁴ All of the women presented with new heart murmurs and either right- or left-sided valvular abnormalities. Eight of the 24 women also developed pulmonary hypertension. Several required cardiac surgery and were found to have plaque-like encasement of the leaflets and chordae, with preservation of valvular structure. These pathologic findings are identical to those described in patients with ergotamine-induced valvular disease and in those with carcinoid valvulopathy. Although subsequent studies confirmed this association, the reported magnitude of risk associated with these drugs has varied.^{85,88,171} Regression of these valvular lesions with cessation of the drugs is reported,²² and limited evidence indicates that the valvular effects are milder than initially described.⁶¹

Primary pulmonary hypertension has been described in association with fenfluramine and dexfenfluramine since 1981.^{8,21,44,111,138} Primary pulmonary hypertension in association with another anorectic, aminorex fumarate, was previously reported in Europe.⁶⁶ In one multicenter case control study of patients with primary pulmonary hypertension, use of anorectics such as dexfenfluramine and fenfluramine for more than 3 months was associated with a 30-fold increased risk of primary pulmonary hypertension in these patients compared with nonusers.¹ Several theories are proposed to explain the mechanism of pulmonary toxicity of these anorectics,²¹ namely, serotonin-mediated constriction of pulmonary arteries,¹¹⁰ serotonin-mediated platelet aggregation, and vasoconstriction in the lungs leading to microembolization, elevated pulmonary vascular resistance, and pulmonary hypertension.¹¹¹

Guar Gum

Guar gum is derived from the bean of the *Cyamopsis psorabides* plant and is a hygroscopic polysaccharide that expands 10- to 20-fold in the stomach, forming a gelatinous mass. The purpose of ingesting guar was to cause gastric distension and create the sensation of satiety, thereby decreasing appetite and food intake. Unfortunately, the use of guar gum resulted in numerous cases of esophageal and small bowel obstruction in patients with both preexisting anatomical lesions such as strictures and in individuals with normal gastrointestinal anatomy. It was withdrawn from the market in 1992.¹⁰²

BARIATRIC SURGERY

Although not a specific toxicologic concern, it is imperative to mention surgical interventions for management of obesity. Surgical interventions to manage obesity have increased in frequency over the past years and may provide a long-term solution for obesity. Roux-en-Y gastric bypass, laparoscopic adjustable banding, and biliary-pancreatic diversion with duodenal switch are the most commonly described techniques.^{2,20,43} The health of these patients is of particular concern because absorption of vitamins, minerals, and drugs is altered.^{91,114,133,144,166} Pharmacokinetics of orally administered

medications may also be altered.^{133,144} Consideration of drug properties should be examined closely prior to initiation in this patient population.⁹¹

SUMMARY

- Obesity is a major health concern and a significant cause of preventable diseases and sequelae. Unproven weight loss modalities are associated with treatment failure and the potential for significant adverse events.
- Some common themes exist; combination drug therapy likely provides the best weight loss; and toxicity from proven and unproven treatments remains a significant concern.
- A balanced weight loss plan that encompasses decreased caloric intake with increased energy expenditure through exercise should be encouraged.
- Clinicians should be aware of the lack of regulation of most available diet remedies and should report adverse events involving these products to poison control centers and to the FDA MedWatch system so that appropriate regulatory actions can be taken to prevent further instances of toxicity.
- A historical review of compounds used as weight loss agents readily uncovers numerous examples of poorly conceived drug regimens, popular misunderstanding of the benefits and risk of the drugs involved, and relatively poor postmarketing surveillance leading to unnecessary morbidity and mortality.

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43 ESSENTIAL OILS

Lauren Kornreich Shawn

INTRODUCTION

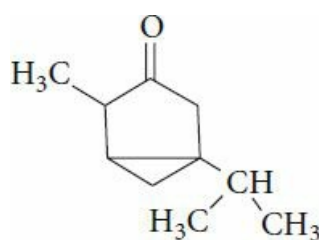
Essential oils are a class of volatile oils that are extracted through steam distillation or are cold pressed from the leaves, flowers, bark, wood, fruit, or peel of a single parent plant. The term essential refers to the essence of a plant, rather than an indispensable component of the oil or a vital biologic function. These organic compounds are a mixture of complex hydrocarbons that give the oil its aroma, therapeutic properties, and occasionally cause toxicity. More than 500 essential oils exist and can be categorized into five chemical groups: terpenes, quinines, substituted benzenes, aromatic/aliphatic esters, and phenols and aromatic/aliphatic alcohols.

HISTORY AND EPIDEMIOLOGY

The potential for toxicity arises from several aspects of oil production, use, and regulation. These oils are not under the US Food and Drug Administration (FDA) regulation; therefore, they may not contain the specific ingredient intended for use or may contain excessive amounts of the active ingredient, other chemicals, or various adulterants. Furthermore, there is no standardized nomenclature for many of these herbs or for the exact chemical composition of specific oil. Even with the strictest production guidelines, oils can vary by the environment the plant was grown in and by part of the plant primarily used in production. Sometimes these differences are utilized to confer a particular property to the oil in terms of aroma or believed therapeutic benefit.

Therapeutic use of essential oils can be traced back thousands of years in history to the ancient Greeks and ancient Egyptians, and it is also described in biblical writings. The first documents detailing an actual distillation process date back to the ninth century, when such oils were imported into Europe from the Middle East.¹⁵⁸ By the 16th century, concepts of separating fatty oils and essential oils from aromatic water became more defined, and oils were used frequently for fragrance, flavoring, and medicinal purposes. By the 19th century, these processes became industrialized, and specific chemicals could be identified and mass produced. Essential oils fell out of favor in the early 20th century, as new medications and a desire for modernization developed. However, in the past 30 years, resurgence in interest and use of essential oils developed as many people deemed natural products to be safer and more environmentally friendly. This chapter highlights some of the most commonly used oils for medicinal purposes that also have the greatest potential for toxicity.

Absinthe



Thujone

History. *Artemisia absinthium* is more commonly known as wormwood because of its use as an anthelmintic in ancient times. It is a member of the Compositae family, which also includes ragweed, chrysanthemums, marigolds, and daisies.¹³⁹ Absinthe is a liqueur composed of ethanol, oil of wormwood, and various other herbs, and it is known for its green color and bitter taste. It became a favorite among the artists and poets of Paris during the city's Belle Époque in the 19th century. Bohemian society enjoyed the drink by pouring water on top of a sugar cube that was suspended over a glass of absinthe. The addition of sugar water not only made the drink more palatable but also enhanced the herbal aroma and green coloration, which was referred to as the "louche effect."¹⁰¹ This ritual was commonly performed in the early evening and

thus the “green hour” was akin to a Parisian “happy hour.”¹⁰

The earliest recorded use of wormwood is found in the Ebers papyrus, which covers writing from 3550 to 1550 B.C. in Egypt.¹⁰ During the first century A.D., Pliny described wormwood’s anthelmintic properties in *Historia Naturalis*. Dioscorides’ *De Materia Medica*, which was considered an authoritative medical text through the Middle Ages, described wormwood’s ability not only to treat intestinal worms but to repel fleas and other pests with topical application.¹⁰ For millennia, wine was commonly fortified with wormwood, and the formulation is still known today, albeit in much more dilute concentrations, as vermouth (derived from the German word for wormwood, Wermut).¹¹⁷

Absinthe was first distilled in Switzerland but came to prominence during the early 19th century, with Pernod’s distillery in France.¹⁰¹ During the French-Algerian wars of the 19th century, absinthe was used medicinally by the French troops to ward off infection and prevent dysentery.¹⁰⁰ Subsequently, the returning troops introduced the drink to French society. As early as 1850, descriptions of toxicity were documented. By the 1910s, many countries had made it illegal. In the 20th century, thujone was discovered to be the toxic component of absinthe. Absinthe is still available as Pernod, a formulation that is free of thujone. However, thujone-containing absinthe, as well as recipes for making it at home, can be obtained over the Internet.

Pharmacology. The bitter taste and anthelmintic properties come from the lactones absinthin and anabsinthin.¹³⁹ However, the toxicity of wormwood is due to its thujone content. Thujone is a monoterpene ketone, which exists in α - and β -diastereoisomeric forms. Oil of wormwood may contain up to 70% thujone (α - and β -thujone).¹³⁹ The amount of the β isomer often exceeds that of α -thujone but is less toxic.⁸¹ After oral absorption, both isomers undergo species specific hydroxylation reactions by the cytochrome (CYP) P450 system and are subsequently glucuronidated and renally eliminated.⁸⁰ α -Thujone is metabolized primarily to 7-hydroxy α -thujone by CYP3A4 in humans, but there are at least six other metabolites, some of which are more prominent in other animal models.⁸⁰ The 7-hydroxy metabolite achieves a higher concentration in the brain, but it is less potent in binding the GABA_A receptor and is less toxic compared to its parent compound.⁸¹

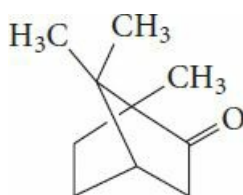
Pathophysiology. α -Thujone is generally accepted to be the more toxic of the two isomers and is a noncompetitive GABA_A receptor antagonist, similar to picrotoxin.⁸¹ This antagonism causes neuroexcitation, which may result as hallucinations or seizures in a dose-dependent fashion. Ethanol enhances GABA activity and may have a protective effect by reducing seizures in mice.⁸¹ In the 1970s, it was speculated that thujone mediated the psychotropic effects of absinthe via cannabinoid receptors. However, further research demonstrated that despite low affinity for the CB1 and CB2 receptors, thujone failed to evoke any chemical signaling from that binding.¹¹² Currently, research suggests that the psychotropic effects may be mediated by α -thujone’s ability to desensitize the 5-HT₃ receptor.⁴⁵

Thujones induce the synthesis of 5-aminolevulinic acid synthetase, leading to increased porphyrin production.¹⁸ Individuals with defects in heme synthesis may develop porphyrialike symptoms upon ingestion of thujones. Some have speculated that Vincent Van Gogh suffered from porphyria secondary to ingestion of absinthe and other volatile oils.

Clinical Features. Clinical features of acute toxicity are similar to those of ethanol intoxication, including euphoria and confusion, which may progress to restlessness, visual hallucinations, and delirium. Seizures have also occurred. Studies in 19th-century France revealed that the oil of wormwood component in absinthe, rather than the ethanol or other aromatic herbs, was responsible for auditory and visual hallucinations and seizures in humans and dogs.^{4,12} Absinthism was recognized as a distinct disease from alcoholism as early as 1850s. It was characterized by delirium, hallucinations, tremors, and seizures. Although thujone is the purported xenobiotic in the development of these symptoms, the patients also drank excessive amounts of ethanol, so differentiating this syndrome from chronic sequelae of alcoholism is difficult.⁴

Rhabdomyolysis and acute kidney injury (AKI) have occurred following ingestion of oil of wormwood intended for preparation as absinthe.¹⁵⁹ The etiology of the rhabdomyolysis has not been elucidated.

Camphor



History. Originally derived from the bark of the camphor tree (*Cinnamomum camphora*), camphor has been widely used for centuries. It was described in writings from Marco Polo’s visits to China, and in the 16th century it was referred to as the “balsam of disease.”¹¹ Camphor has been used as an abortifacient, a contraceptive, a cold remedy, an aphrodisiac, an antiaphrodisiac, a lactation suppressor, and an antiseptic.^{9,69} In the late 19th and early 20th centuries, it was also regarded

as a cardiac stimulant and used extensively to treat congestive heart failure and cardiovascular compromise during influenza outbreaks.^{49,64,67,107,110} By the 1920s, studies demonstrated that camphor was not an effective cardiovascular stimulant, and its use began to fall out of favor.¹¹⁰ In the 20th century, camphor was predominantly used as a topical rubefacient to provide local analgesia and antipruritic effects. It also became a key ingredient in paregoric (camphorated tincture of opium), a common household remedy for diarrhea and cough used until 1970. Throughout the 20th century, camphor was also available as a nonprescription remedy in the forms of camphorated oil, which was 20% camphor in cottonseed oil, and spirits of camphor, which was 10% camphor in alcohol. Consequential toxicity occurred in cases where camphorated oil was mistaken for castor oil and ingested in large amounts.^{12,32,152} In 1982, the FDA limited any product from containing more than 11% camphor as well as placed an outright ban on camphorated oil after numerous reports of significant morbidity and mortality. Today camphor can be found in topical products such as Vick's Vapo-Rub and Tiger Balm. It was also used extensively as a moth repellent. Despite restrictions on its sale by the FDA, concentrated camphor products are still found in the United States. They are illegally sold in various immigrant communities for use as pesticides and medicinal remedies.⁹²

Pharmacology. Camphor is a bicyclic monoterpene ketone that is rapidly absorbed from the gastrointestinal (GI) tract. Serum concentrations can be detected within 15 minutes of ingestion.^{121,125} It is also readily absorbed from the skin and mucous membranes.⁹² It also has been documented to cross the placenta and blood–brain barrier.¹²⁵ A detectable concentration was found in amniotic fluid 20 hours after maternal ingestion.¹²⁵ Camphor is very lipophilic with a large volume of distribution. It is metabolized in the liver by CYP2A6 to 5-exo-hydroxycamphor, but other studies using animal models have cited 5-endo-hydroxycamphor and 3-hydroxycamphor as significant metabolites.^{71,128,152} These metabolites then undergo glucuronidation and are excreted in the urine.¹²⁸

Pathophysiology. The mechanism for seizure activity is still unknown. Camphor desensitizes the transient receptor potential vanilloid subtype 1 (TRPV1) channel, a nonspecific cation channel that mediates thermosensation and nociception in the peripheral nervous system (Fig. 43–1).¹⁶⁴ Similar to other topical analgesics with effects on these channels, it is postulated that desensitization mediates the analgesic and cooling effect of topical camphor products. There are TRPV1 receptors found in the central nervous system (CNS), but it is unknown whether they are implicated in the CNS effect of camphor toxicity. Autopsies of case reports and animal studies have shown neuronal necrosis and degeneration on pathology, but the mechanism of action remains elusive.¹⁴¹

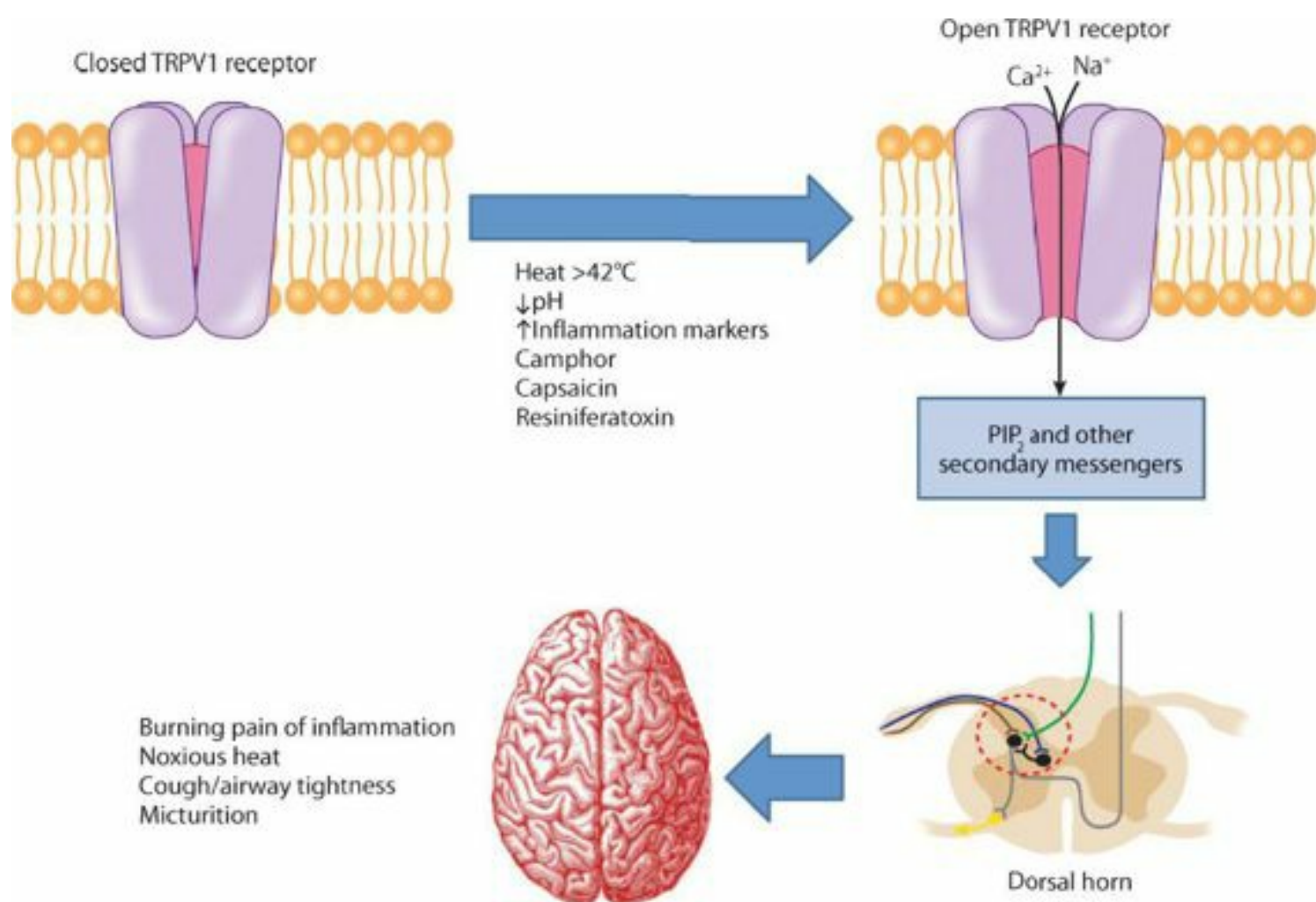


FIGURE 43–1. The transient receptor potential vanilloid subtype 1 (TRPV1) receptor is a nonspecific cation channel that

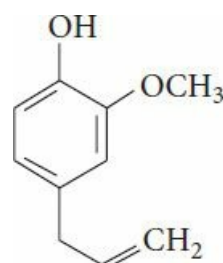
is located on the skin and bladder, in the peripheral nociceptors and the dorsal horn of the spinal cord, and in the airway. Stimulation by heat, acidemia, and inflammation increases its activity, whereas camphor, capsaicin, and resiniferatoxin are direct agonists. Once open, TRPV1 stimulates intracellular signaling via PIP_2 to relay sensation of burning pain, noxious heat, airway tightness, and micturition.

Hepatotoxicity is also reported and can range from a mild elevation in aminotransferase concentrations to fulminant hepatic failure. Children seem to be more susceptible to hepatotoxicity since they have relatively immature liver enzymes and glucuronidation systems. The hepatotoxicity may present similarly to Reye syndrome but does not have the same characteristic findings on biopsy.⁸⁷

Clinical Features. Camphor toxicity is reported after nasal, topical, inhalational, and oral administration.^{32,88,121,137,147,155} Toxicity has developed within 5 to 90 minutes after ingestion.¹² Case reports of delayed onset of symptoms are complicated by unknown time of ingestion or concomitant illness.¹⁰⁹ In a retrospective review of 182 cases, no patient developed symptoms more than 6 hours after ingestion.⁶⁹ The ingestion of 2 g has caused significant toxicity in adults and as little as 0.7 to 1 g of 20% camphorated oil (1 teaspoon) has been fatal in children.^{32,141} Other reports describe children having seizures but surviving after ingesting 0.5 to 6 g of camphor.¹³⁴

Generally, the first symptoms are related to GI irritation and include nausea and vomiting, although patients who were exposed via topical or inhalational administration rarely suffer from GI symptoms. Patients have complained of feeling warm, faint, and vertiginous as well as headaches.⁸⁸ Severe symptoms include confusion, agitation, delirium, and hallucinations.^{20,29,49,147} Seizures are common and usually develop within minutes to a few hours of exposure.¹³⁴ Status epilepticus is reported.^{39,92}

Clove Oil



Eugenol

History. Clove oil is extracted from the plant *Syzygium aromaticum*, also known as *Eugenia aromatica*. This evergreen plant is native to the Maluku islands of Indonesia (traditionally known as the Spice Islands). Its dried, unopened buds are known as cloves, a descriptive name derived from the Latin word *clavus*, meaning nail. During the Chinese Han dynasty, subjects were required to chew cloves in order to mask bad breath when appearing before the emperor. In medieval and Renaissance Europe, cloves were considered to be a valuable commodity. They were used for flavoring and fragrance, as well as for medicinal purposes, and that tradition remains intact today. The first recorded medicinal use of cloves in Western society can be found in *The Practice of Physic*, which was written in French in the 1640s and translated into English in 1687.³⁷ Clove oil is commonly mixed with zinc oxide as a sealant in dentistry, a practice that has been described as far back as 1873.⁸³ Clove oil is still used to alleviate toothaches, and one study found it just as effective as topical benzocaine for analgesia.³

Pharmacology. Typically, clove oil contains 60% to 90% eugenol, which is the primary active component. Eugenol undergoes sulfonation and glucuronidation in the liver, with a minor pathway involving the CYP450 system to form a reactive intermediate that requires glutathione for proper elimination.¹⁴⁹

Pathophysiology. The anesthetic properties of eugenol are mediated by blockade of various ion currents in nerves. This was initially demonstrated by the ability to block conduction of action potentials in frog sciatic nerves.⁹⁷ Given the structural similarity to capsaicin, studies sought to determine if the effects were mediated by a common mechanism. Studies of rat dorsal root ganglion cells suggest that eugenol acts in both a capsaicin receptor mediated pathway and by an independent pathway.¹¹⁵ Capsaicin requires the TRPV1 receptor to inhibit voltage-gated calcium channels in order to desensitize peripheral nociceptors, but eugenol does not (Fig. 43–1).^{103,114} Eugenol also inhibits voltage-gated sodium channels independently of TRPV1, and this likely mediates its anesthetic effects.¹¹⁸ Eugenol similarly can block voltage-gated potassium channels in neurons, which suggests a possible mechanism for the irritating effects of eugenol as potassium efflux is required to terminate action potentials and neurotransmitter release.¹⁰⁵

Studies with rat hepatocytes demonstrated that eugenol can cause glutathione depletion and subsequent hepatotoxicity in

a dose- and time-dependent manner. The loss of glutathione occurred prior to the onset of cell death in these studies.¹⁵⁰ Furthermore, N-acetylcysteine (NAC) was able to prevent glutathione depletion and cell death.

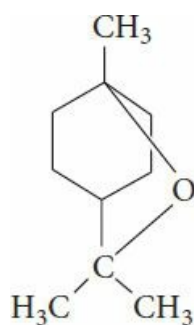
Eugenol inhibits prostaglandin synthetase, which may support its claims as an antiinflammatory agent in dentistry.⁸³

Clinical Features. There are several reports of allergic reactions and local irritation when eugenol zinc oxide was used for dental procedures.^{14,98,132} There are fewer case reports of systemic toxicity from other forms of exposure. However, in case reports of infants and children ingesting clove oil, depressed mental status, anion gap metabolic acidosis, and hepatotoxicity complicated by coagulopathy and hypoglycemia is reported.^{22,56,75,86,102}

A single case report described a 24 year-old woman who developed permanent infraorbital anesthesia and anhidrosis after spilling a small amount of clove oil on her face in an attempt to relieve a toothache.⁸⁴

Acute respiratory distress syndrome is reported with intravenous administration of clove oil. Similar findings of perivascular, interstitial, and alveolar edema are found in animal studies. The proposed mechanism is oxidant mediated, but this has not been verified.^{93,162}

Eucalyptus Oil



Eucalyptol

History. Oil of eucalyptus is derived primarily from *Eucalyptus globulus*, a tree native to Australia. Eighteenth-century British explorers noted that the aboriginal people traditionally used eucalyptus as a fever remedy, so they brought it to England for further examination. The introduction of eucalyptus oil to the West led to an increased demand, because it was increasingly used to treat the symptoms of the common cold and influenza. The oil was believed to be so effective that there were public campaigns to grow the trees in areas of Europe stricken with malaria and other infectious diseases. Great effort was made to determine how best to cultivate these plants in the colder, damper European environment.^{6,126} In the 19th and early 20th centuries, eucalyptus oil was a common household remedy for coughs and fevers, and it was also used as an antiseptic.³⁶ It was even reported as effective in treating hemorrhage, burns, and diabetes.^{7,140,151}

Pharmacology. Eucalyptus oil contains almost 70% eucalyptol, a monoterpene cyclic ether also known as 1,8-cineole. It is rapidly absorbed from the GI tract and metabolized by the 3A family of CYP enzymes, particularly 3A4 and 3A5.⁵⁰ In rats, the main urinary metabolites are 2-hydroxycineole, 3-hydroxycineole, and 1,8-dihydroxycineol-9-oic acids.^{50,108} In humans, only the 2-hydroxy and 3-hydroxy metabolites are found.⁵⁰

Pathophysiology. The effect of eucalyptus on upper respiratory symptoms may be due to a myorelaxant effect as potassium-induced contractions of airway smooth muscle are inhibited.¹⁰⁶ However, it also potentiates acetylcholine-induced contractions of the trachea in vitro, possibly by inhibiting acetylcholinesterase.¹⁰⁶ Some authors have hypothesized that this mediates the upper respiratory irritation that commonly plagues workers who process eucalyptus trees for papers and other materials. Eucalyptol inhibits monocytes from producing several cytokines, particularly tumor necrosis factor (TNF)- α and interleukin (IL)-1 β , from being produced.⁹⁰ It also suppresses arachidonic acid metabolism. Some hypothesize that this makes eucalyptol effective at controlling mucous hypersecretion and a potential adjunct in controlling asthma and chronic obstructive pulmonary disease, for which it is commonly used as an alternative medicine.^{89,90,161}

The mechanism of toxicity has yet to be elucidated. Some research suggests that eucalyptol may affect the autonomic nervous system.⁵⁷ Animal studies have proven to be difficult to interpret as mice seem relative insensitive to the oil and other animals require extremely high amounts to achieve toxic effect.⁴³ Significant morbidity and mortality are rare.

Clinical Features. Typical symptoms include drowsiness, slurred speech, ataxia, nausea, and vomiting.^{58,143} Rarely, seizures and coma can occur.⁷⁰ Symptom onset is usually within minutes to hours and rarely exceeds 4 hours. In children, significant toxicity has been reported after ingesting as little as a teaspoon. Fatalities have been reported in adults who have ingested as little as 4 mL, but a patient survived a 120- to 200-mL ingestion after receiving mannitol infusions and dialysis.^{58,70} Inhalational and dermal exposures seem to have minimal toxicity as long as the patient is promptly removed or

decontaminated from the exposure.¹⁴³

Lavender

History. Lavender is one of the most commonly used essential oils for fragrance and aromatherapy.²⁸ It was used by the ancient Romans and Greeks for its believed antimicrobial, carminative, sedative, and antidepressive properties. The oil is produced by steam distillation of the flower heads and foliage of the *Lavandula* species. However, the chemical composition and fragrance of the oil is determined by the proportion of flowers distilled within a particular batch.

There are four commonly used lavenders: *Lavandula latifolia*, a Mediterranean variety; *Lavandula angustifolia*, commonly known as English lavender (or *L. officinalis*); *Lavandula stoechas*, commonly known as French lavender; and *Lavandula x intermedia*, which is a sterile cross between *L. latifolia* and *L. angustifolia*.²⁸ The lavenders generally have the same major chemical constituents in their oils and ethnobotanical history, but some species have specific therapeutic benefits ascribed to them. For example, *L. stoechas* was traditionally used as a headache remedy, *L. latifolia* as an abortifacient, and *L. angustifolia* as a diuretic.²⁸ However, many of these effects, regardless of species used, have never been substantiated in the medical and scientific literature. Lavender oil is most commonly used in aromatherapy to enhance mood, decrease anxiety, or control pain. Most studies demonstrating improved pain control, decreased anxiety, or improved mood were small studies or poorly controlled.

Pharmacology. The main components of lavender oil contains linalool, linalyl acetate, 1,8-cineole, β -ocimene, terpinen-4-ol, and camphor.²⁸ The proportion of each within a given batch of oil may depend on the plant used and type of distillation. Plants with smaller camphor components, such as *L. angustifolia*, are used more for fragrance and cosmetic purposes because their aroma is considered to be more pleasant. Plants with higher camphor content have been traditionally used for insect repellent and antimicrobial uses.

Linalool and linalyl acetate are the components believed to be responsible for the neuropsychiatric effects of lavender oil, specifically sedative and narcotic effects. These compounds are rapidly absorbed through the skin and can reach peak serum concentrations as soon as 19 minutes postexposure.^{28,85} Linalool inhibits both nicotinic receptor-mediated acetylcholine release and glutamate release.^{122,135}

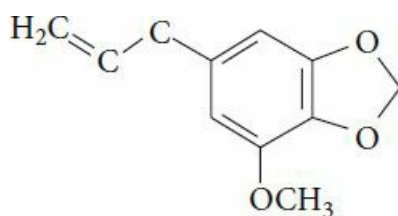
L. angustifolia has activity against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis* as well as other bacteria.¹⁶³ Its potential as an antimicrobial and preservative in cosmetics is demonstrated.⁹⁹

Pathophysiology. Lavender oil is very allergenic. Linalool is not electrophilic or chemically reactive, suggesting it would not be a contact allergen.⁷² Linalyl acetate has an electrophilic center and is a weak allergen in studies.¹³⁸ However, both of these compounds immediately oxidize when exposed to air, generating hydroperoxides, which are strong allergens. This oxidation occurs regardless of whether pure linalool, linalyl acetate, or lavender oil is used.^{72,138}

A case series reported the development of gynecomastia in three prepubertal boys using lavender oil.⁷⁸ All three children had extensive endocrine evaluations, with no abnormalities detected, and in each case the gynecomastia resolved when lavender oil was discontinued. In vitro data showed that lavender oil elicits a dose-dependent increase in estrogen responsivity and antiandrogenic activity in breast cancer cell cultures, similar to the effects of estradiol.⁷⁸

Clinical Features. The predominant clinical feature of exposure is contact dermatitis. Unexplained or “idiopathic” gynecomastia in prepubertal boys with negative endocrine evaluations should prompt questions regarding the use of these essential oils.

Nutmeg



Myristicin

History. Nutmeg and mace originate from the evergreen tree *Myristica fragrans*, which is native to the Maluku islands of Indonesia (Spice Islands) and was imported to Europe as early as the mid-12th century.^{59,136} However, today, nutmeg is more commonly imported to the United States from Malaysia, Grenada, Trinidad and other parts of the Caribbean.¹³⁶ The name nutmeg refers to the seed of the tree, which looks like a glossy brown nut. Mace is derived from the scarlet-colored aril that encloses the seed.

Although nutmeg is a common household spice and flavoring agent, it has been used for centuries for various ailments, including digestive disorders, cholera, rheumatic disease, psychiatric disorders, and pain.⁵⁹ Mace has been used as an aphrodisiac, but nutmeg has been commonly used in Europe and North America, albeit ineffectually, as an emmenagogue and abortifacient.¹²³ Indeed, most of the cases of nutmeg poisoning in the early 20th century were due to women attempting to terminate pregnancies or induce menses.⁶⁸ However, most cases of toxicity today are due to people using nutmeg as a natural high.^{1,27,120,131} The first reported case of nutmeg poisoning is attributed to Lobel, who described delirium in a pregnant woman who ingested 10 or 12 nutmeg seeds in 1576.²⁷ In 1832, the famous scientist Purkinje demonstrated the toxicity of nutmeg by ingesting seeds, causing delirium and then stupor.⁶⁸

Pharmacology. The nutmeg seed yields 7% to 16% volatile oil, 4% to 8% of which is myristicin.⁷³ Myristicin is believed to be the psychoactive component of the oil, but some studies have brought that into question. It was initially hypothesized that myristicin was metabolized to the amphetamine derivative 3,4-methylenedioxy-5-methoxyamphetamine (MMDA) by the addition of ammonia to the allyl side chain. Elemicin, another main ingredient of the volatile oil, would be metabolized to 3,4,5-trimethoxyamphetamine (TMA).¹³³ This was further supported by detection of MMDA by thin layer chromatography of rat liver incubated with myristicin.²⁰ However, in vivo studies could neither replicate these results nor find evidence of the amphetamine derivatives. Gas chromatography of urine from rats and humans exposed to nutmeg, pure myristicin, or elemicin did not detect MMDA, TMA, or evidence of the original compounds.¹⁷ However, other metabolites were found, suggesting extensive liver metabolism. It was later determined that CYP3A4 and CYP1A2 were primarily involved in the formation of myristicin's main metabolite, 5-allyl-1-methoxy-2,3-dihydroxybenzene.¹⁶⁶

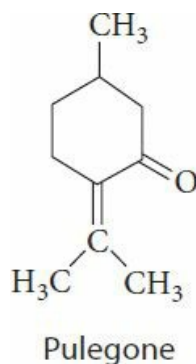
Pathophysiology. Studies in mice suggested that nutmeg and fresh myristicin are monoamine oxidase inhibitors but that excessive doses could reverse that effect,¹⁵⁴ and nutmeg was shown to be not as potent as known monoamine oxidase inhibitors on the market at the time. In the 1960s, nutmeg was studied as a possible antidepressant in five patients with mixed results, but a formal trial of nutmeg as a psychiatric medication was never conducted.¹⁵⁴

Animal data show that nutmeg can induce tachycardia and increase the speed of conduction through the atrioventricular node in the acute setting, but chronic exposure caused bradycardia.¹³⁰ The exact mechanism for this is unknown.

Cats appear to be exquisitely sensitive to nutmeg and develop not only acute mental status changes with nutmeg exposure but liver damage leading to hepatic encephalopathy.¹⁵³ This has not been reported in humans.

Clinical Features. Tachycardia, nausea, and dry mouth are common in acute exposures. Some patients develop GI distress and vomiting. CNS symptoms can range from giddiness to a sense of detachment or impending doom to hallucinations and delusions.^{1,8,38,68,120} Nutmeg ingestion rarely causes significant morbidity or mortality. Only two deaths have been reported. In 1887, an 8 year-old boy became comatose after ingesting two nutmegs and died the next day; however, he also received a wide variety of analeptics that may have been more harmful than the initial exposure.²⁷ The other case involved a detectable serum myristicin concentration on autopsy of a 55 year-old woman who had a toxic serum concentration of flunitrazepam and whose stomach contents smelled strongly of nutmeg.¹⁴⁴ It is unclear if the nutmeg contributed to her death.

Pennyroyal



History. Oil of pennyroyal is derived from the plant *Mentha pulegium* from the Labiatae family. It has a mintlike odor and is still used as a flavoring and fragrance agent in foods and cosmetics. Its initial use was as a flea repellant. Pulegium is derived from the word *pulex*, which is Latin for flea.⁶⁶ Pennyroyal has been used for centuries as an emmenagogue and abortifacient, and most reported toxicity has resulted from women ingesting large quantities to induce these effects. Dioscorides listed pennyroyal as an abortifacient in his *Da Materia Medica*, and the Greek playwright Aristophanes made frequent reference to it in his plays.¹²⁴ Women still use pennyroyal for these purposes today.

Pharmacology. The primary active ingredient in pennyroyal is pulegone, a monoterpene. In particular, R(+)-pulegone is the active isomer.⁶⁵ Pulegone is metabolized by the CYP450 system into several metabolites, including menthofuran, which

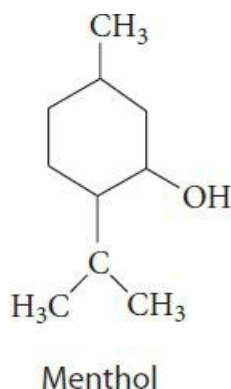
is thought to be the metabolite primarily responsible for hepatotoxicity, although other reactive intermediates are also implicated.^{66,148}

Pathophysiology. In animal studies, pennyroyal causes centrilobular hepatic necrosis.⁶⁵ In a rat model, pulegone depletes glutathione in hepatocytes and in the plasma. Furthermore, hepatotoxicity is significantly increased in glutathione-depleted animals. However, another unknown reactive metabolite has been implicated because blocking the CYP450 system prevents glutathione depletion. Menthofuran had a minimal effect on glutathione concentrations in the plasma and liver, and its ability to cause hepatotoxicity was not affected by glutathione depletion, suggesting a role on another reactive metabolite.¹⁴⁸ R(+)-pulegone also causes necrosis in lung epithelium, but the mechanism remains unknown.⁶⁵

Recently, R(+)-pulegone has been shown to decrease inward current from L type calcium channels as well as block the inward rectifying potassium channels on the rat myocardium.⁴²

Clinical Features. Common initial signs and symptoms are nausea, abdominal pain, and vomiting, often occurring within a few hours of exposure.⁵ CNS toxicity, including seizures and coma, can develop in severe cases.^{19,51} Ingestion of as little as 5 mL has been implicated in severe CNS toxicity. However, in most cases, ingestion of 10 mL is primarily associated with GI symptoms and mild CNS symptoms such as dizziness and lethargy. Fatal cases involving liver failure, kidney failure, and disseminated intravascular coagulation have occurred with ingestion of 15 mL, but these often involve large amounts or multiple doses over a short period of time.^{2,146,156} In reported cases, patients either ingested a tea brewed from the leaves of *M. pulegium*, a tablet containing the herb, oil of pennyroyal, or essence of pennyroyal, which is an alcoholic preparation.^{19,31,51,63} Most cases of severe toxicity involved women ingesting large amounts of the herb in order to induce an abortion; however, two cases involved confusing the leaves of *M. pulegium* for nontoxic mint leaves to make tea.¹³

Peppermint Oil (Menthol)



History. Menthol or peppermint oil is one of the most commonly used flavoring agents in the world. It is derived from the distillation of leaves of the *Mentha piperita* herb, which is native to Europe and parts of Asia but easily grows in North America as well.¹¹¹ Before World War II, menthol was primarily exported from China and Japan, but as those trade routes became disrupted during and after the war, Brazil became the predominate exporter.⁵² Peppermint flavor is common in oral care products, candies, cosmetics, pharmaceuticals, and beverages. Pure crystalline menthol was extracted from plants and introduced as a medicine in the 19th century. In the late 19th century, its use in upper respiratory illness was described, but the author cautioned that more information was needed to “become familiar with its actions and know its limitations.”⁵³ However, menthol is still used today for many remedies with little supporting data. It is sold as an herbal remedy for pruritus, GI disorders such as irritable bowel syndrome, cough and cold symptoms, as well as a topical analgesic.¹⁶⁵ Pure distilled peppermint oil is more expensive and primarily produced by the United States for toothpaste and other dental care products. Corn mint oil, also known for its minty scent and flavor, is derived from *Mentha arvensis* and can contain 70% to 80% menthol. However, menthol derived from this plant has a more herbaceous flavor and is less commonly used commercially.⁵²

Pharmacology. There are four pairs of optical isomers that exist for menthol given its three asymmetric carbons on the central ring of the structure. However, only the –/– menthol form is found in nature and is the most potent.⁵² Peppermint oil typically contains 30% to 55% menthol.⁷⁶

Menthol is very lipid soluble and easily absorbed through the skin. Menthol is rapidly metabolized by the CYP450 system to primarily to p-menthane-3,8 diol and then glucuronidated and eliminated in the urine.⁵² Menthol is a moderate inhibitor of CYP3A4, but its effects on the metabolism of other drugs such as the dihydropyridine calcium channel blockers are not clear.⁴⁸ In human pharmacokinetic studies, only glucuronidated menthol is detected in urine in ranges of 45% to 46% of the menthol ingested.⁶¹ The plasma half-life of menthol glucuronide was determined to be 56.2 minutes and 42.6 minutes, respectively, when mint teas and candies were used.⁶¹

Pathophysiology. In the late 19th century, Goldscheider hypothesized that the cooling effects of menthol involved stimulation of a thermoreceptor. Two independent studies demonstrated the transient receptor potential cation channel subfamily M member 8 (TRPM8) is activated by both menthol and thermal stimuli in the cool to cold range of 46° to 82°F (8°–28°C) (Fig. 43–2).¹¹⁹ TRPM8 is a member of the transient receptor potential family of excitatory ion channels (the same receptor family as TRPV1).¹⁵ Menthol and cold stimuli increase intracellular calcium, which leads to depolarization and generation of an action potential. Currently, there are six known transient receptors that perceive temperatures ranging from noxious heat to noxious cold, depending on the type or combination of receptors activated (Fig. 43–2).^{119,157} These receptors are primarily expressed by small-diameter sensory neurons of the dorsal root ganglion and trigeminal nerves.¹⁵ Some data suggest that menthol’s analgesic properties are mediated by its effects on sodium channels.⁶⁰

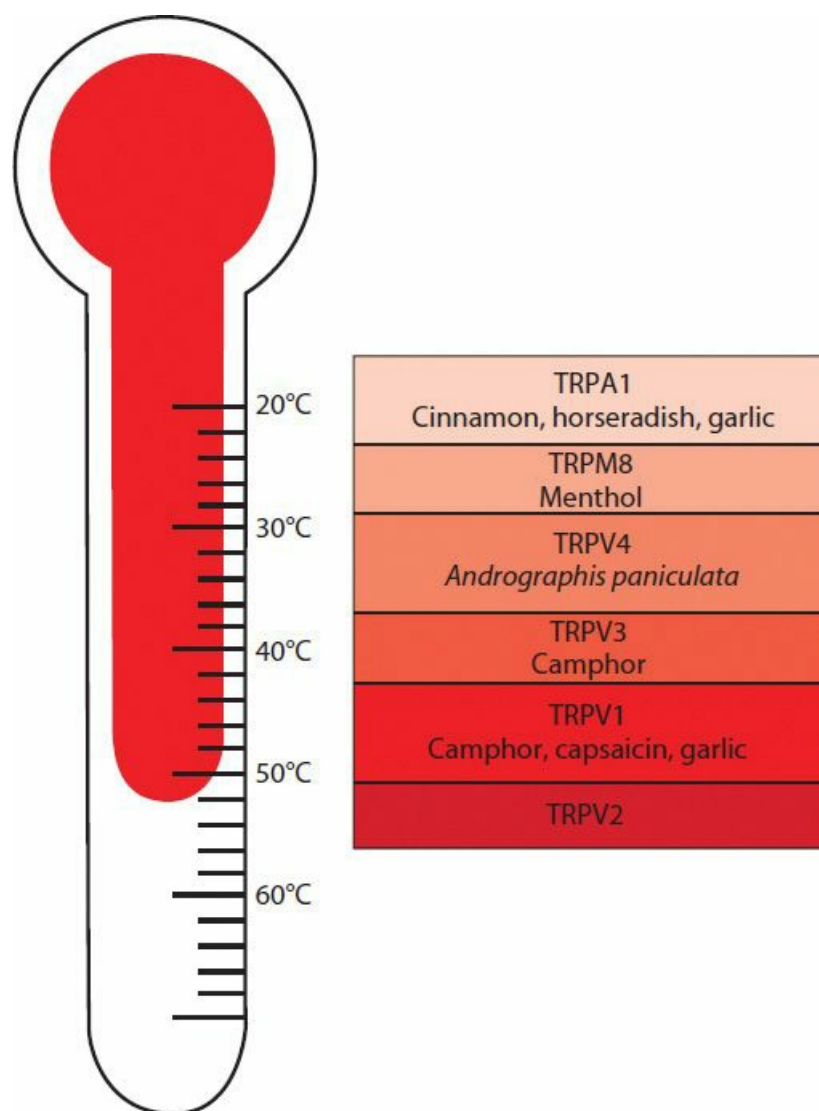


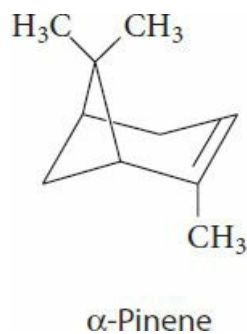
FIGURE 43–2. Schematic of the six known mammalian thermo-TRP channels based on their temperature threshold for activation. Certain natural substances can activate these receptors, which may lead to burning or noxious heat sensation.

Menthol has been investigated as an adjunct to irritable bowel syndrome therapy. In vitro data with isolated animal ileum and jejunum tissue show that menthol reduces contractions by reducing calcium influx, even when such tissue was exposed to acetylcholine, histamine, and serotonin.⁷⁹ In some countries, menthol is sold in an acid resistant preparation as a carminative for irritable bowel symptoms. Menthol and peppermint oil both inhibit 5-HT₃ receptors in vitro as well as reduce serotonin-induced contractions of rat ileum, which could mediate some of the antiemetic effects.⁷⁶

Menthol is commonly used to relieve the symptoms of upper respiratory infections, in particular rhinitis. However, studies have shown that despite the sensation of improved airflow and decreased congestion, menthol actually causes increased nasal congestion.^{53,54} Inhalation of menthol, camphor, or eucalyptus did not decrease nasal resistance to airflow, despite the fact that all of the subjects reported an increased sensation of airflow.²⁴ Similar results were found for nasal menthol lozenges.⁵⁵

Clinical Features. Application of menthol to skin or mucosa causes the sensation of coolness or warmth. Case reports regarding menthol toxicity are rare. One report pertains to Olbas oil, which contains 35% menthol. However, it also contains 35% eucalyptus oil, as well as other oils in smaller amounts. In this report, the child developed ataxia, nystagmus, and altered mental status.¹¹⁶

Pine Oil



History. Pine oil is commonly used as a household cleaner, varnish, and polish. In the past, it had medicinal uses as an expectorant and topical liniment. Turpentine is an oleoresin solvent—a mixture of pine oils and resins distilled from the tree genus *Pinus*. Pine oil is also distilled from the same trees but does not include any resins. Turpentine is used as a degreaser and paint thinner. Pine oil is commonly found in Pine-Sol and similar household cleaners. These cleaners typically include 20% pine oil, 6% to 10% isopropyl alcohol, and other hydrocarbons.

Pharmacology. The lethal dose is in the range of 60 to 120 g in adults.⁹⁶ The major terpene is 1- α -terpineol. The major metabolite is bornyl acetate, which is produced by the enzymatic processes of hydration, hydroxylation, rearrangement, acetylation, and reduction in the liver.⁹⁶ The metabolites are excreted through the kidneys and by exhalation. Pine oil is readily absorbed, and clinical effects usually occur within 2 to 3 hours postingestion.⁹¹

Pathophysiology. Pine oil and turpentine are volatile hydrocarbon compounds with low viscosity. Aspiration and inhalational injury is common when low-viscosity hydrocarbons are ingested or inhaled (Chap. 108). Animals injected with pine oil develop acute respiratory distress syndrome (ARDS), but the mechanism is unknown.¹⁴²

Clinical Features. The most common reported symptoms are impaired mentation, psychomotor agitation, delirium, headache, nausea, ataxia, and GI distress. GI irritation and gastritis are reported, but actual perforation or high-grade lesions have not been found.³³ Acute kidney injury is also reported.⁹⁶ An isolated case report of hemorrhagic cystitis occurring after a patient ingested turpentine for several days to treat a cold is described.⁹⁴ Fatalities are rare, but are more likely to occur when the patient is elderly.¹⁶⁰ The most severe outcomes involve an aspiration pneumonitis that can develop into ARDS or a secondary pneumonia.^{21,91}

Tea Tree Oil

History. Tea tree oil is derived from the distillation of leaves of *Melaleuca alternifolia*, a plant that is native to Australia. The *Melaleuca* genus belongs to the Myrtaceae family and contains more than 230 species. The international standard for tea tree oil does not specify which *Melaleuca* species must be used but rather dictates a certain chemical content.²⁵ Traditionally, *M. alternifolia* has been the primary source for the oil. Nevertheless, synonyms and ambiguous naming of various oils and plants make it difficult to identify the primary plant product. Tea tree oil is also known as melaleuca oil or ti tree oil in many cases. Furthermore, ti tree is the Maori and Samoan common name for plants of the *Cordyline* genus, a completely different plant.²⁵ There are oils from other *Melaleuca* species on the market that possess different chemical properties from that of tea tree oil, further complicating matters. Tea trees can also be known as paperbark trees, but paperbark oil may refer to oil from another type *Melaleuca* tree or even a nonrelated tree such as *Leptospermum* species.

The first reported use of *M. alternifolia* was in Australian Aborigines. Crushed leaves were inhaled to treat coughs and cold symptoms, and poultices of the leaves were applied to wounds. Oral histories describe swimming or bathing in healing lakes composed of decaying fallen tea tree leaves as a treatment for a variety of ailments.²⁵ The oil itself was not distilled until the 20th century, at which time it was touted as an antibacterial agent. Commercial production began after medicinal properties of the oil were first reported in the 1920s. Production slowed after World War II, presumably because of the increased use of antibiotics and decreased desire to use natural products. Renewed interest in the oil began in the 1970s, and production increased as well as became more standardized.

Pharmacology. Data on safety and toxicity are scant. Pharmacokinetic and pharmacodynamic data are even more lacking. Animal studies and case reports of human poisoning demonstrate toxicity with oral exposure. The LD₅₀ for rats is 1.9 to 2.6 mL/kg, and rats dosed with less than 1.5 mL/kg appeared lethargic and ataxic.²⁵

Tea tree oil is comprised of terpene hydrocarbons and contains more than 100 components.²⁵ There can be variability in the composition of oils sold on the market, but there is an international standard stipulating that tea tree oil should contain at least 30% terpinen-4-ol, which is believed to be the primary antimicrobial agent and less than 15% 1,8-cineole, which is believed to be primarily responsible for the irritating properties.²⁵ There are other hydrocarbons found in tea tree oil that

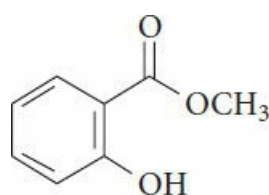
help make up its specific chemotype for the standard, but are less involved in the presumed medicinal properties.

Pathophysiology. Tea tree oil is predominately used as a topical antiseptic, and its antimicrobial effects have been the most studied use of the oil. Studies show that it is bactericidal, and its mechanism of action has been partly elucidated. Tea tree oil, as a lipophilic hydrocarbon, has been found to disrupt the membranes of liposome model systems, supporting the hypothesis that it kills bacteria by disrupting their cell membranes.³⁵ Tea tree oil does not cause bacteria to lyse per se but makes them more susceptible to lysis when exposed to hypertonic medium, or at least it causes an inability to recover from leakage of intracellular contents over time. This is demonstrated by leakage of potassium ions and 260-nm light-absorbing material (a marker of leakage of cytoplasm contents) in *S aureus* and *Escherichia coli*.^{26,34} Tea tree oil also inhibits respiration in *S aureus*.^{26,35} The hydrocarbons 1,8-cineole and terpinen-4-ol were found to be primarily responsible for this phenomena.²⁶ Although 1,8-cineole was initially thought not to play a role in the antimicrobial activity of the oil, it seems to penetrate and disrupt the cellular membranes of bacteria. Terpinen-4-ol and α -terpineol have been shown to have the greatest antimicrobial activity.

Tea tree oil also has antiinflammatory effects. Specifically, it has been shown to inhibit lipopolysaccharide-induced production of the inflammatory mediators TNF- α , IL-1 α , IL-10, and prostaglandin E₂ by monocytes in vitro.⁷⁴

Clinical Manifestations. Skin irritation and allergic reactions are common effects with topical exposure. The allergic reactions are hypothesized to occur after the oil has undergone significant oxidation.¹²⁹ The hydrocarbon 1,8-cineole has been implicated as the main irritating component, but there are little data to support this theory. In some of the cases of prepubertal gynecomastia reported in boys exposed to lavender oil, the patients were also exposed to tea tree oil.⁷⁸ However, it has not been demonstrated that tea tree oil affects the endocrine system. When ingested, tea tree oil commonly causes drowsiness, ataxia, and slurred speech. Case reports of children unintentionally ingesting a 100% concentration of tea tree oil show symptoms developing within 30 minutes of exposure. One child had resolution of symptoms within 5 hours and another had to be intubated but had improvement in neurologic symptoms within 10 hours.^{48,122} In all reported cases of pediatric and adult oral poisoning, patients have responded well to supportive care alone; no deaths have been reported.^{48,122,135}

Oil of Wintergreen



Methyl salicylate

History. Oil of wintergreen was originally derived from *Gaultheria procumbens*, or the Eastern Teaberry, which is a fragrant ground cover plant found in North America. The leaves were steamed and distilled to produce the oil that was used topically to relieve the symptoms of rheumatism. Oil of wintergreen is also obtained from the twigs of Sweet Birch, or *Betula lenta*. The active ingredient in oil of wintergreen is methyl salicylate, which has a pleasant, minty smell and taste, posing a significant hazard to children. Pure oil of wintergreen contains at least 98% methyl salicylate, but most commercial preparations of methyl salicylate contain far less.⁴⁷ FDA regulations require that any drug containing more than 5% methyl salicylate have a warning against using it other than as a topical agent and keeping it out of the reach of children.⁴⁰ Oil of wintergreen has been used as a fragrance and flavoring agent in foods and household products.⁸² It is also found in topical preparations worldwide, such as Tiger Balm and Ben-Gay, which are used to treat inflammation and myalgias. In many Asian countries, topical oils with benign, poetic names such as red flower oil and white flower oil contain high concentrations of methyl salicylate and are quite toxic when ingested.^{29,30} Further confusing consumers and practitioners, there are many other names for this essential oil, including checkerberry oil, sweet birch oil, mountain tea, teaberry, groundberry oil, gaultheria oil, and spicewood oil.⁴⁷

The first reported case of toxicity occurred in 1832, when six soldiers used the oil to flavor their tea.⁴⁶ The seminal case series was reported in the 1930s in which 43 exposures were tabulated, 20 of which involved children under the age of 4 years and had a 75% fatality rate.¹⁴⁵ The smallest lethal dose in this series was 4 mL of oil of wintergreen and 6 mL was reported to be a lethal dose in a 21 year-old man.

Pharmacology. Methyl salicylate is absorbed both from the GI tract and transdermally. Normally, only 12% to 20% of topical salicylate is absorbed from the skin after 10 hours of application.¹²⁷ Heat, inflamed or broken skin, and prolonged use of occlusive dressings can increase absorption.^{23,77,113} Children have died following topical application.²³ Children are presumed to be at greater risk for toxicity due to their higher surface area-to-weight ratio and more permeable skin. Once

absorbed, methyl salicylate enters the circulation and is transported to the liver, where it undergoes hydrolysis to form salicylic acid.⁴¹ Methyl salicylate is a carboxylic acid ester. Most of the studies of salicylate metabolism involve aspirin, which is a phenolic ester. It is assumed that all forms of salicylate have similar properties after they are converted to salicylic acid. The salicylic acid undergoes conjugation with glycine and glucuronic acid, forming salicyluric acid, salicyl acyl, and phenolic glucuronide. Salicylates then undergo renal elimination in the forms of salicyluric acid (75%), free salicylic acid (10%), salicylic phenol (10%) acyl (5%) glucuronides, and gentisic acid (<1%).^{16,41,104}

Pathophysiology. Five milliliters (one teaspoon) of oil of wintergreen is equivalent in salicylate content to 7 g of aspirin, which has been a fatal amount in some reported cases. An extensive discussion of salicylate pathophysiology is given in [Chap. 39](#).

Clinical Features. An overdose of methyl salicylate presents similarly to that of other salicylates such as aspirin. Salicylate poisoning is characterized by diaphoresis, nausea, vomiting, tinnitus, hyperpnea, and tachypnea. Mental status changes are sign of severe toxicity. Symptom onset can be within a few hours given rapid absorption of the oil. Severe toxicity is associated with seizures, cerebral edema, ARDS, coma, and death. Further details on evaluation and management can be found in [Chap. 39](#).

DIAGNOSTIC TESTING

Laboratory testing is of little utility in most essential oil toxicity, and the patient's clinical status will determine what tests are indicated. Some essential oil exposures do require specific studies, and they are listed below. Generally, blood or urine concentrations of the active ingredients are not available in a meaningful time frame and cannot and should not guide management. Patients who present with altered mental status or seizures warrant a complete evaluation that may include a rapid assessment of glucose, basic metabolic studies, a head computed tomography scan, and lumbar puncture for serious potential structural, infectious, or metabolic etiologies. In patients who present with respiratory distress, chest radiographs, and continuous pulse oximetry are warranted.

- **Absinthe:** Laboratory studies should include a complete blood count (CBC), chemistry panel, creatine phosphokinase concentration, and glucose monitoring in patients who present with seizures. Urinalysis should be performed to evaluate for myoglobinuria.
- **Pennyroyal:** CBC and liver function studies, including the aminotransferases, bilirubin, prothrombin time, and partial thromboplastin time, and a β -human chorionic gonadotropin in women are indicated, because many women ingest pennyroyal to terminate unwanted pregnancies.
- **Oil of wintergreen:** Serum salicylate concentrations, blood gas, serum potassium concentration, and urine pH should be sent every 1 to 2 hours to determine extent of toxicity and need for treatment ([Chap. 39](#)).

TREATMENT

The mainstay of treatment of symptomatic essential oil toxicity is supportive care, including monitoring of vital signs, intravenous fluids, and supplemental oxygen as needed. A dose of activated charcoal may be helpful in alert patients with an intact airway, but if there is a concern for seizures, activated charcoal may need to be withheld or deferred until the airway is protected. Dermal exposures should be properly decontaminated to prevent further absorption. Benzodiazepines are the mainstay of treatment in patients who present with agitation and seizures.

A few of the essential oils require specific treatment:

- **Absinthe:** If rhabdomyolysis is present, hydration and urinary alkalization may be appropriate, depending on the clinical severity.
- **Camphor:** Most patients need supportive care with a focus on airway and circulatory management as well as aggressive treatment of seizures. Barbiturates are frequently cited as a first-line treatment of seizures based on one animal study that demonstrated decreased neuronal damage with administration of pentobarbital.¹⁴¹ However, it is likely that appropriate use of benzodiazepines would be just as effective. Given the risk of seizures and altered mental status, inducing emesis is not recommended. There is no proof of any benefit with orogastric lavage, and the rapid absorption of camphor from the GI tract decreases its likelihood of utility. The molecular weight and lipophilic nature of camphor indicates that it would likely be absorbed by activated charcoal. One animal study that underdosed the amount of activated charcoal as well as gave subtoxic doses of camphor indicated that activated charcoal was not effective.⁴⁴ There have been no further studies examining this issue; however, given the risk of aspiration from emesis and seizure, activated charcoal should only be considered in patients with massive life-threatening ingestions and protected airways. There have been case reports of improvement in mental status and seizures with lipid dialysis (using soybean oil) as well as hemoperfusion with either activated charcoal or amberlite resin.^{62,95} However, camphor has a very large volume of distribution (2–4 L/kg), and these cases documented only a small percentage of

body load effectively being removed, thus limiting its utility.

- **Clove oil:** In patients who exhibit signs of hepatotoxicity, NAC should be administered. Although no definitive studies on NAC use in this patient population are available, the suggestion that NAC is protective in the rat model, combined with the safety profile of NAC, warrant its use in the setting of eugenol-induced hepatotoxicity.⁸⁰
- **Pennyroyal:** One case of ingestion of a potentially fatal amount of pennyroyal was successfully treated with lavage, activated charcoal, and NAC.⁵ Given in vitro studies showing glutathione depletion, it would be reasonable to administer NAC in cases of pennyroyal-induced hepatotoxicity. Because there is no established dosing regimen, using the same regimen used for APAP toxicity would be reasonable.¹⁴⁸
- **Oil of wintergreen:** Alkalization with sodium bicarbonate and hemodialysis may be indicated in cases of severe toxicity. Exchange transfusion has been used successfully in children with life-threatening toxicity following methyl salicylate overdose ([Chap. 39](#)).⁴⁷

SUMMARY

- Essential oils are increasingly used as an alternative form of medical therapy.
- These oils contain mixtures of complex hydrocarbons that have the potential to be toxic.
- Cutaneous use of these products in moderation is associated with minimal toxicity. However, ingestion, prolonged inhalation, or excessive topical use may cause significant morbidity and mortality.
- Patients and health care providers should have open dialogues about the therapeutic use of these products and any concerning exposures should be referred to the regional poison centers for guidance in management.

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44 FOOD POISONING

Michael G. Tunik

Each year in the United States there are approximately 9.4 million illnesses, 55,961 hospitalizations, and 1351 deaths from known foodborne agents, and 38.4 million gastroenteritis illnesses, 71,878 hospitalizations, and 1686 deaths from unspecified agents.³⁹ Worldwide food distribution, large-scale national food preparation and distribution networks, limited food regulatory practices, and corporate greed place everyone at risk. Food poisoning causes morbidity and mortality by one or more of the following mechanisms: Infectious agents (bacteria, viruses, parasites) can be transmitted in food; toxins, produced by organisms, can be consumed in food; toxins or chemicals can be inadvertently or purposefully used to contaminate food and be ingested.

This chapter is organized into four major types of food poisoning: foodborne poisoning with neurologic effects, food poisoning with gastrointestinal symptoms, foodborne poisoning with anaphylaxislike effects, and food poisoning used for bioterrorism.

HISTORY AND EPIDEMIOLOGY

In recent years in the United States, *Salmonella* spp and *Escherichia coli* have become the major causes of food poisoning responsible for epidemics that afflict millions, hospitalize hundreds, and kill many unsuspecting people.

The most common causes of foodborne disease include bacteria—*Salmonella* spp, *Campylobacter* spp, *Shigella* spp, and *E. coli*⁶⁶ (Table 44–1). In the last decade, large numbers of people have also suffered from food poisoning due to purposeful placement of chemicals in food,⁴¹ and staphylococcal toxin.¹⁵⁴

TABLE 44–1. Epidemiology of Food Poisoning Reported to the US Centers for Disease Control and Prevention (2009–2010)⁶⁶

<i>Etiology</i>	<i>Cases</i>	<i>Hospitalizations</i>
<i>Bacillus cereus</i>	427	3
<i>Campylobacter</i> spp	600	22
Ciguatoxin	61	6
<i>Clostridium perfringens</i>	3225	9
Hepatitis A virus	47	19
Mushroom poisoning	8	0
Norwalk virus	9737	109
Pesticides	42	2
<i>Salmonella</i> spp	7089	583
Scombrototoxin	76	0
<i>Shigella</i> spp	508	19
<i>Staphylococcus aureus</i>	252	0
<i>Vibrio</i> spp	82	43

FOODBORNE POISONING WITH NEUROLOGIC SYMPTOMS

The differential diagnosis of patients with foodborne poisoning presenting with neurologic symptoms is vast (Tables 44–2 and 44–3). The sources of many of these cases are ichthyosarcotoxic, involving toxins from the muscles, viscera, skin, gonads, and mucous surfaces of the fish; rarely, toxicity follows consumption of the fish blood or skeleton. Shellfish poisoning also must be considered. Most episodes of poisoning are not species specific, although particular forms of toxicity from Tetraodontiformes (puffer fish), Gymnothoraces (moray eel), and newts (*Taricha* and other species) are recognized.

TABLE 44–2. Differential Diagnosis of Possible Foodborne Poisoning Presenting with Neurologic Findings^a

Anticholinergic poisoning

Bacterial food poisoning

Botulism

Eaton-Lambert syndrome

Marine food poisoning (ciguatera, scombroid, tetrodotoxin)

Metals (arsenic, lead, mercury)

Monosodium glutamate

Organic phosphorous compounds

Plant xenobiotics (poison hemlock, buckthorn)

Tick paralysis

^aAltered mental status, motor weakness, sensory changes.

TABLE 44–3. Common Toxicologic Foodborne Neurologic Diseases (Primary Presenting Symptoms)

	<i>Onset/Duration*</i>	<i>Findings</i>	<i>Toxin Source/Toxin*/Mechanism**</i>	<i>Diagnosis**/Therapy*</i>
Ciguatera	2–24 hours *Months to years	t, p, n, v, d	Large reef fish: amber jack, barracuda, snapper, parrot, sea bass, moray (dinoflagellate, source) *Ciguatera toxin **Increased sodium channel permeability	**Clinical, mouse bioassay, immunoassay *Supportive, mannitol, isotonic saline Amitriptyline
Tetrodotoxin	Minutes to hours *Days	p, r, ↓bp	Puffer fish, flugu, blue-ringed octopus, newts, horseshoe crab *Tetrodotoxin **Blocks sodium channel	**Clinical *Respiratory support
Neurotoxic shellfish poisoning	15 min to 18 hours *Days	b, t, n, v, d, p	Mussels, clams, scallops, oysters, <i>P. brevis</i> : “red tide” *Brevetoxin **Increased sodium channel permeability	**Clinical, mouse bioassay of food, HPLC *Supportive
Paralytic shellfish poisoning	30 min *Days	t, p, n, v, d	Mussels, clams, scallops, oysters, <i>P. catenella</i> , <i>P. tamarensis</i> *Saxitoxin **Decreases sodium channel permeability	**Clinical, mouse bioassay of food, HPLC *Respiratory support
Amnesic shellfish poisoning	15 min to 38 hours *Years	a, n, v, d, p, r	Mussels, possibly other shellfish; <i>N. pungens</i> *Domoic acid **Glutamate analog	**Clinical, mouse bioassay of food, HPLC *Respiratory support
Botulism	12–73 hours *Years	v, d, t, w	Home-canned foods, honey, corn syrups, <i>C. botulinum</i> *Botulinum toxin **Binds presynaptically, blocks acetylcholine release	**Clinical immunoassay *Antitoxin, respiratory support

↓bp = hypotension; a = amnesia; b = bronchospasm; d = diarrhea; HPLC = high-pressure liquid chromatography; n = nausea; p = paresthesia; r = respiratory depression; t = temperature reversal sensation; v = vomiting; w = weakness.

In cases of ciguatera poisoning, the major symptoms usually are neurotoxic, and the gastrointestinal (GI) symptoms are minor. Scombroid poisoning, which is exceptionally common, is not associated with focal neurologic manifestations, but facial flushing, headache, and dysphagia are its major signs and symptoms.

Knowing where the fish was caught often helps establish a diagnosis, but refrigerated transport of foods and rapid worldwide travel can complicate that assessment. Travelers to Caribbean and Pacific islands, as well as those traveling

within the United States, have experienced ciguatera poisoning.⁹⁶ In geographically disparate regions of Canada,¹³⁰ individuals have experienced domoic acid poisoning due to ingestion of cultivated mussels from Prince Edward Island.

In the differential diagnosis of foodborne poisons presenting with neurologic findings, activities other than eating must always be considered. In particular, sport divers often perform their activities in high-risk areas such as Florida, California, and Hawaii, and often during the high-risk periods from May through August. In the process, they may sustain a sting from a stingray tail, or laceration (from a deltoid or pectoral fin spine of a lionfish or stonefish) that can cause consequential marine toxicity (Chap. 119).

Ciguatera Poisoning

Ciguatera poisoning is one of the most commonly reported forms of vertebrate fishborne poisonings in the United States accounting for almost one-half of the reported cases.⁶⁶ Ciguatera poisoning is endemic to warm water, bottom dwelling reef fish living around the globe between 35° north and 35° south latitude, which includes tropical areas such as the Indian Ocean, the South Pacific, and the Caribbean. Hawaii and Florida report 90% of all cases occurring in the United States, most commonly from May through August.⁹⁸

More than 500 fish species have caused human cases of ciguatera poisoning, with the barracuda, sea bass, parrot fish, red snapper, grouper, amber jack, kingfish, and sturgeon the most common sources. The common factor is the comparably large size of the fish involved.

Large fish (4–6 lb or more) become vectors of ciguatera poisoning in accordance with complex feeding patterns inherent in aquatic life. Ciguatoxin can be found in blue-green algae, protozoa, and the free algae dinoflagellates. These plankton members of the phylum Protozoa are single-celled, motile, flagellated, pigmented organisms thriving through photosynthesis. Photosynthetic dinoflagellates such as *Gambierdiscus toxicus* and bacteria within the dinoflagellates are the origins of ciguatoxin.^{51,77,104} Dinoflagellates are the main nutritional source for small herbivorous fish, which, in turn, are the major food source for larger carnivorous fish, thereby increasing the ciguatoxin concentrations in the flesh, adipose tissue, and viscera of larger and larger fish.¹¹

Ciguatoxin is heat stable, lipid soluble, acid stable, odorless, and tasteless. When purified, the toxin is a large (molecular weight: 1100 Da) complex ester that does not harm the fish but is stored in its tissues.^{100,105} The molecule binds to voltage-sensitive sodium channels in diverse tissues and increases the sodium permeability of the channel.^{10,159} The ciguatoxins cause hyperpolarization and a shift in the voltage dependence of channel activation, which opens the sodium channels. Ciguatoxins bind selectively to a particular binding site on the neuron's voltage-sensitive sodium channel protein.¹⁰³

Multiple ciguatoxins are identified in the same fish, perhaps explaining the variability of symptoms and differing severity.¹⁰⁴ People can be afflicted after eating fresh or frozen fish that was prepared by all common methods: boiling, baking, frying, stewing, or broiling. The appearance, taste, and smell of the ciguatoxic fish are usually unremarkable. The majority of symptomatic episodes begin 2 to 6 hours after ingestion, 75% within 12 hours, and 96% within 24 hours.¹¹ Symptoms include acute onset of diaphoresis; headaches, abdominal pain with cramps, nausea, vomiting; profuse watery diarrhea; and a constellation of dramatic neurologic symptoms.¹⁷⁵ A sensation of loose or painful teeth may occur. Typically, peripheral dysesthesias and paresthesias predominate. Watery eyes, tingling, and numbness of the tongue, lips, throat, and perioral area occur. A strange metallic taste is frequently reported as is a reversal of temperature discrimination, the pathophysiology of which remains to be elucidated.²⁸ Myalgias, most often in the lower extremities, arthralgias, ataxia, and weakness are commonly experienced.¹¹

Dysuria⁶⁴ and symptoms of dyspareunia and vaginal and pelvic discomfort may occur in women after sexual intercourse with men who are ciguatoxic and whose semen contains the toxin.⁹⁵ Vertigo, seizures, and visual disturbances such as blurred vision, scotomata, and transient blindness) are reported.

Bradycardia and orthostatic hypotension are described.⁶⁰ The GI symptoms usually subside within 24 to 48 hours; however, cardiovascular and neurologic symptoms may persist for several days to weeks, depending on the amount of toxin ingested. Delayed effects may include protracted itching and hiccoughs. Although deaths are reported, internationally none have been documented in the United States.⁶⁶ When it occurs, mortality is a result of respiratory paralysis and seizures not managed with adequate life support. Ciguatoxin may be transmitted in breast milk²⁰ and can cross the placenta.¹²⁸

Laboratory analysis using an enzyme-linked immunosorbent assay (ELISA) test for ciguatera toxin can be performed; alternatively, high-pressure liquid chromatography (HPLC) is accurate. A dipstick immunobead assay test being developed for field use will allow testing of fish without laboratory processing of the toxin-containing tissues.^{10,75,127} A useful approach to diagnosis and management includes laboratory testing to exclude other diagnostic possibilities and determine the need for, or extent of, specific therapeutic interventions.

Initial treatment for victims of ciguatoxin poisoning includes standard supportive care for a toxic ingestion.¹⁷⁵ In most patients, elimination of the toxin is accelerated if vomiting (40%) and diarrhea (70%) have occurred. Administration of

activated charcoal may be of some benefit. In patients with significant GI fluid loss through vomiting, diarrhea, or both, intravenous fluid and electrolyte repletion are essential. The orthostatic hypotension may respond to intravenous fluids and α -adrenergic agonists. Bradycardia may be treated with atropine.⁵⁷

Intravenous mannitol may alleviate neurologic and muscular dysfunctional symptoms associated with ciguatera; however, GI symptoms are not ameliorated.^{126,129} In one randomized controlled trial, mannitol failed to produce any greater improvement in symptoms than did intravenous 0.9% sodium chloride solution.¹⁴⁷ Mannitol should be used with caution because it may cause hypotension. Vascular reexpansion and cardiovascular stability should be initial treatment priorities. Mannitol may work by inhibiting the ciguatoxin-induced opening of sodium channels on the neuron membranes or reducing the neural edema via an osmotic gradient.

Admission to the hospital for cautious supportive care is essential when the diagnosis is uncertain or when volume depletion or any consequential manifestations are present (Tables 44–2 and 44–3). The etiology of the symptoms must be rapidly identified to provide specific therapy, if available. Diaphoresis is a common clinical finding and an important factor in the differential diagnosis. Late in the course of ciguatera poisoning, amitriptyline 25 mg orally twice daily may alleviate symptoms,²³ which may persist up to 1 year. Victims recovering from ciguatera should avoid alcohol and nuts for 3 to 6 months if exposure exacerbates symptoms.

Ciguateralike Poisoning

Moray, conger, and anguillid eels carry a ciguatoxinlike neurotoxin in their viscera, muscles, and gonads that does not affect the eel itself. The toxin is a complex ester that may be structurally very similar to ciguatoxin and is heat stable.¹²³ Individuals who eat these eels may manifest neurotoxic symptoms similar to ciguatoxin or may show signs of cholinergic toxicity, such as hypersalivation, nausea, vomiting, and diarrhea. Shortness of breath, mucosal erythema, and cutaneous eruptions may also occur. These findings may be present in addition to the neurotoxic symptoms.⁷¹ Management is supportive. Mortality is related to the complications of neurotoxicity, such as seizures and respiratory paralysis.

Shellfish Poisoning

Healthy mollusks living between 30° North and 30° South latitude ingest and filter large quantities of dinoflagellates. These dinoflagellates are the major source of available ocean food during the “non-R” months (May through August) in the northern hemisphere. During this time, these dinoflagellates are responsible for the “red tides” that may be seen from California to Alaska, from New England to the St. Lawrence, and across the west coast of Europe.¹¹⁰ The number of toxic dinoflagellates may be so overwhelming that birds and fish die, and humans who walk along the beach may experience respiratory symptoms caused by aerosolized toxin.¹¹²

Ingestion of shellfish, including oysters, clams, mussels, and scallops, contaminated by dinoflagellates or algae may cause neurotoxic, paralytic, and amnesic syndromes. The dinoflagellates most frequently implicated are *Karenia brevis* (originally named *Gymnodinium breve* in 1948, renamed *Ptychodiscus brevis* in 1979, and reclassified again to the current nomenclature in 2000). The diatoms causing neurotoxic shellfish poisoning include *Protogonyaulax catenella* and *Protogonyaulax tamarensis*, which cause paralytic shellfish poisoning; and *Nitzschia pungens*, the diatom implicated in amnesic shellfish poisoning. Proliferation of these diatoms may cause a red tide, but shellfish poisoning may occur even in the absence of this extreme proliferation.

Paralytic shellfish poisoning is caused by saxitoxin. Saxitoxin blocks the voltage-sensitive sodium channel in a manner identical to tetrodotoxin (TTX; see later). The shellfish implicated usually are clams, oysters, mussels, and scallops, but poisoning has occurred through consumption of crustaceans, gastropods, and fish.

The higher the number of shellfish consumed, the more severe the symptoms. Symptoms usually occur within 30 minutes of ingestion. Neurologic effects predominate and include paresthesias and numbness of the mouth and extremities, a sensation of floating, headache, ataxia, vertigo, muscle weakness, paralysis, and cranial nerve dysfunction manifested by dysphagia, dysarthria, dysphonia, and transient blindness. GI symptoms are less common and include nausea, vomiting, abdominal pain, and diarrhea. Fatalities may occur as a result of respiratory failure, usually within the first 12 hours after symptom onset. Muscle weakness may persist for weeks.

Treatment is supportive. Early intervention for respiratory failure is indicated. Orogastric lavage and cathartics were used to remove unabsorbed toxin from the GI tract but probably are not necessary or efficacious.^{26,101,116,152} Activated charcoal may be given. Antibodies against saxitoxin have reversed cardiorespiratory failure in animals,¹⁴ but this therapy is not yet available for humans. Assays for saxitoxin include a mouse bioassay, ELISA, and HPLC. High-pressure liquid chromatography has good interlaboratory accuracy,¹⁷⁰ but the differences in saxitoxin derivatives make standardization of an analytic test difficult.^{9,97}

Neurotoxic shellfish poisoning (NSP) is caused by brevetoxin. Brevetoxin, which is produced by *Karenia brevis* (previously *Gymnodinium brevis*, and subsequently *Ptychodiscus brevis*), is a lipid-soluble, heat-stable polyether toxin similar to ciguatoxin. It acts by stimulating sodium flux through the sodium channels of both nerve and muscle.^{6,29} NSP is

characterized by gastroenteritis with associated neurologic symptoms. GI symptoms include abdominal pain, nausea, vomiting, diarrhea, and rectal burning. Neurologic features include paresthesias, reversal of hot and cold temperature sensation, myalgias, vertigo, and ataxia. Other effects may include headache, malaise, tremor, dysphagia, bradycardia, decreased reflexes, and dilated pupils. Paralysis does not occur. The combination of bradycardia and mydriasis is unusual. The incubation period is 3 hours (range 15 minutes to 18 hours). GI and neurologic symptoms appear simultaneously. Other manifestations of brevetoxin poisoning include mucosal irritation, cough, and bronchospasm, which occur when *P. brevis* is aerosolized by wave action during red tides. The duration of effects averages 17 hours (range 1–72 hours).¹¹⁶

Brevetoxins can be assayed using mouse bioassay, ELISA, and, more recently, antibody radioimmunoassay and reconstituted sodium channels.^{132,167} Treatment is supportive, and severe respiratory depression is very uncommon. Therapy includes removal of the patient from the environment and the administration of bronchodilators. Neurotoxic shellfish poisoning is not fatal.

Amnesic shellfish poisoning is caused by domoic acid, a structural analogue of glutamic and kainic acids produced by the diatom *N. pungens*. The most extensively documented human outbreak occurred in Canada in 1987, when 107 individuals who had consumed mussels harvested from cultivated river estuaries on Prince Edward Island were affected.¹³⁰ Other human outbreaks may have occurred due to a similar diatom—*Pseudonitzschia australis*—which has been isolated in shellfish from other areas.⁵⁸ Pelican deaths caused by domoic acid-laden anchovies were reported in 1991 and Canada instituted monitoring for domoic acid after this outbreak.¹⁶⁴ The death of 400 sea lions in California in 1998 was linked to domoic acid from the same diatom.¹⁴⁸

Amnesic shellfish poisoning is characterized by GI symptoms of nausea, vomiting, abdominal cramps, diarrhea, and by neurologic symptoms of memory loss and, less frequently, coma, seizures, hemiparesis, ophthalmoplegia, purposeless chewing, and grimacing. Other signs and symptoms include hemodynamic instability and cardiac dysrhythmias. Symptoms typically begin 5 hours (range 15 minutes to 38 hours) after ingestion of mussels. The mortality rate is 2%, with death most frequently occurring in older patients, who experience more severe neurologic symptoms. Ten percent of victims may have long-term antegrade memory deficits, as well as motor and sensory neuropathy. Postmortem examinations have revealed neuronal damage in the hippocampus and amygdala.¹⁶³

Tetrodotoxin Poisoning

This type of fish poisoning involves only the order Tetraodontiformes. Although this order of fish is not restricted geographically, it is eaten most frequently in Japan, California, Africa, South America, and Australia.⁷¹ Cases have also occurred in Florida and New Jersey, as well as Europe, the Mediterranean, and Bangladesh. Approximately 100 freshwater and saltwater species exist in this order, including a number of pufferlike fish such as the globe fish, balloon fish, blowfish, and toad fish.¹¹⁸ TTX found in these fish is also isolated from the blue-ringed octopus⁵⁵ and the gastropod mollusk,¹⁷⁷ and has also been responsible for fatalities from ingestion of horseshoe crab eggs.⁸¹ Certain TTX containing newts (*Taricha*, *notophthalmus*, *triturus*, and *cynops*), particularly *Taricha granulosa*, found in Oregon, California, and southern Alaska, can be fatal when ingested. Most newts and salamanders with bright colors and rough skins contain toxins.²⁴ In Japan, fugu (a local variety of puffer fish) is considered a delicacy, but special licensing is required to prepare this exceedingly toxic fish. In 1989, the US Food and Drug Administration (FDA) legalized the importation of puffer fish. However, prior to exportation from Japan, the fish must be laboratory tested and certified by two Japanese organizations to be free of TTX.

TTX is a heat-stable (except in alkaline milieu), water-soluble nonprotein, found mainly in the fish skin, liver, ovary, intestine, and possibly muscle.^{71,143} The ovary has a high concentration of the toxin and is most poisonous if eaten during the spawning season. TTX is detected by mouse bioassay. It is unstable when heated to 212°F (100°C) in acid, distinguishing it from saxitoxin. TTX from fish can be detected using fluorescent spectrometry⁹ or from the urine of poisoned patients using a combination of immunoaffinity chromatography and fluorometric HPLC.⁸²

TTX and saxitoxin are produced by marine bacteria and likely accumulate in animals higher on the food chain that consume these bacteria.¹²² Accumulation of toxins, primarily in the skin, of two species of Asian puffer fish has been documented. Whether this accumulation of toxin is simply an evolutionary adaptation, to remove a toxic substance, or one that has evolutionary advantages of protection is unclear.¹²¹

Neurotoxicity is produced by inhibition of sodium channels and blockade of neuromuscular transmission.^{119,120} The sodium channel is blocked from the external surface of the neuron by the TTX molecule, which contains a guanidinium group that fits into the external orifice of sodium channel. This causes external “plugging” of the sodium channel, although the gating mechanism is functional.^{119,120}

Effects of tetrodotoxin poisoning typically occur within minutes of ingestion. Headache, diaphoresis, dysesthesias, and paresthesias of the lips, tongue, mouth, face, fingers, and toes evolve rapidly. Buccal bullae and salivation may develop. Dysphagia, dysarthria, nausea, vomiting, and abdominal pain may ensue. Generalized malaise, loss of coordination, weakness, fasciculations, and an ascending paralysis (with risk of respiratory paralysis) occur in 4 to 24 hours. Other

cranial nerves may be involved. In more severe toxicity, hypotension is present. In some studies, mortality has approached 50%.¹⁵⁵

Therapy is supportive. Removal of the toxin and prevention of absorption are the essential measures. Supportive respiratory care emphasizing airway protection, including intubation, if necessary, is extremely important.

Less Common Poisonings: Echinoderms

The sea urchin usually causes toxicity by contact with its spinous processes, but this Caribbean delicacy also is toxic upon ingestion. When the sea urchin is prepared as food, the venom containing gonads should be removed because they contain an acetylcholinelike substance that causes the cholinergic syndrome of profuse salivation, abdominal pain, nausea, vomiting, and diarrhea. The sea star is considered edible by some individuals, although an asteriotoxin with saponinlike activity that produces nausea and vomiting is reported.

PREVENTION OF MARINE FOODBORNE DISEASE

Careful evaluation of the symptoms and meticulous reporting to local and state health departments, as well as to the US Centers for Disease Control and Prevention (CDC), will allow for more precise analysis of epidemics of poisoning from contaminated or poisonous food or fish. Many states and countries have developed rigorous health codes with regard to harvesting certain species of fish in certain areas at certain times.

Some examples of actions taken by state and foreign health agencies in controlling epidemics of seafood-borne food poisoning are the following: A 3230-km stretch of Massachusetts coastline was noted to be unsafe for shellfish harvesting due to a red tide bloom. The state declared a health emergency and confiscated shellfish harvested in this area, and prohibited the marketing, export, and serving of shellfish.¹⁰⁹ The health code of Miami, Florida, prohibits the sale of barracuda and warns against eating fillets from large and potentially toxic fish containing ciguatoxin. The Japanese closely regulate preparation and selling of the puffer fish (fugu), requiring that preparers receive special training and licensing. The sale of fugu is now also permitted under strict control in the United States as well. The Canadian government marks the location and time of harvesting of mussels, and mussels are tested for the presence of domoic acid.^{58,130}

FOOD POISONING ASSOCIATED WITH DIARRHEA

The initial differential diagnosis for acute diarrhea involves several etiologies: infectious (bacterial, viral, parasitic, and fungal), structural (including surgical), metabolic, functional, inflammatory, toxin induced, and food induced. The differential diagnosis is described in greater detail in [Chap. 20](#).

An elevated temperature may be caused by invasive organisms, including *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, invasive *E. coli*, *Vibrio parahaemolyticus*, and *Yersinia* spp, as well as some viruses. Episodes of acute gastroenteritis not associated with fever can be caused by organisms producing toxins, including *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*, enterotoxigenic *E. coli*, and viruses.³

Fecal leukocytes typically are found in patients with invasive shigellosis, salmonellosis, *Campylobacter* enteritis, typhoid fever, invasive *E. coli* colitis, *V. parahaemolyticus*, *Yersinia enterocolitica*, and inflammatory bowel disease. In all of these conditions, except typhoid fever, the leukocytes are primarily polymorphonuclear; in typhoid fever, they are mononuclear. No stool leukocytes are noted in cholera, viral diarrhea, noninvasive *E. coli* diarrhea, or nonspecific diarrhea.⁷⁴

The timing of diarrhea onset after exposure or the incubation period can be useful in differentiating the cause. Extremely short incubation periods of less than 6 hours are typical for *Staphylococcus*, *B. cereus* (type I), enterotoxigenic *E. coli*,^{3,107,162} and preformed enterotoxins, as well as roundworm larvae ingestions. Intermediate incubation periods of 8 to 24 hours are found with *C. perfringens*, *B. cereus* (type II enterotoxin), enteroinvasive *E. coli*,^{49,114} and salmonella. Longer incubation periods occur in other bacterial causes of acute gastroenteritis ([Table 44–4](#)).

TABLE 44–4. Common Foodborne Infections: Gastrointestinal (Time of Onset and Primary Presenting Symptom)

Etiology	Onset	Symptoms					Source	Pathogenesis	Therapy
		A	V	Di	Dy	F			
<i>Staphylococcus</i> spp	2–6 hours	+	+	+	–	–	Prepared foods: meats, pastries, salads	Heat stable enterotoxin	Supportive, volume expansion
<i>Bacillus cereus</i>									
Type I	1–6 hours	+	+	+	–	–	Fried rice	Heat labile toxins	Supportive, volume expansion
Type II	12 hours	+	–	+	–	–	Meats, vegetables	Heat labile toxins	
Anisakiasis	1–12 hours	+	+	–	–	–	Raw fish, sushi, (Eustrongyloides), minnows, salmon, cod, herring, squid, tuna	Intestinal larvae	Endoscopy, laparotomy removal
<i>Clostridium perfringens</i>	8–24 hours	+	±	+	±	–	Poultry, heat-processed meats	Heat labile enterotoxin	Volume expansion
<i>Salmonella</i> spp	8–24 hours	±	±	+	±	+	Poultry, egg, pets (turtles, lizards, chicks)	Bacteria, endotoxin (bacteremia)	Antibiotics
<i>E. coli</i>	24–72 hours						Water, food	Enterotoxin, heat stable	Volume expansion
Enterotoxigenic	<6 hours	+	±	+	–	+	Enteric contact		Electrolytes
Invasive	24–72 hours	+	–	+	+	+	Raw produce	Bacteria (invasive)	Antibiotics
Hemorrhagic	24–72 hours	+	+	+	+	±	Under cooked beef, unpasteurized milk	Shiga-like toxin	Renal, hematologic support
<i>Vibrio cholera</i>	24–72 hours	±	±	+	–	±	Water, food enteric contact	Heat labile Enterotoxin	Electrolyte replacement, antibiotics
<i>Shigella</i> spp	24–72 hours	+	±	+	+	±	Institutional food handlers, household, preschool, enteric contact	Bacteria-Endotoxin	Antibiotics
<i>Campylobacter jejuni</i>	1–7 days	+	+	+	±	+	Milk, poultry, unchlorinated water	Bacteria, heat labile enterotoxin	Antibiotics
<i>Yersinia</i> spp	1–7 days	+	+	+	±	+	Pork, milk, pets	Bacteria, enterotoxin	Antibiotics

A = abdominal pain; Di = diarrhea; Dy = dysentery; F = fever; V = vomiting.

The three most likely etiologies of diarrhea are infectious, xenobiotics (chemicals found in an organism, not normally present, frequently a pollutant or contaminant), and foodborne. These three etiologies are not mutually exclusive. The differential diagnosis must be made among these groups. When the time from exposure to onset of symptoms is brief, all of the nonbacterial infectious etiologies (viral, parasitic, fungal, and algal) except for upper GI invasion by roundworm larvae can be eliminated. The possibility of a bacterial etiology with enterotoxin production should be considered (Table 44–4).^{3,21}

EPIDEMIOLOGY

Epidemiologic analysis is of immediate importance, particularly when GI diseases strike more than one person in a group. The questions raised in Table 44–5 must be answered.¹⁴² If available, an infectious disease consultant or infection control officer should be called for assistance. Alternatively, assistance from state and local health departments should be sought. Often, only the CDC or state health department has the resources to investigate and confirm a presumptive diagnosis in an outbreak. Sophisticated techniques such as toxin detection, matching the organism in the food by phage type with a food handler, matching an organism by phage type with other persons, isolating 10 or more organisms per gram of implicated food,^{49,52} or polymerase chain reaction (PCR) identification of bacterial or plasmid DNA are potentially useful, although generally not possible using the laboratory and personnel available in most hospitals.^{27,32,65} Structural, metabolic, and functional causes often can be eliminated. As in these diseases, neither a significant grouping of cases nor a limited clinical history is characteristic. Foodborne parasites such as *Trichinella spiralis* (trichinosis), *Toxoplasma gondii* (toxoplasmosis), and *G. lamblia* (giardiasis) must be considered, although acute GI symptoms are not usually prominent.

TABLE 44–5. Epidemiologic Analysis of Gastrointestinal Disease

1. Is the occurrence of the disease in a large group significant enough to be consistent with foodborne disease (two or more cases)?
2. Is the symptomatology in affected individuals well defined and similar?
3. Is the onset, time, and duration of illness similar among affected group members (incubation)?
4. What are the possible modes of transmission (ie, contact, food, water)?
5. Is there a relationship between the time of exposure of the group and the mode of transmission?
6. Do attack rates differ for age, gender, or occupation?
7. Can it be determined which foods were served and to whom? Can the items that were not eaten by those who did not become ill be identified?
8. What is the food-specific attack rate?
9. How was the food procured? How was it stored?
10. Was cooking technique adequate?
11. Was personal hygiene acceptable?
12. Was there animal contamination?

Salmonella Species

Salmonella enteritidis infections are of great concern in the United States. Two particular outbreaks define very special problems. In the 1980s, recurrent outbreaks associated with grade A eggs or food containing such eggs occurred. In the past, such outbreaks of salmonella enteritis were attributed to infection of the egg with salmonella (from the chicken's GI tract) through cracks in the shell. More recently, outbreaks have involved noncracked, nonsoiled eggs.¹¹⁵ In these cases, presumably the salmonella has infected the eggs before the shell was formed. In either case, people who consume raw or undercooked eggs are at most risk for salmonella enteritis. Raw eggs can be found as ingredients of chocolate mousse, hollandaise sauce, eggnog, Caesar salads, and homemade ice cream. Whole, partially cooked eggs are problematic when eaten sunny side up or poached.³⁷ The second group of outbreaks was associated with raw milk,¹³³ which has become very popular in certain communities. Inadequate microwave cooking may cause small outbreaks.⁵³ These outbreaks are of great concern because they frequently involve multiple drug resistant salmonella infections.⁴⁵ Drinking pasteurized milk may not be protective. An outbreak of salmonellosis resulting in more than 16,000 culture-proven cases was traced to one Illinois dairy. The probable cause of the outbreak was a transfer line connecting raw and pasteurized milk containment tanks.¹³⁹

The contamination of food that is widely distributed places thousands at risk. An outbreak of salmonella food poisoning from peanut butter caused 529 confirmed illnesses in 48 states and Canada, 116 hospitalizations, and possibly eight deaths.⁴⁰ The CDC estimates that the proportion of salmonella infections that are confirmed by laboratory testing is 3% of the total, so the estimated number of infected people affected by this contamination incident may be more than 15,000. News reports state that the peanut butter contamination with salmonella was known, and that the peanut butter was retested for contamination, until no salmonella was reported. The peanut butter was then nationally distributed.⁷³

Additional concern has developed over the widespread use of anti-biotics in animal feed, responsible for meats, poultry, and manure-fertilized vegetables now frequently containing resistant bacterial strains to which virtually the entire population may be exposed.^{45,139} "Household" pets such as chicks, turtles, and iguanas host salmonella and frequently transmit the organism to household contacts, including infants, who are at particular risk for invasive diseases, as well as other family members.¹

FOODBORNE POISONING ASSOCIATED WITH MULTIORGAN SYSTEM DYSFUNCTION

The hemolytic uremic syndrome (HUS) is frequently caused by a bacterial gastroenteritis. The most commonly responsible organism is *E. coli* O157:H7.⁶⁸ Other bacteria and xenobiotics cause the same findings. Typical laboratory findings in HUS include microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.

HUS begins with a prodrome of diarrhea 90% of the time. The diarrhea lasts for 3 to 4 days and frequently becomes bloody. Abdominal pain due to colitis is common, and vomiting, altered mental status (irritability or lethargy), pallor, and low-grade fever frequently occur. At presentation, many have oliguria or anuria, and 10% of children have a generalized seizure at HUS onset.¹⁵¹

HUS is frequently associated with enterohemorrhagic *E. coli* (EHEC) or *E. coli* O157:H7 with postdiarrheal HUS.^{25,109,124,125,137,172} Food products from cattle (ground beef, milk, yogurt, cheese) and water contaminated with fecal

material are EHEC sources.^{48,111} Contaminated water used in gardens and unpasteurized apple cider have caused bloody diarrhea and HUS as a result of EHEC.^{16,44}

EHEC, including *E. coli* O157:H7, produces a toxin similar to the toxin produced by *Shigella dysenteriae* type I, referred to as Shiga-like toxin (SLT) or verotoxin.²¹ The proposed mechanism for SLT damage is intestinal absorption, bloodstream access to renal glomerular endothelium, intracellular adsorption via glycolipid receptors, ribosomal inactivation, and cell death.¹⁶¹ In animal models, organ damage is more severe if endothelial cells have high concentrations of globotriaosylceramide receptors, which have a high binding affinity for Shiga toxin. Other organs with these receptors include the kidney, GI, and central nervous systems, which may explain the pattern of organ damage in children with HUS. Endothelial cell damage and other pathologic processes, including platelet and leukocyte activation, triggering of the coagulation cascade, and the production of cytokines, occur.^{83,169} More than one type of SLT exists; SLT-1, SLT-2, and variants of SLT-2 structure are identified.¹⁷

Detection of *E. coli* O157:H7 through stool culture early in the course of disease is useful. The recovery decreases after the first week of illness.¹⁶¹ *E. coli* O157:H7 almost always produces SLT; therefore, if stool cultures are negative, enzyme immunoassay (EIA) and PCR tests can be used to detect SLT in the stool when *E. coli* can no longer be identified by culture.²⁷

Treatment of HUS should focus on meticulous supportive care, with fluid and electrolyte balance the priority. Dialysis should be instituted early for azotemia, hyperkalemia, acidosis, and fluid overload. Red blood cells and platelet transfusions may be required. Hypertension should be treated with short-acting calcium channel blockers (nifedipine 0.25–0.5 mg/kg/dose orally) and seizures with benzodiazepines. Plasmapheresis has been used in nondiarrheal HUS and in recurrent HUS after renal transplants. Anti-SLT-2 antibodies have protected mice from SLT-2 toxicity, but intravenous immunoglobulin with SLT-2 activity has not improved outcome in children with HUS. A double-blind, placebo-controlled study on the use of synthetic SLT receptors attached to an oral carrier found that mortality or serious morbidity of HUS syndrome did not change as a result.¹⁶⁶

The mortality from HUS with good supportive care is approximately 5%; another 5% of victims suffer end-stage kidney disease or cerebral ischemic events and chronic neurologic impairment. Prolonged anuria (>1 week), oliguria (>2 weeks), or severe extrarenal disease may serve as markers for higher mortality and morbidity.¹³¹

There is some evidence that early treatment with antibiotics increases the risk of development HUS in children with *E. coli* O157:H7 infections.¹⁵⁶ An earlier meta analysis and randomized trial did not find this association.^{134,140} Due to this concern, many experts recommend not treating patients with clinical or epidemiologic presentations consistent with *E. coli* O157:H7 infections (crampy abdominal pain, bloody diarrhea, regional outbreak) until a definitive pathogen can be identified.

Strategies to prevent the spread of *E. coli* O157:H7 and subsequent HUS include public education on the importance of thorough cooking of beef to a “well-done” temperature of 170°F (77°C), pasteurization of milk and apple cider, and thorough cleaning of vegetables. Public health measures include education of clinicians to consider *E. coli* O157:H7 in patients with bloody diarrhea and insuring the routine capability of microbiology laboratories to culture *E. coli* O157:H7 and provide for EIA or PCR determination of SLT. Public health departments should provide active surveillance systems to identify early outbreaks of *E. coli* O157:H7 infection.

Staphylococcus Species

In cases of suspected food poisoning with a short incubation period, the physician should first assess the risk for staphylococcal causes. The usual foods associated with staphylococcal toxin production include milk products and other proteinaceous foods, cream-filled baked goods, potato and chicken salads, sausages, ham, tongue, and gravy. Pie crust can act as an insulator, maintaining the temperature of the cream filling and occasionally permitting toxin production even during refrigeration.⁴ A routine assessment must be made for the presence of lesions on the hands or nose of any food handlers involved. Unfortunately, carriers of enterotoxigenic staphylococci are difficult to recognize because they usually lack lesions and appear healthy.⁷⁶ A fixed association between a particular food and an illness would be most helpful epidemiologically but rarely occurs clinically. Factors such as environment, host resistance, nature of the agent, and dose make the results surprisingly variable.

Although patients with staphylococcal food poisoning rarely have significant temperature elevations, 16% of 2992 documented cases in a published review had a subjective sense of fever.⁷⁶ Abdominal pain, nausea followed by vomiting, and diarrhea dominate the clinical findings. Diarrhea does not occur in the absence of nausea and vomiting. The mean incubation period is 4.4 hours with a mean duration of illness of 20 hours. Two staphylococcal enterotoxin food poisoning incidents involving large numbers of people have been reported. At a public event in Brazil in 1998, one-half of the 8000 people who attended had nausea, emesis, diarrhea, abdominal pain, and dizziness within hours of consuming food. Of the ill patients, 2000 overwhelmed the capacity of local emergency departments, 396 (20%) were admitted including 81 to intensive care units, and 16 young children and elderly participants died.¹⁵⁴ In another report, 328 individuals became ill

with symptoms of diarrhea, vomiting, dizziness, chills, and headache after eating cheese or milk.¹⁵³ In both reports, staphylococcus enterotoxin was found in the food consumed.

Most enterotoxins are produced by *S. aureus* coagulase-positive species. The enterotoxins initiate an inflammatory response in GI mucosal cells and lead to cell destruction. The enterotoxins also may exert a sudden explosive effect on the emesis center in the brain and diverse other organ systems. Discrimination of unique *S. aureus* isolates from those found in foodborne outbreaks can be made using restriction fragment length polymorphism analysis by pulsed-field gel electrophoresis and PCR techniques.¹⁷³

Bacillus cereus

Another foodborne toxin with GI symptoms is associated with eating reheated fried rice. *Bacillus cereus* type I is the causative organism, and bacterial overgrowth and toxin production causes consequential early onset nausea and vomiting.² Infrequently this toxin causes liver failure.¹⁰⁸ *Bacillus cereus* type II has a delayed onset of similar GI symptoms, including diarrhea.⁵⁹

Campylobacter jejuni

Campylobacter jejuni is a major cause of bacterial enteritis. The organism is most commonly isolated in children younger than 5 years and in adults 20 to 40 years of age. *Campylobacter* enteritis outbreaks are more common in the summer months in temperate climates. Although most cases of *Campylobacter* enteritis are sporadic, outbreaks are associated with contaminated food and water. The most frequent sources of *Campylobacter* in food are raw or undercooked poultry products⁵⁴ and unpasteurized milk.¹⁵⁷ Birds are a common reservoir, and small outbreaks are associated with contamination of milk by birds pecking on milk-container tops.¹⁵⁷ Contaminated water supplies are also frequent sources of *Campylobacter* enteritis involving large numbers of individuals.¹⁹ *C. jejuni* is heat labile; cooking of food, pasteurization of milk, and chlorination of water will prevent human transmission.

The incubation period for *Campylobacter* enteritis varies from 1 to 7 days (mean 3 days). Typical symptoms include diarrhea, abdominal cramps, and fever. Other symptoms may include headache, vomiting, excessive gas, and malaise. The diarrhea may contain gross blood, and leukocytes are frequently present on microscopic examination.⁷⁴ Illness usually lasts 5 to 6 days (range 1–8 days). Rarely, symptoms last for several weeks. Severely affected individuals present with lower GI hemorrhage, abdominal pain mimicking appendicitis, a typhoidlike syndrome, reactive polyarthritis (Reiter syndrome), or meningitis. The organism may be detected using PCR identification techniques.⁶² Treatment is supportive, and consists of volume resuscitation, and possibly antibiotics for the more severe cases.³

Group A Streptococcus

Bacterial infections not usually associated with food or food handling are nevertheless occasionally transmitted by food or food handling. Transmission of streptococcal pharyngitis in food prepared by an individual with streptococcal pharyngitis has been demonstrated.⁴⁶ A Swedish food handler caused 153 people to become ill with streptococcal pharyngitis when his infected finger wound contaminated a layer cake served at a birthday party.⁷

Clostridium botulinum

In the last 3 decades, a median of four cases of foodborne botulism, three cases of wound botulism, and 71 cases of infant botulism have been reported annually to the CDC.¹⁵⁰ Home-canned fruits and vegetables, as well as commercial fish products, are among the common foods causing botulism. The incubation period usually is 12 to 36 hours; typical symptoms include some initial GI symptoms, followed by malaise, fatigue, diplopia, dysphagia, and rapid development of small muscle incoordination.⁹⁸ In botulism, the toxin is irreversibly bound to the neuromuscular junction, where it impairs the presynaptic release of acetylcholine.⁹² A patient's survival depends on rapidly diagnosing botulism and immediate initiation of aggressive respiratory therapy. Establishing the diagnosis early may make it possible to treat the "sentinel" or index patient and also others who consumed the contaminated food with antitoxin prior to their developing signs and symptoms (Chap. 41 and Antidotes in Depth: A6). The differential diagnosis of botulism includes myasthenia gravis, atypical Guillain-Barré syndrome, tick-induced paralysis, and certain chemical ingestions (Tables 41–1 and 41–2).

Yersinia enterocolitica

Yersinia enterocolitica causes enteritis most frequently in children and young adults. Typical clinical features include fever, abdominal pain, and diarrhea, which usually contains mucus and blood.^{8,160,171} Other associated symptoms include nausea, vomiting, anorexia, and weight loss. The incubation period may be 1 to 7 days or more. Less common features include prolonged enteritis, reactive polyarthritis, pharyngeal and hepatic involvement, and rash. *Yersinia* is a common

pathogen in many animals, including dogs and pigs. Sources of human infection include milk products, raw pork products, infected household pets, and person-to-person transmission.^{22,70,99} The diagnosis may be based on cultures of food, stool, blood, and, less frequently, skin abscesses, pharyngeal cultures, or cultures from other organ tissues (mesenteric lymph nodes, liver). *Yersinia* may be identified by PCR.⁸⁴ Patients receiving the chelator deferoxamine (Antidotes in Depth: A7) may acquire *Yersinia* infections due to the patients' increased susceptibility. The deferoxamine-iron complex acts as a siderophore for organism growth. Therapy is usually supportive, but patients with invasive disease (eg, bacteremia, bacterial arthritis) should be treated with intravenous antibiotics. Fluoroquinolones and third-generation cephalosporins are highly bacteriocidal against *Yersinia* spp.

Listeria monocytogenes

Listeriosis transmitted by food usually occurs in pregnant women and their fetuses, the elderly, and immunocompromised individuals using corticosteroids or with malignancies, diabetes mellitus, kidney disease, or HIV infection.^{15,34,36,146} Typical food sources include unpasteurized milk, soft cheeses such as feta, and undercooked chicken. Individuals at risk should avoid the usual sources and should be evaluated for listeriosis if typical symptoms of fever, severe headache, muscle ache, and pharyngitis develop. Treatment with intravenous ampicillin and aminoglycoside, or trimethoprim/sulfamethoxazole is indicated for systemic *Listeria* infections.

Xenobiotic-Induced Diseases

In addition to the aforementioned saxitoxin TTX, domoic acid, and ciguatoxin, many other xenobiotics contaminate our food sources. Careful assessment for possible foodborne pesticide poisoning is essential. For example, aldicarb contamination has occurred in hydroponically grown vegetables and watermelons contaminated with pesticides.⁶⁷ Eating malathion-contaminated chapatti and wheat flour resulted in 60 poisonings including a death in one outbreak⁴² (Chap. 113). Insecticides, rodenticides, arsenic, lead, or fluoride preparations can be mistaken for a food ingredient. These poisonings usually have a rapid onset of signs and symptoms after exposure.

The possibility of unintentional acute metal salt ingestion must also be considered. This type of poisoning most typically occurs when very acidic fruit punch is served in metal-lined containers. Antimony, zinc, copper, tin, or cadmium in a container may be dissolved in an acidic food or juice medium.

Mushroom-Induced Disease

Some species produce major GI effects. *Amanita phalloides*, the most poisonous mushroom, usually causes GI symptoms as well as hepatotoxic effects with a delay to clinical manifestations. The rapid onset of symptoms suggests some of the gastroenterotoxic mushrooms (Chap. 120).

Intestinal Parasitic Infections

The popularity of eating raw fish, or sushi, has led to an increase in reported intestinal parasitic infections. Etiologic agents are roundworms (*Eustrongyloides anisakis*) and fish tapeworms (*Diphyllobothrium* spp). Symptoms of anisakiasis may be upper intestinal (occur 1–12 hours after eating) or lower intestinal (delayed for days or weeks). Typical symptoms include nausea, vomiting, and severe crampy abdominal pain; with intestinal perforation severe pain, rebound, and guarding occur. A dietary history of eating raw fish is needed to establish diagnosis and therapy. Visual inspection of the larvae (on endoscopy, laparotomy, or pathologic examination) is useful. Treatment of intestinal infection involves surgical or laparoscopic removal. *Anisakis simplex* and *Pseudoterranova decipiens* are Anisakidae that may be found in several types of consumed raw fish, including mackerel, cod, herring, rockfish, salmon, yellow fin tuna, and squid. Reliable methods of preventing ingestion of live anisakid larvae are freezing at –4°F (–20°C) for 60 hours or cooking at 140°F (60°C) for 5 minutes.^{31,89,106,138,144,176}

Diphyllobothriasis (fish tapeworm disease) is caused by eating uncooked fish that harbor the parasite, including herring, salmon, pike, and whitefish. The symptoms are less acute than with intestinal roundworm ingestions and usually begin 1–2 weeks after ingestion.³⁰ Signs and symptoms include nausea, vomiting, abdominal cramping, flatulence, abdominal distension, diarrhea, and megaloblastic anemia. The diagnosis is based on a history of ingesting raw fish and on identification of the tapeworm proglottids in stool. Treatment with niclosamide, praziquantel, or paromomycin usually is effective.³⁵

Monosodium Glutamate

This clinical presentation is misnamed “Chinese restaurant syndrome” since it results from the ingestion of monosodium glutamate (MSG), which has multicultural use in the preparation of many foods. Affected individuals present with a burning sensation of the upper torso, facial pressure, headache, flushing, chest pain, nausea and vomiting, and, infrequently, life-

threatening bronchospasm,³ and angioedema.¹⁵⁸ Intensity and duration of symptoms are generally dose related but with significant variation in individual responses to the amount ingested.^{145,178} MSG causes “shudder attacks” or a seizurelike syndrome in young children. Absorption is more rapid following fasting, and the typical burning symptoms rapidly spread over the back, neck, shoulders, abdomen, and occasionally the thighs. GI symptoms are rarely prominent and symptoms can usually be prevented by prior ingestion of food. When symptoms do occur, they tend to last approximately one hour. The syndrome is a reaction to MSG, which had been commonly used in Chinese and many other restaurants. MSG is also marketed as an effective flavor enhancer.¹³ Many sausages and canned soups contain large doses of MSG.

MSG (regarded as “safe” by the FDA) can cause other acute and bizarre neurologic symptoms. There is evidence that humans have a unique taste receptor for glutamate.⁹¹ This explains its ability to act as a flavor enhancer for foods. Glutamate is also an excitatory neurotransmitter that can stimulate central nervous system neurons through activation of glutamate receptors, and may be the explanation for some of the neurologic symptoms described with ingestion.¹⁷⁹

Anaphylaxis and Anaphylactoid Presentations

Some foods and foodborne toxins may cause allergic or anaphylactoidlike manifestations,⁸⁵ also sometimes referred to as “restaurant syndromes”¹⁴⁹ (Table 44–6). The similarity of these syndromes complicates a patient’s future approach to safe eating. Isolating the precipitant is essential so that the risk can be effectively assessed. Manufacturers of processed foods should provide an unambiguous listing of ingredients on package labels. Sensitive individuals (or in the cases of children their parents) must be rigorously attentive.^{141,180} Those who experience severe reactions should make sure that epinephrine and antihistamines are always available immediately. Attempts to prevent allergic reactions to dairy products by avoiding dairy-containing foods may fail. Nondairy foods may still be processed in equipment used for dairy products or contain flavor enhancers of a dairy origin (eg, partially hydrolyzed sodium caseinate), both of which can cause morbidity and death in allergic individuals.⁶¹ Individuals with known food allergies do not always carry prescribed autoinjectable spring-injected epinephrine syringes, in some cases from a belief that the allergen is easily identifiable and avoidable.⁸⁵ Food additives that can cause anaphylaxis include antibiotics, aspartame, butylated hydroxyanisole, butylated hydroxytoluene, nitrates or nitrites, sulfites, and paraben esters.¹⁰² Regulation of these preservatives is limited, and xenobiotics such as sulfites are so ubiquitous that predicting which guacamole, cider, vinegar, fresh or dried fruits, wines, or beers contain these sensitizing agents may be impossible.

TABLE 44–6. Epidemiologic Analysis of Gastrointestinal Disease

	Onset	Symptoms/Signs	Cause	Therapy
Anaphylaxis (anaphylactoid)	Minutes to hours	Urticaria, angioedema, bronchospasm, hypotension	Allergens—nuts, eggs, milk, fish, shellfish, peanuts, soy	Oxygen, epinephrine, β_2 -adrenergic agonist, corticosteroids, volume expansion, H_1 , H_2 histamine blockers, avoidance
Monosodium glutamate (MSG)	Minutes	Flushing, hypotension, palpitations, facial pressure, headaches, rhinitis, bronchospasm, shivering	Flavor enhancer of foods	Oxygen, β_2 -adrenergic agonists, volume expansion, avoidance
Metabisulfites	Minutes	Flushing, hypotension, bronchospasm	Preservative in wines, salad (bars), fruit juice, shrimp	See Anaphylaxis, avoidance
Scombroid	Minutes to hours	Flushing, hypotension, urticaria, headache, pruritis, gastrointestinal symptoms	Large fish—poorly refrigerated: tuna, bonito, albacore, mackerel, mahi mahi (histamine)	H_1 , H_2 blockers, supportive care, avoidance
Tyramine	Minutes to hours	Headache, hypertension (INH or MAOI) increases risk	Wines, aged cheeses	Avoidance for those with hypertension, migraines
Tartrazine	Hours	Urticaria, angioedema, bronchospasm	Yellow coloring food additive	See Anaphylaxis, avoidance

INH = isoniazid; MAOI = monoamine oxidase inhibitor.

Scombroid Poisoning

Scombroid poisoning originally was described with the Scombroideae fish (including the large dark-meat marine tuna, albacore, bonito, mackerel, and skipjack). However, the most commonly ingested vectors identified by the CDC are nonscombroid fish, such as mahi mahi and amber jack.³³ All of the implicated fish species live in temperate or tropical waters. Ingestion of bluefish in New Hampshire was the probable cause of scombroid poisoning in five people,⁵² and in a large outbreak, tuna was the offender in 71 cases reported from a military outpost.⁴⁷ The incidence of this disease is

probably far greater than was originally perceived. This type of poisoning differs from other fishborne causes of illness in that it is entirely preventable if the fish is properly stored following removal from the water.

Scombroid poisoning results from eating cooked, smoked, canned, or raw fish. The implicated fish all have a high concentration of histidine in their dark meat. *Morganella morganii*, *E. coli*, and *Klebsiella pneumoniae*, commonly found on the surface of the fish, contain a histidine decarboxylase enzyme that acts on a warm (not refrigerated), freshly killed fish, converting histidine to histamine, saurine, and other heat-stable substances. Although saurine has been suggested as the causative toxin, chromatographic analysis demonstrates that histamine is found as histamine phosphate and saurine is merely histamine hydrochloride.^{56,117} The term saurine originated from saury, a Japanese dried fish delicacy often associated with scombroid poisoning. The extent of spoilage usually correlates with histamine concentrations. Histamine concentrations in healthy fish are less than 0.1 mg/100 g fish meat. In fish left at room temperature, the concentration rapidly increases, reaching toxic concentrations of 100 mg/100 g fish within 12 hours.

The appearance, taste, and smell of the fish are usually unremarkable.⁵ Rarely, the skin has an abnormal “honeycombing” character or a pungent, peppery taste that may be a clue to its toxicity. Within minutes to hours after eating the fish, the individual experiences numbness, tingling, or a burning sensation of the mouth, dysphagia, headache, and, of particular significance for scombroid poisoning, a unique flush characterized by an intense diffuse erythema of the face, neck, and upper torso.⁸⁶ Rarely, pruritus, urticaria, angioedema, or bronchospasm ensues. Nausea, vomiting, dizziness, palpitations, abdominal pain, diarrhea, and prostration may develop.^{43,63,86,113}

The prognosis is good with appropriate supportive care and parenteral antihistamines such as diphenhydramine. H₂-receptor antagonists such as cimetidine or ranitidine may also be useful in alleviating gastrointestinal symptoms.¹⁸ The toxic substance should be removed or absorbed from the gut. Inhaled β_2 -adrenergic agonists and epinephrine may be necessary if bronchospasm is prominent. Patients usually show significant improvement within a few hours.

Elevated serum or urine histamine concentrations can confirm the diagnosis, but are usually unnecessary. If any uncooked fish remains, isolation of causative bacteria from the flesh is suggestive, but not diagnostic. A capillary electrophoretic assay makes rapid histamine detection possible.⁷⁹ Histamine concentrations greater than 50 mg/100 g fish meat are considered hazardous by the FDA; in Europe the concentrations are 100 to 200 mg/100 g.⁷⁹ Isoniazid may increase the severity of the reaction to scombroid fish by inhibiting enzymes that break down histamine.^{78,168}

Patients may be reassured that they are not allergic to fish if other individuals experience a similar reaction to eating the same fish at the same time, or if any remaining fish can be preserved and tested for elevated histamine concentrations. If this information is not available, then an anaphylactic reaction to the fish must be considered. Table 44–6 lists the differential diagnosis of flushing, bronchospasm, and headache. Because many people often consume alcohol with fish, alcohol must be considered an independent variable.

The differential diagnosis of the scombrototoxic flush apart from a disulfiramlike reaction includes ingestion of niacin or nicotinic acid, and pheochromocytoma. The history and clinical evolution usually establish the diagnosis quickly.

Global Food Distribution, Illegal Food Additives

Xenobiotics are given to animals to increase their health and growth. Clenbuterol, a β_2 agonist, has been administered to cattle raised for human consumption. The substance can cause toxicity in humans who eat contaminated animal meat. Tachycardia, tremors, nausea, epigastric pain, headache, muscle pain, and diarrhea were present in 50 poisoned patients. Other findings included hypertension and leukocytosis.¹³⁶ No deaths have been reported. The use of antibiotics, β_2 agonists, and other growth enhancers continues, despite safety concerns and laws against their use, because these practices increase yield and profit.

The globalization of food supplies and international agricultural trade has created a new global threat, the apparent purposeful contamination of food for profit. In 2008, almost 300,000 children in China were affected by melamine contamination of milk. Of these, 50,000 were hospitalized and 6 reported deaths occurred.

The melamine-contaminated milk was sold in China as powdered infant formula, with more than 22 brands containing melamine. The contamination was not limited to China, as melamine has been found in candy, chocolate, cookies, and biscuits sold in the United States, likely due to the adulteration of milk used in preparation of these products.

Melamine is a non-nutritious, nitrogen-containing compound, usually used in glues, plastics, and fertilizers. To increase profits, milk sold in China had previously been diluted, causing protein malnutrition in children. Because the nitrogen content of milk (a surrogate measure for protein content) is now carefully monitored to detect dilution and to prevent another episode of malnutrition, melamine was added to increase the measured nitrogen content and hide the dilution. This purposeful addition of melamine is suspected to be the cause of the melamine contamination of powdered milk in China.

Melamine and its metabolite cyanuric acid are excreted in the kidneys. Kidney stones containing melamine and uric acid were found in 13 children with acute kidney injury, who had consumed melamine containing milk formula.⁶⁹ Both melamine and cyanuric acid appear necessary to cause kidney stones in animals. The combination alone caused renal

crystals in cats.¹³⁵ Melamine found in wheat gluten was added to pet food in 2007 resulted in thousands of complaints, and dozens of suspected animal deaths in the United States.

The melamine milk contamination is one of the largest reported deliberate food adulteration incidents. It affected about 300,000 Chinese infants and young children and caused six deaths.^{41,80}

Food products from all over the world find their way into our foods. Increased vigilance by the agencies responsible for food safety, both in countries where the food originates and in countries that import the food, is needed to prevent other events such as the melamine contaminations.

Vegetables and Plants

Plants, vegetables, and their diverse presentations often are involved in food poisonings.^{72,87,88,93,94} Edible plants and plant products may be poorly cooked or prepared, or they may be contaminated. Extensive discussion of this may be found in Chap. 121.

FOOD POISONING AND BIOTERRORISM

The threat of terrorist assaults has received increased attention and is discussed in Chaps. 132 and 133. The use of food as a vehicle for intentional contamination with the intent of causing mass suffering or death has already occurred in the United States.^{38,90,165} In the first report, 12 laboratory workers had GI symptoms, primarily severe diarrhea, after consuming food purposefully contaminated with *Shigella dysenteriae* type II served in a staff break room.⁹⁰ Four workers were hospitalized; none had reported long-term sequelae. This *Shigella* strain rarely causes endemic disease. Nevertheless an identical strain, identified by pulsed-field gel electrophoresis, was found in eight of the 12 symptomatic workers, as well as in the pastries served in the break room, and in the laboratory stock culture of *S. dysenteriae*. This finding suggests purposeful poisoning of food eaten by laboratory personnel. The person responsible and the motive remain unknown.

The second case series describes a large community outbreak of food poisoning caused by *Salmonella typhimurium*.¹⁶⁵ The outbreak occurred in the Dalles, Oregon, area during the fall of 1984; a total of 751 people suffered salmonella gastroenteritis. The outbreak was traced to the intentional contamination of restaurant salad bars and coffee creamer by members of a religious commune using a culture of *S. typhimurium* purchased before the outbreak of food poisoning. A criminal investigation found a *Salmonella* culture on the religious commune grounds that contained *S. typhimurium* identical to the salmonella strain found in the food poisoning victims. It was identified by using antibiotic sensitivity, biochemical testing, and DNA restriction endonuclease digestion of plasmid DNA. Only after more than one year of investigation was this salmonella outbreak linked to terrorist activity. Reasons for the delay in identifying the outbreak as a purposeful food poisoning included (1) no apparent motive, (2) no claim of responsibility, (3) no pattern of unusual behavior in the restaurants, (4) no disgruntled restaurant employees identified, (5) multiple time points for contamination indicated by epidemic exposure curves, suggesting a sustained source of contamination and not a single act, (6) no previous event of similar nature as a reference, (7) the likeliness of other possibilities (eg, repeated unintentional contamination by restaurant workers), and (8) fear that the publicity necessary to aid the investigation might generate copycat criminal activity.

Publication of the event was delayed by almost 10 years out of fear of unintentionally encouraging copycat activity. On the other hand, use of biological weapons by the Japanese cult Aum Shinrikyo appears to have motivated authorities to release this publication in the hopes of quickly identifying similar deliberate food poisoning patterns in the future.

A third report describes a disgruntled employee who contaminated 200 lb of meat at a supermarket with a nicotine-containing insecticide.³⁸ Ninety-two people became ill, and four sought medical care. Symptoms included vomiting, abdominal pain, rectal bleeding, and one case of atrial tachycardia.

In another case of human greed, a Chinese restaurant owner poisoned the food in his neighbor's restaurant with tetramine. Tetramine or tetramethylenedisulfotetramine is a highly lethal neurotoxic rodenticide, once used worldwide, now illegal in the United States. The snack shop owner caused hundreds to become ill and 38 deaths by spiking his competitors' breakfast offerings (fried dough sticks, sesame cakes, and sticky rice balls). Tetramethylenedisulfotetramine is an odorless and tasteless white crystal that is water-soluble. The mechanism of action is noncompetitive irreversible binding to the chloride channel on the γ -aminobutyric acid receptor complex, which blocks the influx of chloride and alters the neurons' potential. It is referred to as a "cage convulsant" because of its globular structure. Severe toxicity presents with tachycardia, dysrhythmias, agitation as well as status epilepticus and coma. Immediate or early treatment with sodium-(RS)-2,3-dimercaptopropane-1-sulfonate (DMPS) and pyridoxine (vitamin B6) appears to be effective in a mouse model.^{12,50,174}

The capacity of foodborne xenobiotics that are easy to obtain and disburse to infect large numbers of people is clearly exemplified by two specific outbreaks: (1) the purposeful salmonella outbreak in Oregon, (2) the apparently unintentional salmonella outbreak that resulted in more than 16,000 culture-proven cases traced to contamination in an Illinois dairy. The probable cause of the outbreak was a contaminated transfer pipe connecting the raw and pasteurized milk containment tanks.¹³⁹ These events emphasize the vulnerability of our food supply and the importance of ensuring its safety and security.

SUMMARY

- The diverse etiologies of food poisoning involve almost all aspects of toxicology.
- Our concerns center around the natural toxicity of plants or animals, the contamination of which can occur in the field, during factory processing, subsequent transport and distribution, or during home preparation or storage.
- Whether these events are intentional or unintentional, they alter our approaches to general nutrition and society.
- Issues in food safety include the governmental role in food preparation and protection, bacteria such as *Salmonella* and *E. coli* O157:H7, prions in Creutzfeldt-Jacob disease (bovine encephalopathy), and genetically altered materials such as corn.
- Future discussions of food poisonings and interpretations of the importance of these problems may dramatically alter our food sources and their preparation and monitoring.

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45 HERBAL PREPARATIONS

Oliver L. Hung

Although there is increased awareness of the widespread use of herbal preparations in the United States, physicians frequently seek information about their usage only after the patient demonstrates toxicity.

HISTORY AND EPIDEMIOLOGY

Since ancient times and perhaps since prehistoric times, people of all cultures have used herbal preparations to treat disease and promote health.⁴⁰ A 60,000 year-old Iraqi burial site contained eight different medicinal plants, suggesting very early historical usage.¹⁴² The earliest surviving written account of medicinal plants is the Egyptian Ebers papyrus, circa 1500 B.C., which lists dozens of medicinal plants and their intended uses. In India, the Vedas, epic poems written in approximately 1500 B.C., contain references to herbal preparations of the time. In China, the Divine Husbandman's Classic, written in the first century A.D., lists 252 herbal preparations. In ancient Europe, herbal medicines were the mainstay of healing. In the first century, the Greek physician Dioscorides wrote one of the first European herbal books, *De Materia Medica*, which listed 600 herbals and was translated into many languages. Shamans and folk healers from the Americas, Africa, Australia, and Asia continue to include herbals for spiritual and medicinal purposes based on oral traditions passed from generation to generation.

During the Scientific Revolution, European scientists began to isolate purified extracts of plant products for use as medicinal agents. In 1804 and 1832, morphine and codeine were isolated from the sap of the poppy plant *Papaver somniferum*.⁷³ In the mid-eighteenth century, Edward Stone described in a letter to the president of the Royal Society of Medicine the successful use of the bark of the willow tree in curing "agues" (fever).²⁰ In 1829, salicin, the active ingredient of the willow bark, was identified. Its derivative sodium salicylate was marketed in 1875 as a treatment for rheumatic fever and as an antipyretic. The enormous success of this drug led to the synthesis of acetylsalicylic acid in 1899. The original name, aspirin (acetyl-spiric acid), is said to have been derived from *Spiraea*, the plant genus from which salicylic acid once was prepared. Even today, plant preparations still are being investigated for the development of modern drugs. Sweet wormwood (*Artemisia annua*, qing hao) was first described as a treatment for malaria in China in 168 B.C.⁸⁸ In 1971, the active parent compound artemisinin was first isolated by Chinese investigators. Artemisinin, when used in combination with other antimalarials, is considered the best treatment for falciparum-resistant malaria.^{85,107,134} Prescriptions from plant-derived medicines currently represent approximately 25% of prescriptions dispensed in the United States^{2,163} and at least 60% of nonprescription medications contain one or more natural products as ingredients.⁴⁸

Herbal preparations continue to be the dominant form of healing in the developing world because of the high cost of "Western" medical treatment and the scarcity of "Western"-trained medical personnel.^{47,92,95,108} The World Health Organization estimates that 4 billion people, up to 80% of the world population, use herbal preparations for some aspect of primary health care.^{2,166}

Herbal preparations and other dietary supplements are not only sold exclusively in health food stores but are readily available for sale in mainstream retail outlets such as grocery stores, drug stores, complementary medicine practitioners, offices, mail order companies, the Internet, and gasoline stations. US pharmaceutical companies have also entered the herbal market. US herbal dietary supplement sales were estimated at \$5.3 billion in 2011, representing direct sales of \$2.6 billion, natural and health food sales of \$1.8 billion, and \$1 billion from mass-market retailers. Over the last 4 years, sales have continued to increase: 4.5% in 2011, 0.2% increase in 2010, 4.8% in 2009, and 0.9% in 2008.¹⁴ Similarly, worldwide herbal preparation usage continues to grow. The current global herbal supplements and remedies market is valued at \$62 billion and it is predicted to reach \$107 billion by 2017.⁶⁷

Although they often are used by consumers in the hope of preventing or treating medical illness, herbals are not classified as medications; therefore, despite reports of toxicity associated with their usage, no systematic evaluation of herbal efficacy or safety is required. Additionally problematic is that patients often do not consider herbal preparations as medications and may not provide a history of usage unless questioned specifically about herbal usage.

Unfortunately, the medical profession's response to the widespread usage of herbal preparations appears to be inconsistent, with one study suggesting that the medical practitioner's knowledge of current herbal preparation regulations

is grossly inadequate.⁶ Several studies have attempted to determine how US hospitals regulate herbal preparation use in their facilities.^{4,9,43,63} Depending on the study, only 31% to 79% of respondents reported having formal policies governing the usage of herbal preparations in their facilities. Herbal preparation use was completely banned in 11% to 22% of facilities. However, the majority of facilities did allow the use of herbal preparations if they were ordered by an authorized prescriber. Identified concerns addressed in these studies included difficulties in identifying products (particularly “home supply” products), and concerns for appropriate dosing, efficacy, safety, and consistency. The conflicting approaches have been attributed to health care facilities attempting to balance patient-centered care with their legal, medical, and ethical concerns about these products.^{17,63}

In 1998, Congress established the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health to stimulate, develop, and support research in complementary and alternative medicines.¹⁰⁵ So far, NCCAM-funded studies have failed to demonstrate any clinical benefit for using St. John’s wort for depression,⁸¹ hawthorne for congestive heart failure,¹⁷⁰ echinacea for the common cold,¹⁵² glucosamine and chondroitin sulfate for osteoarthritis,⁴² saw palmetto for benign prostatic hypertrophy,¹¹ Ginkgo biloba for dementia,⁵² shark cartilage for lung cancer,¹⁰⁰ and cranberry juice for recurrent urinary tract infections.⁴¹

DEFINITION

The botanical definition of the term herb is specific for certain leafy plants without woody stems. However, the term herbal preparations often includes non-herb plant materials, even animal and mineral products. Thus, in a broad sense, the term herbals includes any “natural” or “traditional” remedy, but these terms also are poorly defined. Although these xenobiotics are often also called medications, this terminology may be inaccurate and misleading. Many herbal preparations purportedly are used for their nonspecific “adaptogenic” properties by permitting the body to return to a normal state by resisting stress, but they lack any specific medicinal effects. Because many herbal users and herbalists do not consider herbal preparations medications, use of the term herbal medicine by the clinician may convey a different, and perhaps unintended, meaning. For these reasons, it may be inappropriate and without benefit to refer to these products as medication, but they are xenobiotics.

Herbal preparations are considered to be a subset of “alternative therapies.” These therapies are defined as interventions that are neither widely taught in US medical schools nor generally available in US hospitals.⁵⁴ When these alternative therapies are used in conjunction with conventional medical therapies, they are also known as complementary and alternative medicine (CAM).¹¹⁷ The NCCAM groups CAM into five domains: whole medical systems (eg, Ayurveda, homeopathy), mind–body medicine (eg, prayer, hypnosis), biologically based practices (eg, herbal preparations, dietary supplements), manipulative and body-based practices (eg, acupressure, acupuncture, chiropractic, massage), and energy medicine (eg, therapeutic touch).¹¹⁷

The study of herbal preparations is complicated by the lack of standardized nomenclature, while the diversity of common, proprietary, and botanical names may increase the confusion. A single plant preparation may have many common names, in addition to its botanical name. For example, *Datura stramonium* is also known as jimson weed, Angel’s trumpet, apple of Peru, Jamestown weed, thornapple, and tolguacha. Likewise, a common name for a plant, such as gordolobo, may refer to several plants, such as *Verbascum thapsus* and *Gnaphalium macounii*.⁸⁰ The mandrake refers not only to the belladonna-alkaloid-containing *Mandragora officinarum* but also the podophyllum-containing *Podophyllum peltatum*. Thus, accurate classification of herbal preparations is very difficult, which limits effective study and increases the risk of adverse effects.

REGULATION OF HERBAL PREPARATIONS

For regulatory purposes the US government classifies herbal preparations as a type of dietary supplement, which means that the US Food and Drug Administration (FDA) classifies them as nutrients with nondrug status.⁴⁵ However, many nonherbals, such as vitamins, minerals, nutritional supplements, and food additives, are also dietary supplements (Chaps. 42, 46, and 47).

In the United States, herbal preparations are not subjected to the same standards as drugs. The FDA has gradually assumed an increased role in its vigilance over the manufacturing, marketing, and sales of herbal preparations. In 1994, Congress passed the Dietary Supplement Health and Education Act, which reduced the oversight by the FDA of products categorized as dietary supplements.⁵⁷ Dietary supplements include vitamins, minerals, herbals, amino acids, and any product that had been sold as a “supplement” before October 15, 1994.⁴⁵ After October 15, 1994, any new ingredient intended for use in dietary supplements requires notification and approval by the FDA at least 75 days in advance of marketing. The FDA must review and determine whether the proposed ingredient is expected to be safe under the intended conditions for use. However, because most ingredients contained in dietary supplements were in use prior to 1994, the vast majority of dietary supplements are not subject to even this weakened premarket safety evaluation. After marketing, if the

FDA determines that a manufactured dietary supplement is unsafe, the agency can warn the public, suggest changes to make the supplement safer, urge the manufacturer to recall the product, recall the product, or ban the product.

On several occasions the FDA has urged manufacturers to stop producing dietary supplements containing unsafe products. In July 2001, the FDA warned dietary supplement manufacturers to stop marketing products containing aristolochic acid because of nephrotoxicity and to remove comfrey products from the market because of hepatotoxicity. In November 2001, the FDA warned the manufacturer of LipoKinetix (containing phenylpropanolamine, caffeine, yohimbine, diiodothyronine, usnic acid) to remove the supplement from the marketplace because of reports of associated hepatotoxicity. In 2002, the FDA warned consumers and health care professionals of the risk of hepatotoxicity associated with the use of kava-containing products.¹⁵⁷ However, the FDA did not ban the development of kava-containing products or ban their sale in the United States. In March 2004, the FDA warned dietary supplement manufacturers to stop manufacturing androstenedione or face enforcement actions.¹⁵⁶ To ban a dietary supplement from the marketplace, the FDA must prove that the product is unsafe. In April 2004, the FDA banned all sales of dietary supplements containing ephedra. This was the first FDA prohibition of a supplement since 1994.¹⁵⁵ In April 2012, FDA warned manufacturers that the stimulant used in some fitness supplements, dimethylamylamine, did not qualify as a legal dietary supplement. One year later, the FDA issued a consumer warning that dimethylamylamine usage is associated with cardiovascular complications with 86 reported illnesses and deaths.¹⁵⁸

Because the law requires the FDA to consider dietary supplements as food products, quality control issues and production methods are governed by the Current Good Manufacturing Practices regulations for foods.¹⁵⁴ However, these regulations only ensure that foods, and thus dietary supplements, are produced under sanitary conditions; they do not guarantee the safety, efficacy, or quality of the product, as is required for pharmaceuticals. Two studies suggest that many herbal preparations do not even contain appreciable quantities of the listed herb. In one study of 54 ginseng products, 60% of those analyzed contained pharmacologically insignificant amounts of ginseng and 25% contained no ginsenosides.⁹⁷ A study of echinacea preparations determined that 10% of preparations contained no measurable echinacea, the assayed species was consistent with labeled content in 52% of the sample, and only 43% met the quality standard described by the label.⁶⁵ From 2004 to 2008, the FDA investigated online sales of dietary supplements purported to treat erectile dysfunction or enhance sexual performance by purchasing and analyzing the ingredients of these products.¹⁵³ One-third of the purchased dietary supplements (six out of 17) contained undisclosed prescription drug ingredients such as sildenafil, vardenafil, or related substances.¹⁵³ In a 2010 press announcement, the FDA revealed that the three most common categories of tainted products marketed as dietary supplements are weight loss products containing active ingredients such as sibutramine, body-building products containing anabolic steroids or steroid analogs, and sexual enhancement products that contain phosphodiesterase type 5 inhibitors such as sildenafil.⁵⁹

Herbal products can be initially marketed without any proof of testing for efficacy or safety. Although packaging that claims to cure or prevent a specific disease is not permitted unless approved by the FDA, claims detailing how a product affects the “body’s structure or function” are permissible. Substantiation of these claims is required only if challenged by regulators,¹⁵⁴ but the methodology and requirements for this substantiation are not well defined.

These findings were corroborated by a study evaluating herbal advertising on the Internet. The study determined that 81% of Web sites marketing dietary supplements made one or more health claims without approval from the FDA, and of these sites, 55% made specific claim to treat, prevent, or cure a specific disease.¹¹³

In March 1999, the FDA implemented new dietary supplement labeling rules. All dietary supplement labels must provide a statement of identity (eg, ginseng), net quantity of contents (eg, 60 capsules), structure–function claims with disclaimers that the product has not been evaluated by the FDA; directions for use; supplements fact panel (list of serving size, amount, and active ingredients), other ingredients list, and name and place of business of manufacturer, packer, or distributor. The Dietary Supplement and Nonprescription Drug Consumer Protection Act was signed into law in December 2006.⁵¹ Under this law, manufacturers, packers, or distributors of nutritional supplements are required to notify the FDA about serious adverse events related to their products. In 2007, the FDA issued its current good manufacturing practices final rule, effective in June 2008. The final rule is more stringent than previous regulations and it contains sections similar to current good manufacturing practices for drugs. Manufacturers are required to evaluate the identity, purity, strength, and composition of their dietary supplements. Yet, unlike the FDA regulations for drugs, the final rule still does not require any proof of efficacy or safety. In essence, the FDA, through its regulations, has gradually shifted dietary supplements from a poorly regulated food product into a unique category between a conventional food product and a drug. This has served to fuel the debate on both sides: those who view dietary supplements as more similar to food groups (eg, chamomile tea) and want less government regulation, and others who argue that herbs contain pharmacologically active drugs (eg, ephedra) that require greater regulation.^{106,114}

The FDA recently released data suggesting that its regulations alone are insufficient in ensuring the safety of dietary supplements sold in the United States. Since it began assessing good manufacturing practice compliance in 2008, the FDA has found violations of manufacturing rules in nearly one-half of the 450 dietary supplement firms it has inspected. One in four inspected companies had violations serious enough to warrant release of an FDA warning letter that could result in a

significant enforcement action such as halting production and distribution. The FDA also believes that adverse events associated with dietary supplements are significantly underreported by manufacturers even though it is required by law. For the first 10 months of 2008, the FDA received approximately 950 reports of adverse events, but the agency estimates the true annual number of adverse events is much higher at 50,000.^{102,151} In 2009, the US Government Accountability Office issued a report to Congress that provided four recommendations highlighting the difficulties the FDA had in ensuring the safety of dietary supplements sold in the United States.¹⁵⁹ First, the FDA should be given the authority to require dietary supplement companies to identify themselves as a dietary supplement company, to provide a list of all dietary supplement products they sell, and to report all adverse events related to dietary supplements. Second, the FDA should issue guidance to clarify when an ingredient is considered a new dietary ingredient, the evidence needed to document the safety of a new dietary ingredient, and appropriate methods to establish ingredient identity. Third, the FDA should provide guidance to the industry to clarify when products should be marketed as either dietary supplements or conventional food formulated with added dietary ingredients. Fourth, the FDA should coordinate with consumer outreach to educate consumers about the safety and efficacy of dietary supplements and to assess the effectiveness in improving consumer understanding about dietary supplement. In 2010, the US Government Accountability Office also conducted an investigation to determine whether storefront and mail-order retailers of herbal preparations are using deceptive or questionable marketing practices and whether herbal dietary supplements are contaminated with harmful substances.¹⁶⁰ The investigation found that many herbal dietary supplement retailers were making improper health claims and in some cases were giving potentially harmful medical advice. The study also found that many herbal dietary supplements contain contaminants. In 37 of the 40 herbal dietary supplements tested, trace contaminants were identified (metals or pesticides), although none were identified in quantities considered to be acutely toxic.

PHARMACOLOGIC PRINCIPLES

The pharmacologic activity of herbal preparations (plant containing or derived) can be classified by five active constituent classes: volatile oils, resins, alkaloids, glycosides, and fixed oils.¹⁴⁴

- **Volatile oils** are aromatic plant ingredients. They are also called ethereal or essential oils, because they evaporate at room temperatures. Many are mucous membrane irritants and have central nervous system (CNS) activity. Examples of herbs containing volatile oils include pennyroyal oil (*Mentha pulegium*), catnip (*Nepeta cataria*), chamomile (*Chamomilla recutita*), and garlic (*Allium sativum*; Chap. 43).
- **Resins** are complex chemical mixtures of acrid resins, resin alcohols, resinol, tannols, esters, and resenes. These substances are often strong gastrointestinal (GI) irritants. Examples of resin-containing herbs include dandelion (*Taraxacum officinale*), elder (*Sambucus* spp), and black cohosh root (*Cimicifuga racemosa*).
- **Alkaloids** are a heterogeneous group of alkaline and nitrogenous compounds. The alkaloid compound usually is found throughout the plant. This class consists of many pharmacologically active and toxic compounds. Examples of alkaloid-containing herbs include aconitum (*Aconitum napellus*), goldenseal (*Hydrastis canadensis*), and Jimson weed (*Datura stramonium*).
- **Glycosides** are esters that contain a sugar component (glycol) and a nonsugar (aglycone), which yields one or more sugars during hydrolysis. They include the anthraquinones, saponins, cyanogenic glycosides, and lactone glycosides. The anthraquinones (senna {*Cassia acutifolia*} and aloe {*Aloe vera*}) are irritant cathartics. Saponins (licorice {*Glycyrrhiza lepidota*} and ginseng {*Panax ginseng* and *P. quinquefolius*}) are mucous membrane irritants, cause hemolysis, and have steroid activity. Cyanogenic glycosides found in apricot, cherry, and peach pits release cyanide. Lactone glycosides (tonka beans {*Dipteryx odorata*}) have anticoagulant activities. Cardiac glycosides defined as cardioactive steroids (Chap. 65) are found in foxglove (*Digitalis* spp) and oleander (*Nerium oleander*).
- **Fixed oils** are esters of long-chain fatty acids and alcohols. Herbs containing fixed oils are generally used as emollients, demulcents, and bases for other products. Generally, they are the least active and least dangerous of all herbal preparations. Examples include olive (*Olea europaea*) and peanut (*Arachis hypogaea*) oils.

Factors Contributing to Herbal Toxicity

The toxicity of a plant may vary widely and depends on conditions such as the time of year and developmental stage at which the plant is collected.⁸⁰ The pyrrolizidine alkaloid content of *Senecio* leaves varies widely from month to month and year to year.⁸⁰ In some cases, only selective parts of a plant used to prepare an herbal preparation are responsible for its toxicity. For example, the pyrrolizidine content of comfrey–pepsin capsules varies from 270 to 2900 mg/kg, depending on whether the leaves or roots were used in the preparation.⁷⁹ The geographical area in which the plant is collected may affect its toxicity. *Senecio longilobus* from Gardner Canyon, Arizona, may contain up to 18% pyrrolizidine alkaloids by dry weight, the highest concentration/amount recorded for any *Senecio* plant species (normal concentration is 0.5%). Finally, conditions and duration of storage may affect its toxicity. The toxicity of *Crotalaria* decreases with storage because of the breakdown of pyrrolizidines.

Few poisonings result from the inherent toxicity of the herbal, because of the low concentration of active ingredient and the known safety of the chosen herb (Table 45–1). Instead, poisonings tend to result from the misuse, overuse (including increased concentration in some commercial derivative products), misidentification, misrepresentation, or contamination of the product. Metal and mineral poisonings from lead, cadmium, mercury, copper, selenium, zinc, and arsenic are associated with herbal preparation usage.^{28,36,46,50,53,121,125,130} High concentrations of these salts sometimes result from contamination during the manufacturing process of some herbal or patent medications (ready-made preparations used by traditional Chinese herbalists). In some cases, as with cinnabar (mercuric sulfide) and calomel (mercurous chloride), these ingredients are intentionally included for purported medicinal benefit.⁸⁶ Patent medications may also contain pharmaceutical medications, such as acetaminophen, aspirin, antihistamines, or corticosteroids.^{37,50} Many of these medicines are not listed on the packaging and may not even be approved for use in the United States. For example, four cases of agranulocytosis followed consumption of Chui Fong Tou Ku Wan, a preparation that contains both aminopyrine (which is not approved for nonprescription sales in the United States) and phenylbutazone (which was withdrawn from the US market in the 1980s), neither of which are listed on the packaging.¹³² Both aminopyrine and phenylbutazone are associated with agranulocytosis.

TABLE 45–1. Laboratory Analysis and Treatment Guidelines for Specific Herbal Preparations

<i>Herbal Preparation</i>	<i>Suggested Laboratory Analysis</i>	<i>Antidote</i>
Cardiac xenobiotics		
Ch'an Su (Bufo Bufo)	Serum digoxin, potassium	Digoxin-specific Fab
Foxglove	Serum digoxin, potassium	Digoxin-specific Fab
Oleander	Serum digoxin, potassium	Digoxin-specific Fab
Squill	Serum digoxin, potassium	Digoxin-specific Fab
Central nervous system xenobiotics		
Henbane	None	Physostigmine
Jimson weed (Datura)	None	Physostigmine
Mandrake	None	Physostigmine
Gastrointestinal xenobiotics		
Aloe	Serum electrolytes	Potassium repletion
Buckthorn	Serum electrolytes	Potassium repletion
Cascara	Serum electrolytes	Potassium repletion
Fo-Ti	Serum electrolytes	Potassium repletion
Senna	Serum electrolytes	Potassium repletion
Hematologic xenobiotics		
Dong Quai	PT	Vitamin K ₁
Tonka bean	PT	Vitamin K ₁
Woodruff	PT	Vitamin K ₁
Hepatic xenobiotics		
Pennyroyal oil	AST/ALT	N-acetylcysteine
Pyrrolizidine alkaloids	AST/ALT	None available
Metals		
	Ag, As, Au, Cd, Cr, Cu, Hg, Pb, Th, or Zn	Metal chelators
	Abdominal radiograph (as appropriate)	
Salicylates		
Medicated oils	Serum salicylate	Sodium bicarbonate, multiple-dose activated charcoal, hemodialysis
Cellular xenobiotics		
Apricot pits (cyanogenic amygdalin)	Lactate	Cyanide antidote
	WBC, BUN	? Glutamic acid
Autumn crocus (colchicine)	Lactate	Cyanide antidote
	WBC, BUN	? Glutamic acid
Elder (cyanide)	WBC, BUN	? Glutamic acid
May apple (podophyllin)		
Periwinkle (vincristine)		
Miscellaneous		
Licorice	Serum potassium	Potassium repletion
Quinine	ECG, serum potassium	Sodium bicarbonate, magnesium

ALT = alanine transferase; AST = aspartate transferase; BUN = blood urea nitrogen; ECG = electrocardiography; PT = prothrombin time; WBC = white blood cell.

CLASSIFICATION OF TOXICITY

Herbal preparations are associated with a wide variety of toxicologic manifestations (Table 45–2). In addition, many

individual herbal preparations are associated with multiple toxicologic effects. To better understand these effects, it is useful to organize herbal toxicity into several general categories.⁵⁹

TABLE 45–2. Selected Herbal Preparations, Popular Use, and Potential Toxicities

<i>Herbal Preparation</i>	<i>Scientific Name</i>	<i>Other Common Names</i>	<i>Traditional and Popular Usage</i>	<i>Active/Toxic Ingredient(s)</i>	<i>Adverse Events</i>
Aconite	<i>Aconitum napellus</i> <i>Aconitum kuznetsovii</i> <i>Aconitum carmichaelii</i>	Monkshood, wolfsbane caowu, chuamwu, bushi	Topical analgesic, neuralgia, asthma, heart disease	Aconite alkaloids (C19 diterpenoid esters) aconitine	GI upset, dysrhythmias
Agrimony	<i>Agrimonia eupatoria</i>	Cocklebur, stickwort, liverwort	Cataract, gallbladder disease, astringent		Photodermatitis
Alfalfa	<i>Medicago sativa</i>		Arthritis, diabetes	L-canavanine	High doses: lupus, pancytopenia
Aloe	<i>Aloe vera</i> and other spp	Cape, Zanzibar, Socotrine, Caracas, Carribyn	Heals wounds, emollient, laxative, abortifacient	Anthraquinones, barbaloin, isobarbaloin	GI upset, dermatitis, hepatitis
Apricot pits	<i>Prunus armeniaca</i>	—	(Laetrile) cancer remedy	Amygdalin	Cyanide poisoning
Aristolochia	<i>Aristolochia clematis</i> <i>Aristolochia reticulata</i> <i>Aristolochia fangchi</i>	Birthwort, heartwort, fangchi	Uterine stimulant, cancer treatment, antibacterial	Aristolochic acid	Nephrotoxin Renal cancer Retroperitoneal fibrosis
Artemisia	<i>Artemisia vulgaris</i> <i>Artemisia dracunculoides</i> <i>Artemisia lactiflora</i>	Mugwort, felon herb, moso, guzhou	Depression, dyspepsia, menstrual disorder, abortifacient	Lactones (sesquiterpenes)	GI upset, allergic reaction (skin, pulmonary)
Astragalus	<i>Astragalus membranaceus</i>	Huang qi, milk vetch root	Immune booster, AIDS, cancer, antioxidant, increase endurance	Astragalosides, trigonoside, and flavonoid constituent	May alter effectiveness of immunosuppressives (eg, steroids, cyclosporine)
Atractylis	<i>Atractylis gummifera</i>	Pinay thistle	Chewing gum, antipyretic, diuretic, gastrointestinal remedy	Potassium atractylate and gummiferin	Hepatitis, altered mental status, seizures, vomiting, hypoglycemia
Atractylodes	<i>Atractylodes macrophala</i>	Baizhu, cangzhu	Appetite stimulant, diuretic, GI upset	Atractylon, atractylol, atractylenolides	None
Autumn crocus	<i>Colchicum autumnale</i>	Crocus, fall crocus, meadow safran, mysteria, vellorita	Gout, rheumatism, prostate, hepatic disease, cancer, gonorrhea	Colchicine	GI upset, renal disease, agranulocytosis
Bee pollen, royal jelly	Derived from <i>Apis mellifera</i>	—	Increase stamina, athletic ability, longevity	Pollen mixture containing hyperallergenic plant pollen or fungi contamination	Allergic reactions, anaphylaxis
Bee venom	Derived from <i>Apis mellifera</i>	—	Immunomodulator	Phospholipase A2 and melittin, hyaluronidases	Allergic reactions, anaphylaxis
Betel nut	<i>Areca catechu</i>	Areca nut, pinlang, pinang	Stimulant	Arecoline	Possible bronchospasm, chronic use associated with leukoplakia and oropharyn- geal squamous cell carcinoma
Bilberry	<i>Vaccinium myrtillus</i>	Whortleberry, black whortles	Diarrhea, night vision, varicose veins	Anthocyanosides	None reported
Bitter orange	<i>Citrus auranti</i>	Changcao, Fructus auranti, green orange, kijiwa, Seville orange, sour orange, Zhi shi	Dyspepsia, increase appetite Weight loss	Synephrines	Cardiovascular toxicity, ephedrinelike effects
Bitter melon	<i>Momordica charantia</i>	Balsam pear	Abortifacient, diabetes, GI disorder, cancer, HIV therapy	Polysaccharide MAP-30 (protein)	None reported
Black cohosh	<i>Cimicifuga racemosa</i>	Black snakeroot, squawroot, bugbane, baneberry	Abortifacient, menstrual irregularity, astringent, dyspepsia	Triterpene glycosides	Dizziness, nausea, vomiting, headache
Black currant oil	<i>Ribes nigrum</i>	Quincy berry, squawcny berry	Immunostimulant, premen- strual syndrome	GLA (γ -linolenic acid) ALA (α -linolenic acid)	None reported
Blue cohosh	<i>Caulophyllum thalictroides</i>	Squaw root, papoose root, blue ginseng	Abortifacient, dysmenorrhea, antigastric	N-methylcytisine (2.5% the potency of nicotine)	Nicotinic toxicity

Boneset	<i>Eupatorium perfoliatum</i>	Thoroughwort, vegetable antimony, feverwort	Antipyretic	Pyrolizidine alkaloids	Possible hepatotoxicity, dermatitis, milk sickness
Borage	<i>Borago officinalis</i>	Beet plant, bee bread	Diuretic, antidepressant, antiinflammatory	Pyrolizidine alkaloids, amabiline	Hepatotoxicity
Boron		Boron	Topical astringent, wound remedy	Boron	Dermatitis, GI upset, renal and hepatic toxicity, seizures, coma, death
Broom	<i>Cytisus scoparius</i>	Scotch broom, Bannal, broom top	Cathartic, diuretic, induce labor, drug of abuse	L-Sparteine	Nicotinic toxicity
Buchu	<i>Agathosma betulina</i>	Bookoo, buku, diosma, buchu, bucco	Diuretic, stimulant, carminative, urine infections, insect repellent	Diosmin, hesperidin, pulegone	None reported
Buckthorn	<i>Rhamnus frangula</i>		Laxative	Anthraquinones	Diarrhea, weakness
Burdock root	<i>Artium lappa</i> <i>Artium minus</i>	Great burdock, gobo, lappa, beggar's button, harebur, niu bang zi	Diuretic, choleretic, induce sweating, skin disorders, burn remedy, diabetes treatment	Atropine (contamination with belladonna alkaloids during harvesting)	Anticholinergic toxicity
Calendula	<i>Calendula officinalis</i>	Marigold, garden marigold, pot marigold, gold blooms, hollygold	Wounds, dysmenorrhea, "radiation" dermatitis		None reported
Cantharidin	<i>Cantharis vesicatoria</i> beetle	Spanish fly, blister beetles	Aphrodisiac, abortifacient, blood purifier	Terpenoid: cantharidin	GI upset, urinary tract and skin irritant, renal toxicity
Caraway	<i>Umbelliferae carvi</i>		Antispasmodic, carminative	D-Carvone	
Carp bile (raw)	<i>Oreopharyngodon idella</i> <i>Cyprinus carpio</i>	Grass carp Common carp	Improve visual acuity and health	† Cyprinol, C27 bile alcohol	Hepatitis, renal failure
Cascara	<i>Rhamnus purshiana</i>	Cascara sagrada	Laxative	Anthraquinones	Diarrhea, weakness
Cat's claw	<i>Uncaria tomentosa</i> <i>Uncaria guianensis</i>	Uña de gato	AIDS, cancer, arthritis, ulcers, dysmenorrhea, wounds, contraceptives	Pentacyclic oxindole alkaloids, tetracyclic oxindole alkaloids	None reported
Catnip	<i>Nepeta cataria</i>	Catania, catnep, catmint	Indigestion, colic, sedative, euphoriant, headaches, emmenagogue	Nepetalactone	Sedative
Ch'an Su	<i>Bufo bufo garpinorum</i> <i>Bufo bufo melanostictus</i>	Stone, limestone, black stone, rock hard, chuan wu, kyeshin	Topical anesthetic, aphrodisiac, cardiac disease	Bufoadienolides, bufotenin	Dysrhythmias, hallucinations
Chamomile	<i>Matricaria inodora</i> , <i>Chamaemelum nobile</i>	Manzanilla	Digestive disorders, skin disorders, cramps	Allergens	Contact dermatitis, allergic reaction, anaphylaxis very rare
Chaparral	<i>Larrea tridentata</i>	Oreosote bush, greasewood, hediondilla	Bronchitis, analgesic, anti-aging, cancer	Homodihydroqualeic acid	Hepatotoxicity (chronic)
Chestnut	<i>Chestnut</i>	Horse chestnut, California buckeye, Ohio buckeye, buckeye	Arthritis, rheumatism, varicose veins, hemorrhoids	Esculetin, nicotine, quercetin, quercitrin, rutin, saponin, shikimic acid	Fasciculations, weakness, incoordination, GI upset, paralysis, stupor
Chuen-Lin	<i>Coptis chinensis</i> , <i>Coptis japonicum</i>	Golden thread, Huang-Lien, Ma-Huang	Infant tonic	Berberine: displaces bilirubin from protein	Neonatal hyperbilirubinemia
Clove	<i>Syzygium aromaticum</i>	Caryophyllum	Expectorant, antiemetic, counterirritant, anesthetic, carminative euphoriant	Eugenol (4-allyl-2-methoxyphenol)	Pulmonary toxicity (cigarettes)
Coltsfoot	<i>Tussilago farfara</i>	Coughwort, horsehood, koandong hua	Throat irritation, asthma, bronchitis, cough	Pyrolizidine alkaloids: tussilagin, senkirkine	Allergy, hepatotoxicity
Comfrey	<i>Symphytum officinale</i> , <i>Symphytum</i> spp., <i>S. x uplandicum</i>	Knitbone, bruisewort, black-wort, slippery root, Russian comfrey	Ulcers, hemorrhoids, bronchitis, burns, sprains, swelling, bruises	Pyrolizidine alkaloids: symphytine, echinidine, laurocarpine	Hepatic veno-occlusive disease

Compound Q	<i>Trichosanthes kirilowii</i>	Guaioogen, GLQ-223, Chinese cucumber root	Fever, swelling, expectorant, abortifacient, diabetes, AIDS	Trichosantin	Pulmonary injury (ALI), cerebral edema, cerebral hemorrhage, seizures, fever
Cordyceps (mushroom)	<i>Cordyceps sinensis</i>	Dong chong xia cao	Genital tonic, aphrodisiac, bronchitis, kidney disorders	Cordyceptic acid, Cordycepin	None reported
Damiana	<i>Turnera diffusa</i> var <i>aphrodisiaca</i>	—	Stimulant, purgative, aphrodisiac, antidepressant	Caryophyllene oxide, caryophyllene, δ -cadinene, elemene, 1,8-cineol	Genitourinary irritation
Dandelion	<i>Taraxacum officinale</i>		Diuretic, detoxifying remedy, bitter	Luteolin	None reported
Deer antler velvet			Erectile dysfunction, infertility, immunostimulant, antiinflammatory, athletic performance	Small amounts of androstenedione, dihydroepiandrosterone, and testosterone	None reported
Dong Quai	<i>Angelica polymorpha</i>	Tang kuei, dang gui	Blood purifier, dysmenorrhea, improve circulation	Coumarin, psoralens, safrole in essential oil	Anticoagulant effects, photodermatitis, possible carcinogen in oil
Echinacea	<i>Echinacea angustifolia</i> , <i>Echinacea purpurea</i>	American cone flower, purple cone flower, snakeroot	Infections, immunostimulant	Echinacoside	CYP1A2 inhibitor
Elder	<i>Sambucus</i> spp	Elderberry, sweet elder, sambucan	Diuretic, laxative, astringent, cancer	Isoquercitrin (cyanogenic glycoside: sambunigrin in leaves)	GI upset, weakness if uncooked leaves ingested
Ephedra	<i>Ephedra</i> spp	Ma-huang, Mormon tea, yellow horse, desert tea, squaw tea, sea grape	Stimulant, bronchospasm	Ephedrine, pseudoephedrine	Headache, insomnia, dizziness, palpitations, seizures, stroke, myocardial infarction, death
Evening primrose	<i>Oenothera biennis</i>	Oil of evening primrose	Coronary disease, multiple sclerosis, cancer, diabetes, rheumatoid arthritis, premenstrual syndrome	Cis- γ -linoleic acid	Lower seizure threshold
Fennel	<i>Foeniculum vulgare</i>	Common, sweet, or bitter fennel	Gastroenteritis, expectorant, emmenagogue, stimulate lactation	Volatile oils: transanethole, fenchone; estrogens: dianethole, photoanethole	Ingestion of volatile oils: vomiting, seizures, pulmonary injury (ALI), dermatitis, estrogen effects
Fenugreek	<i>Trigonella foenum-graecum</i>	Bird's foot, Greek hay seed	Expectorant, demulcent, antiinflammatory, emmenagogue, galactagogue, diabetes	4-hydroxyisoleucine	Hypoglycemia, hypokalemia
Feverfew	<i>Tanacetum parthenium</i>	Featherfew, altamisa, bachelor's button, featherfoil, febrifuge plant, midsummer daisy, nosebleed, wild quinine	Migraine headache, menstrual pain, asthma, dermatitis, arthritis, antipyretic, abortifacient		Oral ulcerations, "postfeverfew syndrome," rebound of migraine symptoms, anxiety, insomnia following cessation of chronic use
Fo-Ti	<i>Polygonum multiflorum</i>	Climbing knotwood, he shou-wu	Scrofula, cancer, constipation therapy, promote longevity	Anthraquinones: chrysophanol, emodin, rhein	Cathartic effects
Foxglove	<i>Digitalis purpurea</i> , <i>Digitalis lanata</i> , <i>Digitalis lutea</i> , <i>Digitalis</i> spp	Purple foxglove, throatwort, fairy finger, fairy cap, lady's thimble, scotch mercury, witch's bells, dead man's bells	Asthma, sedative, diuretic/ cardiotonic, wounds and burns (India)	Cardioactive steroids (eg, digitoxin, gitoxin, digoxin, digitalin, gitaloxin)	Blurred vision, GI upset, dizziness, muscle weakness, tremors, dysrhythmias
Garcinia	<i>Garcinia cambogia</i>	Brindberry, hydroxycitric acid	Weight loss	Hydroxycitric acid	May lower serum glucose concentration in diabetics
Garlic	<i>Allium sativum</i>	Allium, stinking rose, rustic treacle, nectar of the gods, da san	Infections, coronary artery disease, hypertension	Alliin, Ajoene	Contact dermatitis, gastroenteritis, antiplatelet effects

Gentian	<i>Gentiana lutea</i> , <i>Gentiana</i> spp	Bitter root, gall weed Longdancao	Bitter, digestive stimulant, emmenagogue	—	None reported
Germander	<i>Teucrium chamaedrys</i>	Wall germander	Antipyretic, abdominal disorders, wounds, diuretic, cholestatic	Furan neoderodane diterpenes	Hepatotoxicity, hepatitis, cirrhosis
Ginger	<i>Zingiber officinale</i>		Carminative, diuretic, antiemetic, stimulant, motion sickness	Volatile oil, phenol	Possible increased risk of bleeding when taken with anticoagulants
Ginkgo	<i>Ginkgo biloba</i>	Maidenhair tree, kew tree, tebonin, tanakan, rokan, kaveri	Asthma, chilblain, digestive aid, cerebral dysfunction	Ginkgo flavone glycosides and terpene lactones (ginkgolides and bilobalide)	Extracts: GI upset, headache, skin reaction; leaf: antiplatelet; allergic reactions
Ginseng	<i>Pinax ginseng</i> <i>Pinax quinquefolius</i> <i>Pinax pseudoginseng</i>	Ren shen	Respiratory illnesses, gastrointestinal disorders, impotence, fatigue, stress, adaptogenic, external demulcent	Ginsenosides: panaxin, ginsenin	Ginseng abuse syndrome
Glucamannan	<i>Amorphophallus konjac</i>	Konjac, konjac mannan	Weight-reducing agent; "grapefruit diet," increase viscosity, decrease gastric emptying	Polysaccharides	Esophageal and lower GI obstruction
Glucosamine	2-amino-2-deoxyglucose	Chitosamine	Wound-healing polymer, antiarthritic	Glucosamine	None reported
Goat's rue	<i>Goats officinalis</i>	French lilac, French honeysuckle	Antidiabetic	Galagone, paragalegine	Hypoglycemia
Guj	<i>Lycium barbarum, chinense</i>	Wolfberry, gou qi zi	Protect liver, improve eyesight, enhance immune system	Carotenoids, lutein, atropine	May inhibit warfarin metabolism
Goldenseal	<i>Hydrastis canadensis</i>	Orange root, yellow root, tumeric root	Astringent, GI disorders, dysmenorrhea	Berberine, hydrastine	GI upset, Very high doses: paralysis and respiratory failure
Gordolobo yerba	<i>Senecio longiloba</i> <i>Senecio aureus</i> , <i>Senecio vulgaris</i> <i>Senecio spartioides</i>	Groundsel, liverroot	Gargle, cough, emmenagogue	Pyrolizidine alkaloids	Hepatic venoocclusive disease
Gotu Kola	<i>Centella asiatica</i>	Hydnocotyle, Indian pen- nywort, talpetrako	Wound healing, tonic, antibacterial	Asiaticoside, asiatic acid, madecassic acid	Contact dermatitis
Grape seed	<i>Vitis vinifera</i>		Antioxidant: antiaging, peripheral vascular disease	Proanthocyanidins	None reported
Green tea	<i>Camellia sinensis</i>	Green tea	Antioxidant, weight loss, reduce cholesterol	Polyphenols (catechins and epigallocatechin gallate)	Hepatotoxicity from green tea extracts
Hawthorn	<i>Crataegus arjancantha</i> <i>Crataegus laevigata</i> <i>Crataegus monogyna</i>	English hawthorn, haw, maybush, whitethorn	Hypertension, CHF, dysrhythmias, antispasmodic, sedative	Hyperoside, vitesin, procyanidin	Hypotension, sedation
Heliotrope	<i>Crotalaria spectabilis</i> , <i>Heliotropium europaeum</i>	Rattlebox, groundsel, viper's bugloss, bush tea	Cancer	Pyrolizidine alkaloids	Hepatic venoocclusive disease
Herbane	<i>Hieronymus niger</i>	Fetid nightshade, poison tobacco, insane root, stinky nightshade	Sedative, analgesic, antispas- modic, asthma	Hyoscyamine, hyosine	Anticholinergic toxicity
Holly	<i>Ilex aquifolium</i> <i>Ilex opaca</i> <i>Ilex vomitoria</i>	English holly, American holly, and yaupon	Tea, emetic, CNS stimulant, coronary artery disease	Saponins	GI upset

Hoodia	<i>Hoodia gordonii</i>	Xhoba, khoba, Ghaap, hoodia cactus, South African desert cactus	Weight loss, appetite suppressant	PS7	None reported
Horny goat weed	<i>Epimedium grandiflorum</i>	Ying yang huo	Aphrodisiac	Icarin	None reported
Hydrangea	<i>Hydrangea arborescens</i> <i>Hydrangea paniculata</i>	Seven bark, wild hydrangea	Diuretic, stimulant, carminative, cystitis, renal calculi, asthma	Hydrangin, saponin	Dizziness, chest pain, GI upset
Iboga	<i>Lobelia inflata</i>	Ibogaine	Aphrodisiac, stimulant, hallucinogen, addiction treatment	Indole alkaloid: ibogaine	Hallucinations, cholinergic hyperactivity
Ingula	<i>Callipepla laureola</i>		Zulu traditional remedy	Potassium atractylatellike compound	Vomiting, hypoglycemia, centrilobular hepatic necrosis
Jalap	<i>Ipomoea purga</i>	—	Cathartic	Convulxin	Profuse watery diarrhea
Jimsonweed	<i>Datura stramonium</i>	Datura, stramonium, apple of Peru, Jamestown weed, thornapple, tolgucha	Asthma	Atropine, scopolamine, hyoscyamine, stramonium	Anticholinergic toxicity
Juniper	<i>Juniperus communis</i> <i>Juniperus macrocarpa</i>	Oil of sabinol	Toxic, diuretic, urinary antiseptic, emmenagogue, abortifacient	Monoterpenes (terpinen-4-ol)	Renal irritation
Kava kava	<i>Piper methysticum</i>	Awa, kava-kava, kava, tonga	Relaxation beverage, uterine relaxation, headaches, colds, wounds, aphrodisiac	Kava lactones Flavokawin A and B	Mild euphoria, muscle weakness Skin discoloration, hepatic failure
KH-3	Procaine HCl	Gerovital-H3, GH-3, Gerovita	Cerebral atherosclerosis, dementia, arthritis, hair loss, hypertension	Procaine	Procaine toxicity
Khat	<i>Catha edulis</i>	Qat, kat, chaat, Khat es Salabin, Tchaat, Gat	CNS stimulant, depression, fatigue, obesity, ulcers	Cathine, cathinone	Euphoria, dysphoria, stimulation, sedation, psychological dependence, leukoplakia
Kola nut	<i>Cola acuminata</i>	Botu cola, kola nut	Digestive aid, tonic, aphrodisiac, headache, diuretic	Caffeine, theobromine, kolanin	CNS stimulant
Kombucha	Mixture of bacteria and yeast	Kombucha tea, kombucha mushroom, Manchurian tea	Memory loss, premenstrual syndrome, cancer	—	Hepatotoxicity/metabolic acidosis
Levant berry	<i>Anemone cocculea</i>	Fish killer, fishberry, huckle elderberry, Indian berry, louseberry, poisonberry	Vermifuge, malaria	Picrotoxin	CNS stimulant, GI upset
Licorice	<i>Glycyrrhiza glabra</i>	Spanish licorice, Russian licorice, gancan	Gastric irritation	Glycyrrhizin	Flaccid weakness, dysrhythmias, hypokalemia, lethargy
Lipoic acid		D-Lipoic acid, thioctic acid	Antioxidant, diabetes, neuropathy, AIDS	Lipoic acid	Hypoglycemia
Lobelia	<i>Lobelia inflata</i>	Indian tobacco	Antispasmodic, respiratory stimulant, relaxant	Pyridine-derived alkaloids (lobeline)	Nicotine toxicity
Mace	<i>Myristica fragrans</i>	Mace, maceade, seed cover of nutmeg	Diarrhea, mouth sores, insomnia, rheumatism	Myristicin (methoxysafrole)	Hallucinations
Mandrake	<i>Mandragora officinarum</i>		Hallucinogen	Atropine, scopolamine, hyoscyamine	Anticholinergic toxicity
Mate	<i>Ilex paraguayensis</i>	Paraguay tea	Stimulant	Caffeine	Caffeine toxicity

Milk thistle	<i>Cnicus marianus</i> <i>Silybum marianum</i>	Mary thistle	Liver disease, antidepressant, HIV	Silymarin	None
Mistletoe	<i>Viscum album</i> <i>Phoradendron</i> <i>leucarpum</i>	Isador	Antispasmodic, calmative, cancer, HIV	Vicetoxins, lectins	GI upset, bradycardia, delirium
Morinda	<i>Morinda citrifolia</i>	Noni, Indian mulberry, noni/ nono, mengkudu, bajitan	Antioxidant, stress, depression	Polysaccharides, anthraqui- none: damncanthol	None
Morning glory	<i>Ipomoea purpurea</i> <i>L. violacea</i>	Heavenly blue, blue star, flying saucers	Hallucinogen	Lysergic acid lamide Ergine	LSD-like toxicity
Myrrh	<i>Commiphora molmol</i>	Mulmul, ogo, heesabol	Astringent, anesthetic, emmenagogue, antispasmodic, cancer	Sesquiterpenes	None
Nutmeg	<i>Myristica fragrans</i>	Mace, roo dou kou	Hallucinogen, abortifacient, aphrodisiac, GI disorders	Myristicin	Hallucinogen, GI upset
Oleander	<i>Nerium oleander</i>	Adelfa, laurier rose, rosa laurel, rose bay, rose francesca	Cardiac disorders, asthma, coma, cancer, epilepsy	Oleandrin, nerolin, Gentiobi- sycosandrin, odorside A	GI upset, diarrhea, dysrhythmias
Olive leaf extract	<i>Olea europaea</i>		Immunostimulant	Oleuropein	
Ostrich fern	<i>Matteuccia struthiopteris</i>	—	Laxative	—	GI upset if eaten undercooked
Parsley	<i>Petroselinum crispum</i>	Rock parsley, garden parsley	Diuretic, uterine stimulant, abortifacient	Myristicin, apiol, furocouma- rin, psoralen	Uterine stimulant, photosensitization
Passion flower	<i>Passiflora incarnata</i>	Passiflora, maypop	Insomnia, analgesic stimulant	Harmala alkaloids	Sedation
Pau d'Arco	<i>Tibebuia spp</i>	Ipe roxo, lapacho, taheebo tea	Tonic, "blood builder," cancer, AIDS	Naphthoquinone derivative: lapachol	GI upset anemia, bleeding
Pennyroyal oil	<i>Hedeoma pulegioides</i> <i>Mentha pulegium</i>	American pennyroyal, Squawmint, mosquito plant	Abortifacient, regulate men- struation, digestive tonic	Cyclohexanone: pulegone	Hepatotoxicity
Periwinkle	<i>Catharanthus roseus</i>	Red periwinkle, Madagascar or Cape periwinkle, old maid, church-flower, ram-goat rose, "myrtle," magdalena	Hallucinogen, ocular inflammation, diabetes, hemorrhage, insect stings, cancers	Vincristine, vinblastine Indole alkaloid	Vincristine/vinblastine toxicity
Podophyllum	<i>Podophyllum peltatum</i> <i>Podophyllum hexandrum</i> <i>Podophyllum emodi</i>	Mandrake, mayapple, American podophyllum Indian podophyllum guijiu	Cathartic, purgative	Podophyllin	Podophyllin toxicity
Pokeweed	<i>Phytolacca americana</i> <i>Phytolacca decandra</i>	American nightshade, Cancer jalap, inkberry, poke, scoke	Arthritis, emetic, purgative	Saponins: phytolactigenin, jalagonic acid, phytolac- cogenic acid, pokeweed nitrogen	Gastroenteritis, blurry vision, weakness, respiratory distress, seizures, leukocytosis
Pycnogenol (French maritime pine bark extract)	<i>Pinus pinaster</i>	Pine bark extract	Antioxidant, hypertension vascular disease, ADHD	Proanthocyanidins	None reported
Pygeum	<i>Prunus africana</i>	Pygeum africanum, African prune	Impotence, male infertility, prostate cancer, benign prostatic hypertrophy	β -sitosterol, pentacyclic terpenes, ferulic esters	None reported
Quinine	<i>Cinchona succirubra</i> <i>Cinchona calisya</i> <i>Cinchona ledgeriana</i>	Red bark, Peruvian bark, Jesuit bark, China bark Cinchona bark, quinaquina, fever tree	Malaria, fever, indigestion Cancer Hemorrhoids, varicose veins, abortifacient	Quinine	Cinchonism
Red bush tea	<i>Aspalathus linearis</i>	Rooibos tea	Anxiety, allergic dermatitis, indigestion	Aspalathin, isochlorogenic acid, orientin, rutin	None reported
Red clover	<i>Tribulus terrestris</i>	Trefoil, purple clover, wild clover	Boonchitis, cough, eczema, acne, premenstrual syndrome	Isoflavones: biochanin A and farnesochlorogenic	None reported

Rehmannia	<i>Rehmannia glutinosa</i>	Sheng di huang, Chinese foxglove root	Arthritis, asthma, kidney and liver tonic, aplastic anemia, hypopituitarism	Iodoids and iridoid glycosides	None reported
Reishi mushroom	<i>Ganoderma lucidum</i>	Ling zhi, lucky fungus	Hepatitis, promote longevity	Polysaccharide peptides, triterpenes (ganoderic acid)	None reported
Rosavin	<i>Rhodiola rosea</i>	Golden root, cimulin	Weight loss, aphrodisiac, adaptogen, improve cognitive function	Loastralin, rosavin, rosin, rosarin, salidroside	None reported
Rose hips	<i>Rosa canina</i>	Hip berry, rose haws, rose hips, wild boar fruit	Vitamin C supplement, Upper respiratory infection, diarrhea	Vitamin C, vitamin K	May interfere with warfarin
Rue	<i>Ruta graveolens</i>	Herb of grace, herb grass	Emmenagogue, antispasmodic, abortifacient	Furocoumarins, bergapten, xanthoxanthin	Photosensitization
Sage	<i>Salvia officinalis</i>	Garden sage, true sage, scarlet sage, meadow sage	Antiseptic, astringent, hormonal stimulant, carminative, abortifacient	Camphor, thujone	Seizures
St. John's wort	<i>Hypericum perforatum</i>	Klamath weed, John's wort, goatweed, sha-rongye	Anxiety, depression, gastritis, insomnia, promote healing, AIDS	Hyperforin, Hypericin	Occasional photosensitization, drug interaction: CYP3A4
Salvia	<i>Salvia divinorum</i> <i>Salvia miltiorrhiza</i>	Sierra mazateca, diviners sage, magic mint, Maria pastora	Hallucinogen, renal disease	Salvinorin A Lithospermate B	Hallucinations
SAM-e	S-adenosyl-L-methionine		Antidepressant, osteoarthritis, liver disease	S-adenosyl-L-methionine	None reported
Sassafras	<i>Sassafras albidum</i>	Lauraceae	Stimulant, antispasmodic, purifier	Sassafras oil (10% Saffrole)	Hepatotoxicity, carcinogen (?)
Saw palmetto	<i>Serenoa repens</i>	Sabal, American dwarf palm tree, cabbage palm	Genitourinary disorders, increase sperm production, sexual vigor	5- α reductase inhibitor	Diarrhea
Schisandra	<i>Schisandra chinensis</i>	Wu zhi zi, five flavored seed	Tonic, aphrodisiac, liver treatment, sedative	Schisandrins, nigric acid	None reported
Scullcap	<i>Scutellaria lateriflora</i>	Skullcap, helmetflower, hood wort	Tranquillizer, tonic, antispasmodic	Flavone glucuronides and flavanone glucuronides	None reported
Senna	<i>Cassia acutifolia</i> <i>Cassia angustifolia</i>	Alexandrian senna	Stimulant, laxative, diet tea	Anthraquinone, glycosides (sennosides)	Diarrhea, CNS effects
Shark cartilage	<i>Squalus acanthias</i> <i>Sphyrna lewini</i>	—	Cancer: inhibit tumor angiogenesis	Chondroitin sulfate	None reported
Siberian ginseng	<i>Eleutherococcus senticosus</i>	Devil's shrub, eleuthera, eleutherococ	Adaptogens, hypertension, immunomodulator	Ginsenosides	None reported
Slippery elm	<i>Ulmus rubra</i> <i>Ulmus fulva</i>	Elm, elm bark, red elm	Acne, boils, indigestion, abortifacient	Polysaccharide mucilage Oleomin	Contact dermatitis
Soapwort	<i>Saponaria officinalis</i>	Blowwort, bouncing bet, dog doves, fuller's herb, latherwort	Acne, psoriasis, eczema, boils, natural soaps	Saponins	Intravenous: highly toxic Oral: None
SOD	Superoxide dismutase	Ogokein, ormetein, palosein	Improve health, lengthen lifespan, chronic bladder disease, paraquat poisoning	Superoxide dismutase	None reported
Soy isoflavone	<i>Glycine max</i>		Menopausal symptoms, heart disease	Phytoestrogens: genistein, daidzein, glycitein	Cancer
Squill	<i>Urginea maritima</i> <i>Urginea indica</i>	Sea onion Red Squill	Diuretic, emetic, cardiotonic, expectorant	Cardioactive steroid, scillaren A	Emesis, dysrhythmias

Stephania	<i>Stephania tetrandra</i>	Han fang ji	Fever, pain, inflammation, decrease water retention	—	None (misidentification of this herb with aristolochia (Guang fang ji) resulted in cases of Chinese herb nephropathy)
Stevia	<i>Stevia rebaudiana</i>	Sweet leaf of Paraguay	Sugar-free sweetener, diabetes, hypertension, weight-loss aid	Stevioside	None reported
Tu-san-chi	<i>Gymura segetum</i>	—	Tea	Pyrolizidine alkaloids	Hepatic veno-occlusive disease
Tonka bean	<i>Dipteryx odorata</i> , <i>Dipteryx oppositifolia</i>	Tonquin bean, coumaru	Food, cosmetics	Coumarin	Anticoagulant effect
Tung seed	<i>Aleurites moluccana</i> <i>A. fordii</i>	Tung, candlenut, candleberry, barnish tree, balucanat, otahrite	Wood preservative (oil), purgative (oil), asthma treatment (seed)	Saponins, phytotoxins	GI upset, hyporeflexia, death; latex dermatitis
Valerian	<i>Valeriana officinalis</i>	Radix valerianae, Indian Valerian, red valerian	Anxiety, insomnia, antispasmodic	— Valepotriates, valerenic acid	Sedation
Vitex	<i>Vitex agnus-castus</i>	Chasteberry, chaste tree, agnus castus	Premenstrual syndrome, female infertility	—	None reported
White cohosh	<i>Actaea alba</i> , <i>Actaea rubra</i>	Baneberry, snakeberry, doll's eyes, coralberry	Emmenagogue	Protoanemonin	Headache, GI upset, delirium, circulatory failure
White willow bark	<i>Salix alba</i>	Common willow, European willow	Fever, pain astringent	Salicin	Salicylate toxicity
Wild lettuce	<i>Lactuca virosa</i> (<i>Lactuca sativa</i>)	Lettuce opium, prickly lettuce	Sedative, cough suppressant, analgesic	—	None reported
Woodruff	<i>Galium odoratum</i>	Sweet woodruff	Wound healing, tonic, varicose veins, antispasmodic	Coumarin	None reported
Wormwood	<i>Artemisia absinthium</i>	Absinthies	Sedative, analgesic, antihelminthic	Thujone	Psychosis, hallucinations, seizures
Yarrow	<i>Achillea millefolium</i>	Bloodwort, carpenter's grass, dog daisy, nosebleed	Heal wounds, viral symptoms, digestive disorder, diuretic	—	Contact dermatitis
Yew	<i>Taxus baccata</i>	Yew	Antispasmodic, cancer remedy	Taxine (sodium channel blocker)	Dizziness, dry mouth, bradycardia, cardiac arrest
Yohimbe	<i>Pausinystalia yohimbe</i>	Yohimbé, yohimbebe	Body building, aphrodisiac, stimulant	Alkaloid yohimbine from bark	Hypertension, abdominal pain, weakness

(AC = central nervous system, GI = gastrointestinal)

Direct Health Risks

Direct health risks include pharmacologically predictable and dose-dependent toxic reactions, idiosyncratic toxic reactions, long-term toxic effects, and delayed toxic effects. For example, ingestion of aconite tea, in the suggested dose, causes tachydysrhythmias and hypotension. Idiosyncratic toxic reactions cannot be predicted on the basis of principal pharmacologic properties. For example, ingestion of chamomile tea results in anaphylaxis in a small subset of patients with probable allergies to the Compositae family. Long-term toxic effects occur only after chronic usage. For example, chronic use of herbal anthranoid laxatives results in muscular weakness from hypokalemia. Delayed toxic effects include carcinogenicity and teratogenicity. Another example is urothelial cancers in humans as a result of prolonged consumption of Aristolochia.¹¹⁹

Indirect Health Risks

Herbal use may adversely impact health by altering previous conventional prescription medication therapy. A patient may

discontinue or become less compliant with previous therapy, with untoward consequences. Alternatively, the addition of an herbal preparation may affect the pharmacologic effect, principally by altering the bioavailability or clearance of concurrently used medications. Coadministration of St. John wort, an inducer of CYP3A4, with the protease inhibitor indinavir, which is metabolized by this enzyme, may result in decreased plasma indinavir concentrations and potentially decreased antiretroviral activity.¹²⁸

Most Widely Used Herbal Supplements

The most popular herbal supplements (food, drug, and mass-market retail outlets {excluding warehouse buying clubs and convenience store sales}) in the United States in 2011 are listed below in order of sales.¹⁴ The top five represent more than \$100 million of sales.¹⁴

1. **Cranberry** (*Vaccinium macrocarpon*)—Cranberry is a popular remedy for treatment of urinary tract infections, but it appears to be ineffective in preventing recurrent urinary tract infections.⁴¹ Cranberry appears to be safe in appropriate doses.⁷
2. **Soy** (*Glycine max*)—Soy contains two popularly advertised ingredients: protein and isoflavones. Diets high in soy protein are associated with decreased cholesterol and low-density lipoprotein concentrations. Soy isoflavone supplements (genisten, daidzen) are phytoestrogens (plant estrogens) that currently are suggested as alternative remedies for treatment of menopausal symptoms. There is current concern regarding the effect of high concentrations of isoflavones on the risk of developing breast cancer in postmenopausal women and breast cancer survivors.
3. **Saw palmetto** (*Serenoa repens*)—Saw palmetto is a popular remedy for benign prostatic hypertrophy. Saw palmetto inhibits 5- α -reductase. However, a recent study observed that saw palmetto did not improve symptoms or objective measures of benign prostatic hypertrophy.¹¹ Saw palmetto appears to be safe in appropriate doses.^{110,122}
4. **Garlic** (*Allium sativum*)—Garlic has been used as a food and a medicine since ancient times. As a herb, it is used for treatment of infections, hypertension, colic, and cancer.⁶⁴ The intact cells of garlic contain the odorless, sulfur-containing amino acid derivative (+)-S-allyl-L-cysteine sulfoxide, also known as alliin. When crushed, alliin is converted to allicin (diallyl thiosulfinate), which has antibacterial and antioxidant activity and gives the herb its characteristic odor and flavor. Adverse effects of garlic extracts include contact dermatitis, gastroenteritis, nausea, and vomiting. Several constituents of garlic, such as ajoene, possess antiplatelet effects. Consequently, garlic may increase the risk of bleeding in individuals who are also taking antithrombotics.⁶⁴
5. **Ginkgo** (*Ginkgo biloba*)—This herb contains ginkgo flavone glycosides, known as ginkgolides, that are reputed to have antioxidant properties, inhibit platelet aggregation, and increase circulation. It is popularly used to treat or prevent both Alzheimer disease and peripheral vascular disease. However, two studies in 2002 and 2008 failed to demonstrate any improvement in cognitive function in healthy elderly subjects without cognitive impairment.^{52,143} In appropriate doses ginkgo appears to be safe, although it may increase the risk of bleeding in individuals who are also taking antithrombotics or anticoagulants.^{61,110,122}
6. **Milk thistle** (*Silybum marianum*)—Milk thistle contains silymarin and silibinin, and is a popular remedy for treatment of liver dysfunction. It is also an investigational antidote for *Amanita* mushroom poisoning. It appears to be safe (Antidotes in Depth: A36).
7. **Echinacea** (*Echinacea purpurea*, *angustifolia*)—Echinacea is a reputed immunostimulant and is a popular herbal remedy for cold symptoms. However, an NCCAM-funded study was unable to detect any improvement in preventing these symptoms.¹⁵² Echinacea appears to be safe in appropriate doses.⁷¹ Rare individuals develop allergic reactions when taking echinacea.¹¹⁵
8. **Black cohosh** (*Cimicifuga racemosa*)—Black cohosh is used for the treatment of premenstrual syndrome and as alternative estrogen replacement therapy for relief of perimenopausal symptoms. It also is used as a treatment for arthritis and as a mild sedative. Black cohosh appears to be safe in appropriate doses.^{13,78}
9. **St. John wort** (*Hypericum perforatum*)—St. John wort is used to treat depression and is also used as a topical remedy for cuts, bruises, and wounds.¹³⁵ It has lost its popularity as an AIDS treatment because of the lack of clinical efficacy.⁷² The active ingredients are hyperforin and hypericin. Its antidepressant properties likely derive from the ability of hyperforin to inhibit the reuptake of serotonin, dopamine, norepinephrine, γ -aminobutyric acid, and glutamate.²² A major study in 2002 demonstrated that St. John wort is ineffective in treating depression.⁸¹ Acute toxicity appears limited to photosensitization reactions. St. John wort induces CYP3A4 and may interact with medications metabolized by this enzyme (eg, indinavir, oral contraceptives, cycloserine).^{103,128} Hyperforin is a weak monoamine oxidase inhibitor, raising concerns about interactions with the selective serotonin reuptake inhibitors.¹²⁸
10. **Ginseng** (*Panax ginseng*)—Ginseng is the common name for deciduous, perennial plants of the genus *Panax*. *Panax ginseng* is native to Korea, China, Japan, and Russia. *Panax quinquefolius* is the common ginseng species in North America and grows abundantly throughout the central and eastern regions of Canada and the United States. Ginseng

preparations have been used in China for treatment of respiratory illnesses, GI disorders, impotence, fatigue, and stress (“adaptogenic effect”). It is regarded as a tonic and panacea (hence the name *Panax*, meaning “all healing”). Its only recognized use in the United States is as an external demulcent.^{66,96,111} Ginseng provides a good example of the complexity of the biochemistry and pharmacologic effects of herbs. The active components of ginseng are called ginsenosides and include panaxin, panax acid, panaquin, panacen, sapogenin, and ginsenin. Its general metabolic effects include decreasing serum glucose and serum cholesterol concentrations; increasing erythropoiesis, hemoglobin production, and iron absorption from the GI tract; increasing blood pressure and heart rate; GI motility; and CNS stimulation. Ginseng abuse syndrome, which consists of hypertension, nervousness, sleeplessness, and morning diarrhea, has been described following long-term use of ginseng.^{66,139,140} Ginseng use may reduce the anticoagulant effect of warfarin.^{82,169}

11. Valerian (*Valeriana officinalis*)—Valerian is a popular remedy for treatment of anxiety and is also used as a sleeping aid. Valerian appears to be safe in appropriate doses. Valerian may potentiate sedation in patients taking sedative-hypnotics.¹²²

12. Green tea—Green tea is a popular antioxidant used to prevent chronic disease as well as for weight reduction. It is also touted to protect against cancer and decrease cholesterol concentrations. A 2006 study in Japan observed that green tea consumption was associated with a decreased mortality from all causes of cardiovascular disease.⁹¹ Polyphenols contained in green tea including catechins and epigallocatechin gallate are responsible for its antioxidant properties. Although green tea consumption is considered to be safe, recent case reports describing the development of acute hepatitis following ingestion of green tea extracts or infusions suggest that idiosyncratic hepatotoxicity may occur in rare individuals.^{12,15,62,68,83,84}

13. Evening primrose (*Oenothera biennis*)—Evening primrose contain *cis*- γ -linoleic acid, a prostaglandin E₁ precursor. This herb is a popular remedy for treatment of premenstrual syndrome, diabetes, eczema, and rheumatoid arthritis. Evening primrose appears to be safe in appropriate doses. This herb may lower the seizure threshold in epilepsy.

TOXICITY OF SIGNIFICANT HERBAL PREPARATIONS

Cardiovascular Toxins

Aconite. Aconites (caowu, chuanwu, and fuzi) are the dried root stocks of the *Aconitum* plant.¹⁴⁶ In China, aconite usually is derived from *Aconitum carmichaelii* (chuan wu) or *A. kuznezoffii* (caowu). In Europe and the United States, aconite is derived from *A. napellus*, commonly known as monkshood or wolfsbane. The tubers are the most toxic part of the plant. When ingested, both cardiac and neurologic toxicity occur. Aconite poisoning is far more common in Asia, especially China.³⁹ In Hong Kong, it is responsible for the majority of serious poisonings from Chinese herbal preparations.^{35,37,39}

Aconite toxicity is caused by C19 diterpenoid-ester alkaloids, including aconitine, mesaconitine, and hypaconitine.²¹ Aconitine increases sodium influx through the sodium channel, increasing inotropy while delaying the final repolarization phase of the action potential and promoting premature excitation.⁷⁶ Sinus bradycardia and ventricular dysrhythmias can occur.³⁸ Symptoms can occur from 5 minutes to 4 hours after ingestion. Paresthesias of the oral mucosa and entire body may be followed by nausea, vomiting, diarrhea, and hypersalivation, and then by progressive skeletal muscle weakness. Fatalities may occur with doses as low as 5 mL aconite tincture, 2 mg pure aconite, or 1 g dried plant. Atropine may be of value in treating bradycardia or hypersalivation.¹⁴⁷ Although no antidote is available, anecdotal reports suggest the use of amiodarone, flecainide, lidocaine, and procainamide for ventricular tachydysrhythmias.^{147,168} Pharmacologic principles support the use of these sodium channel blockers. One case of aconite-induced refractory tachydysrhythmias was successfully managed with a ventricular assist device.⁵⁶ In a case series of two aconite-poisoned patients, reversal of aconite-induced ventricular dysrhythmias was attributed to the use of charcoal hemoperfusion for aconitine removal.^{98,99}

Ch'an Su. Ch'an Su is a traditional herbal remedy derived from the secretions of the parotid and sebaceous glands of the toad *Bufo bufo gargarizans* or *Bufo melanostictus*. This remedy is traditionally used as a treatment for congestive heart failure.⁸⁹ Ch'an Su contains two groups of toxic compounds: digoxinlike cardioactive steroids consisting of bufadienolides and the alkaloid bufotenin. Clinical findings following ingestion are similar to cardioactive steroid poisoning, including gastrointestinal symptoms and dysrhythmias. It was also marketed as an aphrodisiac for its purported topical anesthetic effects and sold under names such as “Stone,” “Love Stone,” “Black Stone,” and “Rock Hard.” Between 1993 and 1996 in New York City, several fatalities were associated with the ingestion of Ch'an Su marketed as a topical aphrodisiac.²⁵ Severe toxic reactions and death are reported after mouthing toads, “toad licking,” or eating an entire toad, or ingesting toad soup, or toad eggs.¹⁸ Assays for serum digoxin unpredictably cross-react with bufadienolides, but may qualitatively assist in making a presumptive diagnosis (Table 45–1). Digoxin-specific Fab was successfully used to treat Ch'an Su poisoning and should be empirically administered for any suspected case of cardiotoxicity from Ch'an Su or other cardioactive

steroid^{18,141} (Chap. 65).

Central Nervous System Toxins

Absinthe. Wormwood (*Artemisia absinthium*) extract is the main ingredient in absinthe, a toxic liquor that was outlawed in the United States in 1912. This volatile oil is a mixture of α - and β -thujone (Table 45–3).¹⁶⁷ Chronic absinthe use caused “absinthism,” characterized by psychosis, hallucinations, intellectual deterioration, and seizures. The most famous victim of absinthism may have been Vincent Van Gogh, who is thought to have suffered from this disorder in the later part of his life.⁵ A thujone-free wormwood extract now is used for flavoring vermouth and pastis. A case of wormwood-induced seizures, rhabdomyolysis, and acute kidney failure was described involving a patient who purchased from the Internet and consumed approximately 10 mL essential oil of wormwood, assuming it was absinthe liquor.¹⁶⁴ Treatment remains supportive.

TABLE 45–3. Constituent Psychoactive Xenobiotics in Herbal Preparations

Labeled Ingredient	Scientific Name	Usage	Active Ingredients	Effects
Broom	<i>Cytisus scoparius</i>	Smoke for relaxation	L-Sparteine	Sedative-hypnotic
California poppy	<i>Eschscholzia californica</i>	Smoke as marijuana substitute	Alkaloids and glucosides	Euphoriant
Catnip	<i>Nepeta cataria</i>	Smoke or tea as marijuana substitute	Nepetalactone	Euphoriant
Ch'an Su	<i>Bufo bufo gargarizans</i> <i>Bufo bufo melanostictus</i>	Smoke or lick for hallucinations	Bufofenin	Hallucinogen
Cinnamon	<i>Cinnamomum camphora</i>	Smoke with marijuana	?	Stimulant
Dove	<i>Syzygium aromaticum</i>	Smoke in cigarette/"kreteks"	Eugenol	Euphoriant
Damiana	<i>Turnera diffusa</i>	Smoke as marijuana substitute	?	Stimulant/hallucinogen
Goldenseal	<i>Hydrastis canadensis</i>	Ingest to mark detection of opioid, marijuana, or cocaine in urinary drug screen	—	No evidence
Hops	<i>Humulus lupulus</i>	Smoke or tea as sedative and marijuana substitute	Humulone, lupulone → methylbutenol	Sedative (mild)
Hydrangea	<i>Hydrangea paniculata</i>	Smoke as marijuana substitute	Hydrangin, saponin	Stimulant
Ibogaine	<i>Tabernaemontana iboga</i>	Stimulant, hallucinogen	Ibogaine	Hallucinogen
Juniper	<i>Juniperus macrocarpa</i>	Smoke as hallucinogen	?	Hallucinogen
Kava kava	<i>Piper methysticum</i>	Smoke or tea as marijuana substitute	Kava lactones	Hallucinogen
Kola nut	<i>Cola acuminata</i>	Smoke, tea, or capsules as stimulant	Caffeine, theobromine, kolanin	Stimulant
Lobelia	<i>Lobelia inflata</i>	Smoke or tea as marijuana substitute	Lobeline	Euphoriant
Mandrake	<i>Mandragora officinarum</i>	Tea as hallucinogen	Atropine, scopolamine	Hallucinogen
Mate	<i>Ilex paraguayensis</i>	Tea as stimulant	Caffeine	Stimulant
Mormon tea	<i>Ephedra nevadensis</i>	Tea as stimulant	Ephedrine	Stimulant
Morning glory	<i>Ipomoea violacea</i>	Seeds have hallucinogens	D-lysergic acid amide (ergine)	Hallucinogen
Nutmeg	<i>Myristica fragrans</i>	Tea as hallucinogen	Myristicin	Hallucinogen
Passion flower	<i>Passiflora incarnata</i>	Smoke, tea, or capsules as marijuana substitute	Harmala alkaloids	Stimulant (mild)
Periwinkle	<i>Catharanthus roseus</i>	Smoke or tea as euphoriant	Indole alkaloids	Hallucinogen
Prickly poppy	<i>Argemone mexicana</i>	Smoke as euphoriant	Protopine, berberine, isoquinolones	Analgesic
Sahia	<i>Sahia divinatorum</i>	Smoked, chewed	Sahivorium A	Hallucinogen
Snakeroot	<i>Rauwolfia serpentina</i>	Smoke or tea as tobacco substitute	Reserpine	Tranquilizer
Thorn apple	<i>Datura stramonium</i>	Smoke or tea as tobacco substitute or hallucinogen	Atropine, scopolamine	Hallucinogen
Tobacco	<i>Nicotiana spp</i>	Smoke as tobacco	Nicotine	Stimulant
Valerian	<i>Valeriana officinalis</i>	Tea or capsules	Choline, valericine alkaloids	Tranquilizer
Wild lettuce	<i>Lactuca sativa</i>	Smoke as opium substitute	Unknown	Analgesic (mild)
Wormwood	<i>Artemisia absinthium</i>	Smoke or tea as relaxant	Thujone	Analgesic
Yohimbe	<i>Pausanistalia yohimbe</i>	Smoke or tea as stimulant	Yohimbine	Hallucinogen (mild)

Anticholinergics: Henbane, Jimson Weed, Mandrake. Many plants contain the belladonna alkaloids atropine (D,L-hyoscyamine), hyoscyamine, and scopolamine (L-hyoscyne). They may still be used therapeutically for treatment of asthma and occasionally are mistakenly included in herbal teas.³⁴ Signs and symptoms of anticholinergic poisoning include

mydriasis, diminished bowel sounds, urinary retention, dry mouth, flushed skin, tachycardia, and agitation. Mildly poisoned patients usually require only supportive care and sedation with intravenous benzodiazepines. Intravenous physostigmine reverses anticholinergic poisoning; however, its use should be limited to treatment of moderately to severely symptomatic patients because inappropriate use may cause seizures and dysrhythmias (Antidotes in Depth: A9).

Ephedra. Members of the genus *Ephedra* generally consist of erect evergreen plants resembling small shrubs.¹⁵⁰ Common names include sea grape, ma-huang, yellow horse, desert tea, squaw tea, and Mormon tea. *Ephedra* species have a long history of use as stimulants and for management of bronchospasm. They contain the alkaloids ephedrine and, in some species, pseudoephedrine.^{132,150} In large doses, ephedrine causes nervousness, headache, insomnia, dizziness, palpitations, skin flushing, tingling, vomiting, anxiety, restlessness, mania, and psychosis. The treatment is similar to that for other CNS stimulants (Chap. 76). In a published review of 140 reports of adverse events associated with ephedra use submitted to the FDA, 62% of cases (82) were considered “probable” or “possibly” related to ephedra use. Hypertension was the most commonly reported adverse effect (17 cases), followed by palpitations or tachycardia (13 cases), strokes (10 cases), and seizures (seven cases). Ten reported cases resulted in death. Thirteen cases resulted in permanent disability.⁷⁴ In 2002, the FDA banned the sale of ephedra-containing dietary supplements.¹⁵⁵ However, other herbal preparations, such as bitter orange (*Citrus aurantia*), contain ephedra-like alkaloids (synephrine) and are still widely available.^{115,121} Exposures may result in cardiovascular toxicity.^{116,121}

Nicotinics: Betel Nut, Blue Cohosh, Broom, Chestnut, Lobelia, Tobacco. Betel (*Areca catechu*) is chewed by an estimated 200 million people worldwide for its euphoric effect. As an herb, it is used as a digestive aid and as a treatment for cough and sore throat. Its active ingredient is arecoline, a direct-acting nicotinic agonist. The betel leaf also contains a phenolic volatile oil and an alkaloid capable of producing sympathomimetic reactions. Arecoline is a bronchoconstrictor, although weaker than methacholine, and may exacerbate bronchospasm in asthmatic patients chewing betel nut.¹⁴⁹ Treatment for betel nut toxicity is supportive. Long-term use of betel nut is associated with leukoplakia and squamous cell carcinoma of the oral mucosa.¹²⁰

Many other herbal preparations have nicotinic effects. Examples of plants and their nicotinic ingredient include blue cohosh¹³, methylcytisine, broom, l-sparteine, chestnut, esculin, lobelia, lobeline, and tobacco/nicotine (Chap. 85).

Other herbs that have CNS activity include valerian (sedation), kava kava (sedation), Japanese star anise (seizures), nutmeg (hallucinations),¹⁶⁵ mace (hallucinations), and iboga (hallucinations).

Gastrointestinal Toxins

Goldenseal. Goldenseal (*Hydrastis canadensis*) originally was used by the Cherokees and other Native Americans as a dye and an internal remedy.⁶⁹ Today, it is used as an astringent, as a remedy for mucous membranes or GI tract disorders, and as treatment for menorrhagia. Goldenseal is reputed to mask the presence of illicit drugs on urinary drug screens, although multiple studies indicate goldenseal does not affect the results of urinary drug screens.^{44,118,124} This myth originated in the murder-mystery *Stringtown on the Pike* (1900), which was written by the internationally known plant pharmacist Uri Lloyd. In this novel, one of the major characters is accused of murder by poisoning with strychnine but is posthumously exonerated with evidence that hydrastine (the active alkaloid in goldenseal) and morphine cross-react to produce a positive color assay for strychnine.⁶⁰ Appropriate usage of this herb is thought to be safe, but ingestion of large amounts can cause vomiting, diarrhea, convulsions, paralysis, and respiratory failure. In cases of large ingestions, the patient should receive supportive and symptomatic care.

Hepatotoxins

Pennyroyal. Pennyroyal oil is a volatile oil extract from the leaves of *Mentha pulegium* and *Hedeoma pulegioides* plants. Herbalists use pennyroyal oil as an abortifacient and to regulate menstruation. It is also used as a flea/mosquito repellent and as a fragrance. The abortive effect is thought to be caused by irritation and contraction of the uterus.¹⁴⁶ Pennyroyal usually is ingested as a strong tea prepared from the leaves or as the oil itself. It is cited as causative in several well-documented cases of hepatic failure following ingestion of as little as 15 mL of the oil.^{3,8} The postulated mechanism is direct hepatotoxicity following glutathione depletion from the cyclohexanone pulegone and its cytochrome P450 (CYP1A2, CYP2E1, CYP2C19)-dependent toxic metabolites that include menthofuran.⁸⁷ On autopsy, vacuolization of the white matter of the midbrain was reported in both a fatal human exposure and in animal models.^{7,123} Because pulegone depletes hepatic glutathione stores, N-acetylcysteine treatment may be beneficial^{3,19} (Antidotes in Depth: A3). In an animal model, pretreatment with cytochrome P450 inhibitors cimetidine (CYP1A2, CYP2C19) and disulfiram (CYP2E1) reduced pulegone-induced hepatotoxicity.¹⁴⁵ It may be reasonable to consider use of cytochrome P450 inhibitors in the treatment of pennyroyal-poisoned patients; however, evidence of clinical benefit in humans currently is lacking.

Pyrrolizidine Alkaloids. Pyrrolizidine alkaloids are hepatotoxins found in many plants, including heliotrope (*Heliotropium*), ragwort or groundsel (*Senecio*), rattlebox (*Crotalaria*), and comfrey (*Symphytum*).^{127,131} Examples of other

plants and products containing pyrrolizidine alkaloids include borage (*Borago officinalis*), coltsfoot (*Tussilago farfara*), and T'u-san-chi'i (*Gynura segetum*).^{79,90,132} The alkaloids undergo metabolism to pyrroles, which serve as biologic alkylating agents.⁷⁹ The pyrroles cause hepatic sinusoidal hypertrophy and venous occlusion, resulting in hepatic veno-occlusive disease, hepatomegaly, cirrhosis, and possibly hepatic carcinoma. Chronic low dose exposure may cause pulmonary toxicity resulting in pulmonary artery hypertension and right ventricular hypertrophy. Consumption of “bush” tea, prepared from the leaves of the *Crotalaria* plant, is considered an endemic problem in Jamaica. Epidemics have also occurred in Afghanistan and India, where ingestion of contaminated cereals containing *Heliotropium* and *Crotalaria* seeds resulted in reports of 1632 and 60 cases of venoocclusive disease, respectively.^{112,148} In Western countries, ingestion of herbal products containing *Senecio* and comfrey have led to several cases of hepatic venoocclusive disease.¹²⁷ Treatment of hepatic venoocclusive disease is supportive but may require liver transplantation in severe cases.

Several other herbal preparations are associated with hepatotoxicity.⁹³ These preparations include chaparral (*Larrea tridentata*),^{24,70} germander (*Teucrium chamaedrys*),⁹⁴ impilia (*Callilepis laureola*),⁹⁰ atractylis (*Atractylis gummifera*), sassafras (*Sassafras albidum*),¹³⁹ and kava kava (*Piper methysticum*).¹⁵⁷

Metals

Poisonings by metallic salts, including arsenic, cadmium, lead, and mercury, may occur following consumption of various types of herbal preparations^{27,30,46,132} (Chaps. 89, 91, 96, and 98). Treatment consists of ceasing consumption of the herbal product and use of an appropriate chelator when indicated.

Hai-ge-ten (clamshell powder) contamination with copper, chromium, arsenic, or lead is described in several case reports.^{75,104} Pay-loo-ah, a red and orange powder used by the Hmong people as a fever and rash remedy, was contaminated with lead.²⁶ Ayurvedic remedies are either herbal only or *rasa shastra*, which, based upon ancient traditional healing of India, deliberately combines metals such as gold, silver, copper, zinc, iron, lead, tin, and mercury and are used by the majority of the Indian population.^{28,129,130,137} Ghasard, Bola Goli, Kandu, and Moha Yogran Guggulu, traditional Indian remedies for abdominal pain, are associated with lead poisoning.^{27,138} One fatality from lead poisoning from Ghasard, Bola Goli, and Kandu is reported from the United States.²⁷ In one study, 20% of surveyed Ayurvedic products produced in South Asia and sold on a nonprescription basis in stores in the Boston area contained potentially harmful concentrations of lead, mercury, or arsenic.¹³⁶ A follow-up study determined that a similar 21% of Ayurvedic products sold through the Internet also contained potentially harmful concentrations of lead, mercury, or arsenic irrespective of whether manufacture occurred in the United States or India.¹³⁷

These same investigators recently studied the lead, mercury, and arsenic concentrations in the United States and Indian manufactured Ayurvedic medicines sold via the Internet demonstrating that 20% of these were contaminated with one of these metals, all exceeding one or more standards for acceptable daily intake of a toxic metal.¹³⁷ Azarcon (lead tetroxide) and greta (lead oxide) are used by an estimated 7.2% to 12.1% of Mexican-Hispanic families for treatment of *empacho*. In Spanish, *empacho* means “blocked intestine,” but it refers to any type of chronic digestive problem, including such diverse symptoms as constipation, diarrhea, nausea, vomiting, anorexia, apathy, and lethargy.^{31,33} Azarcon and greta are fine powders with total lead contents varying from 70% to more than 90%.^{16,32}

Herbal balls, hand-rolled mixtures of herbs and honey produced in China, are often associated with arsenic and mercury contamination.⁵⁵ Examples include An Gong Niu Huang Wan, Da Huo Luo Wan, and Niu Huang Chiang Ya Wan.

Renal Toxins

Aristolochia. An epidemic of renal failure in Belgium was linked to the substitution of *Aristolochia fangchi*, also known as birthwort, heart-wort, and fangchi, for another Chinese herbal, *Stephania tetrandia*, in the formulation of a weight-loss regimen.^{161,162} Of 70 identified cases of renal fibrosis, 30 patients developed chronic renal failure. Aristolochic acid in *Aristolochia* causes renal fibrosis, which typically becomes clinically apparent 12 to 24 months after the initial injury. Patients with *Aristolochia*-induced nephropathy also have an increased risk for developing urothelial cancer.¹¹⁹

Miscellaneous

Chamomile Tea. Chamomile tea is a popular herbal drink made from chamomile flower heads. Anaphylactic reactions can occur in patients allergic to ragweed, asters, chrysanthemums, or other members of the *Compositae* family.^{10,23} Such reactions are rare but can be life threatening. The patient need not have severe allergies or be highly atopic to experience a cross-reaction.

Chinese Patent Medicines

Chinese patent medicines, a component of traditional Chinese medicine (TCM), contain traditional herbals, formulated into

tablets, capsules, syrups, powders, ointments, and plasters, for easy use. They are produced by poorly regulated Chinese pharmaceutical agencies and are highly susceptible to adulteration (intentional) or contamination (inadvertent). They are often sold by nonherbalists at convenience stores in packages with incomplete documentation of ingredients and often are not labeled in English. Many contain undocumented pharmaceuticals, like to increase their effectiveness, and improve sales among non-TCM users in Western nations. For example, in 2007, 90 Chinese patent medicines randomly purchased in New York City's Chinatown identified five samples containing nine undisclosed Western medications, including chlormethiazole, chlorpheniramine, diclofenac, chlordiazepoxide, hydrochlorothiazide, triamterene, diphenhydramine, and sildenafil citrate.¹⁰⁹

Treatment

A specific treatment strategy should emphasize identification of the specific herbal preparation(s) used by the patient, concurrent medication(s), and medical illness(es). Because herbal preparation toxicity varies greatly depending on the preparation used, careful examination may be aided by knowledge of the herbal preparation. In most cases, supportive care and discontinuation of the herbal preparation(s) are sufficient. Some herbal toxicities require specific laboratory analysis and therapy (Table 45–1).

All adverse events associated with herbal preparations should be reported to the local poison control center or to FDA MedWatch by phone at 1-800-FDA-1088 or online at <https://www.fda.gov/medwatch>.

SUMMARY

- Although most herbal preparation users will experience no ill effects, both herb users and clinicians should be aware that these preparations are pharmacologically active, have the potential for toxicity, and are not as closely regulated by the FDA (or any governmental agency) as pharmaceuticals.
- Herbal preparation users should be aware that these preparations are poorly studied with scientific proof of efficacy lacking for most preparations. No standards exist for their manufacture, quality, or control and many herbal products do not contain the purported amount of the active ingredient. Some herbal products do not even contain the specified active ingredient.
- Many herbal stores are staffed by untrained personnel who may dispense incorrect medical advice and unfounded claims concerning their products.^{126,160}
- Clinicians should be familiar with herbal preparations and their potential for drug interactions and adverse events.

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46 IRON

Jeanmarie Perrone

Iron

Molecular weight	=	55.85 Da
Serum normal concentration	=	80–180 µg/dL
	=	14–32 µmol/L

HISTORY AND EPIDEMIOLOGY

Iron poisoning has become uncommon. This success may underscore the importance of prevention by interventions gleaned from poison center data and poison prevention advocacy. Blister packaging, smaller dosages, and education of parents and health care professionals have led to a great decline in iron poisoning in the past two decades. Unfortunately, however, significant iron poisonings still occur, and clinician must be aware of the nuances of presentation and diagnosis to optimize iron poisoning management. Clinicians must be vigilant for signs of serious iron poisoning and be ready to intervene if gastrointestinal (GI) toxic effects are followed by acid–base disturbances, altered mental status, or hemodynamic compromise.

Iron salts such as ferrous sulfate have been used therapeutically for thousands of years and continue to be available, both with and without prescription, for the prevention and treatment of iron deficiency anemia in patients of all ages. Despite this long history of use, the first reports of iron toxicity only occurred in the mid-twentieth century. Since then, numerous cases of iron poisoning and fatalities have been reported, mostly in children.^{57,59} In 1950, the manufacturer of “fersolate,” an iron supplement, included a package warning: “Excessive doses of iron can be dangerous. Do not leave these tablets within reach of young children, who may eat them as sweets with harmful results.”⁸⁷

The incidence of iron exposures continued to increase in the 1980s, ultimately becoming, in the 1990s, the leading cause of poisoning deaths reported to poison centers among children younger than 6 years (Chap. 136). This problem was publicized in a case series of tragic fatalities involving five toddlers in Los Angeles during a 6-month period in 1992, all of whom were exposed to prenatal vitamins containing iron.⁹⁴ The association between death and prenatal vitamins highlights the availability of these potentially lethal medications in the homes of families with young children, ironically as a result of more attentive prescribing of prenatal iron. A case control study in Canada identified a fourfold increase in the risk of iron poisoning to the older sibling of a newborn during the first postpartum month.⁴² The authors concluded that almost one-half of all hospital admissions of young children for iron poisoning could be prevented by safer storage of iron supplements in the year before and the year after the birth of a sibling.

In 1997, the US Food and Drug Administration (FDA) mandated that all iron salt-containing preparations display warning labels regarding the dangers of pediatric iron poisoning.²³ In addition to the warning labels, the FDA launched an educational campaign to alert caregivers and prescribers of the potential toxicity of iron supplements.²⁴ Other preventive initiatives instituted by the FDA in 1997 included unit dosing (blister packs) of prescriptions for preparations containing more than 30 mg of elemental iron and limitations on the number of pills dispensed (ie, maximum 30 day supply).²⁴ These efforts to prevent unintentional exposure dramatically decreased the incidence of poisoning and were pivotal in decreasing morbidity and mortality associated with iron poisoning⁸¹ (Chap. 135). However, in 2003, the FDA rescinded the blister packaging requirement in response to a lawsuit charging that the FDA did not have jurisdiction over the packaging of dietary supplements.²² Although isolated fatalities continue to occur,⁵⁸ the trend in the National Poison Data System suggests they are becoming less common (Chap. 136). Iron poisoning may also occur after ingestion of other iron salts used in industry, such as ferric chloride.¹⁰² Ingestion of metallic iron does not result in toxicity.

PHARMACOLOGY, PHARMACOKINETICS, AND TOXICOKINETICS

Iron is an element critical to organ function. As a transition metal, iron can easily accept and donate electrons, thereby shifting the ferric (Fe^{3+}) and ferrous (Fe^{2+}) oxidation states (Chap. 12). This redox capacity elucidates the role of iron in multiple protein and enzyme complexes, including cytochromes and myoglobin, although it is principally incorporated into hemoglobin in erythrocytes. Whereas insufficient iron availability results in anemia, excess total body iron results in hemochromatosis.

The body cannot directly excrete iron, so iron stores are regulated by controlling iron absorption from the GI tract. The absorption of iron salts (iron ions as Fe^{2+} or Fe^{3+}) occurs predominantly in the duodenum, and is determined by the iron requirements of the body. In iron deficiency, iron absorption and uptake into intestinal mucosal cells may increase from a normal 10% to 35% to as much as 80% to 95%. After uptake into the intestinal mucosal cells, iron is either stored as ferritin and lost when the cell is sloughed or released to transferrin, a serum iron binding protein. In therapeutic doses, some of these processes become saturated, and absorption into the intestinal cell may be limited. However, in overdose, the oxidative effects of iron on GI mucosal cells lead to dysfunction of this regulatory balance, and passive absorption of iron increases down its concentration gradient⁸⁰ (see Pathophysiology).

Iron supplements are available as the iron salts ferrous gluconate, ferrous sulfate, and ferrous fumarate and as the nonionic preparations carbonyl iron and polysaccharide iron. Additional sources of significant quantities of iron are vitamin preparations, especially prenatal vitamins (Table 46–1). Toxic effects of iron poisoning occur at doses of 10 to 20 mg/kg elemental iron which is defined as the amount of iron ion present in an iron salt (Table 46–1). Significant GI toxic effects occurred in human adult volunteers who ingested 10 to 20 mg of elemental iron/kg.^{9,50} In one volunteer study, six participants who ingested 20 mg/kg elemental iron developed nausea and voluminous diarrhea within 2 hours, and five of the six subjects had serum iron concentrations above 300 $\mu\text{g/dL}$.⁹

TABLE 46–1. Common Iron Formulations and Their Elemental Iron Contents

<i>Iron Formulation</i>	<i>Elemental Iron (%)</i>
Ionic	
Ferrous chloride	28
Ferrous fumarate	33
Ferrous gluconate	12
Ferrous lactate	19
Ferrous sulfate	20
Nonionic	
Carbonyl iron	98 ^a
Polysaccharide iron	46 ^a

^aAlthough these nonionic iron formulations contain higher elemental iron content than ionic formulations, carbonyl iron and iron polysaccharide have better therapeutic-to-toxic ratios due to their limited gastrointestinal absorption rates.

In another study of human volunteers who ingested 5 to 10 mg/kg elemental iron in the form of chewable iron containing vitamins, peak serum iron concentrations occurred between 4.2 and 4.5 hours in all participants.⁵⁰ In overdose, peak concentrations of iron are thought to occur 2 to 6 hours after ingestion, depending on the iron preparation.^{9,50} Chewable vitamins continue to entice children with their sweet taste and recognizable character shapes, increasing the risk of significant exposure. Children’s chewable multivitamins contain less iron per tablet (10–18 mg of elemental iron) than typical prenatal vitamins (65 mg of elemental iron). Iron toxicity still results when large quantities of chewable children’s vitamins are ingested, but the therapeutic-to-toxic ratio is improved.² One animal study paradoxically demonstrates higher iron concentrations after ingestion of equivalent elemental iron doses of chewable versus solid iron tablets.⁶¹ This finding was attributed, in part, to the limited gastric irritation associated with the chewable iron preparations, resulting in less vomiting.

Iron supplements are also available in two nonionic forms, carbonyl iron and iron polysaccharide, both of which appear to be less toxic after overdose than are iron salts,⁷⁶ despite their high elemental iron content.⁴⁶ Carbonyl iron is a form of elemental iron that is highly bioavailable in therapeutic doses compared to other forms of iron because of its high elemental iron content and its very fine, spherical particle size (5 μm).³³ In a rat model of iron toxicity, carbonyl iron had a median lethal dose (LD_{50}) of 50 g/kg compared with an LD_{50} of 1.1 g/kg for ferrous sulfate.⁹⁷ No significant toxicity in humans exposed to carbonyl iron has been reported.⁷⁶ Iron polysaccharide contains approximately 46% elemental iron by weight. It is synthesized by neutralization of a ferric chloride carbohydrate solution. This form of iron also appears to have much lower toxicity than iron salts. The estimated LD_{50} in rats is more than 5 g/kg body weight. Retrospective poison

center data have shown little toxicity from either of these products.⁴⁶

Parenteral iron, such as iron dextran, intravenously administered to patients with kidney failure and chronic anemia, may also result in toxicity, as well as anaphylactoid reactions. Newer parenteral formulations, including iron sucrose and sodium ferrous gluconate, appear to be safer.²¹

PATHOPHYSIOLOGY

Iron is active in many oxidation reduction (redox) reactions. Iron catalyzes the generation of hydroxyl radicals intracellularly through the Fenton reaction and Haber-Weiss cycle and mediates its toxicologic effects as an inducer of oxidative stress and inhibitor of several key metabolic enzymes (Chap. 12). Reactive oxygen species oxidize membrane-bound lipids and cause loss of cellular integrity and tissue injury.^{70,72}

The initial oxidative damage to the GI epithelium produced by iron-induced reactive oxygen species permits iron ions to enter the systemic circulation. Iron ions are rapidly bound to circulating binding proteins, particularly transferrin. After transferrin is saturated with iron, “free” iron (ie, iron not bound to a transport protein) is widely distributed to the various organ systems, where it promotes damaging oxidative processes. A postmortem series of 11 patients who died from iron ingestion substantiated these findings with measurements of elevated iron concentrations in most major organs examined, including the stomach, liver, brain, heart, lung, small bowel, and kidney.⁶⁵ Congestion, edema, necrosis, and iron deposition in the gastric and intestinal mucosa, as well as hemorrhage and congestion in the lungs, are noted on postmortem examination.^{30,31,52}

Iron ions disrupt critical cellular processes such as mitochondrial oxidative phosphorylation. Subsequent buildup of unused hydrogen ions normally incorporated into the synthesis of adenosine triphosphate leads to liberation of H^+ and development of metabolic acidosis (Chap. 13). In addition, absorption of iron from the GI tract leads to conversion of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}). Ferric iron ions exceed the binding capacity of plasma, leading to formation of ferric hydroxide and release of three protons ($Fe^{3+} + 3H_2O \rightarrow Fe(OH)_3 + 3H^+$).^{70,80}

Decreased cardiac output contributes to shock in animals.^{91,100} Although this finding is often attributed to decreased preload and relative bradycardia,⁹¹ a direct negative inotropic effect of iron on the myocardium is also demonstrated in animal models.³ Reports of early coagulopathy unrelated to hepatotoxicity⁸³ led to the identification of free iron as an inhibitor of thrombin formation and the reduction of the effect of thrombin on fibrinogen.⁷³

CLINICAL MANIFESTATIONS

Classic teaching posits five clinical stages of iron toxicity based on the pathophysiology of iron poisoning.^{6,41,68} Although these stages are conceptually important, they are of limited benefit to clinicians managing poisoned patients. Although the stages are typically described in approximate postingestion time frames, a clinical stage should never be assigned based solely on the number of hours postingestion because patients do not necessarily follow the same temporal course through these stages.

The first stage of iron toxicity is characterized by nausea, vomiting, abdominal pain, and diarrhea. These “local” toxic effects of iron predominate, and subsequent salt and water depletion contribute to the ill appearance of the iron poisoned patient. Intestinal ulceration, edema, transmural inflammation, and, in some extreme cases, small-bowel infarction and necrosis may occur.^{25,71,85} Hematemesis, melena, or hematochezia may cause hemodynamic instability. GI symptoms always occur after significant overdose. Conversely, the absence of signs and symptoms, specifically vomiting, in the first 6 hours following ingestion, essentially excludes serious iron toxicity.

The second, or “latent,” stage of iron poisoning commonly refers to the period 6 to 24 hours after ingestion when resolution of GI symptoms occurs, but systemic toxicity has not yet developed. Delineation of this stage may have evolved from early case reports of patients whose GI symptoms had resolved before subsequent deterioration.⁸⁷ This second stage is not a true quiescent phase because ongoing cellular organ toxicity occurs during this phase.⁶ Although clinicians should be wary of patients who no longer have active GI complaints after iron overdose, most such patients have, in fact, recovered and are not in the latent phase. Patients in the latent phase generally have lethargy, tachycardia, or metabolic acidosis. They should be readily identifiable as clinically ill despite resolution of their GI symptoms. In summary, patients who have remained well since ingestion and who have stable vital signs, a normal mental status, and a normal acid–base balance will have a benign clinical course.

Patients who progress to the third, or “shock,” stage of iron poisoning have profound toxicity. This stage may occur in the first few hours after a massive ingestion or 12 to 24 hours after a more moderate ingestion. The etiology of shock may be multifactorial, resulting from hypovolemia, vasodilation, and poor cardiac output,^{91,100} with decreased tissue perfusion and an ongoing metabolic acidosis. Iron-induced coagulopathy may worsen bleeding and hypovolemia.⁸³ Systemic toxicity

produces central nervous system effects with lethargy, hyperventilation, seizures, or coma. The fourth stage of iron poisoning is characterized by hepatic failure, which may occur 2 to 3 days after ingestion.³⁰ The hepatotoxicity is directly attributed to iron uptake by the reticuloendothelial system in the liver, where it causes oxidative damage.^{26,101} The fifth stage of iron toxicity rarely manifests. Gastric outlet obstruction, secondary to strictures and scarring from the initial GI injury, may develop 2 to 8 weeks after ingestion.^{29,36,85}

Patients treated for chronic iron overload are at increased risk for *Yersinia enterocolitica* infection. Iron is a required growth factor for *Y. enterocolitica*; however, the bacterium lacks the siderophore to solubilize and transport iron intracellularly. Because deferoxamine is a siderophore, it fosters the growth of *Y. enterocolitica*. Thus, patients with chronic iron overload or acute poisoning develop *Yersinia* infection or sepsis as a complication of iron poisoning or deferoxamine therapy.^{11,54,57,78} *Yersinia* infection should be suspected in patients who experience abdominal pain, fever, and bloody diarrhea after resolution of iron toxicity. In this setting, cultures should be obtained, fluid and electrolyte repletion accomplished, and fluoroquinolones or third-generation cephalosporin therapy initiated.

DIAGNOSTIC TESTING

Radiography

Iron is available in many forms, and the different preparations vary with respect to radiopacity on abdominal radiography.⁷⁷ Factors such as the time since ingestion and elemental iron content of the tablets are also important.^{60,77} Liquid iron formulations and chewable iron tablets typically are not radiopaque.¹⁹ A retrospective review of iron ingestions in children revealed that abdominal radiographs were positive in only one of 30 patients who ingested chewable iron containing vitamin tablets.¹⁹ Because adult tablet preparations have a higher elemental iron content and do not readily disperse, they tend to be more consistently radiopaque.⁶⁰ Finding radiopaque pills on an abdominal radiograph is helpful in guiding and evaluating the success of GI decontamination.³⁷ However, the absence of radiographic evidence of tablets is not a reliable indicator to exclude potential toxicity.^{60,64} Most patients can be managed without abdominal radiographs, given their lack of sensitivity.

Laboratory Studies

Various laboratory studies are used as surrogate markers to assess the severity of iron poisoning. An anion gap metabolic acidosis and an elevated lactate concentration may develop in patients with serious iron ingestions. Serial electrolyte measurements may be used to assess progression and response to volume replacement. Anemia may result from GI blood loss, but may not be evident initially because of hemoconcentration secondary to plasma volume loss.

Although one small retrospective study of iron-poisoned children found that a white blood cell count (WBC) above 15,000/mm³ or a blood glucose concentration above 150 mg/dL was 100% predictive of iron concentration above 300 µg/dL (a marker for clinical risk),⁴⁹ three subsequent similar studies were unable to validate this association.^{12,48,64} In practice, an elevated WBC or glucose concentration in the setting of a known or suspected iron ingestion should raise concern about an elevated serum iron concentration; however, assessment of the signs and symptoms of the patient is more reliable. Most importantly, normal WBC and glucose concentrations do not reliably exclude toxicity.

Although iron poisoning remains a clinical diagnosis, serum iron concentrations can be used effectively to gauge toxicity and the success of treatment.⁶ In the previously mentioned human volunteer study of six adults who ingested 20 mg/kg of elemental iron, all six adults demonstrated significant GI toxicity, and the four who required intravenous (IV) fluid resuscitation had peak serum iron concentrations in the range of 300 µg/dL between 2 and 4 hours after ingestion.⁹ Serum iron concentrations between 300 and 500 µg/dL usually correlate with significant GI toxicity and modest systemic toxicity. Concentrations between 500 and 1000 µg/dL are associated with pronounced systemic toxicity and shock.⁹⁵ Concentrations above 1000 µg/dL are associated with significant morbidity and mortality.⁹⁵ Although elevated serum iron concentrations may be an additional indicator of potentially serious toxicity, lower concentrations cannot be used to exclude the possibility of serious toxicity. A single serum iron concentration may not represent a peak concentration or may be falsely lowered by the presence of deferoxamine unless an atomic absorption technique is used for measurement.^{28,35}

Total iron-binding capacity (TIBC) is a measurement of the total amount of iron that can be bound by transferrin in a given volume of serum.²⁰ Previously, clinical iron toxicity was thought not to occur if the serum iron concentration was less than the TIBC, because insufficient circulating “free” iron was present to cause tissue damage. Although this is true, the error in interpretation results from the limitations of measuring TIBC values. Most importantly, the in vitro value of TIBC factitiously increases as a result of iron poisoning and thus has a tendency to apparently increase above a concurrently measured serum iron concentration.^{9,86} Because of many confounding issues, the TIBC as currently determined has no value in the assessment of iron-poisoned patients.

MANAGEMENT

Initial Approach

As with any serious ingestion, initial stabilization must include supplemental oxygen, airway assessment, and establishment of IV access. Evidence of hematemesis or lethargy after an iron exposure may be a manifestation of significant toxicity. Intravenous volume repletion should begin while orogastric lavage and whole bowel irrigation (WBI) are considered. In any lethargic patient who likely will deteriorate further, early endotracheal intubation may facilitate safe GI decontamination measures. Abdominal radiography may be used to estimate the iron burden in the GI tract given the caveats discussed earlier. Laboratory values, including chemistries, hemoglobin, iron concentration, coagulation, and hepatic profiles, are necessary in the sickest patients. An arterial or venous blood gas or a lactate concentration rapidly identifies a metabolic acidosis. Patients who appear well and had only one or two brief episodes of vomiting can be observed pending discharge. A serum iron concentration and most other laboratory testing are not needed in patients who have minimal symptoms and normal vital signs.

Limiting Absorption

GI decontamination procedures should be initiated after stabilization. Adequate gastric emptying is critical after ingestion of xenobiotics, such as iron, that are not well adsorbed to activated charcoal. Because vomiting is a prominent early symptom in patients with significant toxicity, induced emesis is not recommended. Orogastric lavage is more effective but may be of only limited value because of the large size and poor solubility of most iron tablets, their ability to form adherent masses,^{25,90} and their movement into the bowel several hours after ingestion.⁴³ The presence and location of radiopaque tablets on abdominal radiography can help guide orogastric lavage. Orogastric lavage will likely not be successful after iron tablets move past the pylorus, so WBI may be more effective (Fig. 46-1).



FIGURE 46-1A. A 17 month-old boy presented to the hospital with lethargy and hematemesis after a large ingestion of iron supplement tablets. Despite orogastric lavage and whole-bowel irrigation, iron tablets and fragments can be visualized in the stomach 4 hours after ingestion.

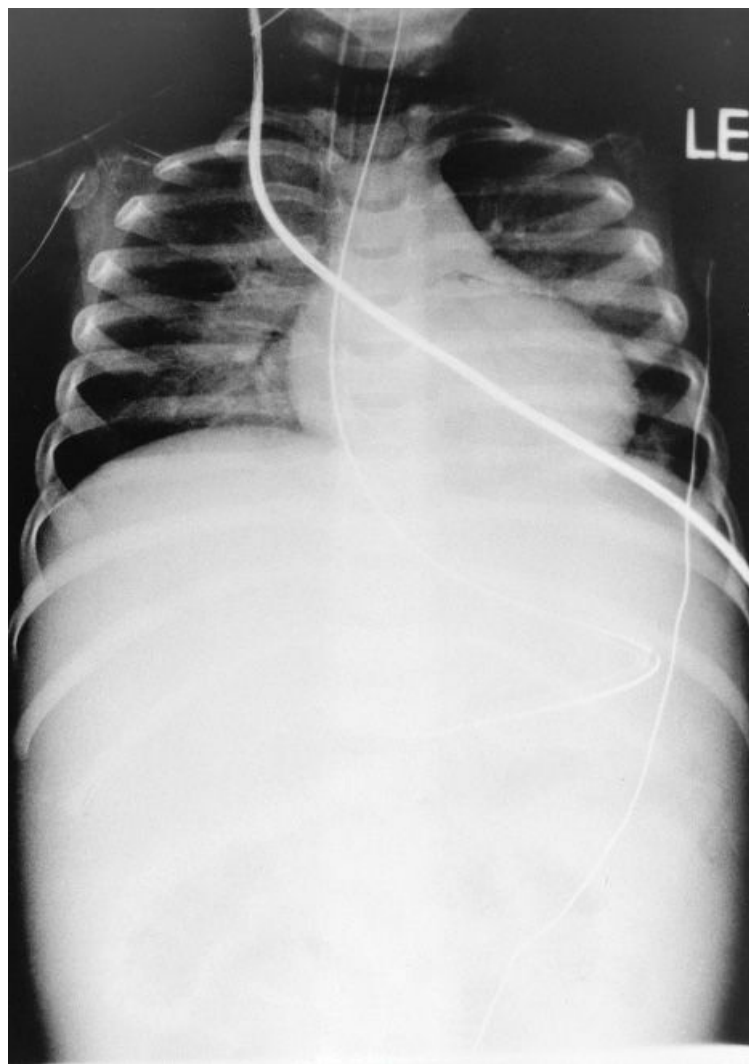


FIGURE 46–1B. The same 17 month-old child 10 hours after ingestion. Persistent iron pills were removed from the stomach by gastrotomy. No further radiopaque fragments can be visualized; however, ARDS is now visible.

Many strategies were used in the past in attempts to improve the efficacy of orogastric lavage. At the present time, no data support the use of oral deferoxamine,^{32,40,98,99,104} bicarbonate,^{15,16} phosphosoda,^{4,27} or magnesium.^{13,75,93} Although some of these techniques demonstrate efficacy, avoidance of the associated risks mandates using only 0.9% sodium chloride solution or tap water for orogastric lavage.

The value of WBI in patients with iron poisoning is supported primarily by case reports and one uncontrolled case series.^{18,43,82,83} However, the rationale for WBI use is logical, especially considering the limitations of other gastric decontamination modalities. The usual dose of WBI with polyethylene glycol electrolyte lavage solution (PEG-ELS) is 500 mL/h in children and 2 L/h in adults. This rate is best achieved by starting slowly and increasing as tolerated, often using a nasogastric tube and an infusion pump to administer large volumes. Antiemetics may be used to treat nausea and vomiting. A large volume (44 L) of WBI was administered safely over a 5-day period to a child who had persistent iron tablets on serial abdominal radiographs⁴³ (Antidotes in Depth: A2 and Chap. 8).

For patients with life-threatening toxicity who demonstrate persistent iron in the GI tract despite orogastric lavage and WBI, upper endoscopy or gastrotomy and surgical removal of iron tablets adherent to the gastric mucosa may be necessary and lifesaving.^{25,66,90}

Deferoxamine

Deferoxamine has been available since the 1960s as a specific chelator for patients with acute iron overdose or chronic iron overload (eg, multiple transfusions). Deferoxamine, which is derived from culture of *Streptomyces pilosus*, has high affinity and specificity for iron. In the presence of ferric iron (Fe^{3+}), deferoxamine forms the complex ferrioxamine, which is excreted by the kidneys,⁴⁴ usually imparting a reddish-brown color to the urine (Fig. 46–2). Deferoxamine chelates free iron and the iron transported between transferrin and ferritin^{51,67} but not the iron present in transferrin, hemoglobin, hemosiderin, or ferritin.^{5,44} Deferoxamine may work by other mechanisms in addition to binding excess systemic iron. Because 100 mg of deferoxamine chelates approximately 8.5 mg of ferric iron, recommended or typical therapeutic dosing of deferoxamine does not produce significant excretion of chelated iron in the urine, yet it does often result in dramatic clinical benefits (Antidotes in Depth: A7). Sufficient evidence suggests that deferoxamine can reach intracytoplasmic and

mitochondrial free iron, thereby limiting intracellular iron toxicity.⁵¹



FIGURE 46–2. These timed sequential urines were obtained from a small child with a serum iron concentration of 990 $\mu\text{g/dL}$ who was treated with intravenous deferoxamine. The characteristic color change is illustrated. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

IV administration of deferoxamine should be considered in iron-poisoned patients with any of the following findings: metabolic acidosis, repetitive vomiting, toxic appearance, lethargy, hypotension, or signs of shock. Deferoxamine administration is indicated for any patient with an iron concentration above 500 $\mu\text{g/dL}$. In patients manifesting serious signs and symptoms of iron poisoning, deferoxamine should be initiated as an IV infusion, starting slowly and gradually increasing to a dose of 15 mg/kg/h. Hypotension is the rate-limiting factor as more rapid infusions are used.^{38,96,98} Patients who appear toxic or have serum iron concentrations above 500 $\mu\text{g/dL}$ should be treated with IV deferoxamine. Patients who have concentrations below 500 $\mu\text{g/dL}$ and who do not appear toxic should be treated supportively without administration of parenteral deferoxamine (Fig. 46–3).

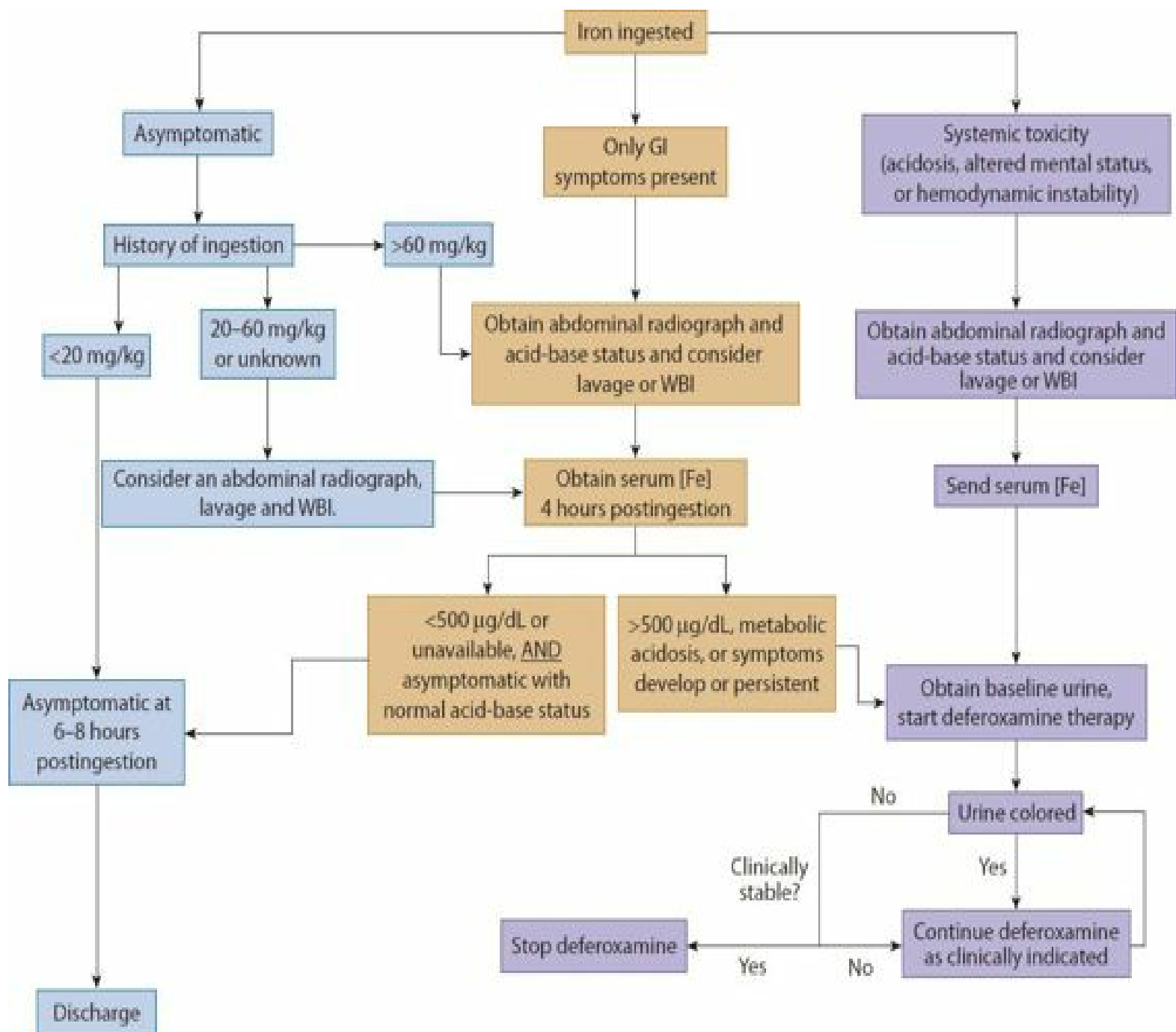


FIGURE 46–3. Algorithm for decision analysis following iron salt ingestion.

Clinicians have attempted to define the earliest clear end points for deferoxamine therapy because of possible deferoxamine toxicity. In one report, a urine iron-to-creatinine ratio (U_I/Cr) was used to determine if free iron excretion into the urine continued during deferoxamine therapy.¹⁰³ This ratio is a more objective measure of the presence of ferrioxamine in the urine than the less reliable and more subjective use of urinary color change.^{17,47,92} This method must be further studied clinically before its use can be advocated. Most authors agree that deferoxamine therapy should be discontinued when the patient appears clinically well, the anion-gap acidosis has resolved, and urine color undergoes no further change.⁵⁵ In patients with persistent signs and symptoms of serious toxicity after 24 hours of IV deferoxamine, continuing therapy should be undertaken cautiously, if at all, and perhaps at a lower dose due to the risk of adverse events (Antidotes in Depth: A7).

Adverse Effects of Deferoxamine. Most adverse effects of deferoxamine are reported in the setting of chronic administration for the treatment of hemochromatosis.^{39,63,74} The same effects, such as acute respiratory distress syndrome (ARDS), are also described after treatment for acute iron overdose.⁸⁴ Four patients with serum iron concentrations ranging from 430 to 620 $\mu\text{g/dL}$ developed ARDS after IV administration of deferoxamine for 32 to 72 hours.⁸⁴ An animal study revealed significantly increased pulmonary toxicity when high-dose deferoxamine therapy was administered in the presence of high concentrations of oxygen (75%–80% FiO_2).¹ The authors suggested that this effect was mediated via an oxygen free radical mechanism (Antidotes in Depth: A7).

Experimental Therapies

Deferasirox is an oral iron chelator approved by the FDA for the treatment of chronic iron overload that was studied as a potential iron antidote in human volunteers following supratherapeutic iron ingestion. In a randomized, double blind, placebo-controlled study, volunteers were administered 5 mg/kg iron followed by deferasirox or placebo.³⁴ Deferasirox resulted in lower iron concentrations in the treated group. However, concerns included the possibility that deferasirox may increase the absorption of iron complex and that the deferasirox dosing may need to be too high in patients with large exposures to effect these results. Further study is warranted before this therapy can be considered.

Patient Disposition

Many patients who ingest iron do not develop significant toxic effects. Recommendations for hospital referral of toddlers who ingest iron range from those with potential exposures of 20 mg/kg up to 60 mg/kg.^{6,47} These wide ranges probably result from the interpretation of retrospective studies in possibly “exposed” toddlers for whom the actual doses were estimated. Many authors suggest that doses were overestimated in patients who subsequently did not develop toxicity (Chap. 136). If a toddler remains asymptomatic or develops minimal or no GI manifestations after a 6 hour observation period in the emergency department, then discharge to an appropriate home situation can be considered. Patients who develop GI symptoms and signs of mild poisoning including vomiting and diarrhea can be observed as inpatients outside the intensive care unit. Patients who manifest signs and symptoms of significant iron poisoning, such as metabolic acidosis, hemodynamic instability, or lethargy, should be monitored and treated in an intensive care unit. Except in the case of carbonyl iron, hospital evaluation is recommended for any child with an estimated unintentional ingestion of more than 20 mg/kg of elemental iron. Children who appear well with unintentional ingestions between 10 and 20 mg/kg elemental iron and fewer than two episodes of vomiting should be closely followed at home in consultation with the poison control center.

Pregnant Patients

The frequent diagnosis of iron deficiency anemia during pregnancy has led to serious and even fatal iron ingestions in pregnant women.^{8,45,62,69,88} In all cases of toxic exposures during pregnancy, maternal resuscitation should always be the primary objective, even if an antidote poses a real or theoretical risk to the fetus. Unproven concerns regarding possible deferoxamine toxicity to the fetus have inappropriately, and at times, disastrously delayed therapy.^{62,79} These fears about fetal deferoxamine toxicity are not supported in either human or animal studies,^{14,53,89} which have demonstrated that neither iron nor deferoxamine is transferred to the fetus in appreciable quantities. An animal study demonstrated that fetal serum iron concentrations were not elevated and fetal deferoxamine concentrations could not be detected in pregnant near-term ewes poisoned with iron and treated with deferoxamine. Fetal demise under these circumstances presumably results from maternal iron toxicity and not from direct iron toxicity to the fetus. Thus, deferoxamine should be used to treat serious maternal iron poisoning and should never be withheld because of unfounded concern for fetal exposure to deferoxamine.

Adjunctive Therapies

Another modality used experimentally for treatment of iron intoxication is continuous arteriovenous hemofiltration (Chap. 10). In a study of five iron poisoned dogs, increased elimination of ferrioxamine in the ultrafiltrate was demonstrated when increasing doses of deferoxamine were infused into the arterial side of the system.⁷ A variant of this approach was utilized successfully in an iron poisoned toddler, who was treated with deferoxamine and venovenous hemofiltration.⁵⁶ Although the authors demonstrated a decreasing serum iron concentration, only a minimal concentration of iron was measured in the ultrafiltrate. This was presumed secondary to the large volumes of infusate used. Theoretically, ferrioxamine in the blood could be dialyzable with new high molecular-weight (large-pore) dialysis filters, but this technique has not been studied.

In toddlers with severe poisoning, exchange transfusion may help to physically remove free iron from the blood while replacing it with normal blood. Exchange transfusion in children is effective for poisonings such as aspirin or theophylline when the volume of xenobiotic distribution is small and removal from the blood compartment can be expected. Treatment with exchange transfusion has been suggested in iron poisoning based on early reports and more recently reported in the successful treatment of an 18 month-old child with iron poisoning.¹⁰ However, removal of blood volume must be performed cautiously because it may not be well tolerated by iron poisoned patients with hemodynamic instability.

SUMMARY

- Iron is available in multiple formulations: prenatal vitamins, ferrous gluconate, ferrous fumarate, and ferrous sulfate are most toxic.
- Iron toxicity is determined by the amount of elemental iron present: signs and symptoms occur following ingestions of 20 mg/kg of elemental iron.
- GI decontamination, including orogastric lavage and WBI using PEG-ELS, should be initiated when indicated as activated charcoal is ineffective in binding iron.

- Abdominal radiography may be helpful in determining the iron burden in the GI tract. However, not all preparations are radiopaque.
- GI signs and symptoms of nausea, vomiting, diarrhea, hematemesis, and abdominal pain are prominent in iron poisoning.
- Systemic iron toxicity leads to metabolic acidosis, hypotension, coagulopathy, and multiorgan system failure.
- Diagnosis and treatment of shock and metabolic acidosis, as well as chelation with deferoxamine, are critical.

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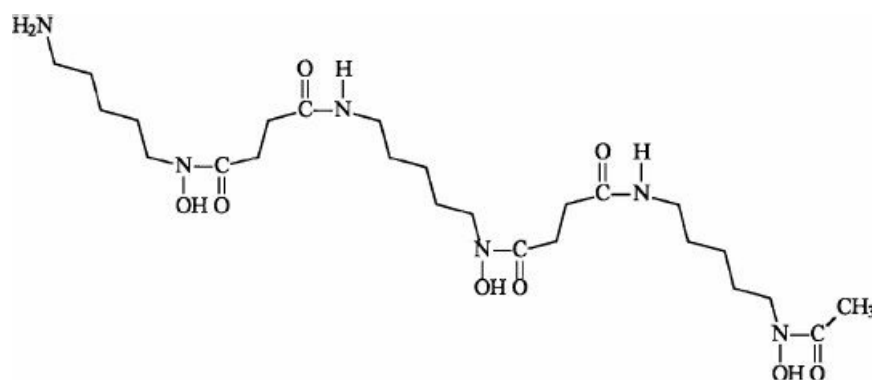
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A7 ANTIDOTES IN DEPTH

Deferoxamine

Mary Ann Howland



INTRODUCTION

Deferoxamine (DFO) is the parenteral chelator of choice for treatment of acute iron poisoning. Considering that DFO has been used to treat patients with acute iron overdose for more than 40 years,³³ there is still much that is unknown. No controlled studies have evaluated the efficacy or dosing of DFO. Animal studies and case series from the 1960s and 1970s form the basis for current use of DFO. This information has been supplemented since then by case reports and clinical experience. DFO is also used for chelation of aluminum in patients with chronic kidney failure. The merits of DFO as a treatment strategy for acute iron overdose is discussed in [Chap. 46](#) and for aluminum toxicity in [Chap. 87](#).

HISTORY

The development of DFO (or desferrioxamine B) resulted from an analysis of the iron containing metabolites of a species of actinomycetes. Ferrioxamine is a brownish-red compound containing trivalent iron (ferric, Fe³⁺) and three molecules of trihydroxamic acid isolated from the organism *Streptomyces pilosus*.³⁸ DFO is the colorless compound that results when the trivalent iron is chemically removed from ferrioxamine B ([Fig. A7-1](#)).³⁸

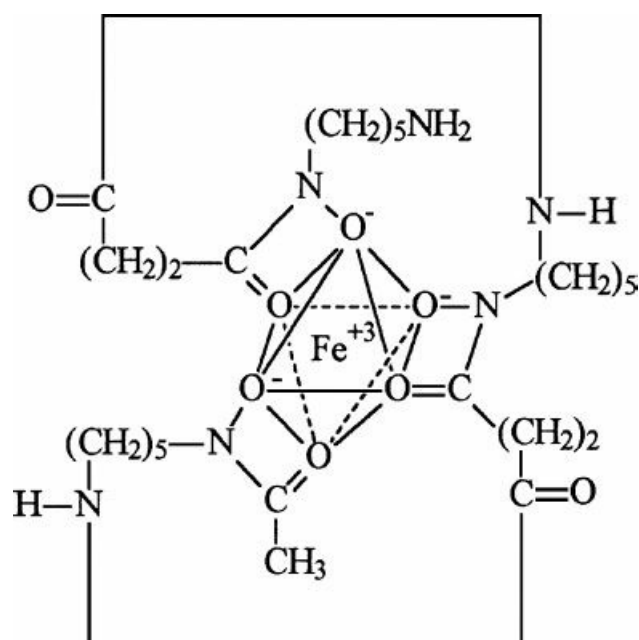


FIGURE A7–1. Ferrioxamine.

PHARMACOLOGY

Chemistry

DFO is a water-soluble hexadentate chelator with a molecular weight of 561 Da. The commercial formulation is the mesylate salt with a molecular weight of 657 Da. One mole of DFO binds 1 mole of Fe^{3+} ; therefore, 100 mg DFO as the mesylate salt theoretically can bind 8.5 mg Fe^{3+} .

DFO has a much greater affinity constant for iron (10^{31}) and aluminum (10^{22}) than for zinc, copper, nickel, magnesium, or calcium (10^2 – 10^{14}).³⁸ Thus, at physiologic pH, DFO complexes almost exclusively with ferric iron.^{28,84}

Related Chelators

Deferiprone, a bidentate oral iron chelator with a molecular weight of 139 Da, was approved by the US Food and Drug Administration (FDA) in 2011 for the treatment of iron overload in patients with thalassemia in whom current treatment is inadequate.²⁴ Three moles of deferiprone are required to bind one mole of ferric ion to form a stable complex, which is excreted in the urine.³² Inappropriate ratios of drug to iron may be ineffective or even harmful because of the formation of potentially toxic intermediates.³² Preliminary animal studies of the use of deferiprone in acute iron toxicity are contradictory.^{10,23,36,39} A dose of 75 mg/kg deferiprone produces 60% of the total iron excretion that can be achieved with 50 mg/kg DFO. All of the iron eliminated with deferiprone occurs in the urine, while DFO eliminates iron in the urine and feces.⁴² It has been proposed that deferiprone is less likely to cause toxicity in patients with low iron stores because it can exchange iron with transferrin. Adverse events include QT prolongation, elevation of hepatic enzymes, gastrointestinal effects, arthralgia, chromaturia. Because of embryofetal toxicity in animals studies it is given an FDA pregnancy category D; DFO also carries a boxed warning for agranulocytosis.²⁴ Deferiprone is now being combined with DFO because studies demonstrate additive or synergistic effects in chronic iron overload syndromes. It is hypothesized that deferiprone, because of its smaller size, can enter and chelate cardiac iron and then transfer it to DFO for elimination.⁴²

Deferasirox, an oral iron chelator that was FDA approved in 2005, is indicated to treat chronic iron overload caused by blood transfusions or in patients with thalassemia and elevated liver iron concentrations. Deferasirox, a tridentate ligand with a molecular weight of 373 Da, binds ferric iron in a 2:1 ratio. Deferasirox is lipid soluble with high protein binding (~99%). Once bound to iron, the complex is predominantly eliminated in the feces. The serum half-life (19 ± 6.5 hours) is considerably longer than DFO and deferiprone (47–137 minutes). Preliminary studies demonstrate a comparable efficacy to DFO in patients with chronic iron overload.⁸⁰ One study utilizing deferasirox in a human model of supraphysiologic iron ingestion demonstrated a reduction in serum iron concentrations when compared with placebo.²⁹ However, the dose of iron ingested was 5 mg/kg, and concerns about achieving the effective dose ratio of deferasirox to iron of 2:1 and the effects of acidemia on the binding of deferasirox to iron in a large overdose limit its use in acute iron poisoning at this time.⁵⁶ In addition, similar to other oral chelators, concerns exist about increasing oral absorption of the deferasirox iron complex, and the toxicity of this complex in the setting of an acute iron overdose.^{22,63,72} Adverse events include boxed warnings for gastrointestinal hemorrhage, kidney failure, and hepatic failure. Advanced age increases these risks.²²

Mechanism of Action

DFO binds Fe^{3+} at the 3 N–OH sites, forming an octahedral iron complex (Fig. A7–1). Once bound, the resultant ferrioxamine is very stable. DFO appears to benefit iron-poisoned patients by chelating free iron (non-transferrin plasma iron), iron in transit between transferrin and ferritin (labile chelatable iron pool),^{32,46,65} and hemosiderin and ferritin, while not directly affecting the iron of transferrin, hemoglobin, and cytochromes.^{20,38} Although in vitro studies suggest that DFO removes iron from ferritin and transferrin with only very little from hemosiderin,⁵¹ in vivo experiments demonstrate that DFO cannot remove iron after the iron is bound to transferrin.⁴ DFO does bind “free iron,” now referred to as non-transferrin bound iron found in the plasma after transferrin saturation, which only occurs acutely after overdose or chronically in iron overload syndromes.³² In vitro studies demonstrate that DFO chelates and inactivates cytoplasmic, lysosomal, and probably mitochondrial iron, preventing disruption of mitochondrial function and injury.^{27,46} An in vitro study suggests that DFO gains access to cytosol and endosomes through endocytosis rather than passive diffusion.²⁷ In chronic iron overload, DFO chelates iron deposited in the reticuloendothelial cells found in the spleen, liver, and bone marrow and excretes iron in the urine as ferrioxamine.³² Whether DFO actually chelates the iron within the reticuloendothelial cells or after liberation into the plasma is unclear. In vitro studies demonstrate that the liver can donate iron to DFO; thus, chelation may also subsequently lead to biliary iron excretion and fecal elimination.^{32,50}

Pharmacokinetics/Pharmacodynamics

The volume of distribution of DFO ranges from 0.6 to 1.33 L/kg.^{38,43,59} Because DFO is water soluble, entry into most cells is limited except for hepatocytes, in which facilitated uptake takes place.^{62a,63} The initial distribution half-life of DFO is 5 to 10 minutes.^{41,71} The terminal elimination half-life of DFO is approximately 6 hours in healthy patients² but approximately 3 hours in patients with thalassemia. DFO is metabolized in the plasma to several metabolites (A–F), of which metabolite B is believed to be toxic.^{38,43,59,61} Unchanged DFO undergoes glomerular filtration and tubular secretion.⁵⁰

By comparison, ferrioxamine has a smaller volume of distribution than DFO. In nephrectomized dogs, the volume of distribution of ferrioxamine was calculated to be 19% of body weight compared with 50% of body weight for DFO.³⁸ This finding implies that DFO has a more extensive tissue distribution. The different pharmacokinetic patterns may be related to the potential for facilitated penetrance of the straight-chain molecule DFO compared with that of the octahedral ferrioxamine.⁶¹ Experiments in dogs with normal kidney function demonstrate that intravenous (IV) ferrioxamine is entirely eliminated by the kidney within 5 hours via glomerular filtration and partial reabsorption.^{36,50}

The pharmacokinetics of DFO and ferrioxamine differ in healthy compared with iron overloaded patients. Whereas plasma DFO concentrations in healthy patients are approximately twice the concentrations noted in patients with thalassemia major, ferrioxamine concentrations are five times greater in patients with thalassemia major compared with healthy patients.^{38,73} The metabolism of DFO is unclear but occurs in the plasma by plasma enzymes and in the liver.²⁰

DFO is hemodialyzable. Some investigators suggest that DFO can be administered during hemodialysis to remove ferrioxamine.⁸⁵ Hemodialysis,^{14,71} particularly high flux hemodialysis⁷⁸ and hemoperfusion,¹⁴ are effective in ferrioxamine removal and are indicated in patients with renal failure.

ROLE IN IRON TOXICITY

Due to the limitations in the amount of iron which DFO can chelate, aggressive gastrointestinal decontamination and supportive measures should accompany its use in iron overdose, as discussed in [Chap. 46](#).

Animal Studies

Guinea pigs given oral lethal doses of ferrous sulfate and oral DFO in a dose calculated to bind most of the iron showed dramatically improved survival rates.⁵¹ Mortality rates in this study and in a swine study¹⁹ directly correlated with the delay to DFO administration.⁵¹

In two canine studies, dogs that received the iron–DFO complex orally had a 40% to 100% mortality.^{84,85} When both oral and IV DFO were administered, the mortality rate was 67%.⁸³ A similar follow-up study demonstrated a 50% mortality rate in dogs given a lethal dose (225 mg/kg) of iron, followed by oral DFO (2.6 g) and IV DFO (0.75–1.5 mg/kg/min for 8–12 hours).⁸⁵ These studies discouraged further investigation in the use of oral DFO despite the more favorable results in other animal models.^{5,34,51,77}

Early Human Use and History of Dosing Recommendations

In one of the earliest case series, 172 hemodynamically stable children who were not severely poisoned were treated with 5 to 10 g oral DFO and either 1 or 2 g intramuscular (IM) DFO every 3 to 12 hours.⁸³ Patients who were in shock or severely ill received 1 g of DFO IV at a maximum of 15 mg/kg/h every 4 to 12 hours for 2 to 3 days as necessary. Of the 28 patients who developed coma, shock, or both, three died. One of the three patients who died had received late treatment with DFO.

This case series was expanded to 472 patients, and guidelines for DFO dosing were formulated as a result of this clinical experience.⁸² The recommended initial dose of DFO was suggested as 1 g IM followed by 0.5 g at 4 and 8 hours later and then every 4 to 12 hours as necessary, not to exceed 6 g in 24 hours. For patients in shock, DFO was recommended at an initial dose not to exceed 1 g IV and a rate not to exceed 15 mg/kg/h followed 4 and 8 hours later by two 0.5-g doses for a total dosage not to exceed 6 g in 24 hours. These recommendations for total dosages were not scientifically developed and appear to be based on arbitrary assumptions. However, the manufacturer continues to recommend these doses.²⁰

Intramuscular Versus Intravenous Administration

Prior to 1976, IM DFO was the preferred route of administration, and IV DFO was reserved for patients in shock. However, when transfusion-induced iron overload was studied and IM and IV DFO administration were compared, IV DFO significantly enhanced urinary iron elimination.⁶⁶ This study provided compelling arguments against IM dosing, as did data showing higher peak and more stable DFO concentrations with IV infusions. A single patient was given 425 mg/kg IV

over 24 hours without incident, although the increase in urinary iron excretion seen when the DFO dose increased from 4 to 16 g/day appeared to be of limited consequence.

Duration of Dosing

The optimum duration of DFO administration is unknown. In canine models, serum iron concentrations peak within 3 to 5 hours and then decrease quickly as iron is transported out of the blood into the tissues.^{79,86} In one human study, initial iron concentrations of approximately 500 µg/dL decreased to approximately 100 µg/dL within 12 hours.⁴⁴ Other case reports also suggest that most of the easily accessible iron is distributed out of the blood compartment by 24 hours.²¹ Although severely poisoned patients have received DFO for more than 24 hours, pulmonary toxicity is associated with prolonged DFO infusions.^{31,57,75} Intuitively, in patients with acute iron overdose, DFO should be administered early and for a shorter duration while the iron is easily accessible in the blood. In patients with chronic iron overload, prolonged infusions of smaller DFO doses are necessary to act as a sink and to slowly remove iron from the limited labile pool and tissue stores.³⁵

ROLE IN ALUMINUM TOXICITY

Patients with severe chronic kidney disease are at high risk for aluminum toxicity.⁸⁸ Acute aluminum toxicity resulting from bladder irrigations with alum for hemorrhagic cystitis is also reported.⁶⁰ Chronic aluminum toxicity is reported from administration of aluminum salts as phosphate binders or from hemodialysis with a water source containing aluminum. DFO binds aluminum to form aluminoxamine, analogous to iron and ferrioxamine. The chelate is a 1:1 octahedral complex with aluminum.⁸⁸ Aluminoxamine is renally excreted. In patients with kidney insufficiency, hemodialysis (especially with a high-flux membrane) is effective in removing the aluminoxamine and should be used to prevent aluminum redistribution to the central nervous system and other tissues.⁵³ The dosing of DFO is unclear but should be tailored to the patient's serum aluminum concentrations, symptoms, and response.⁵³ Electroencephalography monitoring is recommended. DFO doses of 5 to 15 mg/kg/day, infused over several hours and 6 to 8 hours before a 3 to 4 hour run of high flux hemodialysis, have been successful and maximize aluminoxamine removal without exacerbating adverse events.^{53,68} The appropriate duration of this DFO dosing with hemodialysis is unknown and should be based on central nervous system symptoms, serum aluminum concentrations, and kidney function. The correlation of serum aluminum concentrations with toxicity is poorly defined and may depend on the chronicity of aluminum exposure. Patients are treated for days to weeks, with one holiday per week (Chap. 87).

ADVERSE EFFECTS

DFO administration to patients with acute iron overdose is associated with rate related hypotension, hypersensitivity reactions and systemic allergic reactions, pulmonary toxicity, and infection. DFO administration to patients with chronic iron overload is associated with auditory, ocular, and pulmonary toxicity and infection.^{9,35}

Significant hypotension was first noted in 1965 in two children who were administered approximately 80 to 150 mg/kg DFO IV over 15 minutes.⁸⁴ The mechanism for rate-related hypotension is not fully understood, although histamine release is at least partially implicated. Although elevated histamine concentrations were documented in a canine experiment, pretreatment with diphenhydramine was not protective.⁸⁵ Intravascular volume depletion caused by iron toxicity also contributes to hypotension. No experiment has determined the maximum safe rate of DFO administration. Adverse events of DFO, including tachycardia, hypotension, and shock, were reported with rapid infusion.⁸³ These complications resulted in the current recommendations for less rapid IV infusions of DFO not to exceed 15 mg/kg/h.^{83–85} Currently suggested IV infusion rates are somewhat empirical because of the lack of robust evidence. Higher rates were administered successfully in critically ill patients when time was of the essence.^{11,15,21}

Acute respiratory distress syndromes (ARDS) occur in patients with acute iron overdoses who have received IV administration of DFO (15 mg/kg/h) therapy for more than 24 hours.^{3,37,75} Usually, iron concentrations are normal in these patients within 24 hours, and the rationale for continued administration of DFO was not reported. Examination of the nontoxicologic literature reveals other instances of ARDS occurring in patients receiving continuous IV DFO for hemosiderosis and malignancies.^{13,25,81} Administration of continuous IV doses of DFO for prolonged (>24 hours) periods was common to all of these patients. The mechanism for development of pulmonary toxicity after DFO is unknown. Pulmonary toxicity may result from excessive DFO chelation of intracellular iron and depletion of catalase, resulting in oxidant damage,³⁰ or generation of free radicals.¹

DFO therapy may lead to infection with a number of unusual organisms, including *Yersinia enterocolitica*, *Zygomycetes* spp, and *Aeromonas hydrophilia*. The virulence of these organisms is facilitated when the DFO–iron complex acts as a

siderophore for their growth.^{45,49,52} Most cases of septicemia occurred when DFO was used for treatment of aluminum toxicity in patients receiving chronic hemodialysis.⁵⁰ Several cases of *Yersinia* sepsis were reported after acute iron overdose and treatment with DFO.^{49,52}

Ocular toxicity characterized by decreased visual acuity and peripheral visual fields, night blindness, color blindness, and retinal pigmentary abnormalities has occurred in patients who received continuous IV DFO for thalassemia and other nonacute iron and aluminum excess conditions.^{8,12,18,55,58} Ototoxicity documented by abnormal audiograms indicating partial or total deafness is reported.^{61,62} However, neither ocular toxicity nor ototoxicity is reported in the setting of acute overdose treatment. When DFO is used in the absence of iron overload, zinc deficiency and decreases in serum ferritin, mean corpuscular volume and hemoglobin may develop.⁴⁰

Infusion pump malfunctions have occasionally led to acute kidney injury (AKI) due to IV DFO overdose. This has been successfully treated with hemodialysis after failure of medical management.¹⁶ One inadvertent overdose of IV DFO in a patient with severe iron overload associated with sickle cell β thalassemia resulted in AKI within 12 to 18 hours of IV DFO administration. The patient received a planned 45 g (700 mg/kg) 96 hour infusion over 8 hours due to incorrect programming of the infusion pump. High efficiency hemodialysis, instituted after an 8 hour trial of intravenous hydration and mannitol were unsuccessful in restoring kidney function.⁶⁴

PREGNANCY AND LACTATION

A review of the literature identified 61 cases of intentional iron overdose in pregnant women.⁷⁶ Serious iron toxicity with organ involvement was associated with spontaneous abortion, preterm delivery, and maternal death. There is no evidence to indicate that DFO is teratogenic.⁷⁶ Neither iron nor DFO appears to cross the ovine placenta.¹⁷ A case report of a pregnant woman with thalassemia and a review of 40 other pregnant patients with thalassemia treated extensively with DFO found no evidence of teratogenicity.⁶⁹ Thus, DFO should be administered to pregnant women with acute iron overdose for the same indications as for nonpregnant women and is listed as FDA pregnancy category C. Excretion in breast milk is not reported.

DOSING AND ADMINISTRATION

The indications and dosage schedules for DFO administration are largely empirical.^{6,67} Systemic toxicity associated with acute iron poisoning manifested by coma, shock, or metabolic acidosis warrants IV infusion of DFO. The duration of therapy probably should be limited to 24 hours to maximize effectiveness while minimizing the risk of pulmonary toxicity. Some investigators have suggested that more than the recommended dose of 15 mg/kg/h be infused during the first 24 hours for life-threatening iron toxicity, but this recommendation remains to be validated experimentally.³⁵ We recommend starting with 5 mg/kg/h and increasing after 15 minutes if tolerated to 15 mg/kg/h to minimize the risk of hypotension. In adults, after the first 1000 mg is infused, the subsequent doses can be adjusted to infuse the remainder of the 6 to 8 g during the next 23 hours. How exactly this should be done is not clear. Theoretically, an adult patient with significantly elevated serum iron concentrations (>1000 $\mu\text{g/dL}$) who is severely symptomatic, might do better with continuing at a rate of 15 mg/kg/h if tolerated for the first several hours and then reducing the dose to limit the total 24 hours dose to 6 to 8 g. If after the first 1000 mg the patient improved clinically then consideration might be given to administering the remainder of the 5 g over the next 23 hours. In a 70 kg patient, this would be about 3 to 4 mg/kg/h for the next 23 hours. Dosing in obese patients is unknown; however, because DFO is water soluble, limiting the hourly dose in obese adults to 1000 mg is reasonable. The manufacturer recommends not exceeding 125 mg/h after the first 1000 mg has been infused. Although patients with mild toxicity can be treated with IM injections of 90 mg/kg of DFO (maximum of 1 g in children or 2 g in adults), this volume of antidote cannot be given IM with ease or painlessly in children. Therefore, few clinicians administer IM DFO, with most preferring the IV route ([Chap. 46](#)). The total daily parenteral dose is limited by the infusion rate in children (if the manufacturer's recommendations are followed). Conservative recommendations in adults limit the dose to 6 to 8 g/day, although doses as high as 16 g/day with diverse dosing regimens have been administered without incident.^{15,21,47,57,66,74}

URINARY COLOR CHANGE

To further define the role of DFO and the quantitative excretion of urinary iron, investigators studied urinary samples.⁵¹ Several reviews of patients with acute iron poisoning who had received DFO^{48,87} investigated the correlation between urinary iron concentrations and systemic toxicity. Most data suggest that the absence of a urine color change, often referred to as a vin rose color, after DFO administration indicates very little renal excretion of ferrioxamine.²⁶ However, unless a baseline urine color is obtained before DFO administration, post-DFO administration comparisons of urine color are unreliable. DFO administration may not yield a vin rose color despite severe iron toxicity and/or high serum iron

concentrations.⁷⁰ No relationship between urinary iron excretion, clinical iron toxicity, and the effectiveness of DFO has been established.

FORMULATION AND ACQUISITION

DFO mesylate (Desferal) is available in vials containing 500 mg or 2 g of sterile, lyophilized powder.²⁰ Adding 5 or 20 mL of sterile water for injection to either the 500 mg or the 2 g vial, respectively, results in an approximately 100 mg/mL solution. The drug must be completely dissolved before using. The resulting solution is isotonic, clear, and colorless to slightly yellowish²⁰ and can be diluted further with 0.9% NaCl solution, glucose in water, or Ringer lactate solution for IV administration. For IM administration, a smaller volume of solution is preferred. Adding 2 or 8 mL of sterile water for injection to the 500 mg or 2 g vial, respectively, results in a stronger yellow-colored solution containing approximately 200 mg/mL.

SUMMARY

- DFO is the parenteral chelator of choice for treatment of iron poisoning.
- No controlled studies have evaluated its efficacy or dosing.
- IV is the preferred route of administration.
- Early administration captures iron still in the blood compartment.
- Administration for more than 24 hours after ingestion may predispose to acute respiratory distress syndrome.
- DFO is also used for chelation of aluminum in patients with chronic kidney failure.

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47 VITAMINS

Beth Y. Ginsburg

Vitamins are essential for normal human growth and development.⁴⁹ By definition, a vitamin is a substance present in small amounts in natural foods, is necessary for normal metabolism, and whose lack in the diet causes a deficiency disease.⁴²

A standard North American diet is sufficient to prevent overt vitamin deficiency diseases.^{68,77} However, suboptimal vitamin status is common in Western populations and can be a risk factor for chronic diseases such as cardiovascular disease, cancer, and osteoporosis.^{68,77} Groups at particular risk include the elderly, the hospitalized, alcohol-dependent individuals, pregnant women, and others with poor nutritional status. The American Dietetic Association posits that the best strategy for promoting optimal health and reducing chronic disease is to choose a wide variety of nutrient-rich foods, while the use of supplements can help some people meet their nutritional needs.¹⁵⁴ Health care professionals should identify patients with poor nutrition or other reasons for increased vitamin needs and offer guidance on vitamin supplementation. Some suggest that since most people do not consume an optimal amount of vitamins by diet alone, it is prudent for all adults to take vitamin supplements with physician guidance.^{68,77}

Dietary supplement use has increased over time in the United States. National Health and Nutrition Examination Survey (NHANES) data collected from 2003 to 2006 demonstrate that dietary supplement use was reported by 49% of the population age 1 year and older, an increase of approximately 10% from NHANES data from 1988 to 1994, with 79% of users taking them daily for the past 30 days.¹⁵ The categories of dietary supplements included multivitamin, multiminerals (MVMMs), botanicals, and amino acids. Among adults and children, MVMMs were the most commonly reported dietary supplement, with 33% of the population reporting use.

Unfortunately, many individuals share the mistaken beliefs that vitamin preparations provide extra energy or promote muscle growth and regularly ingest quantities of vitamins in great excess of the recommended dietary allowances (RDAs) (Table 47–1). The most commonly used MVMM preparations generally do not exceed 100% of the RDA, but excessive vitamin intake is more likely to occur in MVMM users who also take single vitamin supplements.¹⁹⁹ Excess vitamin intake may also occur in individuals taking an MVMM who ate a healthy diet that included fortified foods and beverages.¹⁶⁸ Some vitamins are associated with consequential adverse effects when ingested in very large doses. Adverse events also may be associated with the use of some vitamins at the RDA or at amounts less than or approaching the established tolerable upper intake level (UL) in certain populations. Those who smoke should avoid products containing large amounts of vitamin A and β -carotene because studies have linked use of these vitamins to an increased risk of lung cancer in smokers.¹⁹⁰ In one study, smokers taking 20 mg/day of β -carotene (UL 36 mg/day) had an 18% higher lung cancer rate than smokers taking a placebo.²²⁴ Individuals taking medications to reduce blood clotting, such as warfarin, should not take supplemental vitamin K since it is involved in blood clotting and may reduce the effectiveness of warfarin and similar medications.

TABLE 47–1. Recommended Dietary Daily Allowances/Adequate Daily Intakes

Age (years)	Vitamin A (μg RAE/1U)	Vitamin D ($\mu\text{g}/10\text{U}$) ^a	Vitamin E (mg α -TA/1U)	Vitamin C (mg)	Vitamin B ₁ (mg)	Niacin (mg NE) ^a
Infants						
0.0–0.5	400/1300 ^a	5/200 ^a	4/4 ^a	40 ^a	0.1 ^a	2 ^a
0.5–1.0	500/1700 ^a	5/200 ^a	5/5 ^a	50 ^a	0.3 ^a	4 ^a
Children						
1–3	300/900	5/200 ^a	6/6	15	0.5	6
4–8	400/1300	5/200 ^a	7/7	25	0.6	8
Males						
9–13	600/2000	5/200 ^a	11/11	45	1.0	12
14–18	900/3000	5/200 ^a	15/15	75	1.3	16
19–50	900/3000	5/200 ^a	15/15	90	1.3	16
51–70	900/3000	10/400 ^a	15/15	90	1.7	16
>70	900/3000	15/600 ^a	15/15	90	1.7	16
Females						
9–13	600/2000	5/200 ^a	11/11	45	1.0	12
14–18	700/2300	5/200 ^a	15/15	65	1.2	14
19–50	700/2300	5/200 ^a	15/15	75	1.3	14
51–70	700/2300	10/400 ^a	15/15	75	1.5	14
>70	700/2300	15/600 ^a	15/15	75	1.5	14
Pregnant						
≤18	750/2500	5/200 ^a	15/15	80	1.9	18
19–50	770/2500	5/200 ^a	15/15	85	1.9	18
Lactating						
≤18	1200/4000	5/200 ^a	19/19	115	2.0	17
19–50	1300/4300	5/200 ^a	19/19	120	2.0	17

^aThese values represent the adequate daily intakes. Values without an ^a represent the recommended dietary daily allowances.

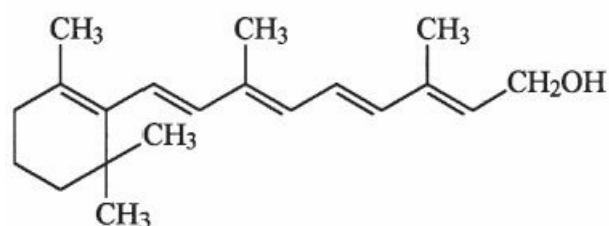
NE = niacin equivalent; RAE = retinol activity equivalents; α -TA = α -tocopherol acetate.

Adapted from Dietary Reference Intakes. Food and Nutrition Board, Institute of Medicine. Available at <http://iom.edu/Reports/2006/Dietary-Reference-Intakes-Essential-Guide-Nutrient-Requirements.aspx>. Last accessed April, 27, 2014.

Vitamins can be divided into two general classes. Most of the vitamins in the water-soluble class have minimal toxicity because they are stored to only a limited extent in the body. Thiamine, riboflavin, cyanocobalamin, pantothenic acid, folic acid, and biotin are not reported to cause any toxicity following oral ingestion.⁴⁹ Ascorbic acid (vitamin C), nicotinic acid (vitamin B₃), and pyridoxine (vitamin B₆) have associated toxicity syndromes. However, the fat-soluble vitamins can bioaccumulate to massive degrees. As a result, the potential for toxicity greatly exceeds that of the water-soluble group. Vitamins A, D, and E (but not K) are associated with toxicity following very large overdose or chronic overuse. The adverse effect secondary to vitamin K is limited to severe, and sometimes fatal, anaphylactoid reactions with rapid administration of the intravenous (IV) preparation.⁷⁵

VITAMIN A

MW = 272.43 Da
 Therapeutic serum concentration = 65–275 IU/dL
 16.6–83.3 µg/dL



History and Epidemiology

Two independent groups discovered vitamin A in 1913.^{157,178} They reported that animals fed an artificial diet with lard as the sole source of fat developed a nutritional deficiency characterized by xerophthalmia. They found that this deficiency could be corrected by adding to the diet a factor contained in butter, egg yolks, and cod liver oil. They named the substance “fat soluble vitamin A.” The chemical structure of vitamin A was determined in 1930.¹²³ Vitamin A is also found naturally in liver, fish, cheese, and whole milk. In the United States and other parts of the world, including some developing countries, many cereal, grain, dairy, and other products, as well as infant formulas, are fortified with vitamin A.^{6,240}

Vitamin A toxicity can occur in people who ingest large doses of preformed vitamin A in their daily diets. Inuits in the sixteenth century recognized that ingestion of large amounts of polar bear liver caused a severe illness characterized by headaches and prostration.⁷⁶ Arctic explorers in the 1800s knew of the poisonous qualities of polar bear liver and described an acute illness following its ingestion.⁸⁵ Explorers also described a condition among the Inuit population known as pibloktoq, or “Arctic hysteria,” characterized by hysteria, depression, echolalia, insensitivity to extreme cold, and seizures, and believed to be related to ingestion of polar bear liver and other organ meats.¹⁸² Vitamin A toxicity is implicated in the etiology of pibloktoq as some somatic and behavioral effects of vitamin A toxicity closely parallel many of the symptoms reported in Inuit patients diagnosed with pibloktoq.¹³² However, the toxic substance in polar bear liver was not identified as vitamin A until 1942.²⁰⁰ The vitamin A content of polar bear liver is as high as 34,600 IU/g (10,400 RAE/g), supporting the view that vitamin A is the toxic factor in liver.²⁰³

Vitamin A toxicity was reported in an adult who chronically ingested large amounts of beef liver,¹¹⁴ as well as following ingestion of the liver of the grouper fish *Cephalopholis boenak*, which has a high content of vitamin A.⁴³ Ingestion of whale and seal liver, as well as the livers of large fish, such as shark, tuna, and sea bass, also is associated with development of vitamin A toxicity.

Vitamin A toxicity usually is not expected to occur following ingestion of large doses of provitamin A carotenoids. Vitamin A induced hepatotoxicity and neurotoxicity was believed to have developed in an 18 year-old girl who maintained a diet nearly limited to foods rich in the carotenoid β -carotene, including pumpkin, carrots, and laver (nori), for several years.¹⁷⁰ However, she also included an unspecified, although reportedly small, amount of fish, red meat, and liver in her diet.

Vitamin A toxicity is rare, with a reported average incidence of less than 10 cases per year from 1976 to 1987.²⁰ The majority of reported cases of vitamin A toxicity result from inappropriate use of vitamin supplements.^{17,20} In the United States, 28% of the population report taking a dietary supplement containing vitamin A.¹⁵

Vitamin A is present in two forms. Preformed vitamin A as retinol is derived from retinyl esters, its storage form, in animal sources of food. Provitamin A carotenoids are vitamin A precursors and are found in plants. Among the carotenoids, β -carotene is most efficiently made into retinol. The term vitamin A was classically only used to refer to the compound retinol. Currently, it is used to describe all retinoids, compounds chemically related to retinol that exhibit the biological activity of retinol. Retinol can be converted in the body to the retinoids retinal and retinoic acid. Synthetic retinoids have been developed via chemical modification of naturally occurring retinoids, often for a specific therapeutic purpose. Vitamin A activity is expressed in retinol activity equivalents (RAEs). One RAE corresponds to 1 µg of retinol or 3.33 IU of vitamin A activity as retinol. One RAE also corresponds to 12 µg of β -carotene.

Vitamin A content varies widely among different food types. A 3 oz serving of cooked beef liver contains 30,325 IU (9100 RAE) of vitamin A, whereas 1 cup of whole milk contains 305 IU (92 RAE) of vitamin A. Fish-liver oils, such as swordfish and black sea bass, have extremely large amounts of vitamin A and may contain more than 180,000 IU (54,050 RAE) of vitamin A per gram of oil. Carotenoids are present in yellow and green fruits and vegetables. A raw carrot has a high β -carotene content of approximately 20,250 IU (6080 RAE). One half cup serving of spinach contains approximately 7400 IU (2220 RAE) of β -carotene, whereas an apricot or peach contains 500 to 600 IU (150–180 RAE). The average American diet provides about one half of its daily vitamin A intake as carotenoids and about one half as preformed vitamin A.⁴⁶ The RDA of vitamin A is 900 µg RAE/day (3000 IU/day) for adult men and 700 µg RAE/day (2300 IU/day) for women (Table 47–1).⁸⁰ The UL for adults is 3000 µg RAE/day (9900 IU/day).

As a group, retinoids have specific sites of action and varying degrees of biologic potency. Retinoic acid is primarily responsible for maintaining normal growth and differentiation of epithelial cells in mucus secreting or keratinizing tissue.¹⁵³ Vitamin A deficiency results in the disappearance of goblet mucous cells and replacement of the normal epithelium with a stratified, keratinized epithelium. Dermal manifestations are the earliest to develop and include dry skin and hair and broken fingernails. In the cornea, hyperkeratization is called xerophthalmia and can lead to permanent blindness. Alterations in the epithelial lining of other organ systems may lead to increased susceptibility to respiratory infections, diarrhea, and urinary calculi. Vitamin A, in the form of 11-cis-retinal, plays a critical role in retinal function.²³⁴ Deficiency results in nyctalopia, which is decreased vision in dim lighting, more commonly known as night blindness.

Vitamin A is prescribed for some people for dermatologic and ophthalmic conditions. Vitamin A toxicity often occurs in adults who continue to use the vitamin without medical supervision.⁸⁶

Isotretinoin (Accutane), 13-cis-retinoic acid, is prescribed for treatment of severe cystic acne. Of great concern is the teratogenicity associated with its use by pregnant women. There has not been any association between male use of isotretinoin during the time of conception and birth defects. The iPLEDGE program is a mandatory US Food and Drug Administration (FDA) risk evaluation and mitigation strategy for the distribution of isotretinoin that was initiated in 2006. Its goals are to inform prescribers, pharmacists, and patients about the serious risks of isotretinoin's and safe-use conditions and to prevent fetal exposure to isotretinoin.²²⁸ Components of the program include mandatory enrollment, documentation of a negative pregnancy test and birth control use, and prescriber, pharmacist, and patient education. The iPLEDGE program replaced the FDA's System to Manage Accutane-Related Teratogenicity (SMART) program that was initiated in 2002. Although both programs share many features, the SMART program was voluntary and did not include mandatory record keeping or reporting. A review after the implementation of the SMART program revealed that there was an increase in the number of pregnant women prescribed isotretinoin compared with the previous year. The review revealed that prescribers were not providing adequate patient education regarding the risk of teratogenicity and that there was not compliance with essential portions of the pregnancy prevention program.¹⁹⁸

All-trans-retinoic acid (ATRA), or tretinoin, is used as a differentiating chemotherapeutic in the treatment of acute promyelocytic leukemia (APL), a disease characterized by the accumulation of promyelocytic blasts in bone marrow due to obstruction of differentiation of granulocytic cells.¹³⁵ ATRA, in combination with anthracycline chemotherapy, improves the complete remission rate, often reported to be greater than 90%, and reduces the incidence of relapse to only 10% to 15% when used as maintenance therapy.⁷¹ APL differentiation syndrome (DS), previously known as ATRA syndrome or retinoic acid syndrome, is the main adverse effect and occurs in up 14% to 16% of patients who receive ATRA with an associated mortality of about 2%.¹⁸⁴ ATRA has also been used for the treatment of myelodysplastic syndrome and acute myelogenous leukemia.

Pharmacology, Pharmacokinetics, and Toxicokinetics

Absorption of vitamin A in the small intestine is nearly complete. However, some vitamin A may be eliminated in the feces when large doses are taken. The majority of vitamin A is ingested as retinyl esters, the storage form of retinol.¹⁵³ Retinyl esters undergo enzymatic hydrolysis to retinol by digestive enzymes in the intestinal lumen and brush border of the intestinal epithelial wall. A small portion of retinol is absorbed directly into the circulation, where it is bound to retinol-binding protein (RBP) and transported to the liver. Most of the retinol is taken into intestinal epithelial cells by RBP.¹⁷⁵ Subsequently, retinol is reesterified and incorporated into chylomicrons, which are released into the blood and taken up by the Ito cells of the liver. After large oral doses, significant amounts of retinyl esters coupled to chylomicrons circulate in association with low-density lipoprotein (LDL) and are delivered to the liver. Approximately 50% to 80% of the total vitamin A content of the body is stored in the liver as retinyl esters.²⁸ The liver releases vitamin A into the bloodstream to maintain a constant plasma retinol concentration and is thus delivered to tissues as needed.

Carotenoid absorption requires bile and absorbable fat in the stomach or intestine. These components combine with carotenoids to form mixed lipid micelles which move into the duodenal mucosal cells via passive diffusion. The majority of β -carotene that is metabolized undergoes central cleavage via oxidation to form retinal, which is then reduced to retinol. Retinol is then esterified with fatty acids and incorporated into chylomicrons, which are transported to the bloodstream via the lymphatics for delivery to the liver. Massive doses of β -carotene are rarely associated with vitamin A toxicity due to decreased efficiency in absorption secondary to saturation of dissolution in bulk lipid, micellar incorporation, and diffusion due to a reduction in the concentration gradient.¹⁸¹ Unabsorbed β -carotene is excreted in the feces. In addition, there is a decrease in the rate of conversion of carotenoids to vitamin A.⁶³ Hypercarotenemia develops when massive doses are ingested. Excess absorbed β -carotene is incorporated with lipoproteins and released into the bloodstream via the lymphatics for delivery to the adipose tissue and adrenals for storage. Hypercarotenemia usually is not associated with morbidity.

The normal serum retinol concentration is approximately 30 to 70 $\mu\text{g/dL}$.²¹⁴ These concentrations are maintained at the expense of hepatic reserves when insufficient amounts of vitamin A are ingested. A normal adult liver contains enough

vitamin A to fulfill the body's requirements for approximately 2 years.¹⁶³ Excessive intake of vitamin A is not initially reflected by elevated serum concentrations because vitamin A is soluble in fat but not in water. Instead, hepatic accumulation is increased. This storage system allows for cumulative toxic effects. Although no quantitative relationship exists between the magnitude of liver stores and serum concentrations of vitamin A, in chronic vitamin A toxicity serum concentrations are generally higher than 3.49 $\mu\text{mol/L}$ (95 $\mu\text{g/dL}$).²⁰ Vitamin A has a half-life of 286 days.^{216,238} Retinoids undergo a variety of metabolic and conjugation pathways and are subsequently eliminated in the feces, urine, or bile.

Clinical toxicity correlates well with total body vitamin A content, which is a function of both dose and duration of administration. A randomized double blind trial, in which 390 women received 400,000 IU (120,000 RAE) of vitamin A as a single dose were compared with 380 women who received placebo, suggested that dosing at this level is well tolerated.¹¹³ Doses of 100,000 IU (30,000 RAE) of vitamin A in infants aged 6 to 11 months and 200,000 IU (60,000 RAE) of vitamin A every 3 to 6 months for infants and children aged 12 to 60 months result in few adverse events.¹⁹ The minimal dose required to produce toxicity in humans is not established. However, an animal study has shown that the median lethal acute dose in monkeys is 560,000 IU (168,000 RAE) per kilogram of body weight.¹⁴⁸ In this study, all monkeys receiving more than 300,000 RAE/kg (999,000 IU/kg) died, whereas none died at a dose of 100,000 RAE/kg (333,000 IU/kg). Hepatotoxicity can occur in humans following an acute ingestion of a massive dose of vitamin A (>600,000 IU {180,000 RAE}).¹²⁹

Vitamin A toxicity may occur more frequently secondary to chronic ingestions of vitamin A. Hepatotoxicity typically requires vitamin A ingestions of at least 50,000 to 100,000 IU/day (15,000–30,000 RAE/day) for months or years.^{6,129} One study found that in patients with vitamin A–induced hepatotoxicity, the average daily vitamin A intake was higher in patients who developed cirrhosis (135,000 IU/day 40,500 RAE/day) compared with patients who developed noncirrhotic liver disease (66,000 IU/day 20,000 RAE/day).⁸⁴ However, case reports have documented hepatotoxicity resulting from vitamin A doses as low as 25,000 IU/day (7500 RAE/day),^{86,129} a dose widely available in nonprescription vitamin A preparations.

Pathophysiology

The mechanism of action for many of the toxic effects of vitamin A may be at the nuclear level. Retinoic acid influences gene expression by combining with nuclear receptors.¹⁵³ Retinoids also influence expression of receptors for certain hormones and growth factors. Thus, they are able to influence growth, differentiation, and function of target cells.¹⁴⁵

In epithelial cells and fibroblasts, retinoids affect changes in nuclear transcription, resulting in enhanced production of proteins such as fibronectin and decreased production of other proteins such as collagenase.¹⁵⁰ Excessive concentrations of retinoids where goblet cells are present lead to the production of a thick mucin layer and inhibition of keratinization. In addition, lipoprotein membranes have increased permeability and decreased stability, resulting in extreme thinning of the epithelial tissue.

In vitro studies in bone demonstrate that high doses of vitamin A are capable of directly stimulating bone resorption and inhibiting bone formation. This effect is secondary to increased osteoclast formation and activity and inhibition of osteoblast growth.^{172,177,209}

Hepatotoxicity may develop secondary to a single large acute overdose or ingestion of smaller doses if taken over a prolonged time.^{86,129} A total of 90% of hepatic vitamin A stores are located in the Ito, or fat-storing, cells of the liver, which are located in the perisinusoidal space of Disse, and are responsible for maintaining normal hepatic architecture.^{99,100} Ito cells undergo hypertrophy and hyperplasia as vitamin A storage increases.¹²⁹ This results in transdifferentiation of the Ito cell into a myofibroblastlike cell that secretes a variety of extracellular matrix components, leading to narrowing of the perisinusoidal space of Disse, obstruction to sinusoidal blood flow, and noncirrhotic portal hypertension (Fig. 47–1).^{54,91,110,124,129,206} Continued ingestion of vitamin A and hepatic storage may lead to obliteration of the space of Disse, sinusoidal barrier damage, perisinusoidal hepatocyte death, fibrosis, and cirrhosis^{110,118,129,204} (Chap. 23).

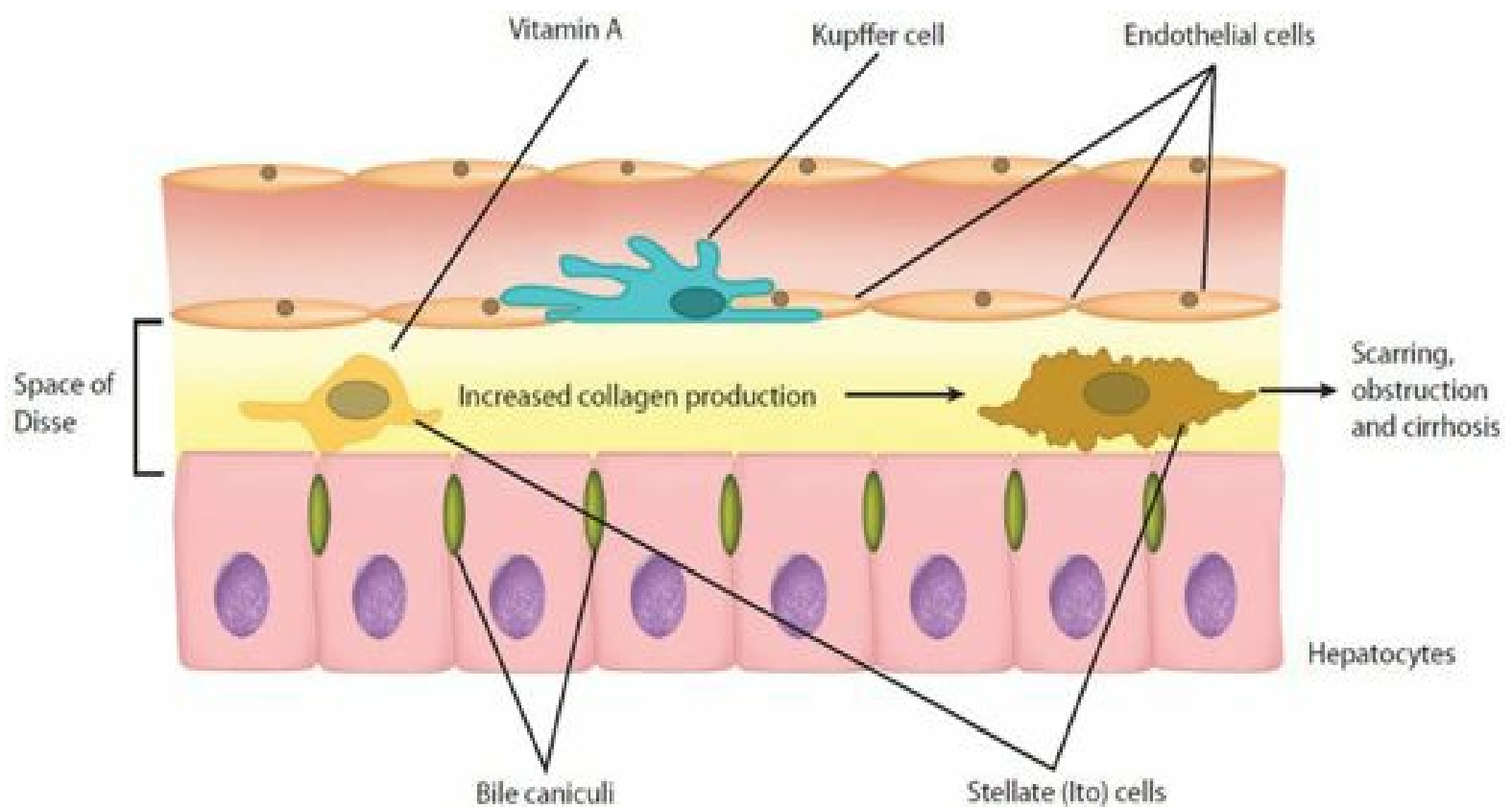


FIGURE 47–1. Schematic demonstration of hepatotoxicity resulting from excessive deposition of vitamin A in the Ito cells of the liver.

Vitamin A toxicity has long been thought to be the cause of the severe headaches and papilledema associated with idiopathic intracranial hypertension (IIH).¹⁹³ Increased concentrations of unbound retinol in the cerebral spinal fluid (CSF) of patients with IIH suggest that vitamin A is involved in the pathogenesis of IIH.^{223,237} However, the mechanisms by which vitamin A leads to increased intracranial pressure (ICP) in IIH are not definitively known.¹⁹³ Unbound, circulating retinol and retinyl esters are proposed to be capable of interacting with cell membranes and producing damage by membranolytic surface-active properties.¹¹⁵ In the central nervous system (CNS), disruption of cell membrane integrity might lead to disruption of CSF outflow, thereby producing signs and symptoms consistent with IIH.^{88,115,127,149} It has also been suggested that vitamin A could lead to intracranial hypertension via enhanced transcription of genes involved in CSF secretion or absorption.⁹² Another explanation for the association of vitamin A with IIH involves the recent recognition of RBP as a signaling molecule altering CSF secretion or absorption.¹⁴²

Clinical Manifestations

Symptoms of an acute overdose of vitamin A often develop within hours to two days after ingestion.¹⁶³ Initial signs and symptoms include headache, papilledema, scotoma, photophobia, seizures, anorexia, drowsiness, irritability, nausea, vomiting, abdominal pain, liver damage, and desquamation.¹⁶³ Nonspecific symptoms include fatigue, fever, weight loss, edema, polydipsia, dysuria, hyperlipidemia, anemia, and menstrual abnormalities.

Hypercarotenemia produces a yellow-orange skin discoloration that can be differentiated from jaundice by the absence of scleral icterus.

Chronic toxicity of vitamin A affects the skin, hair, bones, liver, and brain. The most common skin manifestations include xerosis, which is associated with pruritus and erythema, skin hyperfragility, and desquamation.^{60,61,243} Retinoid toxicity may cause hair thinning and even diffuse hair loss in 10% to 75% of patients.^{79,89,126} In addition, the characteristics of the hair may change after regrowth. Hair sometimes becomes permanently curly or kinky.¹⁰ Nail changes include a shiny appearance, brittleness, softening, and loosening.⁷² Dryness of mucous membranes develops with chapped lips and xerosis of nasal mucosa, which sometimes is associated with nasal bleeding.⁵¹

Findings from epidemiologic studies are consistent with bone loss and a resulting increase in fracture risk. In northern Europe, the region with the highest incidence of osteoporotic fractures, dietary intake of vitamin A is high. A study of this population demonstrated that the risk of first hip fracture was increased by 68% for every 1 mg increase in RAE intake.¹⁵⁹ This study also showed that compared with intake less than 0.5 mg/day, intake greater than 1.5 mg/day reduced bone mineral density by 10% at the femoral neck, 14% at the lumbar spine, and 6% for the total body, doubling the risk of hip fracture. These findings are supported by other studies demonstrating an increased risk of hip fracture among women with

elevated serum vitamin A concentrations and in women ingesting large daily amounts of vitamin A.^{73,176} One study found that among women not taking supplemental vitamin A, a diet rich in vitamin A was also associated with an increased fracture risk.⁷³

Other musculoskeletal findings include skeletal hyperostoses, most commonly affecting the vertebral bodies of thoracic vertebrae, extraspinal tendon and ligament calcifications, soft-tissue ossification, cortical thickening of bone shafts, periosteal thickening, and bone demineralization.^{51,163,165} Many of these findings are apparent on radiographs. Patients often complain of bone and joint pain and muscle stiffness or tenderness. Hypercalcemia, with low or normal parathyroid hormone (PTH) concentrations, likely results from increased osteoclast activity and bone resorption.³⁰ Patients with chronic kidney disease are at increased risk for developing hypercalcemia at vitamin A doses lower than usual toxic doses secondary to decreased renal metabolism of retinol. This complication occurred in an 8 year-old boy with chronic kidney disease following a dose of 12,000 IU/day (3600 RAE/day) for at least 2 years.⁵⁸ Premature epiphyseal closure in children is reported.¹⁸⁹ Teratogenic effects include interference with skeletal differentiation and growth.³⁰

The degree of hepatotoxicity appears to correlate with the dose of vitamin A and chronicity of use. With large doses, cirrhosis develops and may lead to portal hypertension, esophageal varices, jaundice, and ascites.^{55,86,129} Hepatotoxicity may be manifested by elevations in bilirubin, aminotransferases, and alkaline phosphatase concentrations.

Idiopathic intracranial hypertension is characterized by elevated ICP in the absence of a structural anomaly. It occurs in patients with altered endocrine function, systemic diseases, impaired cerebral venous drainage, or ingestion of various xenobiotics, including excessive vitamin A (Table 47–2).⁵ The syndrome is most common in young obese women, but the etiology remains unknown in the majority of cases. The first case of IIH associated with vitamin A toxicity was described in 1954.⁸⁵ However, the symptoms were first described in 1856 by an Arctic explorer who noted vertigo and headache after eating polar bear liver.²¹³ Patients typically present with headache and visual disturbances, including sixth nerve palsies, visual field deficits, and blurred vision, and have a normal mental status. Despite severe papilledema, visual loss often is minimal. However, permanent blindness may result from optic atrophy.¹⁴⁷ Other symptoms of neurotoxicity include ataxia, fatigue, depression, irritability, and psychosis.²⁶

TABLE 47–2. Xenobiotics Associated with Intracranial Hypertension

Antibiotics
Ampicillin
Minocycline
Metronidazole
Nalidixic acid
Nitrofurantoin
Sulfamethoxazole
Tetracycline
Corticosteroid therapy (oral and intranasal) and cessation
Enflurane
Griseofulvin
Halothane
Ketamine
Lead
Lithium
Oral contraceptives and progestins
Phenothiazines

Phenytoin

Tubocurarine

Vitamin A

Isotretinoin is effective in the management of acne. However, its use is associated with teratogenicity. It is thought to interfere with cranial neural crest cells, which contribute to the development of both the ear and the conotruncal area of the heart, and may cause malformed or absent external ears or auditory canals and conotruncal heart defects.¹³¹ Although studies have not shown a teratogenic risk with topical preparations, case reports describe fetal malformations associated with topical preparation use during pregnancy.^{13,36,119,143,212} In addition, mucocutaneous abnormalities, IIH, corneal opacities, hypercalcemia, hyperuricemia, musculoskeletal symptoms, liver function abnormalities, elevated triglyceride concentrations, and spontaneous abortion are reported.^{3,78,84,96,97}

Acute promyelocytic leukemia DS is the main adverse effect of treatment with ATRA. The pathophysiology of DS is not well understood, but involves an inflammatory response. Proposed mechanisms include tissue infiltration of APL cells, particularly in the lungs but also in the liver, spleen, and heart, and leukocyte extravasation.¹³³ Onset of symptoms is typically 2 to 21 days after initiation of ATRA.¹⁸⁴ The hallmarks of DS are fever and respiratory distress.^{184,201} Other common signs and symptoms include elevated white blood count, dyspnea, pulmonary edema, pulmonary infiltrates, and pleural and pericardial effusions.^{184,201} Weight gain, bone pain, headache, hypotension, congestive heart failure, acute kidney injury, and hepatotoxicity occur less commonly.^{184,201} There are no established criteria for diagnosis, but some suggest that three signs and symptoms are needed.²⁰¹ Elevated leukocyte counts at diagnosis or rapidly increasing counts during ATRA treatment predict the development of DS. Addition of dexamethasone to the ATRA treatment regimen decreases the incidence of DS to approximately 15% and its mortality to 1%.⁷⁰ However, other data demonstrated a 17% occurrence of DS despite concurrent use of steroids and not all authors support its use.^{184,242}

Diagnostic Testing

The diagnosis of vitamin A associated hepatotoxicity is supported by histologic evidence of Ito cell hyperplasia with fluorescent vacuoles on liver biopsy.⁸⁶ Laboratory testing should also include serum electrolytes including calcium, hepatic enzymes, a complete blood cell count, and a vitamin A concentration. Because the liver has a large storage capacity for excess vitamin A, hepatotoxicity may occur prior to an elevation in the serum concentration of vitamin A, which may be normal or even low, in the setting of an acute overdose. As the hepatic storage capacity is overwhelmed, the serum concentration may rapidly rise in a nonlinear fashion. Further evaluation should be guided by the clinical presentation and may include bone radiographs, computed tomography of the brain, and lumbar puncture.

Treatment

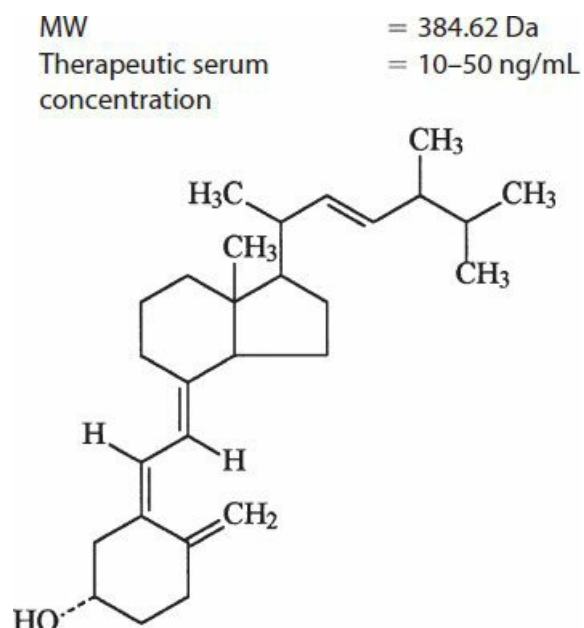
Management of a patient with a recent acute, large overdose should begin with gastrointestinal decontamination. This can be accomplished with a dose of activated charcoal. In extremely large overdoses that are expected to produce significant toxicity, gastric lavage may be considered. Although most signs and symptoms of vitamin A toxicity resolve within one week following vitamin A discontinuation and supportive care, papilledema, desquamation, and skeletal abnormalities may persist for several months. Hypercalcemia should be treated with IV fluids, loop diuretics, and prednisone 20 mg/day.²⁵ Bisphosphonates may be beneficial in refractory cases.

Idiopathic intracranial hypertension may require more aggressive therapy. Indications for treatment include visual field loss and symptoms of elevated ICP.¹⁹³ Acetazolamide, a carbonic anhydrase inhibitor, is the most commonly used treatment for IIH.¹⁹³ It is usually started at a dose of 0.5 to 1 g/day and gradually increased until clinical improvement is seen to 3 to 4 g/day.¹⁹³ Acetazolamide has teratogenic effects in animals and is designated FDA pregnancy category C. Topiramate, a partial carbonic anhydrase inhibitor that is used in the treatment of migraine headaches and epilepsy has demonstrated efficacy comparable to acetazolamide in the treatment of IIH.³⁸ Its adverse effect of weight loss may also be beneficial for patients with IIH. Furosemide is considered second-line treatment, but can be used in patients who cannot tolerate acetazolamide.^{29,193} The role of corticosteroids in the treatment of IIH is controversial and they should not be used chronically for the treatment of papilledema.²⁹ However, a short course of high dose corticosteroids may be used in patients with acute visual loss from fulminant papilledema.¹⁴⁴ Patients with extremely high ICP may benefit from daily lumbar punctures with CSF drainage.

Treatment of DS involves prompt administration of corticosteroids, commonly dexamethasone 10 mg IV twice daily until symptoms resolve followed by a 2-week taper.²⁰¹ In severe cases, ATRA should be discontinued or another chemotherapeutic, typically cytarabine, should be added to ATRA in patients with high white blood cell counts.¹⁸⁴ ATRA

can be reintroduced upon resolution of DS.

VITAMIN D



History and Epidemiology

Rickets, a disease of urban children living in temperate zones, was thought to result from the lack of a dietary factor or adequate sunshine. In 1919, two independent groups demonstrated that rickets could be prevented or cured by either the addition of cod liver oil to the diet or exposure to sunlight.^{112,160} Vitamin D is found in cod liver oil and other foods, including butter, cheese, and cream, which contain 12 to 40 IU/100 g (0.3–1 µg/100 g), eggs, which contain 25 IU/100 g (0.6 µg/100 g), and fatty fish, such as salmon and mackerel, which contain 150 to 550 IU/100 g (4–14 µg/100 g) and 1100 IU/100 g (28 µg/100 g), respectively. Some foods typically are fortified with vitamin D, including cereals, bread, and milk.¹⁰⁵ Many dietary supplements, such as multivitamins, contain vitamin D.

Rickets has been eliminated as a major public health concern in children in Europe and North America since the fortification of milk with vitamin D. Outbreaks of vitamin D poisoning subsequently occurred in Europe in the 1950s because of excessive fortification of milk and cereals to compensate for wartime nutritional deprivation of children.⁵⁶ This vitamin D poisoning led to a period of prohibition of vitamin D fortification of foods.¹⁰⁵ More recently, a study showed that milk and infant formulas rarely contain the amount of vitamin D stated on the label and may be either significantly underfortified or overfortified, leading to vitamin D deficiency or toxicity.¹⁰⁵ One case series demonstrated vitamin D toxicity in eight patients who drank local dairy milk that was excessively fortified with vitamin D₃.¹¹⁷ Many cases of vitamin D toxicity result from continued supplementation of vitamin D and calcium initially prescribed for treatment of hypoparathyroidism, osteoporosis, or osteomalacia but inappropriately continued due among other reasons to inadequate patient physician communication.^{53,137,185} Two reports describe vitamin D toxicity in families secondary to use of a highly concentrated vitamin D preparation in nut oil that was not intended for human consumption.^{59,186} Another case report describes vitamin D poisoning secondary to contamination of table sugar with crystalline vitamin D₃.²³² Vitamin D toxicity has been reported in dogs secondary to vitamin D₃ exposure in the form of rodenticides.⁸¹ Vitamin D deficiency should not occur in individuals who eat a well-balanced diet and are exposed to adequate sunlight. Casual exposure of cutaneous tissues to ultraviolet light during the summer months should produce adequate vitamin D storage for winter months.⁹³ Total body sun exposure provides the vitamin D equivalent of 10,000 IU/day (250 µg/day); the body requires only a total vitamin D supply of 4000 IU/day (100 µg/day).²³⁰ Breast-fed infants may require supplemental vitamin D if they have limited exposure to sunlight because the vitamin D content of human milk is extremely low.⁴⁹ Other groups susceptible to vitamin D deficiency include the elderly, vegans, persons with darkly pigmented skin, and persons without adequate sunlight exposure such as those living in institutions.

The Institute of Medicine (IOM) recently found that although average total vitamin D intake was below the median requirement in North Americans, average serum concentrations of vitamin D were above the 20 ng/mL concentration that the IOM determined to be needed for good bone health. They suggested that sun exposure contributes meaningful amounts of vitamin D and that the majority of the population is meeting its needs for vitamin D.²⁰² Despite this finding, in 2010 the IOM revised its dietary reference intakes with an increase in the RDA for vitamin D across all age groups (Table 47–1).

The new RDA assumes minimal sunlight exposure and is 600 IU/day (15 µg/day) for nonelderly adults. The new RDA may lead to an increased number of persons taking vitamin D either by prescription or in the form of a dietary supplement. In addition, the IOM found that testing for vitamin D deficiency has become widespread.²⁰² However, the measurements or cut-points of sufficiency or deficiency used by laboratories are not based on scientific studies and there is no central regulatory authority determining which cut-point should be used. The IOM found that many laboratories use an inappropriately high cut-point for deficiency, thereby leading to an increased number of diagnoses of vitamin D deficiency and possibly persons taking unnecessary vitamin D supplements.

The use of vitamin D supplements to prevent and treat a variety of illnesses has increased substantially over the past decade.⁹⁵ Vitamin D deficiency is linked to autoimmune disease, cancer, cardiovascular disease, depression, dementia, infectious disease, musculoskeletal decline, and more.⁹⁵ However, the IOM concluded that vitamin D supplementation for indications other than musculoskeletal health is not supported by adequate scientific evidence.²⁰² Vitamin D is used for the prophylaxis and treatment of rickets, osteomalacia, and osteoporosis. It is also used for the treatment of hypoparathyroidism and skin conditions, including psoriasis.

Vitamin D is the name given to both ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃). In humans, both forms of vitamin D have the same biologic potency. One microgram of vitamin D is equivalent to 40 IU of vitamin D.

Pharmacology, Pharmacokinetics, and Toxicokinetics

Vitamin D itself is not biologically active and must go through extensive metabolism to an active form, whether it is ingested from a food source in the form of vitamin D₂ and D₃ or synthesized in the body. Vitamin D₃ is synthesized in the skin from 7-dehydrocholesterol (provitamin D₃) in a reaction catalyzed by ultraviolet B irradiation (Fig. 47–2).¹³⁷ Vitamin D₃ then is bound to vitamin D-binding protein, a protein that also binds vitamin D from the diet, and afterward enters the circulation. In the endoplasmic reticulum of the liver, vitamin D is metabolized to 25-hydroxyvitamin D {25(OH)D} by vitamin D-25-hydroxylase.⁸² Once formed, 25(OH)D is again bound to vitamin D-binding protein and transported to the proximal convoluted tubule in the kidney for hydroxylation to 1,25-dihydroxyvitamin D {1,25(OH)₂D}, or calcitriol, by 25(OH)D-1-α-hydroxylase.⁸² Once formed, 1,25(OH)₂D is secreted back into circulation, bound to vitamin D-binding protein, and delivered to target cells where it binds to receptors.

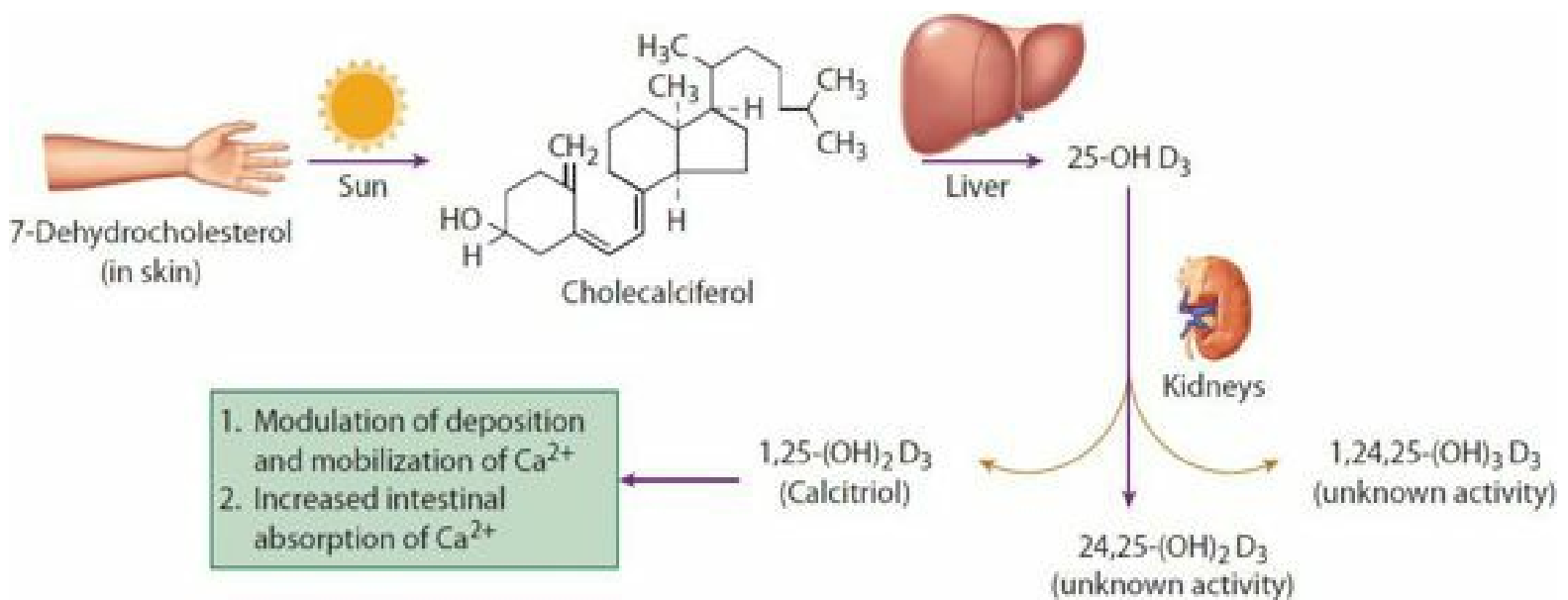


FIGURE 47–2. Schematic representation of the synthesis and physiologic response to vitamin D.

Vitamin D might be more appropriately called a hormone rather than a vitamin because it is synthesized in the body, circulates in the blood, and then binds to receptors in order to evoke its biologic action. The primary role of vitamin D is regulation of calcium homeostasis via interactions with the intestines and bones. Protein bound calcitriol is taken up by cells and then binds to a specific nuclear vitamin D receptor protein that, in turn, binds to regulatory sequences on chromosomal DNA.¹³⁷ The result is induction of gene transcription and translation of proteins that carry out the cellular functions of vitamin D. In the intestines, calcitriol increases the production of calcium binding proteins and plasma membrane calcium pump proteins, thereby increasing calcium absorption through the duodenum.¹²⁰ In the bone, calcitriol stimulates osteoclastic precursors to differentiate into mature osteoclasts.¹⁰⁶ Mature osteoclasts, together with PTH, lead to mobilization of calcium stores from bone, thereby raising serum concentrations of calcium. Given sufficient serum concentrations of calcium, calcitriol promotes bone mineralization by osteoblasts, resulting in increased deposition of

calcium hydroxyapatite into the bone matrix.¹⁰⁶ Calcitriol also binds to a vitamin D receptor in the parathyroid glands, which leads to decreased synthesis and secretion of PTH.¹⁷¹ The vitamin D receptor is present in most cells of the body including lymphocytes, epidermal skin cells, and tumor cells.²⁰⁵ The binding of calcitriol can inhibit proliferation and induce terminal differentiation.¹⁸⁸ Although the role of vitamin D has not been elucidated in all cells, abnormalities present during vitamin D deficiency may help identify the function of vitamin D in various tissues.

Vitamin D deficiency results in hypocalcemia, leading to increased secretion of PTH, which acts to restore plasma calcium concentrations at the expense of bone. In children, this situation leads to rickets in which newly formed bone is not adequately mineralized and results in bone deformities and growth defects. Adults develop osteomalacia, a disease characterized by undermineralized bone matrix. Patients typically present with bone pain and tenderness and proximal muscle weakness. Bone deformities are limited to the advanced stages of disease.

The literature varies regarding the toxic dose of vitamin D, with little scientific data available for corroboration. The current upper level intake is set at 4000 IU/day (100 µg/day) for persons aged 9 years and older, with lower levels set for children younger than 9 years of age.²⁰² This is an increase compared to the previous tolerable upper intake dose of 2000 IU/day (50 µg/day).²³⁰ There also are studies showing that doses as high as 4400 IU/day (110 µg/day) and 100,000 IU (2500 µg) for 4 days did not result in adverse effects.^{219,226,230} Case reports describe toxicity in the setting of vitamin D intake of 50,000 to 600,000 IU or, simply, doses in the milligram range, daily for prolonged periods.^{53,90,146,185}

Pathophysiology

The hallmark of vitamin D toxicity is hypercalcemia. Vitamin D in the form of 1,25(OH)₂D promotes calcium absorption from the gut and mobilization of calcium from bone. Vitamin D toxicity may be associated with a serum concentration of 25(OH)D 20 times higher than normal, whereas the concentration of 1,25(OH)₂D remains exceedingly variable.^{82,186} 25-Hydroxyvitamin D can mimic the action of 1,25(OH)₂D when it is present in excess and can bind to receptors usually specific for 1,25(OH)₂D.^{82,137} Alternatively, 25(OH)D, which has a higher affinity for vitamin D-binding protein compared to 1,25(OH)₂D, may preferentially bind to vitamin D-binding protein when it is present in elevated concentrations, displacing 1,25(OH)₂D and allowing it to circulate in an unbound form, or loosely bound to albumin.²³¹ A study of patients with vitamin D toxicity who had normal or near normal total 1,25(OH)₂D concentrations had elevated free 1,25(OH)₂D concentrations.¹⁸⁶ The availability of 1,25(OH)₂D to its receptors likely is increased, resulting in vitamin D toxicity.

Clinical Manifestations

Patients with vitamin D toxicity present with signs and symptoms characteristic of hypercalcemia.¹³⁷ Early manifestations include weakness, fatigue, somnolence, irritability, headache, dizziness, muscle and bone pain, nausea, vomiting, abdominal cramps, and diarrhea or constipation (Chap. 19). As the calcium concentration increases, hypercalcemia may induce polyuria and polydipsia. Diuresis results in salt and water depletion, further impairing calcium excretion. Severe hypercalcemia may present with ataxia, confusion, psychosis, seizures, coma, and acute kidney injury. In addition, cardiac dysrhythmias result from a shortened refractory period and slowed conduction. Findings on electrocardiography include increased PR intervals, widening of QRS complexes, QT shortening, and flattened T waves (Chap. 16).¹⁷³ Patients can develop metastatic calcification of the kidneys, blood vessels, myocardium, lung, and skin. Several patients with vitamin D toxicity have presented with anemia.^{191,207} Proposed mechanisms for anemia include a direct effect of vitamin D on hematopoietic cells and inhibition of erythropoietin production.¹⁹¹

Diagnostic Testing

Vitamin D toxicity should be considered in patients presenting with signs and symptoms of hypercalcemia. In addition to an elevated serum calcium concentration, laboratory results may reveal hyperphosphatemia given that vitamin D facilitates phosphate absorption in the small intestine, enhances its mobilization from bone, and decreases its excretion by the kidney.¹⁵¹ The diagnosis should be suspected in children with nephrocalcinosis and hypercalciuria even if serum calcium and phosphorus concentrations are normal.¹⁶⁶ Serum 25(OH)D can be measured, but it is unlikely that results will be available quickly. According to the IOM, the desired 25(OH)D concentration range is 20 to 50 ng/mL.²⁰² The IOM also found that concentrations higher than 30 ng/mL were not consistently associated with increased benefit and concentrations higher than 50 ng/mL may be cause for concern.

Management

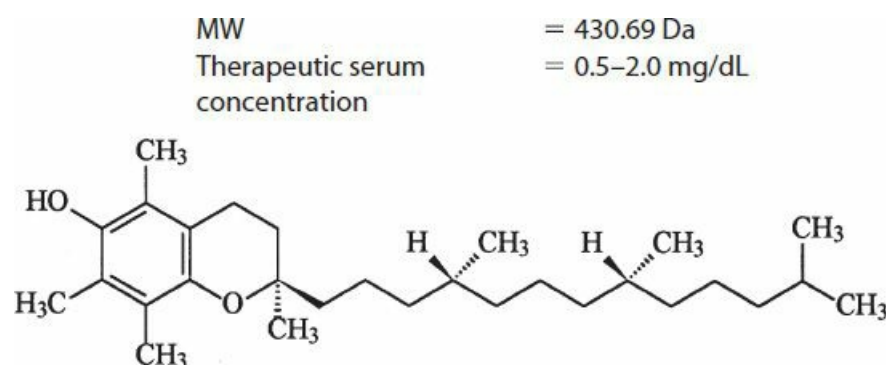
Treatment of hypercalcemia in patients with vitamin D toxicity should include discontinuation of both vitamin D and calcium supplementation, maintenance of a low calcium diet, and administration of adequate volumes of oral or IV fluid to

increase renal calcium clearance.¹³⁷ Many cases of hypercalcemia will respond to such supportive care. Following rehydration, a loop diuretic, such as furosemide, can be added to promote calcium excretion.¹³⁷ Corticosteroids, such as hydrocortisone 100 mg/day or prednisone 20 mg/day, improve hypercalcemia and hypercalciuria in vitamin D poisoning. Studies have attempted to explain this effect as being a result of either decreased intestinal calcium absorption or inhibition of bone resorption.^{125,221} Bisphosphonates, such as pamidronate 90 mg IV and clodronate 600 mg IV, were used successfully in cases of severe hypercalcemia.^{136,196} These drugs inhibit bone resorption via actions on osteoclasts. Their use may preclude the need for hemodialysis in refractory cases of hypercalcemia. Calcitonin, a hypocalcemic hormone secreted by the thyroid gland that directly inhibits osteoclast activity, can be used to decrease bone resorption. Salmon calcitonin was successfully used to treat refractory hypercalcemia in a child with vitamin D poisoning. The dose utilized was 4 units/kg IM twice daily until hypercalcemia resolved at 15 days.¹⁶¹ Of note, studies have led the FDA to conclude that salmon calcitonin in the form of a nasal spray for the treatment of postmenopausal osteoporosis is associated with an increased risk of cancer.³⁷

ANTIOXIDANTS (VITAMINS E AND C)

The antioxidants include vitamins E and C and β -carotene. During the 1990s, the concept that antioxidants had a protective effect against atherosclerosis and carcinogenesis was widely promoted. This notion was based on the “oxidative-modification hypothesis” of atherosclerosis, which proposes that atherogenesis is initiated by lipid peroxidation of LDL.⁵⁷ Unregulated or prolonged production of cellular oxidants leading to oxidant induced DNA damage is thought to be responsible for carcinogenesis.¹²⁸ Epidemiologic evidence seems to support the use of antioxidants for these indications.^{130,194,218} However, several prospective, randomized, placebo controlled clinical trials, designed to test for the effect of antioxidant vitamins on cardiovascular disease and cancer, have consistently shown that commonly used antioxidant regimens do not significantly reduce or prevent overall cardiovascular events or cancer.^{34,98,102,174,224,245}

VITAMIN E



History and Epidemiology

The existence of vitamin E was first demonstrated in 1922 by researchers noting that female rats deficient in a dietary principle were unable to sustain a pregnancy.⁶⁶ Testicular lesions in male rats were described in deficiency states and vitamin E was referred to as the “anti-sterility vitamin.”¹⁵³ Vitamin E was first isolated from wheat-germ oil in 1936.⁶⁵ The richest sources of vitamin E include nuts, wheat germ, whole grains, vegetable and seed oils, including soybean, corn, cottonseed, and safflower, and the products made from these oils. In general, animal products are poor sources of vitamin E. Human milk, by contrast to cow’s milk, has sufficient vitamin E in the form of α -tocopherol to meet the needs of breast fed infants.¹⁵³ Supplementation should not be necessary in persons who consume a well-balanced diet.

Vitamin E deficiency occurs in patients with malabsorption syndromes, which may occur in the presence of pancreatic insufficiency or hepatobiliary disease, such as biliary atresia.²⁷ Patients with abetalipoproteinemia are at risk for vitamin E deficiency.¹⁴ In this rare disease, absorption and transport of vitamin E are impaired secondary to a lack of chylomicron and β -lipoprotein formation. Manifestations of deficiency are variable, but seem to have the most effect in organ systems that rely on vitamin E for normal functioning.¹⁵³ The clinical syndrome is primarily manifested by a peripheral neuropathy and spinocerebellar syndrome that improves with supplemental vitamin E.¹⁶² Symptoms include ophthalmoplegia, hyporeflexia, gait disturbances, and decreased sensitivity to vibration and proprioception.²⁷

Vitamin E is an essential nutrient. It is believed to be necessary for normal functioning of the nervous, reproductive, muscular, cardiovascular, and hematopoietic systems. Use of vitamin E has been proposed for a wide range of conditions. In most cases, scientific rationale for its use is lacking or is based on in vitro or animal data that have not been validated in

humans or have demonstrated equivocal results.²⁷ As examples, vitamin E has been used for treatment of recurrent abortion, hemolytic anemias, claudication, wound healing, tardive dyskinesia, epilepsy, and adult respiratory distress syndrome. In addition, much research over the past decade has focused on the use of vitamin E for the prevention and treatment of cardiovascular disease and cancer, with disappointing results.²²⁵

Vitamin E includes eight naturally occurring compounds in two classes—tocopherols and tocotrienols—that have differing biologic activities. The most biologically active form is RRR- α -tocopherol, previously known as d- α -tocopherol, which is the most widely available form of vitamin E in food. A synthetic form of α -tocopherol, often used in vitamin supplements, contains a mixture of d and l isomers and is designated all-rac- α -tocopherol (previously d,l- α -tocopherol). One IU is equivalent to 1 mg α -tocopherol acetate (ALPHA-TA).

Pharmacology, Pharmacokinetics, and Toxicokinetics

Vitamin E absorption is dependent on the ingestion and absorption of fat. The presence of bile also is essential. Vitamin E is passively absorbed in the intestinal tract into the lymphatic circulation by a nonsaturable process. Approximately 45% of a dose is absorbed in this manner and subsequently enters the bloodstream in chylomicrons, which are taken up by the liver. Vitamin E then is secreted back into the circulation, where it is primarily associated with LDL. Vitamin E is distributed to all tissues, with the greatest accumulation in adipose tissue, liver, and muscle.

The primary biologic function of vitamin E is as an antioxidant. It prevents damage to biologic membranes by protecting polyunsaturated fats within membrane phospholipids from oxidation.³⁵ It accomplishes this task by preferentially binding to peroxy radicals and forming the corresponding organic hydroperoxide and tocopheroxyl radical, which, in turn interacts with other antioxidant compounds, such as ascorbic acid, thereby regenerating tocopherol. Vitamin E may be responsible for cell growth and proliferation by combating the inhibitory effects of lipid peroxidation.¹⁶² Vitamin E may have a negative role in the regulation of cellular proliferation through its nonoxidant properties, such as inhibition of protein kinase C activity.¹⁶²

Large amounts of vitamin E, ranging from 400 to 800 IU/day (400–800 mg/day) for months to years, were previously thought to be without apparent harm.⁴⁹ Vitamin E supplementation results in few obvious adverse effects, even at doses as high as 3200 mg/day (3200 IU/day).²⁰ In several species, the oral median lethal dose was 2000 mg/kg (2000 IU/kg) or more, and significant adverse effects were observed only when daily doses were greater than 1000 mg/kg (1000 IU/kg), equivalent to 200 to 500 mg/kg (200–500 IU/kg) in humans.¹⁶³ However, a meta-analysis reveals that all cause mortality may increase at doses equal to or greater than 400 IU/day (400 mg/day).¹⁶⁴

Pathophysiology

In vitro studies demonstrate that in high doses vitamin E may have a paradoxical prooxidant effect.^{2,33,164} The prooxidant effect of vitamin E on LDLs is related to the production of α -tocopheroxyl radicals, which normally are inhibited by other antioxidants such as vitamin C. High doses of vitamin E may displace other antioxidants, thereby disrupting the natural balance of the antioxidant system and increasing vulnerability to oxidative damage.¹¹¹ High doses of vitamin E may inhibit human cytosolic glutathione S-transferases, enzymes that are active in the detoxification of xenobiotics and endogenous toxins.²²⁹

Clinical Manifestations

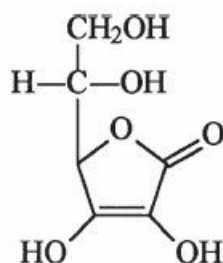
Gastrointestinal symptoms, including nausea and gastric distress, were reported in patients who had received vitamin E 2000 to 2500 IU/day (2000–2500 mg/day).^{103,239} Diarrhea and abdominal cramps were reported in patients who received a dose of 3200 IU/day (3200 mg/day).⁸ Reports of other adverse effects, including fatigue, weakness, emotional changes, thrombophlebitis, increased serum creatinine concentration, and decreased thyroid hormone concentrations, have not been reproduced in other case series or clinical trials.¹⁶³

The most significant toxic effect of vitamin E, at doses exceeding 1000 IU/day (1000 mg/day), is its ability to antagonize the effects of vitamin K.⁴⁹ Vitamin E appears to increase the epoxidation of vitamin K to its inactive form, thereby increasing the vitamin K requirement several fold.^{21,233} Although high oral doses of vitamin E typically do not produce a coagulopathy in normal humans with adequate vitamin K stores, coagulopathy may develop in vitamin K deficient patients or those taking warfarin.^{21,47,69,233} Animal studies demonstrate that absorption of both vitamins A and K is impaired by large doses of vitamin E.^{27,197}

Use of an IV vitamin E preparation (E-Ferol) was associated with a severe epidemic of unexplained thrombocytopenia, kidney dysfunction, hepatomegaly, cholestasis, ascites, hypotension, and metabolic acidosis in low birth weight infants in several neonatal intensive care units in the early 1980s.³² Use of polysorbate 20 and polysorbate 80 for emulsification of lipids and fat-soluble vitamins in this IV vitamin E product was implicated as the cause of this syndrome, rather than vitamin E.

VITAMIN C

MW = 176.12 Da
Therapeutic serum concentration = 0.4–2.0 mg/dL



History and Epidemiology

Vitamin C, also known as ascorbic acid, has long been used as a preventative for the common cold. Interestingly, an extensive review of 14 studies of the role of vitamin C in the treatment of the common cold suggested that only eight were valid investigations, and none of the studies demonstrated any therapeutic benefit.⁴¹ Its function as an antioxidant has led to its use for the prevention and treatment of cardiovascular disease and cancer. Human data from clinical trials have failed to demonstrate that vitamin C significantly reduces or prevents overall cardiovascular events or cancer. Vitamin C may have a role as a reducing agent in the treatment of idiopathic methemoglobinemia ([Chap. 127](#)). However, it is less effective than standard treatment with methylene blue; therefore, it is not routinely indicated.¹⁵² Vitamin C is popularly used to promote wound healing, treat cataracts, combat chronic degenerative diseases, counteract the effects of aging, increase mental attentiveness, and decrease stress.^{47,163} However, little, if any, objective data demonstrate a benefit of treatment for any of these indications.⁴⁹

Vitamin C has long been associated with prevention of scurvy.¹⁵² In 1747, James Lind, a physician in the British Royal Navy, analyzed the relationship between diet and scurvy and confirmed the protective and curative effects of citrus fruits. Vitamin C was isolated from cabbage in 1928 and subsequently shown in 1932 to be the active antiscorbutic factor in lemon juice. It was given the name ascorbic acid to indicate its role in preventing scurvy. Other dietary sources of vitamin C include tomatoes, strawberries, and potatoes. Today, those at risk for developing scurvy include the elderly, alcoholics, chronic drug users, and others with inadequate diets, including infants fed formula diets with insufficient concentrations of vitamin C.¹⁵² Symptoms include gingivitis, poor wound healing, bleeding, and petechiae and ecchymoses. Musculoskeletal signs and symptoms consisting of arthralgias, myalgias, hemarthrosis, and muscular hematomas develop in 80% of cases.⁶⁷ Children experience severe pain in their lower limbs secondary to subperiosteal bleeding.⁶⁷

Pharmacology, Pharmacokinetics, and Toxicokinetics

Following ingestion, intestinal absorption of vitamin C occurs via an active transport system that is saturable.¹⁹⁵ The absorptive capacity is reached with ingestion of approximately 3 g/day, and vitamin C dietary supplements are commonly taken in doses of 500 mg/day. When given as a single oral dose, absorption decreases from 75% at 1 g to 20% at 5 g. Vitamin C is distributed from the plasma to all cells in the body. Tissue uptake is also a saturable process.¹⁶³ Metabolic degradation of vitamin C to oxalate accounts for 30% to 40% of oxalate excreted daily.⁹⁴ Because absorption and metabolic conversion are saturable, large ingestions of vitamin C should not significantly increase oxalate production.²¹¹ Only a small amount of vitamin C is filtered through the glomeruli, and tubular resorption, a saturable process that may compete with uric acid, usually is almost complete.²⁴ Plasma concentrations of vitamin C typically are maintained at approximately 1 mg/dL. The kidney efficiently eliminates excess vitamin C as unchanged ascorbic acid.

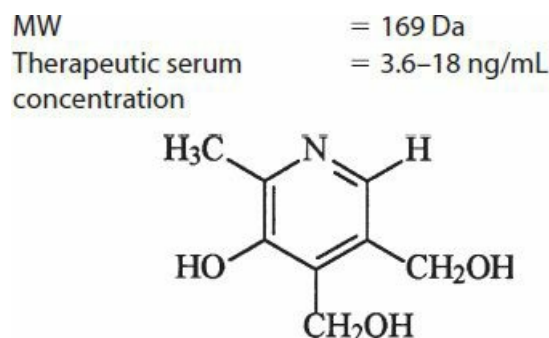
Vitamin C is a cofactor in several hydroxylation and amidation reactions by functioning as a reducing agent.^{139,140} As a result, vitamin C plays an important role in the synthesis of collagen, carnitine, folinic acid, and norepinephrine. It also influences the processing of hormones such as oxytocin, antidiuretic hormone, and cholecystokinin. Vitamin C reduces iron from the ferric to the ferrous state in the stomach, thereby increasing intestinal absorption of iron. Vitamin C may be involved in steroidogenesis in the adrenals. Vitamin C also has a prooxidant effect in vivo.¹⁸⁷ This effect is not believed to occur at doses less than 500 mg/day but may occur in the setting of overdose.

Clinical Manifestations

The possibility of oxalate nephrolithiasis should not be a significant clinical concern.⁸⁴ Nevertheless, conflicting studies and reports exist regarding the association between vitamin C overdose and the development of oxalosis. A prospective study on the risk of kidney stones in men did not support an association between high daily vitamin C intake and stone

formation.⁵⁰ This was also demonstrated in a study involving daily ingestion of 4 g of ascorbic acid for five days in healthy men in which there was no increase in urinary oxalate excretion.¹² Another study did show increased rates of oxalate absorption and endogenous synthesis contributing to hyperoxaluria, but this effect was found in individuals with a prior history of renal calcium oxalate stones and not in individuals without a prior history of calcium oxalate stones.⁴⁰ Some reports of high urine oxalate concentrations likely were erroneous because of conversion of ascorbate to oxalate in alkaline urine samples left standing after collection.^{12,236} By contrast, other reports show an increase in urinary oxalate and calcium oxalate crystallization following ingestion of high doses of vitamin C in both stone-formers and non-stone-formers.^{18,155} Individual case reports documenting the presence of oxalate stones in the setting of vitamin C overdose often have involved IV administration.^{48,83,134,156,222,244} Oxalosis is also more likely to develop in patients with chronic kidney disease.^{16,163} Gastrointestinal effects of high doses of vitamin C may include localized esophagitis, given prolonged mucosal contact with ascorbic acid, and an osmotic diarrhea.^{108,235}

VITAMIN B₆



History

Pyridoxine, pyridoxal, and pyridoxamine are related compounds that have the same physiologic properties. Although all three compounds are included in the term vitamin B₆, the vitamin has been assigned the name pyridoxine. This vitamin was discovered in 1936 as the water-soluble factor whose deficiency was responsible for the development of dermatitis in rats.¹⁵² In humans, deficiency is characterized by cheilosis, stomatitis, glossitis, blepharitis, and a seborrheic dermatitis around the eyes, nose, and mouth.²⁰³ More importantly, pyridoxine deficiency is associated with seizures.

Pyridoxine is found in several foods, including meat, liver, whole-grain breads and cereals, soybeans, and vegetables.¹⁵² Deficiency should not occur in humans who eat a well balanced diet.²¹⁵

Pyridoxine is popularly used as a component of bodybuilding regimens and for treatment of premenstrual syndrome and carpal tunnel syndrome.^{1,62} High doses have been used for treatment of schizophrenia and autism with variable results.^{74,138}

Pharmacology

All forms of vitamin B₆ are well absorbed from the intestinal tract. Pyridoxine is rapidly metabolized to pyridoxal, pyridoxal phosphate (PLP), and 4-pyridoxic acid.²⁴⁶ PLP accounts for approximately 60% of circulating vitamin B₆ and is the primary form that crosses cell membranes.¹⁵² Most vitamin B₆ is renally excreted as 4-pyridoxic acid, with only 7% excreted unchanged in the urine.^{152,246} Experiments in anephric rats demonstrate an up to ten fold increase in susceptibility to pyridoxine induced neurotoxicity, suggesting a need for caution when prescribing pyridoxine to patients with chronic kidney disease.¹⁴¹

Pyridoxal phosphate is the active form of vitamin B₆. It is a coenzyme required for the synthesis of γ -aminobutyric acid (GABA), an inhibitory neurotransmitter. Decreased GABA formation in the setting of pyridoxine deficiency may contribute to seizures.¹⁵² Isoniazid and other hydrazines inhibit the enzyme responsible for conversion of pyridoxine to PLP (Chap. 58).¹⁰⁷ Therefore, pyridoxine should be administered concomitantly with isoniazid to limit the development of a peripheral neuropathy. Seizures resulting from isoniazid overdose often are successfully treated with pyridoxine (Antidotes in Depth: A14).

Pathophysiology

Interestingly, similar to pyridoxine deficiency, pyridoxine toxicity is characterized by neurologic effects. The pathophysiology of pyridoxine neurotoxicity is not well defined. However, studies indicate that the mammalian peripheral sensory nervous system is vulnerable to large doses of pyridoxine.²⁰⁸ Peripheral sensory nerves may be particularly

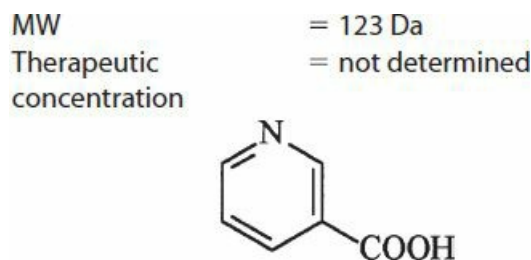
vulnerable to circulating xenobiotics because of the permeability of their associated blood vessels.²⁰⁸ Compared with the CNS, these nerves lack the blood brain barrier. In addition, the nerves of the CNS may be relatively shielded from pyridoxine toxicity because pyridoxine is transported into the CNS by a saturable mechanism.²⁰⁸ In 1942, pyridoxine was recognized to cause severe weakness and pathological changes in peripheral nerves and dorsal root ganglia in dogs and rats.^{9,217} Administration of IV pyridoxine 2 g/kg in two patients for the treatment of mushroom poisoning resulted in permanent dorsal root and sensory ganglia deficits.⁴

Clinical Manifestations

Chronic overdoses are associated with progressive sensory ataxia and severe distal impairment of proprioception and vibratory sensation. Touch, pain, and temperature sensation may be minimally impaired, and reflexes may be diminished or absent. These findings were first described in 1983 in a case series of seven patients who were taking pyridoxine 2–6 g/day for 2 to 40 months for premenstrual syndrome.²⁰⁸ Nerve conduction and somatosensory studies in these patients showed dysfunction in the distal sensory peripheral nerves. Nerve biopsy showed widespread, nonspecific axonal degeneration. This syndrome has since been reported with pyridoxine doses as low as 200 mg/day.¹⁸³ Among 26 patients with elevated serum pyridoxine concentrations, the most common symptoms reported were numbness (96%), burning pain (49.9%), tingling (57.7%), balance difficulties (30.7%), and weakness (7.8%).²¹⁰ In most cases, symptoms gradually improved over several months with abstinence from pyridoxine. However, symptoms may still progress for 2 to 3 weeks after pyridoxine discontinuation.²³

Acute neurotoxicity may occur when a massive amount of pyridoxine is administered as a single dose or given over a few days.⁴ Large overdoses of pyridoxine are associated with incoordination, ataxia, seizures, and death.²²⁷

NICOTINIC ACID



History

Nicotinic acid, or niacin, was discovered to be an essential dietary component in the early 1900s.⁸⁷ A deficiency of this vitamin, also known as vitamin B₃, causes pellagra, which is characterized by dermatitis, diarrhea, and dementia. This disease had been prevalent for centuries in countries that heavily relied on maize as a dietary staple until it was determined that pellagra could be prevented by increasing dietary intake of fresh eggs, milk, and fresh meat, including liver.¹⁵² Other food sources of nicotinic acid include fish, poultry, nuts, legumes, and whole-grain and enriched breads and cereals. Supplementation of flour with nicotinic acid in 1939 probably is responsible for the near eradication of this disease in the United States. Chronic alcohol users still develop pellagra, likely secondary to malnutrition.

Niacin was introduced as a treatment for hyperlipidemia in 1955.⁷ Nicotinic acid reduces triglyceride synthesis, with a resultant drop in very-low-density lipoprotein cholesterol and LDL cholesterol and a rise in high-density-lipoprotein cholesterol.⁸⁷ Therapy usually is started with single doses of 100 to 250 mg. Frequency of dose and total daily dose are gradually increased until a dose of 1.5 to 2.0 g/day is reached. If the LDL cholesterol concentration is not sufficiently decreased with this dosing regimen, then the dose is further increased to 3.0 g/day. These doses of niacin are 100-fold higher than the amount necessary to meet adult nutritional needs.¹⁹²

More recently, the nonmedicinal ingestion of niacin for the purpose of altering or masking the results of urine testing for illicit drugs was noted.^{11,39,167} However, there is no evidence that ingestion of niacin is capable of this effect.

Pharmacology, Pharmacokinetics, and Toxicokinetics

Nicotinic acid is well absorbed from the intestinal tract and is distributed to all tissues. With therapeutic dosing, little unchanged vitamin is excreted in the urine. When extremely high doses are ingested, the unchanged vitamin is the major urinary component. Nicotinic acid ultimately is converted to nicotinamide adenine dinucleotide (NAD⁺) and nicotinamide adenine dinucleotide phosphate (NADP⁺), which are the physiologically active forms of this vitamin. NADH and NADPH, the reduced forms of NAD⁺ and NADP⁺ respectively, act as coenzymes for proteins that catalyze oxidation–reduction

reactions that are essential for tissue respiration.¹⁵²

Clinical Manifestations

The most common adverse effect associated with niacin use is a vasodilatory cutaneous flushing described as a sense of warmth in the face, ears, neck, trunk, and less frequently in the extremities, lasting less than 1 to 2.5 hours.¹¹⁶ Other symptoms include erythema, itching, and tingling. These effects may occur at doses of 0.5 to 1.0 g/day.¹⁵⁸ Symptoms commence within 15 to 30 minutes after ingestion of immediate-release niacin, 30 to 120 minutes after ingestion of extended-release niacin, and at more variable times after ingestion of sustained-release niacin.¹¹⁶ Symptoms are caused by the production of prostaglandin (PG) D₂ and E₂ via the G protein-coupled receptor, GPR109A.²² Flushing occurs because of the predilection of the skin as a site of prostaglandin production after niacin ingestion.²²⁰ PGD₂ and PGE₂ act on receptors DP₁ and EP_{2/4} in dermal capillaries causing vasodilation.¹²² Vasodilatory adverse events occur in almost all of patients, particularly when given an immediate release form of niacin.¹⁵⁸ Many patients discontinue niacin use because of flushing. Long-term tolerance to flushing does develop with continued dosing of niacin, secondary to decreased PGD₂ output.¹¹⁶

Because rapid absorption of niacin seems to be related to development of flushing, modified release preparations of niacin were developed. A meta-analysis of 4000 patients who had used various time-release preparations of niacin showed that among the 70% of patients who experienced flushing, 85% had used immediate release niacin, 66% used extended release niacin, and 26% had used sustained-release niacin.³¹ The modified release preparations are more likely to produce gastrointestinal adverse events, such as epigastric distress, nausea, and diarrhea.¹⁵⁸ In addition, niacin-induced hepatotoxicity occurs more frequently and is more severe in patients treated with modified release niacin rather than immediate-release niacin.^{44,192} Elevated hepatic aminotransferases may occur with doses as low as 1 g/day, whereas symptoms of hepatic dysfunction occur at doses of 2 to 3 g/day.¹⁵⁸ These patients may have elevated serum bilirubin and ammonia concentrations and a prolonged prothrombin time. They may present with fatigue, anorexia, nausea, vomiting, and jaundice. In most cases, liver function improves following niacin withdrawal.^{64,158} Severe cases have progressed to fulminant hepatic failure and hepatic encephalopathy.^{45,104,169}

Niacin also causes amblyopia, hyperglycemia, hyperuricemia, coagulopathy, myopathy, and hyperpigmentation.¹⁰¹ A recent case of a 16 year-old boy who ingested 13 g of niacin over 48 hours described the development of metabolic acidosis, hypoglycemia, elevated hepatic aminotransferases, and coagulopathy.¹¹ The patient also complained of severe myalgias and chest and abdominal pain. His signs and symptoms resolved after 5 days with intravenous fluid resuscitation and bicarbonate infusion.

Management

A dose of 325 mg of aspirin taken 30 minutes before ingestion of niacin diminishes flushing.²⁴¹ This is because aspirin inhibits cyclooxygenase, thereby decreasing production of prostaglandins.

Other strategies for reducing flushing include dosing with meals, and avoidance of alcohol, hot beverages, spicy foods, and hot baths or showers close to or after dosing.⁵² Flushing may also be decreased by starting at a low dose and gradually increasing to the full dose. Tolerance to flushing may develop after several weeks, but flushing will recur if doses are missed.

Laropiprant, a PGD₂ antagonist at receptor DP₁, has demonstrated efficacy in numerous studies (phase 1, 2, and 3 trials) for reducing niacin-associated flushing.¹¹⁶ In Europe, laropiprant was approved for use in 2008 in the form of a combined tablet, 1000 mg of extended release niacin with 20 mg laropiprant, and sold under the trade name Tredaptive (Merck & Co; known outside the United States as MSD). Also in 2008, the FDA did not give approval for a similar product with the trade name Cordaptive made by the same pharmaceutical company. In 2013, the HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) collaborative group reported an increased incidence of myopathy among patients taking simvastatin plus extended release niacin/laropiprant (ERN/LRPT) compared to those taking simvastatin plus placebo.¹⁰⁹ Also, ERN/LRPT in addition to statin therapy did not significantly reduce the risk of major vascular events in patients with well controlled LDL-cholesterol concentrations. As a result, the study was halted and Merck & Co plans to cease production of Tredaptive. Other findings included that 25.4% of participants taking ERN/LRPT stopped their randomized treatment compared with 16.6% taking placebo, mostly due to adverse dermatologic and gastrointestinal effects.

Recent in vitro studies demonstrate that methylnicotinate induces serotonin release from human platelets in addition to PGD₂ release from human mast cells.¹⁷⁹ Animal studies demonstrate the ability of various serotonin antagonists including cyproheptadine to inhibit the niacin-induced temperature increase, associated with flush, by 90%.¹⁷⁹ Flavanoids have been studied as a potential treatment for niacin flush due to their ability to inhibit both niacin-induced plasma PGD₂ and

serotonin increase in a rat model.¹⁸⁰ In a small human study, a dietary supplement containing 150 mg of the flavanoid quercetin decreased the severity and longevity of erythema and burning sensation scores on a visual scale.¹²¹

SUMMARY

- Healthy adults consuming a well-balanced diet do not require vitamin supplementation.
- Vitamins are popularly believed to be a panacea and are commonly taken in supraphysiologic doses.
- Because the therapeutic index is large, toxicity generally does not develop unless very large doses are taken for sustained periods.
- Health care professionals should consider hypervitaminosis in the differential diagnosis when patients present with symptoms consistent with a vitamin toxicity syndrome.
- A thorough history, with emphasis on diet and prescribed and supplemental vitamin use, is important.

Acknowledgment

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C. PHARMACEUTICALS

CASE STUDY 3

History A 27 year-old man was found acting abnormally in a train station. When approached by police, he seemed to be hallucinating and answered questions inappropriately, so emergency medical services was activated. When the paramedics arrived, they recorded a blood pressure of 148/92 mm Hg, a pulse of 142 beats/min, and a respiratory rate of 16 breaths/min. They noted dilated pupils and disorientation, but did not comment on other abnormalities. An intravenous line was inserted, and the patient was given oxygen via nasal canula at 4 L/min during transport to the hospital. No further history could be obtained because the patient could not be understood.

Physical Examination On arrival to the hospital, the patient appeared to be a well nourished, appropriately dressed man in significant distress. Vital signs were: blood pressure, 152/92 mm Hg; pulse, 155 beats/min; respiratory rate, 22 breaths/min; rectal temperature, 99.4°F; oxygen saturation, 100% on nasal canula at 4 L/min; and glucose, 117 mg/dL. Physical examination revealed a normal head without signs of trauma, the pupils were 7 to 8 mm and not reactive (**Fig. CS3–1**), and the extraocular muscles appeared normal. His neck was supple. His chest was clear to auscultation, and other than tachycardia, his heart sounds were normal. His abdomen was slightly distended and tender in the suprapubic area with absent bowel sounds. His skin was warm and dry. The neurologic examination was notable for good strength in all four extremities with intermittent myoclonic jerking, slight symmetrical hyperreflexia, and plantar flexion. He was mumbling incoherently looking about the room as if he were responding to external stimuli and could not answer questions.



FIGURE CS3–1. The patient's right eye demonstrating a large and fixed pupil.

Because the patient could not provide any history, his belongings were searched for possible information. Despite being well dressed, he had no wallet, cell phone, pills, or other useful information in his pockets.

What Is the Differential Diagnosis? The patient's presentation is notable for hypertension, tachycardia, and tachypnea with dilated pupils and hallucinations. The toxicologic differential diagnosis of these findings includes anticholinergics and antihistamines (**Chap. 49**), certain antipsychotics and antidepressants (**Chaps. 70** and **71**), alcohol and sedative–hypnotic withdrawal (**Chap. 81**), sympathomimetics such as cocaine and amphetamines (**Chaps. 76** and **78**), and hallucinogens (**Chap. 82**). However, a more detailed evaluation of the physical examination is suggestive of an anticholinergic toxic syndrome (**Chap. 3**) in that the skin is dry, the pupils are poorly responsive, and the bowel sounds are diminished. All of these findings are inconsistent with sympathomimetics, hallucinogens, and alcohol or sedative–hypnotic withdrawal. Although cyclic antidepressants and some antipsychotics are potent anticholinergics, their toxicity is usually associated with hypotension and somnolence.

Immediate Assessment and Management In the setting of suspected anticholinergic toxicity, the single most important diagnostic test is to obtain an electrocardiogram (ECG). The ECG is used primarily to identify signs of sodium channel

blockade that are characteristic of cyclic antidepressant overdose (Chaps. 16 and 71) but also occur with some phenothiazine antipsychotics (Chap. 70), diphenhydramine (Chap. 49), type IA and IC antidysrhythmics (Chap. 64), cocaine (Chap. 78), and some other xenobiotics. A prolonged QRS complex duration would not only help provide a diagnosis but would also indicate the need to intervene with hypertonic sodium bicarbonate (Antidotes in Depth: A5). The patient's ECG is shown in Fig. CS3–2.

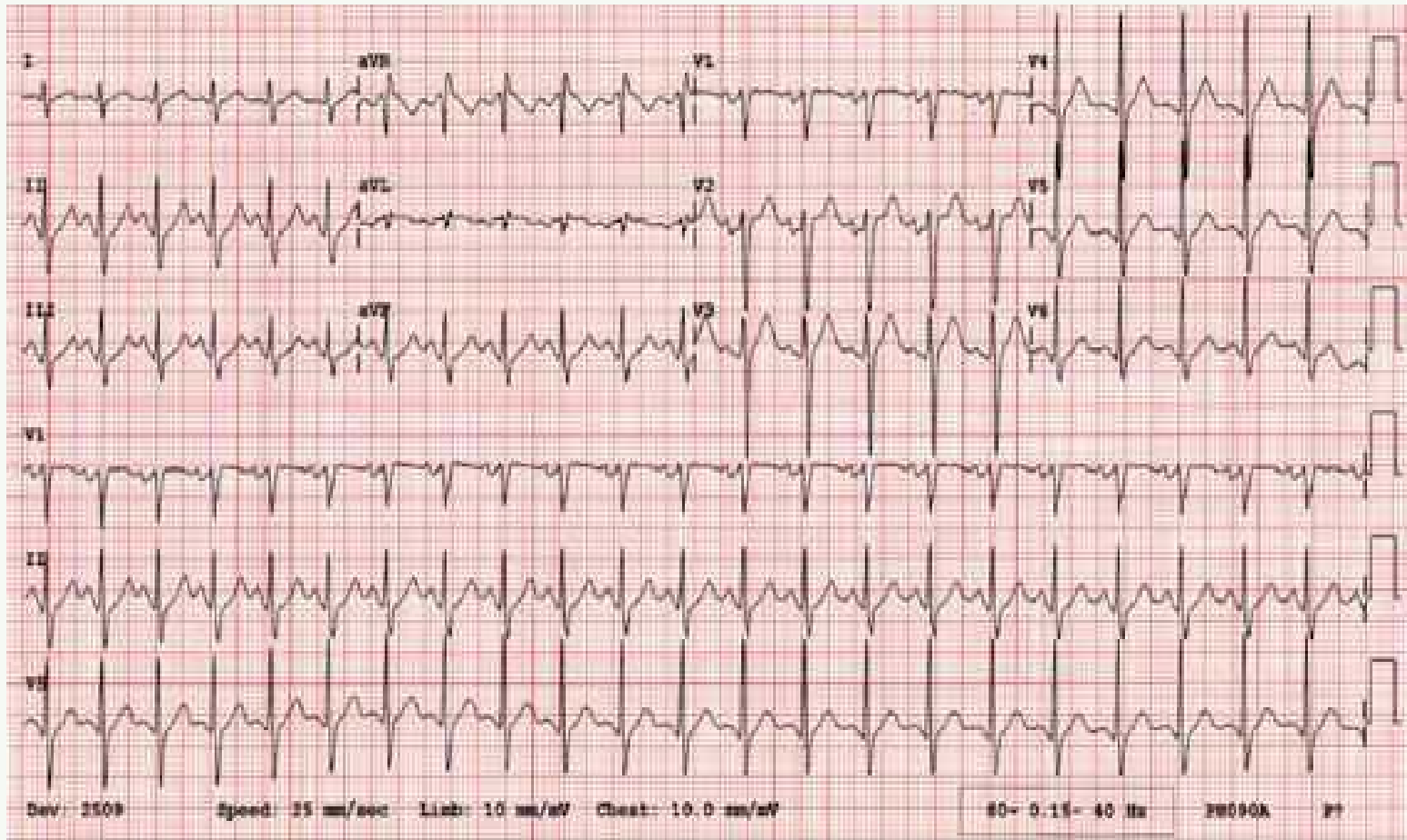


FIGURE CS3–2. ECG showing sinus tachycardia with a QRS duration of 90 msec, a QT interval of 320 msec (QTc 506 msec) and findings consistent with early sodium channel blockade (an S wave in I and an R wave in aVR despite a relatively normal QRS complex duration).

Additional life-threatening conditions that might be associated with anticholinergic toxicity include hyperthermia, seizures, and rhabdomyolysis. These problems should be anticipated. Laboratory analysis was sent for a complete blood count, electrolytes, creatine phosphokinase, and concentrations of acetaminophen and ethanol.

Further Diagnosis and Treatment The combination of a clinical anticholinergic toxic syndrome with subtle markers of sodium channel blockade was most suggestive of diphenhydramine toxicity. Given that the patient was uncomfortable and unable to provide a history, a decision was made to administer physostigmine (Antidotes in Depth: A9). Atropine was brought to the bedside, and the patient was attached to a cardiac monitor. One milligram of physostigmine was infused over 5 minutes. Over the next few minutes, the patient's pupils appeared smaller, and his heart rate dropped to 110 beats/min. He became calm, but his speech was still garbled and incoherent, and his bowel sounds were quiet. A second dose of 1 mg of physostigmine was given over 5 minutes. Shortly thereafter, the patient's voice became clear, and he asked to drink water and use a urinal. He spontaneously voided 800 mL of clear urine. His blood pressure was 132/84 mm Hg, and his pulse was 98 beats/min.

He related that he had no past medical history, no past surgical history, and no allergies to medications and was not taking any prescription, nonprescription, or illicit drugs. The last thing he remembered was that he was early for his train and went to the station bar for a drink with someone he met while waiting.

Case Resolution All of the patient's laboratory tests were within normal limits except for his blood ethanol concentration, which was 32 mg/dL. The health care team was concerned about drug facilitated robbery and had the department social worker meet with the patient. He was offered the opportunity for comprehensive testing as well as filing a report with the police, which he declined. He was observed for 8 hours and remained well, so he was discharged at his own request.

48 ANTIEPILEPTICS

Suzanne Doyon

HISTORY AND EPIDEMIOLOGY

Historically, seizures were treated by a variety of methods, including ketogenic diets, fluid restriction, and surgical excision of scars or irritable cortical foci. The first truly effective antiepileptic therapy was introduced in 1857, when the administration of bromides was noted to sedate patients and significantly reduce their seizures. Phenobarbital, a sedative–hypnotic, was first used to treat seizures in 1912. Most of the subsequently introduced antiepileptics such as primidone had chemical structures similar to that of phenobarbital, and sedation was erroneously believed to be an essential component of antiepileptic therapy.

The search for nonsedating antiepileptics led to the introduction of phenytoin in 1938.¹¹⁶ After 1965, benzodiazepines, carbamazepine, and valproic acid (VPA) were introduced and gained wide use as antiepileptics. These antiepileptics were the only new medications available until the 1990s when gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, felbamate, vigabatrin, lacosamide, and zonisamide were introduced.

Antiepileptics are also currently used for treating mood disorders, refractory pain syndromes such as trigeminal neuralgia, bruxism, migraine headaches, drug withdrawal syndromes, and social phobias. A warning, based on a meta-analysis of placebo-controlled trials, placed the risk of suicide twice as high among patients receiving antiepileptics as compared with those receiving placebo.^{30,78} More specifically, other authors reported an association between mood disorders treated with antiepileptics and suicides.¹³³ Conversely, others observed that rates of depression are high among patients with epilepsy, whether well controlled with antiepileptics or not.⁷

This chapter reviews the toxicity and management of overdoses with antiepileptics other than the benzodiazepines and barbiturates, which are discussed in [Chap. 74](#).

PHARMACOLOGY

The mechanisms of action of antiepileptics are fourfold: sodium or calcium channel inhibition, inhibition of excitatory amines, GABA (γ -aminobutyric acid) related, and binding to synaptic vesicle protein 2A. Some antiepileptics have multiple mechanisms of action.¹¹⁴

During seizures, a high-frequency pattern of neuronal firing is detected. This pattern is uncommon during normal physiologic neuronal activity. Voltage-gated sodium channels (VGSCs) are primarily responsible for this rapid neuronal firing. Under the influence of sodium channel blockers, the VGSCs are maintained partially open with their internal inactivation gates closed. The VGSCs cannot recover from inactivation and are prevented from firing repetitively. Phenytoin, carbamazepine, VPA, lamotrigine, topiramate, oxcarbazepine, and zonisamide all attach themselves to the batrachotoxin binding site (or adjacent area) on the VGSCs, close the inactivation gate, and prolong the recovery from inactivation.^{113,114,194,198} At therapeutic concentrations, VGSC binding is largely selective. At toxic concentrations, selectivity is lost, and both high-frequency and spontaneous sodium channels are inhibited, including those found in cardiac tissue responsible for action potential initiation leading to electrocardiographic (ECG) disturbances such as QRS complex prolongation and atrioventricular blockade.^{27,50,92,127,173,178} Lacosamide is unique as it binds to collapsing response mediator protein 2 (CRMP-2), a phosphoprotein in the VGSC, and slows inactivation of the channel resulting in limited repetitive firing.¹¹⁴

Voltage-gated calcium channels (VGCCs) are multisubunit complexes that are broadly classified into low- and high-voltage groups. The low voltage group encompasses the T-type calcium channels. Zonisamide, VPA, and ethosuximide inhibit flow of calcium through these channels, thus reducing the T current, also known as the pacemaker current.^{136,145} Gabapentin and pregabalin bind to the $\alpha_2\delta_1$ subunit of the presynaptic P/Q VGCC, reducing the calcium required fusion of synaptic vesicles to membranes and reducing the exocytosis of glutamate.¹¹⁴ Levetiracetam inhibits N-type calcium channels, but this is not its major mechanism of action.^{107,109}

The N-methyl-D-aspartate (NMDA) receptor is the glutamate receptor of greatest clinical importance with respect to development of seizures. When stimulated by glutamate, the NMDA receptor activates a ligand-gated ion channel that

permits entry of Na⁺ and Ca²⁺ into the neuronal cells. Suppression of the glutamate–NMDA interaction is protective against seizures.¹¹⁴ VPA is a possible competitive glutamate antagonist at the NMDA receptors. Lamotrigine and possibly high dose phenytoin inhibit glutamate release by binding to presynaptic Na⁺ channels.⁵⁷ Topiramate binds to kainate, as opposed to the NMDA glutamate receptor, and blocks Na⁺ entry into the neuronal cell.¹⁴⁰

GABA acts through fast chloride-permeable ionotropic GABA_A receptors and slower G protein–coupled GABA_B receptors. The recently discovered GABA_c receptors are not well studied. Vigabatrin irreversibly inhibits GABA transaminase, the enzyme primarily responsible for GABA metabolism.^{71,114} VPA may have similar effects.¹¹⁴ Tiagabine inhibits the GABA transporter GAT-1 and thereby prevents reuptake of GABA into presynaptic neurons.^{71,114} Neither gabapentin nor pregabalin, despite their structural similarity to GABA, mimics GABA when iontophoretically applied to GABA neurons.^{114,118}

Lastly, synaptic vesicular 2A (SV2A) proteins are members of the superfamily of proteins called membrane transporters that are an integral part of secretory vesicles in neuronal tissue. Levetiracetam binds with high affinity to SV2A, inducing a conformational change in the protein that leads to inhibition of vesicular exocytosis from the presynaptic neuron.^{74,109} Table 48–1 and Figure 48–1 summarize these findings.

TABLE 48–1. Comparison of Mechanisms of Action of Antiepileptics

Sodium Channel Inhibition	NMDA/Kainate Inhibition
Carbamazepine	Lamotrigine
Lacosamide	Topiramate
Lamotrigine	?High-dose phenytoin
Oxcarbazepine	?Valproic acid
Phenytoin (fosphenytoin)	GABA Related
Topiramate	Tiagabine
Valproic acid	Vigabatrin
Zonisamide	SV2A Related
Calcium Channel Inhibition	Levetiracetam
Gabapentin	
Ethosuximide	
Pregabalin	
Valproic acid	
Zonisamide	

GABA = γ-aminobutyric acid; NMDA = *N*-methyl-D-aspartate.

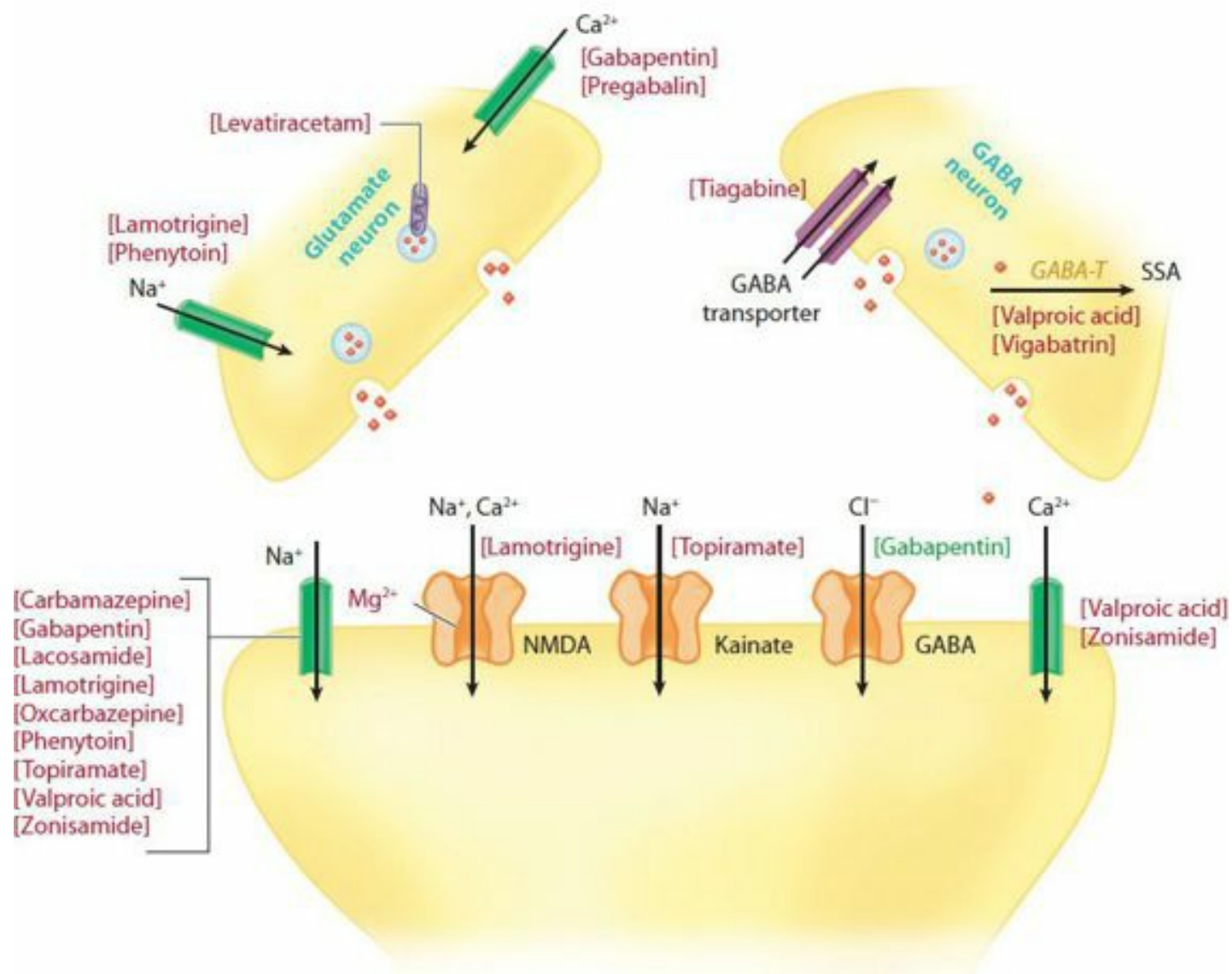


FIGURE 48–1. The mechanisms of action of anticonvulsants can generally be placed into one of four categories: sodium or, calcium channel inhibition, inhibition of excitatory aminoacids GABA agonism and inhibition of presynaptic vesicular exocytosis. GABA = γ -aminobutyric acid; GABA-T = GABA transaminase; NMDA = N-methyl-D-aspartate; SAS = succinic acid semialdehyde.

CARBAMAZEPINE

Carbamazepine is structurally related to the cyclic antidepressants. It is a narrow spectrum antiepileptic. Carbamazepine is a first-line agent for seizures and is a pregnancy category D medication associated with kinked ribs and cleft palate.^{16,50}

Pharmacokinetics and Toxicokinetics

Carbamazepine is lipophilic, with slow and unpredictable absorption after oral administration and rapid distribution to all tissues. Peak concentrations are reached as late as 12 to 24 hours after ingestion, especially after large ingestion of sustained-release preparations.¹⁹⁹ Carbamazepine also possesses weak anticholinergic properties and can decrease gastrointestinal (GI) motility, delaying its own absorption. Hence, no simple relationship exists between the dose and the serum concentration of carbamazepine.

Carbamazepine is metabolized primarily by CYP3A4 to carbamazepine 10,11-epoxide, which is pharmacologically active. This quantifiable metabolite is further degraded by epoxide hydrolase to carbamazepine-diol, a largely inactive compound.⁸³ Elimination of carbamazepine increases over the first few weeks of therapy because of autoinduction, and the half-life during chronic therapy shortens substantially. Therefore, the dose must be increased gradually over a 2- to 4-week period to a final daily dose of 10 to 20 mg/kg for adults and 20 to 70 mg/kg for children. Children require a higher dose because they eliminate the drug more rapidly. During chronic therapy, the elimination half-life ranges from 10 to 20 hours.⁹⁸ Furthermore, at very high serum concentrations, zero-order elimination kinetics are observed¹⁹⁹ (Tables 48–2 and 48–3).

TABLE 48–2. Pharmacokinetics of Antiepileptics after Therapeutic Oral Administration

	Time to Max Serum Concentration (hours)	Therapeutic Serum Concentration		Volume of Distribution (L/kg)	Protein Binding (%)	Urinary Elimination Unchanged (%)	Active Metabolite	Elimination Half-Life (hours)
		(mg/L)	(μ mol/L)					
Carbamazepine	3–24 in overdose	4–12	17–51	0.8–1.8	75	1–2	CBZ 10, 11-epoxide	Acute, 6–20; chronic, 5–12
Gabapentin	3	2–20	12–117	0.8–1.3	0	100	None	5–7
Lacosamide	1–4	5–10?	20–40?	0.6	15	40	None	13
Lamotrigine	1–3	3–14	12–58	0.9–1.2	55	10	None	15–35
Levetiracetam	1–2	10–40	60–240	0.6	10	95	None	5–8
Oxcarbazepine (MHD)	1–5	1–3 3–40	4–12 12–156	0.7	67 47	1 27	MHD	1–2 9
Phenobarbital	1–6	15–40	65–172	0.7	35–50	20–50	None	53–140
Phenytoin	5–24 in overdose	10–20	40–79	0.6	>90	<5	None	6–60
Pregabalin	1	2.8–8.3	18–52	0.5	0	>90	None	2.8–8.3
Tiagabine	1–2	0.01–0.1	0.027–0.27	0.8–2.1	95	<5	None	5–9
Topiramate	1–4	5–25	15–74	0.5–0.8	15	60	None	20–30
Valproic acid	1–24 in overdose	50–120	347–832	0.1–0.4	>90*	<5	None	6–18
Vigabatrin	1	20–80	155–619	0.8	0	70	None	6–8
Zonisamide	2–6	10–40	47–189	1.7–1.8	40–60	85	None	60

*Saturable.

CBZ = carbamazepine; MHD = monohydroxycarbamazepine.

TABLE 48–3. Metabolism of Antiepileptic and by the Cytochrome P450 (CYP) System

	Metabolized by	Induction	Inhibition
Carbamazepine	1A2; 2C8; 2C9; 3A4	2C9; 3A family	None
Gabapentin	None	None	None
Lacosamide	2C19	None	None
Lamotrigine	None	None	None
Levetiracetam	None	None	None
Oxcarbazepine	?	3A4	2C19
Phenytoin	2C9; 2C19; 3A4	2C family; 3A family	None
Tiagabine	3A4	None	None
Topiramate	None	None	2C19
Valproic acid	2C9; 2C19	None	2C19
Zonisamide	3A4	None	None

Clinical Manifestations

Acute carbamazepine toxicity is characterized by neurologic signs and symptoms in association with cardiovascular effects. The initial neurologic disturbances include nystagmus, ataxia, and dysarthria. In patients with a large overdose, fluctuations in level of consciousness and coma are observed.^{68,154,159} Carbamazepine toxicity may cause seizures both in nonepileptic and epileptic patients.^{24,108} The mechanism underlying carbamazepine-induced seizures is poorly understood.^{68,136} In some cases, an increase in seizure frequency, unaccompanied by other neurologic effects, is the

presenting symptom of carbamazepine toxicity. Status epilepticus may complicate acute carbamazepine toxicity.¹⁷⁰ In a large case series, 55% of adult patients with carbamazepine concentrations greater than 40 mg/L developed seizures.⁶⁸ Children may experience seizures at lower concentrations.¹⁶⁹

Cardiovascular effects include sinus tachycardia, which occurs in 35% of overdoses as a result of an anticholinergic mechanism, hypotension with myocardial depression, and cardiac conduction abnormalities.⁶⁸ High concentrations of carbamazepine may cause depression of phases 0, 2, and 4 of the cardiac action potential ([Chap. 16](#)).¹⁷³ In a large case series of carbamazepine overdoses, a 15% incidence of QRS complex prolongation (>100 msec), 50% incidence of QT interval prolongation (>420 msec), and no cases of terminal 40 msec axis deviation of the QRS complex in limb leads were observed.⁶ These abnormalities can be delayed for as long as 20 hours and may occur with chronic therapy.^{6,76} The toxicity of carbamazepine in children differs slightly from that in adults. Children experience a higher incidence of dystonic reactions, choreoathetosis, and seizures and have a lower incidence of ECG abnormalities.^{169,177} Chronic carbamazepine overdose can result in headaches, diplopia, or ataxia. Idiosyncratic adverse events are common.¹⁵¹

The incidence of carbamazepine induced hyponatremia ranges from 1.8% to 40%. Increased antidiuretic hormone secretion (SIADH) or increased sensitivity of peripheral osmoreceptors to antidiuretic hormone are suggested mechanisms^{93,114} ([Chap. 19](#)).

Diagnostic Testing

Serum carbamazepine concentrations should be obtained in all cases of carbamazepine exposure. Because of erratic absorption, the concentrations should be repeated every 4 to 6 hours and closely monitored until a downward trend is observed. In one case report, peak concentrations were reached 106 hours after ingestion in a patient who ingested a sustained-release preparation.²⁴ Serum concentrations greater than 40 mg/L are associated with coma, seizures, respiratory depression, and cardiotoxicity.¹ Carbamazepine may cross-react with toxicology screening for tricyclic antidepressants ([Chap. 71](#)).⁴⁸

Patients receiving multiple antiepileptics, especially combination therapy with VPA and lamotrigine, may develop carbamazepine toxicity at serum concentrations within the therapeutic reference range because of elevated concentrations of the circulating carbamazepine-10,11-epoxide metabolite ([Table 48–4](#)). This finding is attributed to the additive inhibitory effects of VPA and lamotrigine on the enzyme epoxide hydrolase. Carbamazepine-10,11-epoxide concentrations in the 1 to 10 mg/L range are detected.

TABLE 48–4. Antiepileptic Drug Interactions

	Toxicity Increased by	Anticonvulsant Effect Decreased by	Increases Concentrations of	Decreases Concentrations of
Carbamazepine	Allopurinol, amiodarone, cimetidine, danazol, diltiazem, fluoxetine, fluvoxamine, gemfibrozil, INH, ketoconazole, lamotrigine, macrolides, nefazodone, nicotine, propoxyphene, protease inhibitors, verapamil	Benzodiazepines, felbamate, isotretinoin, phenobarbital, phenytoin, primidone, succinimides, VPA	None	Doxycycline, felbamate, haloperidol, lamotrigine, methadone, OCPs, phenytoin, primidone, tiagabine, VPA, warfarin
Gabapentin	Cimetidine	Antacids	Felbamate	None
Lamotrigine	Sertraline, VPA	Antituberculous medications, CBZ, phenobarbital, phenytoin	CBZ epoxide	None
Levetiracetam	None	None	Phenytoin	None
Oxcarbazepine	None	CBZ, phenobarbital, phenytoin	Phenytoin	Lamotrigine, OCPs
Phenytoin	Allopurinol, amiodarone, chloramphenicol, chlorpheniramine, clarithromycin, cloxacillin, cimetidine, disulfiram, ethosuximide, felbamate, fluconazole, fluocuracil, fluoxetine, fluvoxamine, imipramine, INH, methylphenidate, metronidazole, miconazole, omeprazole, phenylbutazone, sulfonamides, ticlopidine, trimethoprim, tolbutamide, tolazamide, topiramate, VPA, warfarin	Antacids, antineoplastics CBZ, calcium, diazepam, diazoxide, ethanol (chronic), folic acid, influenza vaccine, loxapine, nitrofurantoin, phenobarbital, phenylbutazone, pyridoxine, rifampin, salicylates, sulfisoxazole, sucralose, theophylline, tolbutamide, VPA, vigabatrin	Phenobarbital, primidone, warfarin	Amiodarone, CBZ, cardioactive steroids, corticosteroids, cyclosporine, disopyramide, dopamine, doxycycline, furosemide, haloperidol, influenza vaccine, levodopa, methadone, mexiletine, OCP phenothiazines, quinidine, tacrolimus, theophylline, tiagabine, tolbutamide, VPA
Tiagabine	None	CBZ, phenobarbital, phenytoin	None	VPA
Topiramate	None	CBZ, phenobarbital, phenytoin	Phenytoin	OCPs, digoxin
Valproic Acid	Cimetidine, felbamate, cimetidine	Antacids, CBZ, chitosan, chlorpromazine, felbamate, INH, methotrexate, phenobarbital, phenytoin, primidone, salicylates	Felbamate, lamotrigine, phenobarbital, primidone	CBZ, tiagabine
Vigabatrin	None	None	None	Phenytoin
Zonisamide	None	CBZ, phenobarbital, phenytoin	TCBZ	TCBZ

CBZ = carbamazepine; INH = isoniazid; OCP = oral contraceptive; VPA = valproic acid.

Management

Multiple-dose activated charcoal (MDAC) reduces enterohepatic and enteroenteric circulation of carbamazepine.^{15,108,162} In a randomized trial, MDAC was associated with a reduction in the elimination half-life of carbamazepine from 28 to 13 hours, a decrease in need for mechanical ventilation, a shorter coma, and a shorter length of stay in the intensive care unit (ICU).¹⁵ Cardiac monitoring for occurrence of QRS or QT abnormalities is recommended for all patients. Although not formally studied, sodium bicarbonate should be administered if the QRS duration exceeds 100 msec. Carbamazepine-induced seizures are treated with benzodiazepines. Hemodialysis (HD) is relatively ineffective for removal of carbamazepine, mostly because it is poorly water soluble. One study observed increased clearance with HD supplemented with albumin dialysate.³¹ Charcoal hemoperfusion, if available, will increase carbamazepine clearance and may be a useful adjunct in life-threatening overdoses.^{108,138} Continuous venovenous HD and hemodiafiltration were used successfully in a few patients but had no significant effect in others.^{8,64,160,163,201} It must be emphasized that MDAC remains effective in decreasing concentrations, is universally available, is much less invasive, and is associated with good clinical outcomes.^{15,160}

GABAPENTIN

Gabapentin is a narrow-spectrum antiepileptic that has achieved greater popularity as an adjunctive therapy for chronic pain.⁵⁰ It has high water solubility but poor lipid.¹⁷ It is a category C medication with limited human data in pregnancy.¹⁶

Pharmacokinetics and Toxicokinetics

The bioavailability of gabapentin is approximately 60% in the therapeutic dose range. Absorption kinetics are dose dependent with decreasing bioavailability at increased dosage because of saturation of the L-amino acid transport system. Dosage adjustments are necessary in patients with creatinine clearance of 60 mL/min or less. It is not metabolized by and does not affect the CYP450 system and has no significant interactions with other antiepileptics¹¹⁴ (Table 48–3).

Clinical Manifestations

Sedation, ataxia, movement disorders, slurred speech, and GI symptoms are observed after acute gabapentin overdose.^{65,88,141,191} In a case series of 20 patients with gabapentin overdose, lethargy, ataxia, and GI symptoms developed in less than 5 hours and resolved within 4 to 24 hours.⁸⁸ Catatonia after abrupt withdrawal of gabapentin is described.¹⁴⁹

Diagnostic Testing

Effective control of seizures typically occurs at concentrations above 2 mg/L. Because of its large therapeutic index, monitoring of serum gabapentin concentrations may not be necessary.⁹¹

Management

The treatment is largely supportive. The rapid saturation of the transporter system limits bioavailability and absorption in large overdoses. Patients with persistent neurologic symptoms should be admitted to the hospital. HD and hemoperfusion are not generally necessary, but up to 35% is removed by HD in anuric patients.^{41,69}

LACOSAMIDE

Lacosamide is a functionalized amino acid approved for use since 2008. Because of its high water solubility, it was developed for intravenous (IV) and oral use.⁹² It is a category C medication with limited data in human pregnancy.¹⁶

Pharmacokinetics and Toxicokinetics

Lacosamide has a favorable pharmacokinetic profile. It is predominantly excreted unchanged in the urine and undergoes only minor hepatic metabolism (CYP2C19). It displays no significant pharmacokinetic medication interactions, contrary to many other antiepileptics that block VGSC.¹²⁸

Clinical Manifestations

One case report of therapeutic error in IV administration of lacosamide resulted in reversible atrioventricular heart block.²¹ Data suggest a pharmacodynamic interaction between lacosamide and other VGSC blockers.¹²⁸ Chronic lacosamide along with other VGSC blockers is associated with ataxia, diplopia, and sedation.¹²⁸

Management

Activated charcoal (AC) should be considered. ECG monitoring and supportive care is recommended.

LAMOTRIGINE

Clinical Manifestations

Lamotrigine, a broad-spectrum antiepileptic, is approved as an adjunctive medication for treatment of seizures in adults and children. It also is approved for maintenance treatment of bipolar mood disorder. It is a category C medication with limited human data in pregnancy.¹⁶

Pharmacokinetics and Toxicokinetics

The bioavailability of lamotrigine is 98%. It is predominantly glucuronidated to lamotrigine 2-N-glucuronide. The elimination half-life is approximately 25 hours but can be halved in the presence of phenytoin and carbamazepine and doubled in the presence of VPA. Phenytoin and carbamazepine induce glucuronidation. VPA competes with lamotrigine for the same step in the glucuronidation process. Significantly reduced clearance of lamotrigine occurs in patients with Gilbert syndrome (syndrome of defective glucuronidation). Lamotrigine does not affect the CYP450 system or the metabolism of other medications except when it is administered concomitantly with carbamazepine, when it is associated with accumulation of the carbamazepine epoxide metabolite.⁵⁷

Clinical Manifestations

Neurologic manifestations such as lethargy, ataxia, nystagmus, and GI symptoms are described after lamotrigine overdose. Coma, hypokinesia, seizures, status epilepticus, hypertension, tachycardia, and cardiac conduction disturbances may occur.^{103,121} Cardiac conduction abnormalities including QRS complex prolongation, Brugada-like ECG abnormalities, and

third-degree heart block are all related to sodium channel blockade.^{27,50,127,178}

Chronic supratherapeutic dosing resulted in oculoerythric crises in four patients.¹⁹⁰ Chronic therapy is associated with rashes, rhabdomyolysis, elevated hepatic aminotransferases, and serum creatinine phosphokinase concentrations, findings suggestive of a hypersensitivity reaction.¹⁴⁷

Diagnostic Testing

Lamotrigine concentrations greater than 14 mg/L are potentially toxic.

Management

Activated charcoal should be administered. Supportive care and ECG monitoring are recommended. Lamotrigine-induced seizures respond to benzodiazepines.^{22,39,186,195} Data on HD and hemoperfusion are not available, but based on its size, relatively low protein binding, and volume of distribution (1.4 L/kg), lamotrigine should be removed by HD. IV fat emulsion was used successfully in two severe cases of lamotrigine poisoning presenting with coma, seizures, and QRS complex widening.^{27,121} (Antidotes in Depth: A20).

LEVETIRACETAM

Levetiracetam is a broad-spectrum antiepileptic with a wide margin of safety in administration and very favorable pharmacokinetics.⁶³ It is a category C medication with limited human data in pregnancy.¹⁶

Pharmacokinetics and Toxicokinetics

The bioavailability of levetiracetam approaches 100%. The major metabolic pathway involves enzymatic hydrolysis of the acetamide group. This reaction is not dependent on hepatic CYP450 activity. There are no active metabolites. Dosage adjustments are necessary in patients with creatinine clearances of 60 mL/min or less.⁷¹

Clinical Manifestations

Mild central nervous system (CNS) depression, vertigo, and ataxia were reported in one large case series.¹³ Respiratory depression was observed in one case report.¹¹ Two case reports of children with supratherapeutic dosing noted only mild effects such as slight decrease in muscle tone, which reversed immediately after the doses were adjusted.⁹

Diagnostic Testing

Therapeutic concentrations are 10 to 40 µg/mL. Because of its large therapeutic window, routine monitoring of serum levetiracetam concentrations may not be necessary.⁷¹

Management

Activated charcoal should be considered. Supportive care is recommended.

OXCARBAZEPINE

Oxcarbazepine is an analog of carbamazepine that functions as a prodrug. Presystemic 10-ketoreduction rapidly metabolizes oxcarbazepine to monohydroxy carbamazepine (MHD), which is pharmacologically active.¹¹⁴ MHD is subsequently conjugated and renally eliminated. It is a less potent inducer of CYP3A4 than carbamazepine and has minimal effects on its own metabolism.¹¹⁴ It is a category C medication with limited data in human pregnancy.¹⁶ CNS depression and possibly bradycardia and hypotension are reported after overdose.^{135,189} In these cases, serum oxcarbazepine concentrations reached 7 to 32 mg/L (therapeutic, <3 mg/L), yet concentrations of MHD were 46 to 65 mg/L (therapeutic, 10–35 mg/L), less than twofold the therapeutic concentrations. The formation of MHD is a rate-limited process, and this probably contributes to the relatively low MHD concentrations after acute oxcarbazepine overdose.^{53,135,189}

Activated charcoal should be administered, and supportive care should be provided. The rate-limited enzymatic conversion from inactive prodrug to active metabolite may limit its toxicity. HD does not increase the clearance of oxcarbazepine or its metabolite and is not useful.⁵³

PHENYTOIN AND FOSPHENYTOIN

Phenytoin is still widely considered a first-line antiepileptic for the treatment of most seizure disorders except absence seizures. It is a narrow-spectrum antiepileptic that is nonsedating in therapeutic doses and therefore often used successfully for long-term management of epilepsy.⁵⁰ Phenytoin, a pregnancy category D drug, is associated with the fetal hydantoin syndrome and possible hemorrhage at birth.¹⁶

Introduced in 1997, fosphenytoin is a water-soluble phosphate ester prodrug of phenytoin. Advantages include availability for intramuscular (IM) administration and low potential for tissue injury at injection sites.^{18,114}

Pharmacokinetics and Toxicokinetics

Phenytoin is rapidly distributed to all tissues following a two-compartment model. In patients with nondetectable phenytoin serum concentrations, oral loading doses of 20 mg/kg yield therapeutic (>10 mg/L) serum concentrations at 5.6 ± 0.2 hours.¹⁸¹ In cases of very large oral overdoses, GI absorption can be delayed because of capacity limited absorption or decreased GI motility, and peak serum concentrations may take days to be reached.^{28,33} Some authors suggest that phenytoin absorption may continue in the colon because of its lipophilic properties.¹⁷⁵ Additionally, phenytoin occasionally forms concretions in the GI tract.^{28,33}

Phenytoin is extensively bound to serum proteins, mainly albumin. Only the unbound free fraction can cross biologic membranes and is pharmacologically active. A significant fraction of phenytoin remains unbound in neonates, uremic patients, and other patients with hypoalbuminemia, such as patients in ICUs.^{37,61}

Less than 5% of a given dose of phenytoin is excreted unchanged in the urine. The remainder is metabolized in the liver. The major phenytoin metabolite, a parahydroxylphenyl derivative, is inactive but is the putative metabolite responsible for the hypersensitivity reaction associated with phenytoin administration.⁹⁰ The Michaelis-Menten model of saturable enzyme kinetics explains the relationship between phenytoin doses and serum concentrations at steady state. At phenytoin concentrations below 10 mg/L, elimination usually is first order, and elimination half-life ranges between 6 and 24 hours. At higher concentrations, zero-order elimination occurs as a result of saturation of the hydroxylation reaction, and the apparent elimination half-life increases to 20 to 60 hours.¹¹⁴ Therefore, the apparent half-life of elimination of phenytoin is progressively prolonged as plasma concentration increases (Chap. 9).

Fosphenytoin is a prodrug. It is metabolized by tissue and blood phosphatases to phenytoin, phosphate, and formaldehyde. The bioavailability of the derived phenytoin is 100% when compared with intravenously administered phenytoin regardless of the route of administration (IV or IM). The half-life of conversion of fosphenytoin to phenytoin is 7 to 15 minutes. Faster rates of IV infusion and displacement of phenytoin from protein binding sites by fosphenytoin compensate for the conversion-related delay in appearance of phenytoin in serum.⁴⁷ The dose of fosphenytoin is expressed in phenytoin equivalents (PEs).

Clinical Manifestations

Acute phenytoin toxicity produces predominantly neurologic dysfunction that typically affects the cerebellar and vestibular systems. Phenytoin concentrations greater than 15 mg/L usually are associated with nystagmus; concentrations greater than 30 mg/L are associated with ataxia and poor coordination; and concentrations exceeding 50 mg/L are associated with lethargy, slurred speech, and pyramidal and extrapyramidal manifestations.^{33,119} Toxic concentrations rarely cause de novo seizures.¹⁷⁶ Young children and elderly adults may present with atypical manifestations of toxicity. Decreased appetite, poor feeding, diminished activity, abdominal distension, chorea, and opisthotonic posturing are reported after oral overdoses in infants.¹⁰⁵

Cardiotoxicity resulting from oral overdoses of phenytoin is almost never reported.^{44,179} However, IV phenytoin impairs myocardial contractility, decreases peripheral vascular resistance, and depresses myocardial conduction. In a large case series, IV phenytoin was associated with a 3.5% incidence of hemodynamic complications.⁴³ Deaths after IV administration of phenytoin are reported.^{58,152,193,203} Hypotension, dysrhythmias, and cardiac arrest are associated with higher rates of infusion and higher infused doses. All can be at least partially attributed to the propylene glycol (40%) and ethanol (10%), the diluents used in the IV preparation of phenytoin.¹²⁰ Propylene glycol in particular depresses myocardial tissue and decreases peripheral vascular resistance (Chap. 55). Fosphenytoin, available only as a parenteral preparation, does not contain propylene glycol, but the metabolism of this prodrug releases phosphate and formaldehyde. Two reports describe bradycardia, hypotension, and asystole when, five- to 10-fold overdoses of fosphenytoin were administered to infants in error.^{96,148} One infant had a serum phenytoin concentration of 77.2 mg/L and marked hyperphosphatemia (serum phosphate concentration of 25.9 mg/L), although the serum calcium, magnesium, and blood urea nitrogen were normal.¹⁴⁸ Others report hyperphosphatemia after the administration of fosphenytoin to a patient with end-stage kidney disease.¹¹² Another report describes hypocalcemia and prolongation of the QT interval after the administration of fosphenytoin (1500 mg PE) intravenously to an adult patient with normal kidney function; however, no phosphate measurements were obtained.⁸²

Serious soft tissue reactions such as the purple glove syndrome can occur after administration of IV phenytoin and are not always related to problematic infusions or extravasation. The incidence of the purple glove syndrome ranges from 1.7% to 6%.^{21,129} Symptoms begin 2 to 12 hours after administration and include discoloration, edema, and possible blistering distal to the site of administration.²¹ Symptoms may be mild and resolve over days to weeks or may be severe and lead to necrosis, possibly necessitating amputation of digits.^{21,34,43,86,156} The risk of fosphenytoin-induced skin necrosis is lower because of its water solubility.

Chronically elevated phenytoin concentrations may result in gingival hyperplasia, frontal bossing, pseudolymphoma cerebellar effects, behavioral changes, and encephalopathy. Hyperactivity, confusion, lethargy, and hallucinations characterize the behavioral changes. Chronic use of phenytoin is associated rarely with agranulocytosis. Phenytoin may produce hepatotoxicity.

Diagnostic Testing

Serum phenytoin concentrations should be obtained in all cases of phenytoin exposure. Because of unpredictable absorption, phenytoin concentrations should be repeatedly monitored. Therapeutic concentrations are 10 to 20 mg/L. Because of zero-order elimination, high serum phenytoin concentrations may take days or weeks to return to the therapeutic range.^{33,105,119}

Patients with impaired or decreased protein-binding capacity can develop symptoms at total phenytoin concentrations within the therapeutic range. Patients at greatest risk include neonates; elderly adults; hypoalbuminemic, hyperbilirubinemic, and uremic patients; and patients undergoing combination therapy with VPA, salicylates, and sulfonamides because these agents displace phenytoin from its albumin binding sites. In such patients, determination of the free phenytoin concentration is helpful because it compares more reliably with the cerebrospinal fluid concentrations than does the total phenytoin concentration.³⁷ Therapeutic free phenytoin concentrations are 1.0 to 2.1 mg/L.¹⁴

Equation 48–1 approximates the total phenytoin concentration that would be expected on a given measured serum phenytoin concentration and measured albumin concentration.³⁴

$$[\text{Phenytoin}] = \frac{[\text{Measured phenytoin}]}{(0.25 \times [\text{Measured albumin}]) + 0.1} \quad (\text{Eq. 48-1})$$

Management

The treatment of patients with acute or chronic phenytoin overdoses remains largely supportive. Phenytoin-related deaths are rare, even after massive overdoses. MDAC reduces the elimination half-life of intravenously administered phenytoin from 44.5 to 22.3 hours. MDAC also decreased serum concentrations of phenytoin significantly more rapidly than no MDAC in patients with supratherapeutic concentrations from chronic overdose who were randomized to either therapy.¹⁶⁷ HD was performed in four cases of acute phenytoin overdoses and was associated with 3% to 92% reductions in serum concentrations. In only two of the four cases did significant clinical improvement follow HD.^{55,150,161,185} Charcoal hemoperfusion, plasmapheresis, and other extracorporeal techniques such as molecular adsorbents recirculating systems (MARS) are of marginal benefit in the management of phenytoin overdose and are not associated with improved outcomes.^{37,79,119,158} Extracorporeal drug removal is rarely indicated in phenytoin overdoses but may be considered in patients presenting with persistent coma and significantly elevated serum concentrations. All patients admitted to the hospital for phenytoin overdose require neurologic assessments; those who are admitted after an oral exposure do not require routine cardiac monitoring because they do not usually experience dysrhythmias or cardiovascular complications.^{44,105,179} Phenytoin-induced agranulocytosis can be treated successfully with administration of granulocyte colony-stimulating factor.¹⁸⁰

Hypotension, cardiac dysrhythmias, and dyskinesias during IV administration of phenytoin are generally transient and usually resolve in 30 to 60 minutes unless complications occur. Stopping the phenytoin infusion for a few minutes and administering a bolus of 250 to 500 mL of 0.9% sodium chloride solution generally is sufficient to treat the hypotension. Restarting the infusion at half the initial rate is recommended.

Electrocardiographic abnormalities, especially a prolonged QT interval temporally related to fosphenytoin infusions, may be due to hyperphosphatemia and hypocalcemia, and these electrolyte abnormalities should be rapidly corrected. In one case, HD was required to correct the hyperphosphatemia.¹¹² Life-threatening dysrhythmias may require prolonged periods of cardiopulmonary resuscitation.^{96,148}

The management of extravasation is discussed in Special Considerations: SC4.

PREGABALIN

Pregabalin is a second-generation narrow-spectrum antiepileptic agent developed as a more potent analog of gabapentin. It is indicated in the management of epilepsy and neuropathic pain.¹⁵⁵ It has high water solubility and poor lipid solubility.¹⁷

Pharmacokinetics and Toxicokinetics

Pregabalin, contrary to gabapentin, does not have a saturable GI transporter protein and is highly bioavailable with rapid absorption. It is not protein bound, and more than 90% of the medication is excreted unchanged in the urine.¹⁴² Its elimination half-life, similar to that of gabapentin, is short, 4.6 to 6.9 hours. Pregabalin has no significant interactions with other antiepileptic agents except perhaps increasing the steady-state concentrations of tiagabine.¹⁷ It is a category C medication with limited human data in pregnancy.¹⁶

Clinical Manifestations

Overdose experience is limited. Drowsiness, dizziness, tremors, muscle twitching, and seizures are described after overdose.^{131,166} One patient developed third-degree atrioventricular block perhaps because of blockade of L-type calcium channels in the myocardium.¹ Peripheral edema, weight gain, and decompensated congestive heart failure occur after chronic therapy.¹²³

Diagnostic Testing

The proposed therapeutic concentrations are 2.8 to 8.3 mg/L.

Management

Administration of AC is recommended. Pregabalin is cleared by HD.^{91,202}

TIAGABINE

Tiagabine inhibits GABA reuptake and is approved as an adjunctive treatment of seizures. It is also prescribed for a variety of psychiatric disorders. Tiagabine is a narrow-spectrum antiepileptic medication.⁵⁰ It is a category C medication with limited data in human pregnancy.¹⁶

Pharmacokinetics and Toxicokinetics

Tiagabine is quickly and completely absorbed within 2 to 3 hours of ingestion. It is widely distributed and easily crosses the blood-brain barrier.⁸⁷ It is metabolized by the CYP3A4 system to inactive metabolites. The elimination half-life is reduced by 50% in patients taking enzyme-inducing antiepileptics.¹⁰⁶ It has no effect on the CYP450 system.¹⁰⁶

Clinical Manifestations

Lethargy, facial myoclonus (grimacing), nystagmus, and posturing are described in patients who overdose on tiagabine.^{26,171} Seizures and status epilepticus are reported at therapeutic doses as well as in overdose.^{52,70,81,132} One previously healthy girl developed multiple seizures after an unsupervised ingestion of tiagabine.⁸¹ A patient presented in status epilepticus and was believed to be noncompliant with therapy until a tiagabine concentration of 1.87 mg/L was obtained and an acute overdose confirmed.¹³² Stimulation of the presynaptic GABA_B receptors in the thalamus is suggested as the underlying mechanism for tiagabine-induced seizures.¹⁴⁴ Symptoms generally persist for 12 to 24 hours, and permanent neurologic sequelae usually do not occur.^{26,81,132,171}

Diagnostic Testing

Therapeutic tiagabine concentrations are 5 to 70 ng/mL.

Management

Activated charcoal and supportive care are recommended. Seizures respond to administration of benzodiazepines even though the beneficial effects of the GABA agonists such as benzodiazepines seem paradoxical when treating seizures from tiagabine.^{52,70,81,132} Status epilepticus resistant to benzodiazepines should be treated with barbiturates or propofol. Posturing and grimacing are treated with benzodiazepines.²⁶ Data on the use of HD and hemoperfusion are not available, but because of high protein binding, HD will likely not be effective.

TOPIRAMATE

Topiramate is approved as adjunctive therapy for seizures in adults. It is also approved for migraine prophylaxis, infantile spasms, IHH, and other refractory seizure disorders in infants and children. Topiramate is a broad-spectrum antiepileptic. Its sulfamate moiety weakly inhibits carbonic anhydrase, specifically the carbonic anhydrase II and IV isoforms present in the kidneys and CNS.⁴⁰ Topiramate is a pregnancy category D drug because of the risk of oral clefts.

Pharmacokinetics and Toxicokinetics

Topiramate is readily bioavailable. Only 20% of the dose is hepatically metabolized via hydroxylation, hydrolysis, and glucuronidation; the remaining 80% of the medication is eliminated unchanged in the urine (Table 48–2).

Clinical Manifestations

Lethargy, ataxia, nystagmus, myoclonus, hallucinations, coma, seizures, and status epilepticus are all reported after topiramate overdose.^{32,46,101,103,168} Lethargy may be accompanied by abnormal speech patterns, such as echolalia, and word-finding difficulties after acute overdose.^{32,187} In some cases, the clinical effects lasted for days.¹⁰¹ Hyperchloremic metabolic acidosis resulting from inhibition of renal cortical carbonic anhydrase may be present (lowest reported bicarbonate concentration, 12 mEq/L) along with hypocitraturia and high urine pH leading to formation of calcium phosphate stones.⁵⁸ The hyperchloremic metabolic acidosis typically appears within hours of ingestion and can also persist for days.^{32,46,137,187} Clinical effects, especially seizures, mostly occur in acute overdoses and not in acute-on-chronic overdoses or during dose escalation.^{113,115,200}

Diagnostic Testing

A death with a postmortem concentration of 170 mg/L is reported.⁹⁵ Serum chemistry or arterial blood gas analysis should be adequate to evaluate for hyperchloremia, hypokalemia, and metabolic acidosis.

Management

Activated charcoal and supportive care are recommended. Severe hyperchloremic metabolic acidosis should be treated with sodium bicarbonate 1 to 2 mEq/kg intravenously. However, systemic administration of sodium bicarbonate may impair the anticonvulsive effect of topiramate and sodium might increase calcium excretion.^{32,46,58} HD can increase topiramate clearance four- to sixfold.⁵⁴ HD is generally recommended in patients with life-threatening topiramate overdoses presenting with significant neurologic impairment, intractable electrolyte abnormalities, or anuria. Recurrent calcium phosphate stones should be treated with an increase in urine volume, restriction of sodium intake, and possible supplementation with potassium citrate.⁵⁸

VALPROIC ACID

Valproic acid (di-n-propylacetic acid {VPA}) is a simple branched chain carboxylic acid that is used for treatment of seizure disorders, mania associated with bipolar disorder, and in migraine prophylaxis. VPA is a broad-spectrum antiepileptic. It is a category D drug in pregnancy and is associated with neural tube and facial defects.¹⁶

Pharmacokinetics, Toxicokinetics, and Pathophysiology

Valproic acid is well absorbed from the GI tract with a bioavailability of 80% to 90%. Peak concentrations usually are reached in 6 hours, except for enteric-coated and extended-release preparations, with which peaks are delayed for up to 24 hours.^{45,84,117} VPA is 90% protein bound at therapeutic concentrations, but the percentage decreases to 35% as the VPA concentration exceeds 300 mg/L because of saturation of binding sites.^{49,75} (Table 48–2).

Valproic acid is less than 3% excreted unchanged in the urine and undergoes extensive biotransformation in the liver. Hepatic metabolism is complex and uses the same enzymes and cofactors that are needed for mitochondrial lipid metabolism. Glucuronidation, mitochondrial β -oxidation, and cytosolic β -oxidation account for 50%, 40%, and 10%, respectively, of the metabolism of VPA.¹⁶⁴ β -Oxidation occurs in the mitochondrial matrix and starts with passive diffusion of VPA across the double-layer mitochondrial membrane and ends with the transport of metabolites in the opposite direction using acetylCoA and carnitine as transporters^{100,182} (Fig. 48–2 and Table 48–5).

β -Oxidation of VPA depletes carnitine stores through a number of different mechanisms. VPA increases carnitine excretion via formation of valproylcarnitine, which can be renally excreted. Second, valproylcarnitine inhibits the adenosine triphosphate (ATP)-dependent carnitine transporter located on the plasma membrane. Third, VPA metabolites trap mitochondrial CoA. Mitochondrial CoA trapping (or depletion) decreases ATP production, which in turn negatively affects the carnitine transporter.^{100,143} Depletion of carnitine and sequestration of the limited pool of mitochondrial free acetyl-CoA are the end result of excessive β -oxidation.^{164,182} Reduced CoA activity decreases the formation of N-acetylglutamate, an obligatory cofactor for carbamoylphosphate synthetase I (CPS I). CPS I is the primary enzyme responsible for incorporation of ammonia into the urea cycle. The result is impaired ureogenesis and hyperammonemia. Ammonia can injure muscle and brain.^{10,190}

Mitochondrial dysfunction, inhibition of β -oxidation, and depletion of carnitine, acetylCoA, and possibly glutathione stores impair lipid metabolism and lead to fatty acid accumulation, steatosis, lysosomal leakage, formation of reactive oxygen species, and cytotoxicity histologically similar to Reye syndrome.^{139,164} This rare form of hepatotoxicity is often irreversible.¹⁶⁴

Lastly, a number of case reports describe an association between inborn errors of metabolism, seizure disorder, and VPA-induced hyperammonemia and hepatotoxicity after therapeutic dosing.¹⁶⁴

Clinical Manifestations

Overdoses of VPA result in symptoms varying from lethargy to coma associated with cerebral edema. In one large case series, 100% of patients with serum VPA concentrations greater than 850 mg/L manifested coma, 63% manifested respiratory depression requiring intubation and mechanical ventilation, and 25% developed hypotension.^{72,172}

Metabolic complications after acute VPA overdoses include hypernatremia, hypocalcemia, anion gap metabolic acidosis, and hyperammonemia.^{45,165,172} Anion gap metabolic acidosis after overdose is a poor prognostic sign. It results from accumulation of ketoacids and lactic acid, carboxylic, and propionic acid.^{5,35,62,146}

Bone marrow suppression occurs 3 to 5 days after acute massive overdoses of VPA and is characterized by pancytopenia.^{5,172} Hematopoietic disturbances usually resolve spontaneously within a few days.

Pancreatitis, hepatotoxicity, and acute kidney injury are rare manifestations of acute toxicity.^{5,35,85} Chronic VPA therapy may lead to hepatotoxicity and microvesicular steatosis secondary to the aforementioned metabolic aberration in fatty acid metabolism rather than, as with other antiepileptic agents, a hypersensitivity reaction.^{19,42} Clinical findings may vary from asymptomatic elevation of aminotransferase concentrations to fatal hepatitis.

Valproate-induced hyperammonemic encephalopathy is characterized by impaired consciousness with confusion or lethargy, focal or bilateral neurologic signs, and increased seizure frequency. It is not always accompanied by elevated VPA concentrations or hepatotoxicity.¹⁹⁶ The etiology is uncertain, but elevated ammonia concentrations coupled with elevated concentrations of some of the more neurotoxic VPA metabolites may be responsible.^{25,45,192} The differential diagnosis of acute hyperammonemia in the absence of liver disease includes urea synthesis errors, hematologic malignancies, VPA, 5-fluorouracil, and hyperalimentation.¹⁹⁶

Diagnostic Testing

Serum VPA concentrations should be obtained in all cases of VPA exposure and repeated every 4 to 6 hours until a downward trend is observed. Therapeutic concentrations are 50 to 100 mg/L, although some clinicians use higher concentrations.

Many VPA metabolites can be measured in the urine. In large overdoses, the 4-en-VPA concentration may be elevated, indicating a shift toward β -oxidation. The β -oxidation metabolite 2-en-VPA may be low or absent, indicating inhibition of β -oxidation or carnitine depletion. Concentrations of the 2-en-VPA metabolite increase 1 to 3 days after acute ingestion, signaling the return to normal β -oxidation.¹⁶⁴

Electrolytes, blood gases, liver function tests, platelets, and serum lactate and serum ammonia concentrations should be monitored in all patients. Hyperammonemia (>80 $\mu\text{g/dL}$ or >35 $\mu\text{mol/L}$) occurs in up to 80% of patients receiving chronic VPA therapy.¹⁶⁴

Management

Supportive management is sufficient to ensure complete recovery in most patients with VPA overdoses. Discontinuation of all medications that likely affect VPA metabolism is also recommended (Table 48-4).

MDAC is useful in preventing absorption of VPA, especially in overdoses of enteric-coated or extended-release preparations, but MDAC does not significantly affect the elimination of VPA.³ Naloxone does not reverse VPA-induced CNS depression or respiratory depression.^{29,73,188}

Carnitine should be administered if evidence indicates the presence of hyperammonemia or hepatotoxicity.^{77,99,182} Whereas IV carnitine is preferred in symptomatic patients, oral carnitine is sufficient in asymptomatic patients. The loading dose is 100 mg/kg IV over 30 minutes (maximum, 6 g) followed by 15 mg/kg IV over 10 to 30 minutes every 4 hours until clinical improvement occurs (Antidotes in Depth: A8).

Extracorporeal techniques appear to be somewhat useful in increasing elimination of VPA. In large overdoses, the free fraction of VPA is sufficiently high to allow for effective clearance by HD, and HD has reduced the elimination half-life of VPA to 2.5 hours in several cases.^{20,38,67,75,80,89,165} Charcoal hemoperfusion alone and in combination with HD was not superior to HD alone.^{49,110,165} Continuous venovenous hemodialfiltration did not significantly improve elimination in one patient.⁸⁰ HD remains the preferred modality of extracorporeal elimination of VPA. It should be considered for severe VPA overdoses presenting with coma or hemodynamic compromise and serum concentrations greater than 850 mg/L, particularly if severe hyperammonemia is present.⁴

VIGABATRIN

Vigabatrin, or vinyl GABA, is a stereospecific irreversible inhibitor of GABA-transaminase. Although vigabatrin has a short elimination half-life, its duration of action is 24 hours. Dosage adjustments are necessary in patients with creatinine clearance under 80 mL/min.¹¹⁴ It is a category C medication in pregnancy.¹⁶ Agitation, coma, and psychosis are reported after acute ingestion.^{36,97}

Chronic toxicity may result in dizziness, tremor, which usually is mild and transient, and depression and psychosis.⁹⁷ Treatment of vigabatrin toxicity is largely supportive. Severe agitation is best treated with benzodiazepines. Some cases of mild vigabatrin-induced psychosis resolve simply by withdrawal of the medication.⁹⁷ The use of vigabatrin is associated with a risk of retinopathy and visual peripheral field defects.¹⁵⁷

ZONISAMIDE

Zonisamide, a sulfonamide derivative with two decades of use in Japan, is an antiepileptic approved for adjunctive treatment of partial seizures in adults.¹¹⁴ Similar to topiramate, zonisamide also inhibits carbonic anhydrase enzymes.⁵⁸ It is a category C medication in pregnancy.¹⁶ Overdose experience with zonisamide is limited. In one case report, a patient who presented with obtundation, a QTc of 506 msec, and serum concentration of 182 mg/L (therapeutic, 10–40 mg/L) was intubated and placed on a ventilator and recovered in 3 days.⁶⁷ In another, a patient with a serum concentration of 110 mg/L received supportive care and recovered in 48 hours.¹⁹⁷ In one case report, status epilepticus, coma, and death were associated with zonisamide overdose despite a premortem concentration of 44 mg/L and presence of caffeine, diphenhydramine, and mirtazapine in postmortem heart blood.¹⁸³ Recurrence of calcium phosphate stones should be treated with an increase in urine volume, restriction of sodium intake, and possible supplementation with potassium citrate.⁵⁸

DRESS SYNDROME

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, previously named drug hypersensitivity syndrome, is a severe adverse drug event first described in 1950.¹⁸⁴ DRESS syndrome is a distinct severe adverse drug reaction characterized by fever, rash, and solid organ involvement. DRESS syndrome occurs in approximately one of every 1000 to 10,000 uses of antiepileptics, usually aromatic antiepileptics such as phenytoin, carbamazepine, phenobarbital, primidone, and lamotrigine. The literature also supports the inclusion of oxcarbazepine and levetiracetam as causative antiepileptics.⁶⁰ Data suggest a genetic defect in drug metabolism as the causative lesion, for example HLA-A*3101 in Northern Europeans and Japanese individuals.¹³⁴ First-degree relatives of patients with DRESS have a 25% risk of developing this syndrome.^{90,192}

DRESS syndrome occurs most frequently within the first 2 months of therapy and is not related to dose or serum concentration. The pathophysiology is related to the accumulation of reactive arene oxide metabolites resulting from decreased epoxide hydrolase enzyme activity. These metabolites bind to macromolecules and cause cellular apoptosis and necrosis. They also form neoantigens that trigger T cell–mediated delayed (type IV) hypersensitivity reactions. Interestingly, the same metabolite is believed to cause other serious dermatologic reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis¹⁷⁴ (Chap. 18 and Fig. 18–4).

Initial symptoms also include fever (>38.5°C); malaise; and pharyngitis, including tonsillitis. A macular exanthem that is very inflamed and covers more than 50% of the total body surface area, sparing the mucous membranes, is characteristic. Tender lymphadenopathy follows. Multiorgan involvement usually occurs 1 to 2 weeks into the syndrome. The liver is the most frequently affected organ (>80% of cases), although involvement of the CNS (encephalitis), heart (myocarditis), lungs

(pneumonitis), kidney (nephritis), and thyroid (hyperthyroid thyroiditis followed by hypothyroidism) are possible. Liver disturbances range from mildly elevated aminotransferase concentrations to fulminant hepatic failure.^{90,192} Eosinophilia and mononucleosis-type atypical lymphocytosis are common.¹³⁴ DRESS syndrome has been commonly mistaken for sepsis. Fatality rates are reportedly as high as 10%.¹⁸⁴

Skin biopsies reveal nonspecific perivascular lymphocytic infiltration, spongiotic or lichenoid dermatitis, and variable degrees of edema.¹⁹² Lymph node histology reveals benign hyperplasia, atypical lymphoid cells, or lymphoma. Other laboratory abnormalities include positive rheumatoid factor, antinuclear antibodies, antidouble-stranded DNA smooth muscle antibodies, cold agglutinins, and hypo- or hypergammaglobulinemia. A novel lymphocyte toxicity assay and serum thymus and activation-regulated chemokine (TARC) are being studied as potential diagnostic tests.^{126,130}

Prompt discontinuation of the offending antiepileptic is essential to prevent symptom progression. Patients should be admitted to the hospital and receive methylprednisolone 0.5 to 1 mg/kg/d divided in four doses.^{23,192} In one small case series, patients received high-dose methylprednisolone 7 mg/kg/d for 3 days followed by tapering doses of prednisolone for 30 days with associated good outcomes.¹²⁴ Other promising therapies include use of IV immunoglobulins.^{111,153,192} One patient was treated successfully with extracorporeal membrane oxygenation (ECMO) and intraaortic balloon pump after developing life-threatening myocarditis.¹⁰²

In one case series, 90% of patients with DRESS syndrome showed in vitro cross-reactivity to other aromatic antiepileptics.² Based on this evidence, avoidance of phenytoin, carbamazepine, phenobarbital, primidone, lamotrigine, levetiracetam, and oxcarbazepine is recommended; benzodiazepines, VPA, gabapentin, topiramate, and tiagabine are safe alternatives.

SUMMARY

- All antiepileptics produce CNS symptoms in overdose; therefore, differentiation based on clinical findings is difficult. Lethargy, sedation, ataxia, and nystagmus occur after overdoses of almost all the antiepileptics.
- Coma occurs after substantial overdose of all antiepileptics with perhaps the exception of gabapentin. Seizures are more common with tiagabine, lamotrigine, pregabalin, and carbamazepine overdoses.
- Hemodynamic instability and abnormal ECGs are rare findings. Carbamazepine, lamotrigine, and possibly topiramate can cause QRS complex prolongation.
- Except for VPA overdoses, there are no specific antidotes or overdoses of antiepileptics. Supportive care alone usually yields beneficial outcomes.
- Patients with severe VPA overdoses or VPA induced hyperammonemia should be treated with carnitine. Extracorporeal drug removal is rarely necessary and should be reserved for patients with severe carbamazepine toxicity.

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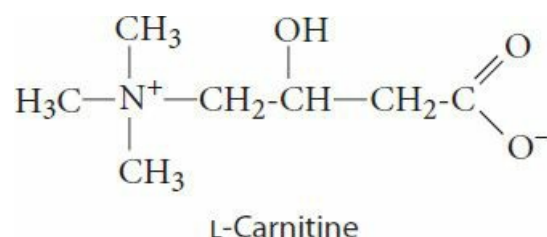
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A8 ANTIDOTES IN DEPTH

L-Carnitine

Mary Ann Howland



INTRODUCTION

L-Carnitine (levocarnitine) is an amino acid vital to mitochondrial utilization of fatty acids. It is approved by the US Food and Drug Administration (FDA) for treatment of L-carnitine deficiency that either results from inborn errors of metabolism or is associated with hemodialysis. L-Carnitine is also used off label to treat carnitine deficiency secondary to valproic acid toxicity or that associated with zidovudine (AZT)-induced mitochondrial myopathy^{10,11,19} and pediatric cardiomyopathy.¹⁷

Based on the proposed mechanism of action of valproic acid–induced hyperammonemia and valproic acid–induced hepatic toxicity, L-carnitine should theoretically help with both of these conditions, but the data to support this are limited. Based on the available evidence, L-carnitine should be considered for patients with valproic acid–induced hyperammonemia and valproic acid–induced hepatic toxicity. Symptomatic patients should receive L-carnitine intravenously; because of limited bioavailability, oral administration should be reserved for patients who are not acutely ill.

HISTORY

L-Carnitine is found in mammals, in many bacteria, and in very small amounts in most plants except for avocado and soy products.³⁶ Carnitine was first discovered in 1905 in extracts of muscle, and its name is derived from *carnis*, the Latin word for flesh.²⁰ Subsequently, its chemical formula and structure were identified, and in 1997, its enantiomeric properties were confirmed.³⁶ Carnitine was formerly known as vitamin BT.

PHARMACOLOGY

Chemistry

Carnitine is a water-soluble amino acid that can exist as either the D or L-form; however, the endogenous L isomer is the active form and should be used therapeutically. L-Carnitine (C₇H₁₅NO₃) has a molecular weight of 161 Da. At physiologic pH, L-carnitine contains both a positively charged quaternary nitrogen ion and a negatively charged carboxylic acid group.¹⁵

Mechanism of Action

Fatty acids provide 9 kcal/g and are important sources of human energy for the body, particularly for the liver, heart, and skeletal muscle. The utilization of fatty acids as an energy source requires L-carnitine–mediated passage through both the outer and inner mitochondrial membranes to reach the mitochondrial matrix, where β-oxidation occurs (Figs. 48–2 and 13–9). Enzymes in the outer and inner mitochondrial membranes (carnitine palmitoyltransferase and carnitine acylcarnitine translocase) catalyze the synthesis, translocation, and regeneration of L-carnitine.³² Binding of L-carnitine to fatty acids occurs through esterification at the hydroxyl group on the chiral carbon.¹⁵ The L-carnitine regenerated in the mitochondrial

matrix can also translocate in the opposite direction, from the matrix and through the inner membrane back to the intermembrane space. Acyl-coenzyme A (CoA) is transported by carnitine from the cytosol to the mitochondria and undergoes β -oxidation in the mitochondrial matrix, generating acetyl-CoA, which then enters the citric acid cycle for the generation of adenosine triphosphate (ATP).

L-Carnitine Homeostasis

Approximately 54% to 87% of the body stores of L-carnitine is derived primarily from meat and dairy products in the diet; the remainder is endogenously synthesized from trimethyllysine.³⁶ This amino acid, found largely in skeletal muscle, is converted to trimethylammonibutanoate (γ -butyrobetaine) and then carried to the liver and kidney for hydroxylation to L-carnitine.²⁰ Synthesis of L-carnitine in the liver and kidney occurs at a rate of approximately 2 $\mu\text{mol/kg/d}$ and is regulated by the amount of diet-derived trimethyllysine.^{20,36} L-Carnitine is filtered by the kidneys, and tubular reabsorption maintains serum L-carnitine concentrations in the normal range, which is approximately 40 to 50 $\mu\text{mol/L}$.³⁷

Pharmacokinetics of Exogenous L-Carnitine

Carnitine pharmacokinetics is very complex and must take into consideration extensive interconversion between L-carnitine and acylcarnitine as well as multicompartmental nonlinear pharmacokinetic modeling.³⁷ The current understanding of L-carnitine pharmacokinetics is largely derived from three major studies.^{9,18,43} L-Carnitine is not bound to plasma proteins. Its volume of distribution (V_d) of the central compartment (V_c) is 0.15 L/kg, approximating extracellular fluid volume. Its V_d is 0.7 L/kg. Both vary depending on the compartment model analyzed. The α half-life is 0.6 to 0.7 hours, with a terminal elimination half-life of 10 to 23 hours, but may be 25% to 50% shorter. The kidneys rapidly eliminate L-carnitine, and as the dose increases, renal clearance increases, reflecting saturation of renal reuptake by organic cation/carnitine transporter.³⁷ Baseline serum concentrations for L-carnitine are 40 $\mu\text{mol/L}$ but increase to a peak concentration of 1000 $\mu\text{mol/L}$ after 2 g of L-carnitine are administered intravenously. Oral (PO) administration of 2 g produces peaks of only 15 to 70 $\mu\text{mol/L}$, demonstrating poor oral bioavailability. The time to peak concentrations after PO administration occurs at 2.5 to 7.0 hours, indicating slow uptake and release by intestinal mucosal cells. After a 2 g carnitine dose, PO absorption is rapidly saturated, and no further absorption occurs after administration of 6 g PO. After a radiolabeled dose, most L-carnitine is metabolized to trimethylamine N-oxide and butyrobetaine, with only approximately 4% to 8% remaining unchanged. The metabolites trimethylamine and trimethylamine N-oxide may accumulate after chronic high-dose PO therapy in patients with severely compromised kidney function.⁹ Fecal excretion of L-carnitine is less than 1% of the total dose. Carnitor (L-carnitine) tablets are bioequivalent to the Carnitor PO solution, with a bioavailability of approximately 15%. After 4 days of dosing at 1980 mg (6 \times 330-mg tablets) twice daily or 2 g twice daily of the PO solution, the maximum serum concentration was 80 $\mu\text{mol/L}$.

ROLE IN VALPROIC ACID AND HYPERAMMONEMIA

Valproic acid may cause hyperammonemia ($>80 \mu\text{g/dL}$ or $>35 \mu\text{mol/L}$) without predictability for symptoms or hepatic dysfunction. Hyperammonemia and hepatic toxicity may be associated either with therapeutic dosing or an acute overdose. Approximately 35% of patients receiving valproic acid demonstrate hyperammonemia, often with corresponding reduced serum L-carnitine concentrations.⁷ In the absence of hepatic dysfunction, the postulated mechanisms for hyperammonemia are unclear but may result from interference with hepatic synthesis of urea or a small increase in ammonia production by the kidney.^{27,44} Valproic acid induces both carnitine and acetyl-CoA deficiencies by combining with L-carnitine as valproylcarnitine and with acetyl-CoA as valproyl-CoA. Ultimately, β -oxidation of all fatty acids is reduced, resulting in decreased energy production. Valproylcarnitine formation may inhibit the renal reabsorption of L-carnitine.³¹

Valproic acid stimulates glutaminase, favoring glutamate uptake and ammonia release from the kidney. Reduced glutamate concentrations lead to impaired production of N-acetylglutamate (NAGA), a cofactor for carbamoyl phosphate synthetase I (CPS I), which is responsible for the synthesis of urea from ammonia in the liver (Fig. 48–2).

In humans taking valproic acid, L-carnitine supplementation reduces ammonia concentrations.^{1,3,5,7,25,34,39,45} The delay for normalization of ammonia concentrations is unknown, but a preliminary report suggests that improved ammonia elimination with L-carnitine (3–15 hours) compared with published controls (11–90 hours), although the difference was not statistically significant.^{41,42}

ROLE IN VALPROIC ACID AND HEPATOTOXICITY

Valproic acid therapy is commonly associated with a transient dose-related asymptomatic increase in liver enzyme concentrations and a rare symptomatic, life-threatening, idiosyncratic hepatotoxicity similar to Reye syndrome.⁴ Liver histology of the latter demonstrates microvesicular steatosis, similar to that described in both hypoglycin-induced Jamaican

vomiting sickness ([Chap. 121](#)) and Reye syndrome. This occurrence presumably results from L-carnitine and acetyl-CoA deficiency, which inhibits mitochondrial β -oxidation of valproic acid and other fatty acids, causing hepatocellular accumulation. One study compared valproic acid administration in mice bred to have decreased carnitine stores with normal mice and found that those with decreased carnitine stores developed microvesicular steatosis of the liver and demonstrated decreased mitochondrial oxidative capacity.²³

Rat studies demonstrate that toxic doses of valproic acid over 7 days cause microvesicular steatosis, mitochondrial swelling, hyperammonemia, and hypocarnitinemia.⁴⁰ When coadministered with L-carnitine, the mitochondrial swelling, hyperammonemia, and carnitine concentrations were similar to control rats, and the microvesicular steatosis was reduced.⁴⁰

The strongest evidence for the benefit of L-carnitine treatment in improving survival from valproic acid–induced hepatotoxicity comes from the retrospective analysis of patients identified by the International Registry for Adverse Reactions to valproic acid.⁶ When 50 patients with acute, symptomatic hepatic dysfunction who were not treated with L-carnitine were compared with 42 similar patients treated with L-carnitine, only 10% of the untreated patients survived, but 48% of the L-carnitine–treated patients survived.⁶ Early diagnosis of patients, prompt discontinuance of valproic acid, and administration of intravenous (IV) rather than PO L-carnitine resulted in the greatest survival rate.⁶ Most patients received 50 to 100 mg/kg/d of L-carnitine regardless of the route of administration.⁶

Acute valproic acid overdose rarely causes hepatotoxicity.⁴¹ However, if a patient were to develop hepatotoxicity after a valproic acid overdose, the general consensus is to administer L-carnitine.^{22,24,25,30,33,38} Because who will go on to develop hepatotoxicity after a valproic acid overdose cannot be predicted, many authors recommend administering prophylactic doses of L-carnitine to patients with severe overdoses, often defined by encephalopathy or a valproic acid concentration > 450 mg/L, with or without evidence of hepatotoxicity.^{25,33,38,41}

L-Carnitine Concentrations

In the serum, 80% of L-carnitine is free, and approximately 20% is acylated.¹⁴ In adults who eat all food groups and children older than 1 year of age, the normal serum concentrations of free L-carnitine are 22 to 66 $\mu\text{mol/L}$ and of total L-carnitine concentrations are 28 to 84 $\mu\text{mol/L}$. Vegetarians have L-carnitine concentrations 12% to 30% lower than omnivores.³⁵

Studies in patients taking valproic acid demonstrate decreases in both free and total serum L-carnitine concentrations³⁴ and decreases in both total and free muscle carnitine concentrations.²

Case studies demonstrate reduced serum free L-carnitine concentrations and abnormal valproic acid metabolite profiles that normalize with L-carnitine supplementation.^{21,28,29} All of these data support the therapeutic use of L-carnitine and provide a potential mechanism for its beneficial effects in valproic acid–induced hepatotoxicity.

ADVERSE EFFECTS AND SAFETY ISSUES

L-Carnitine administration is well tolerated.²⁶ Transient nausea and vomiting are the most common side effects reported, with diarrhea and a fishy body odor noted at higher doses.⁹ After chronic high doses of L-carnitine in patients with severely compromised kidney function, the potentially toxic L-carnitine metabolites trimethylamine and methylamine N-oxide accumulate. The importance of this accumulation is unknown. Trimethylamine and its metabolite dimethylamine may contribute to cognitive abnormalities and the fishy odor.¹³ In a pharmacokinetic study after IV administration of 6 g of L-carnitine over 10 minutes, two of six subjects complained of transient visual blurring; one subject also complained of headache and lightheadedness. The manufacturer of L-carnitine has received case reports of convulsive episodes after L-carnitine use by patients with and without preexisting seizure disorders. No reports of seizures related to L-carnitine use can be found in the human literature. The only data suggesting carnitine-related seizures are found in a rat model.¹⁶

There are no known contraindications to the use of L-carnitine. However, only the L isomer and not the racemic mixture should be used because the DL mixture may interfere with mitochondrial utilization of L-carnitine.

OVERDOSE OF L-Carnitine

No cases of toxicity from overdose have been reported, although large PO doses may cause diarrhea.⁹ The LD_{50} in rats is 5.4 g/kg IV and 19.2 g/kg PO.⁹

PREGNANCY AND LACTATION

L-Carnitine is considered FDA pregnancy category B. There is no information on excretion into breast milk.

DOSING AND ADMINISTRATION

The optimal dosing of L-carnitine for valproic acid–induced hyperammonemia or hepatotoxicity has not been established. Recommendations for IV L-carnitine administration to patients with acute metabolic disorders resulting from L-carnitine deficiency range from 50 to 500 mg/kg/d.^{9,12} A loading dose equal to the daily dose may be given initially followed by the daily dose divided into 4 hourly doses. The 500-mg/kg/d dose was intended for children⁸ and offers no maximum dose. After the loading dose, the author suggests a maximal daily dose of 6 g. The PO dosing of L-carnitine usually is 50 to 100 mg/kg/d up to 3 g/d and should be reserved for patients who are not acutely ill.

For patients with an acute overdose of valproic acid and without hepatic enzyme abnormalities or symptomatic hyperammonemia, L-carnitine administration can be considered prophylactic, and enteral doses of 100 mg/kg/day divided every 8 hours up to 3 g/d are appropriate. For patients with valproic acid–induced symptomatic hepatotoxicity or symptomatic hyperammonemia, IV L-carnitine should be administered. The author suggests a dose of 100 mg/kg IV up to 6 g administered over 30 minutes as a loading dose followed by 15 mg/kg every 6 hours administered over 10 to 30 minutes.

FORMULATION AND ACQUISITION

L-Carnitine is available as a sterile injection for IV use in 1 g/5 mL single-dose vials.⁹ L-Carnitine is supplied without a preservative. After the vial is opened, the unused portion should be discarded. L-Carnitine injection is compatible with and stable when mixed with 0.9% sodium chloride solution or lactated Ringer solution in concentrations as high as 8 mg/mL for as long as 24 hours.⁹ L-Carnitine is also available as 250 and 330 mg tablets; as a PO solution with artificial cherry flavoring, malic acid, sucrose syrup, and methylparaben and propylparaben as preservatives; and as a sugar free PO solution at a concentration of 100 mg/mL.⁸ The PO solution may be consumed without diluting, or it may be dissolved in other drinks to mask the taste. Slow consumption reduces gastrointestinal side effects.⁹

SUMMARY

- L-Carnitine should be administered to patients with valproic acid–induced hyperammonemia, hepatotoxicity, those with valproic acid concentrations above 450 mg/L and encephalopathy.
- Symptomatic patients should receive IV L-carnitine, not the oral preparation.

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49 ANTIHISTAMINES AND DECONGESTANTS

Sophie Gosselin

Antihistamines and decongestants rank among the highest prescription and non prescription xenobiotics used in the United States. In 2011, antihistamines and cough and cold preparations ranked respectively 9th and 11th in substance categories most frequently involved in human exposures related calls to US Poison Control centers. Antihistamines ranked 11th place in categories associated with the largest number of fatalities in 2011 ([Chap. 136](#)).

Popular mythology suggests that expectorants or decongestants depress cough and relieve congestion, and antihistamines also promote sleep. In an effort to retain selected drugs on the nonprescription market, the US Food and Drug Administration (FDA) developed a nonprescription monograph rule allowing some medications in use before 1972 to remain on the market without new clinical trials. As such, many nonprescription decongestants, antihistamines, and expectorants remained available for children without adequate safety or efficacy data in younger age groups. Between the years 1998 and 2007, 8.7% of US parents surveyed reported to have used an antihistamine or decongestant containing remedy for their children younger than 12 years of age in the past week. The majority of these children were younger than 5 years of age. Pseudoephedrine, brompheniramine, and chlorpheniramine are the three most common ingredients used.¹⁷⁸

Unwanted effects associated with their use have posed significant public health problems particularly in children. Fatality studies associated with nonprescription cough and cold medicines reported that although uncommon, most deaths involved nontherapeutic dosages, administration for sedation purposes, and use in children primarily younger than 2 years of age.³⁴ However, the causality of death by cough and cold medicine is often debated. The data needed to prove this relationship are often incomplete because of such factors as the lack of postmortem drug quantification.¹³³ In 2007, a group of pediatricians and pharmacists petitioned the FDA requesting a change in labeling for children younger than 6 years of age on the basis that safety had never been demonstrated in this age group. This petition alerted the general public of the underestimated adverse effects of these xenobiotics.^{143,166} In early 2008, the FDA Public Health Advisory announced that cough and cold products were not recommended for children younger than 2 years of age, and later that same year the Consumer Healthcare Products Association (CHPA), a trade group of generic drug manufacturers, announced that its members were voluntarily modifying product labels for cough and cold medicines to exclude children younger than 4 years of age.¹⁷¹

Despite their widespread use, many reviews of nonprescription medications for cough in adults and children found no evidence for the effectiveness of these xenobiotics.¹⁵⁴ Conclusions are similar regarding the use of antihistamines or decongestants in otitis media.²⁸ Moreover, many well-conducted studies of antihistamines in monotherapy or in combination with a decongestant for patients with upper respiratory illness reported a significant absence of overall symptom improvement.^{154,176} It is also suggested that the majority of any perceived benefit of cough suppressants may be due to the sensory impact of sweetness and the placebo effect as well as the concerning intent of using the known adverse effect of sedation as a therapeutic goal.⁴⁵

A recent systematic review on the toxicity of common cough and cold remedies in children younger than 12 years of age concluded there is sufficient evidence of an unfavorable risk-to-benefit ratio to support measures aimed at restricting use of cough and cold medications in younger age groups.⁷³ As individuals seek to ameliorate the symptoms of an unpleasant illness, official restrictions in younger age groups have yielded concerns of increased off-label use of medicines intended for older age groups or substitution with other xenobiotics. Two recent analyses of both poison center data and emergency department (ED) visits reported significant decreases in annual rates of both therapeutic medication errors and overall ED visits related to cough and cold medicines. However, the rate of unintentional ingestions did not appear to have been modified after the marketing exposure changes in 2007, implying that further efforts to increase packaging safety and parental education are needed.^{88,101,147}

Despite many consumer-directed newsletter and media campaigns, it does not appear that overall use in the general population has decreased. This is indicated by the rising sales in the category “cough- and cold-related” nonprescription medications between 2008 and 2011, reaching \$4.2 billion in 2011, higher than analgesics (\$2.7 billion).²⁹ A survey done in 2010 for CHPA found that 93% of US adults prefer to treat their minor ailments with nonprescription products before seeking professional care, and 85% would do the same for their children.¹⁶⁰

Recreational use of antihistamines and decongestants as “legal highs” was reported as early as the 1970s.¹²⁴ The

popular “T’s and blues,” referring to the combination of pentazocine (Talwin) and the antihistamine tripeleennamine (blue-colored pills), were used intravenously as a substitute for heroin. In 1983, when naloxone was included in pentazocine (Talwin NX), abuse patterns decreased.¹⁰ Nonprescription sympathomimetics, such as pseudoephedrine, are also used as precursors in the synthesis of methamphetamine. Although the rates of potential adverse events are perceived as low, the issue takes on added significance when the magnitude of the exposure rates for these xenobiotics is considered. In a survey of 2528 participants distributed across the United States, 4.5% of adult participants in 2006 reported taking pseudoephedrine within the past week compared with 8.1% in 2002, and 3.8% reported the use of diphenhydramine compared with 4.4% in 2002.^{82,153} Both poison center and clinical experience suggests that recreational use of antihistamines may be increasing. Dextromethorphan-containing products are widely used for recreational purposes (Chap. 38).

Regardless of intent, exposures to these xenobiotics are relatively frequent, as illustrated by the number of calls received to the American Association of Poison Control Centers (AAPCC). Compilation of the National Poison Data System (NPDS) reports for the years 2001 to 2010 shows that although the total number of exposure calls related to antihistamines has increased in the last 10 years, reaching 3% of calls, the percentage of exposure per population covered by AAPCC remains constant at 0.03%. In contrast, both pediatric and adult cough and cold preparation-related calls have decreased since 2007 (Chap. 136).

In combination with each other, analgesics or antipyretics, antihistamines, and decongestants are easily accessible to the public. This availability perpetuates the widespread public impression that nonprescription xenobiotics are “safe” and contributes to their frequent use, misuse, and abuse.

ANTIHISTAMINES

History and Epidemiology

History. After the discovery of histamine, Daniel Bovet and other researchers at the Pasteur Institute attempted to synthesize antagonists to better understand its physiological role. In 1939, pyrilamine was found to be extremely effective in guinea pigs but not safe enough for humans. In 1941, phenbenzamine was the first antihistamine deemed suitable for clinical use.¹⁵⁶ Diphenhydramine was synthesized in 1943, and shortly after, in 1947, orphenadrine was derived. The more pronounced anticholinergic effects of the hydrochloride salt of orphenadrine explain its use in the treatment of Parkinson disease, and the citrate salt is used as muscle relaxant. In the same years, Searle and Company, in Chicago, modified diphenhydramine to reduce drowsiness. Dimenhydrinate, the resulting 8-chlorotheophylline salt, serendipitously cured a patient of her long-standing motion sickness. This benefit was proven in a clinical trial in 1949, in which 25% of the troops crossing the Atlantic from New York who received a placebo experienced seasickness compared with only 4% of those receiving dimenhydrinate.¹⁵⁶

Reports of adverse effects and toxicity were soon published. The first report of a death associated with diphenhydramine occurred in 1948.¹⁴ However, in this patient, several other factors could have been contributory to her demise. Deaths were also reported with methapyrilene, but given its frequent co-ingestion with propoxyphene or scopolamine and the variable postmortem serum concentrations reported, attribution of causality was difficult.¹³⁴ In the 1950s, more pediatric overdose cases were reported, and the resemblance to atropine poisoning was noted. At the time, treatment consisted of phenobarbital, “pressure respirations”, and cooling with tepid water sponges.¹³¹

In the following decade, more than 5000 compounds were synthesized by more than 500 chemists and tried for human use. Daniel Bovet was awarded the Nobel Prize in Physiology or Medicine in 1957 for his work related to the synthesis of compounds blocking the effects of bodily substances such as histamine.¹⁶

Cyclizine, a piperazine rather than a dimethylamine, was developed in the 1960s. It proved to be long acting and was used during the first manned flight to the moon by the National Aeronautic and Space Administration to control space sickness. It is no longer approved for use in the United States, although its derivative, hydroxyzine, remains in use.¹⁵⁶ In the 1970s, terfenadine was synthesized as a tranquilizer, but it lacked central nervous system (CNS) penetration. However, its peripheral antihistaminic effects proved useful. In 1989, more than 773 reactions to terfenadine were reported ranging from long QT interval to convulsions in supratherapeutic ingestions.³⁵ In 1992, the FDA issued a warning for the risk of torsade de pointes with terfenadine when administered with CYP3A4 inhibitors. Fexofenadine, its active metabolite, was marketed instead.¹⁵⁶

None of the initial xenobiotics could antagonize histamine-induced gastric acid secretion, leading to the determination of the existence of more than one type of histamine receptors. The histamine receptor subtypes were identified as H₁ and H₂. H₂ receptors were noted to be located in the stomach. Attempts to identify H₂ receptor antagonists identified guanylhistamine, a partial agonist, and initiated the understanding of the histamine receptors physiology.¹⁵⁵

Cimetidine was synthesized in 1972, but its binding to the heme moiety of the cytochrome P450 with resultant inhibition caused medication interactions as well as altered mental status.¹⁷³ Ranitidine, a less polar molecule, did not enter the CNS

and did not interfere with the P450 cytochromes. It rapidly became one of the best-selling drugs and stayed so for many years.

Seeking to better understand the action of histamine in the CNS, animal studies in the early 1980s postulated the existence of another histamine receptor located presynaptically. The existence of a distinct H₃ receptor inhibiting the neuronal synthesis of histamine (autoreceptor) when stimulated was validated with the development of the selective agonist R- α -methylhistamine and antagonist thioperamide.⁶ A fourth histamine receptor has recently been identified. Its primary function seems to modulate inflammatory and immune responses as well as nociception.⁷⁰ The numerous functions of histamine and its receptors in the nervous system, immune system, and other organs are continually being appreciated. Trials are underway for the use of H₃ and H₄ histamine receptor antagonists in CNS cognitive disorder, obesity, and allergic rhinitis treatments.⁹⁸

Epidemiology. Antihistamines are now available worldwide, and many do not require a prescription. These medications find widespread application in the treatment of conditions such as anaphylaxis, benign positional vertigo, dystonic reactions, hyperemesis gravidarum, gastroesophageal reflux disease, stress gastritis, and other histamine-mediated disorders. They are also used for their ability to act on other receptors in the treatment of serotonin toxicity. Additionally, they are used for symptomatic relief of allergy symptoms as in allergic rhinitis, conjunctivitis, or urticaria and are included in many combination cough and cold preparations as discussed previously. First-generation antihistamines are widely available without prescription and are also marketed as sleep aids. These two factors may contribute to their common ingestion in suicide attempts.¹²⁶ Second- and third-generation H₁ antihistamines are less frequently implicated in suicide attempts. Although reporting is not comprehensive, according to 2011 NPDS data, about one in five antihistamine-related exposures called to poison centers are intentional. A 10-year review of the NPDS statistics shows that although the total number of antihistamine exposures increased steadily from 2001 to 2010, with a peak of adult exposures in 2007. During this time, percentage of exposures per population served by the AAPCC has remained relatively constant. More than 35% of antihistamine exposures are related to diphenhydramine (**Chap. 136**).

H₂ antihistamines have a better safety profile in therapeutic and overdose situations.¹¹¹ Even though many references cite the possibility of bradydysrhythmias, hypotension, and cardiac arrest with massive ingestions or intravenous (IV) administration of H₂ antihistamines, these reports are rare. The incidence of adverse cardiovascular events with H₂ antihistamines is largely unknown. In the largest published review assessing 881 cases of lone cimetidine exposures, most were in children from 12 to 36 months of age, and 76% were unintentional in nature. No fatalities were observed.⁹¹ A review of NPDS reports from 2001 to 2010 did not identify any fatalities from single-product ingestion of cimetidine or other H₂ antihistamines. Only a few case reports of fatalities associated with acute exposures to H₂ antihistamines in adults can be found, mainly in forensic literature with little clinical information.⁷⁸

Children may be at increased risk for antihistamine toxicity. Most of the reported deaths in this age group are with diphenhydramine, but this may well be a reflection of its ubiquity.^{104,114} Fatalities are also reported with other antihistamines, albeit often in combination with dextromethophan and pseudoephedrine, making it difficult to attribute the cause of death to the antihistamine alone.¹⁵ Liquid formulations attractive to children and topical preparations are available, resulting in unintentional ingestions when accessible. First-generation antihistamines are also administered for their sedative properties by parents and prescribed by pediatricians for various purposes, including promoting recovery of sick children or as a relief for working parents.^{2,119} However, the result of a randomized trial of diphenhydramine for this indication showed it was no more effective than placebo for nighttime awakenings or parental happiness.¹⁰⁹

Pharmacology

Histamine Receptor Physiology. H₁ receptors are located in the CNS, heart, vasculature, airways, sensory neurons, gastrointestinal (GI) smooth muscle, immune system, and adrenal medulla. Through H₁ receptors, histamine interacts with G proteins in the plasma membranes. Stimulation of H₁ receptors results in increased synthesis by phospholipases A₂ and C, inositol-1,4,5-triphosphate, and several diacylglycerols (DAGs) from phospholipids located in cell membranes. Inositol-1,4,5-triphosphate causes release of calcium, which then activates calcium-calmodulin-dependent myosin light-chain kinase, resulting in enhanced cross-bridging and smooth muscle contraction. The active and inactive forms of this receptor subtype are in equilibrium at baseline, and histamine shifts the equilibrium to the active conformation.¹⁴⁹

H₁ receptors are most commonly associated with mediation of inflammation. The other functions of histamine and the H₁ receptor include control of the sleep-wake cycle, cognition, memory, and endocrine homeostasis. H₁ receptor stimulation also causes vasodilation, increases vascular permeability, and increases bronchoconstriction. Cardiac histamine H₁ receptor stimulation increases atrioventricular nodal conduction time.³⁶

H₂ receptors are located in cells of the gastric mucosa, heart, lung, CNS, uterus, and immune cells. H₂ receptor stimulation is mediated by adenylyl cyclase activation of cyclic adenosine monophosphate (cAMP)-dependent protein kinase

in smooth muscle and in parietal cells of the stomach and results in increased gastric acidity through stimulation of the H^+ - K^+ -ATPase pump, causing release of H^+ into the gastric lumen. The action of histamine on the H_2 receptor increases sinus node automaticity, ventricular contraction force, and coronary flow as well as vascular permeability and mucus production in the airways.^{70,149}

H_3 receptors are found in neurons of the central and peripheral nervous systems, airways, and GI tract. The action of histamine on H_3 receptors of the CNS decreases further release of histamine, acetylcholine, dopamine, and serotonin. H_3 receptors partly act to prevent excessive bronchoconstriction and are implicated in control of neurogenic inflammation and proinflammatory activity.⁹⁸

H_4 receptors are located in leukocytes, bone marrow, spleen, lung, liver, colon, and hippocampus. The H_4 receptor plays a role in the differentiation of myeloblasts and promyelocytes and in eosinophil chemotaxis.⁹⁸

All four types of histamine receptors are heptahelical transmembrane molecules that transduce extracellular signals via G proteins to intracellular second-messenger systems.¹⁴⁹ Xenobiotics acting at each of the four histamine-modulated receptor sites have been identified. To date, no H_3 or H_4 antihistamines are available for commercial clinical use (Fig. 49–1).

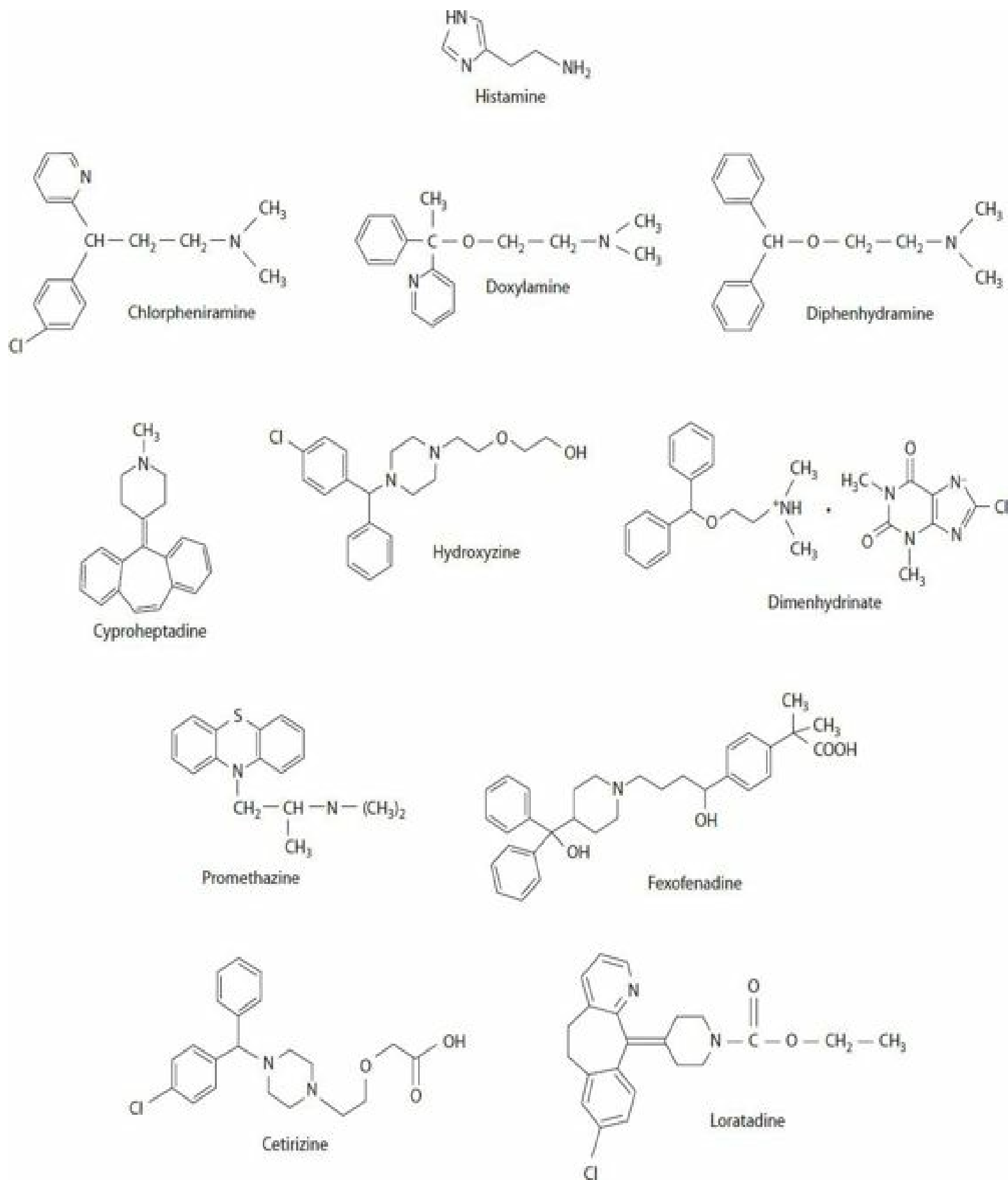


FIGURE 49–1. Structure of histamine and selected H₁ receptor antihistamines.

Histamine Receptors: Inverse Agonists versus Antagonists. All known H₁ histamine antagonists function as inverse agonists and are not simply reversible competitive antagonists. Rather than preventing the binding of histamine to its receptor as in a classical competitive antagonist model, these xenobiotics stabilize the inactive form of the histamine receptor and shift the equilibrium to this inactive conformation¹⁴⁹ (Fig. 49–2).

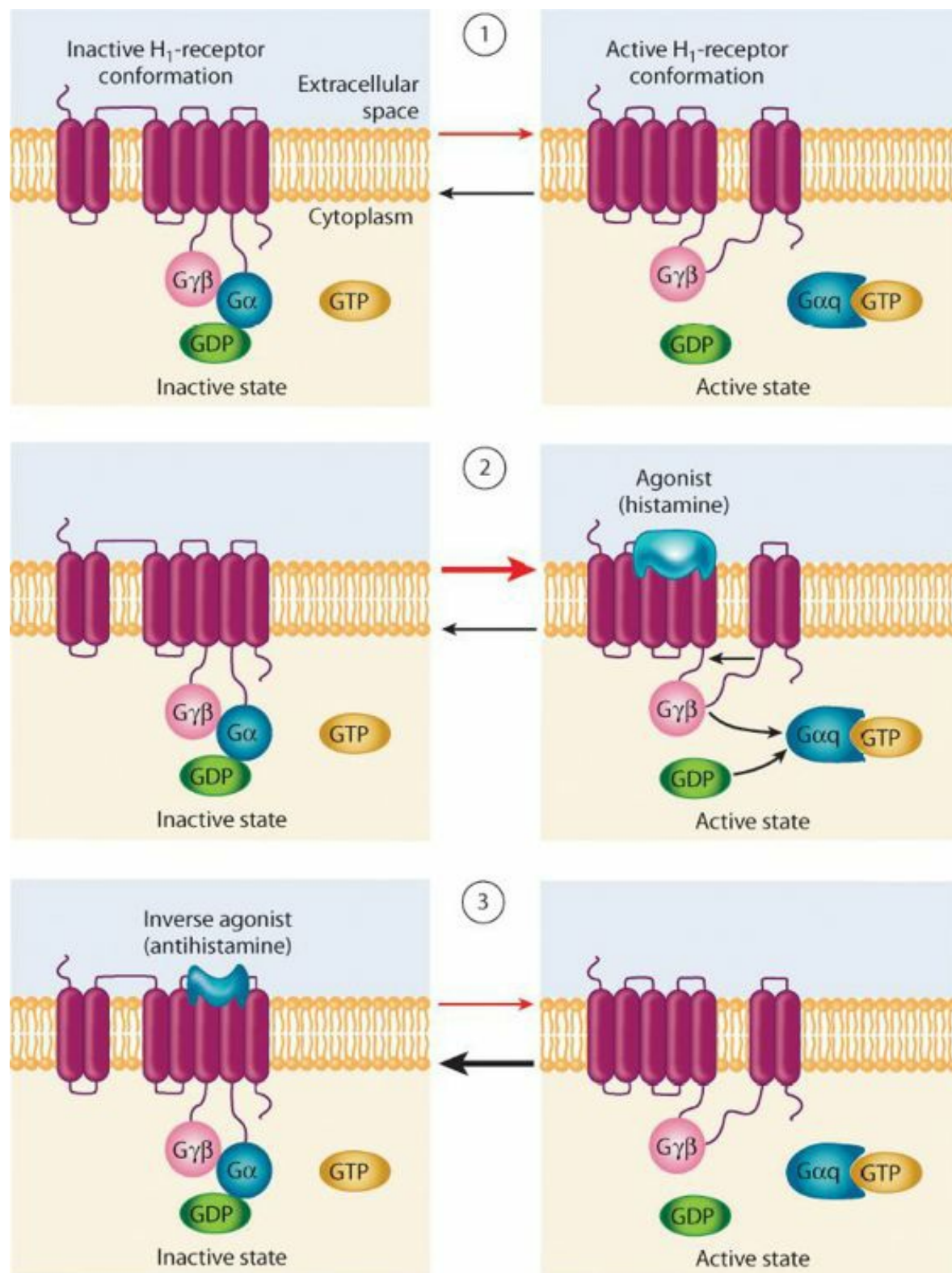


FIGURE 49–2. Action of histamine and antihistamines on the H₁ receptor. Molecular basis of action of histamine and antihistamines. (A) The inactive state of the histamine H₁ receptor is in equilibrium with the active state. (B) The agonist, histamine, has preferential affinity for the active state, stabilizes the receptor in this conformation, and shifts the equilibrium toward the active state. (C) An H₁ antihistamine (inverse agonist) has preferential affinity for the inactive state, stabilizes the receptor in this conformation, and shifts the equilibrium toward the inactive state. GDP = guanosine diphosphate; GTP = guanosine triphosphate. (Reproduced with permission from Simons FE, Simons KJ: Histamine and H₁-antihistamine: celebrating a century of progress. *J Allergy Clin Immunol.* 2011;128:1139–1150. Copyright Elsevier.)

However, for consistency with the medical literature and the current terminology for these xenobiotics, the terms antihistamine or histamine antagonist rather than inverse agonist are used.

H₁ Antihistamines. Antiallergic and antiinflammatory activities of the H₁ antihistamines involve multiple mechanisms. Inhibition of the release of mediators from mast cells or basophils involves a direct inhibitory effect on calcium ion channels, thereby reducing the inward calcium current activated when intracellular stores of calcium are depleted. Inhibition of the expression of cell adhesion molecules and eosinophil chemotaxis involves downregulation of the H₁ receptor–activated nuclear factor (δ B), which binds to promoter or enhancer regions of genes that regulate the synthesis of

proinflammatory cytokines and adhesion proteins.¹⁴⁹

Another classification system of H₁ antihistamines stratifies them by sedating properties and ability to cross the blood–brain barrier and refers to them in terms of generations as they appeared into clinical use. Positron emission tomography (PET) is now the standard method used to assess H₁ receptor occupancy of antihistamines in the CNS.¹⁹⁰

First-generation H₁ antihistamines readily penetrate the blood–brain barrier and produce CNS effects, including sedation and performance impairment. Central effects of the first-generation H₁ antihistamines likely result from their high lipophilicity or lack of recognition by the P-glycoprotein efflux pump on the luminal surfaces of vascular endothelial cells in the CNS. First-generation H₁ antihistamines also bind to muscarinic, serotonin and to α -adrenergic receptors as well as ion cardiac channels. Their binding to the voltage sensitive Na⁺ channels produces use-dependent block because of their much higher affinity to the inactivated Na⁺ channels and their binding to the K⁺ channels (IK_r) alters repolarization (Chap. 16).^{25,149}

Six major classes of H₁ antihistamines are traditionally recognized based on molecular structure. The classes were initially populated by first-generation derivatives of ethylenediamine (mepyramine, tripeleminamine), ethanolamine (diphenhydramine, doxylamine, orphenadrine, dimenhydrinate), alkylamines (pheniramine, chlorpheniramine, brompheniramine), phenothiazines (promethazine), piperazines (hydroxyzine), and piperidines (azatadine). Many of the classic antihistamines are substituted ethylamine structures with a tertiary amino group linked by a two- or three-carbon chain with two aromatic groups. This structure differs from histamine by the absence of a primary amino group and the presence of a single aromatic moiety.

Some H₁ antihistamines have relatively unique properties that have led to special uses or marketing. Although dimenhydrinate, chlorpheniramine, cyproheptadine, promethazine, and pyrilamine have been studied for their local anesthetic properties mediated by sodium channel binding, diphenhydramine is the most used antihistamine for this purpose in dentistry since the 1960s.⁹² Concerns arose with tissue irritation and skin necrosis when diphenhydramine hydrochloride 5% was used. Even though the 1% solution produces erythema without necrosis, its use should be reserved for patients truly allergic to conventional local anesthetics.¹⁵² Diphenhydramine and doxylamine find frequent application in nonprescription sleeping medications because of their sedative effects. Diphenhydramine and dimenhydrinate have relatively strong antimuscarinic activity and are used for the management of motion sickness. Oxatamide, a sedating H₁ antihistamine, may possess mast cell stabilizing properties possibly mediated via calcium-channel blockade and is associated with dyskinesia. Cyproheptadine has 5-HT₂ antagonist properties and is used in the treatment of serotonin toxicity.

Second-generation H₁ antihistamines are peripherally selective and have a higher therapeutic index. Second-generation H₁ antihistamines do not penetrate the CNS well because of their hydrophilicity, their relatively high molecular weight, and recognition by the P-glycoprotein efflux pump on the luminal surfaces of vascular endothelial cells in the CNS.²⁵ Second-generation H₁ antihistamines include astemizole, azelastine, cetirizine, ebastine, ketotifen, levocabastine, loratadine, mizolastine, olopatadine, and terfenadine. They have lower binding affinities for the cholinergic, α -adrenergic, and β -adrenergic receptor sites than do the first-generation antihistamines. Many are prodrugs that need to be converted in the liver to hydrosoluble metabolites.

Although not officially accepted terminology, metabolites or active enantiomers of second-generation H₁ antihistamines such as desloratadine, levocetirizine, and fexofenadine are sometimes referred to as third-generation antihistamines. They have fewer adverse drug reactions, but no study has confirmed their therapeutic advantages over the parent compounds. Fexofenadine, however, does not have the cardiac toxicity of its parent drug terfenadine. In a test of wheal suppression, which correlates better to receptor occupancy than plasma concentrations, fexofenadine had the earliest onset of action, and levocetirizine showed maximal inhibition at 3 and 6 hours.^{37,58}

Cautious prescribing practice may lead to a preference for second-generation H₁ antihistamines in patients whose activities are safety critical and may be affected by any psychomotor impairment (eg, those who operate motor vehicles).^{63,103} In a randomized placebo-controlled driving simulator trial, 60 mg of fexofenadine did not interfere with driving performance. However, 50 mg of diphenhydramine produced poorer driving performance than ethanol (100 mg/dL). Of note, subjective feelings of drowsiness were not predictors of impairment.¹⁸³ Despite these findings, care must be exercised in the selection and use of second-generation H₁ antihistamines because some subjective or objective sedation may still result from their use, especially if higher-than-recommended dosages are taken, particularly with cetirizine.^{38,137} Furthermore, a meta-analysis suggested that the differentiation between sedating and nonsedating H₁ antihistamines may be blurry, with some studies lacking the methodology to correctly distinguish between medication adverse effects and the signs and symptoms of the condition being treated.^{12,163} Overall, it appears that the relative incidence of anticholinergic and CNS adverse effects caused by second-generation H₁ antihistamines may be similar to that produced by placebo.³⁸ Using recommended doses of antihistamines, PET scanning shows that first-generation antihistamines occupy more than 70% of

the H₁ receptors in the frontal cortex, temporal cortex, hippocampus, and pons. In contrast, the second-generation antihistamines occupy less than 20% to 30% of the available CNS H₁ receptors.^{162,163}

H₂ Antihistamines. These structural analogs of histamine are highly selective inhibitors of the H₂ receptor site. Cimetidine is the original antihistamine in this class; it includes the imidazole ring of histamine (Fig. 49–3). Although ranitidine and famotidine have a furan (ranitidine) or thiazole (famotidine) group instead, they retain significant structural similarity to histamine.

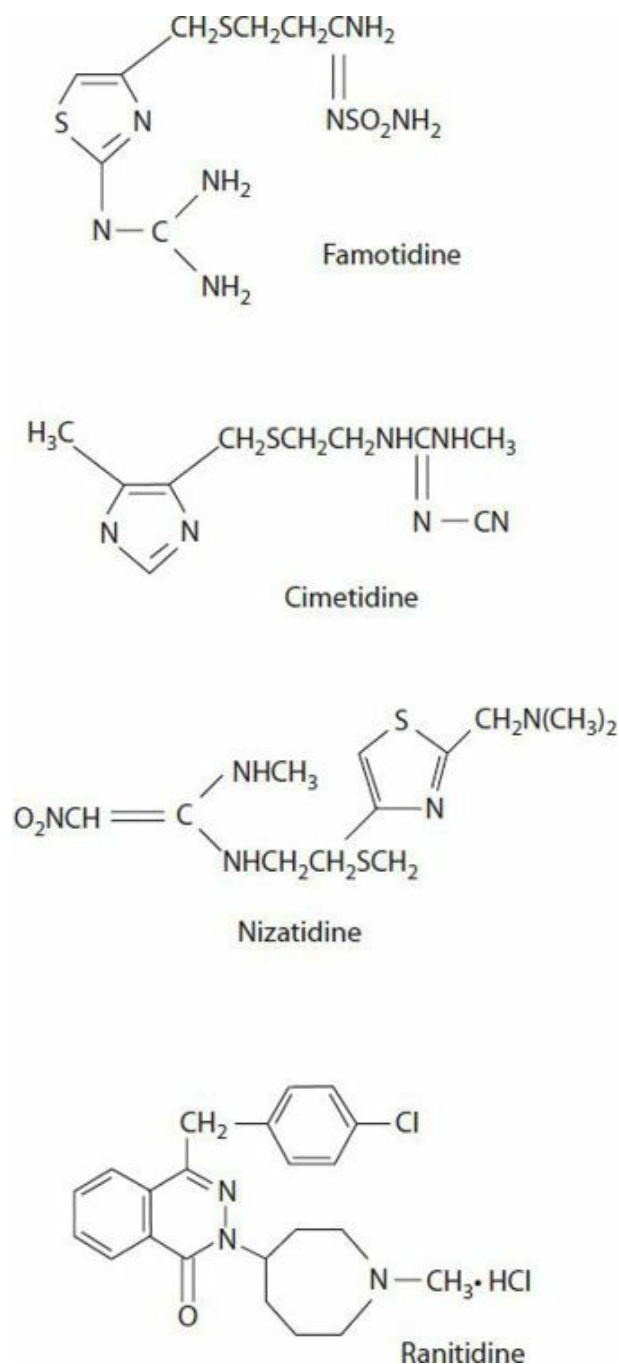


FIGURE 49–3. Structures of H₂ receptor antagonists.

The effectiveness of H₂ antihistamines in the treatment of diseases caused by excessive gastric acid secretion is improved further by their concomitant alteration in the response of parietal cells to acetylcholine and gastrin, two other stimulants for gastric acid secretion (Fig. 49–4). Of note, H₂ antihistamines have little pharmacologic effect elsewhere in the body, and they have weak CNS penetration secondary to their hydrophilic properties.

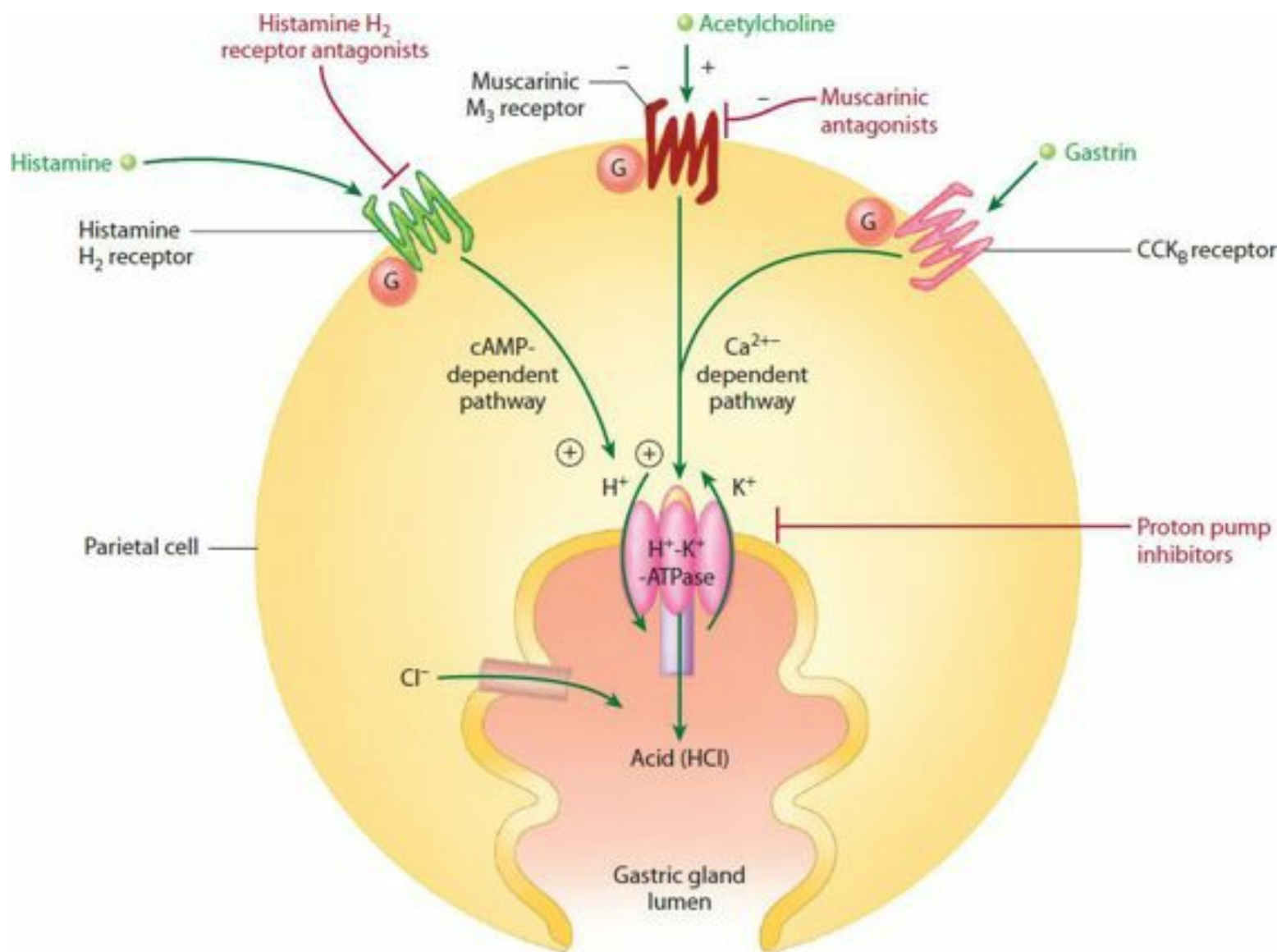


FIGURE 49–4. Schematic representation of a gastric parietal cell demonstrating the mechanism of hydrogen ion secretion into the lumen. Gastric acid is modulated by both the calcium-dependent and cyclic adenosine monophosphate (cAMP)–dependent pathway. Histamine binding to the H_2 receptor increases gastric acidity by increasing cAMP. Both acetylcholine and gastrin increase gastric acidity by increasing the influx of calcium. Whereas acetylcholine binds at the muscarinic 3 (M_3) receptor, gastrin binds the cholecystokinin B (CCK_B) receptor.

H_3 Antihistamines. These xenobiotics are the focus of much research; however, none are currently commercially available.¹⁹² Some prototypical drugs include ciproxifan, clobenpropit, pitolisant, and thioperamide. This category is further divided into the imidazole-based and non-imidazole-based series.¹⁷² Because of nootropic (cognitive enhancement) and stimulant effects, it has been suggested that H_3 antihistamines might play a future role in the treatment of attention deficit and hyperactivity disorder, narcolepsy, depression, or dementia. Pitolisant has been granted orphan drug status in the European Union and United States. Its benefit in the treatment of narcolepsy is contested, and it is currently in clinical trials for Parkinson disease and schizophrenia.¹⁴² Conessine, a herbal used in Ayurvedic medicine for dysentery, is also a selective H_3 antihistamine.^{55,138}

H_4 Antihistamines. No commercially available xenobiotics of this class are currently available. Because of their association with mast cells and eosinophils, H_4 antagonists clinical trials are studying their potential therapeutic benefit in the treatment of allergic rhinitis, asthma, and autoimmune disorders.¹⁴⁹

Atypical Antihistamines

Other xenobiotics have been named atypical antihistamines because of their inhibitory effect on the enzyme histidine decarboxylase, which catalyzes the transformation of histidine to histamine as opposed to action on the H_1 receptor.

Tritoqualine has been commercially available in Europe since the 1960s and is used for persistent allergic rhinitis.¹²⁵ To date, no case report of overdose with atypical antihistamines has been published.

Pharmacokinetics and Toxicokinetics

H₁ Antihistamines

Absorption. H₁ antihistamines are generally well absorbed after oral administration, and most achieve peak plasma concentrations within 2 to 3 hours. Although less well studied, dermal absorption appears to be consequential, especially with extensive or prolonged application to abnormal skin.¹⁶⁷ The maximum antihistaminic effect occurs several hours after peak serum concentrations. In supratherapeutic or overdose circumstances, absorption can be prolonged by the antimuscarinic effect on the GI tract.

Although ingestion is the usual route of exposure, rare cases of topical preparations containing diphenhydramine and promethazine cause agitation attributed to anticholinergic toxicity in children. Blood concentrations in these patients may be above the peak therapeutic concentration of 0.06 mg/L.^{50,72,141,146,188} Many cases were with concomitant varicella infection, blurring the causality of the clinical findings attributed to topical diphenhydramine alone. Lumbar punctures were not done to exclude encephalitis, but symptoms improved with cessation of diphenhydramine. Several cases occurred after a bath, calling into question the role of peripheral vasodilation in increasing dermal absorption. Some patients had concomitant oral diphenhydramine therapy but none exceeding the recommended dose of 5 mg/kg/day. One death solely after exposure to topical diphenhydramine is reported in a child with eczema.¹⁶⁷ All cases of topical antihistamine-induced toxicity involved administration over significant body surface area on abnormal skin.

Distribution. Antihistamines are typically lipid soluble with variable octanol/water partition coefficients. They are also highly bound to plasma protein in therapeutic concentrations. The saturability of protein binding in toxic concentrations is largely unknown. The average volume of distribution is between 0.5 and 12 L/kg but can extend to 30 L/kg with desloratadine.

Metabolism. Hepatic metabolism is the primary route of metabolism for antihistamines.¹²¹ Cetirizine, fexofenadine, and levocetirizine are exceptions. A poor metabolizer phenotype of desloratadine has been identified in children and adults. In these individuals, the apparent half-life of desloratadine is 50 hours or more compared with the average population whose half-life is around 26 hours.¹²⁸ This variability has not been shown to impact the safety profile of desloratadine. Many Asian patients can acetylate therapeutic concentrations of diphenhydramine to a nontoxic metabolite twice as rapidly as white patients, making Asians much less sensitive to both the psychomotor and sedative effects.¹⁵⁸ Results of a study of 100 patients in a sample of 2074 antihistamine users reporting excessive daytime sleepiness after use of H₁ antihistamines (predominantly chlorpheniramine) suggest that the presence of the CYP2D6*10 allele is a risk factor for development of H₁ antihistamine-induced adverse drug reactions.¹³⁹

Excretion. Unchanged antihistamines and metabolites are renally excreted. Chlorpheniramine urinary excretion is increased in acidic urine. Elderly adults (mean age, 69 years) had similar time to peak concentrations but longer elimination half-lives of diphenhydramine compared with young adults.¹⁵¹

Elimination half-life is quite varied for all H₁ antihistamines with chlorpheniramine, hydroxyzine, azelastine, and levocabastine exhibiting the longest termination half-lives up to 24 hours.¹⁴⁹

The duration of action ranges from 3 hours to 24 hours, which is much longer than predicted from the serum elimination half-lives of the antihistamines. One study addressing the pharmacokinetics of diphenhydramine found that children (mean age, 8.9 years) reached peak plasma concentrations faster and had a shorter mean elimination half-life than young adults for the same dosage per kilogram.¹⁴⁹ Similar findings were observed with hydroxyzine.¹⁵⁰ In another volunteer study, desloratadine doses of 1 and 1.25 mg in children between the ages of 6 months and 2 years were found to provide a single dose target exposure (area under the plasma concentration–time curve) comparable with that experienced by adults receiving the recommended 5-mg dose.⁵⁷

Modifications in therapeutic doses may be required for patients with hepatic or renal dysfunction, young people, and elderly adults. Such modifications often must be made empirically because formal studies and recommendations for many xenobiotics are lacking. Patients with renal dysfunction might be more susceptible to developing toxicity from acute ingestion of a second-generation antihistamine, and dose adjustment is recommended for cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine.³³

Drug interactions. Recognized pharmacokinetic drug interactions involving the H₁ antihistamines are generally caused by modulation of CYP450 metabolism (most often CYP2D6 or CYP3A4) or via interference with active transport mechanisms such as P-glycoprotein or organic anion transporter polypeptide (OATP). The currently available second-generation H₁ antihistamines undergo fewer clinically relevant pharmacokinetic interactions than the first-generation H₁ antihistamines.^{9,40}

H₂ Antihistamines

Absorption. Cimetidine is rapidly and completely absorbed after oral administration, but only 40% to 50% of ranitidine and famotidine are bioavailable with a peak concentration within 3 hours. All have reduced absorption when administered concomitantly with food.

Distribution. Cimetidine has a volume of distribution of approximately 2 L/kg. Famotidine and ranitidine have a

variable volume of distribution in different age groups ranging from 1 to 4 L/kg. All have protein binding in the range of 15% to 25%.

Metabolism. Cimetidine has some hepatic metabolism (15%), but ranitidine and famotidine do not (<5%).

Excretion. Up to 70% of ranitidine is eliminated unchanged in the urine, and 10% is eliminated unchanged in the stool. Famotidine and cimetidine are also primarily renally excreted. Renal excretion is lower for oral than for IV administration.

Elimination half-life. The elimination half-life in patients with normal renal function is approximately 2 hours, but the half-life is substantially prolonged with impaired renal function (up to 10 hours) and in elderly adults (4 hours).

Interactions. Cimetidine is responsible for numerous drug–drug interactions because it can inhibit cytochrome P450 activity, thereby impairing hepatic drug metabolism. It can reduce hepatic blood flow, resulting in decreased clearance of drugs that are highly extracted by the liver. None of the other currently available H₂ antihistamines inhibit the cytochrome P450 oxidase system.¹⁰⁵ Additionally, by altering gastric pH, cimetidine and all of the other H₂ antagonists may alter the absorption of acid-labile xenobiotics. Finally, cimetidine and ranitidine are associated with myelosuppression, particularly when administered with xenobiotics capable of causing bone marrow suppression.⁷

Cimetidine is an inhibitor of ethanol-oxidizing activity of gastric alcohol dehydrogenase (ADH) in human isoenzymes, but inhibition by nizatidine and famotidine is negligible. It is likely a result of the thiazole group of these H₂ antihistamines preventing binding to the enzymatic substrate site.¹⁵⁹ In vitro data regarding ranitidine inhibition of gastric ADH yielded conflicting results. However, a human study comparing oral versus IV ethanol kinetics with ranitidine showed a significant reduction in first-pass metabolism.^{19,64} The first-pass metabolism of ethanol is influenced by the gastric mucosa, but it is unclear by which mechanisms ranitidine might influence increases in blood ethanol concentrations.¹¹⁷ The literature on the clinical relevance of these effects is conflicting.¹⁸ A meta-analysis of the effect of H₂ antihistamines on serum ethanol concentrations reported small elevations with cimetidine and ranitidine when administered concurrently, but the overall effect seemed unlikely to be clinically significant related to the accepted legal definitions of intoxication.¹⁸⁴ However, a later study reported raised ethanol concentrations in the range known to impair driving skills when ranitidine was taken regularly for 7 days before drinking.⁵ Asians are known to have increased gastric ADH as well as decreased ALDH-2.¹¹⁸ Combined therapy with H₁ and H₂ antihistamines were tried as a treatment for the “Asian flush” reaction with encouraging results. However, only H₂ antihistamines blocked the flushing reaction¹¹⁰ (Table 49–1).

TABLE 49–1. Pharmacokinetics Properties of Commonly Used Antihistamines in the United States

Antihistamine		Half-Life (hours) ^a	Duration of Action (h) ^a	Hepatic Metabolism	Log D ^c	Vd (L/kg) ^b	Urinary Elimination (%)
H₁ antihistamines							
First generation	Chlorpheniramine	12–43 (urine pH dependent)	24	Yes	1.13	5–7	30
	Cyproheptadine	N/A	4–6	Yes	4.93	N/A	72
	Diphenhydramine	3–14	12	Yes	1.92	3–4	4
	Doxylamine	10–11	N/A	Yes	1.15	2.7	N/A
	Hydroxyzine	13–27	24	Yes	2.21	13–31	15
	Promethazine	9–16	4–6	Yes	2.73	9–19	<1
Second generation	Cetirizine	6.5–10	12–24	<40%	–0.02	0.58	70
	Desloratadine	21–27	>24	Yes	2.95	10–30	41
	Fexofenadine	9–20	12–24	<8%	2.68	12	11
	Levocetirizine	N/A	>24	<15%	–0.83	0.41	85
	Loratadine	3–20	24	Yes	6.23	26–32	
H₂ antihistamines							
	Cimetidine	2	6–10			1.4	35–60
	Ranitidine	2.1	12			1.6–2.4	69
	Nizatidine	1.3	24	Yes	N/A	1.2–1.8	61
	Famotidine	2.6	12			0.9–1.4	67

^aBrunton LB, Lazo JS, Parker KL, eds: Goodman & Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York: McGraw-Hill; 2005. ^bBeale RC: Disposition of Toxic Drugs and Chemicals in Man. 7th edition. Foster City, CA: Biomedical Publications; 2004. ^cLog D is the octanol/water partition coefficient at a pH of 7.

Vd = volume of distribution.

Data from Wilson CJ, Beale JM, Block JH: Wilson and Gilvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. 12th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2011.

Pathophysiology

The pathophysiology of acute H₁ antihistamine overdose is largely an extension of the expected therapeutic and adverse effects. These effects can be classified in broad categories according to the type of receptors involved. Acute H₂ antihistamine toxicity can be explained by a loss of selectivity for the gastric H₂ receptor and inhibition of the cardiac H₂ receptors responsible for positive chronotropy and inotropy.^{84,187}

The pathophysiology of H₁ antihistamine abuse is thought to be multifactorial. Humans are reported to abuse dimenhydrinate and diphenhydramine for their euphoric and hallucinogenic effects as well as for their reported anxiolytic and anticholinergic properties.⁶⁰ Recreational ingestion up to 5 g is reported, although most common recreational doses used to experience euphoria and hallucinations average 1 g.⁵⁹ Promethazine often combined with codeine, is widely abused in certain demographic groups.

However, animal studies of self-administration and conditioned place preferences suggest that antihistamines also have a rewarding potential independent of its euphoric effects, which increases with use. Dimenhydrinate abuse is linked to the stimulant effect of the 8-chlorotheophylline component but alone does not produce rewarding effects. However, diphenhydramine antagonizes muscarinic receptors, modulates serotonin function, enhances dopamine concentrations, and potentiate opioid receptors. It is now thought that the combination of diphenhydramine and the methylxanthine 8-chlorotheophylline as in dimenhydrinate has synergistic effect on the rewarding potential.⁵⁹ The dose–response for this to occur in humans remains to be studied. Older antihistamines such as chlorpheniramine are also selective serotonin receptor inhibitors, which might explain their nonmedical use⁶² (Table 49–2).

TABLE 49–2. Effects of H₁ Antihistamines

<i>Effects</i>	<i>Clinical Result</i>	<i>First Generation</i>	<i>Second Generation</i>
Must cell histamine inhibition	Decreased itching Decreased vascular permeability Vasodilation	Therapeutic	Therapeutic
Calcium ion channel blockage	Decreased mediator release	Therapeutic	Therapeutic
CNS H ₁ receptor occupancy	Sedation Impaired psychomotor performance	Marked effect in therapeutic and overdose	Minimal or no effect reported with cetirizine in overdose
CNS serotonin receptor antagonism	Increased appetite Weight gain	Occurs in therapeutic doses; no significance in overdose	No effect
Peripheral muscarinic receptor antagonism	Dry mucosa Decreased peristalsis Urinary retention Sinus tachycardia Mydriasis	Marked effect in overdose; minimal effect can occur at therapeutic doses	Minimal or no effect
Central muscarinic receptor antagonism	Agitation Delirium Hallucinations	Marked effect in overdose	No effect
α-Adrenergic receptors	Dizziness Hypotension	Marked effect in overdose; minimal effect can occur at therapeutic doses	No effect
Cardiac ion channel blockade	Prolonged QRS (I _{Na}) Prolonged QT interval (I _K)	Marked effect in overdose on Na ⁺ channel	Minimal or no effect at therapeutic doses except terfenadine, astemizole on K ⁺ channel

CNS = central nervous system.

Clinical Manifestations

H₁ Antihistamines. The toxic doses for each antihistamine are not well defined. The oft-cited threshold of toxicity of three to five times the therapeutic dose for first-generation antihistamines as well as cetirizine, loratadine, and fexofenadine originating from algorithms in various articles has never been validated.¹⁶⁴ Extrapolating plasma concentrations to an ingested dose is not accurate in predicting clinical effects for diphenhydramine and doxylamine.^{89,90} A dose-dependent relationship for diphenhydramine toxicity was published indicating a high risk of seizures with ingestions above 1.5 g in

adults.¹²⁹

Neurologic. Acute overdose of first-generation H₁ antihistamine usually results in the onset of toxicity within 2 hours. Dose–response effect accounts for the wide spectrum of altered mental status observed. Drowsiness seen in milder poisoning can rapidly progress to obtundation and seizures with larger ingestions. Compared with adults, children may more commonly present with excitation, irritability, or ataxia as well as being more prone to having hallucinations or seizures.⁸ Patients typically exhibit an anticholinergic syndrome, including mydriasis, tachycardia, hyperthermia, dry mucous membranes, urinary retention, diminished bowel sounds, and altered mental status such as disorientation and hallucinations. The skin may appear flushed, warm, and dry. Hyperthermia occurs in severe cases and correlates with the extent of agitation, ambient temperature and humidity, and length of time during which the patient cannot dissipate heat because of anticholinergic-mediated reduction in sweating ([Chap. 30](#)).

Some patients with high therapeutic dosing or after overdose develop a central anticholinergic syndrome in which CNS anticholinergic effects, such as hallucinations, outlast peripheral anticholinergic effects. At a later stage of ingestion the lack of tachycardia, skin changes, or other peripheral anticholinergic manifestations complicates establishment of the correct diagnosis for antihistamine poisoned patients unless there is a clear exposure history.^{56,182} Ingestion of second-generation H₁ and H₂ antihistamines usually does not result in significant CNS depression or anticholinergic effects except perhaps in pediatric patients or in adults with altered pharmacokinetic parameters. Although dry mouth and mydriasis are common adverse therapeutic effects, sedation is of the greatest concern.

Seizures can occur at any point in time in the course of the poisoning but typically begin in the first few hours and represent severe toxicity. Chlorpheniramine is both a serotonin reuptake inhibitor and a postsynaptic 5-HT_{1A} and 5-HT_{2A} receptor agonist.⁷⁹ Agonism of 5-HT receptors is associated with seizures. All first-generation H₁ antihistamines can produce seizures, although pheniramine seems to be more proconvulsant than others.²¹ Up to 22% of drug-induced seizures in children have been related to an antihistamine exposure, and diphenhydramine is a common cause of recreational drug-induced seizures.^{1,52,165}

Mydriasis develops at both therapeutic and toxic doses, with most patients describing blurred vision or diplopia. Both vertical and horizontal nystagmus may occur in patients with diphenhydramine overdose.⁴⁸

In a review of 136 patients with diphenhydramine overdose, somnolence, lethargy, or coma occurred in approximately 55% of patients, and 15% experienced a catatonic stupor.⁸⁹ Several reports suggest that young children experience more respiratory complications, CNS stimulation, anticholinergic effects, and seizures than do adults.¹¹⁴ In a placebo-controlled study comparing the CNS effects of the first- and second-generation H₁ antihistamines, the second-generation antihistamines caused less cognitive dysfunction and somnolence.^{38,69} This finding was corroborated in the simulated driving model in which loratadine produced significantly less impairment than diphenhydramine.⁶³ Use of diphenhydramine compared with loratadine in a work setting results in significantly higher injury rates.⁵¹ Observational postmarketing cohort studies conducted in England on large numbers of patients reported rates of sedation or drowsiness of fewer than 1% for desloratadine and levocetirizine.^{95,96}

Cardiovascular. Sinus tachycardia is a consistent finding after overdose with an H₁ antihistamine with anticholinergic effects and can persist after other toxic manifestations and delirium have resolved. Both hypotension and hypertension may occur.¹⁰⁰ These findings probably relate more to the patient's age, volume status, and vascular tone than to a specific class of antihistamines. Binding to inactivated channels results in prolongation of both the QRS complexes and QT intervals may occur with any first-generation H₁ antihistamine at doses that are supratherapeutic.^{27,92} Brugada-pattern electrocardiographic (ECG) changes are also reported.^{99,191}

Cardiotoxicity observed with terfenadine and astemizole may result from accumulation of the parent drug in cardiac tissue after inhibition of drug elimination (eg, terfenadine–ketoconazole interaction) and may be exacerbated by electrolyte (eg, Ca²⁺) imbalances or concomitant use of another ion channel blocker.^{13,68} They are no longer approved for use in the United States and many other countries. Second-generation H₁ antihistamines currently available are less dysrhythmogenic.^{65,127} Rare cases of QT interval prolongation have been reported in therapeutic situations, but the incidence of dysrhythmias with second-generation in overdose is unknown.³ One study reported six cases of patients taking amiodarone with loratadine who presented with episodes of torsade de pointes and syncope. Amiodarone accumulation has not been reported with co-treatment with loratadine, and all patients made a full recovery after loratadine was stopped. Loratadine accumulation via P450 CYP3A4 inhibition by amiodarone is the mechanism suspected to explain this occurrence.⁴ QT interval prolongation is reported with cetirizine (mainly with kidney failure or large ingestions), but none has been published with desloratadine or levocetirizine.³

Other. Rhabdomyolysis can occur in patients with extreme agitation or seizures after an H₁ antihistamine overdose.⁵³ Rhabdomyolysis is commonly noted in patients who overdose with doxylamine even in the absence of trauma or other common etiologies such as seizures, shock, or crush injuries. The mechanism remains undefined. A prospective study found

that 87% of patients who ingested more than 20 mg/kg of doxylamine developed rhabdomyolysis, and this dose was the best predictor of this complication.⁷⁵ Another retrospective review found a dose of more than 13 mg/kg to be the only predictive factor of doxylamine-induced rhabdomyolysis.⁸⁶ Rhabdomyolysis is reported as a rare adverse event after diphenhydramine overdose.⁴⁷ One case of compartment syndrome with diphenhydramine alone was published.¹⁷⁷ This complication more commonly occurs in association with other factors such as ethanol intoxication or immobilization. Creatine kinase concentrations are reported as high as 262,000 UI/L without seizure activity.^{42,47,85}

Unless complications such as aspiration or kidney failure develop, most patients are symptomatic for 24 to 48 hours with resolution of cardiac symptoms occurring before neurologic recovery. Anticholinergic delirium and residual sinus tachycardia can last a few days, but generally neither needs cardiac monitoring in intensive care settings. Other adverse effects mostly seen in therapeutic use include pancytopenia and cholestatic jaundice (cetirizine) fixed-drug rash, urticaria, photosensitivity, hyperthermia, transaminitis, or agranulocytosis. Hypersensitivity reaction to antihistamines is exceptionally rare but has been reported.³⁹ Postmortem findings are generally limited to pulmonary and visceral congestion, suggesting cardiogenic causes of death.⁸⁰

Special populations. Elderly patients are more susceptible to adverse events because kidney and liver dysfunction delay antihistamine metabolism.⁶⁹ All H₁ antihistamines cross the placenta, and some are teratogenic in animals. First- and second-generation agents fall into FDA categories B and C and should be individually addressed, avoiding or minimizing exposure when possible ([Chap. 31](#)). Because of their antimuscarinic effects, the first-generation antihistamines are generally contraindicated in patients with glaucoma or benign prostatic hypertrophy.

H₂ Antihistamines. These xenobiotics are well tolerated in overdose even after large ingestions. Patients may develop tachycardia, dilated and sluggishly reactive pupils, slurred speech, and confusion.^{157,173} In a retrospective study of acute cimetidine overdoses, 8.9% of patients had symptoms related to the ingestion, and those with reported moderate medical outcomes had ingested cimetidine with suicidal intent. Severe dysrhythmias, including ventricular fibrillation and bradycardia leading to fatal cardiac arrest in rapid IV infusion of cimetidine, are reported.¹⁴⁵ Deaths are reported in rare instances in large ingestion of cimetidine.⁸⁷

Famotidine and ranitidine produce even fewer dose-related toxicities in overdose. In addition, they are less likely than cimetidine to induce or inhibit the cytochrome P450 enzyme system, thereby producing fewer drug–drug interactions.⁷¹

Diagnostic Testing

The bedside diagnosis of antihistamine toxicity is a clinical one. Antihistamines cause false-positive results on several rapid urine drug screens by immunoassay to amphetamines (ranitidine), methadone (diphenhydramine, doxylamine), and phencyclidine (diphenhydramine, doxylamine). Cyproheptadine, diphenhydramine, and hydroxyzine have given false-positive results to tricyclic antidepressants (TCAs) in serum immunoassays only.¹⁶¹ Such results have caused concerns, particularly in children, and should always be confirmed if malicious intent is suspected.¹³⁵

Comprehensive blood or urine analysis screening with liquid chromatography/mass spectroscopy (LC/MS) or gas chromatography/mass spectroscopy (GC/MS) can provide antihistamine concentrations, but these are more useful in medicolegal or forensic situations. The turnaround time usually needed is unlikely to provide results at the time of initial assessment. Moreover, treatment is based on alleviation or correction of toxic signs or symptoms and should not depend on a concentration result that has not been shown to correlate with toxicity.^{85,89,90} Measurement of antihistamine concentrations in body fluids is not readily available and is generally unnecessary for clinical assessment and management.

Several publications have estimated the toxic diphenhydramine concentration in children to be around 5 mg/L. Fatal antihistamine concentrations are reported with great variability. However, as occurs in adults, toxic effects and fatalities are reported with lower concentrations. Considering diphenhydramine is subject to postmortem redistribution, it would be prudent to obtain blood samples as soon as possible to aid in determining the cause of death in fatalities involving these xenobiotics.⁸

Management

General Management. The initial management of a given exposure can begin by a consultation with a poison control center. Guidelines are published and validated with regards to the evidence-based out-of-hospital management of diphenhydramine and dimenhydrinate exposure allowing for home observation for any ingestion under 7.5 mg/kg in children younger than 6 years of age or under 300 mg or 7.5 mg/kg for adults and older children.^{11,140} Other criteria for medical evaluation for other antihistamines vary according to local practices, but in general, ingestions of less than five times the maximal therapeutic dose is rarely toxic.

Patients presenting to hospitals after exposure of any antihistamine must be triaged and medically assessed quickly, generally within 30 minutes of arrival, because those who will develop severe complications may be initially indistinguishable from those who will have a benign course, and the window for GI decontamination may soon elapse.

The individual should be attached to a cardiac monitor and observed for signs of sodium channel antagonism (increased QRS complex duration), potassium channel blockade (prolonged QT interval), and related dysrhythmias, as well as for seizures. IV access should be established and airway protection ensured.

Gastrointestinal decontamination can be undertaken with care to avoid aspiration in patients with large ingestions of first-generation H₁ antihistamines or early presentations but is generally not needed for H₂ antihistamines. The use of oral activated charcoal (AC), although more effective if administered early with regards to time of ingestion, can be considered even after a delay for ingestion of large amounts that might reduce absorption time. Multiple dose AC or whole-bowel irrigation (WBI) is usually not indicated. Neostigmine administration was used with success in drug-induced ileus, thus facilitating gut decontamination.²⁴

Enhanced elimination techniques do not benefit the toxicity of these xenobiotics because of their large volumes of distribution, extensive protein binding, and absence of enterobiliary circulation. However, exceptional case reports have been published using hemoperfusion and hemodialysis with resolution of the dysrhythmias previously unresponsive to treatment. These patients had ingested 20 mg/kg (adult) and 50 mg/kg (child) of diphenhydramine. All cases reported diphenhydramine concentrations in the fatal range. The mechanism proposed to explain these recoveries is that removal of diphenhydramine from the toxic compartment during extracorporeal treatment might have been enough to improve the distributive shock suspected to be from α -adrenergic blockade.^{106,113,179} Unfortunately, no clearance data, only blood concentrations before and after dialysis, have been reported, thus making conclusions on the efficacy of enhanced removal debatable and not recommended.

Assessment of the serum acetaminophen concentration is important because of its inclusion in many cough and cold products. Other laboratory studies should be obtained as indicated by history or physical signs and symptoms. Kidney function and creatine kinase should be obtained on all patients, particularly in patients with seizures or doxylamine overdose. Serum pregnancy tests should be obtained in women of childbearing age. An ECG should be obtained on all patients during the initial assessment and repeated at regular intervals, particularly if physostigmine use is considered.

The patient's vital signs and mental status must be monitored. Serial assessments of the patient's vital signs, particularly temperature, and mental status should be made. The potential for clinical deterioration necessitates management of symptomatic patients in a monitored environment.

Specific Treatments. **Sedation** can increase the risk for aspiration. Intubation to secure the airway is recommended when excessive sedation compromises ventilation.

Seizures should be treated with an IV benzodiazepine such as 2 to 4 mg (0.05–0.1 mg/kg in children) of lorazepam or 10 mg (0.2–0.5 mg/kg in children) of diazepam with repeated dosing as necessary.^{49,74} Hypertonic saline (3%) has also been shown to be effective in diphenhydramine-induced seizures in an animal model.⁶⁷ Recurrent seizures refractory to benzodiazepines or sodium bicarbonate should be treated with propofol or general anesthesia. Phenytoin use is discouraged as in most toxicologic-induced seizures.

Hypotension generally responds to isotonic fluids (0.9% sodium chloride solution or lactated Ringer solution). If the desired increase in blood pressure is not attained, sodium bicarbonate therapy or vasopressors can be titrated to achieve an acceptable blood pressure. In one instance, cardiogenic shock and myocardial depression resulting from a 10 g ingestion of pyrilamine could only be reversed with an intraaortic balloon counterpulsation device.⁵⁴ This approach should rarely be needed.

The sodium channel blocking (type IA antidysrhythmic) properties of diphenhydramine and other antihistamines may lead to wide-complex **dysrhythmias** that resemble those that occur after TCA overdose ([Chap. 71](#)). Hypertonic sodium bicarbonate reverses diphenhydramine or other antihistamine-associated conduction abnormalities^{27,49,74,144} (Antidotes in Depth: A5).

Type IA (quinidine, procainamide, disopyramide), IC (flecainide), and III (amiodarone, sotalol) antidysrhythmics are contraindicated because of their capacity to prolong the QRS and QT intervals. The use of IV lipid emulsion is reported with an ingestion of 1250 to 2500 mg of diphenhydramine. The common mechanism of action on sodium channels with TCAs and local anesthetics likely explains its success in restoring cardiac activity within minutes of administration after 60 minutes of unsuccessful resuscitation with 50 mEq of sodium bicarbonate, 2 mg of epinephrine, IV glucose, and 1 mg of atropine.⁷⁷

Rhabdomyolysis associated nephrotoxicity should be prevented by early use of IV fluid, NaCl 0.9%, to produce a urine output of 1 to 3 mL/kg/h. Once established, antihistamine-induced rhabdomyolysis is treated with IV fluids.¹²⁰ Although urinary alkalization may be helpful to prevent myoglobin-induced nephrotoxicity, its usefulness is controversial and might be best reserved when urinary pH is lower than 6.5.²⁶ Serum potassium and ECGs should be obtained to exclude significant hyperkalemia from muscle injury or acute kidney injury. Initial hypocalcemia caused by precipitation of phosphate from muscle breakdown should not be replaced unless dangerously low because calcium redistributes into the circulation in later phases.¹²⁰

Cooling via evaporative methods (tepid mist or cooling blanket or fan) is generally sufficient, but patients with severe

hyperthermia should receive more rapid cooling using an ice bath. **Hyperthermic** patients should be monitored for the development of disseminated intravascular coagulation and other complications. The goal is to return the patient to a normothermic state. There is insufficient evidence to recommend therapeutic hypothermia in poisoned patients with antihistamines.

Agitation or psychosis generally responds readily to titration of a benzodiazepine. Although most commonly a direct central effect, other frequent causes of agitation such as urinary retention or bright lights shone into dilated eyes unable to accommodate should not be forgotten. Physostigmine may effectively reverse the peripheral or central anticholinergic syndrome and can be used as a benzodiazepine-sparing strategy, but should only be considered after the initial cardiovascular toxicity, if present, has resolved or is no longer a possibility. It should be used with caution in an attempt to reverse coma or sedation caused by anticholinergic toxicity.

In a retrospective comparison of physostigmine and benzodiazepines, physostigmine was found to be safer and more effective for treating anticholinergic agitation and delirium.²² Contraindications to physostigmine use include wide QRS complex or bradycardia noted by ECG, asthma, and pulmonary disease. The primary benefits of physostigmine use in patients with antihistamine overdose include restoration of GI motility, elimination of agitation, and possible obviation of the need for computed tomography (CT) scan or lumbar puncture if the patient regains a normal mental status and can provide a clear history. The anticipated benefits of physostigmine must outweigh the potential risks before its use.

Before physostigmine is administered, the patient should be attached to a cardiac monitor, and secure IV access should be established. Physostigmine (1–2 mg in adults; 0.5 mg in children) should be administered by IV bolus over 5 to 10 minutes with continuous monitoring of vital signs, ECG, breath sounds, and oxygen saturation by pulse oximetry. The initial dose of physostigmine can be repeated at 5- to 10-minute intervals if anticholinergic symptoms are not reversed and cholinergic symptoms such as salivation, diaphoresis, bradycardia, lacrimation, urination, or defecation do not develop. When improvement occurs as a result of physostigmine, repeated doses of physostigmine at 30- to 60-minute intervals may be necessary, taking into account the fact metabolism of the offending xenobiotic is occurring and that subsequent doses might need to be lowered to avoid cholinergic symptoms. Another alternative for confirmed central anticholinergic symptoms expected to last many hours could be the administration of oral anticholinesterases such as donepezil, tacrine, or rivastigmine.^{37,116} They are noncompetitive reversible anticholinesterases, crossing the blood–brain barrier, with a longer duration of action than physostigmine. Continuous infusion of physostigmine has also been used successfully.¹²³ Benzodiazepines can be used, but excessive sedation with repetitive dosing can present undesirable effects. A dose of IV atropine should be available at the patient's bedside to treat cholinergic toxicity if it occurs (Antidotes in Depth: A9).

DECONGESTANTS

History and Epidemiology

History. Decongestants are xenobiotics acting on α -adrenergic receptors, producing vasoconstriction, decreasing edema of mucous membranes, and improving bronchiolar air movement. Ma Huang, the horsetail plant of the Red Emperor, was used in China for at least 2000 years before it was introduced into Western medicine in the late 19th century by Japanese researchers, who isolated the active ingredient from Ephedra plants. Ephedrine, the first xenobiotic of the sympathomimetic amine class to be used pharmaceutically, was first approved in 1926 by the Council of Pharmacy and Chemistry of the American Medical Association and was very popular in the treatment of asthma. Amphetamines were later synthesized to palliate to a shortage of Ephedra plant availability. Pseudoephedrine is a natural stereoisomer of ephedrine, and phenylephrine was introduced into clinical medicine in the 1930s and in 1949 replaced amphetamines in several compounds. Amphetamine was marketed as nasal decongestant (Benedrine Inhaler), which was eventually withdrawn in the 1960s because of widespread abuse.

Imidazoline decongestants, on the other hand, were derived from piperazine compounds while investigating their use as uric acid remedies to combat gout. As more imidazolines were synthesized for gout treatment, one of the compound, tolazoline, was found to have weak adrenergic blocking activity but its naphthyl analogue produced the reverse effect. Naphazoline was introduced in the 1940s as a decongestant. In the decades that followed, many imidazoline decongestants have been developed and tried for clinical use.¹⁵⁵

Epidemiology. Despite many years of widespread decongestant use in the United States and sporadic case reports of adverse effects, the magnitude and public health significance of adverse effects of this class of medications has only recently been appreciated. From 1991 to 2000, the FDA received 22 spontaneous reports of hemorrhagic stroke associated with phenylpropanolamine (PPA) use, and more than 30 other cases were reported in the literature since 1979. Statistical analysis published in 2000 confirmed that PPA is an independent risk factor for hemorrhagic stroke in women.^{23,83} The FDA recommended removal of PPA from the market in 2000 because of its association with intracranial hemorrhages. Many manufacturers took steps to remove or reformulate PPA-containing products well before the FDA rule-making process could be completed.

Fatality rates with decongestants suffer from the selection bias of case reporting as well as which xenobiotics are

examined. One study addressing the cause of death in children did not include imidazoline derivatives in their search strategy but these xenobiotics might have been included in part of the cases assessed.³⁴ Despite these biases, studies report a positive association between fatalities in children under 2 years of age and pseudoephedrine containing cough and cold medications resulting in high pseudoephedrine concentrations. Additional nonfatal adverse events also occurred in the children during that study period.³⁰

The majority of exposures are unintentional. NDPS data from 2011 report that only one in five cough and cold preparation exposures are intentional. In another study, postmortem analysis of unexpected infant fatalities yielded 10 deaths (ages 17 days–10 months) associated with the use of cough and cold medicines.¹³³ In response to new information and concerns, the FDA required labeling changes on medications aimed toward young children. In January 2012, the US Consumer Product Safety Commission proposed a new rule requiring child-resistant packaging for any nonprescription drug product containing the equivalent of 0.08 mg or more of an imidazoline in a single package.¹⁷⁰

Recreational use of ephedrine-containing stimulants is common, and combinations of these xenobiotics with caffeine or other herbs may be marketed as “herbal ecstasy” (Chap. 45). The sale of dietary supplements containing Ephedra, Ma Huang, *Sida cordifolia*, and pinellia (ephedrine alkaloids) was banned by the FDA in 2004 because of concerns over their cardiovascular effects, including hypertension, seizures, stroke, and dysrhythmias.⁵⁸ Companies challenged this rule in court, but it was finally upheld in 2006. Xenobiotics that contain chemically synthesized ephedrine, traditional Chinese herbal remedies, and herbal teas are not covered by the rule. Specific guidelines as to what constitutes a traditional remedy are still unclear and are currently under the FDA dietary supplement category.¹⁶⁹ Since then, many manufacturers have substituted ephedra by *Citrus aurantium*, whose principal ingredient is p-synephrine, and are marketing products as being “ephedra free.”¹³² The FDA ban on sales of ephedra had a significant reduction on the number of calls to poison centers and in the number of deaths.¹⁹³

Imidazoline abuse is also associated with strokes, although population incidences are not reported.⁹⁷ Of all the decongestants, only ephedrine and pseudoephedrine are on the list of xenobiotics monitored in competitive sports.¹⁸⁹ Phenylephrine and synephrine concentrations in urine are no longer monitored.

The Combat Methamphetamine Act signed into law in March 2006 limited methamphetamine precursor availability and additional precautions in pharmacies such as dispensing limits for nonprescription quantities, requesting personal identification, and storage of the medications behind pharmacy counters. This aimed to reduce potential harm associated with these xenobiotics by closing loopholes contained in the previous 2000 regulations.¹⁶⁸ The success of such stricter measures has yet to be quantified.^{107,115,135} Travel and Internet purchases being more common, it can also be expected that individuals might present with toxicity from xenobiotics not otherwise available in their countries of residence.

Pharmacology

Decongestants can be divided into two categories, sympathomimetic amines and imidazolines.

Sympathomimetics. The decongestants phenylephrine, pseudoephedrine, ephedrine, and PPA reduce nasal congestion by stimulating the α -adrenergic receptor sites on vascular smooth muscle⁷⁶ (Fig. 49–5). Both α_1 and α_2 receptor subtypes are linked to a Gq protein activating smooth muscle contraction via the IP₃ signal transduction pathway (Fig. 49–6). This process constricts dilated arterioles and reduces blood flow to engorged nasal vascular beds. The α -adrenergic mediated decrease in volume ultimately lowers resistance to airflow. Prolonged topical administration may produce rebound congestion upon discontinuation; possible mechanisms include desensitization of receptors and mucosal damage. This damage is caused by α_2 -adrenergic mediated arteriolar constriction resulting in decreased blood supply to the mucosa.

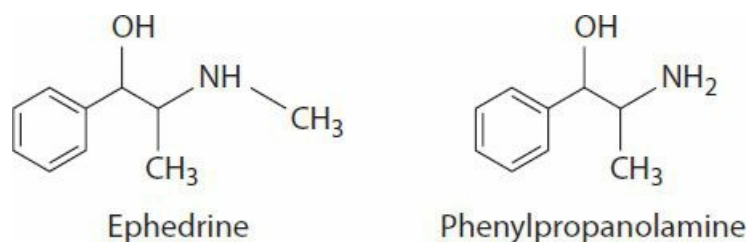


FIGURE 49–5. Structure of ephedrine and phenylpropanolamine decongestants.

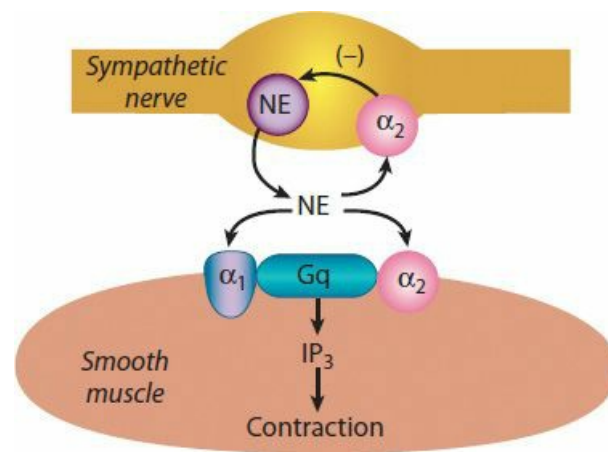


FIGURE 49–6. Mechanism of action of the α -adrenergic decongestants. The α -adrenergic decongestants stimulate postsynaptic α_1 - and α_2 -adrenergic receptors to increase the concentration of inositol triphosphate (IP₃), which mediates vasoconstriction of blood vessels and reduces swollen mucosa. The imidazoline decongestants also bind to postsynaptic α_2 -adrenergic receptors on these blood vessels.

Phenylephrine is a direct α_1 -adrenergic receptor agonist with very little β -adrenergic agonist activity at therapeutic doses. Pseudoephedrine and ephedrine are mixed-acting direct and indirect nonspecific $\alpha_{1,2}$ -adrenergic and $\beta_{1,2}$ -adrenergic receptor agonists. Pseudoephedrine is the D-isomer of ephedrine and has only up to 25% of the adrenergic receptor activity of ephedrine.⁴³ PPA is an $\alpha_{1,2}$ -adrenergic receptor stimulant devoid of β -adrenergic receptor activity. PPA can directly stimulate $\alpha_{1,2}$ -adrenergic receptors and can indirectly stimulate these receptors by causing norepinephrine release.

Imidazolines. The decongestant effects of the imidazoline class of xenobiotics results from their vasoconstrictive action as α -adrenergic agonists, with binding to α_2 -adrenergic receptors on blood vessels. In addition, these medications show high affinity for imidazoline receptors, which are located in the ventrolateral medulla and some peripheral tissues. Three classes of imidazoline receptors are recognized. I₁ receptors mediate the inhibitory actions of imidazolines xenobiotics to lower blood pressure. I₂ receptor is an important binding site for monoamine oxidase, and I₃ receptor regulates insulin secretion from pancreatic cells.⁶¹ The imidazoline receptor field is in expansion as more physiological roles are found for these receptors, namely cell proliferation, regulation of body fat, inflammation, pain and opioid addiction, appetite, epilepsy, and neuroprotection. Table 49–3 summarizes the pharmacologic and toxic effect of available decongestants.

TABLE 49–3. Effects of Decongestants

	<i>Therapeutic</i>	<i>Duration Action (hours)</i>	<i>Toxic</i>
Imidazolines			
Naphazoline	Nasal decongestant	8	Acute: hypertension followed by hypotension, bradycardia, hypoventilation, hypotonia, CNS depression, hallucinations Chronic: mydriasis from ocular administration
Oxymetazoline	Otorrhea reduction	6–7	
Tetrahydrozoline	Nasal decongestant	4–8	
Xylometazoline	Nasal decongestant	5–6	
Sympathomimetic			
Ephedrine	Nasal decongestant	3–5	Hypertension, tachycardia, insomnia, psychosis
Phenylephrine	Nasal decongestant, vasopressor	1	Hypertension, reflex bradycardia
Pseudoephedrine	Nasal decongestant	3–4	Hypertension, tachycardia, insomnia, psychosis

The imidazoline (I) category of direct sympathomimetic receptor agonists is generally reserved for topical application. The agonists in this class are used for their local effects in the nasal passages and the eyes. The more common medications include oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, and naphazoline hydrochloride (Fig. 49–7). The α_1 -adrenergic mediated vasoconstriction is complemented by an additive effect of preferential binding to α_2 -adrenergic receptors located on resistance vessels regulating blood flow. The imidazoline decongestants such as oxymetazoline and naphazoline are pure central and peripheral α_2 -adrenergic receptor agonists; tetrahydrozoline stimulates α_2 -adrenergic receptors and H_2 receptors. These medications are primarily used as nasal decongestants. Tetrahydrozoline is available without a prescription as an ophthalmic preparation to decrease conjunctival injection.

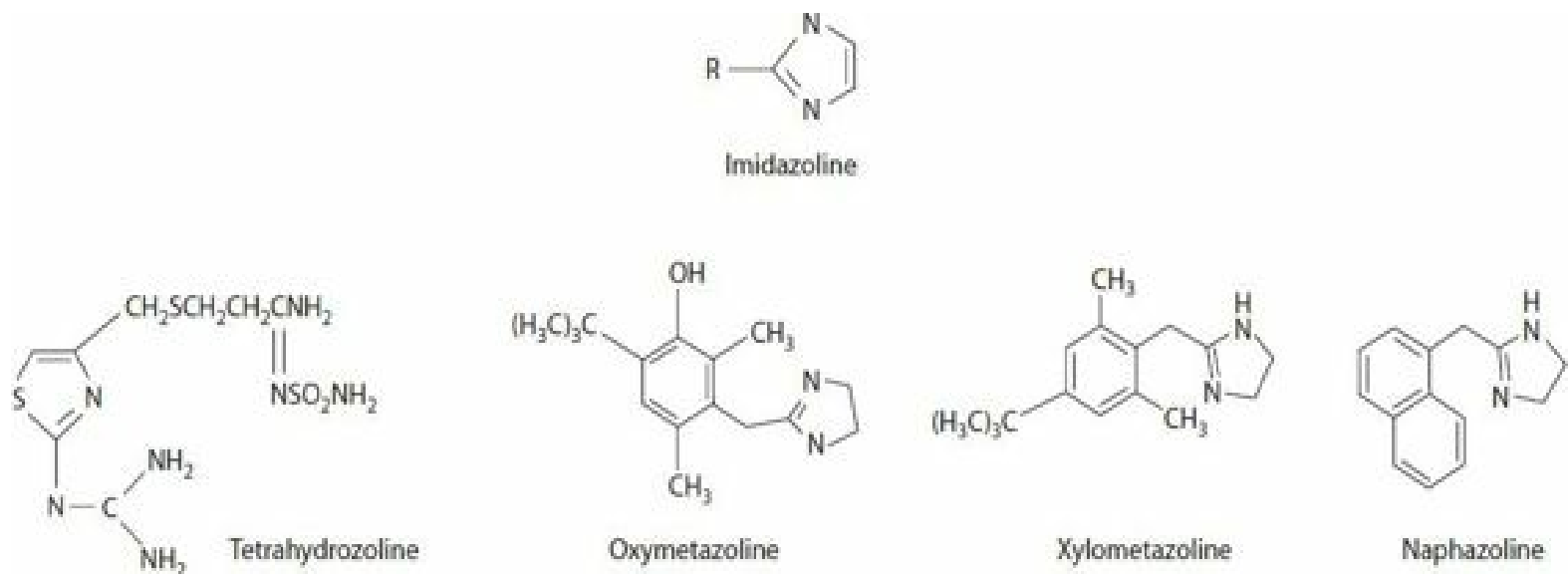


FIGURE 49–7. Structure of imidazoline and the imidazoline decongestants.

Selective α_2 -adrenergic receptor agonists acting on nasal veins for decongestant effect are being developed to minimize toxicity and adverse effects associated with current nonselective decongestants affecting nasal veins and arteries.³¹

Pharmacokinetics and Toxicokinetics

Sympathomimetics. Phenylephrine and other decongestants of this class are pharmacologically active after topical or oral administration. Absorption from the GI tract is rapid, with peak blood concentrations occurring within 2 to 4 hours of ingestion. They have variable hepatic metabolism via monoamine oxidase and mainly renal excretion. Children have shorter elimination half-lives of pseudoephedrine than adults at doses under 60 mg. Urinary elimination of pseudoephedrine is pH dependent.¹⁴⁸ Pseudoephedrine is excreted in breast milk, but use during lactation is considered acceptable.

Toxic effects can occur at therapeutic dosage in population with altered pharmacokinetics such as end-stage kidney disease. A meta-analysis found a dose–response relationship between blood pressure and pseudoephedrine in therapeutic situations.¹³⁶ Toxic symptoms are an extension of the adverse effects and follow a similar dose–response curve.

Imidazolines. The imidazolines are rapidly absorbed from the GI tract and mucous membranes. Despite their use for many decades, their metabolism has been poorly studied.¹⁰² Their elimination half-lives are from 2 to 4 hours. All imidazoline preparations have a relatively rapid onset of action, with 60% of maximum effectiveness occurring after only 20 minutes. Oxymetazoline is the only medication with duration of action more than 8 hours. The other preparations have an average duration of action of approximately 4 hours.

The toxicity of these medications follows a dose–response curve and accentuates the action on receptors. There is no information regarding modification of pharmacokinetics parameters in supratherapeutic conditions.

Pathophysiology

Sympathomimetic. Sympathomimetic decongestants cause their toxic effects via excessive stimulation of the adrenergic system and in effect produce signs and symptoms associated with the sympathomimetic toxidrome. Excessive vasoconstriction can result in end-organ damage to the brain, retina, heart, and kidneys.

Imidazolines. Imidazolines stimulate imidazoline receptors and produce a sympatholytic effect that in supratherapeutic conditions results in marked bradycardia and hypotension as well as a sympathomimetic syndrome.

Clinical Manifestations

Sympathomimetics. Ingestions of less than 1 mg/kg of pseudoephedrine in children have been reported to produce almost no toxicity and are generally managed conservatively without the need for hospital evaluation. A study of acute ingestions in children age 6 months to 5 years reported an absence of symptoms at doses lower than 120 mg and lethargy with doses above 360 mg.¹⁸⁶ After a decongestant overdose of this class, most patients present with a sympathomimetic syndrome with CNS stimulation, hypertension, tachycardia, or reflex bradycardia in response to pure α_1 -adrenergic agonist induced hypertension (**Chap. 76**). Approximately four to five times the recommended dose of pseudoephedrine may be required to cause hypertension.^{43,46} An increase in sinus dysrhythmias is reported in adults with ingestion of 120 mg of pseudoephedrine and moderate exercise.¹⁷ Headache was the most common initial symptom (39%) reported by patients who later developed severe toxicity from PPA. In 45 patients who developed hypertensive encephalopathy from PPA ingestion, 24 patients developed intracranial hemorrhages, 15 developed seizures, and six died.⁹³ Seizures, myocardial infarction, bradycardia, atrial and ventricular dysrhythmias, ischemic bowel infarction, and cerebral hemorrhages are

reported, even with therapeutic dosing.^{23,180} In a review of 500 reports of adverse reactions from patients who had ingested ephedrine and associated stimulants as dietary supplements, eight fatalities from myocardial infarction and cerebral hemorrhage were reported.¹²² Psychosis, agitation, and manic behavior have been reported with acute ingestion.

Imidazolines. When ingested, the imidazoline decongestants naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline are potent central and peripheral α_2 -adrenergic and imidazoline receptor agonists. In overdose, they can cause CNS depression, and initial brief hypertension followed by hypotension, bradycardia, and respiratory depression similar to clonidine (**Chap. 63**).⁶⁶ Children are particularly sensitive to the effects of the imidazoline decongestants. Cases of acute stroke have been reported in adults with naphazoline abuse.³²

Rare cases of cardiomyopathy with apical ballooning (Takotsubo) after large ingestion or chronic use of pseudoephedrine or oxymetazoline are reported.^{181,194} Acute respiratory distress syndrome from vasoconstriction of pulmonary vessels can also occur with both classes of decongestants. Reversible encephalopathy with bilateral posterior hemispheric edema on neuroimaging was reported after nonprescription use of pseudoephedrine albeit in a patient with an autoimmune disorder that might have been a predisposing factor.⁴⁴ Toxic effects usually resolve within 8 to 16 hours. However, they may persist for more than 24 hours if a sustained-release product is ingested.

Diagnostic Testing

The bedside diagnostic of decongestant toxicity is a clinical one. Sympathomimetic decongestants can cause false-positive results on several rapid urine drug screens by immunoassay to amphetamines.¹¹² Comprehensive blood or urine analysis screening test by LC/MS or GC/MS can be obtained for research purposes, in child abuse, or in forensic studies to determine the cause of death. They have no role in the immediate clinical management of poisoned patients.

Management

Patients presenting after an exposure to decongestants should be triaged promptly and brought to a monitored environment. A cardiac monitor should be attached to the patient and observed for dysrhythmias. IV access should be established and airway protection ensured. GI decontamination with AC should be done in large ingestions of pseudoephedrine if no contraindications are present. A retrospective study of xylometazoline ingestion in children reported toxicity above nasal or oral exposure exceeding 0.4 mg/kg body weight. Ingestions of more than 0.1 mg/kg of naphazoline or tetrahydrozoline produced severe toxicity in children. The decision to give AC in these instances should be made individually because liquid formulations are rapidly absorbed and might not be amenable to AC adsorption by the time of presentation.¹⁷⁴ AC administration may be beneficial several hours after ingestion of sustained-release decongestant preparations. More than one dose of AC may be considered to complete GI decontamination in massive ingestion of oral preparations, but multidose AC for enhanced elimination purposes has no role. WBI and renal-enhanced elimination techniques are not indicated.

Specific Treatment

Neurologic toxicity. Patients with extreme agitation, seizures, and psychosis should initially be treated with administration of oxygen and IV benzodiazepines, titrated upward to effect. A patient with a persisting headache, focal neurologic deficits, or abnormal neuropsychiatric examination findings after decongestant ingestion should be evaluated for cerebral hemorrhage by noncontrast head CT. If the timing of the imaging is delayed, reducing the sensitivity of this modality, subsequent lumbar puncture to exclude subarachnoid hemorrhage might be required.

Respiratory toxicity. Children presenting with respiratory depression from imidazoline decongestants have responded to naloxone. These case reports are too few to establish the efficacy of this therapy. Nevertheless, the use of naloxone in imidazoline toxicity seems to pose low risk in non-opioid-dependent patients. Many poison centers do recommend it.^{20,81}

Cardiovascular toxicity. Tachycardia, palpitations, and hypertension can occur in mild poisoning and usually respond to benzodiazepines. A patient who remains hypertensive or is believed to have chest pain of ischemic origin should be treated with phentolamine, an α -adrenergic antagonist, or nicardipine. Labetalol has been proposed and used in some reported cases; however, because of its different affinity for α - and β -adrenergic receptors depending on the route of administration, its use is not recommended when coronary vasospasm is suspected.¹⁷⁵ Labetalol is a more potent β - than α -adrenergic receptor blocker when given intravenously.^{94,108} β -Adrenergic antagonists should be avoided because of concern for unopposed α -adrenergic effects. An ECG is required, and any elevation of the ST segment warrants immediate consultation with a cardiologist.

Patients with ventricular dysrhythmias from sympathomimetic decongestants should be treated with standard doses of lidocaine or sodium bicarbonate. The evidence for efficacy of amiodarone in this setting is still lacking.^{41,130} PPA may cause hypertension with a reflex bradycardia and atrioventricular block that is responsive to standard doses of atropine. Atropine must be used with caution because it can cause a dangerous increase in blood pressure as the reflex bradycardia reverses. Therefore, a vasodilator such as phentolamine is preferred because the stimulus for the bradycardia is corrected with reversal of the hypertension.

Imidazoline-induced hypertension rarely requires therapy, but in the setting of symptomatic hypertension, a short-acting α -adrenergic antagonist such as phentolamine may be administered.¹⁸⁵ However, the hypertension is generally transient and

followed by hypotension. Initial antihypertensive therapy could exacerbate toxicity and should only be reserved for cases in which severe hypertension represents a true urgency for end-organ damage.

SUMMARY

- Anticholinergic toxicity is expected with H₁ antihistamines within a few hours of ingestion.
- Cardiotoxicity via sodium channel antagonism can be fatal and is treated with sodium bicarbonate.
- Physostigmine or other anticholinesterases can be used to reverse anticholinergic effects of H₁ antihistamines.
- H₂ antihistamines rarely result in symptoms or signs of toxicity.
- Decongestants used for recreational purposes can be ingested in doses producing toxic effects. The management is mainly supportive.
- Patients with abnormal mental status or seizures should be investigated to exclude intracranial hemorrhages.
- Topical imidazoline decongestants can produce toxicity.
- Sympathomimetic decongestants follow the same treatment guidelines as amphetamines and other agents of the sympathomimetic class.

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A9 ANTIDOTES IN DEPTH

Physostigmine Salicylate

Mary Ann Howland

INTRODUCTION

Physostigmine is a carbamate that reversibly inhibits cholinesterases in the peripheral nervous system and central nervous system (CNS).⁴⁶ The tertiary amine structure of physostigmine permits CNS penetration and differentiates it from neostigmine and pyridostigmine, which are quaternary amines that have limited ability to enter the CNS. The inhibition of cholinesterases prevents the metabolism of acetylcholine, allowing acetylcholine to accumulate and antagonize the antimuscarinic effects of xenobiotics such as atropine, scopolamine, and diphenhydramine.⁵⁴ Although physostigmine previously was used as an antagonist to the antimuscarinic effects of cyclic antidepressants and phenothiazines, this use is no longer recommended because of a poor risk-to-benefit ratio, given the potential for exacerbation of life-threatening cardiotoxicity. Similarly, physostigmine has a poor risk-to-benefit ratio in the management of presumed γ -hydroxybutyric acid (GHB) toxicity.^{4,48,55} Atypical antipsychotics have complex pharmacologic effects. Although some atypical antipsychotics, such as olanzapine, have significant antimuscarinic side effects, the benefit of treating these anticholinergic effects with physostigmine must be weighed by the potential risks of exacerbating cardiotoxicity.^{19,47,53}

HISTORY

The history of physostigmine dates to antiquity and the Efik people of Old Calabar in Nigeria.^{17,21,24,46} The chiefs in this area used a poisonous concoction made from the beans of an aquatic leguminous perennial plant found in the area to create a judicial test the esere ordeal. Esere was the word used to represent both the bean and the ritual used to test the innocence or guilt of an accused person. They also believed that the esere had the power to detect and kill persons practicing witchcraft. Supposedly, innocent persons quickly swallowed the poison, which resulted in immediate emesis.²⁴ Vomiting allowed the innocent to survive without therapy or to be given an antidote of excrement in water. The guilty, however, hesitated swallowing, leading to speculation that sublingual absorption led to severe systemic symptoms without the benefit of vomiting. These persons were noted to develop mouth fasciculations and died foaming at the mouth. Daniell, a British medical officer stationed in Calabar, brought samples of the bean and the plant back to England in 1840.²⁴ John Balfour, a professor of medicine and botany at the Edinburgh Medical School, characterized the plant, which became known as *Physostigma venenosum* Balfour (family Leguminosae), in 1857. The active alkaloid was isolated by Jobst and Hesse in 1864 and was named physostigmine. Independently, one year later Vee and Leven also isolated and named the active alkaloid eserine.

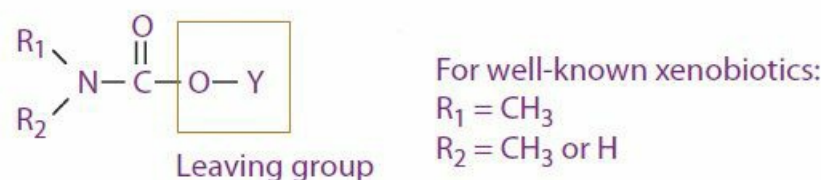
Christison performed the first toxicologic studies, including self-experimentation with increasing doses of the seed. Fraser, Christison's student and successor, originated the concept of antagonism from his experiments with physostigmine and atropine. Fraser plotted the dose relationships between the effects of atropine versus physostigmine on various organs such as the eye and the heart, demonstrating the antidotal effects of atropine for the lethal effects of physostigmine.¹⁷ Subsequent experiments with physostigmine led to the development of the theory of neurohumoral transmission.²¹ By the 1930s, physostigmine was used as a miotic for patients with glaucoma, a treatment for myasthenia gravis, for reversal of the paralytic effects of curare, and an antidote for atropine and insecticides.

PHARMACOLOGY

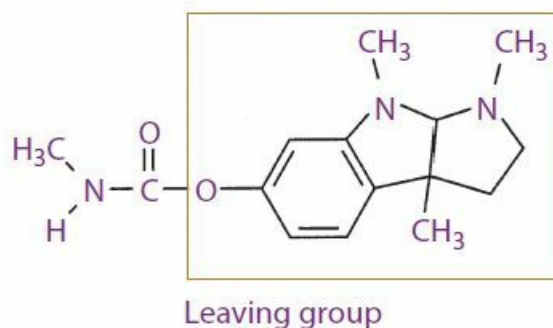
Chemistry

Physostigmine salicylate is the salicylate salt of physostigmine, a carbamate with a molecular weight of 275 Da. **Figure A9-1** shows the general formula for carbamate cholinesterase inhibitors and the chemical structures of physostigmine ($C_{15}H_{21}O_2N_3$), a tertiary amine, and neostigmine, a quaternary amine.

A. General formula for carbamate inhibitors



B. Physostigmine



C. Neostigmine

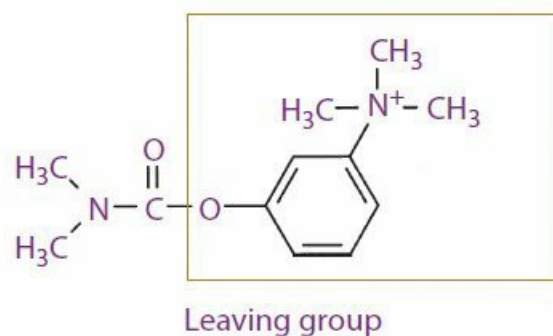


FIGURE A9–1 (A) General formula for carbamate cholinesterase inhibitors. (B) Structure of physostigmine. (C) Structure of neostigmine.

Mechanism of Action

Physostigmine is a reversible acetylcholinesterase inhibitor. Similar to acetylcholine, physostigmine is a substrate for the cholinesterases (choline ester hydrolases), erythrocyte acetylcholinesterase, and plasma cholinesterase. Both acetylcholine and physostigmine bind to cholinesterases to form a complex, from which part of the complex known as the leaving group (ie, choline for acetylcholine) is removed, and the remaining acetylated (for acetylcholine) or carbamoylated (for physostigmine) enzyme is hydrolyzed, regenerating the enzyme and freeing the acetate or carbamate groups, respectively (Figs. 113–2 and 113–3). For acetylcholine, the process is extremely rapid, with a turnover time of 150 msec. In contrast, the half-life for hydrolysis of the carbamoylated enzyme is 15 to 30 minutes.⁴⁶ The I_{50} (molar concentration that inhibits 50% of the enzyme) of physostigmine is 2.3×10^{-7} M for acetylcholinesterase, which is much weaker than for other carbamates at 1×10^{-10} M and many organic phosphorus compounds at 1×10^{-11} M.²² Only the S-isomer of physostigmine inhibits cholinesterases, with plasma cholinesterase slightly more sensitive than acetylcholinesterase.³ Newer xenobiotics used in the treatment of Alzheimer disease¹¹ show selectivity for the CNS and for acetylcholinesterase. This group includes tacrine, donepezil, and galantamine, which are reversible cholinesterase inhibitors, and rivastigmine, considered a pseudoirreversible or slowly reversible inhibitor. These pharmaceuticals and neostigmine²³ have undergone limited study for reversal of anticholinergic poisoning.^{11,23,27,40}

Pharmacokinetics and Pharmacodynamics

Physostigmine is poorly absorbed orally, with a bioavailability of less than 5% to 12%.^{1,37} Cholinesterases rapidly cleave the ester linkage resulting in very little unaltered physostigmine elimination in the urine. Pharmacokinetic parameters after intravenous (IV) administration of 1.5 mg over 60 minutes in nine patients with Alzheimer disease demonstrated the following: volume of distribution, 2.4 ± 0.6 L/kg; half-life, 16.4 ± 3.2 minutes; peak serum concentration, 3 ± 0.5 ng/mL; and clearance, 0.1 L/min/kg (7.7 L/min). There was a threefold interindividual variability in plasma physostigmine concentrations. Plasma cholinesterase concentrations demonstrated inhibition within two minutes of initiating the

physostigmine infusion. The half-life of plasma cholinesterase inhibition was 83.7 ± 5.2 minutes, with full recovery within 3 hours of termination of physostigmine infusion. The effects on plasma cholinesterase inhibition lasted approximately five times longer than the half-life of physostigmine.²⁶ All patients experienced varying degrees of diaphoresis, nausea, vomiting, headache, and generalized fatigue despite pretreatment with 2.5 mg of methscopolamine.^{2,26}

ROLE IN ANTIMUSCARINIC TOXICITY

Physostigmine was first used as an antidote in 1864 to counteract severe atropine poisoning.³³ Today its role is primarily in the treatment of antimuscarinic poisoning. More than 600 xenobiotics respond to physostigmine.¹² Anticholinergics fall into the categories of antimuscarinic (atropine, scopolamine, propantheline, benztropine, trihexyphenidyl), neuromuscular blockers (curare), and ganglionic blockers (trimethaphan). Other xenobiotics (antihistamines, antipsychotics, and antidepressants) have antimuscarinic properties that are not their primary therapeutic actions and are often considered adverse drug effects.

The clinical use of physostigmine has varied over time.⁴² Owing to its ability to cause CNS arousal, physostigmine was used in the 1970s to reverse the CNS effects of a large number of antimuscarinics and used inappropriately to treat toxicity from nonantimuscarinics.^{18,31,32,34,38} The success with regard to antimuscarinics is directly related to the inhibition of cholinesterase. The effects of physostigmine on nonantimuscarinic xenobiotics such as the benzodiazepines, opioids,^{28,39,51} and GHB^{4,48} result from either the direct action of acetylcholine on the reticular activating system or interdependence of central neurotransmitters.³⁴ Few serious adverse effects are reported.⁵⁰ However, asystole followed administration of physostigmine in two patients with tricyclic antidepressant (TCA) overdose.³⁵ This occurrence led to the realization that toxicity from TCA is complex and consists of more than just antimuscarinic effects.³⁵ Cyclic antidepressant induced sodium channel blockade causes myocardial depression, QRS interval prolongation, and ventricular dysrhythmias. Physostigmine augments vagal effects, thus contributing to decreased cardiac output and cardiac conduction defects. An extensive review of the literature concluded that the safety of physostigmine use for seizures or cardiotoxicity in the setting of cyclic antidepressant toxicity was difficult to predict and thus not recommended.⁴⁵ A reevaluation must conclude that the risks of physostigmine use for xenobiotics that are not primarily antimuscarinic often outweigh any benefit.

This analysis is certainly true with regard to GHB ([Chap. 83](#)) as well.⁴⁸ GHB is often used with other xenobiotics, and its effects are highly variable.⁵⁵ Recovery from GHB typically occurs spontaneously within several hours (16 minutes to 6 hours).^{7,8,14,29,48,49} Three patients in whom a presumptive diagnosis of GHB toxicity was made were treated with physostigmine.⁷ The three patients had an improved mental status within 5 to 15 minutes. One of these patients relapsed and then fully awakened 40 minutes later. This patient was incontinent of feces, an adverse effect likely caused by the physostigmine.⁷ All three of the patients were arousable before physostigmine use. Although anesthetic study of GHB in the 1970s is the rationale for current use, it is illogical in the care of those who illicitly use GHB.²⁰

However, in cases of antimuscarinic overdose, physostigmine use clearly is beneficial. A study of 52 patients showed that whereas physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively,⁶ benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium. A shorter time to recovery after agitation was observed in those treated with physostigmine. No significant differences between these groups with regard to side effects or length of stay were noted.⁶

Indications for physostigmine use include the presence of peripheral or central antimuscarinic manifestations without evidence of significant QRS or QT prolongation. Peripheral manifestations include dry mucosa, dry skin, flushed face, mydriasis, hyperthermia, decreased bowel sounds, urinary retention, and tachycardia. Central manifestations include agitation, delirium, hallucinations, seizures, and coma.^{16,30} The peripheral and central findings usually occur simultaneously. In the early phases of overdose, peripheral manifestations typically precede central manifestations, although the central manifestations often are more remarkable.^{1,5,9,13,15,22,41,44} The central findings may persist longer than the peripheral findings, particularly when a patient is recovering from an overdose of an antimuscarinic xenobiotic.

ADVERSE EFFECTS AND SAFETY ISSUES

An excess of physostigmine results in accumulation of acetylcholine at peripheral muscarinic receptors, nicotinic receptors (skeletal muscle, autonomic ganglia, adrenal glands), and CNS sites.²⁵ Muscarinic effects produce stimulation of smooth muscle and glandular secretions in the respiratory, gastrointestinal, and genitourinary tracts, and inhibition of contraction of most vascular smooth musculature. Nicotinic effects are stimulatory at low doses and depressant at high doses. For example, acetylcholine excess at the neuromuscular junction produces fasciculations followed by weakness and paralysis. Its effect on the CNS results in anxiety, dizziness, tremors, confusion, ataxia, coma, and seizures.²⁵ Electroencephalograms demonstrate asynchronous discharges followed by higher voltage discharges and a pattern similar to tonic-clonic

seizures.²⁵ The cardiovascular effects are dose dependent and directly related to the presence of the diverse muscarinic and nicotinic effects.²⁵ In addition to its inhibition of cholinesterase, physostigmine has a direct action on the nicotinic acetylcholine receptor ionic channel.⁴³

Physostigmine toxicity results when physostigmine is used in the absence of antimuscarinic toxicity or when excess doses are administered with regard to the antimuscarinic xenobiotic exposure. Patients overdosed with physostigmine should be managed with intensive supportive care, including mechanical ventilation if needed; IV atropine⁵² titrated to reverse bronchial secretions; and, rarely, pralidoxime to reverse skeletal muscle effects.¹⁰

Contraindications to physostigmine use include reactive airway disease, peripheral vascular disease, intestinal or bladder obstruction, intraventricular conduction defects, and atrioventricular block and in patients receiving therapeutic doses of choline esters and succinylcholine.^{36,37} It is unclear why the package insert also lists diabetes as a contraindication.³⁶ Drug interactions with cholinergic agonists (eg, ophthalmic pilocarpine); depolarizing neuromuscular blockers; or other anticholinesterases such as carbamates, organic phosphorous compounds, and pyridostigmine are expected to be additive when taken concomitantly with physostigmine. The actions of xenobiotics metabolized by plasma cholinesterases such as cocaine, succinylcholine, or mivacurium are expected to be prolonged.

Physostigmine salicylate injection contains sodium metabisulfite.³⁶ Sulfites may cause life-threatening anaphylactoid reactions in susceptible individuals.

PREGNANCY AND LACTATION

Physostigmine is US Food and Drug Administration pregnancy category C. Little information is available regarding the effects of physostigmine in pregnancy. Transient muscular weakness occurred in 10% to 20% of neonates whose mothers received anticholinesterase treatment for myasthenia gravis.³⁷ Physostigmine should only be given when the benefit clearly outweighs the risk. Safety in lactation has not been established.

DOSING AND ADMINISTRATION

The dose of physostigmine is 1 to 2 mg in adults and 0.02 mg/kg (maximum, 0.5 mg) in children intravenously infused over at least 5 minutes. The onset of action usually is within minutes.²² The dose can be repeated after 10 to 15 minutes if an adequate response is not achieved and muscarinic effects are not noted. Rapid administration may cause bradycardia, hypersalivation leading to respiratory difficulty, and seizures. Although the half-life of physostigmine is approximately 16 minutes, its duration of action usually is much longer (often >1 hour) and is directly related to the duration of cholinesterase inhibition.² After reversal of anticholinergic symptoms, additional doses may be required if clinical relapse occurs. The effective dose depends on the ingested dose and duration of action of the antimuscarinic xenobiotic. Although a total of 4 mg in divided doses usually is sufficient in most clinical situations,¹⁶ significant interindividual variability exists. Atropine should be available at the bedside and titrated to effect should excessive cholinergic toxicity develop. A dose of atropine administered at half the physostigmine dose is recommended.

FORMULATION AND ACQUISITION

Physostigmine is available in 2-mL ampules containing 1 mg/mL of physostigmine salicylate. The vehicle contains sodium metabisulfite and benzyl alcohol.³⁶

SUMMARY

- Physostigmine is used extensively in the fields of anesthesiology, emergency medicine, and medical toxicology.
- The only evidence-based use of physostigmine is for the management of patients with an antimuscarinic syndrome, particularly those without cardiovascular compromise who have an agitated delirium and a normal QRS duration.
- In these patients, physostigmine has an excellent risk-to-benefit profile.

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50 CHEMOTHERAPEUTICS OVERVIEW

Richard Y. Wang

Although overdoses of chemotherapeutics are infrequent, these events are of greater consequence than overdoses of many other xenobiotics because most chemotherapeutics have narrow therapeutic indices. This is evident from survey data from poison centers in the United States. From 1988 to 2010, the median annual number of people exposed to chemotherapeutics reported to US poison centers was about 1000. In the past 5 years, the number of annual exposures to these chemotherapeutics has steadily increased to slightly over 1500 (Chap. 136). These exposures represent about one per 1000 cases of exposures to pharmaceuticals, or one per 2000 cases of all exposures annually reported to US poison centers. Approximately two-thirds of the people exposed to chemotherapeutics in these reports were adults, one-fourth of the group was young children, and the remainder was adolescents. The annual trend for the proportion of exposures among adults and children appears to have remained at approximately 70% and 25%, respectively, from 2001 to 2010. Children and adolescents between the ages of 6 and 19 years accounted for approximately 7% of the population annually exposed, and this frequency did not change between these years. Although these differences among age groups can represent the incidence of cancer in these populations, further analysis is warranted to better define the reasons for these observations because they are not apparent.

Among single exposures to chemotherapeutics reported to US poison centers from 2006 to 2010, the annual percentage of unintentional exposures was slightly above 97%, and the annual percentage of exposures resulting in moderate or major severity in toxicity remained at approximately 6%. The mortality rate was about two per 1000 single exposures in this same period. These observations are consistent with a hospital-based survey and can be attributed to the increased toxicity of these chemotherapeutics.²⁴ The prevalence of the exposure to chemotherapeutics is expected to continue to increase because of the increased availability of oral formulations⁷⁶ and their expanding therapeutic indications.

MEDICATION ERRORS WITH CHEMOTHERAPEUTICS

The importance of understanding the occurrence of medication errors is to prevent future events of a similar nature. Fortunately, medical errors related to the use of chemotherapeutics occur infrequently. The reported medical error rate for the chemotherapeutics varies from 0.04% to 5.5% based on data from US medical centers,^{13,22,24,71} although the true prevalence of these events remains unknown. The rates reported by international medical centers are similar.^{25,41,43,44,53,66} These reported estimates vary by the clinical setting (hospital vs. outpatient) and the patient population (adults vs. children). The outpatient setting and the treatment of children present several unique challenges to the health care system, including increased volumes, decreased control measures, increased workload, and unique dosing schemes such as dose based on body surface area.^{24,69} In a satellite pharmacy setting, two of the potentially lethal overdoses of cisplatin were a result of errors in duration of administration (100 mg/m² for 3–4 consecutive days instead of for 1 day).¹⁹ Lack of health care provider familiarity with the chemotherapeutics and dosing errors are major causes of these events. Chemotherapeutics used frequently, recently added to the formulary, and used in complex protocols can contribute to these errors.⁵²

The factors contributing to the occurrence of medication errors with chemotherapeutics and the measures identified to prevent these events, such as centralization of services (medical oncology, pharmaceutical) and the use of standardized protocols, are similar to those for other pharmaceuticals, and they are discussed elsewhere (Chap. 140).^{6,8,66} The centralization of services can reduce chemotherapeutic errors by 25% and the institution of information technology (IT), such as electronic prescribing protocols, production, and bedside scanning of barcodes for proper identification, can reduce medication error by 10%,⁸ although drug labeling errors continue to occur.^{41,44} Additional strategies to reduce these errors include tracking and following up on errors and increased patient education and participation.⁶⁰ Many of these preventive efforts can also improve worker safety by reducing occupational exposures. As more chemotherapeutics become available and their indications broaden, unintentional exposures and unintended dosing regimens will likely increase in number and frequency. The adoption of safety standards for the administration can limit these errors.³¹

Aside from unintentional exposures, additional factors leading to increased toxicity associated with chemotherapeutics include age, sex, comorbidities, compromised host state such as ascites, and diminished kidney and liver functions. Diminished hepatic clearance caused by altered enzyme expression can be accounted for by age, sex, smoking status, and

the concurrent use of other xenobiotics. Differences in sex can contribute to varying pharmacokinetic parameters, including bioavailability, distribution, metabolism, and elimination. Women treated with 5-fluorouracil (5-FU) for colon cancer had a twofold higher frequency of drug-related toxicity than men.⁷³ The manifestations included leukopenia, diarrhea, and stomatitis. Although the basis for this difference in toxicity between sexes is not known, it may result from a decreased 5-FU clearance in women.⁷⁹ Dihydropyrimidine dehydrogenase (DPD) inactivates more than 80% of fluorouracil by metabolizing it to 5-fluorodihydrouracil, and low or absent activity of this enzyme can result in hematologic and gastrointestinal (GI) toxicity from treatment with 5-FU or its prodrug capecitabine.

At an individual level, genetic polymorphisms can contribute to differences in xenobiotic response with resultant toxicity by altering targets, transporters, and enzyme complexes. Such variations have been characterized for several enzymes that are involved in the metabolism of chemotherapeutics. Two examples of this type of toxicity include irinotecan used for the treatment of metastatic colon cancer and amonafide used for the investigational treatment of secondary acute myeloid leukemia. Irinotecan is a topoisomerase I inhibitor that works through its active metabolite, SN-38, which can cause diarrhea and neutropenia at elevated concentrations.⁷⁵ A genetic variant of uridine diphosphate glucuronosyltransferase (UGT1A1) containing the T7 allele glucuronidates SN-38 at a slower rate than other variants, which results in increased SN-38 concentrations and increased toxicity.^{3,30} Amonafide, which is a topoisomerase II inhibitor, and its active metabolite, N-acetyl amonafide is formed by N-acetyltransferase 2 (NAT2). Patients capable of “rapid acetylation” have a genetic variation of NAT2 and are more likely to develop myelotoxicity than are slow acetylators.⁵⁴ There are additional polymorphisms in metabolism associated with chemotherapeutics.²¹ however, further work is necessary to define their clinical significance. Because of the narrow therapeutic index of the chemotherapeutics, the significance of such findings demonstrates the benefit of individual drug monitoring and genetic screening for use to maximize the therapeutic efficacy while limiting host toxicity.

CLASSES OF CHEMOTHERAPEUTICS

Most chemotherapeutics can be grouped into one of five categories: alkylating agents, antimetabolites, antimitotics, antibiotics, and platinum-based complexes (Table 50–1). Some new chemotherapeutics target specific proteins located on the cell membrane, such as growth factor receptors, to inhibit the proliferation of tumor cells^{36,55} (Fig. 50–1). They can be categorized as monoclonal antibodies (MABs) and protein kinase inhibitors (NIBs) based on their therapeutic approach. The antimetabolites are grouped by the substrates with which they interfere. Methotrexate (MTX) is a folate antagonist. Other xenobiotics with similar mechanisms but lesser toxicity include trimethoprim and pyrimethamine. The antimitotics are plant alkaloids, and they exert toxic effects by interrupting microtubule assembly. Others are naturally derived and include the antibiotics and the enzyme L-asparaginase, which can be isolated from bacteria. The alkylating agents are more commonly used than other antineoplastics and cause covalent binding to nucleic acids, which inhibits DNA activity (replication and transcription) (Fig. 50–2). The more notable chemotherapeutics in this class, including those with similar activity, are the nitrogen mustards, nitrosoureas, and platinum-based complexes. The antimetabolites and the alkylating agents are cell-cycle active, meaning that they only affect cells undergoing cell division. Some xenobiotics are phase specific; that is, they affect the cell only at a period during cell division. The cell cycle consists of the S phase (DNA replication) and the M phase (mitosis). DNA regulation and chromosomal separation occur during mitosis. Vincristine is M-phase specific, and cytarabine is S-phase specific in their sites of action. Other antineoplastics inhibit topoisomerase, which is necessary for DNA replication because it allows for reversible DNA strand breaks.

TABLE 50–1. Classification of Chemotherapeutics, Their Adverse Effects and Antidotal Therapy

<i>Class</i>	<i>Chemotherapeutic</i>	<i>Adverse Effects</i>	<i>Overdose</i>	<i>Antidotes</i>
Alkylating agents	Busulphan	Hyperpigmentation, pulmonary fibrosis, hyperuricemia	Myelosuppression	
	Dacarbazine	Hypotension, hepatocellular toxicity, influenzalike syndrome		
	Nitrogen mustards Chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan	Hemorrhagic cystitis, encephalopathy, pulmonary fibrosis	Seizures, encephalopathy, myocardial necrosis, kidney injury, hyponatremia	MESNA; methylene blue
	Nitrosoureas Bendamustine, carmustine, lomustine, semustine, streptozocin	Pulmonary fibrosis, hepatocellular toxicity, kidney injury	Myelosuppression (delayed onset and prolonged duration)	
	Procarbazine	MAOI activity		
	Temozolomide		Myelosuppression	
Antibiotics	Anthracycline Daunorubicin, doxorubicin, epirubicin, idarubicin	Dilated cardiomyopathy	Dysrhythmias, cardiomyopathy, CHF, myelosuppression	Dexrazoxane
	Bleomycin	Pulmonary fibrosis		
	Dactinomycin	Hepatocellular toxicity		
	Mitomycin C	Hemolytic uremic syndrome		
	Mitoxantrone	Dilated cardiomyopathy	Cardiomyopathy, CHF	None
Antimetabolites	Methotrexate	Mucositis, nausea, diarrhea, hepatocellular toxicity	Mucositis, myelosuppression, kidney injury	Leucovorin (folinic acid); Glucarpidase (carboxypeptidase G2)
	Purine analogs Fludarabine Mercaptopurine	Encephalopathy, muscle weakness Hyperuricemia, pancreatitis, cholestasis	Myelosuppression, hepatocellular toxicity	
	Pentostatin Thioguanine	Hepatocellular toxicity Hyperuricemia		
	Pyrimidine analogs Cytarabine	Acute respiratory distress syndrome, neuropathy, cerebellar ataxia		
	Fluorouracil, capecitabine	Cardiogenic shock, cardiomyopathy, cerebellar ataxia, diarrhea, mucositis, myelosuppression, neuropathy	Mucositis, myelosuppression, myocardial ischemia, cardiac conduction disorders	Uridine triacetate
Antimitotics	Taxenes Docetaxel, paclitaxel	GI perforation, peripheral neuropathy, dysrhythmias		
	Vinca alkaloids Vinblastine, vincristine, vindesine	Peripheral neuropathy, hyponatremia (SIADH)	Encephalopathy, seizures, autonomic instability, paralytic ileus, myelosuppression	
Enzyme	L-Asparaginase	Hypersensitivity, pancreatitis, coagulopathy	No reports	None
Monoclonal antibodies	Many: gemtuzomab, trastuzumab	Hypersensitivity specific to the site of action and infection	No reports	None
Platinum-based complexes	Cisplatin, carboplatin, oxaliplatin	Kidney injury, peripheral neuropathy, hypomagnesemia, hypocalcemia, hyponatremia, ototoxicity, myelosuppression	Seizures, encephalopathy, ototoxicity, retinal toxicity, myelosuppression, peripheral neuropathy	Amifostine; thiosulfate

Protein kinase inhibitors	Many: Gefitinib, sorafenib, erlotinib	GI (nausea, diarrhea), acneiform rash (folliculitis), nail fragility, and xerosis (EGFR inhibitor), interstitial lung disease (erlotinib, gefitinib), hypertension (inhibitors of VEGF and PDGF), hypothyroidism (sunitinib), and infection	Nausea, vomiting, facial rash, edema	None
Topoisomerase inhibitors	Camptothecins Irinotecan Topotecan Epipodophyllotoxins Etoposide, teniposide	Neutropenia, mucositis, diarrhea, early onset cholinergic syndrome (irinotecan) CHF, hypotension	Myelosuppression	None

CHF = congestive heart failure; EGFR = epidermal growth factor receptor; GI = gastrointestinal; MAOI = monoamine oxidase inhibitor; MESNA = mercaptoethane sulfonate; PDGF = platelet-derived growth factor; SIADH = syndrome of inappropriate antidiuretic hormone secretion; VEGF = vascular endothelial growth factor.

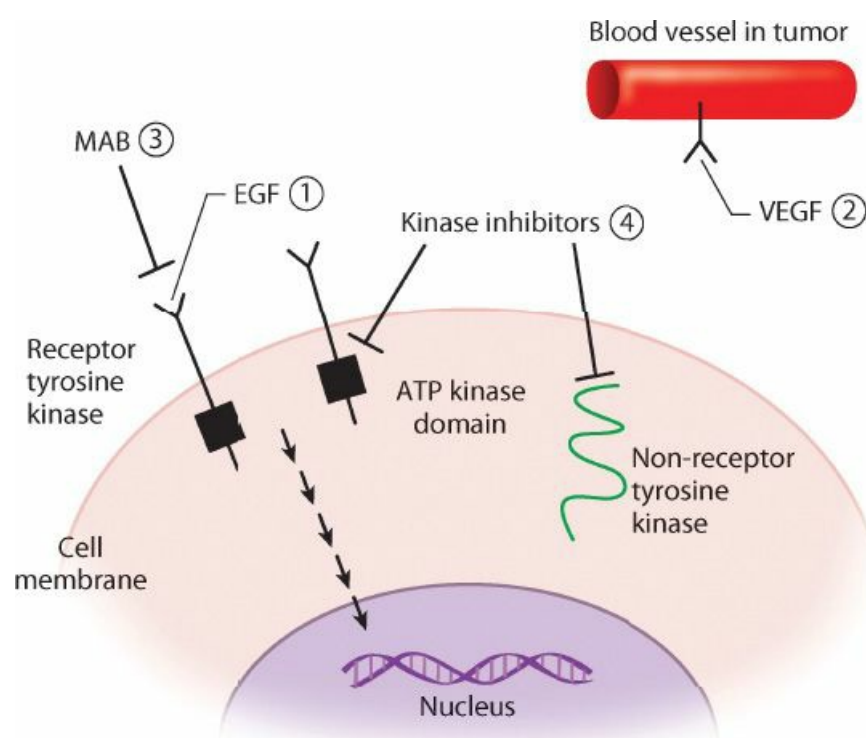


FIGURE 50–1. Sites of action of selected targeted agents. Tyrosine kinases initiate signal transduction pathways and production of transcription factors that are responsible for cellular processes, including proliferation, survival, angiogenesis, and progression. Growth factors, such as endothelial growth factor (EGF) and vascular endothelial growth factor (VEGF), bind and activate transmembrane tyrosine kinases by causing receptor dimerization and phosphorylation (1). VEGF promotes endothelial cell mitogenesis and migration, which leads to vascular proliferation (2). Tyrosine kinases can be inhibited by monoclonal antibody (MAB) binding at the cell surface receptor site (3) or by kinase inhibitors at the adenosine triphosphate (ATP) binding site or substrate-binding site or by causing a change in the conformation of the enzyme (NIB) (4).

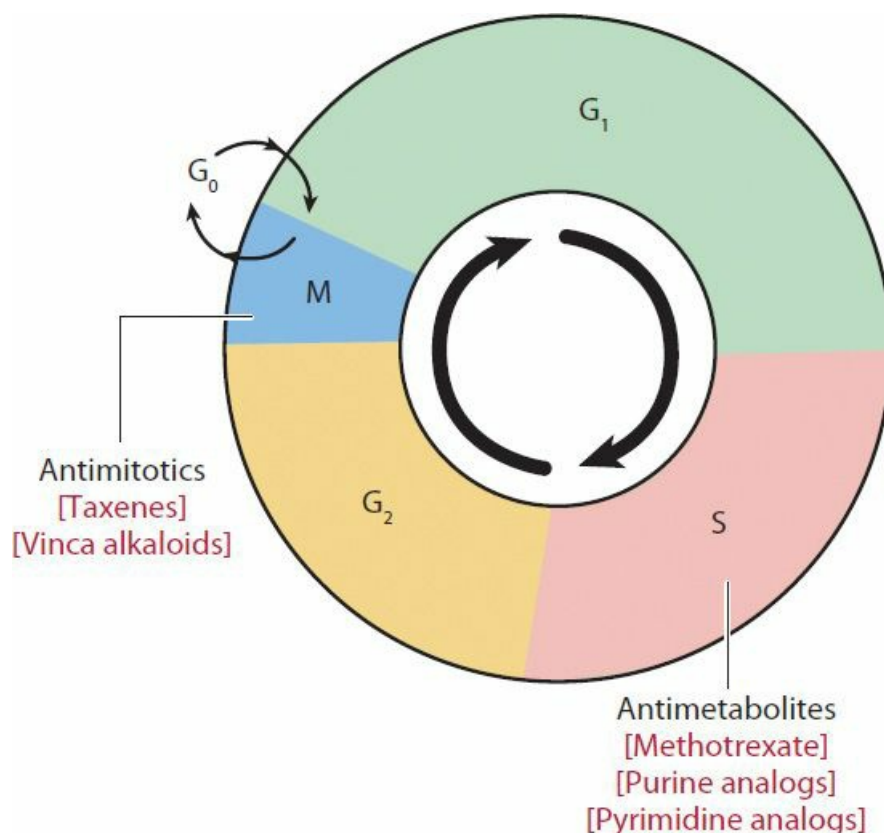


FIGURE 50–2. Selected classes of cell cycle phase-specific chemotherapeutics and their sites of action in the cell cycle. Arrows represent the progression of the cell cycle by phases. G₀ (resting), G₁ (gap 1), G₂ (gap 2), M (mitosis), and S (DNA synthesis).

Because the majority of the cases of chemotherapeutics overdoses involve MTX, vincristine, mitoxantrone (related to the anthracyclines),⁶⁴ nitrogen mustards, and cisplatin, the discussion in this section focuses on these xenobiotics (see [Chap. 36](#) for a discussion of the Vinca alkaloids).

MECHANISMS OF ACTION

The mechanisms responsible for the cytotoxic effects of the antineoplastics are the disruption of cellular replication and proliferation, which impairs DNA function by causing strand breaks, inhibiting strand relaxation, and serving as inhibitory analogs of essential cofactors and nitrogenous bases of nucleic acids. For example, alkylating agents form reactive intermediates that covalently bind to nitrogenous bases on the DNA structure, which leads to the formation of strand breaks and mispairings. Cross-linkages between strands can occur with the nitrogen mustards because they contain two reactive chloroethyl side chains. The planar anthracycline antibiotics can intercalate with DNA to alter replication and cause strand breaks through oxidative damage induced by a reactive semiquinone intermediate. DNA strand relaxation can be impaired by topoisomerase inhibitors, such as topotecan. Topotecan is derived from camptothecin, which is isolated from the tree *Camptotheca acuminata*. Single methyl transfer reactions and base pairings are essential activities during DNA synthesis that are affected by the antimetabolites, which include structural analogs to folate, pyrimidines, and purines.

Recent cancer therapy includes chemotherapeutics that limit cellular proliferation by inhibiting growth factor receptor activation and enhancing cell lysis by antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. MABs to tumor cell surface antigens, such as CD20, CD52, and CD33, and the C1q complement are used to direct host defense mechanisms or deliver chemotherapeutics to these sites. For example, gemtuzumab ozogamicin is an antibody conjugated to the antibiotic calicheamicin, and it is directed at CD33-positive leukemic blast cells. Other antibody conjugates include radioactive isotopes and diphtheria toxin. In addition to these antigens, MABs against tumor growth factor receptors are available.

Tumor growth factors promote cell progression, proliferation, and differentiation by angiogenesis. Their receptors located at the cell membrane are characterized for certain tumors, such as epidermal growth factor receptor (EGFR) (lung, kidney, and GI tumors) and human epidermal growth factor receptor 2 (HER2) (breast). Vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) are active in angiogenesis. Inactivation of these receptors can be accomplished with therapeutic MABs and protein kinase inhibitors. MABs prevent the activation of these receptors by inhibiting substrate binding to the receptor located at the extracellular surface. Kinase inhibitors are considered to be small molecule therapeutics that impair the adenosine triphosphate (ATP) activation of growth factor receptors, tyrosine kinase inhibitors, and certain signal transduction proteins responsible for tumor cell division, such as serine/threonine kinase inhibitors. The disruption of the proliferation of keratinocytes and GI mucosa and epithelial cells at

these tissue sites can account for the anticipated toxic effects from the use of MABs and kinase inhibitors directed at EGFR. The therapeutic use of the protein kinase inhibitors of VEGFR and PDGFR, such as sunitib and sorafenib, is associated with hypertension, which can be caused by endothelial dysfunction and diminished microvascular regrowth.

These MABs are derivitized from human and chimeric (human and murine) sources, which contribute to the toxicity. Immunologic responses to the presence of foreign proteins include rigors, nausea, vomiting, and rashes. Some organ-specific effects of varying antibodies include bone marrow, skin (via EGFR), kidney (hypomagnesemia via EGFR), GI (via EGFR), and cardiac (via HER2, trastuzumab).

MANIFESTATIONS OF TOXICITY

The chemotherapeutics are known for their toxicity to cells with a high level of mitotic activity, such as malignant cells. This characteristic feature accounts for their common clinical manifestations of toxicity, including mucositis, alopecia, and bone marrow suppression. They can also cause protracted vomiting because of their ability to stimulate the chemoreceptor trigger zone in the medulla by vagal and sympathetic pathways either directly or indirectly through the GI tract. The likelihood for vomiting depends on the dose, the route of administration, and the type of antineoplastic. Although the onset of emesis typically occurs within 6 hours and lasts for 24 hours, late onset emesis can occur with cisplatin cyclophosphamide, carboplatin, and doxorubicin. The time of onset for the other manifestations is typically in the first week after treatment, with mucositis preceding leukopenia, which varies depending on the antineoplastic and is dose dependent. For example, the nadir and recovery for neutropenia are about 7 to 13 days and 21 to 24 days, respectively, but more prolonged delays to recovery occur for busulfan and carmustine given at higher doses. Anthracyclines and platinum-based complexes are likely to cause severe neutropenia, and MTX, 5-FU, bleomycin, and doxorubicin are likely to cause mucositis and severe salt and water depletion because of the amount of GI fluid loss from diarrhea and vomiting. Death usually results from overwhelming sepsis as enteric organisms traverse compromised GI epithelium, enter the bloodstream, and attack a host with neutropenia from bone marrow suppression. Some of the unique manifestations for certain chemotherapeutics involve the skin, heart, central and peripheral nervous systems, and kidneys.

Dermatologic manifestations caused by chemotherapeutics can be due to hypersensitivity reactions, extravasations (Special Considerations: SC4), or cytotoxicity from the use of tyrosine kinase inhibitors for the EGFR (eg, gefitinib, erlotinib).⁸¹ Patients commonly develop pruritus, xerosis, erythema, and folliculitis or an acneiform rash that can desquamate during therapy. These reactions develop within the first week of treatment and continue for several weeks. The folliculitis is a dose-dependent response and typically resolves within weeks after treatment. The dermal response appears to be more intense with MABs than with the kinase inhibitors for the EGFR. The other kinase inhibitors (ie, sunitinib, sorafenib) involved with growth factor receptors for angiogenesis (ie, VEGFR, PDGFR) are associated with a “hand–foot” skin reaction, which is a painful erythema and edema of the palm and sole that leads to desquamation.

The cardiovascular manifestations of toxicity depend on the antineoplastic, and the common ones include congestive heart failure (CHF), dysrhythmias, and hypertension. The anthracyclines, cyclophosphamide, 5-FU, and arsenic trioxide can cause cardiac toxicity (Table 50–2). Although the anthracyclines are known for their late-onset cardiomyopathy, they can also cause acute cardiac manifestations. Those occurring within 24 hours of therapy include dysrhythmias, ST segment and T wave changes on electrocardiogram (ECG), diminished left ventricular ejection fraction (LVEF) leading to CHF, pericarditis, myocarditis, and sudden death.^{9,61,62,69,80} Arsenic trioxide (As_2O_3) used for the treatment of acute promyelocytic leukemia can cause dose-dependent prolongation of the QT interval and ventricular tachydysrhythmias, including torsade de pointes, during the course of treatment.⁵ Inorganic arsenic inhibits the slow (I_{Ks}) and rapid (I_{Kr}) delayed rectifier K^+ channels of ventricular myocytes, which impairs the efflux of potassium ions during ventricular repolarization (Chaps. 16 and 89). These ECG changes tend to develop after several days of drug therapy, reverse upon discontinuation of the drug, and occur more frequently during intravenous (IV) than oral therapy because of the increased blood concentration of arsenic from the IV route of administration.⁶⁵ Patients at increased risk for cardiac conduction disorders during arsenic trioxide therapy include those with hypokalemia and hypomagnesemia, taking medications that prolong the QT interval, and with underlying cardiac conduction disorders. Myocardial ischemia leading to cardiogenic shock can occur from the high-dose infusion of 5-FU.⁷⁴ The metabolite fluoroacetate⁴ is purported to cause endothelial damage and result in vasospasm.²⁸ Normalization of ECG findings, including diminished QRS voltage and abnormal ventricular wall motion, are expected by 48 hours after the discontinuation of infusion therapy.¹⁵ Within a few days of exposure, cyclophosphamide can cause CHF, hemorrhagic pericarditis, tamponade, and death at high doses from therapy during bone marrow transplant or the overdose setting. The cardiomyopathy from anthracyclines involves biventricular failure, and its onset is variable, from months to years. Although this period is usually 1 to 4 months, it tends to be longer for the less toxic anthracycline analogs.^{26,32,66} Trastuzumab is associated with a slight increase incidence of CHF from diminished LVEF among patients previously treated with anthracyclines or with underlying heart disease.²⁷ A potential mechanism for the enhanced cardiac toxicity from the drug interaction is that trastuzumab disrupts the HER2-neuregulin compensatory response by the heart to the exposure to anthracyclines.¹⁶ Lapatinib is another antineoplastic targeting HER2,

but by inhibiting phosphorylation at the tyrosine kinase domain, and it can lead to a slight decrease in LVEF.⁵⁰

TABLE 50–2. Cardiovascular Manifestations of Toxicity of Selected Chemotherapeutics

<i>Chemotherapeutic</i>	<i>Time of Onset since Treatment</i>	<i>Manifestation</i>
Anthracycline	<24 hours	Dysrhythmias, ST-segment and T-wave changes on ECG; diminished LVEF leading to CHF, pericarditis, myocarditis, and sudden death
	Months to years, typically at 1–4 months	Dilated cardiomyopathy
Arsenic trioxide	Days	Prolongation of QT interval on ECG leading to ventricular tachydysrhythmia (torsade de pointes)
Cyclophosphamide	Days	CHF, hemorrhagic pericarditis, tamponade, and death
5-Fluorouracil	Hours to days	Myocardial ischemia, cardiac conduction disorders, and cardiogenic shock

CHF = congestive heart failure; ECG = electrocardiogram; LVEF = left ventricular ejection fraction.

The neurologic toxicities of chemotherapeutics include central and peripheral manifestations. The acute manifestations of toxicity include both alterations in mental status and seizures, which occur from the systemic administration of high doses of nitrogen mustards (cyclophosphamide, ifosfamide, and chlorambucil), nitrosureas (lomustine), MTX, and vincristine. The inappropriate intrathecal administration of vincristine and MTX can cause central nervous system toxicity (Special Considerations: SC3). Patients with prior seizure disorders, delayed drug clearance, and altered drug pharmacokinetics (eg, nephrotic syndrome)⁵⁸ are at increased risk for seizures. L-Asparaginase, 5-FU, and procarbazine are associated with alterations in mental status.⁷⁷ Cerebellar ataxia is described in 5% of patients treated with 5-FU,⁵¹ and high-frequency ototoxicity can occur with cisplatin toxicity. The delayed onset manifestations of neurotoxicity from chemotherapeutics include leukoencephalopathy and peripheral neuropathies. Leukoencephalopathy from MTX typically presents as a delayed onset of behavioral and progressive dementia and is irreversible. Peripheral neuropathy involving both sensory and motor findings is seen with the Vinca alkaloids (vincristine) and bortezomib, but only sensory involvement is noted with cisplatin and paclitaxel.³⁹

Kidney failure from tubulointerstitial pathology can occur from MTX, cisplatin, ifosfamide, or nitrosureas in a dose-dependent manner. The nitrosurea semustine can cause glomerular injury leading to sclerosis. Kidney damage is attributed to the formation of insoluble intratubular precipitates of drug metabolites (7-OH MTX, the metabolite of MTX) or reactive intermediates (cisplatin, nitrosureas) that lead to cell death. The nitrosureas can also form isocyanate, which can impair DNA repair enzymes and lead to irreversible kidney damage.³⁸ The onset, severity, and reversibility of renal toxicity depend on the administered dose and the antineoplastic. For example, streptozocin is more nephrotoxic than the other nitrosureas, semustine, lomustine, and carmustine. Patients at increased risk for worsening renal function from these chemotherapeutics include those with prior kidney disease, increased age, salt and water depletion, hypotension, and concomitant use of nephrotoxic xenobiotics, such as aminoglycosides. Young children (younger than 5 years old) appear to

be more vulnerable to ifosfamide-induced proximal tubular toxicity leading to urinary loss of phosphate and bicarbonate than older patients.^{42,70} Also, patients with third-space fluid, such as ascites and pleural effusions, and aciduria are at increased risk for MTX-induced acute kidney injury (AKI) because of the prolonged half-life of the drug and the increased likelihood of the formation of insoluble precipitates in the renal tubules at a low urinary pH. The AKI from MTX, cisplatin, and streptozocin typically presents within 1 to 2 weeks, unlike in patients treated with semustine, who can present with renal compromise months to years after exposure.⁷⁸ Patients can develop fluid and electrolyte abnormalities from these chemotherapeutics, causing renal tubular disorders, and from vincristine, causing centrally mediated syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Chaps. 19 and 36).

DIAGNOSTIC TESTING

The determinations of chemotherapeutic concentrations in clinical specimens are not routinely available, except for MTX. At certain research centers,¹¹ the testing for busulfan,⁶⁸ cisplatin (platinum),¹⁸ fluorouracil, vincristine,¹⁷ and topotecan can be available. These concentrations can be used to assist in confirming exposure and monitoring drug clearance but should not be relied on to determine initial management because of the difficulty in obtaining these tests and the limited ability to correlate the concentrations with clinical toxicity.

For certain chemotherapeutics, the presence of typical clinical manifestations strongly suggests their toxicity, for example, cisplatin (AKI and ototoxicity), Vinca alkaloids (peripheral neuropathy, central autonomic instability, and SIADH), anthracyclines (CHF and dilated cardiomyopathy), ifosfamide (encephalopathy and seizures), and MTX (AKI, mucositis, and pancytopenia). The diagnosis of a patient with toxicity from these xenobiotics is based on a historical evidence for exposure, clinical manifestations, and laboratory findings that support toxicity or exposure. For patients presenting with delayed onset symptoms, the association between toxicity and exposure requires an increased level of awareness to establish the causation.²⁶ Additional studies can be obtained to evaluate for specific disorders noted on the clinical examination, such as electromyography and nerve conduction studies for peripheral neuropathies, electroretinography for retinopathies, and echocardiography for cardiac dysfunction.

GENERAL MANAGEMENT

The initial management of these patients includes hemodynamic stabilization, decontamination, antidotal therapy, and enhanced elimination when feasible. Maximal benefits from antidotes and enhanced elimination can be obtained through their timely institution. Hypotension can result from dehydration, cardiac dysfunction, or sepsis. Patients with myocardial ischemia from 5-FU can be treated with coronary vasodilators, such as nitrates and calcium channel blockers. Seizures are treated with benzodiazepines, barbiturates, and propofol. Encephalopathy from high-dose ifosfamide has been treated with methylene blue (Antidotes in Depth: A42).⁴⁹ Patients with blood dyscrasias, including neutropenia and thrombocytopenia, should be evaluated for GI bleeding and infections. Those at risk for overwhelming sepsis should be started on broad-spectrum antibiotics and granulocyte colony-stimulating factor (G-CSF) as indicated. Oral activated charcoal can be administered to patients soon after an oral exposure to limit the gut bioavailability of the chemotherapeutic. Repeat oral doses of activated charcoal can enhance the clearance of MTX in patients with AKI or CKD.²³

Patients with vomiting are typically difficult to manage. Combination therapy involving multiple antiemetics is needed to treat patients exposed to chemotherapeutics with high emetogenic potential (eg, cisplatin, doxorubicin, cyclophosphamide, lomustine) or excessive doses of chemotherapeutics with low emetogenic potential (eg, Vinca alkaloids, fluorouracil). Therapy can include 5-HT₃ receptor antagonists, corticosteroids, dopamine receptor antagonists, a neurokinin-1 receptor antagonists, or benzodiazepines.⁴⁰ Serotonin receptor antagonists are effective for vomiting starting within 6 hours of exposure and are used with dexamethasone and aprepitant in patients with protracted vomiting. When the 5-HT₃ receptors are saturated, additional doses are no longer effective. Aprepitant, when used in combination with a corticosteroid, such as dexamethasone, is effective for managing delayed-onset vomiting, which can last for 5 days. Dopamine receptor antagonists, 5-HT₃ receptor antagonists, or dexamethasone at a higher dose can be used to treat breakthrough vomiting. Benzodiazepines can be used in this setting, but they are most effective for the prevention of vomiting. A basic metabolic panel, complete blood count, urinalysis, and ECG should be obtained for patients with a significant overdose to evaluate toxicity and to establish baseline values. Pregnant women exposed to chemotherapeutics require individualized care.⁴⁶ The patient's peripheral blood count should be followed for up to 2 weeks after a chemotherapeutic is administered because of the potential delayed onset of myelosuppression.

Gastrointestinal fluid losses from vomiting, diarrhea, and mucosal ulcerations can lead to salt and water depletion, which should be treated with IV fluids. IV fluids are important for patients with cisplatin and MTX toxicity to promote the renal elimination of toxic metabolites. Patients with cisplatin toxicity should be treated with 0.9% sodium chloride and an osmotic diuretic to maintain an adequate chloride gradient to promote the renal elimination of cisplatin. Urinary alkalization is indicated for patients with MTX toxicity to limit the precipitation of drug metabolites in the renal tubules.

Antidotal therapy is available for only a few xenobiotics, including anthracyclines (dexrazoxane), MTX (leucovorin, glucarpidase), cisplatin (amifostine, thiosulfate), 5-FU (uridine triacetate),⁴⁵ and ifosfamide (methylene blue, mercaptoethane sulfonate). Uridine triacetate as uridine triphosphate competes with 5-FU as fluorouridine triphosphate during RNA synthesis to limit toxicity (Fig. 50–3). These antidotes permit the use of higher doses of antineoplastics in cancer patients. However, patients with overdoses from antineoplastics can also benefit from the use of these antidotes, which should be initiated soon after the decision to treat has been made. Additional information regarding them can be found in Chaps. 51 and 52 and Antidotes in Depth: A10, A11, A39, and A42.

FIGURE 50–3. 5-Fluorouracil, capecitabine, and tegafur chemotherapeutic mechanisms of action and uridine triacetate antidotal rescue. 5'-DFCR = 5'-deoxy-5-fluorocytidine; 5'-DFUR = 5'-deoxy-5-fluorouridine; 5-FdUMP = fluorodeoxyuridine monophosphate; 5-FU = 5-fluorouracil; 5,10-methylene-FH4 = 5,10-methylenetetrahydrofolate; CYP2A6 = cytochrome P450, family 2, subfamily A, polypeptide 6; DHFR = dihydrofolate reductase; DHFU = 5,6-dihydrofluorouracil; DNA Pol = DNA polymerase; DPD = dihydropyrimidine dehydrogenase; dTMP = deoxythymidine monophosphate; dTTP = deoxythymidine triphosphate; dUMP = deoxyuridine monophosphate; FdUTP = fluorodeoxyuridine triphosphate; FH2 = dihydrofolate; FUDR = floxuridine; FUTP = fluorouridine triphosphate; RNA Pol = RNA polymerase; TKase = thymidine kinase; TPase = thymidine phosphorylase; TYMS = thymidylate synthase; UTP = uridine triphosphate. (Used with permission of Silas W. Smith, MD.)

The decision to use myeloid growth factors in patients with agranulocytosis depends on the severity and nature of the neutropenia, the anticipated speed of recovery, and the tumor type. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been used for several patients with overdoses such as cisplatin, melphalan, bleomycin, fluorouracil, and MTX.^{14,29,33–35,37,45,48,67} Typically, if promyelocytes and myelocytes are present in the bone marrow, neutrophil recovery will occur spontaneously in 4 to 7 days after the withdrawal of the offending antineoplastic.²⁰ However, when granulopoiesis is completely absent, neutrophil recovery cannot be expected for at least 14 days. The use of G-CSF or GM-CSF can accelerate neutrophil recovery during cytotoxic antineoplastic therapy. When myeloid precursors are present in the bone marrow, G-CSF can accelerate neutrophil recovery in 1 to 4 days. If myeloid precursors are absent, neutrophil recovery with G-CSF can take longer, but it will be enhanced. GM-CSF is indicated for use in neutropenic patients after

induction antineoplastic therapy for acute myelogenous leukemia because GM-CSF enhances the response of macrophages, neutrophils, and eosinophils. Serum concentrations of the antineoplastic should be below detection before institution of G-CSF to gain maximal response. Typically, G-CSF is initiated within 24 hours of the completion of the treatment cycle. The initial dose is 5 µg/kg/d IV or subcutaneously, and it should be continued beyond the expected white blood cell (WBC) nadir for approximately a 2 week course, although it can be prolonged for lomustine overdoses.^{1,72} The dose may be adjusted, depending on the patient's WBC response, but should be discontinued when the postnadir absolute neutrophil count is greater than 10,000 cells/mm³. Bone pain can be anticipated from the use of colony-stimulating factors, presumably because of the increase in cellularity in the marrow space. Additional side effects can be expected from GM-CSF therapy, including myalgia, fever, and pericarditis.

GM-CSF can produce a transient beneficial response in the WBCs in patients with aplastic anemia.¹² However, when the anemia is severe, the GM-CSF therapy is not effective. Another hematopoietic growth factor, erythropoietin (epoetin alfa and darbepoetin alfa), is approved for use in patients with anemia associated with cancer chemotherapy.^{7,57} Although the purpose of this therapy is to decrease the need for red blood cell transfusions, it does not replace the need for red blood cell transfusion when indicated.

CHEMOTHERAPEUTICS IN THE WORKPLACE

Pharmacists, nurses, physicians, and others involved in the preparation and dispensing of chemotherapeutics and those who may be exposed to the body fluids of patients treated with antineoplastics are at increased risk for toxicity. Several studies demonstrate they can be detected in the work environment and measured in workers,⁵⁹ and there is concern about the possible genotoxic effects from these exposures.⁶³ Workers may absorb these xenobiotics by the dermal, inhalational, or GI route. The factors determining the amount of worker exposure include the nature of the work, the amount of chemotherapeutic used, the frequency and duration of exposure, the physical and chemical nature of the chemotherapeutic, and the use of ventilated cabinets and personal protection equipment during the handling of these chemotherapeutics. The workplace guidelines for chemotherapeutics fall under the broader category of hazardous agents. The National Institute for Occupational Safety and Health (NIOSH) defines a “drug” as a “hazardous agent” if it is carcinogenic, teratogenic, genotoxic, associated with developmental or reproductive toxicity, or toxic to organs at low dose. A sample list of drugs considered to be hazardous by NIOSH is available.¹⁰

Regulatory and workplace recommendations for exposure levels and the waste management of these xenobiotics are available from various agencies and organizations. These recommendations are limited in scope because only a small number of xenobiotics or adverse health effects are adequately studied, and many xenobiotics do not meet the current definition for inclusion. The US Environmental Protection Agency (Resource Conservation and Recovery Act, 40 CFR §§260–279)⁵⁶ regulates nine chemotherapeutics (arsenic trioxide, chlorambucil, cyclophosphamide, daunomycin, melphalan, mitomycin C, naphthylamine mustard, streptozocin, and uracil mustard) and the equipment and devices associated with their preparation or delivery, as well as their disposal, as hazardous waste.⁵⁶ The current recommendations for worker safety with these xenobiotics in the workplace include the proper management of the work environment (eg, storage, handling, preparation, administration, use of personal protection equipment, decontamination, and waste disposal) and the institution of a medical surveillance program with approved laboratory testing.^{2,47,63}

SUMMARY

- The chemotherapeutics are a unique therapeutic class because their cytotoxicity is a direct effect.
- The majority of serious chemotherapeutic overdoses are iatrogenic, involving misreading of the product label, and errors in dosing and transcription of orders. A key element is the lack of familiarity of the health care provider with the use of these select xenobiotics.
- Clinical manifestations of chemotherapeutic toxicity depend on the mechanism of action, route of administration, and duration of exposure. The gut epithelium and bone marrow are extremely susceptible to toxicity because of their high mitotic activity. They are important because their failure will lead to overwhelming sepsis and death.
- Treatment remains primarily supportive in nature. The early institution of cytoprotectants, such as leucovorin and glucarpidase for MTX, amifostine for cisplatin, uridine triacetate for 5-FU, and dexrazoxane for anthracyclines, as antidotal therapy in overdosed patients can limit further toxicity. However, further work is needed to better define their optimal use in these situations.
- The best treatment for chemotherapeutic overdoses is prevention, which can be accomplished by maintaining a heightened awareness when working with these xenobiotics, educating patients and health care providers regarding their use, and providing increased skilled and standardized care.

Disclaimer

The findings and conclusions in this chapter are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

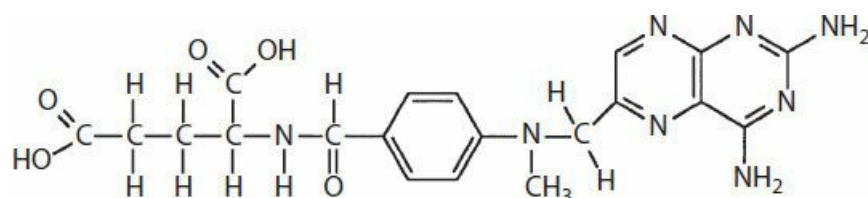
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51 CHEMOTHERAPEUTICS: METHOTREXATE

Richard Y. Wang



Methotrexate (MTX) is commonly used in the treatment of cancers and noncancerous conditions. Its immunosuppressive activity allows it to also be used for rheumatoid arthritis, organ transplantation, psoriasis, trophoblastic diseases, and therapeutic abortion.^{12,33}

Risk factors for MTX toxicity include impaired kidney function (primary route of drug elimination), third compartment spacing, ascites and pleural effusions, concurrent use of nephrotoxins (such as nonsteroidal antiinflammatory drugs (NSAIDs) aminoglycosides⁴²) and certain intravenous (IV) radiologic contrast dyes^{18,26}, age, folate deficiency, and concurrent infection.⁶⁵ MTX toxicity depends on the dose but even more on the duration of exposure.

PHARMACOLOGY

The therapeutic and toxic effects of MTX are based on its ability to limit DNA and RNA synthesis by inhibiting dihydrofolate reductase (DHFR) and thymidylate synthetase (Fig. 51–1). Thymidylate synthesis is inhibited by polyglutamic derivatives of MTX. DHFR reduces folic acid to tetrahydrofolate (FH4), which serves as an essential cofactor in the synthesis of purine nucleotides. Reduced folate is also required by thymidylate synthetase to serve as a methyl donor in the formation of thymidylate. Thymidylate is then used for DNA synthesis. MTX, a structural analog of folate, competitively inhibits DHFR by binding to the enzymatic site of action. This inhibits reduced folate production, which is necessary for nucleotide formation and DNA/RNA synthesis.

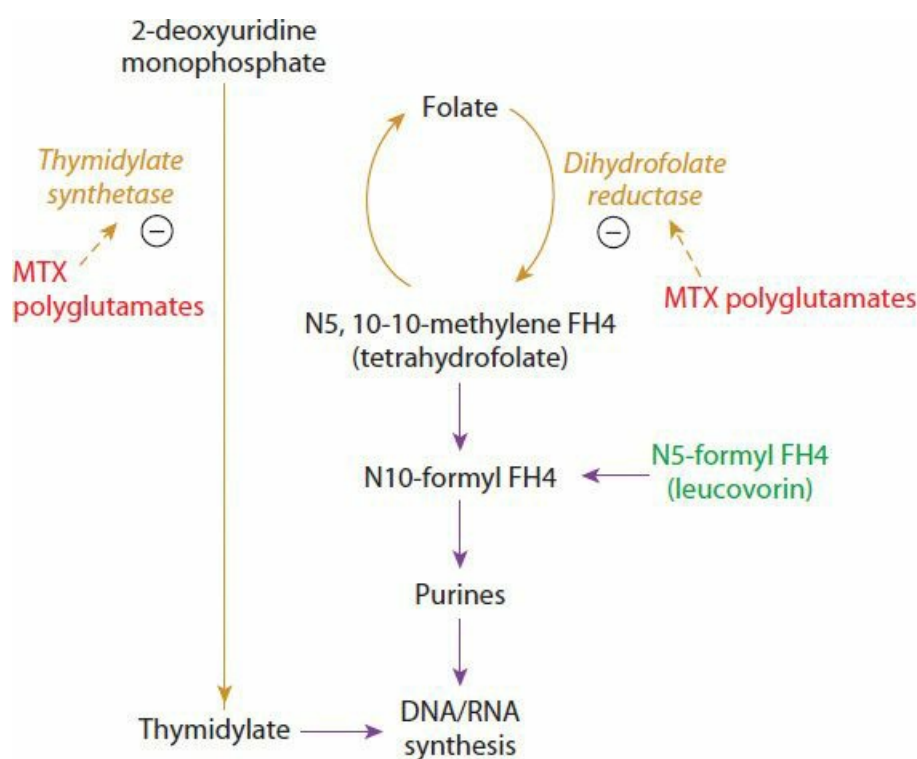


FIGURE 51–1. Mechanism of methotrexate (MTX) toxicity. MTX and MTX polyglutamates inhibit dihydrofolate reductase (DHFR) and thymidylate synthetase, which are necessary for DNA and RNA synthesis. Leucovorin bypasses DHFR blockade to allow for continued synthesis.

The bioavailability of MTX appears to be limited by a saturable intestinal absorption mechanism. At oral doses less than 30 mg/m², the absorption is 90%; at doses greater than 80 mg/m², the total absorption is less than 10% to 20%.⁹ The weekly adult dose used for the treatment of psoriasis and rheumatoid arthritis is low and can be administered orally. However, the dose used to induce abortion is higher (50 mg/m²) and must be administered parenterally to achieve an effective drug concentration. MTX dosing regimens for chemotherapy are variable but can be generally classified as low (40 mg/m²), moderate range, and high doses (1000 mg/m²). Conventional IV doses of up to 100 mg/m² can be administered without leucovorin rescue. Doses of 1000 mg/m² are considered potentially lethal. Much higher doses (2–3 g/m²) can be given when MTX is followed by leucovorin to prevent life-threatening toxicity. The mortality rate from high-dose MTX is approximately 6% and occurs primarily when MTX concentrations are not closely monitored.^{65,68}

Methotrexate has a triphasic plasma clearance. The initial plasma distribution half-life is short at 0.75 hours. The second half-life is 2 to 3.4 hours and represents renal clearance of the drug. The third phase has a half-life of about 8 to 10.4 hours and represents tissue redistribution into the plasma. This third phase can be prolonged in the setting of kidney failure and is associated with bone marrow and gastrointestinal (GI) toxicity. The volume of distribution is 0.6 to 0.9 L/kg, and protein binding is 50%. Healthy kidneys eliminate 50% to 80% of MTX unchanged within 48 hours of administration. When the creatinine clearance is less than 60 mL/min, MTX clearance is delayed.^{58,70}

PATHOPHYSIOLOGY

At high doses, drug and insoluble drug metabolites (7-hydroxy methotrexate {7-OH-MTX} and 2,4-diamino-N10-methylpteroic acid {DAMPA}) accumulate and may precipitate in the renal tubules, causing reversible acute tubular necrosis. MTX is one-tenth as soluble at a pH of 5.5 as it is at a pH of 7.5.^{9,59} Expressed another way, the serum concentration threshold for nephrotoxicity is 2.2 mmol/L when the urine pH is 5.5 and 22 mmol/L when the urine pH is 6.9. Thus, patients who are either inadequately hydrated or have not had urinary alkalinization are at risk for acute kidney failure from high-dose MTX treatment.^{3,34} MTX is excreted unchanged in the urine by both glomerular filtration and active tubular secretion. Folic acid blocks renal MTX reabsorption and can enhance elimination during leucovorin rescue.²⁷ A small amount of MTX is metabolized intracellularly to polyglutamate derivatives, which inhibit DHFR and thymidylate synthetase and are believed to be responsible for the persistent cytotoxic effect of MTX because they do not easily diffuse outside of the cell.

CLINICAL MANIFESTATIONS

In the course of MTX therapy, a variety of disorders can occur, resulting from either increased patient susceptibility to toxicity or excessive administration. The clinical manifestations of MTX toxicity include stomatitis, esophagitis, kidney failure, myelosuppression, hepatitis, and central nervous system dysfunction. In a group of 23 patients who received 45 courses of high-dose MTX therapy with leucovorin rescue, the most commonly observed signs included increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (81%), nausea and vomiting (66%), mucositis (33%), dermatitis (18%), leukopenia (11%), thrombocytopenia (9%), and creatinine elevation (7%).⁵⁵

Nausea and vomiting, considered rare after low-dose cancer therapy (40 mg/m²), typically begin 2 to 4 hours after high-dose therapy (1000 mg/m²) and last for about 6 to 12 hours. Mucositis, characterized by mouth soreness, stomatitis, or diarrhea, usually occurs in the first week of therapy, continues to evolve in the second week of therapy, and can last for 4 to 7 days. Other GI effects resulting from MTX therapy include pharyngitis, anorexia, GI hemorrhage, and toxic megacolon.⁶ Hepatocellular toxicity, as identified as increased AST (>1000 IU/L) or ALT (>1000 IU/L), and hyperbilirubinemia, can occur with both acute and chronic therapy.^{47,49} It is usually associated with high dose regimens. Laboratory abnormalities improve within 1 to 2 weeks of discontinuation of MTX. The mechanism is incompletely understood, but toxicity is attributed to reduced liver folate stores.⁷ Factors associated with hepatotoxicity include sustained high serum concentrations, increased cumulative dosages, chronic therapy, and host factors such as an increase in age, obesity, diabetes, and alcoholism.⁷¹

Pancytopenia usually occurs within the first 2 weeks after an acute exposure. Pancytopenia can also occur with chronic MTX therapy for rheumatoid arthritis and psoriasis.^{16,40,47,57}

When used in low-dose IV doses of 40 to 60 mg/m², MTX is not associated with appreciable nephrotoxicity. However, at doses greater than 5000 mg/m² (~130 mg/kg for an adult), several investigators report severe kidney damage, with oliguria, azotemia, and kidney failure.⁸ The kidney function can normalize over time. Patients at risk for nephrotoxicity include elderly adults; those with underlying kidney disease defined as a glomerular filtration rate of less than 50 mL/min; and those who receive concurrent drug therapy that can delay MTX excretion, which includes xenobiotics that reduce renal blood flow such as NSAIDs, nephrotoxins such as cisplatin and the aminoglycosides, and weak organic acids such as salicylates and piperacillin that inhibit renal secretion.^{32,65}

The neurologic complications associated with either high-dose systemic MTX therapy or intrathecal administration are the most consequential manifestations. The incidence of neurologic toxicity from high-dose MTX therapy is approximately 5% to 15%.³⁵ The manifestations of toxicity usually occur from hours to days after the initiation of therapy and include hemiparesis, paraparesis, quadraparesis, seizures, and dysreflexia.^{35,46,66,69} These events are reversible to varying degrees.² Clinical findings occurring within several hours (usually within 12 hours) of therapy are attributed to chemical arachnoiditis, and they include acute onset of fever, meningismus, pleocytosis, and increased cerebrospinal fluid (CSF) protein concentration.²⁸ Leukoencephalopathy is associated with the onset of behavioral disorders and progressive dementia from months to years after treatment and is irreversible, although manifestations presenting soon after treatment can be reversible depending on the extent of involvement.^{5,74} Patients with increased age and prior cranial radiation are at increased risk for this disorder.²³ Patients with leukoencephalopathy have findings consistent with edema and demyelination or necrosis of the white matter on computed tomography (CT) and magnetic resonance imaging (MRI) of the brain.⁵

DIAGNOSTIC TESTING

Serum MTX concentrations are monitored during therapy to limit toxicity. For example, patients with a serum concentration greater than 1.0 $\mu\text{mol/L}$ at 48 hours after treatment are considered at risk for bone marrow and mucosal toxicities.⁶⁵ The measurement of MTX concentrations in the clinical setting is routinely conducted using an enzyme immunoassay or fluorescence polarization immunoassay (FPIA). These measurements can be performed on serum, plasma, and CSF. The presence of MTX metabolites, such as 7-OH-MTX and DAMPA, folic acid, and certain drugs, such as trimethoprim and aminopterin, can diminish the specificity of the analytical method for MTX.^{4,11,19,53,60} The amount by which these xenobiotics affect the MTX concentration depends on the assay. Leucovorin demonstrated a crossreactivity for MTX of less than 1% at a concentration of 1000 $\mu\text{mol/L}$ with the FPIA (monoclonal antibody {MAB}) method¹ and approximately 8% at a concentration of 1.69 $\mu\text{mol/L}$ with a modified enzyme immunoassay method.¹⁰ The advantages of high-performance liquid chromatography (HPLC) over these other methods include improved sensitivity, specificity, and ability to detect metabolites; however, HPLC takes longer to run than the routine clinical methods because it is not an automated procedure. When patients are treated with glucarpidase (carboxypeptidase) (Antidotes in Depth: A11), it is preferable to use the HPLC method to measure MTX because of the presence of metabolites. The FPIA method with MABs is not recommended for use in patients who have developed antibodies to mouse MABs or elevated concentrations of DAMPA.⁴¹

An elevated CSF MTX concentration ($>100 \mu\text{mol/L}$) is indicative of an excessive intrathecal dose or delayed CSF outflow obstruction.⁵⁰ Radiologic imaging of the brain, such as CT and MRI, can be obtained to evaluate for meningeal inflammation, demyelination and necrosis of the white matter, or other pathologies such as a cerebrovascular accident.

MANAGEMENT

In the event of an oral overdose of MTX, the initial concern should be GI decontamination. Activated charcoal adsorbs MTX and should be administered as soon as possible to limit absorption.²⁴ The administration of multiple-dose activated charcoal or cholestyramine^{17,62} can significantly decrease the elimination half-life of MTX by interrupting the enterohepatic circulation.^{21,24} This approach can increase MTX clearance but is of most benefit to patients with diminished creatinine clearance.

Adequate hydration with 0.9% sodium chloride solution as well as urinary alkalization with IV sodium bicarbonate (to urine pH of 7 to 8) (Antidotes in Depth: A5) is also important to prevent kidney failure that results from the precipitation of MTX and metabolites.¹³ The complete blood count should be monitored on days 7, 10, and 14 to assess the impact on the bone marrow.⁴³ Granulocyte-macrophage colony-stimulating factor (GM-CSF) was used in a patient with a chronic MTX overdose and pancytopenia.⁶⁴ The patient had a serum MTX concentration of 1.25 $\mu\text{mol/L}$ on admission and was in kidney failure. Bone marrow biopsy showed promyelocytes but no mature white cells and a marked reduction of megakaryocytes. Because of deteriorating conditions, GM-CSF (125 $\mu\text{g/m}^2/\text{d}$) was administered when the MTX concentration fell below the reference limit for toxicity. Seven days after the initiation of GM-CSF, the white blood cell count rose and reached normal values within 10 days.

Patients presenting with meningismus or altered mental status after MTX therapy require an initial MRI of the brain and then CSF analysis for infection.³⁸ Although not considered standard, the CSF can be assayed for MTX if excessive exposure to this compartment is suspected. The CSF MTX concentration is about 0.1 mol/L ($1 \times 10^5 \mu\text{mol/L}$) and lasts for 48 hours after an IV MTX dose of 1500 mg/m^2 and 100 mol/L ($1 \times 10^8 \mu\text{mol/L}$) for the peak therapeutic concentration after a 12-mg intrathecal MTX dose.⁵¹ MRI of the brain can demonstrate a high signal throughout the pachymeningeal (dura mater) region, which is consistent with chemical meningitis,²⁰ or a high signal of the white matter with a decreased

diffusion coefficient in a diffusion-weighted image to indicate the presence of edema, which is an early finding of leukoencephalopathy.

ANTIDOTES

The available rescue agents for MTX toxicity include folinic acid (leucovorin) (Antidotes in Depth: A10) and glucarpidase (carboxypeptidase) (Antidotes in Depth: A11). The effectiveness of these therapies depends on both the timing of administration and the dose, which warrants the monitoring of serum MTX concentrations during the use of these antidotes. Folinic acid rescue therapy limits bone marrow and GI toxicity by allowing essential biochemical processes that are dependent on reduced folates to continue. The purpose of the initial dose of leucovorin is to achieve a serum concentration equal to the MTX; subsequent doses should be adjusted according to serum MTX concentrations at 12, 24, and 48 hours after exposure (Fig. 51–1).^{39,60} Leucovorin treatment is continued until the MTX concentration is less than 0.01 $\mu\text{mol/L}$.¹² In patients with marrow toxicity and no cancer, leucovorin therapy should be continued until marrow recovery occurs even if serum MTX is no longer detectable⁴⁵ because intracellular MTX activity can still be ongoing because of the presence of cytosolic MTX polyglutamates. Among 36 patients undergoing MTX therapy (the amount varied from 2.0–13.0 mg of MTX per week) for rheumatoid arthritis, all of these patients had indirectly detectable MTX polyglutamates in their red blood cells and nondetectable MTX in the serum (FPIA, MAB).^{29,30}

Glucarpidase (carboxypeptidase G₂, Voraxaze) is a recombinant bacterial enzyme that is used as a rescue therapy to inactivate MTX by hydrolyzing it to DAMPA and glutamate. Glucarpidase is available for use as an adjunctive therapy in patients receiving high-dose MTX and those experiencing MTX toxicity or who are at risk for MTX toxicity (diminished kidney function or delayed MTX clearance based on serum MTX concentrations). After glucarpidase therapy, serum MTX concentrations need to be monitored because residual concentrations of MTX in the blood after initial enzymatic therapy can result from an inadequate dose of glucarpidase. This occurs in patients with large MTX exposures or the redistribution of MTX from tissue stores to the blood compartment.^{11,60,72} Glucarpidase can also be successfully administered intrathecally to reduce elevated MTX concentrations in the cerebrospinal space (Special Considerations: SC3).⁷³

EXTRACORPOREAL ELIMINATION

There are several reports of the use of hemodialysis or hemoperfusion (or both) for patients with MTX toxicity.^{37,48,56,67,70} Although the volume of distribution (0.6–0.9 L/kg) and protein binding (50% that is not concentration dependent) suggest that MTX is dialyzable, older clinical evidence suggested otherwise.⁶⁴ In one report, less than 10% of an initial 700 mg dose of MTX was cleared in 12 sessions of hemodialysis.⁶⁷ The measured clearance was only 38 mL/min, which can be compared with 5 mL/min for peritoneal dialysis,²⁵ 0.28 to 24 mL/min for continuous venovenous hemodiafiltration,^{36,39} and 180 mL/min for normal renal clearance.⁴⁴ Using plasma exchange transfusion to remove MTX is not recommended because MTX has limited protein binding, limiting any potential efficacy of this procedure.^{8,39,52,67}

Acute intermittent hemodialysis with a high-flux dialyzer membrane (F-80B Fresenius Dialyzer) yielded an effective mean serum MTX clearance of 92 ± 10.3 mL/min in six patients with kidney failure that was a result of either chronic disease or high-dose MTX therapy.⁷⁰ These patients received high-dose MTX therapy and had predialysis serum MTX concentrations ranging from 1.45 to 1813 $\mu\text{mol/L}$. The time of dialysis initiation after MTX treatment was from 1 hour to 6 days in these patients. A postdialysis serum MTX concentration of 0.3 $\mu\text{mol/L}$ was used as an end point for dialysis. The reported MTX clearance by this technique closely approximates normal renal MTX clearance and is indicated to enhance the clearance of MTX in patients with diminished renal clearance and an elevated serum MTX concentration.⁵⁸

Charcoal hemoperfusion removed more than 50% of MTX in four patients with impaired renal MTX clearance during high-dose MTX therapy.¹⁵ This was thought to have prevented severe skin and mucosal toxicity. Sequential hemodialysis and hemoperfusion were used for a patient with substantial MTX toxicity.²⁴ These procedures decreased the half-life of elimination from 45 hours to 7.6 hours. In experimental animals, hemoperfusion significantly reduced the terminal half-life of MTX. In surgically anephric dogs, hemoperfusion decreased the half-life from more than 20 hours to 1.3 hours.³¹ Consequently, hemoperfusion is recommended over hemodialysis when it is available; otherwise, high-flux hemodialysis is preferred.⁵⁶

In vitro studies indicate that the toxic effects of 100 $\mu\text{mol/L}$ of MTX cannot be reversed by 1000 $\mu\text{mol/L}$ of folinic acid.⁵⁴ This suggests the need for extracorporeal elimination after massive doses or enzymatic cleavage (or both) to lower persistent serum MTX concentrations of greater than 100 $\mu\text{mol/L}$.⁵⁶ It is important to perform high-flux hemodialysis early before distribution into tissues. Rebound of MTX concentrations from tissues can be expected after hemodialysis, which can begin at 2 hours after dialysis and plateau at 16 hours.^{22,25,70} Patients who are at the greatest risk for developing MTX toxicity despite folinic acid treatment should be considered for glucarpidase therapy. This includes patients with progressively diminishing renal clearance.⁶⁵ High-flux hemodialysis can offer the additional benefit of correcting fluid and

electrolyte disorders resulting from kidney failure. Other treatment options to limit additional organ toxicity, including leucovorin and urinary alkalization, should be continued during extracorporeal MTX removal. Folic acid is water soluble and can be removed by hemodialysis.^{14,56,61,63} This is probably also applicable for folinic acid, and replacement doses of leucovorin postdialysis should be considered.

SUMMARY

- The number of patients with MTX exposures and resultant toxicity is anticipated to increase because of the expanding therapeutic indications and available multiple formulations of this antineoplastic.
- Clinicians need to have a greater awareness of the clinical presentations, acute and chronic, and management of MTX toxicity to improve outcomes.
- Patients with associated chronic illnesses, diminished renal clearance, and chronic toxicity are at greatest risk for increased morbidity from overwhelming sepsis.
- Management includes supportive care, monitoring serum MTX concentrations, urinary alkalization to limit kidney toxicity, enhanced elimination, and antidotal therapy with leucovorin and enzymatic cleavage with glucarpidase when indicated.
- The early recognition of these patients and institution of these therapies can offer the patient the best outcome.

Disclaimer

The findings and conclusions in this chapter are those of the author and do not necessarily represent the views of Centers for Disease Control and Prevention.

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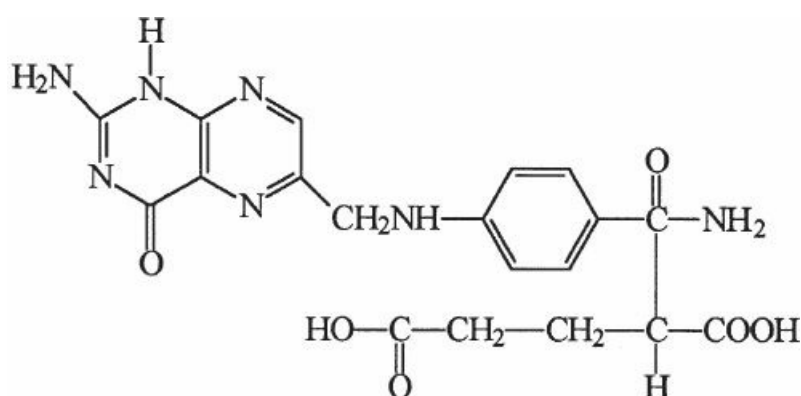
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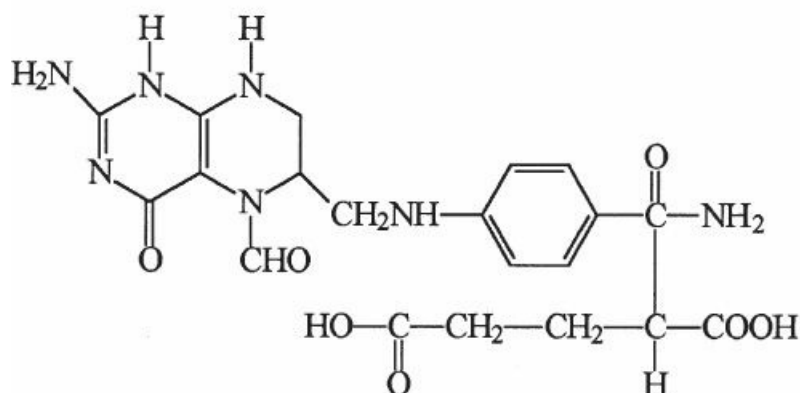
A10 ANTIDOTES IN DEPTH

Folates: Leucovorin (Folinic Acid) and Folic Acid

Mary Ann Howland



Folic Acid



Folinic Acid

Folates refer to the metabolically active reduced forms of folic acid, including dihydrofolate and tetrahydrofolate. These folates are vital to cellular biochemistry, including the synthesis of purines and DNA. Folic acid must be reduced in vivo by dihydrofolate reductase to tetrahydrofolate. Dihydrofolate reductase inhibitors such as methotrexate prevent this reduction. Leucovorin (folinic acid) and levoleucovorin, and compared with folic acid, they do not require dihydrofolate reductase for activation. Therefore, either leucovorin or levoleucovorin is the primary antidote for a patient who receives an overdose of methotrexate or another dihydrofolate reductase inhibitor.

Methanol is metabolized to the active and toxic formic acid. Folates, including folic acid and leucovorin, speed up the conversion of formic acid to nontoxic metabolites. Because methanol does not interfere with the synthesis of tetrahydrofolate, either folic acid or leucovorin is acceptable for a patient poisoned by methanol who necessitates enhanced formate metabolism. Preliminary evidence also suggests a role for folic acid to enhance arsenic elimination.

HISTORY

In the early 1930s when Lucy Wills went to Bombay to study pregnant textile workers with macrocytic anemia, she found that a yeast extract given to these poor people with a nutritionally deficient diet corrected and prevented their anemia.¹¹ Mitchell isolated the active ingredient from spinach in 1941 and named it folic acid from the Latin folium meaning leaf.¹¹ Subsequently, folic acid was synthesized and its chemical structure identified. Since then, the many roles of folate and natural or induced folate deficiency continue to be studied.

PHARMACOLOGY

Folic acid (pteroylglutamic acid), an essential water-soluble vitamin, consists of a pteridine ring joined to PABA (para-aminobenzoic acid) and glutamic acid.¹⁰ Folic acid is the most common of the many folate congeners that exist in nature and perform essential cellular metabolic functions. Folic acid is often called vitamin B₉. After absorption, folic acid is reduced by dihydrofolic acid reductase (DHFR) to dihydrofolic acid and then tetrahydrofolic acid (THF), which accepts one carbon groups. Tetrahydrofolic acid serves as the precursor for several biologically active forms of folic acid, including 5-formyltetrahydrofolic acid (5-formyl THF), which is best known as folinic acid, leucovorin, and citrovorum factor. These biologically active forms of folate are enzymatically interconvertible and function as cofactors, providing the one carbon groups necessary for many intracellular metabolic reactions, including the synthesis of thymidylate and purine nucleotides, which are essential precursors of DNA.^{29,32,36,38,43} The minimum daily requirement of folic acid is normally 50 µg, but pregnant women and nutritionally deprived, acutely ill patients may require 100 to 200 µg.^{10,12}

Leucovorin is a mixture of the active and inactive diastereoisomers of 5-formyl THF of which the levo form is active and available as levoleucovorin.⁶ Both are available as the calcium salt, with the same chemical formula, C₂₀H₂₁CaN₇O₇, and a molecular weight (MW) of 511 Da. Both are rapidly metabolized to several active folates, including 5-methyltetrahydrofolate (5-CH₃-THF). The dose of levoleucovorin is half of leucovorin.

After a DHFR inhibitor such as methotrexate inhibits the formation of tetrahydrofolic acid, the intracellular machinery for the synthesis of indispensable thymidylate and purine nucleotides comes to a halt, and DNA production ceases. Leucovorin and levoleucovorin are biologically active forms of folic acid and bypass this inhibition of DHFR caused by methotrexate.

Folate catalyzes the formation of carbon dioxide and water from formic acid, the final metabolic step in methanol elimination. Because there is no inhibition of the formation or recycling of active folate, either folic acid or leucovorin is beneficial.

Early investigations suggest that folic acid may aid in the methylation and subsequent elimination of arsenic. Folate supplementation in folate-deficient subjects was done to enhance the elimination of arsenic and potentially decreased chronic arsenic toxicity.^{5,7,8,30} Studies remain to be performed to determine whether folate supplementation in folate-replete individuals is beneficial.

Leucovorin Pharmacokinetics

Whereas leucovorin is naturally formed in the body as the active (l) isomer, the commercial preparation is the racemic mixture, which means it consists of equal amounts of the inactive (d) and active (l) isomers. The pharmacokinetics of the racemic mixture of leucovorin and its active metabolite were studied after a single intravenous (IV) infusion and as a constant infusion in normal human volunteers.^{39,40} During constant infusion of 500 mg/m²/d, the steady-state concentration for the active isomer was 2.33 µmol, the half-life was 35 minutes, and the volume of distribution (Vd) was 13.6 L. The active isomer is metabolized to an active metabolite (l-5-CH₃-THF) that achieved a steady-state concentration of 4.85 µmol and a half-life of 227 minutes. Similar values were achieved for half-life and Vd after single IV doses ranging from 25 to 100 mg. The inactive d-isomer achieved higher concentrations and had a much longer half-life with oral administration, which is saturable and stereoselective, resulting in absorption of the active isomer that is four to five times greater than that of the inactive isomer. Studies of stereospecific oral absorption demonstrate that 100% of the l-leucovorin is absorbed, but only 20% of the d-leucovorin is absorbed at this dose.¹⁹ One study detected no adverse effects of the inactive isomer on the intracellular uptake of the active isomer and concluded that giving the active isomer provided no pharmacokinetic advantage over the racemic mixture.³⁵

Two hundred milligrams of levoleucovorin was compared to 400 mg of leucovorin, each administered as a 2 hour IV infusion as a crossover study in 40 healthy volunteers. The area under the curve and the maximum serum concentrations of l-5-CH₃-THF were similar for both.

Preliminary evidence suggests that l-5-CH₃-THF enters the CSF after systemic administration of both leucovorin and levoleucovorin. However, the concentration achieved is one to three orders of magnitude less than is normally obtained after intrathecal methotrexate. Intrathecal administration of leucovorin and levoleucovorin is contraindicated.

The pharmacokinetics of IV leucovorin was compared with intramuscular (IM) and oral administration in male volunteers given 25 mg. The mean peak of the active 1-5-CH₃-THF concentration was 258 ng/mL (5.5×10^{-1} μmol/L) at 1.3 hours after IV administration compared with 226 ng/mL at 2.8 hours for IM and 367 ng/mL at 2.4 hours for oral administration.

The pharmacokinetics of orally administered leucovorin was studied in healthy, fasted male volunteers in single doses ranging from 20 to 100 mg and 200 mg IV over 5 minutes compared with 200 mg orally.^{23,31} Bioavailability decreased from 100% for the 20-mg dose to 78% for the 40 mg dose and ultimately to 31% for the 200 mg dose. A microbiologic assay was used to measure total tetrahydrofolates (reduced and active folates). Normal serum folate concentrations are approximately 0.05 μmol/L.¹⁴ The 200 mg oral dose produced a peak serum concentration of 1.82 μmol/L compared with 0.66 μmol/L for the 20-mg oral dose and 27.1 μmol/L for the 200 mg IV dose.^{23,31}

ROLE IN METHOTREXATE TOXICITY

Methotrexate, an antimetabolite, is a structural analog of folic acid, differing only in the substitution of an amino group for a hydroxyl group at the number 4 position of the pteridine ring (Chap. 51). Methotrexate binds to the active site of DHFR, rendering it incapable of reducing folic acid to its biologically active forms and incapable of regenerating the necessary active forms required for the synthesis of purine nucleotides and thymidylate.³⁷ At physiologic pH, the binding between methotrexate and DHFR is competitive, with an inhibition constant of about 1 μmol/L.³⁴ Leucovorin is a reduced, active form of folate. As such, it does not require DHFR for enzymatic interconversion to the form required for purine nucleotide and thymidylate formation. Folic acid is unable to counteract methotrexate toxicity because after methotrexate therapy, DHFR is unavailable to convert folic acid to an active reduced form. Leucovorin rescue is the term used to describe the practice of limiting the toxic effects of high-dose methotrexate therapy.

ROLE IN METHANOL TOXICITY

Monkeys experimentally made folate deficient develop methanol toxicity at lower methanol concentrations.²⁴ Administering folic acid to normal monkeys accelerates formate metabolism.²⁴ Pretreatment with folic acid or leucovorin decreased both formate concentrations and the accompanying metabolic acidosis without affecting the rate of methanol elimination.²⁴ Leucovorin remained effective in hastening the metabolism of formate when given 10 hours after methanol administration.²⁷

The hepatic concentrations of total folate, leucovorin, and folate dehydrogenase (which increases leucovorin concentrations) are all diminished in methanol poisoned humans.¹⁶ In an analysis of a single methanol-poisoned patient who was given folic acid, ethanol, and hemodialyzed, the half-life of formate was 1.1 hours.²⁸ In another methanol poisoned patient treated without folic acid, the formate half-life was 2.8 hours.¹³ These comparative data are inadequate to draw definitive conclusions but may support the therapeutic role of folate in addition to that of fomepizole (Antidotes in Depth: A30) and hemodialysis.

ROLE IN ARSENIC TOXICITY

Arsenic contamination of drinking water has plagued millions, causing increased manifestations of chronic arsenic toxicity, including cancer and cardiovascular, dermatologic, and neurologic problems. Arsenic is methylated to monomethylarsonic acid (MMA) and then to dimethylarsinic acid (DMA). Early evidence suggests that nutritional deficiencies facilitate arsenic methylation, encouraging further study of folate supplementation along with other nutrients with the hope of diminishing the chronic health effects of arsenic toxicity.^{5,7,8,30} The absolute methylation amount and product probably also depends on the degree of upregulation.^{9a}

ADVERSE EFFECTS AND SAFETY ISSUES

Reports of adverse reactions to parenteral injections of folic acid, leucovorin, or levoleucovorin are uncommon. However, adverse reactions may include allergic or anaphylactoid reactions.¹⁰ Seizures are rarely associated with leucovorin or levoleucovorin administration.^{6,25} The calcium content of leucovorin and levoleucovorin warrants a slow IV infusion at a rate not faster than 160 mg/min in adults. There is 0.004 mEq of calcium per milligram of leucovorin calcium injection. Extremely large doses of leucovorin on the order of 1000 mg every 3 hours might lead to hypercalcemia.⁴⁴ Neither leucovorin nor levoleucovorin should be administered intrathecally.^{15,18,33,42}

Leucovorin and levoleucovorin are not antidotes for 5-fluorouracil (5-FU), and both can enhance both the therapeutic and toxic effects of fluoropyrimidines such as 5-FU.^{19,22} Both leucovorin and levoleucovorin are readily converted to 5,10-

methylenetetrahydrofolate, which enhances the binding of the active metabolite of fluorouracil to thymidylate synthase, thereby potentiating the inhibition.

Many protocols recommended separating leucovorin and levoleucovorin from glucarpidase by 2 hours (Antidotes in Depth: A11); otherwise, leucovorin acts as a substrate for glucarpidase.

There is a potential for dosing errors when interchanging leucovorin and levoleucovorin. The dose of levoleucovorin is half the dose of leucovorin.

PREGNANCY AND LACTATION

Leucovorin and levoleucovorin are Food and Drug Administration (FDA) pregnancy category C drugs. Human studies are lacking, and animal reproductive studies have not been conducted. Breast milk excretion is unstudied.

Folic acid is an FDA category A drug and is safe during pregnancy and compatible with breastfeeding.

DOSING AND ADMINISTRATION

After overdose of methotrexate, a dose of leucovorin estimated to produce the same plasma concentration as the methotrexate dose should be given as soon as possible, preferably, within one hour. One mole of methotrexate weighs 455 Da, and 1 mol of leucovorin calcium weighs 511 Da, with the MW of the leucovorin portion equal to 471 Da. Because of the safety of leucovorin and because of the toxicity of methotrexate, underdosing leucovorin should be avoided. Although serum methotrexate concentrations are often closely followed in patients on diverse oncologic regimens,^{2,3} in the overdose setting, or in methotrexate toxicity related to treatment for tubal pregnancies, it is inappropriate to wait for a serum concentration before initiating treatment with leucovorin.¹ The toxic threshold for methotrexate is reported to be 1×10^{-8} mol/L (0.01 μ mol/L or 10 nmol/L).⁴ Normal serum folic acid concentrations are in the range of 13 to 43 nmol/L. If the patient's exposure to methotrexate is not for therapeutic purposes there is no need to permit any methotrexate to remain unantagonized by leucovorin.

As an example, if a child unintentionally ingests 100 (2.5 mg) methotrexate tablets for a total dose of 250 mg, only part of this dose is absorbed because methotrexate absorption is saturable.⁹ The bioavailability of methotrexate decreases from 100% with doses less than 30 mg/m² to approximately 10% to 20% with doses greater than 80 mg/m². In this case, it is safe to assume that a bioavailability of 50% would result in an absorbed dose of methotrexate of less than 125 mg. For this exposure, an IV dose of 125 mg of leucovorin should be given over 15 to 30 minutes. This dose of IV leucovorin would be expected to produce serum concentrations in excess of that of the methotrexate, given that the Vd of leucovorin is about 25% less than methotrexate and the MWs are similar. This dose of IV leucovorin should be repeated every 3 to 6 hours until the serum methotrexate concentration is less than 0.05 μ mol/L, preferably zero. This differs from recommendations in patients receiving methotrexate therapeutically (see later discussion). The methotrexate half-life may vary from 5 to 45 hours, depending on the dose and the patient's kidney function. For this reason, leucovorin therapy should be continued for 12 to 24 doses (3 days) or longer if methotrexate concentrations are unavailable. Patients who may develop third-space storage in ascites or pleural effusions may also require leucovorin dosing for an extended period of time. Patients with bone marrow toxicity require more prolonged dosing because plasma half-lives of methotrexate do not reflect persistent intracellular concentrations.

Systemic Methotrexate Toxicity

The routine dose of leucovorin for "leucovorin rescue" after high-dose methotrexate therapy with doses of 12 to 15 g/m² ranges from 10 to 25 mg/m² IM or IV every 6 hours for 72 hours to 150 mg/m² every 3 hours in patients with renal compromise and delayed elimination. If a neonate must be treated, a benzyl alcohol-free preparation must be used because of the toxicity of benzyl alcohol in neonates (Chap. 55).⁴¹ For methotrexate overdoses, equimolar serum leucovorin concentrations should provide adequate protection, but because precise determinations are invariably delayed, leucovorin administration should be initiated without delay.

As a rough guide, a single dose of 25 mg of IV leucovorin in an adult produces a peak concentration of the active 1-5-CH₃-THF metabolite of approximately 258 ng/mL, which is 0.55 μ mol/L.¹⁹ A dosage of about 150 mg every 4 hours in an adult achieves a steady-state concentration of about 4.85 μ mol/L.³⁹ And although the dose of leucovorin can be as high as 1000 mg/m² every 6 hours, this is rarely warranted and cannot adequately compete with serum concentrations of methotrexate above 100 μ mol/L under these circumstances, glucarpidase should be strongly considered. An IV leucovorin dose of 150 mg/m² every 3 to 6 hours should be effective in all but the most severe overdoses and should be administered IV as soon as possible over 15 to 30 minutes but not faster than 160 mg/min in adults because of the calcium content. This dose should be continued a minimum of several days or until the serum methotrexate concentration falls below 0.05 μ mol/L in the absence of bone marrow toxicity. One case series of 11 patients receiving methotrexate over 4 hours at 10 to 12 g/m²

for osteosarcoma or 3.5 g/m^2 for central nervous system lymphoma required high-dose leucovorin rescue for methotrexate concentrations at high risk for toxicity at 24, 48, or 72 hours, usually because of acute kidney injury. The dosage of leucovorin ranged from 0.24 to 10 g/day and was titrated downward as the methotrexate concentration fell. It took an average of 11 ± 3 days for the methotrexate concentration to drop below $0.1 \text{ } \mu\text{mol/L}$ (Table A10–1).

TABLE A10-1. Guidelines for Leucovorin Dosage and Administration^a

<i>Clinical Situation</i>	<i>Laboratory Findings</i>	<i>Leucovorin Dosage</i>
Normal methotrexate elimination	Serum [methotrexate] $\sim 10 \text{ } \mu\text{mol/L}$ at 24 hours after administration, $1 \text{ } \mu\text{mol/L}$ at 48 hours, and $<0.2 \text{ } \mu\text{mol/L}$ at 72 hours	15 mg PO, IM, or IV every 6 hours for 60 hours (10 doses starting at 24 hours after the start of methotrexate infusion)
Delayed late methotrexate elimination	Serum [methotrexate] remaining $>0.2 \text{ } \mu\text{mol/L}$ at 72 hours and $>0.05 \text{ } \mu\text{mol/L}$ at 96 hours after administration	Continue 15 mg PO, IM, or IV every 6 hours until [methotrexate] is $<0.05 \text{ } \mu\text{mol/L}$
Delayed early methotrexate elimination or evidence of acute renal injury	Serum [methotrexate] of $\geq 50 \text{ } \mu\text{mol/L}$ at 24 hours or $\geq 5 \text{ } \mu\text{mol/L}$ at 48 hours after administration or a $\geq 100\%$ increase in serum [creatinine] at 24 hours after methotrexate administration (eg, an increase from 0.5 to $\geq 1 \text{ mg/dL}$)	150 mg IV every 3 hours until methotrexate level is $<1 \text{ } \mu\text{mol/L}$; then 15 minutes IV every 3 hours until [methotrexate] is $<0.05 \text{ } \mu\text{mol/L}$

^aLeucovorin should not be administered intrathecally.

IM = intramuscular; IV = intravenous; PO = oral.

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The package insert for leucovorin rescue after high-dose methotrexate as well as the methotrexate package insert suggest the following guidelines when methotrexate concentrations are drawn 24 hours or more after the start of the methotrexate infusion (Table A10–1):^{19,26}

An IV leucovorin dose of 100 mg/m^2 every 3 to 6 hours should be effective in all but the most severe overdoses. A constant IV infusion of $21 \text{ mg/m}^2/\text{h}$ has been safely administered for 5 days. Figure A10–1 offers a nomogram for pharmacokinetically guided rescue after high-dose methotrexate.² A transition to oral administration of leucovorin depends on the serum concentration of methotrexate and whether adequate serum concentrations of leucovorin can be achieved orally. In adults, a 200 mg oral dose of leucovorin produces a peak serum concentration of $1.82 \text{ } \mu\text{mol/L}$ compared with $27.1 \text{ } \mu\text{mol/L}$ with a 200 mg IV dose.

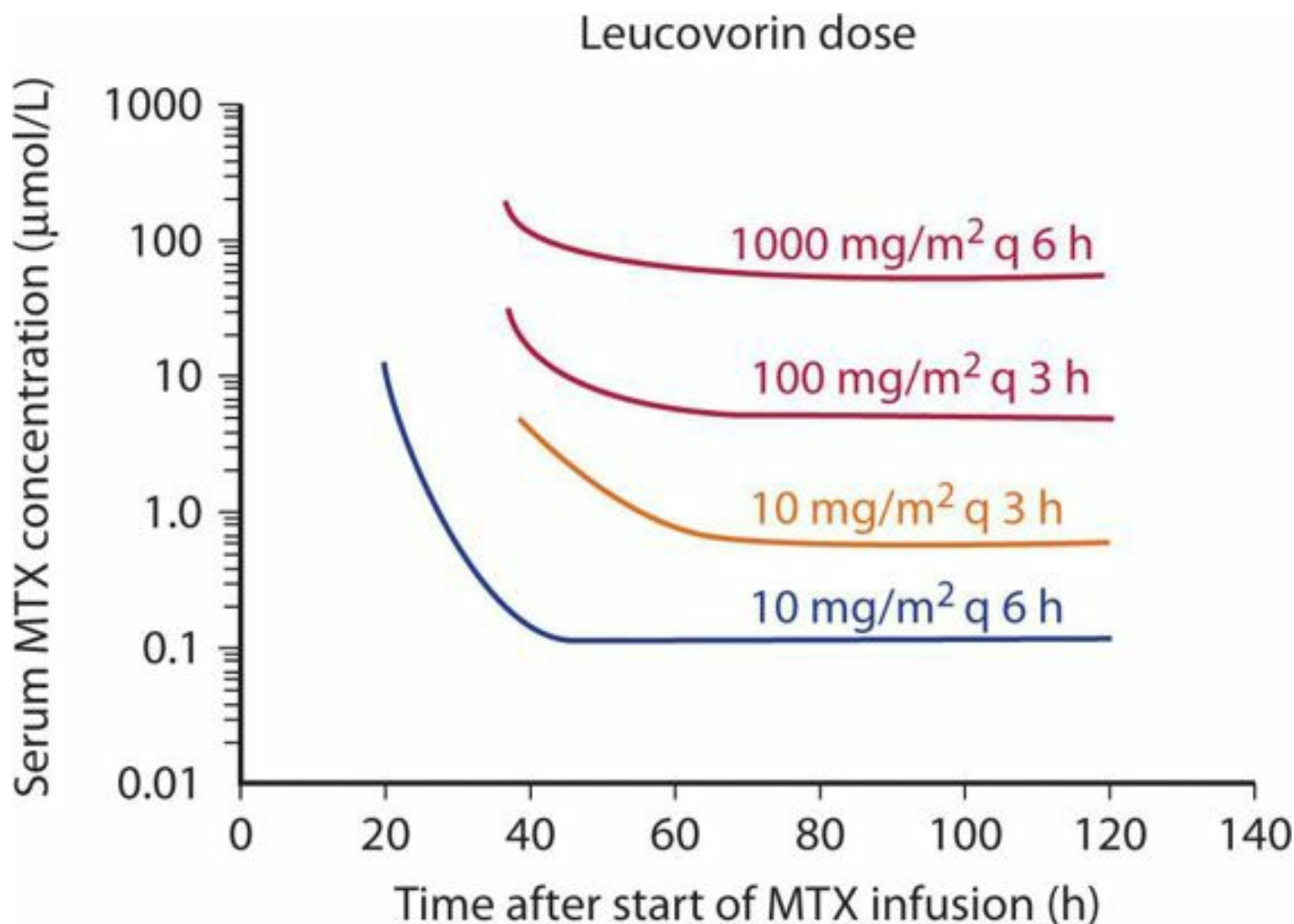


FIGURE A10–1. Example of a nomogram developed by Bleier² for pharmacokinetically guided leucovorin rescue after high-dose methotrexate (MTX) administration.

Levoleucovorin, the active l isomer of folinic acid, is available and should be dosed at half the dose of the racemate leucovorin.⁶

Administration of activated charcoal (AC) precludes the subsequent administration of oral leucovorin. In addition to leucovorin, other modalities to treat patients with methotrexate overdoses include AC and urinary alkalinization as well as glucarpidase (carboxypeptidase G) and extracorporeal removal ([Chap. 51](#)).

Intrathecal Methotrexate Overdose

Unintentional overdose with intrathecal methotrexate is potentially quite serious and is dose dependent.^{15,20} In these cases, IV leucovorin and not intrathecal leucovorin should be administered. Intrathecal leucovorin was considered a major factor in the death of a child given a slightly higher dose of intrathecal methotrexate than was prescribed.¹⁸ Not all intrathecal methotrexate overdoses require aggressive intervention, but consultation with experienced hematologists/oncologists and medical toxicologists is warranted (Special Considerations: SC3).¹⁷ Consideration should be given to providing intrathecal glucarpidase.

Methanol Toxicity

Either folic acid or leucovorin (folinic acid) should be administered parenterally at the first suspicion of methanol poisoning. Folic acid is most commonly used. No complications are reported with the use of 50 to 70 mg of IV folic acid every 4 hours for the first 24 hours in the treatment of methanol-poisoned patients.²⁸ The precise dosage necessary is unknown, but 1 to 2 mg/kg every 4 to 6 hours is probably sufficient. Folic acid should be continued until the methanol and formate are eliminated. Because the first dose is usually administered before hemodialysis, a second dose should be administered at the completion of hemodialysis because this highly water-soluble vitamin will have been eliminated.

FORMULATION AND ACQUISITION

Leucovorin (folinic acid) powder for injection is available in 50, 100, 200, and 350-mg vials. Each milligram of leucovorin contains 0.004 mEq of calcium. Reconstitution with sterile water for injection—5 mL to the 50 mg vial, 10 mL to the 100-mg vial, or 20 mL to the 200 mg vial—results in a final concentration of 10 mg/mL. Adding 17.5 mL of sterile water for injection to the 350-mg vial results in a final concentration of 20 mg/mL. These lyophilized products contain no preservatives. The only inactive ingredient is sodium chloride added to adjust tonicity. Reconstitute with Sterile Water for Injection, USP, when doses greater than 10 mg/m² are used and use immediately. Further dilute in 100 to 1000 mL of 0.9% sodium chloride or D₅W for infusion.²¹ Leucovorin is also available in a single-use vial as a solution for injection at a concentration of 10 mg/mL in a 50-mL vial. Because of the calcium content, the rate of IV administration should not be faster than 160 mg/min in adults.¹⁹ Leucovorin is also available orally in a variety of strengths, including 5, 10, 15, and 25 mg tablets.

Levoleucovorin⁶ lyophilized powder for injection is available in a single-use 50 mg vial containing the equivalent of 50 mg of levoleucovorin as the calcium pentahydrate salt and 50 mg of mannitol. Reconstitution with 5.3 mL of 0.9% sodium chloride injection, yields a concentration of 10 mg/mL.⁵ Levoleucovorin is also available as a sterile solution in a single-use 175 mg vial that contains 17.5 mL of sterile solution in which each milliliter contains levoleucovorin calcium pentahydrate equivalent to 10 mg of levoleucovorin and 8.3 mg of sodium chloride. Because of the calcium content, the rate of IV administration should not be faster than 160 mg/min (16 mL of reconstituted solution/min).⁶ Further dilution to concentrations of 0.5 mg/mL in 0.9% sodium chloride injection or 5% dextrose injection is acceptable but should be used within 4 hours when stored at room temperature.⁶

Folic acid is available parenterally in 10 mL multidose vials with 1.5% benzyl alcohol in concentrations of 5 or 10 mg/mL from a variety of manufacturers. After it has been opened, the vial must be kept refrigerated.

If administration to neonates is necessary, a benzyl alcohol–free preparation must be used because of the toxicity of benzyl alcohol in neonates ([Chap. 55](#)).

SUMMARY

- Leucovorin (folinic acid) is the primary antidote for a patient who receives an overdose of methotrexate.
- Leucovorin is the biologically active, reduced form of folic acid, the synthesis of which is prevented by methotrexate.
- Only leucovorin (folinic acid) is an acceptable antidote for a patient with methotrexate toxicity, but either folic acid or leucovorin is acceptable for a patient poisoned by methanol.
- After a methanol overdose, folic acid enhances the elimination of formate ([Table A10–2](#)).

TABLE A10–2. Rapid Calculations

1 mole = 1 g molecular weight

1 Molar = 1 mole/L

1×10^{-3} moles = 1 millimole = 1 mmol

1×10^{-6} moles = 1 micromole = 1 μ mol

1×10^{-9} moles = 1 nanomole = 1 nmol

1 mole of methotrexate weighs 455 Da; 1 mole methotrexate = 455 g

1 Molar methotrexate = 455 g/L = 455 mg/mL

1×10^{-8} Molar methotrexate = 455×10^{-8} g/L = 455×10.8 mg/mL = 455×10^{-5} μ g/mL = 455×10^{-2} ng/mL = 4.55 ng/mL

Data from Methotrexate Injection, USP [package insert]. Bedford, Ohio: Manufactured by Bedford Labs; 2012.

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A11 ANTIDOTES IN DEPTH

Glucarpidase (Carboxypeptidase G₂)

Silas W. Smith

Glucarpidase (carboxypeptidase G₂, CPDG₂) is indicated for the management of methotrexate (MTX) toxicity. When given intravenously or intrathecally, it rapidly enzymatically inactivates MTX, folates and folate analogues. It does not substitute for and must be used in conjunction with leucovorin (Antidotes in Depth: A10). Leucovorin should not be administered within two hours before or after a dose of glucarpidase.

HISTORY

Soon after the description of the structure and synthesis of folate,⁶ a *Flavobacterium* species capable of removing the glutamate moiety of folate was discovered.³⁷ From 1955 to 1956, the inactivation of folate analogues (including by the chemotherapeutic aminopterin) was demonstrated in bacteria and yeasts.^{51,72} Purification of “carboxypeptidase G,” a pseudomonad-derived, zinc-dependent enzyme responsible for MTX cleavage, was reported in 1967.^{28,38} Other bacterial carboxypeptidases that differed in their substrate specificity and kinetics were isolated and purified in 1971 (*Pseudomonas stutzeri* carboxypeptidase G₁),⁴³ 1978 (*Flavobacterium* carboxypeptidase),⁵ and 1992 (*Pseudomonas* spp M-27 carboxypeptidase G₃).⁸⁰ By 1976, carboxypeptidase G₁ was scaled to pilot manufacturing production.¹⁸ Carboxypeptidase G₁ was initially explored as a chemotherapeutic to deprive growing tumors of folate.^{8,9,15,34} Human usage of CPDG₁ for this purpose was reported in 1974.⁹ The antidotal potential of carboxypeptidase was first suggested in 1972 when it was noted that carboxypeptidase G₁ rapidly decreased MTX concentrations and improved survival in mice injected with lethal MTX doses.¹⁶ CPDG₁ was subsequently used to selectively eliminate systemic MTX in patients treated with high dosages targeting central nervous system (CNS) malignancies.^{1,2} CPDG₁ was first used for rescue in a patient receiving MTX with kidney failure in 1978.³² Unfortunately, the enzyme source of CPDG₁ was then lost.^{4,82} The carboxypeptidase currently used in clinical practice (carboxypeptidase G₂) was cloned from *Pseudomonas* strain R16 and sequenced, characterized, and expressed in *Escherichia coli* in the early 1980s.^{46–48,63} The preliminary crystal structure was provided in 1991, with a complete characterization (at 2.5 Å) and description of the active site and biochemical mechanism of action in 1997.^{39,59,69} After the renewed availability of the recombinant CPDG₂ product, it underwent nonhuman primate testing for both intravenous (IV) and intrathecal (IT) rescue of MTX overdose.^{3,4} Reports of successful use in human IV and IT MTX overdose rapidly emerged.^{7,14,19,21,29,32,35,36,40,49,52,53,56,60,62,64,66,67,71,74,76–78,82} The US Food and Drug Administration designated glucarpidase an orphan product in 2003 and ultimately granted marketing approval in January 2012.¹³

PHARMACOLOGY

CHEMISTRY AND PREPARATION

Glucarpidase is produced by recombinant DNA technology. The enzyme cloned from *Pseudomonas* strain R16 is expressed in *E. coli* strain RV308.²⁴ The xenobiotic is manufactured in Belgium, and the final commercial product is filled, freeze dried, and packaged in the United States.^{24,31}

Mechanism of Action

Glucarpidase is a dimerized protein structure with two domains, a β-sheet interaction site and a zinc dependent catalytic domain.⁵⁹ The catalytic domain hydrolyzes C-terminal glutamate residues of folate and folate analogues such as MTX. Molecular modeling suggests that the two zinc (2+) ions bind a water molecule, promoting its polarization and nucleophilic

attack on the carbonyl group of the substrate (Fig. A11–1).⁷⁰ MTX and its metabolite 7-OH-MTX are thus split into inactive DAMPA (2,4-diamino-N¹⁰-methylpteroic acid) and OH-DAMPA plus glutamate.⁷⁹ DAMPA undergoes subsequent hepatic metabolism. Glucarpidase similarly inactivates leucovorin and folate by cleaving their terminal glutamate residues (Fig. A11–1).⁵

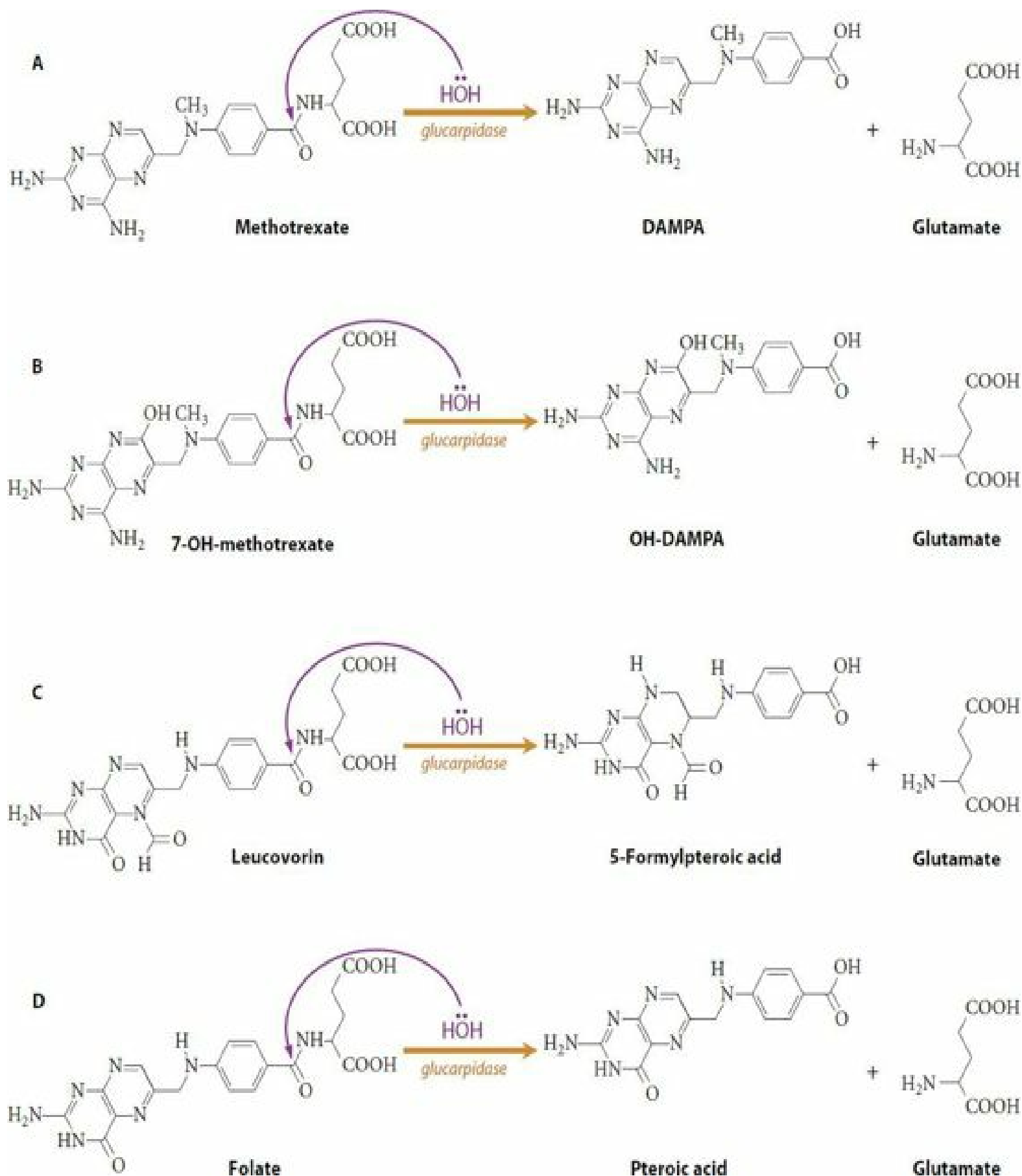


FIGURE A11–1. The catalytic domain of glucarpidase permits hydrolysis of the C-terminal glutamate residue of folate and folate analogues such as methotrexate (MTX) via hypothesized nucleophilic attack of a zinc bound water molecule.⁷⁰ (**A** and **B**) MTX and its metabolite 7-OH-MTX are split into inactive DAMPA (2,4-diamino-N¹⁰-methylpteroic acid) and OH-DAMPA plus glutamate. Glucarpidase similarly inactivates leucovorin (folinic acid) (**C**) and folate (**D**) by cleavage of

terminal glutamate residues.

Pharmacokinetics

In one study, 50 units/kg of glucarpidase was given IV to eight volunteer subjects with normal kidney function and four volunteers with impaired function (calculated creatinine clearance <30 mL/min; range, 9.8–27.4 mL/min).⁵⁷ Those with normal kidney function achieved a mean maximum serum concentration of glucarpidase of 3.1 µg/mL, with a mean half-life of 9.0 hours. These values were essentially unaffected in the setting of impaired glomerular filtration rate (GFR); therefore, renal dosing is not recommended.¹³ Glucarpidase restriction to the plasma compartment was implied by a volume of distribution of 3.6 L.⁵⁷ The large protein size (83 kDa dimer) of glucarpidase precludes traversing the blood brain barrier, crossing the cell membrane to act intracellularly, acting on MTX in the gut lumen, or treating MTX extravasation.^{1,16,19}

Pharmacodynamics

One unit of glucarpidase activity catalyzes the hydrolysis of 1 µmol of MTX per minute at 37°C.³ The mean enzymatic activity half-life of glucarpidase was 5.6 hours in normal volunteers and 8.2 hours in those with impaired GFR.⁵⁷ Its optimum activity pH is between 7.0 and 7.5, compatible with human physiology. After glucarpidase administration, a rapid decline of serum MTX concentrations by 71% to 99% occurred within minutes with the original Center for Applied Microbiology and Research (CAMR) product, with the concurrent appearance of inactive DAMPA in both serum and urine.^{14,36,62,64,73,74,76} DAMPA undergoes subsequent hepatic metabolism and renal elimination (~50%).⁷⁹ Commercial glucarpidase rapidly decreases serum MTX concentrations by greater than 97% within 15 minutes (Table A11–1).^{13,17,25,64} In one study, a reduction greater than 95% was sustained for up to 8 days in 20 of 22 patients.²⁵

TABLE A11–1. Glucarpidase Efficacy Trials^a

Trial	FDA T-001, ¹³ 2000–2003, "Berlin" ¹³	FDA T-002 ¹³ , 1993–2004, "NCI" ^{13,17}	FDA T-003, ²⁵ 1997–2002, "Bonn" ¹³	FDA T-006, ¹³ 2004–2007, "NCI" ¹³	FDA T-016, ¹³ 2007–2010, "BTG IND 11557" ¹³	2008–2010, "St. Jude" ¹⁷
Lot	CAMR	CAMR	CAMR	Commercial	Commercial	Commercial
Sites (n)	29	149	50	55	NR	1
Safety data (n)	43	214	65	149	141	20
Malignancies	ALL: 13; L: 12; +CNS: 16; others: 2	L/L: 111; OS/S: 75; others: 3	ALL: 26; NHL: 21; OS: 12; others: 6	L/L: 93; OS/S: 47; others: 9	L/L: 88; OS/S: 46; others: 7	ALL: 10; OS: 6; L: 4
Age (years)	18–78 (54)	0.4–82 (17)	0.9–71.8 (15.4)	0.08–85 (18)	0.5–85 (16)	4.1–20.4 (12.1)
TTT (hours)	27–176 (56)	NR	25–178 (52)	27–86 (48)	NR	26.3–95 (45.9)
Dose (U/kg)	10–58 (50)	NR	33–60 (50)	18–98 (49)	6–189 (50)	13–65.6 (51.6)
[MTX] (μmol/L)	1–1187	1–849 (35)	0.52–901 (11.93)	1.9–708 (38.9)	NR	1.3–590.6 (29.1)
[MTX] ↓ from baseline (%)	n = 24 18–99 (>97%)	n = 70 NR	n = 25 73–99 (97%)	n = 22 ≥97%	NR	n = 6 99.2–99.9 (99.6)
[MTX] RSCIR	83%	57%	NR	45%	NR	67%
Leucovorin dosing	mg = [MTX] (μM) × (kg); [MTX] _t ≤5 μM: 15–75 mg/m ² Q 6	1 g/m ² IV every 6 hours; then 250 mg/m ² Q 6 x 48 hours	None 4 hours prior; after 1 hour at 100 mg/m ² Q 6 x 24 hours	NR	NR	NR
Heme/myelo	60.4%	NR	4.6%	NR	NR	10%
Infection	16.2%	NR	12.5%	NR	NR	20%
Mucositis	34.9%	NR	15.3%	NR	NR	5%
Nephrotoxicity	18.6%	NR	34.1%	NR	NR	35%
Hepatotoxicity	16.2%	NR	32.9%	NR	NR	NR
MTX—death ^a	23.2%	5.1%	6.1%	4.0%	2.1%	0%

^aStatistical values denote medians. ^bOr not specifically reported as malignancy related.

ALL = acute lymphoblastic leukemia; CAMR = Center for Applied Microbiology and Research (UK) lot 004; FDA = Food and Drug Administration; heme/myelo = hematological toxicity/myelosuppression; L/L = leukemia/lymphoma; MTX = methotrexate; NC = National Cancer Institute; NHL = non-Hodgkin lymphoma; NR = not reported in FDA summary; OS/S = osteosarcoma/sarcoma; RSCIR = rapid and sustained clinically important reduction; T = Trial (FDA identifier); TTT = time to treatment.

ROLE IN METHOTREXATE TOXICITY

Patients receiving high-dose MTX therapy are routinely “rescued” with leucovorin (eg, 10 mg orally every 6 hours).⁸¹ Treatment nomograms and institutional algorithms recommend higher leucovorin doses when MTX concentrations are excessive or the elevation of the concentration is prolonged (Antidotes in Depth: A10).^{10,73,81} However, at MTX concentrations above 100 μmol/L (1×10^{-4} mol/L), data suggest that adequate leucovorin concentrations cannot be achieved for competitive and complete reversal of toxicity.^{14,36,41,58} Also, leucovorin administration provides 0.004 mEq of calcium per milligram of leucovorin and may be rarely associated with hypercalcemia in extremely high-dose therapy.⁸²

Glucarpidase is labeled for patients with serum MTX concentrations greater than 1 μmol/L in the setting of impaired kidney function (ie, an MTX concentration not within 2 standard deviations of the mean MTX excretion curve specific for the administered MTX dose).¹³ In the absence of an MTX concentration, significant mucositis, gastrointestinal (GI) distress, myelosuppression, hepatitis, or neurotoxicity should prompt consideration of glucarpidase in addition to aggressive leucovorin therapy while awaiting confirmation (off label).

Several efficacy and safety studies in both adults and children are summarized in Table A11–1. The CAMR product, used in several initial clinical trials,^{14,62,75} was not bioequivalent to the current commercial product.²⁵ Although no trial has yet demonstrated the superiority of glucarpidase as adjuvant therapy to leucovorin and supportive care alone, the pharmacodynamic efficacy is clear: baseline MTX concentration decreases by greater than 97%. Rapid and sustained clinically important reduction (RSCIR, [MTX] <1 μmol/L) occurred somewhat less frequently in 45%²⁵ and 67%¹⁷ of

patients. In exploratory analysis, patients with osteosarcoma—who received higher MTX doses (eg, 8–12 g/m²)—experienced less benefit with glucarpidase.²⁵ One analysis concluded that glucarpidase did not prevent fatal MTX toxicity in 3% of patients.¹³ However, data support the use of glucarpidase to treat those at risk of toxicity from MTX due to either persistently elevated MTX concentrations or kidney dysfunction.^{14,29,62,74} The use of glucarpidase to manage MTX toxicity has also permitted early resumption of MTX chemotherapy.^{7,17,21,67}

Intracellular MTX is polyglutamated, which hinders transmembrane transport and increases intracellular half-life. This MTX pool is inaccessible to glucarpidase (and hemodialysis) and can persist, causing cytotoxicity and a rebound in serum MTX concentrations for up to 85 hours after glucarpidase administration.^{27,62,75,77} Delaying glucarpidase more than 96 hours after MTX initiation, after intracellular MTX is established, is associated with failure to prevent significant MTX toxicity.^{62,75} This emphasizes the need for close monitoring of MTX concentrations and for early consideration for glucarpidase. Persistent intracellular MTX requires ongoing leucovorin therapy for 48 hours at the same leucovorin dose as that before glucarpidase and then repeated until the MTX concentration is below the leucovorin treatment threshold for a minimum of 3 days.¹³ Some authors continue leucovorin until the MTX concentration is less than 50 nanomol/L (0.05 μmol/L; 0.05×10^{-6} molar).⁷³

In the setting of oral MTX overdose, GI decontamination should be considered because glucarpidase has no intraluminal activity.

Because leucovorin is contraindicated for IT administration,^{23,33,68} IT glucarpidase provides an effective means to rapidly lower cerebrospinal fluid MTX concentrations in cases of overdose or prolonged persistence.^{3,52,77} The manufacturer is anticipated to pursue this indication under the “Animal Rule.”²⁵

Inadvertent or intentional MTX exposure^{50,65} is also an appropriate indication for glucarpidase, particularly before drug distribution. Additionally, glucarpidase has been proposed as an antidote for toxicity associated with pemetrexed (a folate antimetabolite).¹¹ In international patent applications, experiments demonstrated glucarpidase cleavage of pemetrexed and raltitrexed.^{44,45}

ADVERSE EFFECTS AND SAFETY ISSUES

Antidotal Compromise

The affinity of carboxypeptidase for MTX is 10 to 15 fold higher than for leucovorin; however, its affinity for the active metabolite of leucovorin, 5-methyltetrahydrofolate (5-mTHF) and folate are similar.^{5,22,63} Although racemic leucovorin is commonly prescribed, the active enantiomer is also commercially available. Because glucarpidase cleaves active levo-(6S)-leucovorin approximately 50% faster than inactive dextro-(6R)-leucovorin,³⁰ glucarpidase may compromise leucovorin rescue if both antidotes are administered contemporaneously. Fifteen minutes after administration of glucarpidase, median leucovorin and active 5-mTHF concentrations dropped by 8% and greater than 97%, respectively; the remaining leucovorin was likely the inactive d-isomer.^{73,75} Healthy volunteers provided leucovorin 2 hours after glucarpidase had their leucovorin concentrations decreased by 50%, and activated levo-5-mTHF was undetectable. When leucovorin therapy was delayed 26 hours after glucarpidase administration, enzymatic cleavage by glucarpidase still decreased leucovorin and 5-mTHF concentrations by 80% and 75%, respectively.²² In another study, when leucovorin was administered 2 hours after glucarpidase, maximum leucovorin concentration and area under the curve decreased by 54% and 33%, respectively; maximum (6S)-5-mTHF concentration and area under the curve decreased more significantly by 93% and 92%, respectively.²⁵ Thus, leucovorin should not be administered for at least 2 hours before or after glucarpidase is provided.

Immunogenicity

Initial studies reported adverse effects in four of nine patients treated with CPDG₁, including development of inactivating antibodies, “sensitization” to CPDG₁, and anaphylactoid reactions.^{1,2,9,32} In patients administered CPDG₂ fused to a murine single chain Fv antibody, 36% (11 of 30) developed anti-CPDG₂ antibodies, but no antimurine antibodies were detected.⁴² Studies using the noncommercial (CAMR) lot reported antiglucarpidase antibody (AGA) development in none of 28 patients⁷⁵ and in three of seven patients,⁶² respectively. In clinical trials using the commercial product, 15% (12 of 78) developed AGAs after a single glucarpidase dose, and 22% (4 of 18) developed AGAs after two doses.^{13,25} The current recombinant glucarpidase (CPDG₂) imparts a much lower incidence of adverse effects than the initial CPDG₁ enzyme, including paresthesias (2%), flushing (2%), nausea or vomiting (2%), hypotension (1%), headache (1%), and rash (0.3%).^{13,25} However, in intentional repeated dosing of glucarpidase with HDMTX, two of four patients experienced allergic reactions.²⁵

Although AGAs might decrease clinical efficacy or predispose to allergic reaction upon reexposure,^{2,4,22,62} many patients have been successfully treated with more than one dose of glucarpidase for persistently elevated MTX concentrations.^{14,19,36,53,56,62,66,78,82}

Other Considerations

Because “inactive” DAMPA has a pH-dependent urinary solubility eight to ten times less than MTX,^{30,74} alkalization and saline diuresis must be continued to prevent DAMPA precipitation and further renal compromise. Although the supplied product contains lactose and Tris-HCl with zinc buffer, lactose intolerant patients can receive glucarpidase. Previous concerns of allergic reactions to lactose-containing xenobiotics and patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosemia, or glucose–galactose malabsorption are unaddressed in prescribing guidelines.¹³

PREGNANCY AND LACTATION

Glucarpidase carries a pregnancy category C designation, although formal human and animal data are lacking. The excretion of glucarpidase in breast milk is unknown.

DOSING AND ADMINISTRATION

Glucarpidase is dosed in units per kilogram in both children and adults. After reconstituting each 1000 unit vial with 1 mL of sterile 0.9% sodium chloride, a single dose of 50 units/kg is administered immediately by bolus IV injection over 5 minutes. Although clinical studies permitted additional glucarpidase doses 24 to 48 hours later in cases of persistent MTX, repeat administration has not demonstrated significant efficacy.^{13,14,54,61} In cases of IT MTX overdose, a fixed dose of glucarpidase (2000 units) reconstituted in sterile 0.9% sodium chloride has been administered intrathecally (off label) over 5 minutes.^{52,77} A lack of compatibility studies precludes glucarpidase mixing with other xenobiotics.

Monitoring

False elevations of MTX concentrations are reported with all of the various immunoassay techniques after glucarpidase administration.^{21,30,36,56,78,82} The DAMPA product significantly cross-reacts with both MTX radioimmunoassay and competitive dihydrofolate reductase binding assays.²⁰ Both MTX metabolites (7-OH-MTX and DAMPA) appreciably interfere with fluorescence polarization immunoassay (FPIA) and enzyme multiplied immunoassay technique (EMIT) assays. For DAMPA, the cross-reactivity rates are 100% (EMIT) and 36% to 44% (FPIA).⁵⁵ 7-OH-MTX cross-reactivity using EMIT is 4% to 31%, and 0.6% to 3% with FPIA.^{26,55} Clinically, the concentrations of DAMPA detected are comparable to those of MTX after administration of CPDG₂.¹⁹ Thus, the use of high-performance liquid chromatography (HPLC) to determine actual MTX concentrations is mandated when glucarpidase is given.¹²

FORMULATION AND ACQUISITION

Branded glucarpidase (Voraxaze) is available in single use glass vials containing lyophilized glucarpidase (1000 units) with lactose monohydrate (10 mg), buffered to pH 6.5 to 8.0 with Tris-HCl (0.6 mg) and zinc acetate dihydrate (0.002 mg). It should be maintained at 36° to 46°F (2°–8°C) but not frozen. The manufacturer’s website details acquisition information for inside and outside of the United States (<http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze> and <http://www.btgplc.com/contact-us/contacts>, respectively).

SUMMARY

- Glucarpidase is a bacterially derived metalloenzyme used in the treatment of MTX toxicity. It cleaves MTX in the serum compartment to rapidly reduce serum MTX concentrations.
- Glucarpidase does not substitute for leucovorin, which must be continued to counteract persistent intracellular and CNS MTX.
- Do not administer leucovorin within two hours before or after a dose of glucarpidase to avoid the enzymatic destruction of folate and leucovorin.
- The measurement of MTX concentrations after glucarpidase administration will be unreliable unless HPLC is used.

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SC3 SPECIAL CONSIDERATIONS

Intrathecal Administration of Xenobiotics

Rama B. Rao

Cerebrospinal fluid (CSF) is produced by the choroid plexus that lines the cerebral ventricles at a rate of 15 to 30 mL/h, or approximately 500 mL/d in adults.⁵⁰ CSF flows in a rostral to caudal direction and is resorbed through the arachnoid villi directly into the venous circulation. The estimated total volume of CSF is 130 to 150 mL in healthy adults and 35 mL in infants.^{50,66,89}

For more than 100 years, a variety of experimental and therapeutic xenobiotics have been delivered directly into the CSF^{57,116} (Table SC3–1). The most common current indications for intrathecal administration include analgesia, anesthesia, and treatment of spasticity or central nervous system (CNS) neoplasms. The clinical advantages of this route of administration include targeted delivery and lower medication dosages with fewer systemic effects. Medications are usually administered via a spinal needle or an indwelling intrathecal catheter. Catheters may be attached to either an external or subcutaneous pump. Less commonly, medications are administered into a reservoir of an intraventricular shunt. The distribution of intrathecal xenobiotics is determined by a variety of factors. Some authors speculate that the xenobiotic movement is often attributed to both diffusion and convection, and they suggest that the dilution of xenobiotics administered via a lumbar catheter is attributed to the outflow of CSF from the fourth ventricle.⁸² In a radiolabeled tracer study of five patients with lumbar catheters, individuals received the hydrophilic radiolabeled diethylene triamine pentaacetic acid (¹¹¹In-DTPA) intrathecally. Neuroimaging revealed a drop in concentration of the tracer as the fluid moved rostrally.⁵⁹ The steady-state lumbar to cervical concentration for hydrophilic xenobiotics is 4:1 with marked interindividual variability.⁸⁶ Depending on the lipophilicity, the xenobiotic reaches the brain within a few minutes to 1 hour. Patient position and interindividual variations in lumbosacral CSF volume may affect xenobiotic distribution and may account for the differences in the level of spinal anesthesia among patients administered the same local anesthetic dosages.⁴⁸ Baricity, which is the ratio of the specific gravity of the xenobiotic to the specific gravity of CSF at 98.6°F (37°C), is also a consequential variable. Hyperbaric xenobiotics typically distribute in accordance with gravitational forces.⁴⁸ However, in overdose or administration of xenobiotics unintended for intrathecal administration, distribution, resorption, and clinical effects may not follow predictable models.

TABLE SC3–1. Xenobiotics Administered Intrathecally^a

Analgesics/anesthetics
Anesthetics (local)
Ketamine ⁴⁶
Morphine ⁶³
Opioids ⁷⁰
Zinconitide ¹⁷
Antimicrobials
Amikacin ^{14, 26}
Amphotericin B
Arbekacin ³⁸
Cefotetan

Ceftriaxone²²
Gentamicin¹⁰¹
Levofloxacin¹⁴
Penicillin
Polymyxin E¹³
Vancomycin^{1, 71}
Antiinflammatory
Corticosteroids
Antispasmodic
Baclofen
Chemotherapeutics
Liposomal cytarabine¹⁶
Methotrexate
Vasoactive
Epinephrine
Papaverine¹⁰⁶
Phenylephrine
Other
Bethanecol⁸⁴
Clonidine²¹
Colistin¹¹²
Midazolam¹¹⁹
Neostigmine⁶³
Octreotide^{79, 85}
Somatostatin
Tetanus immunoglobulin²

^aFew of these xenobiotics are approved by the US Food and Drug Administration for intrathecal administration. Most were utilized in clinical trials or as rescue therapy for refractory central nervous system disorders.

Complications can occur from preparation and dosing errors or inadvertent penetration of the dura and admixture with the CSF during epidural anesthesia or analgesia.^{25,47,48} Medications intended for intrathecal delivery may be administered into the wrong port of a pump delivery system, resulting in a massive overdose (see Pump Malfunction and Errors, below). Another potentially fatal error involves inadvertent administration of the wrong medication into the CSF.⁵³ This error occurs with misidentification or mislabeling of medications during pharmacy preparation or at the bedside. For patients with indwelling devices, medications intended for intravenous delivery may be inadvertently connected to the intrathecal

catheter, which also currently operates the same via Luer lock system.

Several factors affect the clinical toxicity of intrathecal medication errors.¹¹⁷ The properties of the medication are important. Ionized xenobiotics are likely to disrupt normal neurotransmission and cause toxicity, as may hyperosmolar or lipophilic xenobiotics. The site of administration may be important as well. Patients administered the wrong xenobiotic into an Ommaya reservoir (an intraventricular catheter with a subcutaneous access port on the scalp) may suffer immediate alterations in mental status depending upon the xenobiotic administered. Although intrathecal administration of preservatives and excipients have been investigated in animal models, the characteristics of these adjuvants in medication errors is not likely to be of value in predicting clinical effect.⁴⁹

Patients may present with exaggerated symptoms, typically associated with the xenobiotic. For example, patients with intrathecal morphine overdose may present with symptoms of opioid toxicity.⁵⁵ Other manifestations of intrathecal errors, regardless of the xenobiotic, include pain and paresthesias, often ascending in nature; autonomic instability, especially with extremes of blood pressure; and hyperreflexic myoclonic spasms similar to those that occur in patients with tetanus. Seizures or a depressed level of consciousness may also occur. The time of onset of these life-threatening symptoms may be determined by the dose and characteristics of the xenobiotic. For example, a woman inadvertently administered intrathecal potassium chloride complained immediately of severe back pain.⁷² Myoclonic spasms, seizures, and coma followed, and the patient died within 3 hours despite a normal serum potassium concentration. Patients with inadvertent vincristine exposures may be asymptomatic for many hours and die within a few days to a few weeks. In another example, a patient with an inadvertent intrathecal administration of aminophylline immediately developed leg cramps. He recovered and was discharged, only to return 24 hours later for leg weakness progressing to irreversible paraplegia.⁷

XENOBIOTIC RECOVERY FROM CEREBROSPINAL FLUID

Once a medication delivery error is identified, rapid intervention is mandatory, especially for ionized xenobiotics, chemotherapeutics, or iodinated water-soluble contrast agents because these xenobiotics usually reach the brain within an hour. In cases in which outcome is uncertain or not previously described, the exposure should be treated as potentially fatal. Any existing access to the CSF, ideally in the lumbosacral area, should be maintained.¹¹⁰ Immediate withdrawal of CSF, in volumes as high as 75 mL in adults, is indicated. This can be replaced with isotonic solutions: lactated Ringer, 0.9% normal sodium chloride, or Plasma-Lyte, or a combination of these. Older cases utilized Elliot B solution. Some authors recommend the initial large volume removal be performed in 20 to 30 mL aliquots. For children, multiple aliquots of 5 to 10 mL can be removed and replaced with isotonic fluid. If the patient can tolerate an upright position, this may limit cephalad movement of xenobiotics, but positioning for any critical life support measures should take precedence.

Delays to initial CSF drainage should be minimized as the interval between the exposure and CSF drainage may also affect the total xenobiotic recovered (see below). In the interim, a neurosurgical consultation should be obtained to consider the placement of cerebral ventricular access for the performance of continuous CSF lavage. This procedure, also known as ventriculolumbar perfusion, involves continuous instillation of an isotonic solution into the cerebral ventricular system with CSF drainage through a lumbar site. Another intervention involves placement of an epidural catheter into the intrathecal space at a space above the lumbar drainage site. An isotonic solution can be perfused through the catheter and drained caudally. This serves as a readily available, rapid intervention for patients awaiting placement of an emergent ventriculostomy.^{74,103}

For ventriculolumbar perfusion, lavage flow rates can be as great as 150 mL/h. Fresh frozen plasma can be added to the lavage fluid after several hours to increase the CSF protein content. The ideal lavage fluid, protein components, and infusion rates are not known.⁴⁴ Some protocols previously utilized are listed in [Table SC3–2](#). Although artificial CSF formulations exist, their role in the treatment of such medication errors is not evaluated.⁷⁶

Table SC3–2. Inadvertent Intrathecal Exposures

<i>Xenobiotic</i>	<i>Age/Sex</i>	<i>Mechanism</i>	<i>Clinical Findings/Effects</i>	<i>Intervention</i>	<i>Outcome</i>
Amisophylline ¹	64/M	Medication error	Muscle cramps initially Paraplegia at 24 hours	Observation	Paraplegia Death in 2 years
Backfen ²⁸	8/M	Probable pump malfunction	Coma, vomiting, bradycardia	20 mL CSF removed at undetermined time	Survived
Bortezomib ^{33,34}	Unknown	Medication error			Three deaths
Bupivacaine ⁴	34/M	Inadvertent dural puncture	Hypotension Ascending paralysis at 10 minutes		Survived
Cefotetan ¹⁸	66/M	Catheter misconnection	Dyspnea, hypotension, myoclonic spasm, pain at 2 hours	10 mL CSF removed at 20 hours	Rhabdomyolysis Survived
Ceftriaxone ²⁷	74/F	Overdose	Bilateral lower extremity pain	240 mL CSF removed in 20 mL aliquots, with 0.9% NaCl replacement therapy Started at unknown time	Survived
Cytarabine ⁸	4/M	Overdose	Mydriasis, delayed onset, gait impairment, tremor	50 mL CSF removed in 5-mL aliquots, with 0.9% NaCl replacement therapy Started at 65 minutes Estimated 27%–36% cytarabine recovery	Died of unknown cause
Dactinomycin ⁹	5/F	Medication error	Hypotonia, fasciculations, hyperreflexia at 2 hours	50 mL CSF removed with 0.9% NaCl replacement at 1 hour, then VI perfusion started at 1.5 hours using 0.9% NaCl 100 mL/h with 2.5 mg/mL hydrocortisone for 26 hours Other adjuncts	Ascending paraplegia, obstructive hydrocephalus Survived
Doxorubicin ¹	12/F	Medication error	Fever, headache, vomiting at 12 hours, seizures, hydrocephalus	No attempt at removal	Survived without sequelae at 56 days
Doxorubicin ¹⁹	31/F	Medication error	Hypoesthesia, paraparesis, incontinence over 7 days, T8 sensory level, bowel, bladder incontinence, meningismus, adhesive arachnoiditis at 3 weeks	CSF exchange at 20 mL/h for 500 cm ³ per publication; methyl prednisolone 500 mg/d and immunoglobulin 22 g/d initiated at 1 week Treatment of arachnoiditis with VP shunt placement	Lower extremity weakness 3/5 at 8 months, eventual ambulation with resolution of incontinence at 14 months
Furosemide ¹⁸	36/M	Medication error	None	No attempt at removal	Survived
Gadolinium ⁷	64/M	Medication error: gadopentetate dimeglumine	Confusion, nausea, vomiting, ataxia, nystagmus, hallucinations, blurred vision, depressed mental status	Not described	Survived
Gallamine ¹²	48/M	Medication error	Hyperreflexic myoclonic spasm, onset 1 hour 45 minutes; fever, hypertension, tachycardia, miosis, coma at 3 hours	15 mL CSF drainage started at 6 hours	Survived
Iohexol ¹⁶	52/M	Dural perforation	ATCS at 30 minutes, coma, hypoxia, fever		Survived
Ionic contrast media cases ¹⁰	Various	Medication errors	ATCS starting at 30 minutes to 6 hours	Variable	3/7 patients died; fractures, rhabdomyolysis
Iopamidol ¹⁹	Various	Medication error	Cranial neuropathy		Survived
Iothalamate Contrast ¹⁰	48/M	Medication error	ATCS, opisthotonos	Sitting position, intubation 145 mL CSF removal in 10–20 mL aliquots Other adjuncts	Survived
Leucovorin ²⁷	11/M	Therapeutic error	Seizures		Died day 5
Lidocaine, epinephrine, fentanyl ¹⁰²					
Patient 1	28/F	Dural perforation	Hypotension, numbness at 5 minutes	20 mL CSF drained within 5 minutes 51% lidocaine recovery, 4% fentanyl recovery	Survived
Patient 2	68/F	Dural perforation	C ₁ –C ₅ sensory impairment at 18 minutes	30 mL CSF drained at 18 minutes 39% lidocaine recovery; 7% fentanyl recovery	Survived

Magnesium sulfate ⁶⁵	23/F	Medication error	Backache, lower extremity weakness, intact sensation, normotension	Fowler position	Recovery within 7 hours
Mercury ⁶⁶	69/F	Inadvertent (Mercurochrome) injection into CSF fistula	Local pain, nuchal rigidity, coma at 24 hours	Lumbar drain, parenteral chelation	Sensorimotor polyneuropathy Survived
Methotrexate ⁶⁷	2/F	Overdose	Headaches	Varied	Survived
Methotrexate ⁶⁸	34/M	Overdose	Confusion, seizures, ARDS, coma at 2 hours	200 mL CSF drained and replaced with 0.9% NaCl started at 6 hours in aliquots over 48 hours, then another 150 mL CSF exchange over 36 hours (patient also inappropriately received an intrathecal leucovorin)	Cognitive and motor deficits
Methotrexate ⁶⁹	9/M	Overdose	Lower extremity numbness, seizures, flaccid paralysis, cranial neuropathy, posturing	200 mL CSF drained in 30–40 mL aliquots, replacement with Eliott's B solution Started at 45 minutes 78% drug recovery	Died
Methotrexate series I ⁷⁰		Overdose			
Patient 1	12/M		Headache, vomiting at 45 minutes	30 mL CSF drained and replacement with 20 mL of Eliott's B solution started at 2 hours 28% drug recovery	Survived until relapse leukemia
Patient 2	4/M			10 mL CSF drained at 45 minutes 20% drug recovery	Survived
Methotrexate series II ⁷¹					
Patient 1	4/M			250 mL CSF drained in 20 mL aliquots, replacement with 0.9% NaCl Started at 5 hours	Survived
Patient 2	11/M			20 mL CSF withdrawn then 210 mL CSF drained in 5-mL aliquots, replacement with 0.9% NaCl Started at 3 hours 37% drug recovery	Survived
Methotrexate ⁷²	3/F	Medication error: 125 mg	Seizures at 3 hours	No CSF exchange; IV leucovorin rescue and dexamethasone	Survived
Methotrexate ⁷³	26/M	Medication error: 625 mg	Immediate pain in leg, followed by coma and flaccid paralysis, renal failure	70 mL CSF drained at 2 hours; VL perfusion with 240 mL 0.9% NaCl over 3 hours; intrathecal administration of 1000 units CPDG ₂ at 8.5 hours 32% recovery in initial drainage fluid 58% recovery from perfusion drainage	Survived
Methotrexate ⁷⁴	Case series n = 7	Medication errors: 155–600 mg	5/7 patients with seizures, some with headache, nausea, vomiting	Various interventions including VL perfusion started within 1 hour with 500 mL 0.9% NaCl over 4 hours	All survived
Methylene blue ⁷⁵	Case series: n = 14	Direct toxicity due to dye or pH: 10–100 mg	Pain headache, paralysis	Not described	11/14 residual paraplegia or weakness
Methylene blue ⁷⁶	39/M	6 mL 1% solution; as above	Vomiting, hypotension day 1; paralysis and urinary retention	Not described	Paraplegia and death at 5 years
Morphine ⁷⁷	45/F	Inadvertent filling wrong port of subcutaneous infusion pump; 450 mg	Seizures, hypertension, subarachnoid hemorrhage	12 mL CSF withdrawn, then 550 mL CSF drained at 10 mL/h by gravity over 2–3 days	Survived
Morphine ⁷⁸	81/M	Inadvertent: 5 mg	Coma at 4 hours	50 mL CSF drained over 6 minutes, replacement with 50 mL 0.9% NaCl	Survived
Morphine ⁷⁹	47/F	510 mg into wrong port of pump	Myoclonic spasms, coma, seizures, cranial neuropathy, hypertension then hypotension	No CSF interventions	Survived

Neostigmine ⁶¹	26/M	Medication error		None	Survived
PEG asparaginase ⁶²	12/M	Wrong route	None	None	Survived
Penicillin ⁶³	22/M	Dosing error into Ommaya reservoir	Coma, hyporeflexia, tonic-clonic seizures, absence seizures, hypotension at 30 minutes	10 mL CSF withdrawal, then VL CSF drainage; replacement with LR over 30 minutes	Survived
Potassium chloride ⁶⁴	42/F	Medication error during labor	Immediate cramps, pain, seizures, normal serum potassium	None	Maternal-fetal death at 3 hours
Tamadol ⁶⁵	75/F	Connection error	Diaphoresis, hypotension at 10 minutes; myoclonic spasms, opisthotonos	None	Fatal at 48 hours
Tranexamic acid ⁶⁶	49/F	Medication error, wrong route	Immediate back pain, hypertension; seizure at 2 minutes; ventricular fibrillation	None	Fatal at 1.5 hours
Vincristine ⁶⁷	5/F	Medication error: 0.9 mg	Headache at 10 hours, opisthotonos, nystagmus, flaccidity	None	Fatal on day 18
Vincristine ⁶⁸	2.5/F	Medication error: 3 mg	Opisthotonos day 2	200 mL CSF drainage in 10 mL aliquots; replacement with 0.9% NaCl	Fatal on day 3
Vincristine ⁶⁹	27/F	Medication error into Ommaya reservoir	Ascending paralysis	Detail limited: CNS "washout" FFP and "lactate solution" in undefined quantities; timing not described	Fatal on day 10
Vincristine ⁷⁰	16/M	Mislabeled	Ascending paralysis at 2 hours, fever, coma	None	Fatal
Vincristine ⁷¹	Adult	Medication error	Ascending paralysis	CSF drainage unreported quantity and replacement with LR immediately; VL perfusion 150 mL/h for >24 hours then 25 mL FFP in 1 L isotonic solution at 75 mL/h for undefined time 95% recovery of vincristine	Lower extremity neuropathy
Vincristine ⁷²	4/F	Medication error: 1.5 mg	Nystagmus, encephalopathy, ascending paralysis, transient improvement	Immediate drainage 18 mL CSF in 3 mL aliquots; replacement 0.9% NaCl; an additional 30–40 mL drained over 30 minutes, starting at 10 minutes; VL perfusion using Plasma-Lyte to replace 200 mL CSF over at unknown rate, then 6 mL FFP in 250 mL Plasma-Lyte at 50 mL/h for 4 hours	Fatal on day 13
Vincristine ⁷³	1.25/M	Medication error: 0.7 mg	Fetile and irritable at 10 hours then lower extremity pain, nuchal rigidity, opisthotonos, ileus, hypotonia at day 2; ascending paralysis, encephalopathy by day 5; respiratory arrest at day 7	Intrathecal corticosteroids at 10 hours	Death on day 75 (withdrawal of life support)
Vincristine ⁷⁴	7/F	Medication error: 0.5 mg	Ascending weakness, pain, paraplegia	Upright position; immediate drainage 75 mL CSF within 15 min, replaced with LR; VL perfusion started within 2 hours with 150 mL/h of LR for 10 hours, then FFP 15 mL in 1 L LR as irrigant at 55 mL/h for 24 hours Other efforts	Paraplegia, neurogenic bladder Survived
Vincristine ⁷⁵	12/F	Medication error: 2 mg	Asymptomatic for 48 hours, then ascending paralysis, hiccups, cranial neuropathy, coma	35 mL CSF drained at 30 min, then additional drainage of 15 mL CSF replaced with LR; VL perfusion at 3 hours using FFP 15 mL in 1 L LR for total drainage of 615 mL CSF over 10 hours 0.785 mg recovered	Death on day 83
Vincristine ⁷⁶	23/M	Medication error: 2 mg	Headache day 1; leg weakness day 2–3; ascending myeloencephalopathy with coma at day 10; seizures	Drainage of 100 mL CSF at 10 minutes, "large volume lumbar punctures" on day 2 and 3	Prolonged coma, death at 11 months
Vincristine series ⁷⁷		Medication error			
Patient 1	5/F		Ascending paralysis, opisthotonos, coma	Not described	Death on day 7
Patient 2	57/M		Ascending paralysis	"Flushing the subarachnoid space"	Death at 4 weeks

Vincristine [®]	3/M	Medication error	Day 1: leg pain Day 2: headache, nuchal rigidity Day 3: bladder dysfunction, fever, lower extremity paralysis, opisthotonos and coma	Not described	Death on day 6
Vincristine [®]	59/F	Medication error into Ommaya reservoir; 2 mg	Nausea, vomiting day 1; altered mental status, tremor, chills, hiccups, nystagmus, coma over 1 week	50 mL CSF drainage at 10 minutes followed by 75 mL CSF drainage at 30 minutes; VL perfusion with LR and FFP over 24 hours	Death on day 40
Vincristine [®]	10/F	Medication error	Asymptomatic for 6 days, then ascending paralysis with incontinence	Immediate drainage of CSF for 15 minutes; epidural catheter above the lumbar drainage site with lumbolumbar irrigation using 12.5 mL FFP in 500 mL LR with 96 mL drained; VL perfusion within 90 minutes for 24 hours	Survived with sensory-motor deficits of the extremities and urinary incontinence
Vincristine [®]	5.5	1.2 mg	Headache, vomiting and backache at 3 hours, nystagmus, extremity weakness at 72 hours, autonomic instability, hiccups, encephalopathy	Drainage of 20 mL CSF at 30 minutes, repeated on day 2, intrathecal corticosteroids, 23% recovery of dose	Death on day 12
Vincristine [®]	29/F	2 mg	Headache, ascending paraplegia, cranial neuropathy, coma	Intrathecal infusion 5 mL 0.9% NaCl with drainage of 10 mL CSF, positioned upright, additional 60 mL CSF drained at 3 hours	Death on day 14, pulmonary embolus at autopsy
Ziconotide series [®]		Overtitration of therapeutic dosage in each case		Stopped medication in each case	Improved days-weeks later
Patient 1	47/M		Nystagmus, auditory and visual hallucinations, dysmetria, ataxia		Retrograde amnesia
Patient 2	62/M for pain of multiple sclerosis		Agitation, disorientation, waxing and waning mental status, hallucinations, allodynia, bradycardia		Resolution with discontinuation of medication
Patient 3	45/M		Nausea, lightheadedness, nystagmus, bradycardia, agitation		Resolution with discontinuation

AICS = ascending tonic clonic syndrome (myoclonus, hyperreflexia on minimal stimulation, beginning in the lower extremities); CNS = central nervous system; CPG2 = calcitonin receptor-like receptor 2; CSF = cerebrospinal fluid; FFP = fresh frozen plasma; LR = lactated Ringer's solution; VL = ventriculolumbar; VP = ventriculoperitoneal.

Depending on the xenobiotic exposure, specific antidotes or rescue agents can be employed. With most intrathecal exposures, these rescue agents will be administered via oral, intramuscular, or intravenous routes. Extreme caution should be undertaken to avoid delivery of antidotes directly into the CSF, unless specific data support their use. Immediate, aggressive CSF removal and lavage resulted in nearly 95% recovery of vincristine in the lavage fluid of a patient with inadvertent exposure. Of the published cases in which xenobiotic recovery is reported, percentages relate to both the lavage method and quantity of CSF removed. For example, withdrawal of 10 mL of CSF 45 minutes after a methotrexate overdose in a 4 year-old patient recovered 20% of the initial dose.³ Withdrawal of 200 mL of CSF in aliquots 45 minutes after methotrexate overdose in a 9 year-old patient recovered 78% of the initial dose.³¹ The specific xenobiotic may affect recovery as well. For example, a patient underwent withdrawal of 30 mL of CSF 18 minutes after an overdose of simultaneously administered lidocaine, epinephrine, and fentanyl. Approximately 39% of lidocaine was recovered, whereas the recovery of fentanyl was only 7%.¹⁰²

SPECIFIC EXPOSURES

Ionic Contrast

Several xenobiotics have been utilized historically for contrast myelography. Many of these xenobiotics were abandoned because of their propensity to cause adhesive arachnoiditis chronic pain syndromes or other complications (Thorotrast). Low osmolar, nonionic contrast media are currently utilized, but unfortunately, other hyperosmolar ionic media are readily available in radiographic suites and sometimes inadvertently administered. Patients may develop cranial neuropathies.³⁶ Exposed patients become symptomatic within 30 minutes to 6 hours after administration, with hyperreflexia and myoclonic spasms following minimal stimulation.^{91,93,107} Clinical symptoms typically begin in the lower extremities and move in a cephalad direction, sometimes progressing to opisthotonos. This is likely due to alterations in inhibitory neurotransmission

occurring in patients with tetanus; this condition is called ascending tonic-clonic syndrome (ATCS). In one review, three of seven patients with ATCS died as a result of their exposures.⁹¹ Immediate large volume CSF drainage should be performed in 20 mL aliquots with isotonic fluid replacement. Ventriculolumbar perfusion should be considered in severe cases.

Chemotherapeutics

Methotrexate is administered intrathecally for the prevention and treatment of leukemic meningitis or other CNS neoplasms.⁹ Errors are generally dose related.^{3,29-31,44,51,62,90,108} In most reported cases, aggressive drainage of as great as 250 mL of CSF in aliquots with isotonic fluid replacement was utilized without ventriculolumbar perfusion. Experimental treatment of patients with intrathecal carboxypeptidase G₂ (CPDG₂) has been described without obvious adverse events.^{77,114} The patients underwent lumbar drainage followed by intrathecal CDPG₂. Drainage removed between 32% and 58% of the methotrexate, and the antidote reduced the methotrexate concentrations by 98%. The patients received 2000 units of intrathecal CDPG₂ in 12 mL of 0.9% sodium chloride solution over 5 minutes (Antidotes in Depth: A11).

Intrathecal leucovorin is absolutely contraindicated as its use results in fatalities. Following intrathecal methotrexate overdose, the intravenous administration of leucovorin is appropriate^{52,109} (Antidotes in Depth: A10).

Vincristine is typically administered intravenously and does not cross the blood brain barrier. There are no therapeutic indications for intrathecal vincristine, and such errors are almost invariably fatal.^{4-6,15,27,35,39,41,60} In most cases, the error is the result of confusion of either syringes or catheter access. As soon as the exposure is identified, immediate CSF drainage should be instituted, and rapid neurosurgical consultation should be obtained. The few known survivors with cognitive function underwent early neurosurgical intervention for ventriculolumbar perfusion.^{5,29,74,87,123} One of the patients had an epidural catheter placed intrathecally above the drainage site for lumbolumbar perfusion while awaiting ventriculostomy. This method of intrathecal perfusion should be considered in all patients with intrathecal vincristine exposures until definitive ventriculolumbar perfusion can be established. Ideally, tubing systems should be readily available to prevent intrathecal medication errors.^{80,105} Other rescue medications are discussed in Chaps. 36 and 52.

PUMP MALFUNCTIONS AND ERRORS

Some implantable pumps contain two access sites, one of which is contiguous with the intrathecal space and allows for CSF withdrawal or injection of nonionic contrast media for imaging. The other access site is a depot port that is intermittently filled with concentrated amounts of drug (usually an opioid analgesic or baclofen) to be delivered through a programmable pump. In some patients, a template must be placed on the skin overlying subcutaneous pumps to ascertain the proper medication port. Errors occur when a concentrated bolus is inadvertently injected into the wrong port resulting in a massive, sometimes fatal, overdose.^{53,118} Massive intrathecal morphine overdose can have severe rapid symptoms, including hypertensive crises. Either reaccessing the CSF port immediately or placing a spinal needle into the intrathecal space at another site is critical for the withdrawal of CSF. Large-volume drainage with isotonic fluid replacement is required, as well as other supportive measures such as intravenous naloxone if opioid toxicity is present. The patients usually require intubation and care in an intensive care unit. The clinical service that placed the pump should be consulted to assist in further CSF access and perform interrogation of the pump in cases where malfunction is suspected.²⁸ If the consultant is not readily available, emptying the depot port will automatically cause the pump motor to stop.

The other pump problem encountered is sudden, insufficient delivery of either baclofen or an opioid analgesic.⁸⁸ This may occur because of pump malfunction. Alternatively, the intrathecal catheter may kink, migrate, or become obstructed by an inflammatory mass.^{23,24,53,81} Patients with chronic use of baclofen or morphine may suffer severe withdrawal symptoms when intrathecal delivery is disrupted.¹¹³ Intrathecal doses are 100 to 1000 times more potent than the equivalent dose administered intravenously.⁵⁶ The patients may therefore require very high oral or intravenous doses to treat withdrawal until intrathecal delivery can be reestablished. The clinical service that implanted the pump should be consulted, and a thorough neurologic examination should be performed to evaluate for spinal cord compression symptoms.⁵³ An anteroposterior and lateral radiograph can be obtained to assess for kinking or fracture of the catheter.

ERROR PREVENTION

All intrathecal medication errors are preventable.⁴² Mechanisms for prevention are well described.^{32,69} They include trained pharmacists and administering physicians, specialized packaging and handling, use of minibags for intrathecal medications whenever feasible, preadministration of any intravenous medications, removal of all syringes and other medications from the area, and a checklist and time out with two persons reviewing all labels. More recently non-Luer lock systems are being explored to limit connection errors,⁷⁸ but these are predicted to be available in 2015. Any adopted system of prevention should include steps for intrathecal administration of required xenobiotics in all settings, including

treatment wards, outpatient clinics, radiology suites, and the operating room, as well as by all intrathecal routes such as implantable pumps, Ommaya reservoirs and lumbar or other access points.

SUMMARY

- Intrathecal medication errors can be life threatening.
- Errors may occur during preparation or administration.
- Rapid intervention with CSF drainage should be considered when a dosing or medication error occurs.
- More aggressive therapies may be required for chemotherapeutics, depending on the administered chemotherapeutics.

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SC4 SPECIAL CONSIDERATIONS

Extravasation of Chemotherapeutics

Richard Y. Wang

Extravasation injuries are among the most consequential local toxic events. When certain chemotherapeutics leak into the perivascular space, significant necrosis of skin, muscles, and tendons can occur with resultant loss of limb or function. The initial manifestations may include swelling, pain, and a burning sensation that can last for hours. Days later, the area can become erythematous and indurated, followed by resolution or progression to ulceration and necrosis.³⁵ These early findings can be difficult to distinguish from other forms of local drug toxicity, such as irritation and hypersensitivity, which can result from the chemotherapeutic or its vehicle (ethanol, propylene glycol). For example, fluorouracil, carmustine, cisplatin, and dacarbazine are considered as local irritants. The local irritation and hypersensitivity manifestations are self-limiting and typified by an immediate onset of a burning sensation, pruritus, erythema, and a flare reaction of the vein being infused. Hypersensitivity reactions are reported with daunorubicin, doxorubicin, idarubicin, and mitoxantrone. Pretreatment with an antihistamine can prevent some of the hypersensitivity manifestations.⁴³ When a local reaction cannot be differentiated from an extravasation, it is prudent to presume extravasation has occurred and manage the situation accordingly.

The occurrence of extravasations appears to be about 50 times more frequent with inexperienced clinicians.¹⁹ Factors associated with extravasation injuries from peripheral intravenous lines include (a) poor vessel integrity and blood flow, such as those found in the elderly and in patients with numerous venipuncture attempts or who have received radiation therapy to the site; (b) limited venous and lymphatic drainage caused by either obstruction or surgical resection; and (c) the use of venous access overlying a joint, which increases the risk of dislodgments because of movement.^{20,35} Extravasation injuries from implanted ports in central venous vessels can occur from inadequate placement of the needle, needle dislodgement, damaged septum in the port, fibrin sheath formation around the catheter, perforation of the superior vena cava, and fracture of the catheter.³⁷ When extravasation from a central venous port is suspected and radiographic studies are not diagnostic, a computed tomography scan of the chest with contrast is necessary for evaluation.¹

The factors associated with a poor outcome from extravasation injuries include (a) areas of the body with little subcutaneous tissue, such as the dorsum of the hand, volar surface of the wrist, and the antecubital fossa, where healing is poor and vital structures are more likely to be involved; (b) increased concentrations of extravasate; (c) increased volume and duration of contact with tissue; and (d) the type of chemotherapeutic.^{35,36} Vesicants, such as doxorubicin, daunorubicin, dactinomycin, epirubicin, idarubicin, mechlorethamine, mitomycin, and the vinca alkaloids, result in more significant local tissue destruction than other types of chemotherapeutics, such as irritants. Mitomycin infusions can cause dermal ulcerations at venipuncture sites remote from the location of administration.³³ The anthracycline antibiotics are associated with a higher incidence of significant injuries and delayed healing, which can be a result of their slow release from bound tissue into surrounding viable tissue. Doxorubicin extravasation is associated with local tissue necrosis in approximately 25% of reported cases. The extravasation injuries from taxanes appear similar to the vesicants but are less severe in response and more delayed in presentation.^{3,34} Prevention is the best therapy for these injuries. Specialized nursing care and the use of indwelling central venous catheters limit the extent of these injuries.

MANAGEMENT

The treatment for extravasation injuries is controversial, varying from conservative care to early surgical débridement and the use of selective antidotes.³⁷ This uncertainty is a result of the limited number of clinical cases available for study and the discordance between animal studies and human experience. However, general and specific management guidelines for an extravasation and their theoretical foundations exist (Table SC4–1).^{6,9}

Once extravasation is suspected, the infusion should be immediately halted. A physician should be notified, and the chemotherapeutic, its concentration, and the approximate amount infused should be noted. The venous access should be maintained to permit aspiration of as much of the infusate as possible and administration of an antidote, if indicated. Injection of 0.9% sodium chloride into the catheter to dilute the extravasate can be beneficial.^{12,17,23,37} The intermittent local application of ice and elevation of the extremity should be done for 48 to 72 hours to limit further progression of the xenobiotic and the development of dependent edema. Cooling the affected area is believed to prevent cell injury by

reducing the amount of chemotherapeutic absorbed by the tissue and lowering the cellular metabolic rate.^{24,42} With just cold application and strict elevation, only 13 of 119 patients (11%) with mild extravasations required surgical intervention for their injuries.²⁷ In the past, heat was recommended to disperse the xenobiotic, but investigations with animals treated with intradermal doxorubicin demonstrated that this can increase the area of skin ulceration.^{11,27} However, dry, warm compresses are still recommended to promote the systemic uptake of the vinca alkaloids (vincristine and vinblastine) and etoposide.⁷ This is combined with the immediate and local infiltration with hyaluronidase to enhance absorption (Table SC4–1). Human recombinant hyaluronidase (Hyalenex) comes as 150 units/mL and it can be administered as five separate and equally spaced subcutaneous injections of 0.2 mL (30 units) using a 25-gauge or smaller needle at the leading edge of the infiltrate.^{13,14,18} Wounds that are either cancerous or infected should not be treated with hyaluronidase. Patients treated with hyaluronidase need to be monitored for allergic reactions, such as anaphylaxis, although the human recombinant form is less allergenic than animal-derived hyaluronidase.

The wound should be observed closely for the first 7 days and a surgeon consulted if either pain persists or evidence of ulceration appears.³⁵ However, in severe extravasations—where there is a high likelihood of necrosis because of the chemotherapeutic (doxorubicin), the volume or concentration, and any area in which there may be significant long-term morbidity (over joints)—early surgical consultation is recommended. If tissue ulceration occurs, initial management may be restricted to sterile dressings to prevent secondary infections. Once the area of necrotic skin can be clearly delineated from surviving tissue, surgical débridement can be beneficial to limit secondary infection. The use of intravenous fluorescein or other dye indicators can aid in identifying viable tissue.² The patient can require surgical reconstruction or skin grafts depending on the extent of the injury.

ANTIDOTES

Antidotal therapy should be considered when the extravasated xenobiotic is known to respond poorly to conservative care. The antidotal treatments can be categorized by their mechanism of action. Topical corticosteroids have been used to reduce the inflammatory response, including hypersensitivity reactions, from extravasated xenobiotics.^{23,44} However, this therapy remains a controversial practice for chemotherapeutics that are known to cause necrosis, such as doxorubicin and vinca alkaloids,^{4,19,28,40} because the initial injury is not attributed to the presence of inflammatory cells.⁸ Corticosteroids should not be added to doxorubicin infusions, because these drugs are chemically incompatible.³⁹ The administration of 5 mL of 8.4% sodium bicarbonate for extravasations with doxorubicin was advocated in 1980 because it could decrease the DNA binding of doxorubicin by altering the pH of the environment.⁵ However, this treatment is no longer routinely performed due to the intrinsic hyperosmolality of the bicarbonate solution, which can cause tissue necrosis.¹⁶ Sodium thiosulfate is recommended for mechlorethamine extravasations and is believed to inactivate the xenobiotic by reacting with the active ethylenimmonium ring.^{20,32} The site should be infiltrated with 2 mL of a sterile 4% (isotonic) sodium thiosulfate solution for each milligram of mechlorethamine, followed by intermittent ice compresses for 48 to 72 hours.⁶

Finally, there are antidotes, such as dimethyl sulfoxide (DMSO), that scavenge the free radicals that are believed to cause tissue damage from chemotherapeutics, such as doxorubicin. DMSO was shown to be beneficial for anthracycline extravasations in both animal and human clinical trials.^{7,11,28,32,38} DMSO was used at a concentration varying from 55% to 99% (w/v) and it was applied topically and then followed with intermittent cool compresses.^{7,15,28,31} Additional beneficial properties of DMSO are its antiinflammatory, analgesic, and vasodilatory effects, as well as its ability to promote systemic absorption of the chemotherapeutic at local sites.²⁹ However, the role for DMSO in the treatment of anthracycline extravasations has become secondary since dexrazoxane was approved by the FDA for use in the treatment of anthracycline extravasation in adults.²² Also, DMSO is not recommended in conjunction with dexrazoxane for the treatment of anthracycline extravasations. Dexrazoxane is believed to limit free radical cellular damage by chelating iron and directly acting as an antioxidant. The systemic administration of dexrazoxane limited anthracyclines-induced skin lesions in a murine model²⁵ and was used successfully in patients following doxorubicin^{10,26,41} and epirubicin^{21,25} extravasations. In two prospective, open-label, single-arm, multicenter clinical trials, the systemic administration of dexrazoxane within 6 hours of anthracycline extravasation resulted in the need for surgical resection of the wound site in only 1 of 54 (1.8%) patients.³⁰ Dexrazoxane was given to these patients over 3 days intravenously at a starting dose of 1000 mg/m², which was infused over 15 to 30 minutes at a site distant to that of the extravasation because of its irritating property. Cool compress at the site of the extravasation was discontinued for 15 minutes prior to therapy to promote the antidote's perfusion at the site. The dose of dexrazoxane (Table SC4–1) is decreased for patients with diminished renal function (creatinine clearance < 40 mL/min). Patients need to be monitored with serial CBCs and serum AST/ALTs because dexrazoxane can cause reversible bone marrow suppression and elevated liver enzymes. Additional clinical evidence needs to be gathered to better define the medical management of other chemotherapeutic extravasations. The overall incidence of extravasations with chemotherapeutics is likely small, the associated morbidity can be significant.

TABLE SC4–1. Management of Extravasational Injuries^{6,22}

	<i>Therapy</i>	<i>Purpose/Mechanism</i>
<i>General</i>		
	Stop infusion and maintain intravenous cannula at the site.	
	Aspirate extravasate from the site by accessing the original intravenous cannula.	Minimizes amount of chemotherapeutic localized at the site
	Irrigate subcutaneous tissue at the site with 0.9% sodium chloride by accessing the original intravenous cannula.	
	Apply dry cool compresses for 1 hour, every 8 hours for 3 days. ^a	Localizes area of involvement and diminishes cellular uptake of the chemotherapeutic
	Elevate extremity and administer analgesia.	Promotes drainage, prevents dependent edema, and provides comfort
<i>Chemotherapeutic Specific</i>		
Anthracyclines	Dexrazoxane 1000 mg/m ² , daily (max. 2000 mg per day), on days 1 and 2, and 500 mg/m ² on day 3 (max. 1000 mg); dose is decreased for patients with kidney disease	Limits free radical formation
Mechlorethamine	Sodium thiosulfate: Take 1.6 mL of 25% sodium thiosulfate and add to 8.4 mL of sterile water for injection to make a 4% solution Infiltrate the site of extravasation with 2 mL of 4% sodium thiosulfate per milligram of mechlorethamine in the extravasate.	Prevents tissue alkylation
Mitomycin	Dimethyl sulfoxide (DMSO): 55%–99% (w/v) applied topically and allowed to air dry	Free radical scavenger
Vinca alkaloids and epipodophyllotoxins	Hyaluronidase: inject, subcutaneously, 150 units/mL into the site as five separate and equally spaced injections of 0.2 mL using a 25 gauge or smaller needle at the leading edge of the infiltrate Dry warm compresses	Hyaluronic acid enhances systemic absorption Promotes systemic absorption

^aExcept for Vinca alkaloids and epipodophyllotoxins.

SUMMARY

- Prevention is the best form of therapy for these injuries.
- Immediately stop the infusion following a suspected extravasation.
- Aspirate, irrigate the site with 0.9% sodium chloride, apply dry cool compresses, elevate the extremity and administer

analgesia.

- Consider a specific antidote.

Disclaimer

The findings and conclusions in this chapter are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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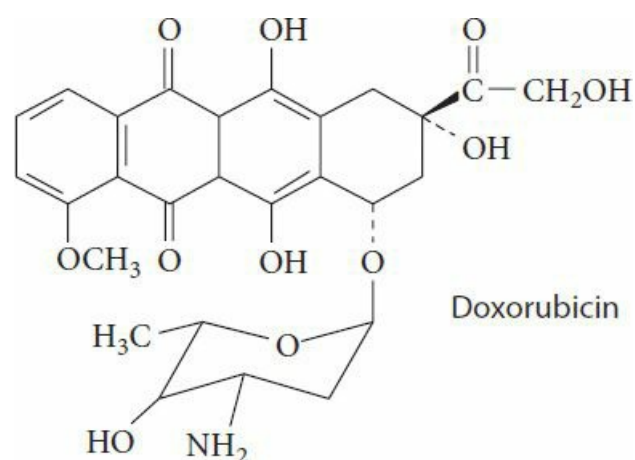
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52 MISCELLANEOUS CHEMOTHERAPEUTICS

Richard Y. Wang

The anthracyclines,^{24,120} nitrogen mustards,^{1,38,55,60,90,130} and platinum-based complexes^{32,35,59,64,68,83,108,111,124} are discussed in this chapter because of their increased likelihood for overdose based on past reports and current clinical use.

ANTHRACYCLINES



Daunorubicin and doxorubicin share many common indications for cancer therapy, but they differ in that doxorubicin is used in solid tumors such as breast carcinoma, and daunorubicin is used in hematogenous malignancies, such as acute myelogenous leukemia and acute lymphocytic leukemia. The clinical toxicity of the older anthracyclines is limited by the use of less toxic structural analogs (eg, epirubicin, idarubicin) and liposome-encapsulated formulations (pegylated liposomal doxorubicin).

Pharmacology

The chemotherapeutics derived from the bacterium *Streptomyces* are dactinomycin, daunorubicin, doxorubicin, bleomycin, mitomycin, and plicamycin. Only plicamycin crosses the blood–brain barrier. Doxorubicin has a protein binding of 75% to 80%, a volume of distribution of 28.0 ± 3.3 L/kg, and a terminal elimination half-life of approximately 30 hours.⁴³ The liposome encapsulated formulation of doxorubicin has a prolonged terminal half-life of 50 hours because of a slower clearance compared with the nonencapsulated formulation. Doxorubicin and daunorubicin are both eliminated by the liver, and their dosages are decreased in patients with hepatic insufficiency. Delayed drug elimination contributes to increased area under the concentration versus time curve and peak concentration, both of which are associated with myelosuppression and cardiac toxicity, respectively.⁶⁶ The mechanism of therapeutic action of the anthracyclines is attributed to DNA intercalation¹⁰¹ and inactivation of topoisomerase II.¹¹⁷ These xenobiotics are metabolized to active metabolites, which have lesser degrees of activity than their parent compounds. The liposomal-encapsulated formulation of doxorubicin has limited selective activity at the tumor compared to nontumor sites in the body, such as the heart and bone marrow because of its particle size (100 Å).^{86,98} A typical dose schedule for daunorubicin is 30 to 60 mg/m² daily for 3 days; for doxorubicin, 45 to 60 mg/m² every 18 to 21 days; and for pegylated liposomal doxorubicin, 50 mg/m² every 28 days.

Pathophysiology

The red anthracycline antibiotics—dactinomycin and doxorubicin—are associated with cardiotoxicity, which limits their therapeutic use. The associated toxicity is caused by a different mechanism than the therapeutic effects.¹¹⁷ The purported mechanism of cardiac toxicity is from the formation of free radicals and impaired intracellular calcium.^{84,91} Doxorubicin and dactinomycin are quinone derivatives and can be reduced to free radicals. These metabolites are extremely cytotoxic through the promotion of lipid peroxidation in a manner similar to paraquat and bleomycin. The limited efficacy of free

radical scavengers (α -tocopherol, N-acetylcysteine) for anthracycline cardiotoxicity led to an understanding of the importance of iron as a cofactor for these free radical-producing reactions.⁸⁵ The anthracyclines have a high affinity for metal ions. Doxorubicin has an iron (Fe^{3+}) binding constant of 10^{41} , which is comparable to deferoxamine.⁴¹ The heart's increased susceptibility to free radicals is attributed to its lack of sufficient enzyme activity responsible for free radical scavenging.²⁹

Clinical Manifestations

The cardiotoxic manifestations can be divided into those occurring acutely or those of late onset. Acute toxicity is characterized by dysrhythmias, ST and T-wave changes on the electrocardiogram (ECG), diminished ejection fraction that usually resolves over 24 hours, or sudden death.^{12,113} Abnormal findings on ECG are present in 41% of patients receiving doxorubicin.^{103,113} These abnormalities are neither dose related nor associated with the development of cardiomyopathy. Acute pericarditis and myocarditis resulting in conduction defects and congestive heart failure (CHF) are also reported.¹³ Animal studies with doxorubicin demonstrate beneficial effects of adrenergic antagonists for toxicity because of elevated concentrations of catecholamines.¹³

Significant cardiotoxicity results from elevated peak serum concentrations and led to therapeutic decisions based on continuous or periodic infusion delivery. The anthracycline antibiotics can cause a congestive cardiomyopathy with systolic dysfunction that typically presents at 1 to 4 months after exposure.⁵³ The condition is irreversible and is associated with a 48% mortality.⁹⁴ This drug induced CHF is associated with pathognomonic changes on electron microscopy that can distinguish this type of cardiomyopathy from that of infectious and ischemic etiologies. These histologic changes include reduced numbers of myocardial fibrils, and mitochondrial and cellular degeneration.¹⁰ The incidence of late onset cardiotoxicity for doxorubicin is between 1% and 10% when the cumulative dose is less than 450 mg/m^2 , and this incidence becomes greater than 20% when more than 550 mg/m^2 (comparable to dactinomycin, 950 mg/m^2 , and epirubicin, 720 mg/m^2) is administered.^{79,127} Daunorubicin and mitoxantrone are associated with a 2% incidence at the cumulative doses of 600 mg/m^2 and 140 mg/m^2 , respectively.

The best way of monitoring cardiac function during therapy is to measure the left ventricular ejection fraction (LVEF) by radionuclide cineradiography or echocardiography.⁴ However, the radionuclide method is more sensitive to small decreases in the LVEF than the method using sonography.³⁶ Therapy should be discontinued when the ejection fraction falls below 50%. Two dimensional echocardiography can demonstrate left ventricular wall thickening and fractional shortening from anthracycline overexposure. Newer approaches used to determine early or subclinical signs of cardiac dysfunction include the evaluation of cardiac specific contractile protein, troponin, cardiac natriuretic peptide, and radionuclide tagged monoclonal antibody imaging.^{37,65,71}

Factors associated with an increased risk of cardiotoxicity include mediastinal irradiation, preexisting cardiac disease in children, age older than 70 years, and the concomitant use of cyclophosphamide, paclitaxel, and other anthracyclines.¹³ The recent therapeutic use of the monoclonal antibody to human epidermal growth factor receptor 2 (HER2), trastuzumab, with anthracyclines appears to enhance cardiac toxicity.²⁶ Children are at risk for developing increased left ventricular afterload from doxorubicin toxicity because of the ability of the drug to inhibit myocardial growth, which can lead to a disproportionate ratio of left ventricular wall thickness to left ventricular chamber size.⁶⁹ Fatalities are reported with minimum doses of 150 to 333 mg/m^2 and occur within 1 to 16 days following exposure.²⁴

Myelosuppression and mucositis from the use of the anthracyclines typically occur in 1 to 2 weeks.⁷ The white cells are affected more than either the red cells or platelets. Patients with diminished drug clearance due to hepatic failure are at risk for the development of these findings.

Mitoxantrone is less toxic than doxorubicin and daunorubicin. Major organs of toxicity remain the heart, bone marrow, and gut. Gastrointestinal effects are less severe and less frequent with mitoxantrone than with doxorubicin.¹¹⁰ Four cases of mitoxantrone overdose are reported in the literature.^{45,110} Common to these events is a 10-fold error in dosing (100 mg/m^2 instead of 10 mg/m^2), early onset of nausea with vomiting, and myelosuppression with fever. Acute decreased cardiac contractility was observed by echocardiography in an asymptomatic patient.⁴⁵ No patients developed dysrhythmias, congestive heart failure, ECG changes, or elevated creatine phosphokinase concentrations. Unfortunately, three patients developed fatal CHF from 1 to 4 months later.¹¹⁰

Management

Patients receiving anthracyclines require monitoring for cardiotoxicity and pancytopenia. A baseline chest radiograph, ECG, and echocardiography to determine LVEF (at rest and/or with stress) are necessary. Endomyocardial biopsy and cardiac catheterization can assist in distinguishing other causes of cardiac dysfunction. Left ventricular function is the best predictor for cardiomyopathy.^{34,104} A 10% absolute decrease in the LVEF or a decrease in LVEF of 50% from baseline is

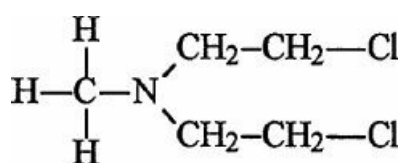
an indication to discontinue anthracycline therapy.¹⁰⁴ Treatment is largely supportive and includes the use of dexrazoxane, which is a specific antidote for doxorubicin toxicity. Dexrazoxane is a cardioprotectant that limits the adverse cardiac effects of doxorubicin by chelating intracellular iron, which mediates the formation of free radical cellular damage.

In clinical trials, patients receiving dexrazoxane had smaller decreases in LVEF per dose of doxorubicin or epirubicin, had fewer histologic changes on cardiac biopsy, were better able to tolerate doxorubicin doses greater than 600 mg/m², and had a lower occurrence of CHF than did patients who were not pretreated with dexrazoxane.^{40,71,72,112,115,116,123} The current role of this chelator is to limit cardiotoxicity in patients receiving more than 300 mg/m² of doxorubicin.¹⁰⁶ It is administered 30 minutes before doxorubicin in a ratio not greater than 10:1 to limit dexrazoxane-induced granulocytopenia and thrombocytopenia.^{112,115,116} The early institution of β -adrenergic antagonists (carvedilol) or angiotensin-converting enzyme inhibitors can reduce cardiac dysfunction from anthracycline therapy, but they are less effective than dexrazoxane.^{42,58,70} Further investigations are required to determine the optimal use of dexrazoxane in patients with unintentional excessive exposures.

Enhanced Elimination

The anthracyclines are highly protein bound and have a large volume of distribution, which limits the use of hemodialysis. However, the early institution of hemoperfusion may enhance elimination. In an animal model, serum doxorubicin clearance could be enhanced up to 20 fold with hemoperfusion.¹²⁹ Factors determining this were duration of therapy, rate of flow, and the use of a 2% acrylic hydrogel coated cartridge. Three patients with a doxorubicin overdose were treated with hemoperfusion, one with an Amberlite cartridge, and all had a rapid reduction in their serum concentrations.²⁴ One survived a 10 fold error in dosing. In a patient with an intravenous mitoxantrone overdose of 98 mg, hemoperfusion was begun within hours, but in two sessions, only 0.287 and 0.236 mg of drug were removed.⁴⁵ The role of double-filtration plasmapheresis to enhance the elimination of liposomal encapsulated doxorubicin in the overdosed patient remains exploratory.⁹⁵

NITROGEN MUSTARDS



Mechlorethamine

Pharmacology

The nitrogen mustards include cyclophosphamide, ifosfamide, chlorambucil, mechlorethamine, and melphalan. Their indicated uses include immunosuppression (eg, controlling graft-versus-host rejection, collagen vascular diseases) and chemotherapy. The tumoricidal activity of these xenobiotics results from the formation of reactive intermediates that bind to chemotherapeutic moieties on DNA, which inactivates DNA synthesis. Mechlorethamine is the original compound from which all of the others were derived. It is highly reactive when it comes in contact with water and undergoes rapid chemical transformation. Local reactions caused by mechlorethamine spillage (eg, extravasation) include tissue injury and thrombophlebitis (Special Considerations: SC4). Nonenzymatic hydrolysis is the major route by which the nitrogen mustards are metabolized, thus accounting for their relatively short elimination half-lives (<3 hours).⁹ Unlike the other xenobiotics in this class, cyclophosphamide and ifosfamide are prodrugs and require cytochrome P450 (CYP2B6 and CYP3A4) activation to achieve their alkylating properties. The pharmacokinetic parameters estimated for ifosfamide are elimination half-life in blood, 4.5 hours (range, 3.4–6.1); volume of distribution, 0.56 L/kg (range, 0.29–0.82); clearance, 79 mL/min (range, 59–116); and protein binding, 20%.⁶⁷ Cyclophosphamide, ifosfamide, and chlorambucil have active metabolites, which prolong their alkylating activity after administration.⁵⁶

Clinical Manifestations

Chlorambucil and ifosfamide can cause altered mental status and myoclonic or tonic-clonic seizures from therapeutic use or from an overdose.^{15,16,38} Both chemotherapeutics undergo hepatic N-dechloroethylation to produce chloroacetaldehyde, which is a presumed nervous system toxin.⁶³ Encephalopathy occurs in 9% of patients receiving 5 g/m² of ifosfamide and is more frequent with oral than with intravenous (IV) administration because of the first-pass effect and increased chloroacetaldehyde production.⁷⁸ Seizures are more commonly associated with chlorambucil than other nitrogen mustards.

Acute overdoses reported from oral exposures range from 1.5 to 6.8 mg/kg (therapeutic is 0.1–0.2 mg/kg).^{5,16} The seizures occur within 6 hours, can appear as generalized tonic–clonic activity or staring spells, and last for up to 24 hours. However, in one instance in which therapeutic dosing was increased, seizures occurred 17 hours later. This delay can be attributed to a lower serum concentration, a slower time to peak than in the overdose setting, or accumulation of active metabolites. A similar reasoning could explain why a patient with a chronic overdose of 4.1 mg/kg over 5 days did not demonstrate central nervous system toxicity.³¹ Patients with increased likelihood for seizures include those with underlying seizure disorders or with nephrotic syndrome, which can alter pharmacokinetics.¹⁰¹ Myelosuppression can present as late as 41 days postexposure in patients with acute or chronic overdoses. Hematopoietic recovery is expected within one week of the nadir, and granulocyte colony stimulating factor treatment may be necessary.⁵⁵ Kidney failure from an acute overdose with ifosfamide is reversible following the immediate institution of hemodialysis.³⁸

Cyclophosphamide and its analog ifosfamide are metabolized to acrolein, which can result in cellular damage from the production of reactive oxygen and nitrogen species^{61,97} and cause hemorrhagic cystitis in approximately 5% to 10% of patients receiving therapy.^{15,23} The incidence of cystitis does not appear to be related to the total dose and administration route, age, or sex. The condition is usually self-limiting, although blood transfusions can be required. Water retention is typically observed in patients within 6 to 8 hours of receiving more than 50 mg/kg of cyclophosphamide. However, it can occur at a lower dose.^{27,52} This effect is attributed to the activity of the alkylating metabolite on the renal tubule or the release of endogenous vasopressin (syndrome of inappropriate antidiuretic hormone). The patient typically develops decreased urinary output, increased urine osmolality, and decreased serum osmolality, which is self-limiting and lasts for about 12 to 16 hours.

In overdose, cyclophosphamide can cause dysrhythmias, myocardial necrosis, hemorrhagic pericarditis, and death. ECG changes tend to occur at doses of 120 mg/kg, with heart failure and myocarditis at doses greater than 150 mg/kg.^{6,81} Diminished QRS voltage on the ECG is attributed to myocardial edema or hemorrhage. An ordering error led to the death of one patient and to irreversible cardiac damage in another patient from cyclophosphamide overdose. These two patients received 6520 mg daily for four consecutive days, as opposed to that amount divided over 4 days.¹⁰⁰ The onset of heart failure can be sudden, and patients older than 50 years of age and those with a history of cardiac dysfunction or prior treatment with anthracyclines are at greatest risk for cardiac toxicity.¹¹⁴

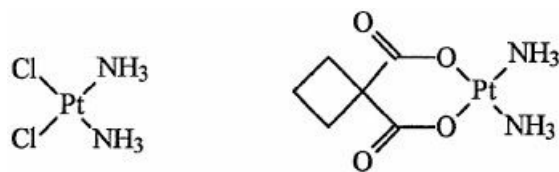
Management

Recommendations for patients with an acute oral chlorambucil overdose include routine gastrointestinal decontamination, 6 hour observation, determination of a complete blood count (CBC) and hepatic enzymes, and weekly CBCs for 4 weeks during follow-up.¹²² Ifosfamide-induced encephalopathy can be managed with the early administration of methylene blue (1–2 mg/kg IV as a 1% solution), although the mechanism by which methylene blue acts is unknown.^{63,132} Potential explanation for the role of methylene blue is as a free radical scavenger⁹³ and an inhibitor of guanylyl cyclase,^{76,102} which can limit the loss of cerebral vascular autoregulation and edema caused by nitric oxide synthesis and cyclic guanosine monophosphate production from the administration of ifosfamide^{61,102,118} (Antidotes in Depth: A42). Seizures are reported to be more effectively managed with benzodiazepines and barbiturates than with phenytoin.^{5,130}

When gross hematuria from cyclophosphamide or ifosfamide therapy persists, treatments can include electrocauterization, systemic vasopressin,⁹⁶ intravesical administration of silver nitrate,⁶⁹ formalin,^{39,107} prostaglandin F₂,¹⁰⁹ and hydrostatic pressure.⁵⁰ Strategies to preventive hematuria include adequate hydration for dilution effect, frequent bladder emptying, IV administration of 2-mercaptoethane sulfonate sodium (MESNA), and intravesical administration of N-acetylcysteine.¹⁵ The thiol group of N-acetylcysteine is believed to directly interact with acrolein and limit its irritating effect on the bladder epithelium. MESNA is believed to work by inactivating acrolein to an inert thioether.⁵¹ The IV dose of MESNA is 20% of the cyclophosphamide or ifosfamide amount (wt/wt) and administered during therapy and at 4 and 8 hours after chemotherapy. In overdose, MESNA does not protect patients from nephrotoxicity and hemodialysis is indicated. Hemodialysis effectively enhances the elimination of ifosfamide and its metabolites when instituted soon after exposure, and it is more effective than hemoperfusion (Adsorba 300 C, Gambro 300 g active carbon) in removing ifosfamide.³⁸

Patients with excessive exposures to cyclophosphamide require baseline ECGs and echocardiograms. IV fluid restriction, a cardiac inotrope (digoxin), and furosemide were successfully used to treat a patient with cyclophosphamide induced congestive cardiomyopathy.¹²⁶

PLATINUM-BASED COMPLEXES



Pharmacology

The cytotoxic effects of the platinum based complexes were first recognized in 1965. Of the many types developed, cisplatin, carboplatin, and oxaliplatin are of clinical utility.⁸² The latter two were designed to reduce the incidence of nephrotoxicity and to counter drug resistance to cisplatin. Cisplatin is an inorganic and carboplatin an organic compound. Similarities exist in their mechanism of toxicity, which is the binding of platinum to DNA to form inter- and intrastrand bonds, resulting in DNA dysfunction and strand breakage. These xenobiotics are eliminated from the body primarily in the urine. The amount eliminated at 24 hours is 25% for cisplatin and 90% for carboplatin. Patients with decreased creatinine clearance (<30 mL/min) have prolonged elimination half-lives of these complexes.³⁰

Pathophysiology

Kidney failure from renal tubular necrosis occurs with cisplatin in a dose-dependent manner. Upon entering the cell, cisplatin forms a cationic reactive complex, which covalently binds to DNA to disrupt replication and transcription, resulting in cell death. The formation of the hydrated platinum complex is favored by a low chloride concentration in the environment; thus, a sodium chloride infusion promotes the native state of cisplatin by preventing hypochloremia. The presence of α_1 -microglobulin, β_2 -microglobulin, retinol-binding protein, alanine aminopeptidase, or N-acetyl-D-glucosaminidase in the urine can be early indicators of renal tubular damage.^{25,46}

The sensory neuropathy associated with platinum containing chemotherapeutics that commonly are attributed to their accumulation and toxicity at the dorsal root ganglion, which is due to the water solubility and chemical reactivity of these xenobiotics.¹⁰⁵ Pathologic evaluation demonstrates increased platinum content at the dorsal root ganglion following cisplatin therapy, which suggests that the increased vascularity and fenestration of the endothelium at this tissue site contributes to the uptake of cisplatin.^{44,54}

Clinical Manifestations

The more common manifestations of toxicity with cisplatin with therapeutic dosing are kidney dysfunction, auditory impairment, and peripheral sensory neuropathy. The other chemotherapeutics that commonly cause a peripheral neuropathy are the Vinca alkaloids and the taxoids. Oxaliplatin induced neuropathy is triggered or enhanced by exposure to cold and can resolve over several months.³³ Myelosuppression is a dose-limiting factor for carboplatin and iproplatin, but it does not occur with cisplatin. At a carboplatin dose of 800 mg/m², 25% of patients develop bone marrow toxicity.⁸⁸ The marrow effects are delayed, with the nadir occurring 3 to 5 weeks after the start of therapy. Patients developing an anemia within the first week of cisplatin therapy should be evaluated for hemolysis.²⁰

The types of therapeutic dosing errors associated with cisplatin are frequency of administration (total dose versus divided dose), confusing cisplatin for carboplatin, and ordering an inappropriate dose.^{21,92} Manifestations in the overdose setting include neurologic, visual, hearing, bone marrow, pancreatic, and kidney disorders.¹⁰⁸ The most common kidney disorder is kidney failure, which is dose-related; it begins at 50 mg/m² and typically occurs at 1 to 2 weeks posttreatment. At this dose, approximately 30% of patients treated with cisplatin develop acute kidney injury (AKI) and a rise in serum blood urea nitrogen and creatinine concentration with subsequent electrolyte disorders, including hypomagnesemia, hypocalcemia, and hyponatremia.³² Hyponatremia is an uncommon finding with cisplatin exposure and is attributed to sodium-wasting nephropathy from renal tubular dysfunction (Chap. 19). At doses greater than 200 mg/m², seizures, encephalopathy, and irreversible peripheral sensory neuropathy are of concern.^{8,22,48,87-89} In addition, visual impairment, including temporary visual loss with permanent loss of color discrimination, can occur within the first week of therapy at this dose.^{19,75,128} Physical examination of the anterior chamber and fundus of the eye will be normal; however, an electroretinogram can demonstrate postphotoreceptor neural dysfunction.⁵⁹ Other possible ocular disorders are papilledema and retrobulbar neuritis. High-frequency (2000 Hz) hearing loss is evident 2 to 3 days after exposure to doses greater than 500 mg/m².¹⁷

Management

Renal protection and enhanced elimination of platinum are the goals in the initial management of a cisplatin overdose, followed by expectant management for myelosuppression and neurotoxicity. Hydration with 0.9% sodium chloride solution and an osmotic diuretic, such as mannitol, should be administered to achieve a high urine output (eg, 1–3 mL/kg/h) for 6 to

24 hours postexposure. Sodium chloride diuresis both promotes the inactive state of cisplatin and decreases the urine platinum concentration, which can limit nephrotoxicity.^{2,125} In the setting of nonoliguric AKI, careful hydration is recommended to maintain urinary output, because renal platinum excretion is directly related to urinary flow and independent of creatinine clearance.¹⁹ Kidney function can be monitored by determining the creatinine clearance or glomerular filtration rate.^{99,119}

Amifostine (Ethyol) and sodium thiosulfate are effective nephroprotectants. Amifostine is approved by the US Food and Drug Administration to prevent cisplatin induced nephrotoxicity, and additional benefits can include the limitation of myelosuppression, mucositis, and neurotoxicity.³ Unlike thiosulfate, amifostine is activated intracellularly by alkaline phosphatase to scavenge free radicals, regenerate glutathione, prevent cisplatin-DNA adduct formation, and facilitate DNA repair.⁶² The patient requires adequate hydration during amifostine infusion because hypotension can occur. Sodium thiosulfate is effective postexposure. Thiosulfate remains in the extracellular space to bind free platinum and limit cellular damage at the renal tubules. Little or no renal toxicity occurred in patients receiving as much as 270 mg/m² of cisplatin when thiosulfate was given as an IV bolus of 4 g/m² followed by infusion of 12 g/m² over 6 hours.^{47,90} In a 14 year-old patient with AKI from cisplatin, thiosulfate was continued at 2.7 g/m² a day until urinary platinum concentration was below 1 µg/mL.³² Thiosulfate can offer the additional benefit of limiting neurotoxicity^{74,121} and should be administered to all patients within 1 to 2 hours after a platinum-based complex chemotherapeutic overdose for it to be most effective (Antidotes in Depth: A40). N-Acetylcysteine and BNP7787 (2,2'-dithio-bis-ethanesulfonate) are under investigation as alternative rescue xenobiotics for cisplatin toxicity.^{11,28,80} BNP7787 also is under clinical investigation to limit peripheral neuropathy from paclitaxel therapy.⁷⁷

Hemodialysis is ineffective in patients with cisplatin overdoses, likely as a result of high protein binding.¹⁴ Plasmapheresis with plasma exchange was performed in five adults, and there was a decline in blood and plasma platinum concentrations with clinical improvement.^{18,19,49,57,131} In one incident, a patient received an overdose of 280 mg/m² and was plasmapheresed on day 12 of exposure.¹⁹ After three daily treatments, the serum platinum concentration decreased from 2900 to 200 ng/mL, and the patient had noticeable improvement in gastrointestinal and visual symptoms. On day 20, the serum platinum concentration rebounded to 700 ng/mL, and the symptoms worsened. Further plasmapheresis lowered the concentration to 290 ng/mL by day 27, and symptoms improved. In another event, a patient received 300 mg/m² of cisplatin and received four daily treatments of plasmapheresis starting on day 6 postexposure.⁵⁷ The serum platinum concentration declined from 2979 to 430 ng/mL, and the patient became more awake and less nauseated. On day 11, platinum concentrations rebounded to 834 ng/mL and fell to 279 ng/mL on reinstitution of plasmapheresis. The amount of platinum removed by three trials in this patient was approximately 4.6 mg. The author of the paper contends that plasmapheresis prevented the need for hemodialysis in kidney failure. Other reports have noted an improvement in patients' mental status and hearing loss following the decline in the serum cisplatin (platinum) concentration from plasmapheresis.^{18,49} Thus, plasmapheresis with plasma exchange should be immediately considered after a cisplatin overdose. Patients who remain symptomatic days later also may benefit.

SUMMARY

- Anthracyclines, nitrogen mustards, and the platinum based complexes are common chemotherapeutic overdoses.
- The primary clinical manifestations of toxicity for these xenobiotics include dilated cardiomyopathy (anthracyclines), encephalopathy and seizures (nitrogen mustards), and kidney failure (platinum based xenobiotics).
- The management for patients with these overdoses includes supportive care, enhanced elimination using plasmapheresis with plasma exchange for cisplatin, and antidotal therapy, such as dexrazoxane for anthracyclines and amifostine for platinum based complexes.
- Specialists in poison information and medical toxicologists must maintain a current level of understanding of these exposures so they can better assist their patients and provide consultation to other healthcare professionals.

Disclaimer

The findings and conclusions in this chapter are those of the author and do not necessarily represent the views of Centers for Disease Control and Prevention.

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53 ANTIDIABETICS AND HYPOGLYCEMICS

George M. Bosse

Glucose	
MW	= 180 Da
Normal fasting range (plasma)	= 60–100 mg/dL
	= 3.3–5.6 mmol/L

HISTORY AND EPIDEMIOLOGY

Insulin first became available for use in 1922 after Banting and Best successfully treated diabetic patients with pancreatic extracts.¹⁰ In an attempt to more closely simulate physiologic conditions, additional “designer” insulins with unique kinetic properties have been developed, including a rapid-acting basal insulin that mimics baseline insulin secretion known as lispro.^{67,140} Several oral delivery systems for insulin have been studied.⁹⁴ However, the development of an oral delivery system for use in humans has not been successful because of poor intestinal absorption and degradation of the oral form of insulin by digestive enzymes. Using zonula occludens toxin, modulation of intestinal tight junctions in animal models significantly increases enteral absorption of insulin.⁴² An inhaled form of insulin was withdrawn from the market due to poor sales and inability to demonstrate better glucose control than short-acting insulins.⁹⁰

The hypoglycemic activity of a sulfonamide derivative used for typhoid fever was noted during World War II.⁷⁶ This discovery was verified later in animals. The sulfonylureas in use today are chemical modifications of that original sulfonamide compound. In the mid-1960s, the first generation sulfonylureas were widely used. Newer second generation drugs differ primarily in their potency.

Although insulin is widely used for treating diabetes mellitus, oral hypoglycemic exposures are more commonly reported to poison centers than are insulin exposures, based on 15 years of data from 1996 to 2010 (Chap. 136). In an older review of 1418 medication-related cases of hypoglycemia, sulfonylureas (especially the long-acting chlorpropamide and glyburide) alone or with a second hypoglycemic accounted for the largest percentage of cases (63%).¹³⁰ Only 18 of the sulfonylurea cases in this series involved intentional overdose. However, hypoglycemia is reported in as many as 20% of patients using sulfonylureas.⁵⁹ In a study of 99,628 emergency hospitalizations for adverse drug events in adults older than 65 years of age, 14% were due to insulin and 11% were due to oral hypoglycemics. The majority (95%) of the hospitalizations related to these groups of endocrine agents were due to hypoglycemia.¹⁹ Other causes of hypoglycemia are listed in Table 53–1.

TABLE 53–1. Causes of Hypoglycemia

Artifactual	Medical Conditions	Neoplasms	Hypoglycin (Ackee)
Chronic myelogenous leukemia	Acquired immunodeficiency syndrome (AIDS)	Carcinomas (diverse extrapancreatic)	Indomethacin
Polycythemia vera	Alcoholism	Hematologic	Pentamidine
Endocrine Disorders	Anorexia nervosa	Insulinoma	Propoxyphene
Addison disease	Autoimmune disorders	Mesenchymal	Quinidine
Glucagon deficiency	Burns	Multiple endocrine adenopathy type 1 (Werner syndrome)	Quinine
Graves disease	Diarrhea (childhood)	Reactive Hypoglycemia	Ritodrine
Panhypopituitarism (Sheehan syndrome)	Leucine sensitivity	Xenobiotics	Salicylates
Hepatic Disease	Muscular activity (excessive)	β-Adrenergic antagonists	Streptozocin
Acute hepatic atrophy	Postgastric surgery (including gastric bypass)	Alloxan	Sulfonamides
Cirrhosis	Pregnancy	Antidiabetics	Vacor
Galactose or fructose intolerance	Protein-calorie malnutrition	Cibenzoline	Valproic acid
Glycogen storage disease	Rheumatoid arthritis	Disopyramide	Venlafaxine
Neoplasia	Septicemia	Ethanol	
Kidney Disease	Shock	Gatifloxacin	
Chronic hemodialysis	Systemic lupus erythematosus		
Chronic kidney insufficiency			

The biguanides metformin and phenformin were developed as derivatives of *Galega officinalis*, the French lilac, recognized in medieval Europe as a treatment for diabetes mellitus.⁸ Phenformin was used in the United States until 1977, when it was removed from the market because of its association with life-threatening metabolic acidosis with hyperlactatemia (64 cases/100,000 patient-years). However, phenformin still is available outside the United States.¹¹⁰

Development of the α -glucosidase inhibitors began in the 1960s when an α -amylase inhibitor was isolated from wheat flour.¹²⁶ Acarbose was discovered more than 10 years later and approved for use in the United States in 1995. Troglitazone and repaglinide were approved for use in the United States in 1997. The US Food and Drug Administration subsequently directed the manufacturer of troglitazone to withdraw the product from the US market in 2000 because of associated liver toxicity. Exenatide, a synthetic form of a compound found in the saliva of the Gila monster, is an incretin mimetic. Liraglutide is a synthetic analog of human incretin. Other newer xenobiotics include the gliptins and the amylin analog pramlintide.

PHARMACOLOGY

Insulin is synthesized as a precursor polypeptide in the β islet cells of the pancreas. Proteolytic processing results in the formation of proinsulin, which is cleaved, giving rise to C-peptide and insulin itself, a double-chain molecule containing 51 amino acid residues. Glucose concentration plays a major role in the regulation of insulin release.¹¹⁶ Glucose is phosphorylated after transport into the β islet cell of the pancreas. Further metabolism of glucose-6-phosphate results in the formation of ATP. ATP inhibition of the K^+ channel results in cell depolarization, inward calcium flux, and insulin release. After release, insulin binds to specific receptors on cell surfaces in insulin-sensitive tissues, particularly the hepatic, muscle, and fat cells. The action of insulin on these cells involves various phosphorylation and dephosphorylation reactions.

Figure 53–1 depicts the chemical structures of select antidiabetics. The sulfonylureas stimulate the β cells of the pancreas to release insulin and are often referred to as insulin secretagogues. They are ineffective in type 1 diabetes mellitus that results from islet cell destruction (Fig. 53–2). This stimulatory effect diminishes with chronic therapy. All the sulfonylureas bind to high-affinity receptor sensors on the pancreatic β cell membrane, resulting in closure of K^+ channels.^{40,47,48} Inhibition of potassium efflux mimics the effect of naturally elevated intracellular ATP and results in insulin release. High-affinity sulfonylurea receptors also present within pancreatic β cells are postulated to be either located on granular membranes or part of a regulatory exocytosis kinase. Binding to these receptors promotes exocytosis by direct interaction with secretory machinery not involving closure of the plasma membrane K^+ channels.^{40,47,48}

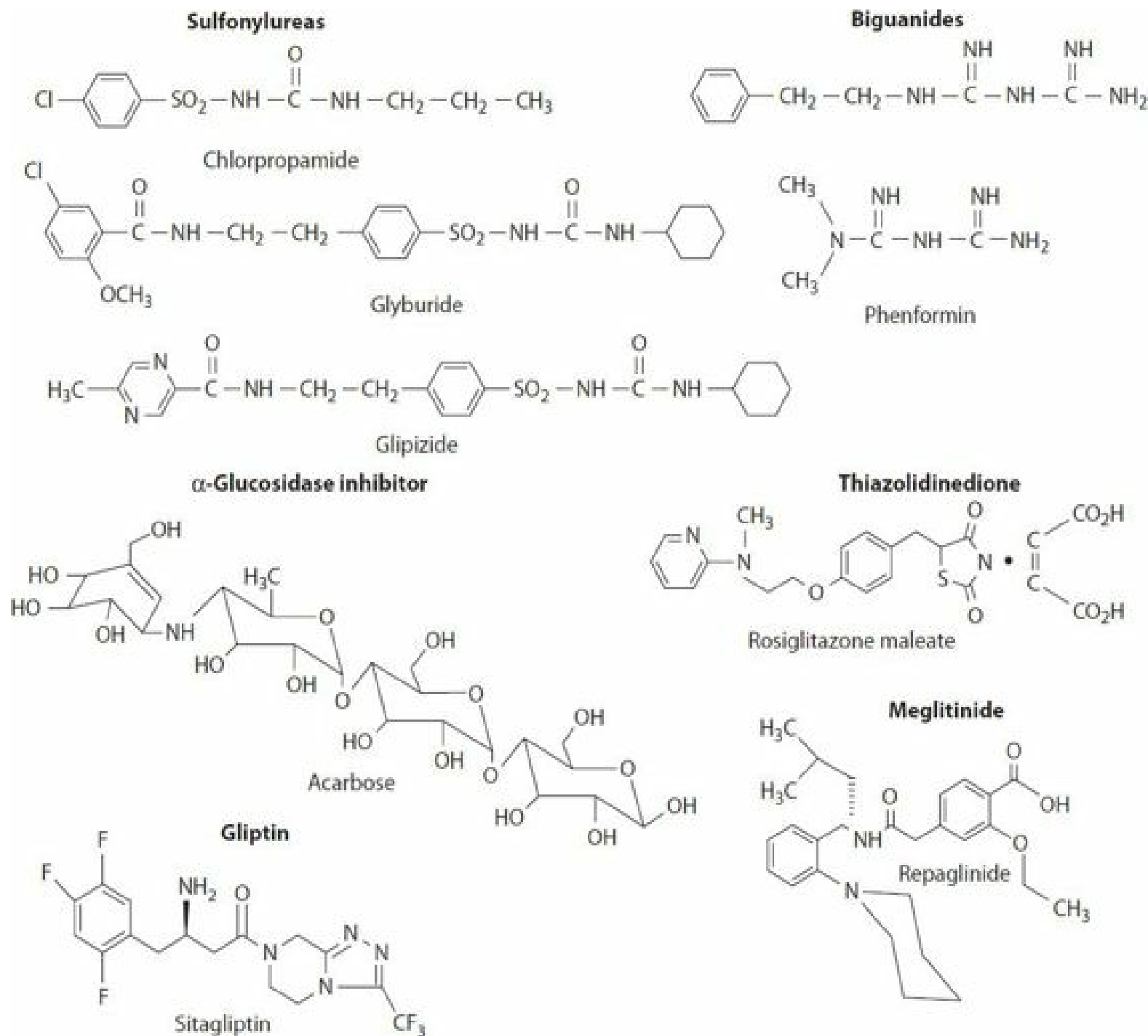


FIGURE 53–1. Chemical structures of representative oral antidiabetics. The glucagonlike peptide (GLP-1) analogs and amylin analogs are large polypeptides. Their structures are not shown here.

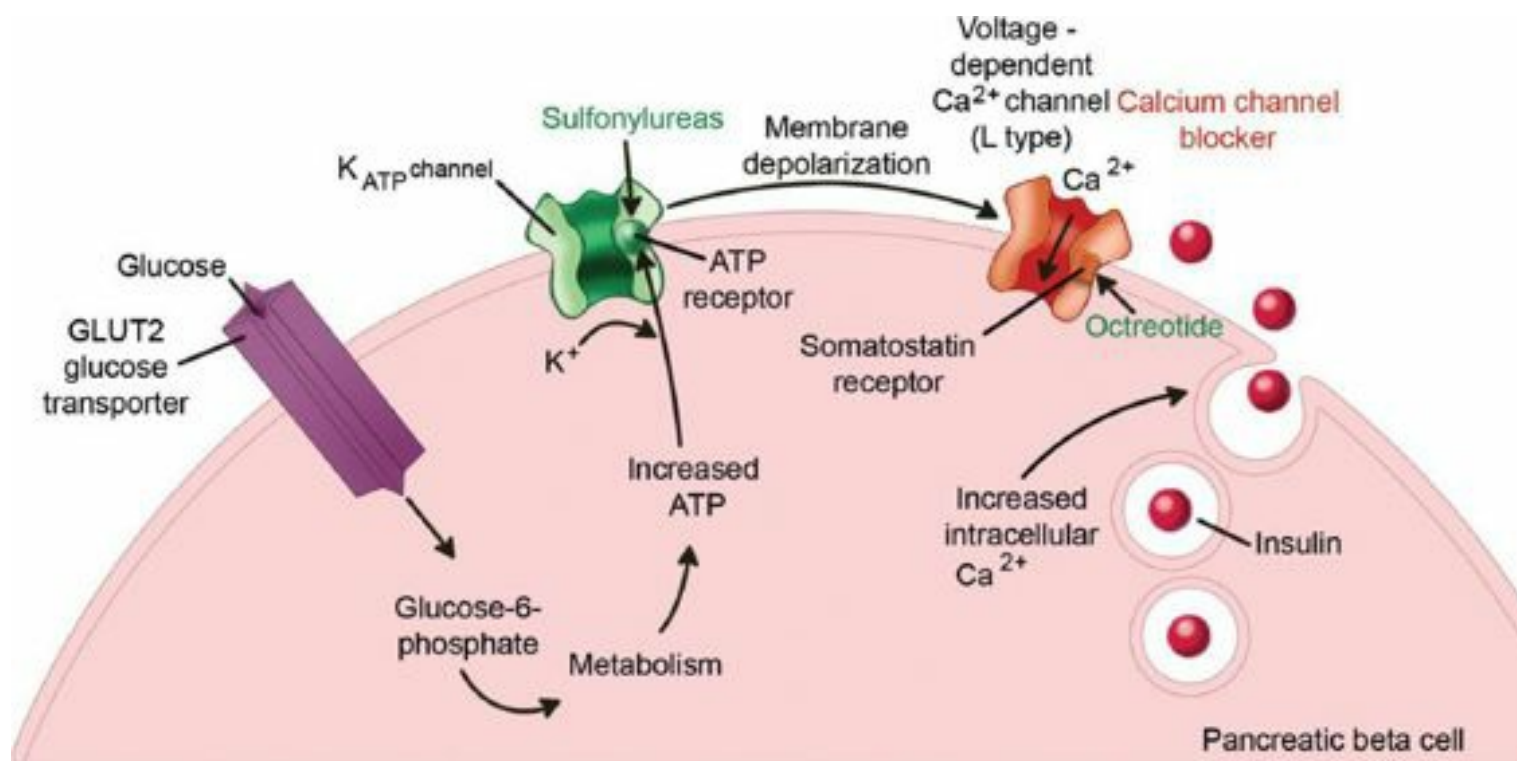


FIGURE 53–2. Under normal conditions, cells release insulin in response to elevation of intracellular ATP concentrations. Sulfonyleureas potentiate the effects of ATP at its “sensor” on the ligand gated K⁺ channels and prevent efflux of K⁺. The subsequent rise in intracellular potential opens voltage-gated Ca²⁺ channels, which increases intracellular calcium concentration through a series of phosphorylation reactions. The increase in intracellular calcium results in the release of insulin. Release of insulin is also caused by binding of sulfonyleureas to postulated receptor sites on regulatory exocytosis kinase and insulin granular membranes. Octreotide inhibits calcium entry through Ca²⁺ channel thereby inhibiting insulin release. GLUT = membrane bound glucose transporter.

The linkage of two guanidine molecules forms the biguanides. Metformin is an oral biguanide approved for treatment of type 2 diabetes mellitus. Its glucose-stabilizing effect is caused by several mechanisms, the most important of which appears to involve inhibition of gluconeogenesis and subsequent decreased hepatic glucose output. Enhanced peripheral glucose uptake also plays a significant role in maintaining euglycemia. The ability of metformin to lower blood glucose concentrations also results from decreased fatty acid oxidation and increased intestinal use of glucose.^{9,142} In skeletal muscle and adipose cells, metformin enhances activity and translocation of glucose transporters. Although the details are unclear, the mechanism by which this process occurs involves an interaction between metformin and tyrosine kinase on the intracellular portion of the insulin receptor. **Figure 53–3** depicts the mechanism of action of metformin.

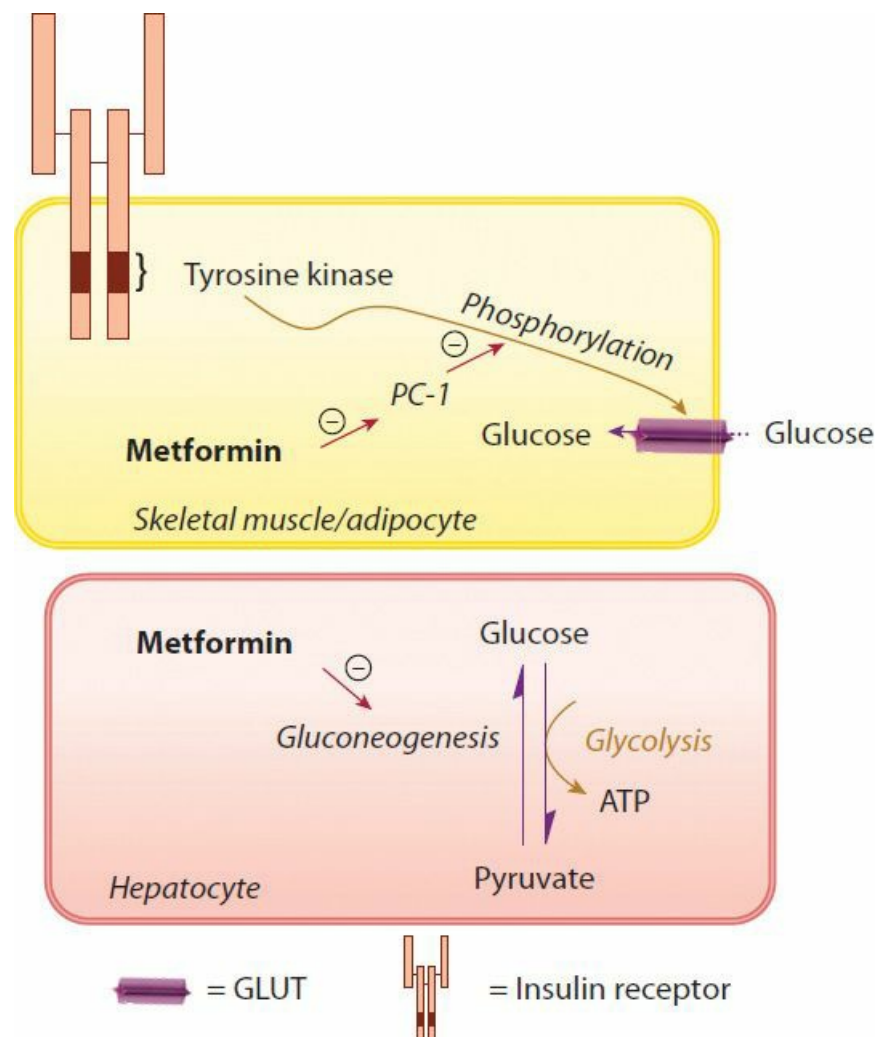


FIGURE 53–3. Under normal conditions, insulin binding to its receptor on myocytes and adipocytes activates tyrosine kinase, resulting in phosphorylation and activation of the membrane-bound glucose transporter GLUT. Non–insulin dependent diabetes mellitus is causally associated with an increased activity of PC-1, a glycoprotein that inhibits tyrosine kinase activity and thus reduces myocyte and adipocyte glucose uptake. Metformin reduces PC-1 activity in these cells, enhancing peripheral glucose utilization. In addition, gluconeogenesis in hepatic cells is reduced through interference with pyruvate carboxylase, the enzyme responsible for conversion of pyruvate to oxaloacetate.

Acarbose and miglitol are oligosaccharides that inhibit α -glucosidase enzymes such as glucoamylase, sucrase, and maltase in the brush border of the small intestine. As a result, postprandial elevations in blood glucose concentrations are blunted.¹⁴⁹ Delayed gastric emptying may be another mechanism for the antihyperglycemic effect of these oligosaccharides.¹²⁰

Insulin resistance in patients with type 2 diabetes mellitus may occur because of secretion of biologically defective insulin molecules, circulating insulin antibodies, or target tissue defects in insulin action.¹⁰³ The thiazolidinedione derivatives decrease insulin resistance by potentiating insulin sensitivity in the liver, adipose tissue, and skeletal muscle. Uptake of glucose into adipose tissue and skeletal muscle is enhanced, while hepatic glucose production is reduced.^{17,58}

Repaglinide (Prandin) and nateglinide (Starlix) are oral representatives of the meglitinide class that also bind to K^+ channels on pancreatic cells, resulting in increased insulin secretion.¹²¹ Compared to the sulfonylureas, the hypoglycemic effects of the meglitinides are shorter in duration.

Exenatide and liraglutide are structurally similar to glucagonlike peptide-1 (GLP-1), an incretin that is released in response to an oral glucose load. GLP-1 enhances the release of insulin, delays gastric emptying, and reduces food intake. GLP-1 is metabolized very rapidly, rendering it therapeutically ineffective. Exenatide and liraglutide have much longer half-lives, rendering them useful in the treatment of type 2 diabetes mellitus.¹⁴⁶ Sitagliptin, saxagliptin, and linagliptin inhibit dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for the inactivation of GLP-1.¹ Pramlintide is an amylin analog. Amylin is produced in the pancreatic β cell and acts in conjunction with insulin to inhibit gastric emptying, decrease postprandial glucagon secretion, and promote satiety.⁷⁷

PHARMACOKINETICS AND TOXICOKINETICS

Pharmacokinetic parameters of the hypoglycemics are given in [Tables 53–2 and 53–3](#). The onset and duration of action in

therapeutic doses vary considerably among preparations. Insulin overdose usually occurs after administration by the subcutaneous or intramuscular route. As might be predicted based on slow onset and prolonged duration of action of some of the preparations, insulin overdose may result in delayed and prolonged hypoglycemia. However, hypoglycemia may also occur with short acting forms because of some unusual toxicokinetic features. Some of these unpredicted responses may be caused by a depot effect following intramuscular or subcutaneous administration, and poor absorption may be further potentiated by the poor perfusion that can occur during periods of hypoglycemia.^{95,139} Further complicating the prediction of the clinical course is the delayed release of insulin from adipose tissue at the injection site(s). Because there are a finite number of insulin receptors, insulin overdoses of varying amounts probably are equivalent in terms of the degree of resultant hypoglycemia once receptor saturation occurs, but not in terms of its duration. A comparison can be made with the current treatment of diabetic ketoacidosis, in which lower doses of insulin are as effective as the higher doses used in the past.⁶⁶

Many of the sulfonylureas have long durations of action, which may explain the unusually long period of hypoglycemia that can occur in both therapeutic use and overdose. Second generation sulfonylureas (glimepiride, glipizide, glyburide) have half-lives that approach 24 hours and are characterized by substantial fecal excretion of the parent drug. These drugs frequently cause hypoglycemia (Table 53–2). Like insulin, the sulfonylureas may cause delayed onset of hypoglycemia following overdose.^{104,118} The reason for the potential delayed onset of effects with sulfonylureas cannot be simply explained by known kinetic principles but may be related to effective counterregulatory mechanisms that fail over time.

TABLE 53–2. Characteristics of Noninsulin Antidiabetics

<i>Xenobiotic</i>	<i>Duration of Action (hours)</i>	<i>Active Hepatic Metabolite</i>	<i>Active Urinary Excretory Product (% of Dose)</i>	<i>Fecal Excretion (% of Dose)</i>	<i>Likelihood of Hypoglycemia in Overdose</i>
I. Sulfonylureas					
First generation					
Acetohexamide (Dymelor)	12–18	Hydroxyhexamide (+++)	Hydroxyhexamide (65%) Acetohexamide (2%)	Negligible	Anticipate
Chlorpropamide (Diabinese)	24–72	2-Hydroxychlorpropamide (+) 3-Hydroxychlorpropamide (+)	Chlorpropamide (20%) 2-Hydroxychlorpropamide (55%) 3-Hydroxychlorpropamide (2%)	Negligible	Anticipate
Tolazamide (Tolinase)	16–24	Hydroxytolazamide (++)	Hydroxytolazamide (35%) Tolazamide (7%)	Negligible	Anticipate
Tolbutamide (Orinase)	6–12	Hydroxytolbutamide (+)	Hydroxytolbutamide (30%) Tolbutamide (2%)	Negligible	Anticipate
Second generation					
Glimepiride (Amaryl)	24	Cyclohexylhydroxy ethyl derivative (++)	Cyclohexylhydroxy methyl derivative (63%)	15%	Anticipate
Glipizide (Glucotrol, Glucotrol XL)	16–24	None	Glipizide (3%)	12%	Anticipate
Glyburide (Micronase, Glynase, DiaBeta)	18–24	4-Hydroxyglyburide (++)	4-Hydroxyglyburide (36%) Glyburide (3%)	50%	Anticipate
II. Biguanides					
Metformin (Glucophage, Glucophage XR)	1.3–4.5	None	Metformin (90%)	Negligible	Unlikely
Phenformin	6–8	None	Phenformin (66%)	Negligible	Unlikely
III. α-Glucosidase Inhibitors					
Acarbose (Precose)	2	None	4-Methyl pyrogallol derivative (<2%)	None	Unlikely
Miglitol (Glyset)	2	None	100%	None	Unlikely
IV. Thiazolidinedione Derivatives					
Pioglitazone (Actos)	16–24	Hydroxy derivative++ Keto derivative++	<15%–30%	70%	Unlikely
Rosiglitazone (Avandia)	12–24	None	None	23%	Unlikely
V. Meglitinides					
Nateglinide (Starlix)	2–4	Isoprene derivative (++) Hydroxylation metabolites (+)	– 16% as parent	10%	Anticipate
Repaglinide (Prandin)	1–3	None	None	90%	Anticipate
VI. GLP-1 Analogs					
Exenatide (Byetta, Bydureon)	6–8	None	None	Negligible	Unlikely
Liraglutide (Victoza)	24	None	None	5%	Unlikely
VII. Glitins					
Sitagliptin (Januvia)	24	None	Sitagliptin (70%–80%)	16%–20%	Unlikely
Saxagliptin (Onglyza)	24	5-hydroxy derivative (++)	Saxagliptin (24%) 5-hydroxy (36%)	22%	Unlikely
Linagliptin (Tradjenta)	24	None	Linagliptin (5%)	80%	Unlikely
VIII. Amylin Analog					
Pramlintide (Symlin)	3	None	None	Negligible	Unlikely

Metformin metabolism is negligible, and the majority of an absorbed dose is actively secreted in the urine unchanged. Plasma protein binding is also negligible.⁹ Repaglinide and nateglinide are prandial glucose regulators characterized by rapid onset and short duration of action. Overdose experience and toxicokinetic data for repaglinide are lacking. It is not clear whether hypoglycemia would be prolonged or delayed in onset following overdose. In one case of nateglinide overdose, hypoglycemia occurred early and was short lived.⁹⁶ Exenatide and liraglutide are available only for parenteral

(subcutaneous) injection. Sitagliptin, saxagliptin, and linagliptin have long half-lives and cause pronounced inhibition of DPP-4, resulting in a long duration of action (approximately 24 hours) after therapeutic doses.⁷⁴ Pramlintide is available only for parenteral (subcutaneous) injection and has a half-life of approximately 40 minutes when used in therapeutic doses.²⁶

PATHOPHYSIOLOGY OF HYPOGLYCEMIA

To varying degrees, the antidiabetics may all produce a nearly identical clinical condition of hypoglycemia. The etiologies of hypoglycemia are divided into three general categories⁴⁴: physiologic or pathophysiologic conditions (Table 53–1), direct effects of various hypoglycemics (Tables 53–2 and 53–3), and potentiation of hypoglycemics by interactions with other xenobiotics (Table 53–4).

TABLE 53–3. Characteristics of Various Forms of Insulin

<i>Insulin</i>	<i>Onset of Action (hours)</i>	<i>Duration of Action (hours)</i>	<i>Peak Glycemic Response (hours)</i>
Rapid Acting			
Aspart (NovoLog)	0.25	3–5	0.75–1.5
Glulisine (Apidra)	0.5	<5	1.5–2
Lispro (Humalog)	0.25–0.5	<5	0.5–2.5
Short Acting			
Regular (Humulin-R, Novolin-R)	0.5–1	5–8	2.5–5
Intermediate Acting			
Lente (Humulin-L, Novolin-L)	1–3	18–24	6–14
NPH (Humulin-N, Novolin-N)	1–2	18–24	6–14
Long Acting			
Detemir (Levemir)	1.5	24	No true peak
Glargine (Lantus)	1.1	24	No true peak
Ultralente (Humulin-U)	4–6	20–36	8–20

TABLE 53–4. Xenobiotics Known to React with Hypoglycemics Resulting in Hypoglycemia

- β-Adrenergic antagonists
- Angiotensin-converting enzyme (ACE) inhibitors
- Allopurinol
- Anabolic steroids
- Chloramphenicol
- Clofibrate
- Disopyramide
- Ethanol
- Fluoroquinolones
- Haloperidol
- Methotrexate

Monoamine oxidase inhibitors

Pentamidine

Phenylbutazone

Probenecid

Quinine

Salicylates

Sulfonamide

Trimethoprim-sulfamethoxazole

Warfarin

Hypoglycemia usually results in decreased insulin secretion, with production of alternate fuels, particularly ketones. Ketone production occurs as a result of fatty acid metabolism.⁷⁰ Nonketotic hypoglycemia can occur in a hyperinsulinemic state such as insulinoma.¹⁰⁶

Central nervous system (CNS) symptoms predominate in hypoglycemia because the brain relies almost entirely on glucose as an energy source. However, during prolonged starvation, the brain can utilize ketones derived from free fatty acids. In contrast to the brain, other major organs such as the heart, liver, and skeletal muscle often function during hypoglycemia because they can use various fuel sources, particularly free fatty acids.¹³²

Emphasis on tighter glucose control as a means of preventing microvascular effects carries with it an increased risk for hypoglycemia.^{32,33} Regulation of glucose control to near-normal glucose concentrations, the characteristics of each individual's awareness of hypoglycemia, and the individual counterregulatory mechanisms define the frequency and intensity of hypoglycemia.¹³¹ The Diabetic Control and Complications Trial research group reported 62 episodes of blood glucose concentration less than 50 mg/dL with CNS manifestations requiring assistance for every 100 patient-years in patients undergoing an intensive insulin therapy regimen. This was in comparison to a conventional therapy group, which had 19 such episodes per 100 patient-years.^{32,33} The intensive therapy group received three or more insulin injections per day or used a pump in an effort to achieve a glucose concentration as close to normal as possible, whereas the conventional therapy group received one or two daily insulin injections.

There has also been a recent emphasis in tighter control of glucose in critically ill patients, even in the absence of known diabetes mellitus. Hyperglycemia occurs in critically ill patients due to several mechanisms and is associated with increased mortality in patients with a variety of medical and surgical diagnoses.⁶⁸ In a study of critically ill surgical patients, tight control of glucose was associated with decreased morbidity and mortality.¹⁵¹ However, such benefits in other studies are not always clearly replicated, and significant hypoglycemia is reported.^{41,150}

The autonomic nervous system regulates glucagon and insulin secretion, glycogenolysis, lipolysis, and gluconeogenesis. β -Adrenergic antagonists affect all of these mechanisms and can result in hypoglycemia. In the presence of kidney failure, β -adrenergic antagonist-induced hypoglycemia is a particular risk⁵¹ secondary to increased insulin half-life and reduced renal gluconeogenesis.¹⁰⁷ In addition, the clinical presentation of hypoglycemia may be muted when β -adrenergic antagonists are present because the expected autonomic responses of tachycardia, diaphoresis, and anxiety may not occur. Although this is assumed to be true, an adverse effect on hypoglycemic awareness could not be demonstrated in healthy volunteers given metoprolol, atenolol, and propranolol.⁶⁴

The concept of hypoglycemia-associated autonomic failure in diabetes mellitus is well described.³⁰ Recurrent episodes of hypoglycemia result in autonomic failure by causing defective glucose counterregulation and possibly hypoglycemic awareness. As glucose concentrations fall, normal sensing mechanisms result in decreased insulin secretion and increased glucagon and epinephrine secretion. These counterregulatory defenses against hypoglycemia are defective in most people with type 1 diabetes mellitus and in many with type II diabetes mellitus.

Although various nonantidiabetic xenobiotics can cause hypoglycemia (Table 53–1), salicylates and ethanol are particularly notable for their unintended hypoglycemic effects. The mechanism of ethanol-induced hypoglycemia is discussed in Chap. 80. Salicylate inhibition of prostaglandin synthesis in the β cell of the pancreas is postulated to result in enhanced insulin secretion.¹¹ Salicylates may also cause hypoglycemia by poorly defined mechanisms that do not involve enhanced insulin secretion.

CLINICAL MANIFESTATIONS

Hypoglycemia and its secondary effects on the CNS (neuroglycopenia) are the most common adverse effects related to insulin and the sulfonylureas. It is essential to remember that hypoglycemia is primarily a clinical, not a numerical, disorder. Clinical hypoglycemia is the failure to maintain a plasma glucose concentration that prevents signs or symptoms of glucose deficiency. The clinical presentations of patients with hypoglycemia are extremely variable. Hypoglycemia must be considered to be the etiology of any neuropsychiatric abnormality, whether persistent or transient, focal or generalized. The cerebral cortex usually is most severely affected. These findings are categorized below¹¹⁵:

- Delirium with subdued, confused, or manic behavior.
- Coma with multifocal brainstem abnormalities, including decerebrate spasms and respiratory abnormalities, with preservation of the oculocephalic (doll's eyes), oculovestibular (cold-caloric), and pupillary responses.
- Focal neurologic deficits simulating a cerebrovascular accident (CVA) with or without the presence of coma. During a 12-month study period, 3 of 125 (2.4%) hypoglycemic patients presented with hemiplegia.⁸³ There are numerous reports^{4,135} and series^{128,148} of patients with focal neurologic deficits.
- Solitary or multiple seizures.

These neuropsychiatric symptoms are usually reversible if the hypoglycemia is corrected promptly. The morbidity resulting from undiagnosed hypoglycemia is related partly to the etiology and partly to the duration and severity of the hypoglycemia. Because the etiologies of hypoglycemia encompass both severe diseases such as fulminant hepatic failure and benign problems such as a missed meal by an insulin-requiring diabetic, the literature with regard to outcome is confusing. Although a study of 125 emergency department (ED) cases of symptomatic hypoglycemia reported an 11% mortality rate,⁸³ only one death (0.8%) was attributed directly to hypoglycemia. In that same study, nine patients (7.2%) presented with seizures (focal in one case), three patients (2.4%) presented with hemiparesis, and four survivors (3.2%) suffered residual neurologic deficits. In one tertiary care medical center, 1.2% of all admitted patients had hypoglycemia (defined as a glucose concentration less than 50 mg/dL). The overall mortality was 27% for this group of 94 patients.⁴⁴ The longer and more profound the hypoglycemic episode, the more likely permanent CNS damage will occur.⁷

No absolute criteria available from the physical examination or history distinguish one form of metabolic coma from another. Moreover, the findings classically associated with hypoglycemia, such as tremor, sweating, tachycardia, confusion, coma, and seizures, frequently may not occur.⁵⁶ The glycemic threshold is the glucose concentration below which clinical manifestations develop, a threshold that is host variable. In one study, the mean glycemic threshold for hypoglycemic symptoms was 78 mg/dL in patients with poorly controlled type 1 diabetes compared to 53 mg/dL in those without the disease.¹⁵

Patients with well-controlled type 1 diabetes may be unaware of hypoglycemia. It appears that even in the presence of numerical hypoglycemia, diabetics with near-normal glycosylated hemoglobin concentrations maintain near-normal glucose uptake by the brain, thereby preserving cerebral metabolism and limiting the response of counterregulatory hormones. The result of this limited response is unawareness of hypoglycemia.^{14,15} A threshold is likely achieved below which the glucose concentration is inadequate, but this may be a concentration so close to that causing serious neuroglycopenia that patients have limited opportunity for corrective action.¹⁴ Hypoglycemia unawareness is most likely in diabetics with chronic use of hypoglycemics because of hypoglycemia-associated autonomic failure.³⁰ Acute ingestion of hypoglycemics in nondiabetic patients likely would cause more classic signs and symptoms.

Sinus tachycardia, atrial fibrillation, and ventricular premature contractions are the most common dysrhythmias associated with hypoglycemia.^{75,102} An outpouring of catecholamines, hypoglycemia itself, transient electrolyte abnormalities, and underlying heart disease appear to be the most likely etiologies. Based on their mechanisms of action, both insulin and the sulfonylureas are expected to promote the shift of potassium into cells, and hypokalemia after insulin overdose is well documented.^{6,139} Other cardiovascular manifestations include angina and ischemia, which rarely may be the sole manifestations of hypoglycemia.³⁸ Both are directly related to hypoglycemia.^{12,112} Increased release of catecholamines during hypoglycemia increases myocardial oxygen demand and may decrease supply by causing coronary vasoconstriction.

Hypothermia may occur in hypoglycemic patients.^{45,63,141} If present, hypothermia usually is mild (90°–95°F {32°–35°C}), unless coexisting conditions such as environmental exposure, infection, head injury, or hypothyroidism are present. In a study comparing two groups of patients with depressed mental status, hypothermia was almost exclusively limited to the hypoglycemic patients; of these patients, 53% with demonstrated hypoglycemia showed hypothermia.¹⁴¹ The central hypothalamic response to hypoglycemia stimulated by the sympathetic nervous system may actually “overshoot” normal temperatures, resulting in hyperthermia following recovery.²⁷

Besides decreasing glucose concentrations, the hypoglycemics can produce a number of adverse effects, both in overdose and in therapeutic doses. Older sulfonylureas, predominantly chlorpropamide, cause a syndrome of inappropriate antidiuretic hormone secretion⁶¹ and disulfiram-ethanol reactions.¹¹³ These adverse effects are exceedingly uncommon with the newer second-generation sulfonylureas.

Hypoglycemia may not occur until 18 hours after lente insulin overdose,⁹⁵ may persist for up to 53 hours after subcutaneous insulin glargine overdose,¹⁸ and may persist up to 6 days after ultralente insulin overdose.⁸⁴ Death after insulin overdose cannot be correlated directly with either the dose or preparation. Some patients have died with doses estimated in the hundreds of units, whereas others have survived doses in the thousands of units.¹²⁷ Mortality and morbidity may correlate better with delay in recognition of the problem, duration of symptoms, onset of therapy, and type of complications, as opposed to the absolute degree of hypoglycemia or persistence of elevated insulin concentrations. A significant correlation exists between the amount of insulin injected and either the total amount of dextrose used for treatment or the duration of dextrose infusion.¹³⁹ In a retrospective study of insulin overdose, 7 of 17 cases (41%) developed recurrent hypoglycemia between 5 and 39 hours after overdose despite oral feeding and intravenous dextrose infusion ranging from 5 to 17 g of dextrose per hour.

In a retrospective review of 40 patients with sulfonylurea overdoses, the time from ingestion to the onset of hypoglycemia, when known, was variable.¹⁰⁵ The longest delay was 21 hours after ingestion of glyburide and 48 hours after ingestion of chlorpropamide. In a retrospective poison center review of 93 cases of sulfonylurea exposures in children, 25 patients (27%) developed hypoglycemia, with a time of onset ranging from 0.5 to 16 hours and a mean of 4.3 hours.¹¹⁸ In a prospective poison center study of sulfonylurea exposures in children, 56 of 185 (30%) patients developed hypoglycemia, with a time of onset ranging from 1 to 21 hours and a mean of 5.3 hours.¹³⁶ Single-tablet ingestions of chlorpropamide 250 mg, glipizide 5 mg, and glyburide 2.5 mg can result in hypoglycemia in young children,¹¹⁸ and the hypoglycemia may be delayed.¹⁴³ Hypoglycemia did not occur until 45 hours after ingestion of a 10 mg extended-release glipizide tablet in a 6 year-old child.¹⁰⁸

Hypoglycemia is reported in at least two cases of metformin overdose.¹⁴⁴ In both cases, metabolic acidosis with elevated lactate was evident on initial presentation. Hypoglycemia was present initially in one of the cases but did not develop until 7 hours later in the second case. Hypoglycemia and metabolic acidosis with hyperlactatemia are reported in a case of overdose with metformin, atenolol, and diclofenac.⁵² Hypoglycemia is reported in a case of metformin-associated metabolic acidosis with hyperlactatemia related to therapeutic use.⁶⁹ Insufficient evidence supports the concept that metformin-associated hypoglycemia can develop in a patient who is not critically ill without metabolic acidosis. Because many patients receiving metformin also take sulfonylureas, hypoglycemia should be anticipated after overdose. Phenformin is similar to metformin in that ingestion alone rarely causes hypoglycemia, in overdose or following therapeutic use.¹³⁰

The α -glucosidase inhibitors, thiazolidinediones, meglitinides, GLP-1 analogs, gliptins, and amylin analogs are xenobiotics for which overdose data are limited. Acarbose and miglitol are not likely to cause hypoglycemia based on their mechanism of action of inhibiting α -glucosidase. The most common adverse effects associated with therapeutic use of these xenobiotics are gastrointestinal, including nausea, bloating, abdominal pain, flatulence, and diarrhea. Elevated aminotransferase concentrations were noted after use of acarbose in clinical trials.⁵⁷ Most patients were asymptomatic, and the aminotransferase concentrations returned to normal after the drug was discontinued. The therapeutic use of acarbose in some cases reportedly led to hepatotoxicity that resolved after the drug was discontinued.^{5,24}

Hypoglycemia would not be expected after thiazolidinedione overdose. The most serious adverse effect of troglitazone is the development of liver toxicity with therapeutic doses, which in some cases was severe enough to require liver transplantation.^{49,99} Liver toxicity related to therapeutic use of rosiglitazone^{3,46} and pioglitazone is also reported.^{82,85} Therapeutic use of pioglitazone and rosiglitazone may precipitate fluid retention in patients with underlying congestive heart failure.⁹⁸ A meta-analysis concluded that rosiglitazone therapy is associated with an increased risk of myocardial infarction and death from cardiovascular causes.¹⁰¹

Hypoglycemia should be anticipated after repaglinide and nateglinide ingestion. Hypoglycemia is reported after nateglinide overdose,⁹⁶ and a case of intentionally self-induced hypoglycemia secondary to repaglinide is reported.⁵⁵ Hypoglycemia did not occur in a recently published case of intentional overdose with a total of 90 μ g exenatide.²⁹ “Severe hypoglycemia” was reported in a phase III clinical trial after inadvertent administration of 10 times the normal dose of exenatide. The specific glucose concentration is not noted in the report.²² Pramlintide is used therapeutically in conjunction with insulin, and hypoglycemia in this setting is more likely than with insulin use alone.⁷⁷

DIAGNOSTIC TESTING

Suspicion of hypoglycemia, particularly neuroglycopenia, is important in any patient with an abnormal neurologic examination. The most frequent reasons for failure to diagnose hypoglycemia and mismanaging patients are the erroneous conclusions that the patient is not hypoglycemic but rather is psychotic, epileptic, experiencing a CVA, or intoxicated because of an “odor of alcohol” on the breath (Chap. 80). Compounding the problem of misdiagnosis is the erroneous assumption that a single bolus of 0.5 to 1 g/kg of hypertonic dextrose will always be sufficient.

Plasma glucose concentrations are accurate, but treatment cannot be delayed pending the results of laboratory testing.

Glucose reagent strip testing can be performed at the bedside. The sensitivity of these tests for detecting hypoglycemia is excellent, but these tests are not perfect. Several interfering substances may cause false elevation of bedside glucose reagent strip concentrations, including maltodextrin, acetaminophen, bilirubin, triglyceride, and uric acid.^{39,65} Bedside glucose testing is discussed in more detail in Antidotes in Depth: A12.

Diagnostic studies other than determinations of glucose concentrations may be indicated, depending on the clinical situation. In some instances, determination of serum ethanol concentration may be helpful in confirming alcohol as a contributing or sole etiologic factor. Kidney function tests may indicate the presence of kidney impairment as a causative factor of hypoglycemia. This commonly occurs in diabetics taking insulin, who often develop kidney failure after they have had the disease for several years. Insulin half-life increases as kidney function declines. Measures of hepatic function may be a clue to liver disease as a cause of hypoglycemia, although liver disease may also be evident on physical examination. Seizures are commonly associated with hypoglycemia, but other studies, such as electrolytes, calcium, magnesium, and imaging of the brain, may be indicated if doubt about the etiology exists.

In the majority of overdose cases, laboratory testing for specific antidiabetics is not helpful. Exceptions might include malicious, surreptitious, or unintentional overdoses (discussed in the next section). Metformin concentrations vary and do not necessarily correlate with the clinical condition.^{2,71,72}

For known diabetics in whom overdose is not suspected, the clinician must search diligently for the cause of hypoglycemia. Sometimes it is as simple as a missed meal in an insulin user or an unusually strenuous exercise routine, but in many cases the cause cannot be clearly defined. Numerous medical conditions, as well as a variety of medications, may be involved (Table 53–1), and diagnostic testing must be individualized for each episode depending on the clinical suspicion. Diagnosing the etiology as “idiopathic” is never acceptable.

EVALUATION OF MALICIOUS, SURREPTITIOUS, OR UNINTENTIONAL INSULIN OVERDOSE

The physical examination may provide helpful clues to the evaluation of a suspected malicious, surreptitious, or unintentional insulin overdose. A meticulous search may reveal a site that is erythematous, hemorrhagic, atypically boggy in nature, or even painful if the subcutaneous (or intramuscular) injection of insulin was particularly large. A simple unexplained needle puncture mark in the appropriate clinical setting may suggest insulin injection.

An understanding of how the β cells of the pancreas secrete insulin in response to glucose concentrations in the blood is essential to understanding the investigation of fasting hypoglycemia.³¹ When the plasma glucose concentration is less than 45 mg/dL, insulin secretion should be almost completely suppressed, so plasma insulin concentrations should be minimal or absent.¹¹⁴ Moreover, insulin is secreted as proinsulin, which is cleaved in vivo to form insulin (a double stranded peptide) and C-peptide, which are released into the blood in equimolar quantities. Insulin is biologically active, whereas proinsulin has limited activity, and C-peptide has no activity. Although insulin is normally cleared during hepatic transit, C-peptide is not. For this reason, C-peptide can be utilized as a quantitative marker of endogenous insulin secretion. In contrast, commercially available exogenous human insulin does not contain C-peptide fragments (Table 53–5). When plasma glucose concentration falls to hypoglycemic concentrations (usually less than 60 mg/dL), insulin concentration should fall to less than 6 μ U/mL. If hypoglycemia is caused by exogenous insulin administration, plasma C-peptide concentrations should be less than 0.2 nmol/L in the presence of insulin concentrations that are substantially higher than insulin concentrations resulting from an insulinoma. With insulinoma, insulin concentrations generally are greater than 6 μ U/mL in the presence of hypoglycemia. Insulinoma results in elevations of both C-peptide and insulin concentrations. Sulfonylurea overdose is expected to have similar effects, but concentrations in reported cases of sulfonylurea-induced hypoglycemia vary considerably.³⁶ In the face of uncertainty, sulfonylurea concentrations are available from reference laboratories. Animal insulin can be distinguished from human insulin by high performance liquid chromatography.⁵⁰ However, this technique has limited use because of the virtually exclusive use of human insulin at present.

TABLE 53–5. Laboratory Assessment of Fasting Hypoglycemia

Clinical State	Insulin ^a (Serum) (μU/mL)	C-Peptide (Serum) (nmol/L)	Proinsulin Serum (pmol/L)	Antinsulin Antibodies ^d
Normal	<6	<0.2	<5	–
Exogenous insulin	Very high	Low (suppressed)	Absent	Present ^c
Insulinoma	High	High	Present	Absent
Sulfonylurea ingestion ^d	High	High	Present	Absent
Autoimmune	Very high (artifact)	Low (or) high (artifact)	Present	Present
Decreased glucose production	Low	Low	Present	Absent
Neoplasia (non-β-cell)	Low	Low	Present	Absent

^aInsulin concentrations are determined during fasting induced hypoglycemia at low concentrations, preferably <60 mg/dL of plasma glucose. ^bThe antinsulin antibodies produced spontaneously differ from those of treated (exposed to exogenous insulin) and those of untreated insulin dependent diabetics. ^cThe presence of antinsulin antibodies occurs less frequently in those exposed only to human insulin. ^dSulfonylurea ingestion is diagnosed by detection of the drugs or their metabolites in serum or urine.

In summary, patients with exogenous insulin induced hypoglycemia will have high insulin concentrations, the presence of insulin-binding antibodies (if chronic insulin users),⁴³ and low C-peptide concentrations. Those who have taken sulfonylureas will have high insulin concentrations, absent insulin-binding antibodies, high C-peptide concentrations, and presence of urinary sulfonylurea metabolites (Table 53–5). The issues of evidence collection that are appropriate to document malicious or surreptitious use of insulin successfully are described⁸⁰ (Chap. 141).

MANAGEMENT

Treatment centers on the correction of hypoglycemia and the anticipation that hypoglycemia may recur. Symptomatic patients with hypoglycemia require immediate treatment with 0.5 to 1 g/kg concentrated intravenous dextrose in the form of D₅₀W in adults, D₂₅W in children, and D₁₀W in neonates. Occasionally, patients require a larger dose to achieve an initial response. If hypoglycemia is suspected but not confirmed, as in the absence of rapid reagent strip availability or when such readings are “borderline,” dextrose should be administered. Theoretical risks are associated with use of concentrated dextrose in the setting of cerebral ischemia, but failure to rapidly correct hypoglycemia may lead to deleterious neurologic effects. Appropriate emergency and toxicologic uses of hypertonic dextrose are covered in detail in Antidotes in Depth: A12.

Glucagon should not be considered as an antihypoglycemic except in the uncommon situation where intravenous access cannot be obtained. Glucagon has a delay to onset of action and may be ineffective in patients with depleted glycogen stores, as in the elderly, cancer patients, or alcoholics. Glucagon also stimulates insulin release from the pancreas, which may lead to prolonged hypoglycemia in settings such as sulfonylurea ingestion and insulinoma.¹⁴⁵

Numerous studies have evaluated approaches for treating insulin reactions with carbohydrates in tablet, solution, or gel forms in a well-defined diabetic population.¹³³ None of these forms is appropriate for the undifferentiated, possibly hypoglycemic patient if intravenous access is available.

A common occurrence involves symptomatic hypoglycemic patients who receive intravenous dextrose in the prehospital setting and subsequently refuse transport to the hospital. The authors of a retrospective review of 571 paramedic runs involving hypoglycemic patients concluded that out-of-hospital treatment of hypoglycemic diabetic patients is safe and effective even when transport is refused.¹³⁴ However, of the 159 patients who agreed to hospital transport, 40% were admitted. The admitted group was older than those released from the ED. The admission rate for transported patients on oral hypoglycemics was higher than those on insulin. The reasons for admission are not otherwise detailed. The authors of a prospective study involving 132 hypoglycemic diabetic patients who refused transport after therapy concluded that most such patients have good short-term outcome, but they still encouraged transport because of the risk of recurrent hypoglycemia.⁹¹ One patient died in each of these two studies. A prospective study in 35 patients with 38 hypoglycemic events related to insulin use concluded that most patients were successfully treated in the prehospital setting without transport.⁷⁸ However, two patients developed recurrent hypoglycemia that they treated themselves, and one of these patients required placement in a long-term care facility for posthypoglycemic encephalopathy. We therefore recommend that all hypoglycemic patients should be transported to EDs.

Emesis, lavage, and catharsis are of limited benefit in the management of patients who overdose on hypoglycemics. The extensive affinity between chlorpropamide, tolazamide, tolbutamide, glyburide, glipizide, and activated charcoal is demonstrated in vitro.⁶² The affinities ranged from 0.45 to 0.52 g/g activated charcoal at pH 7.5 and were higher at pH 4.9. Single-dose activated charcoal should be beneficial in the management of these overdoses. Although affinity studies are

lacking for the other oral hypoglycemics, their chemical characteristics are such that single-dose activated charcoal is expected to be beneficial for these overdoses as well. Multiple-dose activated charcoal and whole-bowel irrigation may be of benefit and should be considered after overdose of modified-release antidiabetics and hypoglycemics, but outcome studies are not available.

In patients who overdose on insulin, case reports describe the use of surgical excision of the injection site.^{23,79,87} However, this technique has not been studied in a systematic fashion, until then, it is expected that IV dextrose should be sufficient. Needle aspiration of a depot site is less invasive and should be considered.

Urinary alkalinization to a pH of 7 to 8 can reduce the half-life of chlorpropamide from 49 hours to approximately 13 hours. Urinary alkalinization is not useful for other hypoglycemics because of their limited renal excretion.¹⁰⁰

MAINTAINING EUGLYCEMIA AFTER INITIAL CONTROL

After the patient is awake and alert, further therapy depends on the xenobiotic involved and pancreatic islet cell function. Some patients, particularly those with prolonged hypoglycemia, may have persistent altered mental status despite euglycemia. Whether the event was unintentional or intentional with suicidal or homicidal intent must be determined. One problem associated with dextrose administration occurs in individuals who can produce insulin via glucose-stimulated insulin release (nondiabetics and those with type 2 diabetes mellitus), placing them at substantial risk for recurrent hypoglycemia. This complication can occur with insulin overdose but is particularly problematic with overdoses of sulfonylurea or meglitinide because these hypoglycemics stimulate insulin release. Treatment with hypertonic dextrose solutions can be expected to result in dramatic yet only transient increases in glucose concentrations, with a subsequent fall in plasma glucose concentration, possibly back to hypoglycemic concentrations.

For diabetics who unintentionally inject an excessive amount of insulin and are not neuroglycopenic, feeding should be initiated and intravenous access maintained while avoiding routine dextrose infusion. In the event of recurrent symptomatic hypoglycemia, a concentrated dextrose bolus should be used. Overdose in the setting of suicidal or homicidal intent likely involves significant quantities of insulin. Nondiabetics may be particularly prone to significant hypoglycemia because they lack insulin resistance. Feeding should be initiated and glucose concentrations maintained in the 100 to 150 mg/dL range using a concentrated dextrose infusion (D₁₀W or greater) as needed.

Central venous lines should be used when D₂₀W infusion is instituted, because concentrated dextrose solutions are substantial venous irritants. The presence of glycosuria is not an adequate indicator of euglycemia; frequent serial blood or reagent strip glucose concentrations should be obtained. The appropriate timing of glucose monitoring varies depending on the clinical situation. Mental status must be observed. As a rough guide, glucose monitoring every 1 to 2 hours after initial control is reasonable, with subsequent spacing of the intervals to once every 4 to 6 hours. Phosphate concentrations should be monitored because glucose loading may lead to hypophosphatemia.⁹² Potassium concentrations should be monitored because glucose administration may lead to hypokalemia in nondiabetics and hyperkalemia in patients with impaired insulin secretion.²⁸ The duration of sampling depends on the stability of the patient, the underlying metabolic disorders, the extent of overdose, and the rate of improvement. When the patient begins to eat an adequate diet and the initial hypoglycemia is controlled, the plasma glucose concentration will rise, and the concentration and rate of dextrose infusion can be tapered. Many patients may actually develop significant hyperglycemia.

The therapeutic approach differs for patients who overdose on sulfonylureas or meglitinides. After initial control of hypoglycemia with concentrated dextrose, the patient should be fed. Intravenous access is necessary, but routine dextrose infusion should be avoided. As with insulin overdose, frequent monitoring of glucose concentrations and mental status is critical. We recommend early use of octreotide in this setting because of the significant risk of glucose stimulated insulin release.

Octreotide, a semisynthetic long-acting analog of somatostatin with an intravenous half-life of 72 minutes, inhibits glucose-stimulated β cell insulin release via receptors coupled to G proteins on β islet cells.¹³ Somatostatin is present in diverse tissues such as the hypothalamus, pancreas, and gastrointestinal tract. It alters the secretion of growth hormone and thyroid-stimulating hormone, gastrointestinal secretions, and the endocrine pancreas (glucagon and insulin).^{122,123} Octreotide was compared to intravenous hypertonic dextrose and to diazoxide and concomitant dextrose in normal subjects brought to hypoglycemia using glipizide.¹³ Fewer episodes of recurrent hypoglycemia occurred after octreotide therapy, and overall dextrose requirements were lower than in the dextrose-alone and dextrose-plus-diazoxide groups. Several successful clinical experiences with octreotide are reported with quinine-induced hypoglycemia resulting from malaria therapy,¹¹¹ insulinoma,⁵⁴ nesidioblastosis of infancy,³⁴ hypoglycemia related to therapeutic use of gliclazide,¹⁶ and tolbutamide overdose.¹³ In a retrospective study of nine patients with hypoglycemia resulting from either glyburide or glipizide, octreotide effectively reduced the risk of recurrent hypoglycemia.⁸⁸

Octreotide appears to be relatively free of serious side effects. The most likely adverse effects are injection-site discomfort if it is administered subcutaneously and gastrointestinal symptoms such as nausea, bloating, diarrhea, and constipation.⁸¹ The suggested adult octreotide dose is 50 μ g subcutaneously every 6 hours (Antidotes in Depth: A13). The

patient should be monitored for 12 to 24 hours after the last dose of octreotide. This observation will ensure that recurrence of hypoglycemia does not occur. Like octreotide, diazoxide may be effective in patients with refractory sulfonylurea-induced hypoglycemia.^{60,104} However, because of its potential to cause hypotension, diazoxide should be considered only if octreotide is unavailable.

ADMITTING PATIENTS TO THE HOSPITAL

The decision to admit a patient may be complex, but several guidelines can be followed. Admission is required for hypoglycemia related to sulfonylureas, ethanol, starvation, hepatic failure, and kidney failure and for hypoglycemia of unknown etiology. The decision to admit a patient often depends on finding an etiology for hypoglycemia, particularly in the setting of insulin use. In most cases, if a diabetic patient on therapeutic doses of insulin develops hypoglycemia after a missed meal, the patient can be discharged after a 4 to 6 hour observation period during which the individual eats a meal and remains asymptomatic with no evidence of hypoglycemia. Patients receiving therapeutic doses of insulin require inpatient evaluation of recurrent and unexplained hypoglycemic episodes. All patients with hypoglycemia after unintentional overdose with long-acting insulin should be admitted. Hospitalization is recommended after unintentional overdose with ultrashort-acting, short-acting, or intermediate-acting insulin if hypoglycemia is persistent or recurrent during a 4 to 6 hour observation period in the ED. Many factors may be responsible for unintentional insulin overdose, such as patient error because of impaired vision, syringe structure, and prescription error; hospital admission may be warranted. Admission is indicated for any patient, regardless of serum glucose concentration or presence or absence of symptoms, who intentionally overdoses on a sulfonylurea or any form of injected insulin, because delayed, profound, and protracted hypoglycemia may result. Although intravenous insulin overdose is expected to result in more immediate symptoms, experience with this scenario is limited. Admission in this setting is advised unless short-acting insulin is involved. Glargine is expected to act like regular insulin when administered intravenously. It is long-acting when administered subcutaneously due to the formation of microprecipitates which are absorbed slowly. Hypoglycemia related to sulfonylurea use in any setting requires hospitalization.²⁰

Patients with possible intentionally self-induced hypoglycemia should be admitted. Intentionally self-induced hypoglycemia is most commonly recognized by members of the medical profession. Administration of insulin to a nondiabetic child is a form of child abuse or an attempt at homicide³⁷ (Chap. 32). Children who have been given an inappropriate dose of insulin, as well as any patient who may be a victim of attempted homicide, should be admitted.

A 4 to 6 hour observation period is recommended after metformin overdose. Further observation or hospital admission is not required for patients who remain asymptomatic during this period with no evidence of metabolic acidosis or hypoglycemia. Patients who overdose on α -glucosidase inhibitors are not expected to have delayed or serious systemic toxicity, and routine medical admission is unnecessary. There are limited data regarding the risk of hypoglycemia and other adverse events after thiazolidinedione ingestion. Based on the mechanism of action and existing clinical experience, hypoglycemia is possible but uncommon after thiazolidinedione overdose. Delayed onset of hypoglycemia or other serious clinical manifestations is unlikely. A 4 to 6 hour observation period after thiazolidinedione overdose is recommended. Significant hypoglycemia is reported with nateglinide overdose,⁹⁶ and with repaglinide used in a setting of intentionally self-induced hypoglycemia.⁵⁵ Meglitinides are expected to behave pharmacologically like sulfonylureas. For this reason alone, hospital admission after meglitinide overdose is advisable, even when the patient is asymptomatic. Admission after exenatide, liraglutide, sitagliptin, saxagliptin, linagliptin, and pramlintide overdose is advised until more overdose data are obtained. Delays in onset of clinical manifestations, particularly hypoglycemia, are not expected, but there is currently limited clinical experience with regard to overdose.

Children who unintentionally ingest one or more sulfonylurea tablets should be hospitalized for 24 hours. Although this recommendation may be controversial and some authors suggest shorter observation periods²¹ or even home monitoring in some cases,¹²⁴ we believe that delayed hypoglycemic effects of sulfonylurea ingestion in children are well documented^{118,136,143} and convincing enough to support admission in all cases. Asymptomatic children with single tablet exposures to sulfonylureas are best managed without prophylactic intravenous dextrose, which could contribute to delayed onset of hypoglycemia.²¹ Elevations in glucose concentrations stimulate insulin release by the pancreas. Such patients instead are best managed by early feeding, frequent checks of glucose concentrations, and observation of mental status.

METFORMIN-ASSOCIATED METABOLIC ACIDOSIS WITH HYPERLACTATEMIA

Throughout this chapter, the term metabolic acidosis with hyperlactatemia is used rather than metformin-associated lactic acidosis. The biochemical and pathophysiologic processes involving lactate are complex, but a few points are worth summarizing. Hyperlactatemia occurs in various diseases and can be present in the absence of acidosis. The production of lactic acid does not result in a net increase in hydrogen ion concentration unless there is associated impairment of oxidative

metabolism. Impaired oxidative metabolism leads to an increase in hydrogen ion production through the hydrolysis of ATP.⁹³ In a pig overdose model, metformin caused metabolic acidosis with hyperlactatemia, mitochondrial dysfunction, and inhibition of oxygen consumption. Infusion of lactic acid alone did not cause inhibition of oxygen consumption.¹¹⁷

The biguanides are uniquely associated with the occurrence of metabolic acidosis with hyperlactatemia. Phenformin causes lactic acid production by several mechanisms, including interference with cellular aerobic metabolism and subsequent enhanced anaerobic metabolism. Phenformin suppresses hepatic gluconeogenesis from pyruvate and causes a decrease in hepatocellular pH, resulting in decreased lactate consumption and hepatic lactate uptake. Metformin-associated metabolic acidosis with elevated lactate occurs 20 times less commonly than that occurring with phenformin. In isolated perfused rat liver, metformin inhibits both hepatic lactate uptake and conversion of lactate to glucose.¹¹⁹ Metabolic acidosis with hyperlactatemia related to metformin usually occurs in the presence of an underlying condition, particularly kidney impairment.^{25,69} In this setting, increased tissue burden of metformin, which is renally eliminated, probably occurs. Other risk factors include cardiorespiratory insufficiency, septicemia, liver disease, history of metabolic acidosis with hyperlactatemia, advanced age, alcohol abuse, and use of radiologic contrast media.^{9,25} Iodinated contrast material may induce acute kidney injury, leading to accumulation of metformin and subsequent risk of development of metabolic acidosis with hyperlactatemia. However, the risk of developing metabolic acidosis with hyperlactatemia after contrast administration is low in patients taking metformin who have normal kidney function and no other risk factors.^{86,97}

Severe metabolic acidosis with hyperlactatemia occurs after acute metformin overdose^{72,89,104,144} but appears to be uncommon. In one case,⁸⁹ metabolic acidosis was not diagnosed until 14 hours after metformin overdose. The patient had early symptoms of repeated vomiting at 1 hour postingestion. Metabolic acidosis with hyperlactatemia occurred in two of 65 adult metformin overdose cases reported to a poison center¹³⁷ and was not reported in a poison center series of 55 pediatric metformin exposures.¹³⁸ In a retrospective review of 398 cases of acute metformin overdose from two poison centers, metabolic acidosis with hyperlactatemia occurred in 9.1% of single product overdose and in 0.7% of polypharmacy overdoses.¹⁵²

A systematic review from the Cochrane Library concluded that therapeutic use of metformin is not associated with an increased risk of metabolic acidosis with hyperlactatemia compared with other antidiabetic treatments if no contraindications are present.¹²⁵ This conclusion was based on a review of prospective comparative trials and observational cohort studies. However, the risk of metformin-associated metabolic acidosis with hyperlactatemia in the setting of overdose setting or kidney insufficiency was not assessed. Although metabolic acidosis with hyperlactatemia after overdose is not common, it does occur with sufficient frequency to require vigilance on the part of the treating physician. Case reports were not used in the Cochrane review, and a few cases of metformin-associated metabolic acidosis with hyperlactatemia in the setting of therapeutic use with no underlying risk factors are reported.^{25,109,147}

It is difficult to predict outcome after metformin overdose. A retrospective literature review found no deaths in cases with a nadir serum pH greater than 6.9, a peak serum lactate concentration less than 25 mmol/L, or a peak serum metformin concentration less than 50 µg/mL.³⁵ However, a retrospective review of intensive care unit patients with metabolic acidosis with hyperlactatemia found no association between metformin concentrations in survivors and nonsurvivors.¹²⁹ There was an association between mortality and lactate concentrations and pH.

Metformin associated metabolic acidosis with hyperlactatemia is a potentially lethal condition. Recognition and awareness of this disorder are important. Symptoms may be nonspecific and include abdominal pain, nausea, vomiting, malaise, myalgia, and dizziness. However, gastrointestinal symptoms are common adverse effects associated with therapeutic use of metformin and do not necessarily require discontinuation of the drug. More severe clinical manifestations of metformin-associated metabolic acidosis with hyperlactatemia include confusion, blindness, mental status depression, hypothermia, respiratory insufficiency, and hypotension. Serum metformin concentrations can be obtained as a diagnostic aid, but these may not correlate with the clinical condition in both the acute overdose setting and in the setting of therapeutic metformin use.^{71,72}

Aggressive airway management and vasopressor therapy may be required. Indications for use of intravenous sodium bicarbonate in critically ill patients with metabolic acidosis with hyperlactatemia of various etiologies are poorly defined and controversial. Rather than using an arterial pH cutoff, we recommend using sodium bicarbonate given evidence of impaired buffering capacity based on a serum bicarbonate threshold concentration of less than 5 mEq/L. Based on case reports, hemodialysis may be effective in improving acid–base status and clinical outcome in patients with significant metabolic acidosis with hyperlactatemia.^{53,69,73} In some of these cases, metformin concentrations were measured and remained abnormally high after dialysis. Clinical improvement despite inadequate removal of metformin may be related to correction of acid–base status.

SUMMARY

- Numerous xenobiotics and medical conditions may cause hypoglycemia.

- Hypoglycemia is the predominant adverse effect related to therapeutic use and overdose of many of the drugs used for treatment of diabetes mellitus.
- Various clinical manifestations, particularly neurologic, may occur and can be confused with conditions such as ethanol intoxication, psychosis, epilepsy, and cerebrovascular accidents.
- The potential for delayed and prolonged hypoglycemia must be recognized in overdose situations.
- Although several treatment options exist, rapid intravenous administration of dextrose is the most important measure.
- Octreotide is useful for patients with recurrent hypoglycemia following sulfonylurea or meglitinide overdose.

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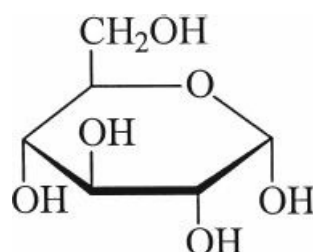
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A12 ANTIDOTES IN DEPTH

Dextrose (D-Glucose)

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Dextrose (D-glucose)

INTRODUCTION

Hypoglycemia is a common cause of altered mental status. Although classically associated with tachycardia, tremor, and diaphoresis, the predictive value of these manifestations is too low to be relied upon. As a result, all patients with altered consciousness require either rapid point-of-care testing of their glucose concentrations or empiric treatment for presumed hypoglycemia. When rapidly diagnosed and treated, hypoglycemic patients typically recover without sequelae. However, delayed or incomplete therapy may lead to permanent neurologic dysfunction ([Chap. 53](#)).

HISTORY

In 1891, Fisher performed the unbelievable feat of identifying the 16 possible different spatial configurations of aldohexose ($C_6H_{12}O_6$), the most prominent member being dextrose or D-glucose.³⁸ This discovery won him the 1902 Nobel Prize in chemistry. The diverse manifestations of hypoglycemia and the treatment of severe cases with intravenous (IV) dextrose have been appreciated for decades.⁶⁸

PHARMACOLOGY

Chemistry

Sugar is the general term used for sweet carbohydrates that are used as food. Simple sugars are called monosaccharides and include glucose (also known as dextrose, or D-glucose, as the L-isomer is hardly found in nature), fructose (also known as fruit sugar, the sweetest), and galactose. The disaccharides include maltose, lactose, and sucrose (sucrose is also known as table or granulated sugar).

Sugars are found in the tissues of most plants, but are only present in sufficient concentrations for efficient extraction in sugarcane and sugar beet. Commercially, glucose is produced from the hydrolysis of starch. Several crops serve as the starch source, with maize being the most common in the United States.

In humans, carbohydrates are absorbed and transported via two main systems. Sodium-dependent glucose transporters (SGLT1-6) are responsible for the intestinal glucose absorption.¹³ Their discovery represented the first description of the mechanism of “flux coupling” or cotransporting, in which transporting one substrate down its concentration gradient creates energy that can then be used to transport a second substrate against a concentration gradient. Other facilitative sugar transporters include GLUT1 to GLUT14 and HMIT.¹⁰⁷ GLUT4 is expressed in insulin-sensitive tissues and regulates whole-body glucose homeostasis.⁷⁸ GLUT3 is found in neurons and in the placenta and has a high affinity for glucose, allowing for transport even in low substrate conditions.⁷ GLUT5 is responsible for the absorption of fructose in the small intestine.⁹ The GLUT5 transporter has wide variability and is dependent on the amount of glucose ingested relative to the fructose. Decreased fructose absorption can lead to abdominal bloating and osmotic diarrhea in susceptible individuals.⁵⁵

Binding of glucose to one of the GLUT receptors causes a conformational change that results in glucose translocation across the membrane.⁵⁴

Related Xenobiotics

Besides the mono and disaccharides mentioned above, sugars are also found in polymer forms. Maltodextrins are oligosaccharides of D-glucose used as food additives. Starch and cellulose are the polymers of glucose found in plants. Glycogen and chitin are found in animals. Some of the polymers are used to store energy (starch and glycogen) and some are used for structural support (chitin and cellulose).

Mechanism of Action

Glucose reaching the liver, adipose tissue, and muscle cells is absorbed and stored as glycogen (under the influence of insulin) or used by all cells to produce adenosine triphosphate (ATP) and pyruvate via glycolysis. Hepatic glycogen can later be converted to glucose and returned to the blood when insulin is low or absent. In contrast, glycogen found in muscle and adipose cells is utilized internally and not released into the systemic circulation. Some glucose is converted to lactic acid by astrocytes and then utilized as an energy source. The brain can use both exogenous and endogenous lactate as an alternative energy source.^{94,105,112} Finally, glucose is also directly used by intestinal cells and red blood cells.

Pharmacokinetics

Accurate prediction of the amount of dextrose required to effectively treat patients with hypoglycemia is difficult. At equilibrium, 25 g of dextrose distributed in total body water in a 70 kg adult is calculated to increase the serum glucose concentration by about 60 mg/dL.⁵¹ In the few clinical studies performed, the magnitude of glucose elevation after oral or IV dextrose loading was unpredictable. In one study, 25 g (50 mL) of D₅₀W administered to adults (both diabetics and nondiabetics) resulted in a mean blood glucose elevation of 166 mg/dL when measured in the opposite extremity 3 to 5 minutes after the bolus; however, the range of this elevation was 37 to 370 mg/dL above baseline.¹ In a human model of insulin-induced hypoglycemia, oral administration of 10 or 20 g of dextrose increased the serum glucose concentration from 60 to 120 mg/dL over one hour.¹¹⁹ Another study used 25 volunteers and administered 25 g of IV dextrose as D₅₀W. Glucose concentrations were measured at 5, 15, 30, and 60 minutes. Volume of distribution formulas could not accurately predict postinfusion glucose concentrations. The serum glucose elevation was statistically significant from baseline at 5 and 15 minutes, and glucose concentrations returned to baseline at 30 minutes postinfusion.⁵

Pharmacodynamics

ATP provides the metabolic energy that fuels all critical cellular processes in all organs. In the adult brain, the anaerobic and aerobic metabolism of glucose through glycolysis and the citric acid cycle, respectively, are the primary sources of ATP (Chap. 13). Although the adult brain can use fatty acids, amino acids, lactate, and ketones as alternate substrates for ATP synthesis, these are not adequate to sustain normal cerebral function in the setting of glucose deprivation. In contrast, in fetal and neonatal brains, glucose is the only substrate for ATP production.^{88,113}

Hypoglycemia cannot be defined by strict numerical values. Rather, it is best defined by organ dysfunction in the setting of inadequate glucose concentrations. The onset of hypoglycemia in both adults and children is followed rapidly by global cerebral dysfunction. In individuals with diabetes, the density and sensitivity of neuronal insulin receptors vary as a function of glycemic control, so that diabetic patients with poor glycemic control have fewer and less sensitive neuronal insulin receptors and may experience hypoglycemic symptoms at much higher concentrations of glucose than those who are normally euglycemic. An important study of diabetic patients demonstrated that the mean blood glucose concentration for symptomatic hypoglycemia in poorly controlled patients was 78 ± 5 mg/dL compared with $53 \pm$ mg/dL in well-controlled patients.⁸ This differential response to hypoglycemia is also described at higher glucose concentrations in poorly controlled versus intensely controlled diabetic patients.⁵⁷ Thus, neuroglycopenia may occur despite “normal” peripheral blood glucose concentrations.¹¹⁵ In rare cases, glucose-consuming cancer cells can produce large amounts of lactate (Warburg effect), which can be used by the brain as an alternate source of energy. Even in the presence of profound hypoglycemia, such patients remain asymptomatic.³²

Hypoglycemia may cause a myriad of neuropsychiatric sequelae that are clinically indistinguishable from those of other toxic-metabolic and structural brain injuries.^{19,27,72,76,97,114,121} In a case series, preexisting signs and symptoms included dizziness and tremulousness (8%); focal stroke syndromes (2%), movement disorders or seizures (7%), irritability, confusion, or bizarre behavior (30%), delirium, stupor, or coma (52%); and irreversible encephalopathy.⁷² These numbers are similar to those in a case series of patients with insulinomas.¹⁸ In cases of undifferentiated coma, both the absence of pupillary light reflex (sensitivity 83% and specificity 77%, positive predictive value {PPV} 70 and negative predictive value {NPV} 87, likelihood ratio {LR} 3.56) and the presence of anisocoria (sensitivity 39% and specificity 96%, PPV 86

and NPV 70, LR 9) are helpful in distinguishing structural from metabolic causes.¹¹⁰ Hypoglycemic hemiplegia is a well-recognized, although rare entity, and therein lies the relevance of a serum glucose measurement in patients with focal neurologic symptoms.⁷²

The heart is partially dependent on glucose as an energy substrate. Hypoglycemia causes myocardial stress that may manifest as angina and or dysrhythmias. There are two mechanisms postulated for hypoglycemia induced dysrhythmias. First, it causes K⁺ current inhibition, which results in QT prolongation.⁸⁰ This is aggravated by the systemic catecholamine response to hypoglycemia, which results in increased intracellular calcium, another dysrhythmogenic stimulus.^{29,67,75,79–81} Nocturnal hypoglycemia is associated with the “dead in bed” syndrome. The postulated mechanisms are hypotonia of the respiratory muscles with an impaired awakening, mediated by orexin-A neurons, and QT prolongation and other dysrhythmogenic effects of hypoglycemia.^{42,82} Counterregulatory hormone responses to hypoglycemia are also impaired by sleep.^{26,58}

ROLE IN HYPOGLYCEMIA

Table A12–1 summarizes some causes of hypoglycemia.

TABLE A12–1. Xenobiotics and Medical Conditions Associated with Hypoglycemia	
Xenobiotic	Medical Condition
Ackee fruit (<i>Blighia sapida</i>)	Hyperinsulinism
Jamaican vomiting sickness	Inborn errors of carbohydrate metabolism (eg, glycogen storage disease)
β-Adrenergic antagonists	Kidney disease
Angiotensin-converting enzyme inhibitors (rare)	Liver disease
Bitter melon (<i>Momordica charantia</i>)	Malignancy
Disopyramide	Malnutrition
Ethanol	Sepsis
Haloperidol (rare)	Shock
Insulin	Starvation
Insulinlike growth factor	Transient neonatal hypoglycemia
Pentamidine	
Quinine and quinidine	
Quinolones (especially gatifloxacin)	
Ritodrine	
Salicylate	
Streptozocin	
Sulfonylureas and other classes	
Trimethoprim-sulfamethoxazole	

Empiric Treatment Considerations

The history and physical examination do not reliably detect patients who are hypoglycemic.⁵⁰ Tachycardia, diaphoresis, pallor, hypertension, tremors, hunger, and restlessness tend to predominate when the decline in serum glucose concentration is rapid. However, neuroglycopenia, even when severe, may not trigger autonomic responses.¹⁹ Signs and symptoms may be further blunted or absent in the setting of concurrent use of β-adrenergic antagonists. Central nervous system signs of neuroglycopenia are also nonspecific. They may include visual disturbances, psychiatric disturbances, confusion, stupor, coma, seizures, and focal neurologic findings.^{72,98} In children, the only sign of neuroglycopenia may be lethargy or irritability.¹²³

The bedside diagnosis of hypoglycemia is limited by the sensitivity and specificity of reagent strips, which do not have the reliability and accuracy of laboratory analysis.⁸⁴ Sensitivities of commonly available reagent strips for detection of hypoglycemia range between 92% and 97% in various studies.^{11,12,56,66,71,96} The accuracy of these point-of-care testing methods is affected by the source of blood, whether arterial, venous, or capillary, and by the poor perfusion associated with shock and cardiac arrest.^{4,14,28,41,59,62,64,70,106}

False-positive capillary hypoglycemia occurs in shock and cardiac arrest. Hypoglycemia was identified by capillary samples in 8 of 50 patients with cardiac arrest. Only three of these were confirmed to be hypoglycemic by laboratory

determination of serum glucose. Reagent strip testing of venous blood correctly classified these patients. There were no false negative results.¹⁰⁶ A critical care unit study that evaluated patients in shock showed that 32% were incorrectly diagnosed as hypoglycemic when capillary blood was used. All these patients were either normoglycemic or hyperglycemic. Results of reagent strip tests of venous blood correlated well with laboratory results, correctly classifying all patients. No cases of hypoglycemia were missed.⁴ Therefore, capillary determinations of glucose should be used with caution in the critically ill population, recognizing that false positive detections of hypoglycemia are common.⁷⁰ When feasible, laboratory measurements should be obtained in these populations. A second best alternative is reagent strip testing of venous blood rather than capillary samples. However, it is important to know the specific test being used at a particular institution, as more recent reports have shown improved correlation between point-of-care testing and laboratory glucose measurements.^{60,64,117}

Several studies have compared the accuracy of standard reagent strips for the detection of hypoglycemia from capillary and venous blood compared with the gold standard of the laboratory. Two studies, one with 97 subjects⁴¹ and one with 270 subjects,⁶² evaluated the agreement between reagent strip determinations of capillary and venous blood glucose in healthy normoglycemic volunteers. In the larger study, 18% of subjects had a more than 15 mg/dL difference between capillary and venous reagent strip tests. In this study, capillary measurements were better correlated with the laboratory values. Whether these results have any clinical significance is not clear because none of the subjects were outside of the euglycemic range. However, the results suggest that the capillary blood glucose test has greater accuracy in the euglycemic range and in healthy individuals.

The “safe” number at which no cases of symptomatic hypoglycemia are missed by reagent strip testing is a subject of debate, because of the inherent risk of error from lack of sensitivity. In one study in which hypoglycemia was defined as a blood glucose concentration below 60 mg/dL, 2 of 33 hypoglycemic patients were not detected at the bedside. A cutoff of 90 mg/dL would have detected 100% of numerically hypoglycemic patients.⁶⁶ Based on these studies, it can be argued that a bedside reagent measurement of 90 mg/dL is a conservative cutoff for assurance of clinical euglycemia in all patients.

With reagent strip testing, variations in hematocrit and the presence of isopropyl alcohol in the sample may alter the accuracy of the test.^{6,46} In some specific tests, such as the one using glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ), accuracy may be affected by a number of interfering xenobiotics, such as serum acetaminophen concentrations greater than 80 mg/dL, a serum bilirubin concentration greater than 20 mg/dL, a serum galactose concentration greater than 10 mg/dL, a maltose concentration greater than 16 mg/dL, a serum uric acid greater than 10 to 16 mg/dL, serum triglycerides greater than 5000 mg/dL, and the presence of D-xylose in the sample. All of these result in falsely elevated glucose measurements.³¹ There are reports of interference with the use of IV fat emulsion therapy as an antidote.⁴⁷ Notably, icodextrin, an ingredient in peritoneal dialysis fluids, may result in overestimation of glucose measurements because it is metabolized to maltose. In several case reports and at least 18 cases reported in a review, this overestimation resulted in excess insulin administration and subsequent hypoglycemia.^{31,39,61,90} Glucose monitoring systems that use the GDH-PQQ method should not be used in patients using icodextrin in the peritoneal dialysis fluid.¹¹¹ Maltose is also contained in some immunoglobulin solutions, and the same interference can be expected.^{34,104} Glucose measurements by the GDH-PQQ and the amperometric methods are also affected by the hematocrit.^{103,117} Whereas hematocrits lower than 20% may result in falsely elevated glucose measurements, hematocrits higher than 55% may result in falsely low measured glucose concentrations.³¹ In a retrospective review of patients admitted to a hospital over a 12-month period, 1.2% were identified as having interfering substances. Of these, 36% had active orders for insulin. In this review, the most common interferences identified were a low hematocrit (44% of patients) and a high serum uric acid (29% of patients).³¹

One final consideration is in patients with salicylate toxicity ([Chap. 39](#)), in which serum glucose is not an accurate reflection of tissue glucose concentrations.¹⁰⁸ Salicylate poisoning is a relatively uncommon cause for drug-induced hypoglycemia.¹⁰² Salicylates uncouple oxidative phosphorylation, which results in increased intracellular glucose demands. Patients may demonstrate symptoms of neuroglycopenia despite normal serum glucose concentrations. Dextrose administration reverses the signs and symptoms,⁶³ and can improve survival.¹⁰⁸

Advances in monitoring technology include continuous glucose monitoring, which uses a sensor placed under the skin that measures interstitial fluid glucose.⁸⁹ These sensors are generally accurate at normal glucose concentrations. However, in situations where the serum glucose is fluctuating, changes in the interstitial glucose concentration may lag for up to 15 minutes. Patients are encouraged to measure the capillary blood glucose before making treatment decisions.¹²⁰ A noninvasive device that also measures interstitial glucose concentrations has been approved by the US Food and Drug Administration.²⁵

Patients with asymptomatic or minimally symptomatic hypoglycemia should be treated with oral carbohydrates (juice, milk, candy, or glucose tablets). For adults, the recommended dose of 20 g should result in symptom improvement in 15 to 20 minutes.¹⁵ Since this improvement may be transient, it is recommended that the initial glucose intake should be followed by a more substantial meal. For the patient unable (coma, seizures) or unwilling (from neuroglycopenia) to receive oral glucose, the IV route must be used. In an adult a bolus dose of 0.5 to 1.0 g/kg of IV dextrose is recommended. The

subsequent improvement in glucose concentration is transient and the patient should be monitored closely for recurrence.¹⁵ Generally, a dextrose infusion should follow the initial dextrose bolus,¹⁵ with the recognition that this supplies very little caloric content.

Rapid increases in serum glucose are sufficient to stimulate insulin release from the pancreas and may result in reactive (or rebound) hypoglycemia. Therefore, glucose concentrations must be closely followed after a bolus of concentrated glucose solutions. This effect is exaggerated in the patients who have ingested sulfonylureas.^{44,48}

ROLE IN ETHANOL DISORDERS

Alcoholic ketoacidosis (AKA) is a metabolic emergency. It occurs when drinkers cease or significantly decrease their food intake and have some degree of vomiting. The result is salt and water depletion with an anion gap metabolic acidosis that is typically accompanied by a normal to low serum glucose (unlike diabetic ketoacidosis). In children, hypoglycemia may occasionally ensue after exposure to ethanol and ethanol-containing household products.^{35,87} Newborns and young infants, in contrast to adults, may present with irritability, feeding problems, lethargy, cyanosis, tachypnea, and/or hypothermia.⁴⁹

The management of AKA consists of rehydration using isotonic crystalloids, parenteral thiamine administration, dextrose infusion using D₅W or D₁₀W, potassium replacement, and addressing the underlying medical problem that led to AKA.⁴⁰

Chapter 80 has an in-depth discussion of AKA.

ROLE IN SALICYLATE POISONING

As discussed in the previous section, salicylates uncouple oxidative phosphorylation, which results in increased intracellular glucose demands.¹⁰⁹ Patients with salicylate toxicity may demonstrate symptoms of neuroglycopenia despite normal serum glucose concentrations. Dextrose administration has been shown to reverse these signs and symptoms of neuroglycopenia.⁶³

Chapter 39 provides an in-depth discussion of salicylate toxicity and its management.

ROLE IN CARDIOVASCULAR TOXICITY

Hyperinsulinemia/euglycemia is one of the cornerstones of management of patients with drug induced cardiovascular toxicity. Insulin improves carbohydrate utilization by the cells and restores calcium fluxes. This improves cardiac contractility and allows for improved vascular tone.⁷⁴ The available data strongly support this approach in patients with calcium channel blocker toxicity, and there are also reports that describe benefit in cases of β -adrenergic antagonist toxicity.^{69,124} The initial bolus of 1 unit/kg and subsequent 1 unit/kg/h of regular insulin must be supplemented with sufficient dextrose to maintain euglycemia. The use of continuous dextrose infusions with insulin (insulin–euglycemia) as antidotal therapy for cardiovascular toxicity is reviewed in Antidotes in Depth: A17.

ROLE IN HYPERKALEMIA

Hyperkalemia occurs commonly in the emergency department, most often as a result of end stage kidney disease. It can represent an adverse medication reaction. IV insulin is used to redistribute potassium inside the cell. A dose of 10 units of regular insulin is usually followed by 25 g of IV 50% dextrose.¹¹⁸ The initial dextrose dose should be followed by a dextrose infusion, as a single bolus is not sufficient to prevent hypoglycemia at one hour.² The onset of action is less than 15 minutes and peaks at 30 to 60 minutes.¹¹⁸ This regimen results in an average serum potassium decrease of about 0.6 mEq/L.¹¹⁸

ADVERSE EFFECTS AND SAFETY ISSUES

The most serious complications associated with hypoglycemia are directly attributable to the failure to recognize and treat it. Most complications due to the administration of concentrated IV dextrose are either clinically insignificant or exceedingly rare. Phlebitis and sclerosis of veins may occur. Tissue necrosis may occur after soft tissue extravasation of D₅₀W and after inadvertent intraarterial injection.^{3,24} Inappropriately large boluses of D₅₀W in children are associated with seizures, brain hemorrhage, and hyperosmolar coma.⁹⁹ Anaphylactoid reactions are also rarely reported after the administration of D₅₀W.¹⁶

While prolonged glucose infusions without thiamine supplementation are associated with Wernicke encephalopathy in

at-risk patients, this does not occur if thiamine is administered proximate to the time of dextrose administration. Correction of hypoglycemia should not be delayed in order to administer thiamine (Antidotes in Depth: A24).⁹²

Dilute dextrose solutions should not be administered with blood as they can cause pseudoagglutination of erythrocytes. These solutions can also result in electrolyte dilution and excess intravascular volume. Most dextrose products are derived from corn, so they should not be used in patients with of severe corn allergy.

One final important consideration is the development of rebound hypoglycemia when dextrose is used to treat sulfonylurea-induced hypoglycemia (Chap. 53). In these cases, serial measurements of glucose and close patient monitoring should follow any dextrose boluses.⁷³

Concerns Regarding Elevated Blood Glucose Concentrations in Patients with Cerebral Ischemia

Studies of ischemic brain injury in a variety of animal models consistently demonstrate that higher blood glucose concentrations are associated with more extensive cerebral injury and worse outcomes.^{17,20–22,43,52,65,86,100,101} The clinical literature also demonstrates that the presence of hyperglycemia upon admission is associated with poorer outcomes in patients with acute ischemic stroke.^{23,33,53,83,85,116,122,125}

While concerns previously existed regarding provision of dextrose in the clinical scenario of potential cerebral ischemia, rapid bedside testing has essentially eliminated this consideration. Although underpowered, the Glucose Insulin in Stroke Trial—United Kingdom (GIST-UK) failed to show any mortality benefit from treatment of hyperglycemia in acute stroke patients.^{45,95} Additionally, it is now clear that attempts at intensive glucose control are associated with higher rates of hypoglycemia, which is related to increased mortality.^{36,37,91,93}

PREGNANCY AND LACTATION

Dextrose is a pregnancy category C (IV) and A (oral); studies have not been conducted regarding its safety to the fetus. Hypoglycemia is a serious concern for fetal well being, and the best evidence suggests that hypoglycemia in a pregnant woman should be approached in the same manner as in any nonpregnant patient. Although there are no data regarding the use of hypertonic dextrose in lactation, it is unlikely to be a concern, because even if the concentration of glucose in subsequent breast milk is a significantly increased, the effect will be transient.

DOSING AND ADMINISTRATION

In most cases, the rapid correction of hypoglycemia by the administration of 0.5 to 1 g/kg of concentrated IV dextrose (Table A12–2) immediately reverses neurologic and cardiac effects. However, prolonged or severe hypoglycemia may result in permanent brain injury, myocardial infarction, and death.^{10,30,77} Glucose should be monitored after concentrated dextrose administration. This is usually done within an hour after administration or if there is a change in the patient’s condition.

TABLE A12–2. Dosing of Dextrose

Age	Concentration	Bolus	Dose in mL/kg
Adult	D ₅₀ W (50% = 0.5 g/mL)	0.5–1.0 g/kg	1–2
Child	D ₂₅ W (25% = 0.25 g/mL)	0.5–1.0 g/kg	2–4
Infant	D ₁₀ W (10% = 0.1 g/mL)	0.5–1.0 g/kg	5–10

FORMULATION AND ACQUISITION

Dextrose is available as a 5%, 10%, 20%, or 50% solution for IV use. Concentrations greater than 10% should be infused via a central venous catheter, except in emergencies. Table A12–3 summarizes the most commonly available intravenous and oral preparations.

TABLE A12–3. Dextrose Preparations for Clinical Use

<i>Preparation</i>	<i>Volume (mL)</i>	<i>Concentration or Amount</i>
Dextrose 2.5% for injection, USP	1000	0.025 g/mL
Dextrose 5% for injection, USP	25, 50, 100, 150, 250, 500, 1000	0.05 g/mL
Dextrose 10% for injection, USP	5, 250, 500, 1000	0.10 g/mL
Dextrose 20% for injection, USP	500, 1000	0.20 g/mL
Dextrose 25% for injection, USP	10	0.25 g/mL
Dextrose 50% for injection, USP	50	0.50 g/mL
Dextrose 70% for injection, USP	70	0.70 g/mL
Oral		
Glucose tablets		1 or 4 g/tablet
Glucose gel		0.4 g/mL (40%)
Dextrose liquid		15 g/59 mL
Dextrose 5% oral solution		0.05 g/mL

USP = US Pharmacopeial Convention.

SUMMARY

- Dextrose is an effective antidote for patients with hypoglycemia and has additional indications in those with alcoholic ketoacidosis and as an adjunct to high-dose insulin therapy for cardiovascular drug toxicity.
- Hypoglycemia can mimic many syndromes, producing any alteration in consciousness, including focal neurologic syndromes.
- The currently available reagent strips reliably demonstrate the absence of significant hypoglycemia at readings greater than 90 mg/dL. Profound neurologic impairment likely is not the result of hypoglycemia with such concentrations, even in diabetic patients.
- Dextrose should be administered to all patients with altered levels of consciousness and numerical hypoglycemia (glucose concentration <90 mg/dL).
- Dextrose should be empirically administered to patients with altered levels of consciousness in the rare cases where bedside reagent strips are not readily available.

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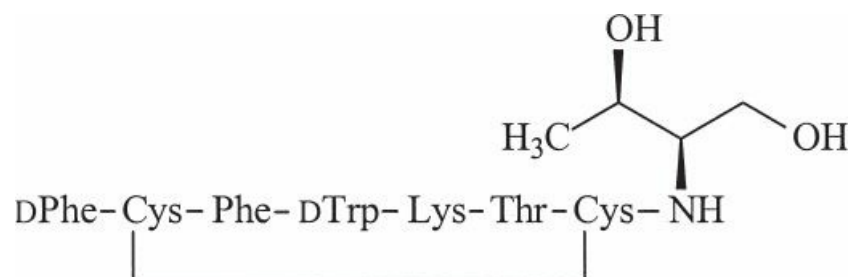
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A13 ANTIDOTES IN DEPTH

Octreotide

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INTRODUCTION

Octreotide is a long-acting, synthetic octapeptide analog of somatostatin that inhibits pancreatic insulin secretion. It currently is the essential complement to dextrose for the treatment of refractory hypoglycemia induced by overdoses of insulin secretagogues (eg, sulfonylureas) and quinine. Although not formally approved by the US Food and Drug Administration (FDA) for this indication, octreotide currently is used in toxicology for the treatment of hypoglycemia from insulin secretagogues.

HISTORY

Somatostatin is a collective term for shorter fragments (SRIF-28, SRIF-25, and SRIF-14) cleaved by tissue specific enzymes from preprosomatostatin (116 amino acids) and prosomatostatin (92 amino acids).¹⁴ Somatostatin was identified in 1973, during the search for growth hormone releasing factor.⁸ In addition to its effects on growth hormone and insulin secretion, somatostatin has far-reaching effects as a central nervous system (CNS) neurotransmitter and as a modulator of hormonal release.^{45,54} The importance of somatostatin on insulin secretion led to the need to create an analog as a therapeutic tool as somatostatin is limited because of its short duration of action.

Octreotide was synthesized in 1982 in an effort to develop a longer-acting analog of somatostatin.⁵ Octreotide is currently approved by the FDA for the treatment of acromegaly, carcinoid tumors, and vasoactive intestinal peptide tumors. It is also used therapeutically for the treatment of pituitary adenomas, pancreatic islet cell tumors, portal hypertension, esophageal varices, and secretory diarrhea.⁴⁵ Octreotide is being investigated for its inhibitory effects on tumor cell proliferation through stimulation of apoptosis, antiangiogenesis, immunomodulatory effects, and the suppression of tumor-stimulating growth factors.^{42,45,55}

PHARMACOLOGY

Mechanism of Action on Insulin Secretion and Other Hormones

The effects of somatostatin are mediated by high-affinity binding to membrane receptors on target tissues. Five different somatostatin receptor subtypes that belong to a superfamily of G-protein coupled receptors are identified and assigned numbers (SSTR1–SSTR5) according to their order of discovery.¹⁴ Octreotide, lanreotide, and vapreotide have high binding affinity for subtype SSTR2, a lower affinity for SSTR5 and SSTR3, and almost no affinity for SSTR1 and SSTR4.⁴⁵ The pancreas contains all five subtypes, but in mice SSTR5 is more prevalent in the β -cells and SSTR2 is more prevalent in the α -cells in animal studies.⁶⁹ SSTR5 is found in many tissues, including the brain, pituitary, stomach, intestine, thyroid, and adrenal gland; SSTR2 is found in the brain, pituitary, stomach, liver, kidney, lung, intestine, spleen, thymus, uterus, prostate, and adrenal gland.^{45,50,58,69} A variety of pituitary and gastroenteropancreatic tumors contain varying percentages of the SSTR subtypes. Recently in comparison to studies in mice SSTR2 was found to be the functionally dominant somatostatin

receptor in human pancreatic β - and α -cells.³⁶

Octreotide, similar to the natural hormone somatostatin, but with a longer duration of action, is a potent inhibitor of growth hormone, glucagon, and insulin. It also suppresses the response of luteinizing hormone to gonadotropin releasing hormone; decreases splanchnic blood flow; and inhibits the release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, thyroid-stimulating hormone, and pancreatic polypeptide.⁵⁴

Experiments in both healthy human volunteers and an isolated perfused canine pancreas model demonstrate the ability of somatostatin to inhibit glucose-stimulated insulin release.^{2,26} Experiments using a whole-cell patch clamp technique on a hamster β -cell line suggest that somatostatin inhibits insulin secretion by a G-protein-mediated decrease in calcium entry through voltage-dependent Ca^{2+} channels.³⁴ No evidence indicates that somatostatin inhibits insulin release by promoting K^{+} efflux through K_{ATP} channels at physiologic concentrations as do the oral hypoglycemics (Fig. 53–2).^{22,47,56} Instead somatostatin, like epinephrine, stimulates a pertussis toxin sensitive Gi-coupled receptor that inhibits adenylate cyclase and production of cyclic adenosine monophosphate (cAMP), decreasing intracellular calcium and thereby reducing insulin secretion.³² Simultaneous distal reduction in phosphorylation of specific proteins may also be involved in reducing insulin secretion.^{22,32,43} This latter mechanism appears to be independent of Ca^{2+} .^{22,32} More recent experiments in human pancreatic β - and α -cells indicate somatostatin agonism via SSTR2 hyperpolarizes human β -cells and decreases depolarized evoked exocytosis in both α - and β -cells via several mechanisms.³⁶ First, increased current through G-protein gated inward rectifying potassium (GIRK, Kir3.x) channels can be demonstrated. This effect is independent of the ATP-sensitive K^{+} (K_{ATP}) channel, and thus it remains effective when the K_{ATP} channel is antagonized by an oral sulfonylurea. Second, somatostatin inhibits a depolarization leak current (mediated by an as yet unidentified channel). Third, somatostatin reduced voltage-gated P/Q-type Ca^{2+} currents. Lastly, somatostatin directly inhibited calcium dependent exocytosis.

Activation of SSTR5 on the β -cell of the pancreas also reduces insulin biosynthesis.²² One study in human volunteers confirms the ability of somatostatin to inhibit the increased insulin response to both glucose and glucagon.²⁶ Intravenous (IV) infusion of 1 g of tolbutamide over 2 minutes caused insulin concentrations to rise and serum glucose concentration to drop sharply. Similarly, in the presence of somatostatin and tolbutamide, administration of IV glucagon caused a rise in glucose concentration without the expected subsequent glucose stimulated rise in insulin. The effects of somatostatin were short lived. Within 5 minutes of stopping the somatostatin, the insulin releasing effects of tolbutamide continued, and within 15 minutes the serum glucose concentration fell. Peak insulin concentrations were achieved within 25 minutes.

Studies comparing octreotide to somatostatin in rats and monkeys demonstrate that octreotide is 1.3 times as potent as somatostatin in inhibiting insulin secretion by 50%. Likewise, compared with somatostatin, octreotide was 45 times more potent in inhibiting growth hormone secretion and 11 times more potent in inhibiting glucagon release.⁷ Comparable results were found using a hyperglycemic glucose clamp technique.³⁹ Octreotide blocks the counterregulatory response to the effects of 0.1 unit/kg IV insulin by preventing an increase in glucagon and growth hormone. The effects of octreotide on the responses of adrenocorticotropin, cortisol, prolactin, luteinizing hormone, and follicle-stimulating hormone to insulin-induced hypoglycemia all remained intact.⁴⁷ In contrast, growth hormone²⁰ and thyroid stimulating hormone are significantly inhibited.⁴⁷

Related Xenobiotics. Lanreotide and vapreotide are very long-acting, FDA approved somatostatin analogs. However, their use in sulfonylurea induced insulin secretion is not warranted based on the time action profiles of the sulfonylureas.

Pharmacokinetics

The pharmacokinetics of IV and subcutaneous (SC) octreotide were studied in eight healthy adult volunteers.⁴¹ Subjects received 25, 50, 100, and 200 μg IV octreotide over 3 minutes and 50, 100, 200, and 400 μg SC octreotide in random order. Following IV administration, the distribution half-life averaged 12 minutes, and the elimination half-life ranged from 72 ± 22 minutes to 98 ± 37 minutes and was linear. V_i (volume of distribution of the central compartment) was dose dependent and increased from approximately 5.7 L at 25, 50, and 100 μg IV to 10 L at 200 μg IV doses.⁴¹ The V_d (volume of distribution determined by area under the curve) ranged from 18 ± 6 L to 30 ± 30 L and showed no dose dependency.⁴¹ Approximately 30% of elimination was renal, and this was reduced in the elderly and in those with chronic kidney disease.⁵⁴

After SC administration, bioavailability was 100%, and peak concentrations were achieved within 30 minutes with an absorption half-life of 5 to 12 minutes. The elimination half-life was 88 to 102 minutes. Peak serum concentrations after SC administration ranged from 2.4 ng/mL at doses of 50 μg to 23.5 ng/mL at doses of 400 μg . After IV administration, peak serum concentrations ranged from 9.6 ng/mL at doses of 50 μg to 27.8 ng/mL at doses of 200 μg .⁴¹

The pharmacokinetics in patients with pathologic conditions may differ from the pharmacokinetics in healthy volunteers as exemplified by a lower peak concentration and a higher steady state V_d in patients with acromegaly.⁵⁴ In patients with reduced kidney function and those with liver cirrhosis and fatty liver disease, the half-life ranges from 2.5 to 3.7 hours depending on the extent of impairment. The half-life in the elderly is also prolonged by about 50%.⁵⁴

Pharmacodynamics

The duration of action of octreotide is variable. When used for tumor suppression, the duration may last up to 12 hours.⁵⁴ The duration of action for inhibition of insulin secretion is unknown but presumed to be somewhere between 6 to 12 hours.

ROLE OF OCTREOTIDE FOR INSULIN SUPPRESSION

Controlled studies in animals given oral gliclazide demonstrate that a single dose of octreotide 50 µg or 100 µg SC results in fewer hypoglycemic events and dextrose boluses.³¹ Octreotide has been studied in humans in several clinical conditions, including insulinomas and hypoglycemia of infancy.^{3,27,37,65,67} In most instances, octreotide suppressed insulin concentrations and glucose concentrations rose. However, worsening hypoglycemia has been reported when suppression of α cell glucagon release outlasts suppression of β cell insulin release.^{8,13,25,33,53,65} Another reason for variable effects in these conditions includes the absence of octreotide-susceptible SSTR receptor subtypes.¹⁹ Octreotide currently is used in toxicology for treatment of hypoglycemia from insulin secretagogues.

In controlled studies of healthy volunteers, octreotide suppressed the release of insulin associated with quinine.⁶¹ Life-threatening hypoglycemia is a well-recognized complication of quinine treatment of *Plasmodium falciparum* malaria; quinine blocks the K_{ATP} channel in an analogous manner to sulfonylureas.⁹ In this setting, hypertonic dextrose and diazoxide therapy are frequently inadequate, with ensuing refractory hypoglycemia. In an investigation of the potential hypoglycemia sparing effect of octreotide given for treatment of quinine induced hypoglycemia, healthy adults were given 50 µg/h octreotide or placebo as a continuous IV infusion for 4 hours, followed at the first hour by infusion of 490 mg quinine base.⁶⁰ In the control subjects, serum insulin concentrations rose and serum glucose concentrations fell significantly, whereas in the octreotide group, insulin concentrations fell and glucose concentrations remained constant. This effect of octreotide began within 30 minutes and persisted for 2 hours after octreotide was stopped. Octreotide was used successfully to treat refractory hypoglycemia in a woman receiving 600 mg quinine dihydrochloride IV for malaria.⁶⁰ A subsequent treatment study⁶¹ confirmed these findings and noted that its volunteer arm, a single 100 µg dose suppressed quinine induced hypoglycemia within 15 minutes. Because quinolone antibiotics share a 4-quinolone nucleus with quinine, they are also associated with rare hypoglycemia due to K_{ATP} inhibition.⁴⁶ Octreotide has been used to reverse quinolone associated hypoglycemia.³⁸

Octreotide efficacy for sulfonylurea-induced hypoglycemia was demonstrated in an early experimental study. Eight healthy volunteers were given 1.43 mg/kg glipizide orally and randomized to receive either a variable dextrose infusion to remain euglycemic, diazoxide 300 mg IV over 30 minutes and repeated every 4 hours with dextrose, or octreotide 30 ng/kg/min IV continuously.¹⁰ Following administration of glipizide, hypoglycemia of 50 mg/dL was achieved within 30 to 165 minutes.¹⁰ Insulin concentrations in the diazoxide group were comparable with those in the glipizide group and were four to five times higher than in the octreotide group. Four of the eight patients in the octreotide group did not require supplemental dextrose. At the fifth hour of the protocol, an IV bolus of 50 mL of 50% dextrose was given to the octreotide group to study the response to hyperglycemia. Approximately 6.5 hours was necessary for the serum glucose concentration to drop to 85 mg/dL, whereas only 3 hours was necessary in the dextrose and diazoxide groups.¹⁰ This demonstrates that octreotide can suppress the ability of hyperglycemia to result in the endogenous release of insulin. Diazoxide infusion was associated with higher norepinephrine concentrations, while epinephrine concentrations were similar in all groups.¹⁰ All xenobiotics were stopped at 13 hours, and serum glucose concentrations fell to less than 65 mg/dL within 1.5 hours in subjects who received the dextrose and diazoxide, whereas the serum glucose concentrations remained greater than 65 mg/dL in six of the eight octreotide subjects for the 4 hour observation period. Without additional octreotide, hypoglycemia recurred for as long as 30 hours after the initial glipizide administration. One prospective, randomized controlled trial of 40 hypoglycemic, poisoned patients (using a single octreotide 75 µg dose subcutaneously) demonstrated consistently higher glucose values for the duration for which octreotide would be expected to be effective (6–8 hours).²³ The failure to control for carbohydrate intake and combined exposure to insulin complicate interpretation of the results.

Many case studies, two case series of 15 patients, and recent reviews^{15,21,28} support the efficacy of octreotide following overdoses of glipizide, glyburide, gliclazide, glimepiride, tolbutamide, and nateglinide. These cases encompass both intentional and unintentional overdoses in children and adults with and without diabetes.^{10,12,16–18,24,29,30,35,39,48,51,52,59,63,68} In these case reports, therapeutic doses ranged considerably, and the most frequent doses were 50 to 100 µg subcutaneously repeated every 8 to 12 hours in the adult patients and 1 to 2 µg/kg SC or IV as a starting dose in pediatrics and repeated every 6 hours as needed.^{15,28}

ADVERSE EFFECTS AND SAFETY ISSUES

Octreotide is generally well tolerated, but toxicologic experience is limited. Adverse reactions occurring with short term

administration usually are local or gastrointestinal (nausea, abdominal cramps, diarrhea, fat malabsorption, and flatulence).⁴⁵ Stinging at the injection site occurs in approximately 7% of patients but rarely lasts more than 15 minutes.⁷⁰ Healthy volunteers receiving octreotide noted no side effects when given IV doses of 25 or 50 µg or SC doses of 50 or 100 µg. At higher doses, early transient nausea and later appearing but longer lasting diarrhea and abdominal pain frequently occur.^{40,41} Healthy volunteers were given IV bolus doses of octreotide as high as 1000 µg and infusion doses of 30,000 µg over 20 minutes and 120,000 µg over 8 hours without serious adverse effects. Single doses in healthy volunteers resulted in decreased biliary contractility and bile secretion.⁵⁴ Long term therapy lasting weeks to months results in biliary tract abnormalities.^{54,71} Octreotide use to reverse sulfonylurea induced hypoglycemia has rarely resulted in bradycardia, hypokalemia, anaphylactoid reactions, hypertension, and apnea.^{18,66} Product information suggests the potential for acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, and pancreatitis.⁵⁴

Octreotide alters the balance among insulin, glucagon, and growth hormone. Serum glucose concentrations must be serially monitored. Hyperglycemia often occurs, but cases of hypoglycemia are reported. A revision in the precautions section of the package labeling states that symptomatic hypoglycemia occurs in patients with type I diabetes and their insulin requirements will likely be reduced. The most likely explanation is suppression of counterregulatory hormones, in particular when glucagon suppression, is more persistent than insulin suppression.⁵⁴

Other adverse effects reported with long-term administration of octreotide or for octreotide in circumstances other than sulfonylurea-induced hypoglycemia include hypothyroidism, cardiac conduction abnormalities, worsening congestive heart failure and QT prolongation (in at-risk patients with acromegaly), bradycardia, pancreatitis, substantial hyperglycemia and bradycardia in an infant with congenital hyperinsulinemia, hypoxemia and pulmonary hypertension in premature neonates, necrotizing enterocolitis,⁴⁴ altered fat absorption, hyperkalemia in a hemodialysis patient,¹ and decreased vitamin B₁₂ concentrations.^{4,6,54}

Drug interactions are expected with xenobiotics that affect glucose regulation. Octreotide may significantly decrease oral absorption of cyclosporine and increase the bioavailability of bromocriptine. Because octreotide may suppress the activity of the cytochrome P450 enzymes, in particular CYP3A4, drugs with narrow therapeutic indices metabolized by these enzymes should be monitored more closely.⁵⁴

PREGNANCY AND LACTATION

Octreotide is considered a category B drug. Pregnant women must be carefully monitored for recurrent hypoglycemia. Use of octreotide should not diminish this vigilance. Studies in breastfeeding have not been performed.

DOSING AND ADMINISTRATION

No controlled trials have evaluated the optimal dose of octreotide for the management of sulfonylurea overdose. In adults, a 50 µg SC dose of octreotide given every 6 hours is suggested. In children, a dose of 4 to 5 µg/kg/d SC divided every 6 hours, up to the adult dose, can be used for initial therapy. This pediatric dose is derived from the literature on treatment of persistent hyperinsulinemic hypoglycemia of infancy.²⁷ In situations where compromised peripheral blood flow is expected, octreotide should be administered IV in the same dose but every 4 hours instead of every 6 hours. An increase in the dose is rarely required. Further toxicologic experience should permit a better delineation of dosing recommendations.

While the optimal duration of octreotide therapy awaits definitive study, several principles and patient factors help guide management. First, the duration of action of every single sulfonylurea except tolbutamide exceeds 12 hours, and this might be altered with extended-release formulations, sulfonylureas with enterohepatic recirculation, in overdose, and with coingestions or coadministrations.^{23,59,62} Second, the onset of hypoglycemia may be significantly delayed following ingestion (as late as 21 to 48 hours, depending upon the hypoglycemic).^{57,64} Third, acute or chronic kidney dysfunction (whether intrinsic or secondary to insufficient perfusion as in cases of congestive heart failure), which may have predisposed to sulfonylurea induced hypoglycemia in the first place, alters elimination of both oral sulfonylureas and antidotal octreotide. Fourth, a controlled animal study demonstrated the failure of single dose octreotide to eliminate recurrent late (9–24 hour) hypoglycemic episodes.³¹ Fifth, human data suggest potential inadequacy of single or few octreotide doses. In one case series, failure occurred 14 hours after a patient's last dose of octreotide (more than 30 hours after the ingestion of glyburide), and an additional failure occurred 36 hours after a single dose of octreotide (40 hours after ingestion of extended-release glipizide).⁴⁸ In humans administered glipizide, after 13 hours of continuously provided octreotide therapy, two of eight subjects (25%) had decreases in glucose more than 3 hours after stopping octreotide. Without ongoing octreotide, hypoglycemia persisted for as long as 30 hours and hyperinsulinemia persisted for greater than 16 hours after the initial glipizide administration.¹⁰ Treatment failures (episodes of glucose <60 mg/dL) occurred in 10 of 22 patients (45%) in a prospective, randomized controlled employing a single-dose octreotide strategy; two events occurred at 12 and 13 hours after octreotide administration.²³ Thus, although one or two octreotide doses might prove

adequate, the available pharmacokinetic, animal, and human data suggest that this may be insufficient, and several days of therapy may be required, depending on the particular xenobiotic, quantity of ingestion, coingestants, and individual patient factors. All patients must be carefully monitored for recurrent hypoglycemia during octreotide therapy and for 12 to 24 hours following termination of octreotide therapy before discharge.¹⁰ The potential for unrecognizable recurrent hypoglycemia during sleep necessitates that patients must not be discharged during the high risk circadian phase (eg, evening or night), unless the patients have been monitored for an adequate amount of time off of octreotide and after a dextrose challenge (which may increase the release of insulin). Other patients at risk for hypoglycemia unawareness (defective glucose counterregulation and hypoglycemia without warning symptoms)⁵ should also be managed conservatively.

Both SC and IV administration are acceptable, although the usual route is SC.⁵⁴ The SC administration sites should be rotated. For IV infusion, octreotide can be diluted in sterile 0.9% sodium chloride solution or D₅W and infused over 15 to 30 minutes or by IV bolus over 3 minutes.⁵⁴ Rapid IV bolus may be indicated for carcinoid crisis.⁵⁴

Refrigeration of octreotide is recommended for prolonged storage, although octreotide is stable at room temperature for 14 days when protected from light. Active warming of refrigerated octreotide is not recommended, although passive warming to room temperature prior to administration is suggested and may reduce the pain of SC administration.⁴⁹

Using the smallest volume possible also reduces the pain with SC administration. A depot formula designed to last for 4 weeks is available (Sandostatin LAR Depot). Although the depot formula is useful for patients with insulinomas, its duration of action far exceeds that of any insulin secretagogue, making it an inappropriate and unnecessary choice for management of xenobiotic-induced hypoglycemia. Vapreotide (Sanvar IR) and lanreotide (Somatuline Depot) are analogs of somatostatin that are available in the United States but are inappropriate for use in the setting of xenobiotic induced insulin secretion.

FORMULATION AND ACQUISITION

Octreotide acetate (Sandostatin) injection is available in ampules and multidose vials ranging in concentration from 50 to 1000 µg/mL. The multidose vials contain phenol. It should not be confused with the long-acting formulation—Sandostatin LAR.

SUMMARY

- The available evidence indicates that octreotide is useful for preventing the reoccurrence of hypoglycemia induced by the insulin secretagogues sulfonylureas and quinine that cause endogenous release of insulin.
- Octreotide is more effective than diazoxide in suppressing insulin release and is better tolerated.
- Octreotide is not a substitute for IV dextrose for the immediate treatment of hypoglycemia or and does not decrease the need for frequent glucose assessments.
- Before discharge, the following should be ensured: the effects of octreotide have dissipated, the patient remains euglycemic following an adequate oral dextrose challenge, and there has been a sufficiently prolonged observation time since ingestion to ensure that hypoglycemia will not occur in a fasting or sleeping patient.

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54 ANTIMIGRAINE MEDICATIONS

Jason Chu

PATHOPHYSIOLOGY OF MIGRAINE HEADACHES

A migraine headache is a neurovascular disorder often initiated by a trigger and characterized by a headache, which is preceded by a visual aura 20% of the time. The headache may be accompanied by a variety of multiple organ system symptoms, such as allodynia, nausea, vomiting, and urinary frequency. There are various types of migraine, the diagnostic criteria for which are established by the International Headache Society.⁴ The types of migraine are divided into two groups: migraine without aura (“common migraine”) and migraine with aura (“classic migraine”). Further subdivisions include migraine with typical aura with or without headache, familial hemiplegic migraine, sporadic hemiplegic migraine, basilar type migraine, and retinal migraine.⁴

The initiation of migraines is not fully understood, but likely involves genetic abnormalities in central nervous system (CNS) ion channels that predispose patients to specific triggers. Patients with familial hemiplegic migraine, an autosomal dominant disorder, have missense mutations in the α_1 subunit of brain specific P/Q voltage-gated calcium channels resulting in altered function of these channels. During migraines, the upper brainstem has increased blood flow and is implicated as a “migraine generator.” After activation, a wave of cortical depression spreads across the cortex from a caudal to rostral fashion followed by a spreading wave of oligemia, which can produce the auras that occur in 20% of migraineurs.^{26,36,86} Current theories suggest that this spreading wave also occurs in patients who do not experience visual auras but spares the visual cortex.

Cephalalgia begins during vasoconstriction prior to vasodilation. Antidromic activation of the afferent neurons of the ophthalmic division of the trigeminal nerve and branches of the C1 and C2 nerves (first order neurons) located on dural arteries at the base of the brain releases inflammatory neuropeptides such as calcitonin gene-related polypeptide (CGRP), vasoactive intestinal peptide (VIP), and neurokinin A. Vasoactive neuropeptides, including serotonin, nitric oxide, substance P, neurokinin A, and calcitonin gene-related peptide (CGRP), are released during this process, which exacerbates the vasodilation and irritates the meninges at the base of the brain, causing further pain. CGRP from trigeminal A- δ -fibers produces dural vasodilation, while substance P and neurokinin A from trigeminal C-fibers increase dural vessel permeability.^{24,26} Pain impulses are relayed orthodromically to the trigeminal nucleus caudalis (second order neurons) in the lower medulla and upper cervical spinal cord, then to the thalamus (third order neurons) via the quintothalamic tract, and finally to higher cortical areas (fourth order neurons probably located in the limbic cortex).^{26,34} The trigeminocervical complex also produces retrograde parasympathetic impulses from the sphenopalatine ganglion and the superior salivatory nucleus in the pons through the pterygopalatine, otic, and carotid ganglia to the cerebral vessels.³⁴

Treatment of migraines encompasses a wide variety of xenobiotics that can be broadly classified as prophylactic or abortive therapies (Table 54–1). Current abortive therapies include analgesics (nonsteroidal antiinflammatory drugs, acetaminophen {APAP}, opioids), antiemetics, ergots alkaloids, triptans, oxygen, magnesium sulfate, and intranasal lidocaine. Triptans are considered the drugs of choice for abortive migraine therapy. Prophylactic therapies with the evidence for established efficacy include antiepileptics (topiramate, valproic acid), β -adrenergic antagonists (metoprolol, propranolol, timolol) and triptans (for menstrually related migraines).⁷⁵

TABLE 54–1. Xenobiotics Used in Migraine Treatment^a

<i>Prophylactic</i>	<i>Abortive</i>
β-Adrenergic antagonists	Acetaminophen
Antiepileptics: Gabapentin, lamotrigine, levetiracetam, topiramate, valproic acid, zonisamide	Antiemetics: metoclopramide, ondansetron, prochlorperazine
Antipsychotics: Aripiprazole, olanzapine, quetiapine	Aspirin
Benzodiazepines	Butalbital
Butterbur root	Butyrophenones: droperidol, haloperidol
Calcium channel blockers	Caffeine
Candesartan	Corticosteroids
Coenzyme Q10	Ergots
Cyclic antidepressants	Lidocaine (intranasal)
Cyproheptadine	Magnesium (intravenous)
Enalapril	Nonsteroidal antiinflammatory drugs
Feverfew	Opioids
Flunarizine	Oxygen
Hormonal contraceptives	Sedative-hypnotics
Isometheptene/dichloralphenazone/acetaminophen (Midrin)	Triptans
Lisinopril	Valproic acid
Magnesium (oral)	
Monoamine oxidase inhibitors	
Melatonin	
Memantine	
Nefazodone	
OnabotulinumtoxinA (Botox A)	
Pizotifen	
Riboflavin	
Selective serotonin reuptake inhibitors	

*Prophylactic xenobiotics are usually taken to prevent triggering of migraines, and abortive xenobiotics are usually taken to stop the clinical manifestations of migraines once they are triggered. However, the separation between the two groups of xenobiotics is not strict, and some xenobiotics may be used in both roles. Triptans are currently considered the drug class of choice for migraine treatment.

ERGOT ALKALOIDS

History and Epidemiology

Ergot is the product of *Claviceps purpurea*, a fungus that contaminates rye and other grains. The spores of the fungus are both windborne and transported by insects to young rye, where they germinate into hyphal filaments. When a spore germinates, it destroys the grain and hardens into a curved body called the sclerotium, which remains the major commercial source of ergot alkaloids.⁷¹ The *C. purpurea* fungus produces diverse substances, including ergotamine, histamine, lysergic acid, tyramine, isomylamine, acetylcholine, and acetaldehyde.

In 600 B.C. an Assyrian tablet mentioned grain contamination believed to be by *C. purpurea*. In the Middle Ages, epidemics causing gangrene of the extremities, with mummification of limbs, were depicted in the literature as blackened limbs resembling the charring from fire and caused a burning sensation expressed by its victims. The disease was called holy fire or St. Anthony's fire, but the improvement that reportedly occurred when victims went to visit the shrine of St. Anthony was probably the result of a diet free of contaminated grain on the journey.³⁷ Abortion and seizures were also reported to result from this poisoning. On the other hand, as early as 1582, midwives used ergot to assist in the childbirth process. In 1818, Desgranges was the first physician to use ergot for obstetric care, and in 1822 Hosack reported that ergot could be used for the control of postpartum hemorrhage.⁸⁴ Since 1950, the clinical use of ergot derivatives is almost entirely limited to the treatment of vascular headaches. Ergonovine, another ergot derivative, is used in obstetric care for its stimulant effect on uterine smooth muscle and was formerly used in cardiac stress tests. Methylergonovine is used for

postpartum uterine atony and hemorrhage. Cabergoline is used for hyperprolactinemia and in the treatment of Parkinson disease. Ergot derivatives were also used as “cognition enhancers,”⁸⁷ to help manage orthostatic hypotension,⁷⁸ and to prevent the secretion of prolactin.⁷¹

Currently in the US, human poisoning epidemics from ergot grain infestations are prevented by government inspections of grain fields. If a grain field contains more than 0.3% affected grain, then it is rejected for commercial sale; in some years, as much as 36% of the grain was rejected.⁷¹ However, elsewhere in the world ergot toxicity remains a problem predominantly in animals.^{9,48}

Pharmacology and Pharmacokinetics

All ergot alkaloids are derivatives of the tetracyclic compound 6-methylergoline. They can be divided into three groups: amino acid alkaloids (ergotamine, ergotoxine), dihydrogenated amino acid alkaloids, and amine alkaloids (Fig. 54–1).

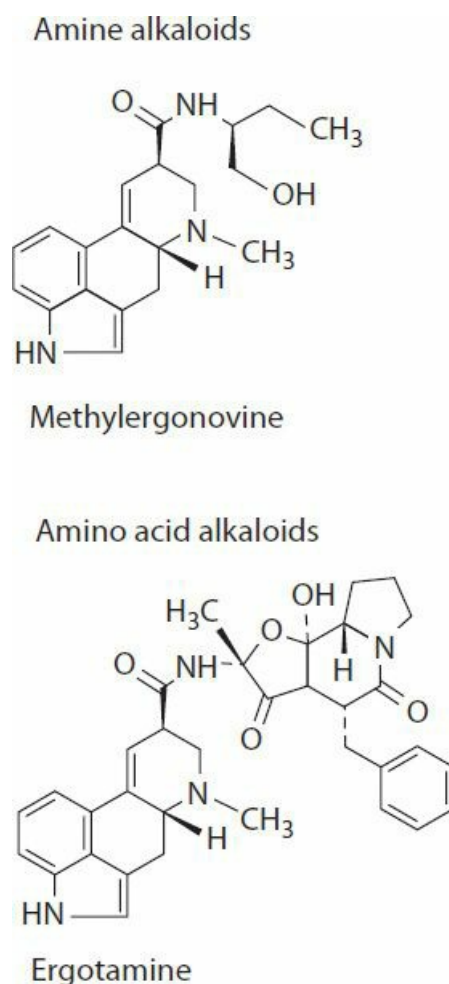


FIGURE 54–1. Chemical structures of two ergot derivatives representative of the amine and amino acid alkaloids.

The pharmacokinetics of the ergot alkaloids are well defined by controlled human volunteer studies, whereas the toxicokinetics are essentially unknown (Table 54–2). Almost all of the ergots are poorly absorbed orally and there is considerable first-pass hepatic metabolism, resulting in highly variable bioavailability. Intramuscular absorption is unpredictable and actions are often delayed.⁶³ Peak plasma concentrations with oral ergotamine occur within 45 to 60 minutes.⁶³ The volume of distribution of ergotamine is approximately 2 L/kg and the half-life varies from 1.4 to 6.2 hours. Ergot alkaloids are metabolized in the liver, probably by CYP3A4, and the metabolites are excreted in the bile.^{7,71}

TABLE 54–2. Pharmacokinetics of Ergots

Ergot Derivative	Clinical Use	$t_{1/2}$ (hours)	Duration of Action (hours)	Bioavailability (%)	Metabolism/Elimination
Bromocriptine	Parkinsonism, amenorrhea/prolactinemia syndrome	60 (PO)	1 week (suppression of prolactin)	28 (PO)	Liver
Dihydroergotamine	Migraine	2.4	3–4 (IM)	100 (IM) 40 (Nasal) <5 (PO)	Liver metabolism Bile excretion
Ergonovine	Testing for coronary vasospastic angina	1.9	3	(IV) 100	Liver
Ergotamine	Migraine	2 (1.4–6.2)	22 (IV)	100 (IV) 47 (IM) <5 (PO)	Liver metabolism Bile excretion
Methylexgonovine	Postpartum hemorrhage	1.4–2.0	3	78 (IM) 60 (PO)	Liver
Methysergide	Migraine	2.7/10 hours (PO)	8–24	13 (PO)	Liver—metabolized to methylexgonovine

IM = intramuscular; IV = intravenous; PO = oral.

The pharmacologic effects of the ergot alkaloids can be subdivided into central and peripheral effects (Table 54–3). In the CNS, ergotamine stimulates serotonergic receptors, potentiates serotonergic effects, blocks neuronal serotonin reuptake, and has central sympatholytic actions.^{37,71} Ergotamine and dihydroergotamine interact with the 1A, 1B, 1D, 1F, 2A, 2C, 3, and 4 serotonin receptor subtypes, dopamine receptors and adrenergic receptors.⁸ The result is increased intrasynaptic serotonin activity in the median raphe neurons of the brainstem.⁶⁸ Ergotamine and dihydroergotamine decrease the neuronal firing rate and stabilize the cerebrovascular smooth musculature, which make them useful drugs for both abortive and prophylactic treatment of migraine headaches.

TABLE 54–3. Pharmacology of Ergot Derivatives

Ergot Derivative	Interactions with Tryptaminergic (Serotonergic) Receptors	Interactions with Dopaminergic Receptors	Interactions with α -Adrenergic Receptors
Bromocriptine (amino acid alkaloid)	Weak antagonist	CNS: Partial agonist/antagonist; inhibits prolactin secretion; emetic (high)	Vasculature: Antagonist
Dihydroergotamine (dihydrogenated group)	Smooth muscles: Partial agonist/antagonist CNS: Agonist lateral geniculate nucleus	CNS: Emetic (mild) Sympathetic ganglia: Antagonism	Vasculature: Partial agonist (veins); antagonist (arteries) Smooth muscles: Antagonism CNS/PNS: Antagonism
Ergonovine and methylexgonovine (amine alkaloid)	Smooth muscles: Potent antagonist Vasculature: Agonist in umbilical and placental vessels CNS: Partial antagonist/agonist	CNS: Emetic (mild); inhibits prolactin (weak); partial agonist/antagonist Vasculature: Weak antagonist	Vasculature: Partial agonist
Ergotamine (amino acid alkaloid)	Vasculature: Partial agonist Smooth muscles: Nonselective antagonist CNS: Poor agonist/antagonist	CNS: Emetic (potent)	Vasculature: Partial agonist/antagonist Smooth muscles: Partial agonist/antagonist CNS: Antagonist PNS: Antagonist
Methysergide (amine alkaloid)	Vasculature: Partial agonist CNS: Potent antagonist	None	None

CNS = central nervous system; PNS = peripheral nervous system.

Peripherally, ergotamine and dihydroergotamine are α -adrenergic, 5-HT_{2A} and 5-HT_{1B} agonists and vasoconstrictors.⁷⁶ The amino acid ergot alkaloids (ergotamine, ergotoxine) exhibit α -adrenergic agonism, and dehydrogenation

(dihydroergotamine) of the lysergic acid nucleus increases the potency of this effect.⁷¹ Ergotamine is a more potent constrictor of peripheral arteries, whereas dihydroergotamine is a more potent vasoconstrictor.¹⁶ Table 54–3 summarizes the pharmacologic actions of selected ergot alkaloids currently used in clinical medicine. The spectrum of effects depends on dose, host response, and physiologic conditions.

The clinical effects following overdose are an extension of the therapeutic effects. At toxic doses, extreme vasoconstriction produces the characteristic ischemic changes that occur in ergotism.

The cerebrovascular effects of ergot alkaloids are not as clearly understood. In migraine treatment, for example, therapeutic doses of ergotamine produce mild vasoconstriction via α -adrenergic agonism. This may be more pronounced in intracranial vessels that are already dilated during a migraine. In toxic doses, cephalic vasodilation may occur but the mechanism for this effect is unknown. One hypothesis is that toxic doses initially produce cerebral vasoconstriction and ischemia, just as occurs in the periphery, but since the cerebral vasculature cannot tolerate hypoxia and hypercapnia, rapid vasodilation then ensues to improve local perfusion. In addition, α -adrenergic receptors in the CNS function differently from those in the periphery, and it may be that CNS vascular tone cannot be maintained in the setting of local tissue hypoxia.

Clinical Manifestations

Ergotism, a toxicologic syndrome resulting from excessive use of ergot alkaloids, is characterized by intense burning of the extremities, hemorrhagic vesiculation, pruritus, formication, nausea, vomiting, and gangrene (Table 54–4). Headache, fixed miosis, hallucinations, delirium, cerebrovascular ischemia, and convulsions are also associated with this condition, which has been called “convulsive” ergotism.³⁷ Chronic ergotism usually presents with peripheral ischemia of the lower extremities, although ischemia of cerebral, mesenteric, coronary, and renal vascular beds are well documented.^{3,27,28,69,70} Ergotism can also result from interactions of ergot derivatives with CYP3A4 inhibitors such as macrolide antibiotics and protease inhibitors, which increase bioavailability of ergots.^{6,7}

TABLE 54–4. Clinical Manifestations of Ergotism

Central Effects	Peripheral Effects
Agitation	Angina
Cerebrovascular ischemia	Bradycardia
Hallucinations	Gangrene
Headaches	Hemorrhagic vesications and skin bullae
Miosis (fixed)	Mesenteric infarction
Nausea	Myocardial infarction
Seizures	Renal infarction
Twitching (facial)	
Vomiting	

The vascular effects ascribed to ergot alkaloids are complex and sometimes conflicting (Table 54–3). Subintimal and medial fibrosis, vasospasm, and arteriolar and venous thrombi (stasis related) are all reported.⁵⁶ Angiography can demonstrate distal, segmental vessel spasm with increased collateralization in patients with chronic ergotism. The coronary, renal, cerebral, ophthalmic, and mesenteric vasculature,⁷⁰ as well as the vessels of the extremities, may also be affected.⁷³ Neuropathic changes may be secondary to ischemia of the vasa nervorum.

Bradycardia is a characteristic effect of the ergot alkaloids, and is believed to be a reflex baroreceptor-mediated phenomenon associated with vasoconstriction, but a reduction in sympathetic tone, direct myocardial depression, and increased vagal activity may also be factors.⁷¹

Myocardial valvular abnormalities are reported with ergot alkaloids. Ergotamine, methysergide, pergolide, and cabergoline cause mitral and aortic valve leaflet thickening and immobility resulting in valvular regurgitation.^{29,69,90}

Treatment

The treatment for a patient with ergot alkaloid toxicity depends on the nature of the clinical findings. Gastric emptying should rarely be used, if at all, because vomiting is a common early occurrence, and the ingestion may be complicated by seizures. After an acute oral overdose, 1 g/kg of activated charcoal should be administered orally. If emesis is present, antiemetics such as ondansetron or metoclopramide should be administered intravenously to facilitate the administration of activated charcoal. In mild cases, characterized by minimal pain of the extremities, nausea, or headache, supportive measures such as hydration and analgesia are all that are needed. Patients who develop mild symptoms of vasospasm, such as dysesthesias and minimal ischemic pain of the digits, should be treated with immediate release nifedipine 10 mg every 8

hours orally.¹⁵ With more serious cases, severe peripheral vasoconstriction may produce ischemic changes that include angina, myocardial infarction, cerebral ischemia, intermittent claudication, and internal organ/mesenteric ischemia. Intravenous sodium nitroprusside at a starting dose of 0.5 µg/kg/min is recommended and should be titrated until resolution of vasoconstriction.^{3,12,62} Phentolamine should be considered as well. Immediate release oral nifedipine at a dose of 10 mg every 8 hours can be administered as a second line therapy. Methylprednisolone at a dose of 1 mg/kg was reported to reverse ergotamine induced lower extremity arterial vasospasm that was not responsive to sodium nitroprusside and heparin.⁶⁶

Heparin or low molecular weight heparins should be administered to prevent sludging and subsequent clot formation. Benzodiazepines should be used to treat seizures or hallucinations.

TRIPTANS

In 1974, investigations began on a new class of compounds that produced vasoconstrictive effects via 5-HT receptors. The first compound successfully used in this way was 5-carboxamidotryptamine (5-CT). When applied to an isolated dog saphenous vein, 5-CT caused potent venoconstriction and induced significant hypotension in vivo. The next compound developed, AH25086 [(3-2-aminoethyl)-N-methyl-1-H-indole-5-acetamide], also constricted saphenous veins in dogs but had more 5-HT receptor selectivity. AH25086 was effective against acute migraine in human volunteers, but further research was stopped because it was deemed less suitable for development in humans, possibly owing to the fact that it was highly polar, lipophobic, and unsuitable for oral use.^{41,72} In 1984, sumatriptan was synthesized and its clinical success led to the rapid development of six other triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan, and one triptan combination medication (sumatriptan/naproxen; Fig. 54-2; Table 54-5).

TABLE 54-5. Pharmacokinetics of Triptans

Triptan	<i>t</i> _{1/2} (hours)	Duration of Action (hours)	Lipophilicity	Bioavailability (%)	Metabolism/Elimination
Almotriptan	3.0–3.7	24	Unknown	70–80	CYP3A4, CYP2D6 MAO-A (minor)
Eletriptan	3.6–6.9	14–16	High	50	CYP3A4
Frovatriptan	25	24	Low	24–30	CYP1A2 Kidney
Naratriptan	4.5–6.6	Unknown	High	63–74	Kidney (major) P450
Rizatriptan	1.8–3.0	25	Moderate	40–45	MAO-A
Sumatriptan	2.0–2.5	4	Low	14 (PO); 96 (SC)	MAO-A
Zolmitriptan	1.5–3.6	18	Moderate	40–49	CYP1A2 MAO-A (minor)

MAO = monoamine oxidase; PO = oral; SC = subcutaneous.

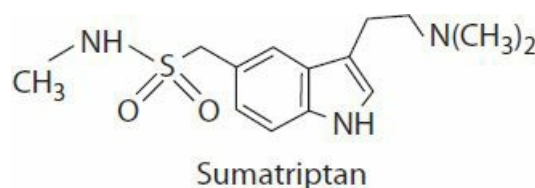


FIGURE 54-2. Representative chemical structure of the triptans.

Pharmacology

The triptans are all primarily 5-HT_{1B} and 5-HT_{1D} receptor agonists and have less activity at 5-HT_{1A} and 5-HT_{1F} receptors³⁰ (Chap. 14). In the CNS, 5-HT_{1B} receptors are located on cerebral vessels.³⁵ Stimulation of these receptors results in cerebral vasoconstriction,¹⁷ reversing abnormal cerebral vasodilation. In contrast, the 5-HT_{1D} receptors are located presynaptically on trigeminal neurons, and act as “autoreceptors” to decrease neurotransmitter release from central trigeminal nerve terminals.⁴⁵ The triptans also inhibit dural neurogenic inflammation by preventing the release of

vasoactive neuropeptides from peripheral trigeminal nerves.^{58,74} Peripherally, triptans cause vasoconstriction systemically through the 5-HT_{1B} receptor^{19,52} (Fig. 54–3).

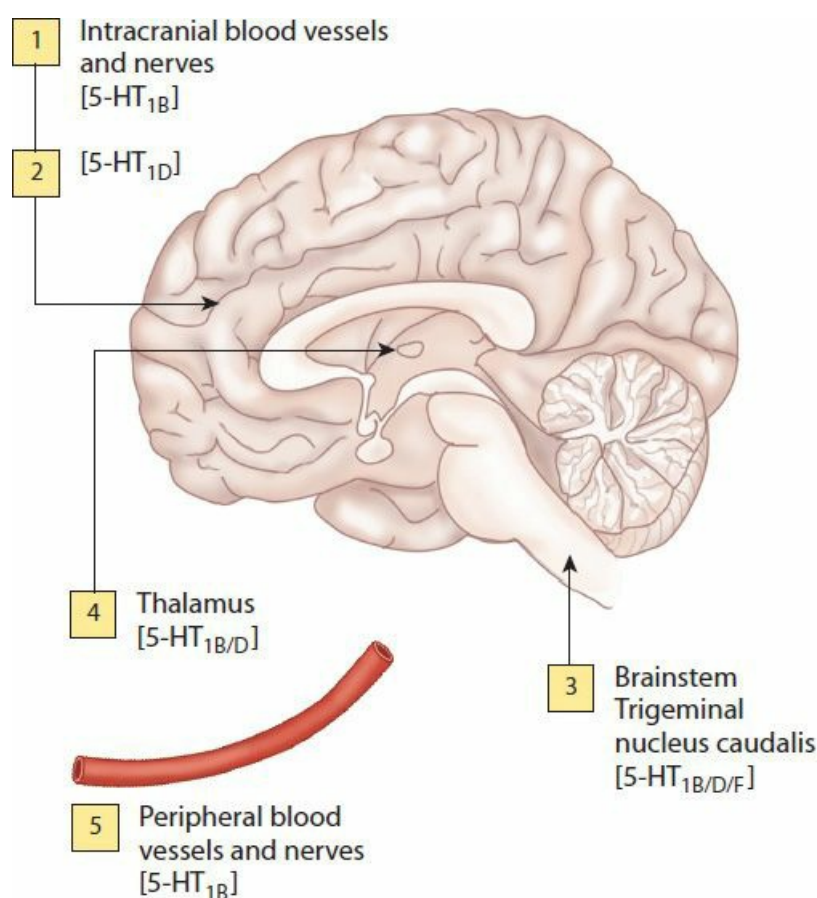


FIGURE 54–3. Mechanism of action of triptans. Vasoconstriction of intracranial [1] and peripheral [5] blood vessels via 5-HT_{1B} receptor agonism. Inhibition of vasoactive peptide release [2] from trigeminal nerve terminals at dural vessels via 5-HT_{1D} agonism. Modulation of nociceptive transmission to trigeminal nucleus caudalis [3] and thalamus [4].

Sumatriptan has poor oral bioavailability but good subcutaneous bioavailability (96%), and is therefore preferentially given by this route. The newer triptans differ substantially from sumatriptan with regard to oral bioavailability, plasma half-life, time to maximum effect, and recurrence rate of headaches. All triptans are pharmacodynamically similar but pharmacokinetically different (Table 54–5).

Clinical Manifestations

With appropriate therapeutic use, the common adverse effects associated with the triptans are less common and include nausea, vomiting, dyspepsia, flushing, and paresthesias.^{18,71} However, the most consequential adverse effects are chest pressure and vasoconstriction. Chest pressure symptoms are reported in up to 15% of sumatriptan users.^{11,65} Although triptans reduce coronary artery diameter by 10% to 15%, chest pressure symptoms are not believed to be secondary to cardiac ischemia. Alternate hypotheses for the chest pressure sensations include a generalized vasospastic disorder in migraineurs, esophageal spasm, bronchospasm, alterations of skeletal muscle energy metabolism, and central sensitization of pain pathways.²⁰ Although the triptans show some degree of coronary artery constriction in vitro, studies demonstrate, and hence recommendations state, that there is no need for routine stress tests in low-risk patients prior to therapy with triptans.^{21,51,83}

However, triptans can cause ischemia due to vasoconstriction. Therapeutic sumatriptan use is associated with myocardial ischemia and or infarction, dysrhythmias, renal infarction, splenic infarction, and ischemic colitis.^{1,5,14,46,53,59,61,64} Cephalic vasoconstriction is the desired effect of sumatriptan, but there are reports of strokes, hemorrhages, and infarctions.^{13,44,50,57} Extrapyramidal symptoms, such as akathisia and dystonia, may also occur.⁴⁹ Therapeutic use of other triptans has caused spinal cord infarction, renal infarction, myocardial infarction, ischemic colitis, and seizures.^{32,47,55,85,88}

Animal studies showed a wide margin of safety with oral sumatriptan. Subcutaneous administration of 2 g/kg of sumatriptan to rats was lethal. Death was preceded by erythema, inactivity, and tremor.⁴² Dogs survived 20 mg/kg and 100 mg/kg subcutaneous doses, but developed hind limb paralysis, erythema, tremor, salivation, and loss of vocalization.⁴¹ Reactions in other animals include seizures, inactivity, reduced respiratory rate, cyanosis, ptosis, ataxia, mydriasis,

salivation, and lacrimation.^{42,79}

Excessive triptan use is associated with vasoconstrictive adverse effects. A 43 year-old man who used 23 (25 mg) tablets of sumatriptan and 32 tablets of a combination preparation of isometheptene 65 mg, dichloralphenazone 100 mg, and APAP 325 mg over 7 days for headaches developed a left occipital infarction with a right hemianopsia. Digital subtraction angiography revealed segmental narrowing in multiple cerebral vessels. The hemianopsia and vessel findings resolved after cessation of the sumatriptan and Midrin and treatment with nicardipine.⁵⁷ A 35 year-old woman who used 300 mg of sumatriptan orally and 12 mg subcutaneously developed ischemic colitis.⁴⁰ Two patients who received four times and 10 times the recommended dose of naratriptan developed severe hypertension.⁶⁰ However, not all triptan overdoses result in toxicity. One 36 year-old man reportedly used 66 (6 mg) doses of sumatriptan subcutaneously over 4 weeks for his cluster headaches and had no adverse effects.⁸¹ The maximum recommended dosage of sumatriptan is 12 mg subcutaneously in a 24-hour period. Patients who took single doses of 100 to 150 mg of almotriptan did not have any adverse effects.²

In 2006, the US Food and Drug Administration (FDA) issued an alert, warning of an increased risk of serotonin toxicity with triptans used in combination with selective serotonin reuptake inhibitors (SSRIs) or selective serotonin-norepinephrine reuptake inhibitors. The alert was based on 27 cases reported to the FDA Adverse Events Reporting System between 1998 and 2002.²⁵ The cases involved triptan use in conjunction with SSRIs that were coded as serotonin syndrome or symptoms indicative of serotonin toxicity.⁷⁷ A case series of serotonin toxicity from migraine medications described three cases associated with sumatriptan use alone, sumatriptan with sertraline, and sumatriptan with methysergide, lithium, and sertraline.⁵⁴ Other medications that might precipitate serotonin toxicity when used in conjunction with triptans include monoamine oxidase inhibitors (Chaps. 73 and 75).

Treatment

Treatment of triptan-induced vasoconstriction is dependent on the route of exposure and the organ system affected. Decontamination is not feasible after subcutaneous exposures, but can be effective following overdose of oral preparations. Gastrointestinal decontamination should be performed with activated charcoal. Because vomiting is not as prominent with triptan exposure as with exposure to the ergot alkaloids, gastric emptying procedures, such as orogastric lavage, may be considered early, but only following massive ingestion. The oral forms of rizatriptan and zolmitriptan are formulated to dissolve on the tongue, limiting the effectiveness of gastrointestinal decontamination.

Many reported cases of triptan induced vasoconstriction compromise responded to intravenous hydration and analgesia.^{46,32} Triptan-associated myocardial ischemia should be treated with aspirin, heparin, and intravenous nitroglycerin.⁶⁴ Coronary angiography should be performed for transmural myocardial infarctions with ST segment elevations on electrocardiography.^{53,61}

ISOMETHEPTENE

Isometheptene is a mild vasoconstrictor marketed as a combination preparation (Midrin) that includes dichloralphenazone, a muscle relaxant, and APAP. It has indirect α - and β -adrenergic agonist effects as well as minor direct α -adrenergic agonist effects on the peripheral vasculature.⁸² When administered early during a migraine exacerbation, it is as effective as sumatriptan in relieving migraine headache.³¹ Cerebral vasoconstriction is reported after therapeutic and excessive isometheptene use.^{59,67} Autonomic dysreflexia, which presented as hypertension, headache, diaphoresis, and flushing, was also reported in a man with spinal cord injury who used isometheptene for treatment of a migraine headache.⁸⁹ Treatment of isometheptene-induced vasoconstriction should include discontinuation of the medication and reversal of the vasoconstriction with calcium channel blockers or vasodilators, such as sodium nitroprusside, nitroglycerin, or phentolamine.

CGRP ANTAGONISTS

During migraines, CGRP is among the many vasoactive peptides released from activated trigeminal nerves.³³ CGRP is a potent vasodilator¹⁰ and is involved in the transmission of nociceptive signals from cerebral vessels to the central nervous system.²² CGRP receptors are found in nerve fibers in cerebral and dural vessels and in multiple areas of the central nervous system postulated in migraine genesis—the cerebral cortex, periaqueductal gray, locus coeruleus, dorsal raphe nuclei, solitary tractus nucleus, spinal dorsal horn, dorsal root ganglia, and trigeminal ganglia.⁸⁰ Treatment of active migraine with sumatriptan decreased CGRP concentrations to normal.³³

Two CGRP antagonists were developed for migraine therapy—olcegepant and telcagepant—neither olcegepant nor telcagepant is available. Based on two high dosing administrations, olcegepant has a volume of distribution of 20 L in an adult with a terminal half-life of 2.5 hours and minor renal excretion.⁴³ Adverse events reported with olcegepant include

paresthesia, flushing, fatigue, headache, abdominal pain, diarrhea, flatulence, rhinitis, dry mouth, and abnormal vision.^{23,43} Adverse effects reported with telcagepant include nausea, dizziness, somnolence, dry mouth, fatigue, paresthesia, and asthenia.^{38,39} Systemic vasoconstrictive adverse effects did not occur in the phase 2 and 3 trials with either olcegepant or telcagepant.

SUMMARY

- Migraine therapies include many xenobiotics for prophylaxis or for abortive therapy. Triptans have supplanted ergots as the primary abortive treatment for patients with migraines.
- Ergots interact with multiple 5-HT, dopamine, and adrenergic receptors, which can cause severe vasoconstriction and end organ ischemia.
- Ergot and triptan induced peripheral ischemia should be managed with vasodilators, calcium channel blockers, and heparin anticoagulation.
- Triptans are more selective and interact only with 5-HT_{1B/D/F} receptors but can also cause peripheral vasoconstriction and end organ ischemia. Triptan induced myocardial ischemia should be treated with anticoagulation, nitrates, and coronary angiography for transmural infarctions.
- Triptan use in conjunction with other serotonin increasing xenobiotics can increase the risk of serotonin toxicity.

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55 PHARMACEUTICAL ADDITIVES

Sean P. Nordt and Lisa E. Vivero

HISTORY AND EPIDEMIOLOGY

During the last century there were several outbreaks of toxicity in the United States associated with pharmaceutical additives ([Chap. 2](#)). The 1937 Massengill sulfanilamide disaster is the most notorious of these epidemics. Diethylene glycol, an excellent solvent and potent nephrotoxin, was substituted for the additives propylene glycol and glycerin in the liquid formulation of a new sulfanilamide antibiotic because of lower cost.^{25,62,69} As a result, more than 100 people died from acute kidney failure.²⁵ Outbreaks of acute kidney failure occurred when diethylene glycol was used to solubilize acetaminophen in South Africa, Bangladesh, Nigeria, and Haiti, cough syrup in Panama, and teething powder in Nigeria.^{20,28,30,71,81,122,133}

In December 1983, a new parenteral vitamin E formulation (E-Ferol) was introduced. It contained 25 units/mL of α -tocopherol acetate, 9% polysorbate 80, 1% polysorbate 20, and water for injection. At the time, no premarketing testing was required for new formulations of an already approved drug. Several months after its release, a fatal syndrome in low-birth-weight infants, characterized by thrombocytopenia, acute kidney injury, cholestasis, hepatomegaly, and ascites, was described.^{1,109} Thirty-eight deaths and 43 cases of severe symptoms were attributed to E-Ferol. Vitamin E was thought to be the cause and E-Ferol was recalled from the market 4 months after its release. It is now believed that the polysorbate emulsifiers were responsible.¹

Although these additive-related occurrences are rare, relative to the frequency of pharmaceutical additive use, they illustrate the potential of pharmaceutical additive toxicity.

Pharmaceuticals are labeled specifically to focus attention on the active ingredient(s) of a product, thus giving the misimpression that additive ingredients are inert and unimportant. Additives, or excipients as they are more properly termed, are necessary to act as vehicles, add color, improve taste, provide consistency, enhance stability and solubility, and impart antimicrobial properties to medicinal formulations. Although it is true that most cases of excipient toxicity involve exposure to large quantities, or to prolonged or improper use, these adverse events are nonetheless related to the toxicologic properties of the excipient.

Prior to selecting the specific additives and quantity necessary for a drug formulation, the drug manufacturer must consider several factors, including the active ingredient's physical form, its solubility and stability, the desired final dosage form and route of administration, and compatibility with the dispensing container materials. The same active ingredient may require different excipients to impart appropriate pharmacokinetic characteristics to different dosage forms, such as in long-acting and immediate-release formulations. Similarly, multiple-dose injection vials containing the same active ingredients as single dose vials specifically require the addition of a bacteriostatic xenobiotic not necessary for single dose vials.

Unlike requirements for active ingredients, there is no specific US Food and Drug Administration (FDA) approval system for pharmaceutical excipients. As such, the FDA determines the amount and type of data necessary to support the use of a specific excipient on a case by case basis. Under current practice, only excipients that were previously permitted for use in foods or pharmaceuticals are defined as generally recognized as safe (GRAS), or "GRAS listed." All components of a pharmaceutical product, including excipients, must be produced in accordance with current good manufacturing practice standards to ensure purity. The Safety Committee of the International Pharmaceutical Excipients Council developed guidelines for the toxicologic testing of new excipients.¹⁶¹ Because of patent protection laws, it was not until very recently that manufacturers were required to provide a list of inactive ingredients contained in all pharmaceutical products. Although it is becoming easier to identify pharmaceutical additives in products, information on their effects and the mechanisms by which they cause adverse responses are often unknown or difficult to obtain.

This chapter summarizes the available literature on commonly used additives associated with direct toxicities ([Table 55–1](#)). Data on pharmacokinetics and mechanism of toxicity are presented where data are available. Although many additives are associated with hypersensitivity reactions, including anaphylaxis, these are not discussed because of their nonpharmacologic basis. However, excipients should always be considered as possibly causative in patients who develop hypersensitivity reactions.

TABLE 55–1. Potential Systemic Toxicity of Various Pharmaceutical Excipients

Cardiovascular

Chlorobutanol

Propylene glycol

Fluid and electrolyte

Polyethylene glycol

Propylene glycol

Sorbitol

Gastrointestinal

Sorbitol

Neurologic

Benzyl alcohol

Chlorobutanol

Polyethylene glycol

Propylene glycol

Ophthalmic

Benzalkonium chloride

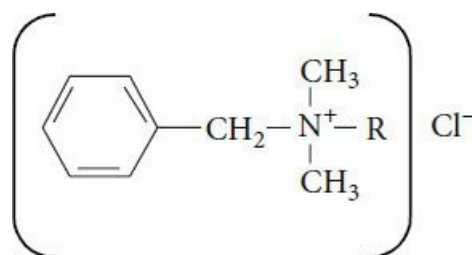
Chlorobutanol

Renal

Polyethylene glycol

Propylene glycol

BENZALKONIUM CHLORIDE



Benzalkonium chloride (BAC, BAK), or alkyldimethyl (phenylmethyl) ammonium chloride, is a quaternary ammonium cationic surfactant composed of a mixture of alkyl benzyl dimethyl ammonium chlorides. Although it is the most widely used ophthalmic preservative in the United States, it is also considered the most cytotoxic ([Table 55–2](#)).^{87,94} Benzalkonium chloride is also used in otic and nasal formulations, and in some small-volume parenteral preparations. The antimicrobial activity of BAC includes Gram-positive and Gram-negative bacteria, and some viruses, fungi, and protozoa. Because of its rapid onset of action, good tissue penetration, and long duration of action, BAC is preferred over other preservatives. The concentration of BAC in ophthalmic medications usually ranges from 0.004% to 0.01%.⁹⁴ Strong BAC solutions (> 0.1%) can be caustic ([Chap. 106](#)).

TABLE 55–2. Benzalkonium Chloride Concentrations of Common Ophthalmic Medications

<i>Medication</i>	<i>Percent</i>
Apraclonidine	0.01
Artificial tears	0.005–0.01
Betaxolol	0.01
Brimonidine/timolol	0.005
Carteolol	0.005
Ciprofloxacin	0.006
Cyclopentolate	0.01
Dexamethasone	0.02
Dorzolamide/timolol	0.075
Epinephrine	0.01
Gentamicin	0.01
Ketorolac	0.006
Levobunol	0.004
Naphazoline	0.01
Ofloxacin	0.005
Phenylephrine	0.005–0.01
Pilocarpine	0.01
Polymyxin B sulfate/trimethoprim	0.004
Tetrahydrozoline	0.01–0.02
Timolol	0.05–0.01
Tobramycin	0.01
Tropicamide	0.01

Ophthalmic Toxicity

Corneal epithelial cells harvested from human cadavers within 12 hours of death were exposed to a medium containing 0.01% BAC.¹⁵⁸ The surfactant properties of BAC resulted in intracellular matrix dissolution and loss of epithelial superficial layers. Following exposure to the medium, mitotic activity ceased and degenerative changes to corneal epithelium were noted. During a 24-hour observation period, epithelial cell cytokinetic or mitotic activity did not occur. Patients with compromised corneal epithelia may be at increased risk for the adverse effects of BAC.¹⁵⁸

Two case reports demonstrate the potential toxicity of BAC and highlight the difficulty of diagnosing BAC toxicity. A 36 year-old woman complained of decreased vision when she inadvertently switched from Lensrins, a contact lens cleaning solution, to Dacriose, an isotonic boric acid solution preserved with BAC. After 3 days, she had inflammation, pain, and decreased visual acuity. Examination of the cornea revealed many superficial punctate erosions of the epithelium. An in vitro experiment identified significant binding of BAC to soft contact lenses.⁵⁷ In the second case, a 56 year-old man diagnosed with keratoconjunctivitis sicca was treated with topical antibiotics and artificial tears containing BAC. Following one year of continual use, the patient developed intractable pain, photophobia, and extensive breakdown of the corneal epithelium. Not suspecting the BAC containing products, the patient continued to use the artificial tears solution for another 9 years despite continued pain and decreasing visual acuity. Replacement with a preservative free saline solution resulted in resolution of pain, photophobia, and corneal changes.⁹⁴ Furthermore, there are newer ophthalmic medication preservatives available (eg, polyquaternium-1, stabilized oxychloride complex, sodium perborate, Sof Zia), which appear to be less toxic than BAC and may ultimately replace BAC.⁴

A case series of corneal endothelial injury following the inadvertent intraocular use of balanced salt solution (BSS) preserved with BAC instead of preservative free BSS in 12 patients undergoing phacoemulsification, a surgical technique to remove cataract lenses. The BSS, was instilled in the anterior chamber. The operating room had run out of preservative free BSS and, unbeknownst to the surgeon, it was replaced with the BAC containing BSS, which contained 0.013% BAC. This is in excess of recommended concentration for intraocular use and is associated with corneal endothelial injury and edema. Within 48 hours of instillation of the BSS, the visual acuity in all 12 patients was limited to only being able to count fingers at two feet. This persisted in 11 of the patients at a 6 month follow-up evaluation after the instillation of the BSS. One patient did have improvement at 6 months of visual acuity to 20/120 and 20/30 without and with pinholes, respectively.⁹⁶

Nasopharyngeal and Oropharyngeal Toxicity

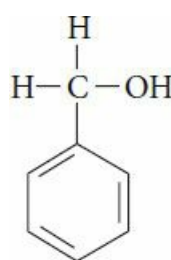
Human adenoidal tissue was exposed to oxymetazoline nasal spray preserved with BAC at concentrations ranging from 0.005 to 0.15 mg/mL for 1 to 30 minutes.¹⁵ Irregular and broken epithelial cells occurred at all concentrations; however, these findings developed earlier and more frequently with the higher concentrations. The number of beating ciliary bodies also decreased as the duration and the concentrations increased. Benzalkonium chloride may decrease the viscosity of the normal protective mucous lining of the naso- and oropharynx, resulting in cytotoxicity.

Administration of one of three nasal corticosteroid sprays, beclomethasone dipropionate, flunisolide, budesonide, preserved with either 0.031% or 0.022% BAC in the right nostril of rats twice daily for 21 days caused squamous cell metaplasia and a decrease in the number of goblet cells, cilia, and mucus.¹⁶ No histologic changes occurred in rats receiving any of the preservative-free steroids or in tissue exposed to 0.9% sodium chloride solution administered into the left nostril as the control. Similarly, in another study, epithelial desquamation, inflammation, and edema occurred when 0.05% and 0.10% BAC was applied hourly to the nasal cavities of rats for 8 hours.⁹⁰ No lesions developed in the nasal cavities of rats receiving 0.01% BAC.

In an in vitro study, cultured human nasal epithelial cells were exposed to varying concentrations of BAC compared with another preservative, potassium sorbate (PS), with phosphate-buffered saline (PBS) as a control. Cell viability was greatly reduced at the higher concentrations of BAC compared with no decrease in cell viability in the PS or PBS groups. Additionally, at concentrations used clinically loss of microvilli, destruction of cell membranes, and poor cytoskeletal alignment demonstrated by electron microscopy occurred.⁷⁸

An in vitro study of human nasal mucosa exposed mucosa to either fluticasone or mometasone preserved with either BAC or PS at various concentrations with subsequent measure of ciliary beat frequency. While PS did not affect ciliary beat frequency at any concentration, BAC adversely affected ciliary beat frequency. At lower concentrations, BAC slowed ciliary beat frequency and brought it to standstill at higher concentrations.⁷⁹

BENZYL ALCOHOL



Benzyl alcohol (benzene methanol) is a colorless, oily liquid with a faint aromatic odor that is most commonly added to pharmaceuticals as a bacteriostatic agent (Table 55–3). In 1982, a “gasping” syndrome, which included hypotension, bradycardia, gasping respirations, hypotonia, progressive metabolic acidosis, seizures, cardiovascular collapse, and death, was first described in low-birth-weight neonates in intensive care units.^{21,64,101} All the infants had received either bacteriostatic water or sodium chloride solution containing 0.9% benzyl alcohol to flush intravenous catheters or in parenteral medications reconstituted with bacteriostatic water or saline.^{21,64} The syndrome occurred in infants who had received more than 99 mg/kg of benzyl alcohol (range, 99–234 mg/kg).⁶⁴ The World Health Organization (WHO) currently estimates the acceptable daily intake of benzyl alcohol to be not more than 5 mg/kg body weight.²³

TABLE 55–3. Benzyl Alcohol Concentration of Common Medications

Medication	Percent	Average Dose (mL) ^a
Amiodarone	2.0	0.42 ^b
Atracurium	0.9	0.03
Bacteriostatic saline for injection	1.5	—
Bacteriostatic water for injection	1.5	—
Bumetanide	1.0	0.03
Chlordiazepoxide	1.5	0.03
Diazepam	1.5	0.03
Enalaprilat	0.9	0.01
Etoposide	3.0	0.14
Glycopyrrolate	0.9	0.01
Lorazepam	2.0	0.02
Methotrexate	0.9	0.01
Midazolam	1.0	0.01
Prochlorperazine	0.75	0.01
Vecuronium	0.9	0.01

^aBased on dosage for a 70-kg person. ^bBased on 24-hour dosage.

Pharmacokinetics

In adults, benzyl alcohol is oxidized to benzoic acid, conjugated in the liver with glycine, and excreted in the urine as hippuric acid. Preterm babies have a greater ability to metabolize benzyl alcohol to benzoic acid than do term babies, but are unable to convert benzoic acid to hippuric acid, possibly because of glycine deficiency. This results in the accumulation of benzoic acid (Fig. 55–1).⁶⁴ A fatal case of metabolic acidosis was reported in a 5 year-old girl who had received 2.4 mg/kg/h diazepam preserved with benzyl alcohol for 36 hours to control status epilepticus. Elevated benzoic acid concentrations were identified in serum and urine samples. The estimated daily dosage of benzyl alcohol was 180 mg/kg.^{64,97}

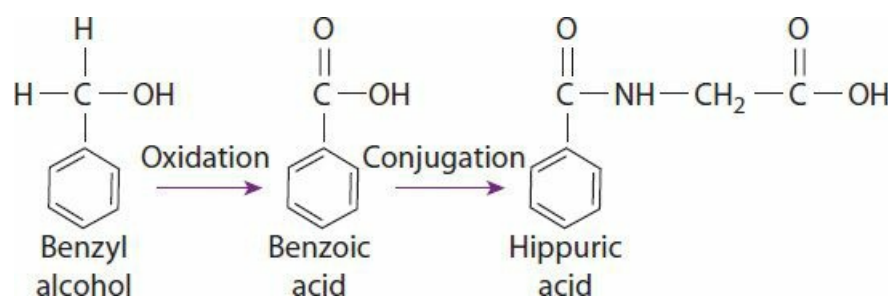


FIGURE 55–1. Oxidative metabolism of benzyl alcohol.

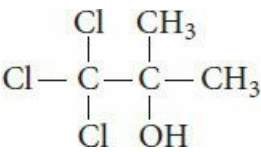
Neurologic Toxicity

Benzyl alcohol is believed to have a role in the increased frequency of cerebral intraventricular hemorrhages and mortality reported in very-low-birth weight (VLBW) infants (weight < 1000 g) who received flush solutions preserved with benzyl alcohol.⁷⁷ An increased incidence of developmental delay and cerebral palsy was also noted in the same VLBW patients, suggesting a secondary damaging effect of benzyl alcohol.¹³

There are several case reports of transient paraplegia following the intrathecal or epidural administration of chemotherapeutics or analgesics containing benzyl alcohol as a preservative.^{9,39,70,139} The local anesthetic effects are most likely responsible for the immediate paraparesis and limited duration of effects, rather than actual demyelination of nerve roots. In a rat study, lumbosacral dorsal root action potential amplitudes were measured after exposure to 0.9% or 1.5% benzyl alcohol solutions in either 0.9% sodium chloride solution or distilled water.⁷⁰ Rats exposed to all benzyl alcohol solutions for less than one minute had inhibited dorsal root action potentials. This was attributed to the local anesthetic

effects of benzyl alcohol as function was 50% to 90% restored after rinsing the nerves with 0.9% sodium chloride solution. Chronic intrathecal exposure to benzyl alcohol 0.9% over 7 days resulted in scattered areas of demyelination and early remyelination. The 1.5% benzyl alcohol solution–exposed dorsal nerve roots showed greater changes with widespread areas of demyelination and fatty degeneration of nerve fibers.

CHLOROBUTANOL



Chlorobutanol, or chlorbutol (1,1,1-trichloro-2-methyl-2-propanol), is available as volatile, white crystals with an odor of camphor. Chlorobutanol has antibacterial and antifungal properties and is widely used as a preservative in injectable, ophthalmic, otic, and cosmetic preparations at concentrations up to 0.5% (Table 55–4). Chlorobutanol also has mild sedative and local anesthetic properties and was formerly used therapeutically as a sedative-hypnotic.¹⁹ Because chlorobutanol is a halogenated hydrocarbon, theoretically it can sensitize the myocardium to catecholamines, although no cases of ventricular dysrhythmias are described in the literature to date. The lethal human chlorobutanol dose is estimated to be 50 to 500 mg/kg.¹¹⁷

TABLE 55–4. Chlorobutanol Concentrations of Common Medications and Doses

Medication	Percent	Dose (mg)
Chloramphenicol ophthalmic solution	0.5	—
Epinephrine injection	0.5	5
Epinephrine ophthalmic solution	0.5	—
Isoniazid injection	0.25	7.5
Methadone injection	0.5	10
Phenylephrine nasal spray	0.15	—
Thiamine injection	0.5	5
Procaine injection	0.25	87
Pyridoxine HCl	0.5	5
Tobramycin ophthalmic ointment	0.5	—
Vasopressin 20 U/mL injectable	0.5	5
Vitamin A injection	0.5	5

Central Nervous System Toxicity

Chlorobutanol has a chemical structure similar to trichloroethanol (Fig. 74–1), the active metabolite of chloral hydrate, and is believed to exhibit similar pharmacologic properties. Central nervous system depression was reported in a 40 year-old alcoholic man who chronically abused Seducaps, formerly available in Australia and several other countries, a nonprescription hypnotic containing chlorobutanol as the active ingredient.¹⁹ On admission to the emergency department he had drowsiness, dysarthria, slurred speech, and occasional episodes of myoclonic movements. His peak serum chlorobutanol concentration was 100 µg/mL, decreasing to 48 µg/mL over 2 weeks, with a half-life of 3 days based on serial declining levels. This is similar to human volunteer pharmacokinetic data following oral administration of chlorobutanol demonstrating an elimination half-life of 10.3 ± 1.3 days.¹⁵⁹ His speech abnormality resolved after 4 weeks. Only chlorobutanol was detected in the patient’s urine or serum. In a second case, a possible central nervous system depressant effect from chlorobutanol was suggested in a 19 year-old woman treated with high doses of intravenous morphine preserved with chlorobutanol.⁴⁵ She received approximately 90 mg/h of chlorobutanol for several days. Her peak serum chlorobutanol concentration was 83 µg/mL, a concentration similar to that in the previous case report¹⁹; however, the

coadministration of morphine precludes the effects being attributed to chlorobutanol alone.

Ketamine is neurotoxic when administered intrathecally to animals.^{106,107} The potential neurotoxic effects of chlorobutanol as a preservative in ketamine compared with preservative-free ketamine was studied in rabbits.¹⁰⁷ Forty rabbits were given 0.3 mL intrathecally of either 1% preservative-free ketamine, 1% ketamine, 0.05% chlorobutanol, or 1% lidocaine as control. The rabbits were observed and hemodynamically monitored for 8 days and then euthanized. Histologic evaluation of the spinal cord as well as for blood brain barrier (BBB) lesions was performed. Seven of the 10 rabbits given intrathecal chlorobutanol showed both white and grey matter histologic changes as well as diffuse BBB injury. No histologic changes were seen in either ketamine groups or the lidocaine group, and only one rabbit in each ketamine group had BBB injury. These results suggest chlorobutanol should not be administered intrathecally.¹⁰⁷

A case series of five patients were given intraarterial papaverine preserved with 0.5% chlorobutanol,¹⁴⁶ which is used to prevent cerebral vasospasm in patients with subarachnoid hemorrhage. Immediately after administration of papaverine in either the left, right, or bilateral anterior cerebral arteries, patients had an acute deterioration in neurologic status. Subsequent brain magnetic resonance imaging identified selective grey matter toxicity in the territories treated with papaverine. Postmortem brain histology analysis in one patient also identified grey matter changes. The authors state the absence of white matter changes is not consistent with ischemic infarction but suggest direct toxic effect of either the papaverine or chlorobutanol. The manufacturer of the papaverine stated that no other reports had been made and the papaverine used came from two different lots; therefore, it is unclear if an unidentified independent variable caused these effects, but the authors caution using intraarterial papaverine in patients with subarachnoid hemorrhage.¹⁴⁶

Ophthalmic Toxicity

Chlorobutanol is a commonly used preservative in ophthalmic preparations and is less toxic to the eye than benzalkonium chloride.¹²¹ Chlorobutanol increases the permeability of cells by impairing cell membrane structure.¹⁵⁸ An in vitro experiment using corneal epithelial cells harvested from human cadavers demonstrated arrested mitotic activity following chlorobutanol exposure.¹⁵⁸ At the commonly formulated concentration of 0.5%, chlorobutanol may cause eye irritation, most likely due to cellular contraction of epithelial microfilaments, cessation of normal cytokinesis, cell movement, and mitotic activity.⁴⁸ Degeneration of human corneal epithelial cells specifically manifested as membranous blebs, cytoplasmic swelling, and occasional breaks in the external cell membrane has also occurred at this concentration.⁴⁸

LIPIDS

In general, there are three types of commercial intravenous lipid drug-delivery systems available: lipid emulsion, liposomal, and lipid complex (Table 55–5). Lipid emulsions are immiscible lipid droplets dispersed in an aqueous phase stabilized by an emulsifier (eg, egg, soy lecithin). Liposomes differ from emulsion lipid droplets in that they are vesicles comprised of one or more concentric phospholipid bilayers surrounding an aqueous core. Lipophilic drugs can be formulated for intravenous administration by partitioning them into the lipid phase of either an emulsion or liposome. Liposomes are capable of encapsulating hydrophilic xenobiotics within their aqueous core to exploit lipid pharmacokinetic properties.¹⁵³ Attaching a therapeutic drug to a lipid to form a lipid complex is another way to take advantage of lipid pharmacokinetics.

Table 55–5. Lipid Carrier Formulations of Common Medications

Medication	Lipid Carrier
Amphotericin B (Abelcet)	Lipid complex
Amphotericin B (AmBisome)	Liposome
Amphotericin B (Amphotec)	Cholesteryl complex
Cytarabine (DepoCyt)	Liposome
Daunorubicin (DaunoXome)	Liposome
Doxorubicin (Doxil)	Liposome (stealth)
Propofol (Diprivan)	Emulsion

Lipid carriers are biocompatible because of their similarity to endogenous cell membranes. They can be created with stable lipid membranes resistant to hydrolysis or oxidation, to decrease toxicity, and to enhance therapeutic efficacy by altering drug pharmacokinetic and pharmacodynamic parameters. The biodistribution, and the rate of release and metabolism of a drug incorporated in a lipid formulation can be regulated by the type and concentration of oil and

emulsifier used, pH, drug concentration dispersed in the medium, the size of the lipid particle, and the manufacturing process.^{123,152} Intravenous formulations are usually isotonic and have a pH of 7 to 8.¹⁵³

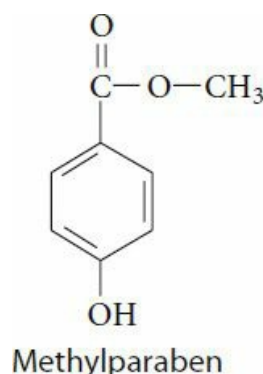
The rate of clearance of a lipid carrier from the blood depends on its physicochemical properties and the molecular weight of the emulsifier. Electrically charged lipid carriers are removed more rapidly than neutral particles.^{24,123} Smaller lipid particle size and high-molecular-weight emulsifiers decrease clearance. Stealth liposome formulations incorporate a polyethylene glycol coating that prevents rapid detection and clearance of liposomes by the reticuloendothelial system prolonging circulation time.¹²³ Active drug targeting can be achieved by conjugating antibodies or vectors to side chains on the emulsifier.^{24,123} For a therapeutic drug available in more than one lipid-carrier formulation (eg, amphotericin B), it is important to note that any change in the lipid formulation can alter the drug's pharmacokinetic, pharmacodynamic, and safety parameters; consequently, they are not equivalent dosage formulations ([Chap. 57](#)).

The physicochemical properties of lipid emulsions not only affect the therapeutic drugs carried by them, but the lipids themselves may also have direct pharmacologic effects on the central nervous¹⁷⁰ and immune systems.⁹³ Lipid fatty acid mediators can affect the membrane receptor channels of N-methyl-D-aspartate (NMDA) receptors, potentiating synaptic transmission.^{110,111,126,156} Dogs given a medium-chain triglyceride emulsion intravenous infusion developed dose-related central nervous system metabolic and neurologic effects, accompanied by electroencephalographic changes consistent with encephalopathy observed when serum octanoate concentration reached 0.5 to 0.9 mM.¹¹⁰ In an in vitro model, three of nine lipid emulsions tested (Abbolipid, 20% soya and safflower oil; Intralipid, 20% soya oil; and Structolipid, 20% structured triglycerides) demonstrated a dose-related activation of cortical neuronal NMDA receptor channels.¹⁷⁰ The lipid source for all but one (Omegaven, 10% fish oil) of the emulsions tested was made up solely or partially by soya oil. The authors could not explain why the other six lipid emulsions did not induce membrane currents. Adequate control for the nonlipid constituent contribution of these emulsions is lacking. In another in vitro study, the same authors found that NMDA-induced neuronal currents are reduced by an unknown factor in the aqueous portion of Abbolipid.¹⁷¹ This suggests that lipid emulsions may pharmacologically enhance the anesthetic effect of hypnotics such as propofol. The clinical relevance of these studies remains to be assessed.

Triglycerides in parenteral nutrition emulsions are implicated in altering the immune system, leading to an increased susceptibility to infection,^{56,168} and altering lung function and hemodynamics in patients with acute respiratory distress syndrome.⁹³ Phospholipid activation of phospholipase A₂ may be an initiating cause.^{56,93,168} However, it is not clear if these immunologic effects are a consequence of factors other than the lipid in the emulsion.

More recently, the sequestering properties of fat emulsions have been employed in the treatment of poisonings in both animal models and human case reports ([Antidotes in Depth: A20](#)).^{11,125,145}

PARABENS



The parabens, or parahydroxybenzoic acids, are a group of compounds widely employed as preservatives in cosmetics, food, and pharmaceuticals because of their bacteriostatic, fungistatic, and antioxidant properties ([Table 55–6](#)).¹⁴⁰ A survey conducted by the FDA identified the parabens as the second most common ingredients in cosmetic formulations, with water being the most common.⁹⁸ Parabens are often used in combination, because the presence of two or more parabens are synergistic.⁹⁸ Methylparabens and propylparabens are most commonly used.¹⁴⁰ Pharmaceutical paraben concentrations usually range from 0.1% to 0.3%.¹³⁴

TABLE 55–6. Paraben Concentrations of Common Medications and Doses

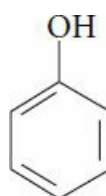
Medication ^a	Percent	Dose (mg)
Bupivacaine HCl 0.25% injection	0.1	—
Droperidol injection	0.2	2
Flumazenil injection	0.2	4
Haloperidol injection	0.2	2
Labetalol injection	0.09	4
Lidocaine injection	0.1	—
Methyldopa injection	0.17	8
Naloxone injection	0.2	2
Neostigmine injection	0.2	2
Ondansetron injection	0.14	3
Pentazocine injection	0.1	1
Pseudoephedrine/brompheniramine elixir	0.2	20
Sulfacetamide ophthalmic solution	0.06	—
Vincristine injection	0.15	4

^aAmount varies depending on volume used (contains 1 mg/mL paraben).

Widespread usage of parabens since the 1920s has shown that they have a relatively low order of toxicity.⁹⁸ However, because of their allergenic potential they are currently considered less suitable for injectable and ophthalmic preparations.¹³⁴ Based on long-term animal studies, the WHO has set the total acceptable daily intake of ethylparabens, methylparabens, and propylparabens to be 10 mg/kg body weight.¹³⁴ In addition to allergic reactions, parabens have the potential to cause other adverse effects. Bilirubin displacement from albumin binding sites occurred with administration of methyl- and propylparabens preserved gentamicin when serum parabens concentrations were 3 to 15 µg/mL.⁴¹ Gentamicin alone has no effect on bilirubin displacement.⁹² Spermicidal activity was demonstrated in an in vitro study of human semen specimens exposed to local paraben concentrations of 1 to 8 mg/mL.¹⁵⁰ Possible interference with conception and potential adverse effects on fertility were not investigated.

More recently, concern has arisen regarding the potential estrogenic and antiandrogenic effects of the parabens and their common metabolite, p-hydroxybenzoic acid. Xenobiotics with these effects are commonly referred to as endocrine disrupting substances. It has been suggested that methylparaben is less toxic than butyl and benzyl-parabens with regard to oxidative stress and resultant cytotoxicity.^{42,143} However, the clinical significance of these effects is not elucidated.^{32,43,131,132,164}

PHENOL



Phenol (carbolic acid, hydroxybenzene, phenylic acid, phenylic alcohol) is a commonly used preservative in injectable medications (Table 55–7). Phenol is a colorless to light pink, caustic liquid with a characteristic odor. When exposed to air and light, phenol turns a red or brown color.³⁸ Phenol exerts antimicrobial activity against a wide variety of microorganisms, such as Gram-negative and Gram-positive bacteria, mycobacteria, and some fungi and viruses.³⁸ Phenol is well absorbed from the gastrointestinal tract, skin, and mucous membranes, and is excreted in the urine as phenyl glucuronide and phenyl sulfate metabolites.³⁸ Although there are numerous reports of phenol toxicity following intentional ingestions or unintentional dermal exposures (Chap. 106), adverse reactions to its use as a pharmaceutical excipient are uncommon, most likely because of the small quantities used.³⁸

TABLE 55–7. Phenol Concentration of Common Medications

Medication	Percent	Dose (mg)
Antivenom (Crotaline)	0.25	25 (per vial)
Antivenom (<i>Micrurus fulvius</i>)	0.25	25 (per vial)
Dryvax (smallpox) vaccine	0.25	2.5
Pneumovax 23 (pneumococcal) vaccine	0.25	1.25
Prostigmin (neostigmine) injection	0.45	4.5
Quinidine gluconate injection	0.25	18.75
Typhoid Vi vaccine	0.25	1.25

Cutaneous Absorption

Systemic toxicity from cutaneous absorption of phenol is reported. Ventricular tachycardia was observed in an 11 year-old boy following application of a chemical peel solution containing 88% phenol in water and liquid soap. The solution was applied to 15% of his body surface area for the treatment of xeroderma pigmentosum. Immediately following the onset of the ventricular tachycardia, the phenol-treated areas were irrigated, an infusion of 0.9% sodium chloride solution was begun, and two intravenous lidocaine boluses were given followed by a lidocaine infusion. The dysrhythmia persisted for 3 hours. The urinary phenol concentration the following day was 58.9 mg/dL.¹⁶² In a similar case, multifocal premature ventricular contractions were observed in a 10 year-old boy after application of a chemical peeling solution of 40% phenol, 0.8% croton oil in hexachlorophene soap, and water for the treatment of a giant hairy nevus.¹⁶⁹ The premature ventricular contractions were refractory to intravenous lidocaine but resolved with intravenous bretylium. No phenol concentrations were obtained to confirm systemic absorption. In a case series of 181 patients undergoing chemical face peeling with phenol-based solutions, 12 demonstrated cardiac dysrhythmias. This occurred more commonly in patients with comorbid diabetes mellitus, hypertension or treatment with antidepressants. These authors recommend prophylactic administration of propranolol prior to phenol application to mitigate these dysrhythmias citing a reduction in dysrhythmia incidence in their patients.⁹¹ Despite the risk of toxicity, phenol chemical peels are still used in some cases because phenol penetrates deep into tissues providing both long-lasting and good cosmetic results. Most commonly phenol chemical peels are used for deep acne scars and other severe skin disorders.

Drowsiness, respiratory depression, and blue-colored urine were noted in a 6 month-old infant 12 hours after topical application of magenta paint over most of the body for seborrheic eczema.¹³⁶ Magenta paint (also known as Castellani paint) was widely used for seborrheic eczema and contained 4% phenol, magenta, boric acid, resorcinol, acetone, and methylated spirit. Further investigation found that phenol was detected in urine samples of four of 16 other infants with seborrheic eczema who had approximately 11% to 15% of their body surface area painted with magenta paint for 2 days.

POLYETHYLENE GLYCOL

Polyethylene glycols (PEGs; Carbowax, Macrogol) include several compounds with varying molecular weights (200–40,000 Da).¹³⁰ They are typically available as mixtures designated by a number denoting their average molecular weight. PEGs are stable, hydrophilic substances, making them useful excipients for cosmetics, and pharmaceuticals of all routes of administration (Table 55–8). Pegylation, a process that modifies the pharmacokinetics of therapeutic liposomes and proteins (eg, peginterferon- α), is the most recent application of PEG. At room temperature, PEGs with molecular weights less than 600 are clear, viscous liquids with a slight characteristic odor and bitter taste. PEGs with molecular weights heavier than 1000 are soluble solids and range in consistency from pastes and waxy flakes to powders.¹³⁰ Commercially available products used for bowel cleansing preparations and whole bowel irrigation are solutions of PEG 3350 sometimes combined with electrolytes and known as PEG electrolyte lavage solution (PEG-ELS; Antidotes in Depth: A2).

TABLE 55–8. Common Medications Containing PEG

<i>Medication</i>	<i>PEG Molecular Weight (Da)</i>
Dexamethasone ophthalmic ointment	400
Etoposide injection	300
Lorazepam injection	400
Medroxyprogesterone depot	3350
Mupirocin ointment	400, 3350
PEG electrolyte solution	3350
Peginterferon α -2a	40,000

PEG = polyethylene glycol.

The solid, high-molecular-weight PEGs are essentially nontoxic. Conversely, low-molecular-weight PEG exposures have caused adverse effects similar to the chemically related toxic alcohols ethylene and diethylene glycol²⁸ (Special Considerations: SC7).

Pharmacokinetics

High-molecular-weight PEGs (> 1000) are not significantly absorbed from the gastrointestinal tract, but low-molecular-weight PEGs may be absorbed when taken orally.^{47,147,148} Topical absorption can occur when PEGs are applied to damaged skin.^{22,154} Once in the systemic circulation, PEGs are mainly excreted unchanged in the urine⁴⁷; however, low-molecular-weight PEGs (eg, PEG 300, PEG 400) are partially metabolized by alcohol dehydrogenase to hydroxyacid and diacid metabolites. The pharmacokinetics of intravenously administered PEG 3350 has not been studied; however, it did not appear to have any systemic effects when unintentionally given by this route.¹³⁵

Nephrotoxicity

In rats fed various PEGs (200, 300, and 400) in their drinking water for 90 days, a solution of 8% PEG 200 produced renal tubular necrosis in all of the animals, followed by death within 15 days; however, a 4% PEG 200 solution resulted in only two of nine rats dying within 80 days. A 16% PEG 400 solution killed all animals within 13 days; however, both 8% and 4% PEG 400 solutions had no observable effect except for a decrease in kidney weight when compared to control animals.¹⁴⁹ A more recent study administering daily high dose PEG 400 intravenously, up to 8.45 g/kg/day, in a canine model failed to show serious renal toxicity. However, edema of kidney cells and increased glomerular volume occurred at these dosages but were reversible.⁹⁵ Acute tubular necrosis has been reported with oliguria, azotemia, and an anion gap metabolic acidosis following oral and topical exposures to low-molecular-weight PEGs (200 and 300). Acute kidney failure occurred in a 65 year-old man with a history of alcohol abuse and seizure disorder after ingestion of the contents of a lava lamp containing 13% PEG 200.⁴⁹ About 48 hours after admission (approximately 50–72 hours postingestion), the patient became oliguric with an anion gap metabolic acidosis and acute kidney failure. Blood sample analysis confirmed traces of the lava lamp fluid; no traces were detected in the urine. After clinical complications from ethanol withdrawal and aspiration pneumonitis, the patient was discharged 3 months later with residual kidney dysfunction attributed to the PEG component of the lamp contents. Acute tubular necrosis was noted on autopsy of six burn patients treated with a topical antibiotic cream in a PEG 300 base.^{22,154} Mass spectrometry detected hydroxyacid and diacid metabolites in serum and urine samples. Oxalate crystals were seen in two cases. These effects were reproduced with the topical application of PEG for 7 days to rabbits with full-thickness skin defects.¹⁵⁴

Neurotoxicity

There are reports of neurologic complications, such as paraplegia and transient bladder paralysis, following intrathecal corticosteroid injections containing 3% PEG as a vehicle.^{14,18} In an in vitro experiment, rabbit vagus nerves were exposed to concentrations of PEG 3350 ranging from 3% to 40% for one hour.¹⁴ A total of 3% and 10% PEG had no effect on nerve action potential amplitude or conduction velocity. A dose of 20% and 30% PEG significantly slowed nerve conduction and had varying effects on the amplitudes of action potentials. Forty percent PEG completely abolished action potentials. These changes were reversible and thought to be related to PEG-induced osmotic effects. More recently, the administration of PEG 1800 is being studied as a potential therapy for spinal cord injury by repairing damaged axons through cellular fusion of damaged cells following the short-term (2 minutes) application, in a guinea pig model. This increases compound action potential conduction.¹⁴⁴ Interestingly, administering a similar dose of PEG continuously for 25 minutes decreased compound action potentials approximately 64% in both damaged and non-damaged isolated mammalian spinal cords

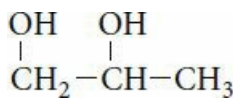
suggesting dose-response toxicity.³⁶

Fluid, Electrolyte, and Acid–Base Disturbances

Hyperosmolality was reported in three patients with burn surface areas ranging from 20% to 56% following repeated applications of Furacin, a topical antibiotic dressing containing 63% PEG 300, 32% PEG 4000, and 5% PEG 1000.²² PEG produces an osmotic effect that is greater than expected for its molecular weight.¹⁴¹ It is theorized that PEG increases osmolality by sequestering water through hydrogen binding, which reduces the availability of water to interact with solutes, thus increasing the chemical and osmotic activity of the solute. Hyperosmolality following the administration of a PEG-containing substance may suggest systemic PEG absorption.

Two cases of metabolic acidosis were reported following administration of therapeutic dosages of an intravenous nitrofurantoin solution containing PEG 300.¹⁵⁵ Similarly, an otherwise unexplained increased anion gap was reported in three patients being treated with a topical PEG-based burn cream.²³ Metabolism of the lower-molecular-weight PEGs by alcohol dehydrogenase to hydroxyacid and diacid metabolites can explain the metabolic acidosis.⁷⁴

PROPYLENE GLYCOL



Propylene glycol (PG), or 1,2-propanediol, is a clear, colorless, odorless, sweet, viscous liquid employed in numerous pharmaceuticals (Table 55–9), foods, and cosmetics. Propylene glycol is used as a solvent and preservative with antiseptic properties similar to ethanol. The WHO has set the daily allowable intake of PG at a maximum of 25 mg/kg,¹⁷² or 1.75 g/d for a 70-kg person.

TABLE 55–9. Propylene Glycol Concentration of Common Medications

Medication	Percent	Average Dose (g) ^a
Amprenavir oral solution	55	57.75
Chlordiazepoxide injection	20	0.08
Diazepam injection	40	0.4
Digoxin injection	40	0.4
Esmolol injection	25	2.5
Etomidate	35	3.6
Lorazepam injection	80	0.64
Multivitamins injection	30	0.45
Nitroglycerin injection	30	0.3
Pentobarbital	40	1.2
Phenobarbital sodium injection	67.8	0.7
Phenytoin injection	40	4.8
Trimethoprim-sulfamethoxazole injection	40	10 ^b

^aBased on dosage for 70-kg person. ^bBased on 24-hour dosage.

Pharmacokinetics

Propylene glycol is rapidly absorbed from the gastrointestinal tract following oral administration and has a volume of distribution of approximately 0.6 L/kg.^{108,151} When applied to intact epidermis, the absorption of PG is minimal. Percutaneous absorption may occur following application to damaged skin (eg, extensive burn surface areas).

Approximately 12% to 45% of PG is excreted unchanged in the urine,⁴⁶ the remainder is hepatically metabolized sequentially by alcohol dehydrogenase to lactaldehyde, which is metabolized further by aldehyde dehydrogenase to lactic acid. Lactic acid is also formed by another metabolite, methylglyoxal.¹²⁰ Lactic acid may be oxidized to pyruvic acid and then to carbon dioxide and water.¹²⁰ The terminal half-life of propylene glycol is reported to be between 1.4 and 5.6 hours in adults and as long as 16.9 hours in neonates.^{46,153}

Cardiovascular Toxicity

Intravenous preparations of phenytoin contain 40% PG to facilitate the dissolution of phenytoin. Nine years after intravenous phenytoin became available, several deaths were attributed to the rapid administration of phenytoin used for the treatment of cardiac dysrhythmias.^{63,160,182}

Cardiovascular effects reported in these cases included hypotension, bradycardia, widening of the QRS interval, increased amplitude of T waves with occasional inversions, and transient ST elevations. Studies in cats¹⁰⁰ and calves⁶⁷ confirmed PG as the cardiotoxin. Bradycardia and depression of atrial conduction were not observed in cats pretreated with atropine, or in those with vagotomy following rapid intravenous infusion of PG, suggesting that these effects are vagally mediated.¹⁰⁰ Amplification of the QRS complex was noted in these same pretreated cats, also suggesting a direct cardiotoxic effect of PG. Similar results were reported in calves pretreated with atropine that received oxytetracycline in a PG vehicle.⁶⁷

Neurotoxicity

Smaller infants appear to have a decreased ability to clear PG when compared with older children and adults.¹⁰¹ An increased frequency of seizures was reported in low-birth-weight infants who received PG 3 g daily in a parenteral multivitamin preparation.¹⁰¹ Seizures developed in an 11 year-old boy receiving long-term oral therapy with vitamin D dissolved in PG.⁷ Serum calcium, magnesium, electrolytes, and blood glucose were normal. Seizures abated after the product was discontinued. Propylene glycol possesses inebriating properties similar to ethanol. Central nervous system depression was reported following an intentional oral ingestion of a PG-containing product.¹⁰⁸

A black-box warning was added to the product information for amprenavir (Agenerase), an oral protease inhibitor solution, because of concerns over its high PG (550 mg/mL) vehicle content.¹³⁸ The recommended daily dosage of amprenavir supplies 1650 mg/kg/day of PG. A 61 year-old man experienced visual hallucinations, disorientation, tinnitus, and vertigo after receiving a 750-mg dose (474 mg/kg PG) of amprenavir solution.⁸⁵

Ototoxicity

Otic preparations can contain up to 94% PG in solutions and 10% in suspensions as part of their vehicles.⁵² In animal studies, application of high concentrations of PG (> 10%) to the middle ear can produce hearing impairment^{113,114,166} and morphologic changes, including tympanic membrane perforation, middle ear adhesions, and cholesteatoma.^{113,154,177} Although the effects of PG in the human middle ear have not been studied, all medications applied to the external ear canal are contraindicated in patients with perforated tympanic membranes.

Fluid, Electrolyte, and Acid–Base Disturbances

Patients receiving continuous or large intermittent quantities of medications containing PG can develop high PG concentrations, particularly those with renal or hepatic insufficiency.^{27,46} Propylene glycol–induced electrolyte and metabolic disturbances are evidenced by hyperosmolality, and an elevated osmolar gap attributed to the osmotically active properties of PG. In most cases, an elevated anion gap, with an otherwise unexplained elevated lactate concentration, is also present. Metabolic acidosis and hyperlactatemia result from PG metabolism.²⁶ These adverse effects are typically reported with intravenous preparations such as lorazepam,^{5,80,179} diazepam,¹⁷³ etomidate,¹⁶³ nitroglycerin,⁴⁶ pediatric multivitamins,⁶⁵ and topical silver sulfadiazine.^{12,53,89}

Systemic absorption of PG from topical application of silver sulfadiazine cream⁵³ resulted in hyperosmolality in patients with burn surface areas greater than 35% of their body.^{12,53,89} In one study, nine of 15 burn patients had osmolar gaps (> 12) after application of the cream.⁸⁹

Hyperosmolality occurred in five infants receiving a parenteral multivitamin that provided a daily PG dose of 3 g.⁶⁵ After 12 days, one premature infant had a PG concentration of 930 mg/dL and an osmolar gap of 136. Anion gap and lactic acid concentrations were normal. In a study, 11 intubated children aged 1 to 15 months who were receiving continuous lorazepam infusions over 3 to 14 days, accumulated serum PG concentrations of 17 to 226 mg/dL did not result in significant increases in osmolar gap or serum lactate concentrations from baseline.³³ This was attributed to normal renal

function and the low cumulative PG doses received (mean, 60 g).

Several small studies have found a strong correlation between elevated PG concentrations and increased osmolar gap measurements in critically ill patients receiving intravenous lorazepam and/or diazepam.^{6,174,178,179} An osmolar gap greater than 10 has been suggested as a marker for potential PG toxicity and also indicates when to consider obtaining a serum PG concentration.¹⁷⁸ An osmolar gap of 20 corresponds to a serum PG concentration of approximately 48 mg/dL.⁶ This equation should be used cautiously, as larger, more comprehensive studies are needed to validate it. There are rare cases where PG accumulation did not result in an osmolar gap.^{66,179} In addition, elevated anion gap measurements and lactate concentrations occur. As PG toxicity can mimic sepsis in these critically ill patients, sepsis should always be considered as the potential etiology of increased lactate, hypotension, and worsening renal function when considering PG toxicity. Both hemodialysis and fomepizole have been used to treat PG toxicity.^{124,181}

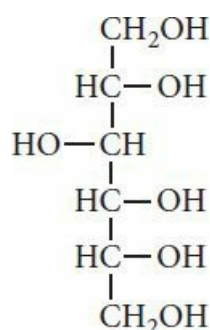
Nephrotoxicity

Human proximal tubular cells exposed in vitro to PG concentrations of 500 to 2000 mg/dL exhibited significant cellular injury and membrane damage within 15 minutes of exposure.¹¹⁶ Repeated exposure for up to 6 days produced dose-dependent toxic effects at lower concentrations (76, 190, and 380 mg/dL).¹¹⁵

The chronic administration of PG may contribute to proximal tubular cell damage and subsequent decreased kidney function. In a retrospective study of eight patients who developed elevations in serum creatinine concentration while receiving continuous lorazepam infusions, serum creatinine rose within 3 to 60 days (median, 9 days).¹⁷⁹ The magnitude of serum creatinine rise was found to correlate with the serum PG concentration and duration of infusion. Serum creatinine decreased within 3 days of discontinuing the infusion. Patients with chronic kidney disease are at greater risk for accumulating PG because 45% of PG is eliminated unchanged by the kidneys⁴⁶; the remainder is metabolized by the liver. Caution should be used when prolonged administration of a PG-containing medication is necessary in the presence of renal or hepatic dysfunction.¹¹⁶

Propylene glycol induced renal tubular necrosis has been reported in several cases. Daily PG vehicle dosages of 11 to 90 g/day over 14 days was associated with rising serum creatinine concentrations (0.7–2.1 mg/dL), elevated serum lactate concentrations, osmolar and anion gaps, and a serum PG concentration of 21 mg/dL.¹⁸⁰ Urine sediment analysis revealed numerous granular, muddy-brown-colored casts and no eosinophils, suggesting an acute renal tubular necrosis. Kidney biopsy and electron microscopy showed extensive dilation of the proximal renal tubules, with swollen epithelial cells and mitochondria. Numerous vacuoles containing debris were also noted. A kidney biopsy of another case with a serum PG concentration of 30 mg/dL showed disrupted brush borders of the proximal renal tubules after a sudden rise in serum creatinine concentration (3.1 mg/dL), nonoliguric kidney failure, and metabolic acidosis. This was attributed to an average daily PG dose of 70 g for 17 days.⁷²

SORBITOL



Sorbitol (D-glucitol) is widely used in the pharmaceutical industry as a sweetener, moistener agent, and as a diluent (Table 55–10). Sorbitol occurs naturally in the ripe berries of many fruits, trees, and plants, and was first isolated in 1872 from the berries of the European mountain ash (*Sorbus aucuparia*).¹¹⁸ It is particularly useful in chewable tablets because of its pleasant taste. In addition, it is widely used by the food industry in chewing gums, dietetic candies, foods, and enteral nutrition formulations. Sorbitol is approximately 50% to 60% as sweet as sucrose.¹¹⁸

TABLE 55–10. Common Medications Containing Sorbitol

<i>Medication</i>	<i>Percent</i>	<i>Dose (g)</i>
Amantadine syrup	64	6.4
Calcium carbonate suspension	28	1.4
Carbamazepine syrup	17	0.85
Chloral hydrate syrup	40	2
Cimetidine syrup	46	2.3
Digoxin elixir	21	0.1
Ferrous sulfate infant drops	31	0.2
Furosemide solution	35	1.75
Guaifenesin/dextromethorphan syrup	64	6.4
Methadone HCl solution	14	5.6
Potassium chloride solution	17.5	1.35
Pseudoephedrine syrup	35	1.75
Sodium polystyrene in sorbitol	50	20

Pharmacokinetics

Unlike sucrose, sorbitol is not readily fermented by oral microorganisms and is poorly absorbed from the gastrointestinal tract. Any absorbed sorbitol is metabolized in the liver to fructose and glucose.¹¹⁸ Sorbitol has a caloric value of 4 kcal/g and is better tolerated by diabetics than sucrose; however, because some of it is metabolized to glucose, it is not unconditionally safe for people with diabetes and is obviously not “dietetic”.¹¹⁸

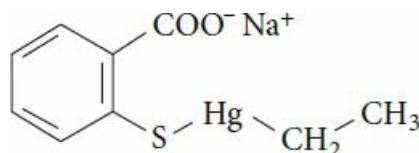
There is a concern of potentially fatal toxicity for individuals with hereditary fructose intolerance (HFI) receiving sorbitol-containing xenobiotics.⁵⁴ HFI is an autosomal recessive disorder caused by a deficiency of fructose-1,6-bisphosphonate aldolase in the liver, kidney, cortex, and small intestine.⁸⁶ This results in the accumulation of fructose-1-phosphate, which prevents glycogen breakdown and glucose synthesis causing hypoglycemia. The prevalence of HFI is most commonly reported to be one in 20,000 persons, but can range between one in 11,000 and one in 100,000.^{2,84,86}

In individuals with HFI, the prolonged administration of sorbitol, fructose, or sucrose can result in death from liver or kidney failure.^{37,142} Dietary exclusion of fructose, sucrose, and sorbitol prevents the adverse effects. This condition should not be confused with the more common disorder of dietary fructose intolerance, which is caused by a defect in the glucose-transport protein 5 system. This leads to the breakdown of fructose to carbon dioxide, hydrogen, and short-chain fatty acids by colonic bacteria, resulting in abdominal pain and bloating.⁹² Dietary fructose intolerance symptoms are minimized by limiting sorbitol, fructose, and sucrose in the diet.

Gastrointestinal Toxicity

In large dosages, sorbitol can cause abdominal cramping, bloating, flatulence, vomiting, and diarrhea. Sorbitol exerts its cathartic effects by its osmotic properties, resulting in fluid shifts within the gastrointestinal tract. Iatrogenic osmotic diarrhea is reported following administration of many different liquid medication formulations containing sorbitol.^{76,102} In a human volunteer study, 42 healthy adults ingested 10 g of a sorbitol solution. Sorbitol intolerance was detected in up to 55% of participants.⁸³ One theoretical explanation for why all participants did not experience the gastrointestinal adverse effects is unrecognized dietary fructose intolerance. Diarrhea resulting from sorbitol-containing medications is common and often overlooked as a possible etiology.^{31,73} Ingestion of large quantities of sorbitol (> 20 g/day in adults) is not recommended (Antidotes in Depth: A2).¹¹⁸

THIMEROSAL



Thimerosal (Merthiolate, Mercurothiolate), or sodium ethylmercurithiosalicylate, is an organic mercury compound that is approximately 49% elemental mercury (Hg^0) by weight.^{137,167} It is metabolized to ethylmercury and thiosalicylate. Thimerosal has a wide spectrum of antibacterial activity at concentrations ranging from 0.01 to 0.1%; however, higher concentrations are sometimes also used.^{88,112} Thimerosal has been widely used as a preservative since the 1930s in contact lens solutions, biologics, and vaccines, particularly those in multidose containers (Table 55–11). The use of thimerosal, which is necessary for the production process of some vaccines (eg, pertussis, influenza), may leave trace amounts in the final product.¹⁰ High-dose thimerosal exposure has resulted in neurotoxicity and nephrotoxicity. Although concerns exist regarding infant exposure to low-dose thimerosal through vaccinations and its effects on neurodevelopment, including possible links to causes of autism,¹⁷ these concerns are unfounded (Chap. 98).⁴⁴

TABLE 55–11. Thimerosal Concentration of Common Medications

Medication	Percent	Dose (mg)
Injectable		
Antivenom (crotaline polyvalent immune) Fab	0.003	0.03 (per vial)
Antivenom (<i>Latrodectus mactans</i>)	0.01	0.25 (per vial)
Antivenom (<i>Micrurus fulvius</i>)	0.005	0.5 (per vial)
Diphtheria and tetanus toxoids ^a	Trace	< 0.3 μg
Influenza virus vaccine ^b (various)	0.01	0.025
Menomune-A/C/Y/W-135 ^b (meningococcal vaccine)	0.01	0.025
Tetanus toxoid (adsorbed)	0.01	0.025
Topical		
Mersol (thimerosal tincture)	0.1	—
Neosporin (triple antibiotic) ophthalmic solution	0.001	—
Ocufen (flurbiprofen) ophthalmic solution	0.005	—

^aTrace defined by the US Food and Drug Administration as < 1 μg mercury each dose. ^bMultidose.

Because specific guidelines for ethylmercury exposure have not been developed, regulatory guidelines for dietary methylmercury exposure were applied to monitor ethylmercury exposure from injected thimerosal-containing vaccines. Methylmercury is a similar, but more toxic, organic mercury compound (Chap. 98). Maximum daily recommended methylmercury exposures range from 0.1 μg Hg/kg (US Environmental Protection Agency {EPA}) to 0.47 μg Hg/kg (WHO).^{3,30,35}

An FDA review of thimerosal-containing vaccines revealed that some infants, depending on the immunization schedule, vaccine formulations, and infant's weight, might be exceeding the EPA exposure limit of 0.1 μg Hg/kg/day for methylmercury. Over the first 6 months of life, a total cumulative dose of up to 187.5 μg Hg total from thimerosal-containing vaccines was possible. The US Public Health Service and the American Academy of Pediatrics jointly responded by recommending the preemptive reduction or removal of thimerosal from vaccines wherever possible.^{3,29} The WHO and European regulatory bodies have made similar recommendations.⁵⁵ To date, thimerosal has been removed from most US-licensed immunoglobulin products. All vaccines routinely recommended for children younger than 7 years of age are either thimerosal-free or contain only trace amounts (< 0.5 μg Hg/dose), with the exception of some inactivated influenza vaccines. Multidose vials requiring thimerosal preservative remain important for immunization programs in developing countries due to lack of consistent ability to refrigerate vaccines. Although efforts continue to eliminate all sources of mercury exposure, complete elimination of thimerosal from all vaccines is unlikely in the near future.¹⁰ When a thimerosal-containing vaccine is the only alternative, the benefits of vaccination far exceed any theoretical risk of mercury toxicity.¹¹⁹

Prior to thimerosal use in pharmaceuticals, evidence for its safety and effectiveness was provided in several animal species and in 22 humans.¹²⁹ Only limited data exist on infant mercury exposure from thimerosal-containing vaccines. Clinical studies that assess the effects of thimerosal exposure on neurodevelopment and renal and immunologic function are lacking. Based on a comprehensive review of epidemiologic data from the United States,^{34,58,61,157,167} Denmark,^{104,105}

Sweden,¹⁵² and the United Kingdom,^{5,75} the Institute of Medicine's Immunization Safety Review Committee,¹¹⁹ the Global Advisory Committee on Vaccine Safety,¹⁷⁶ and the European Agency for the Evaluation of Medicinal Products⁵⁰ have all concluded that no causal relationship exists between thimerosal-containing vaccines and autism. Continued surveillance of autistic spectrum disorders as thimerosal use declines will be conducted to evaluate any associated trends.

Pharmacokinetics

Limited pharmacokinetic data exist for thimerosal and ethylmercury. Once absorbed, thimerosal breaks down to form ethylmercury and thiosalicylate. Some ethylmercury further decomposes into inorganic mercury in the blood, and the remainder distributes into kidney and, to a lesser extent, brain tissue.^{104,105} Because of its longer organic chain, ethylmercury is less stable and decomposes more rapidly than methylmercury, leaving less ethylmercury available to enter kidney and brain tissue.¹⁰⁴ Ethylmercury crosses the blood–brain barrier by passive diffusion.¹⁰⁵ Intracellular ethylmercury decomposes to inorganic mercury, which accumulates in kidney and brain tissues.¹⁰⁵ The half-life of thimerosal is estimated to be about 18 days.¹⁰⁶ Thimerosal is eliminated in the feces as inorganic mercury (Chap. 98).¹²⁸

Mercury or Thimerosal Toxicity

Oral Administration. A case report described a 44 year-old man who ingested 5 g (83 mg/kg) of thimerosal in a suicide attempt; within 15 minutes he began vomiting spontaneously. Gastric lavage was performed and chelation therapy begun with dimercaptopropane sulfonate. Gastroscopy revealed a hemorrhagic gastritis. Polyuric acute kidney injury was noted on the day of admission and persisted for 40 days. Four days after admission, the patient developed fever and a maculopapular exanthem attributed to thimerosal. The patient also developed an autonomic and ascending peripheral polyneuropathy that persisted for 13 days. Chelation therapy was continued for a total of 50 days with dimercaptopropane sulfonate followed by succimer. Elevated blood and urine mercury concentration persisted for more than 140 days. The patient was discharged 148 days following the ingestion with only sensory defects in his toes. No other neurologic sequelae were noted.¹²⁷

Oral absorption of thimerosal resulted in the fatal poisoning of an 18 month-old girl from the intraotic instillation of a solution containing 0.1% thimerosal and 0.14% sodium borate. Tympanostomy tubes placed one year earlier allowed the irrigation solution to flow through the auditory tube into the nasopharynx, and subsequently to be swallowed and absorbed through the oral mucosa and gastrointestinal tract. A total of 1.2 L of solution (500 mg Hg) was instilled over a 4 week period, resulting in severe mercury poisoning. Four days after admission, the serum mercury concentration was 163 µg/dL. The patient also received 1.7 g of boric acid. It is unclear what contribution, if any, the boric acid made to the serum mercury concentration. Chelation therapy with N-acetyl-D-penicillamine was initiated on day 51. Despite increased urinary mercury concentrations following administration of the N-acetyl-D-penicillamine, her neurologic function and blood mercury concentrations remained unchanged. The child died 3 months after admission. An autopsy was not performed.¹³⁷

Intramuscular Administration. Urine mercury concentrations of 26 patients with hypogammaglobulinemia, who received weekly intramuscular immunoglobulin G (IgG) replacement therapy preserved with 0.01% thimerosal were studied. The dosages of IgG ranged from 25 to 50 mg/kg, containing 0.6 to 1.2 mg of mercury per dose.⁶⁸ The total estimated dose of mercury administered ranged from 4 to 734 mg over a period of 6 months to 17 years. Urine mercury concentrations were elevated in 19 patients, ranging from 31 to 75 µg/L; however, no patients had clinical evidence of chronic mercury toxicity.⁶⁸

Six cases of severe mercury poisoning resulting in four deaths were reported following the intramuscular administration of chloramphenicol preserved with thimerosal. A manufacturing error produced vials containing 510 mg of thimerosal (250 mg Hg) instead of 0.51 mg per vial. Two adults received 4 g and 5.5 g of mercury each and four children received 0.2 to 1.8 g each. All six patients had extensive tissue necrosis at the site of injection. Fever, altered mental status, slurred speech, and ataxia were noted. Autopsy identified widespread degeneration and necrosis of the renal tubules; however, creatine kinase concentrations were not reported, so pigment-induced nephrotoxicity cannot be excluded. Elevated mercury concentrations were found in the injection site tissues, and in the kidneys, livers, and brains.⁸

Topical Administration. Thirteen infants were exposed to nine to 48 topical applications of a 0.1% thimerosal tincture for the treatment of exomphalos. Analysis for elevated mercury concentrations was performed in 10 of 13 infants who unexpectedly died. Mercury concentrations were determined in various tissues from six of the infants. Mean tissue concentrations in fresh samples of liver, kidney, spleen, and heart ranged from 5152 to 11,330 ppb, suggesting percutaneous absorption from these repeated topical applications.⁵¹

Ophthalmic Administration. Nine patients undergoing keratoplasty were exposed to a contact lens stored in a solution containing 0.002% thimerosal.¹⁷⁵ After 4 hours, the lens was removed and mercury concentrations of the aqueous humor and excised corneal tissues were determined. Mercury concentrations were elevated in both aqueous humor (range, 20–46 ng/mL higher) and corneal tissues (range, 0.6–14 ng/mL higher) as compared with eyes that had not been fitted with contact lenses. Only residual amounts of mercury remained on the contact lenses after 4 hours of wear. The authors noted that

although the aqueous humor concentrations were in the same range as those measured in 10 patients with vision loss from systemic mercury poisoning (11–104 ng/mL), adverse effects did not occur.

A possible drug interaction between orally administered tetracyclines and thimerosal was reported to result in acute, varying degrees of eye irritation in contact lens wearers using thimerosal-containing contact lens solutions who started treatment with tetracycline.⁴⁰

SUMMARY

- The benefits of pharmaceutical excipients include improved xenobiotic solubility, stability, and palatability, antimicrobial activity, the availability of various dosage forms, the provision of products with long-term storage, and the availability of multiple-dose packaging. While excipients are essential and effective, they are suggested to possess no pharmacologic or toxicologic properties but may actually be responsible for severe—and sometimes fatal—adverse effects.
- The toxicity of pharmaceutical excipients should be considered for patients requiring high doses or prolonged administration of any medication containing excipients, particularly those additives known to have toxicities.
- Under circumstances in which there is no option but to continue treating a patient with a particular xenobiotic, switching to a preservative-free product, or to another brand without the offending excipient, may obviate the need for discontinuation of an effective xenobiotic. In addition to inherent toxicities, many excipients may also be responsible for allergic reactions.
- In the majority of cases, pharmaceutical excipients are safe and effective, and their benefits far exceed their potential for adverse effects when properly administered.

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56 THYROID AND ANTITHYROID MEDICATIONS

Nicole C. Bouchard

HISTORY AND EPIDEMIOLOGY

Long before the thyroid was recognized as a functional endocrine gland, it was believed to serve a cosmetic function, especially in women. Egyptian paintings often emphasize the full and beautiful necks of women with enlarged thyroid glands. Early theories on the physiologic function of the thyroid gland included lubrication of the trachea, diversion of blood flow from the brain, and protection of women from “irritation” and “vexation” from men.³³ Although poorly defined in historical accounts, symptoms resembling hypothyroidism and myxedema that were successfully treated with ground sheep thyroid were described 500 years ago. In the 16th century, Paracelsus described the association between goiter (thyroid gland enlargement) and cretinism.⁶⁹ A syndrome of cardiac hyperactivity, goiter, and exophthalmos was first described in 1786.⁸² Graves and von Basedow³³ further detailed this syndrome and its relationship to the thyroid gland 50 years later.

In 1891, injection of ground sheep thyroid extract was formally described as a treatment for myxedema.³³ Shortly afterward, oral therapy was determined to be equally effective. Seaweed, which contains large amounts of iodine, was used to treat goiter (hypothyroidism) in Chinese medicine as early as the third century A.D. In 1863, Trousseau¹⁰¹ fortuitously discovered a treatment for Graves disease when he inadvertently prescribed daily tincture of iodine instead of tincture of digitalis to a tachycardic, thyrotoxic young woman.

Sir Charles R. Harington described the chemical structure and performed the first synthesis of thyroxine (tetraiodothyronine {T₄}) in 1926.⁸⁴ Triiodothyronine (T₃) was not isolated and synthesized until the 1950s.³³ Prior to this, desiccated thyroid gland from animal sources was commonly used to treat hypothyroidism. Despite becoming essentially obsolete in the modern medical community, unprocessed, desiccated thyroid can be easily purchased via the Internet and in health food stores as a thyroid supplement.⁹⁵ A pharmaceutical grade porcine derived thyroid supplement originally produced by Armour, is still available by prescription from several manufacturers. Unfortunately, the misguided use of both organic and synthetic thyroid supplements as vitality agents, stimulants, and weight-loss aids has become increasingly common. Two epidemics of “hamburger thyrotoxicosis” that occurred in the United States in the mid 1980s secondary to consumption of ground beef contaminated with bovine thyroid gland demonstrated the potential widespread toxicologic sequelae after a community unknowingly ingested thyroid hormone.^{38,51}

Today, hypothyroidism and hyperthyroidism are relatively common endocrine disorders. The global incidence of neonatal hypothyroidism is one per 3000 to 4500 births. It is estimated that hypothyroidism affects 1% to 5% of US adults. It is more prevalent in whites than people of Hispanic or African American descent. In the elderly, the prevalence of hypothyroidism increases to 15% by the age of 75 years. Worldwide, iodine deficiency is the leading cause of hypothyroidism. According to US retail pharmaceutical statistics for prescription drugs, levothyroxine (both generic and brand combined; T₄) has consistently ranked in the top five prescription count, with an average 67 million per year. Because of widespread availability of thyroid replacement therapy, many cases of intentional and unintentional overdoses with thyroid hormone are reported.⁶³ However, despite the profound effects of thyroid hormones on physiologic homeostasis and the widespread use and access to exogenous thyroid hormone, morbidity and mortality from overdose is very low and clinically significant overdoses with thyroid hormone preparations are uncommon.

PHARMACOLOGY

Physiology

To properly understand the impact of thyroid supplements and antithyroid xenobiotics on the function of the human body, an understanding of thyroid physiology is required. Thyroid function is influenced by the following: (1) the hypothalamus, (2) the pituitary gland, (3) the thyroid gland, and (4) the target organs for the thyroid hormones (Fig. 56–1).

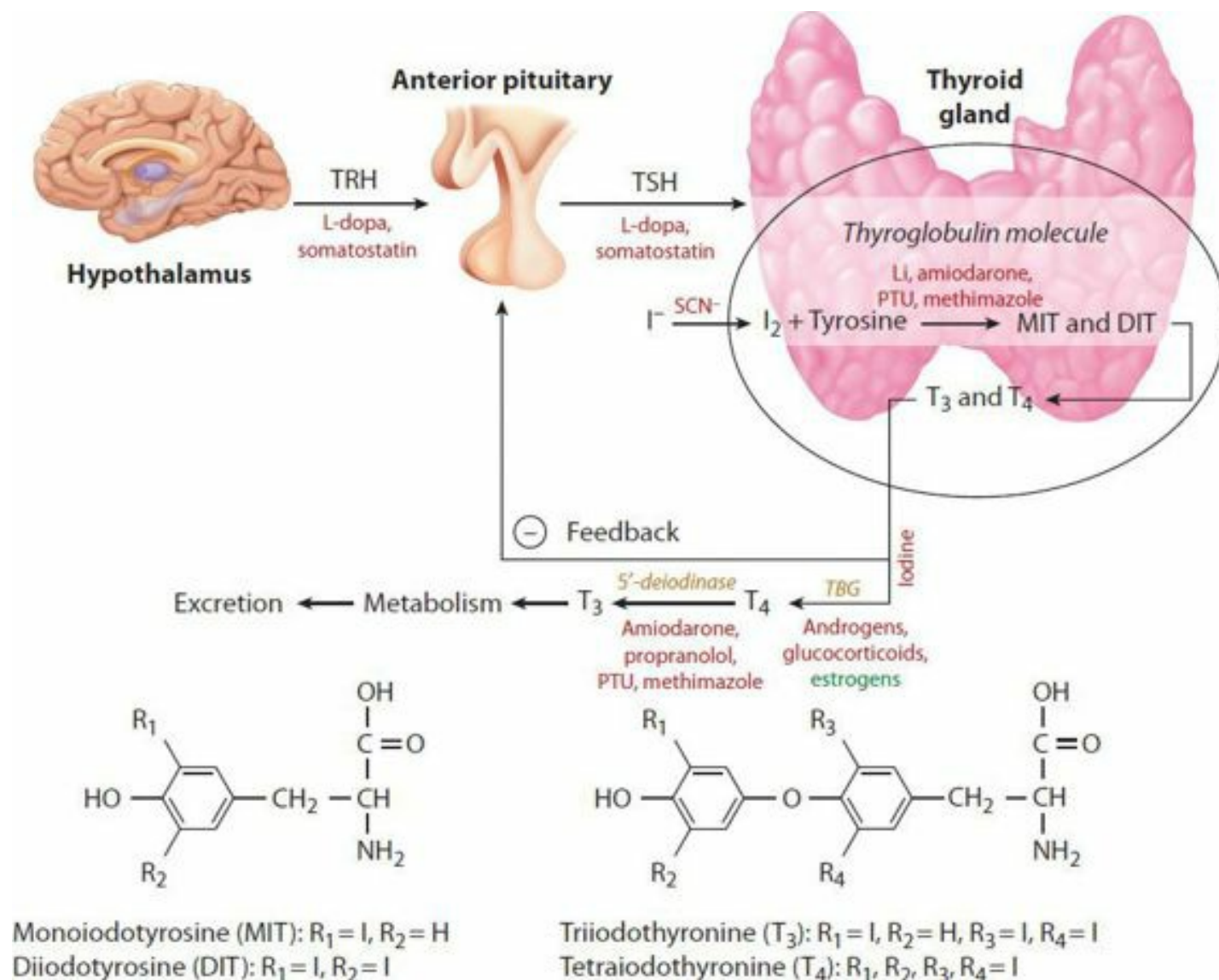


FIGURE 56–1. Thyroid hormone synthesis: its control, metabolism, and molecular structures. PTU = propylthiouracil; SCN⁻ = thiocyanate; TBG = thyroxine binding globulin; TRH = thyrotropin releasing hormone; TSH = thyroid stimulating hormone.

The hypothalamus, viewed by some as the “master gland,” is an intermediate between cerebral centers and the pituitary gland. When the hypothalamus receives specific neurotransmitter stimulation, thyroid-releasing hormone (TRH) is produced, which is then transported through the venous sinusoids to the pituitary gland, which then releases thyroid-stimulating hormone (TSH). TSH enters the circulation and stimulates the production and release of the thyroid hormones T₃ and T₄ from the thyroid gland. Thyroid physiology exhibits classic autoregulation or “negative biofeedback” of hormonal function. When adequate thyroid hormones are present, they exert an inhibitory effect on the pituitary gland, diminishing production of TSH (Fig. 56–1). Suppression or upregulation of TSH production is a frequently used laboratory marker in the evaluation of hyperthyroidism and hypothyroidism, respectively.

Thyroid hormones are tyrosine molecules with iodine substitutions. Two forms of the hormone are physiologically active: T₃ and T₄ (Table 56–1). Synthesis of thyroid hormones is a multistep process. The amino acid tyrosine is concentrated in the follicles of the thyroid gland, which consist of an epithelial layer surrounding a proteinaceous colloidal substance called thyroglobulin. Thus, thyroglobulin contains a large amount of tyrosine. After absorption, iodide (I⁻) is concentrated in thyroid cells by an active transport process called iodide trapping. Absorbed I⁻ is then oxidized to iodine (I₂) by thyroid (iodide) peroxidase. Iodine rapidly iodinates tyrosine residues to form monoiodotyrosine and diiodotyrosine. These substituted tyrosine molecules then combine to form T₃ and T₄. The ratio of T₃ to T₄ in thyroglobulin is 1:5. T₃ and T₄ (thyroxine) ultimately are released into circulation from the thyroglobulin matrix.

TABLE 56–1. Pharmacokinetic Properties of Thyroid Hormones

Pharmacokinetic Property	T_3	T_4
Oral bioavailability (exogenous drug), %	95	80
Volume of distribution (L/kg)	40	10
Half-life (days)	1	7
Protein binding (normal adult), %	99.96	99.6
Relative potency	4	1

Iodide trapping can be inhibited pharmacologically by monovalent anions such as thiocyanate (SCN^-), pertechnetate (TcO_4^-), and perchlorate (ClO_4^-). Thyroid peroxidase is inhibited by high concentrations of intrathyroidal iodide and by thioamide drugs. High intrathyroidal iodide concentrations also can inhibit the release of thyroid hormone into circulation (Table 56–2).

TABLE 56–2. Xenobiotic Interactions: Effects on Thyroid Hormones and Function^{6,26,30,100}

Xenobiotic	Interaction	Effect
Dopamine, levodopa, somatostatin	Inhibit TRH and TSH synthesis	No clinical hypothyroidism
Iodides (including amiodarone), lithium, aminoglutethimide	Inhibit thyroid hormone synthesis or release	Hypothyroidism
Monovalent anions (SCN^- , TcO_4^- , ClO_4^-)	Inhibit iodide uptake to thyroid gland	Hypothyroidism
Estrogens, tamoxifen, heroin, methadone, mitotane	Increase TBG	Altered thyroid hormone transport in serum ↑ Total measured thyroid hormone (vs free hormone)
Androgens, glucocorticoids	Decrease TBG	Altered thyroid hormone transport in serum ↓ Total measured thyroid hormone (vs free hormone)
Salicylates, mefenamic acid, furosemide	Displace T_3 or T_4 from TBG	Transient hyperthyroxinemia
Thioamides (methimazole, propylthiouracil)	Inhibit thyroid peroxidase	Decrease thyroid hormone synthesis
Phenytoin, carbamazepine, phenobarbital, rifampin, rifabutin	Induction of hepatic enzymes	↓ Total thyroid hormone measurements
Iopanoic acid, ipodate, amiodarone, propranolol, corticosteroids, propylthiouracil	Inhibition of 5'-deiodinase	Decrease peripheral conversion of T_4 (↓ T_3 , ↑ rT_3)
Cholestyramine, colestipol, aluminum hydroxide, sucralfate, ferrous sulfate, some calcium preparations, infant soy formula	Interfere with GI absorption of T_4	Decreased oral bioavailability of T_4
Interleukin- α , interleukin-2	Induction of autoimmune thyroid disease	Hyperthyroidism or hypothyroidism

GI = gastrointestinal; TBG = thyroid-binding globulin; TRH = thyroid-releasing hormone; TSH = thyroid-stimulating hormone.

Approximately 95% of circulating or peripheral thyroid hormone is T_4 ; the remainder is T_3 . Only 15% of the peripheral T_3 is secreted directly by the thyroid; the balance results from the peripheral (meaning outside the thyroid gland) conversion of T_4 to T_3 . When circulating T_4 enters the cell, it is deiodinated to T_3 . Deiodination of the T_4 molecule occurs by monodeiodination of either the outer ring or the inner ring by 5'-deiodinase or 5-deiodinase, yielding 3,5,3'- T_3 and 3,3',5'-triiodothyronine (reverse T_3 { rT_3 }), respectively.⁵⁶ T_3 has approximately four times greater hormonal activity than T_4 , whereas rT_3 is metabolically inactive. T_3 exerts its effects by binding to thyroid hormone receptors inside the nucleus. This interaction with nuclear receptors regulates gene transcription and protein synthesis, which ultimately increases oxygen consumption and underlies the thermogenic effects of thyroid hormones.

Propranolol, corticosteroids, ipodate (iodinated oral contrast agent), starvation, and severe illness inhibit 5'-deiodinase, which results in decreased production of metabolically active T_3 and preferential monodeiodination to metabolically inactive rT_3 leading to a syndrome known as “sick euthyroid” (Table 56–2). This energy conserving effect allows attenuation of the thermogenic effects of thyroid hormones in times of physiologic stress.⁹⁹

T_4 and T_3

Thyroid supplementation for treatment of hypothyroidism is in widespread use both in human and veterinary medicine. Thyroid hormones historically were derived from animal origin, but now are largely synthetically produced. Desiccated and processed porcine thyroid contains both T₃ and T₄. Because it is less pharmacologically stable and carries a risk of allergic reaction and thyrotoxicity from T₃, its use has largely been supplanted by the safer synthetic alternatives.

Levothyroxine is the preparation of choice because of its low immunogenicity, 7-day half-life, and easy dosing regimen. It is also available in an intravenous (IV) formulation. Synthroid is the commercial name of the most commonly prescribed form of T₄. Liothyronine (T₃ preparation, Cytomel or Triostat, available in oral {PO} and IV) and liotrix (combination T₃/T₄ preparations, preparations of Thyrolar, available PO) are synthetic preparations that are seldom used clinically because of their short half-lives, high cost, unique therapeutic indication, and increased risk of thyrotoxicosis.

Steady state with regard to suppression of TSH and elevation of T₄ is reached approximately 6 to 8 weeks after initiation of therapy. Doses usually are titrated in increments of 12.5 or 25 µg/day after 2 to 6 weeks based on TSH measurements. [Table 56–3](#) gives typical levothyroxine doses. Different sources suggest that the bioequivalence of Synthroid may or may not be equivalent to generic levothyroxine.¹⁷ As a result, thyroid hormone concentrations and the patient’s clinical status should be followed when transitioning between levothyroxine formulations because the switch may present a risk for an adverse drug event.

TABLE 56–3. Typical Levothyroxine Doses^a

<i>Age Group</i>	<i>Dose (µg/kg/day)</i>	<i>Usual Daily Dose^b (µg/day)</i>
Infants <6 months	8–10	25–50
Infants 6–12 months	6–8	50–75
Children 1–5 years	5–6	75–100
Children 6–12 years	4–5	100–150
Children >12 years	2–3	Until 150 (adult dose)
Adults	1.7	100–150
Elderly	Enhanced sensitivity to thyroxine excess	12.5–50

^aAll levothyroxine dosing is titrated by laboratory assessment. ^bThis dose is a fixed dose estimate (alternative).

PHARMACOKINETICS AND TOXICOKINETICS

Gastrointestinal absorption of exogenous thyroid hormone occurs primarily in the duodenum and ileum. Gastrointestinal absorption can be decreased by variations in intestinal flora and binding by xenobiotics ([Table 56–2](#)). In circulation, T₃ and T₄ both are highly but reversibly bound to plasma proteins—approximately 99.6% and 99.96%, respectively (in nonpregnant adults). Thyroxine-binding globulin binds approximately two-thirds of the circulating thyroid hormones; albumin and other proteins bind the remainder. It is estimated that only 0.4% of T₃ and 0.04% of T₄ exist in the free form. Exogenously derived thyroid hormones exhibit similar binding characteristics when dosed in a physiologic range. The amount of thyroid hormone bound to proteins varies greatly with different physiologic and pharmacologic conditions, for example, increasing in pregnancy and levothyroxine overdose and decreasing in chronic disease.⁴⁰ These changes in protein binding must be considered when measuring total thyroid hormone concentrations in the blood (see Diagnostic Testing). [Table 56–1](#) lists some important pharmacokinetic properties of thyroid hormones.

Thyroid hormones undergo their ultimate metabolism peripherally. Intracellular sequential deiodination accounts for approximately two-thirds of inactivation. Most of the remaining third undergoes hepatic metabolism by glucuronidation or sulfation. Xenobiotics that induce hepatic microsomal metabolism, such as rifampin, phenobarbital, phenytoin, and carbamazepine, increase the metabolic clearance of T₃ and T₄ ([Table 56–2](#)).

PATHOPHYSIOLOGY

Thyroid hormones are critical for optimal physiologic growth and function. Thyroid function is the most important determinant of basal metabolic rate. In addition, the thyroid exerts a permissive effect on many hormones, notably catecholamines and insulin.

Hyperthyroidism is a condition characterized by excess active thyroid hormone. Most aspects of carbohydrate, protein, and lipid metabolism are increased in the presence of thyroid hormone excess. The disorder is characterized by manifestations of increased metabolism such as hyperthermia, weight loss, diarrhea, heat intolerance, and diaphoresis, along with tachycardia, widened pulse pressure, tremor, anxiety, other behavioral changes, and sometimes tachydysrhythmias such as rapid atrial fibrillation, extrasystoles, and high output congestive heart failure.^{23,53,92} This constellation of symptoms, called thyrotoxicosis, may result from overproduction of the hormone, increased conversion from T₄ to T₃, or intake of exogenous hormone. Graves disease (diffuse toxic goiter), an autoimmune disorder, is the most common cause of excess thyroid hormone secretion. It accounts for approximately two-thirds of cases and often is accompanied by exophthalmos and diffusely enlarged, nontender thyroid gland. Toxic multinodular goiter, toxic thyroid adenoma, iodine or amiodarone exposure (which can also cause hypothyroidism; [Table 56–4](#)), thyrotoxicosis factitia, and thyroiditis (eg, postpartum, Hashimoto, DeQuervain) are some other etiologies of hyperthyroidism.³¹ Severe thyrotoxicosis with significant rapid clinical decompensation is referred to as thyroid storm or thyrotoxic crisis. Thyroid storm typically occurs when untreated or undertreated hyperthyroidism occurs simultaneously with a physiologic stressor such as trauma, infection, diabetic ketoacidosis, or surgery. In early stages, patients are hyperthermic and markedly tachycardic, tremulous, agitated, or psychotic with nausea, vomiting, and diarrhea. As the disease progresses, stupor, coma, and hypotension may ensue. General treatment strategies include early airway control, crystalloid fluid resuscitation, β -adrenergic antagonist administration, parenteral corticosteroids if adrenal insufficiency is suspected, and antithyroid medications such as propylthiouracil and methimazole. β -Adrenergic antagonists such as propranolol are the mainstay of treatment, with propranolol the preferred choice because it decreases peripheral conversion of T₄ to T₃. Mortality in thyroid storm, even with treatment, can approach 20%.^{23,90}

TABLE 56–4. Common Xenobiotics That Alter Thyroid Function and Cause Clinically Important Effects^{11,26,35,36,55,100,107}

<i>Xenobiotic</i>	<i>Effect</i>	<i>Mechanism</i>
Lithium	Goiter (in 37% of patients) Hypothyroidism (in 5%–15% of patients)	Mechanism unclear
Amiodarone (37% iodine by weight)	1. Hypothyroidism (in 25% of patients) 2. Hyperthyroidism, type 1: in patients with preexisting goiters from low iodine intake 3. Hyperthyroidism, type 2: in patients with previously normal thyroid function	1. Inhibition of 5'-deiodinase 2. Type 1: iodine excess stimulates thyroid hormone production 3. Type 2: causes thyroid inflammation
Propranolol	↓ Peripheral conversion of T_4 to T_3	Inhibition of 5'-deiodinase
PTU (propylthiouracil) or methimazole	Decreased thyroid hormone synthesis ↓ Peripheral conversion of T_4 to T_3	Inhibition of thyroid peroxidase Inhibition of 5'-deiodinase
Corticosteroids	↓ Peripheral conversion of T_4 to T_3	Inhibition of 5'-deiodinase
Iodine	1. Low dose: transient or no effect 2. High doses (>10 mg/day): ↓ thyroid hormone secretion 3. Transient thyrotoxicosis (ie, Jod-Basedow effect) With rapid correction of hypothyroidism from iodine deficiency from topical iodine 4. Delirium 5. Caustic injury	1. Transiently stimulates thyroid hormone secretion 2. Inhibition of thyroid hormone synthesis 3. Increases thyroid hormone synthesis 4. Mechanism unclear 5. Direct cytotoxic injury to cells
Iodinated contrast material	1. Rapid ↓ peripheral conversion of T_4 to T_3 (adjunctive treatment in thyroid storm) 2. Prolonged suppression of T_4 to T_3 3. Causes thyrotoxicosis and thyroid storm 4. Iodide "mumps"	1. Inhibition of 5'-deiodinase 2. Mechanism unclear 3. Mechanism unclear 4. Idiopathic, toxic accumulation of iodide
Radioactive iodine	Treatment of hyperthyroidism, causes hypothyroidism	Uptake into thyroid follicles causes local destruction
Anion inhibitors ^a	↓ Iodine uptake into thyroid follicle, used in iodide-induced hyperthyroidism	Blocks uptake of iodide into the thyroid gland by competitive inhibition

^aAlso referred to as monovalent anions, ie, thiocyanate (SCN^-), perchlorate (ClO_4^-), and periodate (IO_4^-).

Since plasma catecholamine concentrations are normal or decreased in hyperthyroid states, an increase in sensitivity to catecholamines is thought to be responsible for the increased inotropy and chronotropy produced by thyroid hormones.^{14,88} Several general mechanisms are proposed for the direct cardiac effects of thyroid hormones, although their relative contributions are uncertain^{3,16,52,103}:

- T_3 increases the number of β -adrenergic receptors in various tissues, including cardiac cells.¹⁶ This process occurs via upregulation of β -adrenergic receptor synthesis at the level of the β -adrenergic gene.⁴
- T_3 modulates myocyte intracellular signaling mechanisms that lead to increased catecholamine effects. Enhancement of intracellular signaling activity involving protein kinase A, cyclic adenosine monophosphate, G proteins, and increased phosphorylation of thyroid hormone receptor proteins all are implicated to varying degrees.^{22,53,86,87,91,98,104}
- Enhancement of myocardial transmembrane and sarcoplasmic reticulum ion channel function, L-type voltage-gated Ca^{2+} channels, and accelerated Ca^{2+} entry into the sarcoplasmic reticulum also are suggested.^{49,50,74,97} Whether the effects on intracellular signaling represent a direct effect of T_3 on intracellular signaling mediators or T_3 induced augmentation of the individual β -adrenergic receptor response to catecholamines with a secondary change in postreceptor signaling is unclear.³

In addition to these mechanisms, T_3 upregulates synthesis of cardiac thyroid hormone receptors (at TR- α and TR- β genes), and the thermogenic effects of thyroid hormones can cause decreased systemic vascular resistance leading to a reflex (and indirect) increase in cardiac output. Comprehensive reviews on this topic explore the more complex cellular aspects of thyroid hormones and their effects on the cardiovascular system.^{15,53,80}

Hypothyroidism, a condition characterized by decreased basal metabolic rate and decreased catecholamine effects, is a common disorder, especially in women and the elderly. Worldwide, dietary iodine deficiency remains the leading cause of

hypothyroidism. In certain parts of the world, particularly mountainous regions such as the Andes, Alps, and Himalayas, goitrous hypothyroidism remains endemic. Untreated congenital thyroid deficiency and severe dietary iodine deficiency (goitrous hypothyroidism) in young children result in profound, irreversible mental retardation and dwarfism (also referred to as cretinism). In developed nations, the iodization of table salt has essentially eliminated dietary iodine deficiency as a cause of hypothyroidism leaving autoimmune etiologies as the most common cause, although thyroid function diminishes significantly with age in many patients. Treatment of Graves disease with radioactive iodine typically results in hypothyroidism within one year. Thyroiditis (eg, postpartum, Hashimoto, DeQuervain) may cause hypothyroidism (or hyperthyroidism) as may exposure to certain xenobiotics such as amiodarone and lithium (Table 56–4). Myxedema and myxedema coma are potentially life-threatening emergencies that represent extremes of hypothyroidism. Hypothyroidism is not discussed in more detail in this chapter, except to note that treatment of hypothyroid emergencies, especially with T₃, can result in thyrotoxic signs and symptoms. Comprehensive reviews of hypothyroidism are available.⁹⁴

CLINICAL MANIFESTATION

Symptoms of toxicity from exogenous thyroid hormone resemble those of catecholamine excess. Pronounced catecholaminelike effects occur in the cardiovascular system, especially tachycardia, tachydysrhythmias (usually atrial fibrillation or flutter), thromboembolism (from both atrial fibrillation and endothelial activation), and cardiac failure.^{23,53,92} Interestingly, although hyperthyroid patients typically are anxious, restless, or agitated, patients with thyroid storm may present with a decreased level of consciousness or even coma.^{8,43,57,89,96} Hyperthermia can occur secondary to the thermogenic effects of thyroid hormones and psychomotor agitation. Hyperthermia can be extreme (ie, > 106°F {> 41°C}). The tachycardia associated with thyrotoxicosis often is disproportionately elevated when compared to the temperature elevation.

Acute Toxicity

Acute overdoses with thyroid hormone preparations most commonly occur with oral levothyroxine. Significant ingestions of levothyroxine do not typically manifest clinically until 7 to 10 days after exposure, but rarely can occur as early as 2 to 3 days postingestion.^{32,66,90} The delay of peripheral conversion of T₄ to the metabolically active T₃ and the time required to activate nuclear receptors and protein synthesis account for this clinical latency. By contrast, acute overdoses involving preparations containing T₃ may be clinically manifest within the first 12 to 24 hours after exposure.⁶²

In children, acute thyroxine overdoses almost universally are benign because the ingestions are typically unintentional and of a low dose. Most children remain asymptomatic or develop only mild symptoms. No deaths have been reported.^{20,27,45,58,63,66,100} In a series of 15 pediatric patients with unintentional ingestion, only 3 children developed mild symptoms; these mild signs and symptoms developed within 12 to 48 hours of the exposures and resolved within 24 to 60 hours.⁶⁰ Similarly, a case series that involved 41 children (ages 1–5 years) with unintentional exposures to thyroxine (estimated doses ranged from 40 to 800 µg) found mild signs and symptoms (hyperactive behavior, tachycardia, fever, vomiting, diarrhea, diaphoresis, and flushing) in only 27%. All children had good clinical outcomes. The degree of symptoms did not correlate with the amount ingested or measured serum thyroxine concentrations (measured 1–5 hours postingestion) for most cases in that series (see Diagnostic Testing).²⁷ Two other series involving 78 and 92 cases of unintentional exposures in children found that mild symptoms developed in only four and eight patients, respectively.^{66,105} A report involving an intentional exposure of 9900 µg in a 13 year-old boy treated empirically with activated charcoal, dexamethasone, and oral propranolol described only mild tremors and anxiety.⁶⁵ A 2.5 year-old boy exposed to an estimated 7600 µg and was treated with activated charcoal approximately one hour after exposure and released home. He returned approximately 24 hours with mild tachycardia and hyperthermia and decrease in appetite. No other treatments were administered. Over the next month he experienced desquamation of the palms and soles and irritability.⁴² Only three cases of severe toxicity in children are reported: one child without a history of a seizure disorder had two seizures 7 days after a levothyroxine ingestion (18,000 µg),⁵⁶ another 2.5 year-old developed thyroid storm with lethargy on postingestion day 5 (estimated ingestion was 6000 µg, no activated charcoal was administered, and he was treated with oral propranolol)⁵⁸ and another child became gravely ill for a 12-hour period (blood pressure, 120/68 mm Hg; pulse, 200 beats/minute; temperature 104°F {40°C}) 6 hours after ingesting a large amount (3.2 g, or 50 grains) of a desiccated thyroid preparation containing both T₃ and T₄.⁶¹ All of these children made a full recovery.

Exposures in adults have a wide range of toxicity. Many patients are asymptomatic or mildly symptomatic.^{29,64,77} Severe sequelae occur more frequently in adults than in children. Symptoms resemble thyrotoxicosis and, in extreme cases, thyroid storm. Hyperthermia,^{32,58,96} dysrhythmias,^{5,58,96} and severe agitation³³ are well described. Hemiparesis,⁸ muscle weakness,^{8,96} coma,^{8,58,96} respiratory failure,²⁵ sudden death,⁷ myocardial infarction,⁷ cardiac failure,⁸ focal myocarditis,⁷ rhabdomyolysis with muscle necrosis,⁸ delayed palmar desquamation (> 2 weeks postingestion),^{8,96} and hematuria³² are also described. Because patients are expected to be asymptomatic shortly after ingestion and laboratory tests correlate

poorly with the degree of symptoms, clinical and laboratory findings early in the course of the ingestion are not reliable indicators of which patients will become ill (see Diagnostic Testing).

Chronic Toxicity

Following chronic excessive thyroid hormone ingestion, patients may present with thyrotoxicosis or have a more subtle and insidious presentation. Classically, chronic ingestion of excess thyroid hormone occurs in patients with hypothyroidism, psychiatric disorders, and eating disorders. Persons who ingest thyroid hormones chronically may develop significant weight loss, anxiety, and accelerated osteoporosis.⁷⁶ More severe manifestations, such as cardiac dysrhythmias, tachycardia, cardiac failure, and psychosis, also occur. As in patients with hyperthyroidism, intercurrent illness and physiologic stressors can trigger thyroid storm in these patients.

Numerous miniepidemics of hyperthyroidism and thyrotoxicosis have resulted from the consumption of ground meat containing neck muscle contaminated with thyroid gland.^{18,38,51} Investigators in one of these epidemics had three volunteers consume a single large portion of “well-cooked” epidemic implicated ground beef that previously had been frozen. Although all volunteers remained asymptomatic, the mean serum peak T₄ (8–12 hours postingestion) was elevated approximately 15 µg/dL, and TSH remained undetectable for 4 to 17 days.³⁸ The practice of gullet trimming (using larynx muscles for beef) that led to these outbreaks has since been prohibited in US slaughter houses. However, the risk for sporadic cases remains, especially when laryngeal muscles are used or when farmers and hunters butcher their own meat.⁸¹ Until an exogenous source of thyroid hormone is suspected or identified, such patients often are misdiagnosed with painless thyroiditis or thyrotoxicosis factitia.

Thyrotoxicosis factitia is a symptomatic disorder that mimics physiologic disease. It occurs with intentional chronic ingestion of exogenous thyroid hormone. The pattern of ingestion typically is surreptitious and maladaptive. Patients frequently have comorbid psychiatric disorders, such as Munchausen syndrome or eating disorders, or are taking thyroid hormone for secondary gain.³⁴ Patients with thyrotoxicosis factitia tend to be either health care professionals with access to medications or prescriptions or persons with access to thyroid medications being taken by relatives, friends, or pets.^{28,34,70}

In recent years, thyroid hormones have gained popularity among dieters and athletes who use the hormones as weight loss aids and as stimulants. Severe consequences can occur. Sudden death was reported in three patients suspected of chronic ingestion of thyroid hormone for weight loss and energy enhancement (for which there is a black box warning).⁷ In 2002, the heavily promoted Singaporean diet pill (Slim 10) was linked to hepatotoxicity and hyperthyroidism in numerous patients.³⁸ Investigators found the proprietary herbal preparation was adulterated with significant amounts of the undeclared ingredients T₄, T₃ (from thyroid gland extract), and fenfluramine (a drug banned by the US Food and Drug Administration). The medication was promptly withdrawn and the manufacturers convicted under the Singapore Poisons Act.³⁷ Similar cases were reported from Hong Kong, Japan, and France following ingestion of “slimming pills” containing animal thyroid extract.^{48,78,85} Unfortunately, thyroid hormone-containing supplements are promoted and are readily available to the general public without a prescription through the Internet and in stores selling nutritional supplements (Chap. 45).⁹⁵

DIAGNOSTIC TESTING

Traditionally, thyroid testing involved combinations of measurement of total T₄ and some measurement of hormone binding (T₃ uptake). Free T₄ and T₃ also can be measured by equilibrium dialysis (free T₄), analogue assays (ie, competitive analogs of either free T₃ or free T₄ that competitively bind for spaces on the serum-binding proteins), and antibody capture assays (ie, sequential assays that capture a representative portion of the free fraction of thyroid hormone). Assessment of pituitary production of TSH has improved greatly in recent years. Since supersensitive TSH assays can readily detect suppression of TSH production, TSH is now the primary test for screening thyroid function. Suppressed or elevated concentrations of TSH can be reflexively followed up with a free T₄ assay and, if necessary, a free T₃ assay (Table 56–5).

TABLE 56–5. Diagnostic Tests for Thyroid Hormone and Thyroid Function

<i>Diagnostic Test</i>	<i>Normal Values^a</i>	<i>Comments</i>
TSH	0.5–4.7 IU/mL	Available assays with respective detection limits: First-generation 1.0 IU/L Second-generation 0.1 IU/L Third-generation 0.01 IU/L
Total T ₄ by RIA	4.5–12.5 µg/dL (58–161 nmol/L)	↑ In pregnancy, estrogens, oral contraceptives
Total T ₃ by RIA	80–200 ng/dL (0.9–2.8 nmol/L)	↑ In pregnancy, estrogens, oral contraceptives
Free T ₄	8–18 pg/mL (10–23 pmol/L)	↑ In hyperthyroidism, exogenous thyroxine ingestion
Free T ₃	2.3–4.2 pg/mL (3.5–6.5 pmol/L)	↑ In hyperthyroidism, exogenous thyroid hormone (T ₃ or T ₄)

^aInterlaboratory and interassay variations may occur.

RIA = radioimmunoassay; TSH = thyroid-stimulating hormone.

The clinical manifestations of thyrotoxicosis and thyroid storm are well known to occur at normal, low, moderate, and high concentrations of T₃ and T₄.¹⁰ This lack of correlation between symptoms and serum concentrations is also true for exogenous thyroid hormone ingestion.^{8,27,32,38,56,62,66,77,105} In a large case series of children with unintentional exposures of thyroxine estimated to be between 40 and 800 µg, serum T₄ concentrations were drawn in 11 (1–5 hours postingestion). Serum T₄ concentrations were normal in five of these children and were slightly elevated in six (mean, 16 µg/dL). In this series, one infant who was estimated to have ingested 4500 µg had a significantly higher concentration (55 µg/dL at 4.5 hours) but developed only a transient episode of diaphoresis and a “staring spell” 7 days postingestion. Another child who ingested an estimated 4200 µg had a concentration of 12 µg/dL and developed significant tachycardia and hyperthermia.²⁸ A young child (estimated ingestion 18,000 µg levothyroxine) had a serum T₄ concentration of 117 µg/dL 8 hours postingestion and 38 µg/dL on day 7, when he was symptomatic.⁵⁶ Similar trends were observed for both T₃ and T₄ in three other massive levothyroxine ingestions in children.^{4,65,68} In an adult with a massive ingestion of levothyroxine (720,000 µg), serum T₄ concentrations were higher than 30 µg/dL and free T₄ was above 13 ng/dL (normal range, 0.7–1.86 ng/dL). In this case, TSH remained undetectable until postingestion day 32.³² Overall, the observed symptoms following thyroid hormone ingestion correlate poorly with the amount ingested or with measured serum T₄ concentrations. Prolonged suppression of TSH is common following ingestion of excess thyroid hormone.

Routine analysis of laboratory thyroid function tests in the setting of acute thyroid hormone overdose likely will not affect management. Analysis of thyroid hormone concentrations is indicated only if confirmation of a suspected ingestion is desired and in massive ingestions when early and severe symptoms may occur. Suppression of TSH and elevated thyroid hormone concentrations with a low serum thyroglobulin concentration may help to differentiate between thyrotoxicosis factitia and true endogenous disease.⁷⁰

MANAGEMENT

Based on the existing literature, conservative management is adequate in most cases of acute unintentional thyroxine ingestions in both adults and children. Most children with acute overdose are managed with home observation and follow-up appointments. In cases where the acute thyroxine dose is estimated to be greater than 4000 µg, patient follow-up by regular telephone contact for 10 days is suggested.²⁷ Historically, most children with unintentional ingestions have been treated with GI decontamination with activated charcoal and/or syrup of ipecac, or by gastric lavage,^{27,45,56,58,66,63} but these procedures (especially emesis and lavage) are probably unnecessary. Based on two large series of unintentional exposures in children in which no toxicity was observed in the vast majority of cases, clinically significant toxicity is not expected with estimated ingestions less than 4000 µg.^{27,107} Because children almost uniformly develop no more than minor symptoms, activated charcoal administration should be considered only if the ingestion is greater than 5000 µg of thyroxine. Aspiration risks are minimal in awake, alert children who are able to protect their airways and take activated charcoal

orally, without nasogastric tube placement.^{58,105} By extension, adults with acute ingestions greater than 5000 µg of thyroxine also should be treated with activated charcoal. Except in early presentations with massive thyroxine ingestions (>10,000–50,000 µg) in suicidal adults or ingestions of preparations containing large amounts of T₃, gastric emptying procedures such as orogastric lavage are unwarranted.^{8,32} Similarly, patients with massive ingestions (>10,000–50,000 µg) or ingestion of T₃-containing products should be admitted for observation in anticipation of developing significant symptoms.^{8,32,56,61}

Treatment should be based on the development of toxicity and should include rehydration, airway protection, and control of sympathomimetic symptoms, mental status alterations, and hyperpyrexia. β-Adrenergic antagonism with propranolol has been used for sympathomimetic symptoms in numerous cases.^{24,45,56,66,77,100} Empiric treatment with β-adrenergic antagonists is not recommended. Treatment is only indicated for clinically significant tachycardia, dysrhythmias, and other signs and symptoms of catecholaminelike excess.²⁴

Agitation

If sedation is required, parenteral benzodiazepines and barbiturates are recommended. Rapid-acting benzodiazepines, such as midazolam, or diazepam should be used to control severely agitated or symptomatic patients. Phenobarbital should be considered as an additional treatment in intubated patients or as an adjunct in patients requiring sedation because it offers the added theoretical benefit of inducing enhanced hepatic elimination of thyroxine (Table 56–2). Because of the general risks of sedation and the lack of evidence regarding the clinical use of enhanced hepatic elimination from phenobarbital, sedation with phenobarbital for the sole purpose of enhanced elimination is not indicated. Sedation with antipsychotics such as haloperidol and droperidol should be avoided because their significant anticholinergic properties can exacerbate thyrotoxic symptoms. In addition, the tendency for this class of drugs to prolong the QT interval and predispose to malignant dysrhythmias is of concern in the already catecholaminergic patient. Antipsychotics should be reserved for medically stable patients with psychiatric behavioral disturbances.

Catecholaminelike Excess and Cardiovascular Symptoms

The principal therapeutic role of β-adrenergic antagonists in hyperthyroidism is for their sympatholytic effects.⁷⁶ In addition, propranolol inhibits 5'-deiodinase, thereby decreasing peripheral conversion of T₄ to T₃ (Table 56–2). The clinical significance of decreased peripheral conversion in the setting of overdose is unknown. Propranolol is the most frequently used β-adrenergic antagonist in thyrotoxic patients,^{27,45,56,66,77,100} and should be used parenterally when signs and symptoms are severe or when rapid control of heart rate is required. Starting doses of 1 to 2 mg IV propranolol every 10 to 15 minutes are recommended. Higher doses have been reported in massive thyroxine overdose, where a patient received 23 mg propranolol IV over one hour on initial presentation, then required an average of 30 mg/day IV for 5 more days.³² Oral propranolol can be used for persistent symptoms in patients who are both hemodynamically and medically stable and are not acutely agitated. High oral doses in the range of 20 to 120 mg every 6 hours may be required. Other β-adrenergic antagonists, such as atenolol, nadolol, metoprolol, and esmolol, can be used for symptoms of adrenergic excess, but these may not inhibit the peripheral conversion of T₄ to T₃. Continuous electrocardiographic and hemodynamic monitoring are indicated when parenteral β-adrenergic antagonists are used or when patients require hospitalization.

When nonspecific β-adrenergic antagonists are contraindicated, as in patients with asthma or severe congestive heart failure, β₁-selective antagonists (such as atenolol or metoprolol) or calcium channel blockers can be used as an alternative. Among calcium channel blockers, diltiazem is the most studied for the management of thyrotoxicosis.^{68,88} A double-blind, crossover trial that compared propranolol to diltiazem for thyrotoxic symptoms found that diltiazem was well tolerated and appeared as effective as propranolol.⁷³ Another study successfully used diltiazem as the sole treatment of cardiovascular signs and symptoms in 11 thyrotoxic patients.⁹³ Oral doses of 60 to 120 mg diltiazem three to four times daily or 5 to 10 mg/h parenterally have been used.^{73,93} A possible explanation for the efficacy of calcium channel blockers in thyrotoxicosis is that thyroid hormone enhances Ca²⁺ uptake by L-type voltage-gated Ca²⁺ channels, accelerates Ca²⁺ entry into the sarcoplasmic reticulum, and increases cellular Ca²⁺ storage capacity.^{49,50,74,97} The net effect of these changes is increased inotropy and chronotropy. Calcium channel blockers, particularly diltiazem and verapamil, attenuate these effects. However, the use of parenteral β-adrenergic antagonists in combination with parenteral calcium channel blockers is contraindicated because of the risk for profound hypotension and cardiovascular collapse.⁷⁹

Hyperthermia

Antipyretics are not recommended for hyperthermia associated with catecholamine excess and thyrotoxic condition. Aspirin, particularly high doses (1.5–3 g/day), should be avoided because it carries a theoretical risk of increased thyrotoxicity from displacement of T₃ and T₄ from thyroxine-binding globulin (Table 56–2). Note, however, that hyperthermia, especially extreme hyperthermia (> 106°F {> 41°C}), is most likely secondary to psychomotor agitation and excess heat production from the hypermetabolic, catecholaminergic, and thyrotoxic conditions. Extreme hyperthermia

should be considered a medical emergency and should be rapidly and aggressively treated with active external cooling with ice baths and with β -adrenergic antagonism, sedation with benzodiazepines and/or barbiturates, and endotracheal intubation with paralysis if necessary (Chap. 30).

Other Therapies

Bile acid sequestrants, such as cholestyramine and colestipol, and aluminum hydroxide (antacids) and sucralfate bind to exogenous T_4 and decrease GI absorption (Table 56–2). Because the evidence supporting their effectiveness is poor, they are not routinely recommended for thyroid hormone overdose.⁵⁸

Oral iodine containing contrast media is known to decrease peripheral conversion of T_4 to T_3 . Doses of 1 to 2.5 mg/kg iodine PO daily are routinely used for thyroid storm (oral drops commonly referred to as saturated solution potassium iodide {KI}). Thioamides, such as propylthiouracil (PTU) and methimazole, and the corticosteroids are thyroid gland inhibitors that are used for treatment of non drug related hyperthyroidism. In addition, thioamides inhibit peripheral conversion of T_4 to T_3 . Evidence from limited case reports suggests poor efficacy of both thioamides and corticosteroids in acute overdose^{8,25,58} (see Thioamides and Iodides).

Although use of antithyroid drugs such as PTU, corticosteroids, and iodine contrast media in thyroxine overdose has theoretical benefits, these xenobiotics are not validated, potentially harmful, and unlikely to offer additional benefit, or be superior to conventional therapy with activated charcoal, β -adrenergic antagonism, and sedation. These treatments are not recommended as adjunctive therapies for treatment of exogenous thyroxine overdose.

Extracorporeal Drug Removal

Extracorporeal drug removal procedures, such as plasma exchange or plasmapheresis, exchange transfusion (in children), and charcoal hemoperfusion, have been used in extreme cases of thyroid hormone overdose and thyroid storm.^{1,8,9,25,39,46,54,58,62,71,75,102,106} Overall, results regarding improvement of clinical condition and plasma clearances of thyroid hormones with these methods are conflicting. The largest series of acute ingestions involved six patients who became critically ill after massive thyroxine ingestions of prescribed capsules containing a 1000-fold concentration excess of thyroxine (dose range, 50,000–125,000 $\mu\text{g/day}$ for 2–12 days). Charcoal hemoperfusion and plasmapheresis were used in all patients. Plasmapheresis was found to be more effective than hemoperfusion in the extraction of thyroxine. The authors suggest this intervention may shorten the duration of thyrotoxicosis. Rebound elevations in plasma concentrations occurred 24 hours later, suggesting redistribution between extravascular and intravascular compartments.⁸ This redistribution is expected given the large volume of distribution for thyroid hormones (Table 56–1). There may be a role for early plasmapheresis in the exceptional situation of a known massive ingestion of thyroid hormone. Because the outcomes from most ingestions of thyroid hormone will be favorable with good supportive care, sedation, and β -adrenergic antagonism, the risks of plasmapheresis should be evaluated on a case by case basis after consultation with a medical toxicologist.

XENOBIOTICS WITH ANTITHYROID EFFECTS

Thioamides

Antithyroid drugs are used to decrease the amount of thyroid hormone in hyperthyroidism, most commonly in Graves disease. Thioamides are a group of chemicals with the basic structure of R-SCN. Methimazole and propylthiouracil (PTU) are the two principal thioamides used for treatment of hyperthyroidism. Carbimazole, which is bioactivated methimazole, is available in Europe and China. Methimazole and PTU both inhibit the activity of thyroid peroxidase in the thyroid gland.¹⁰³ PTU has the added effect of inactivating 5'-deiodinase, which decreases the peripheral conversion of T_4 to the metabolically more active T_3 .^{19,60} Because thioamides act primarily by decreasing thyroid hormone synthesis (vs release), a lag time of 3 to 4 weeks may occur before T_4 is depleted. The oral bioavailability of PTU is 50% to 80%. It is rapidly absorbed from the gastrointestinal tract and may undergo first-pass effect by the liver. Although its plasma half-life is only 1.5 hours, its effects are long lasting because of accumulation in the thyroid gland. PTU is inactivated by glucuronidation and is renally eliminated. Methimazole is completely absorbed, is concentrated in the thyroid, and is more slowly eliminated than PTU (48 vs 24 hours). Doses of PTU are in the range of 100 mg orally every 6 to 8 hours. Methimazole can be given 30 mg PO daily. Although PTU is 10 times less potent than methimazole, it is more commonly used. The indications for its use are mild-to-moderate hyperthyroidism.

The two thioamides traverse the placenta (methimazole more than PTU) and should not be administered during pregnancy. However, they are minimally secreted in breast milk. Adverse effects occur in 3% to 12% of patients taking thioamides. The most common adverse effect is a maculopapular pruritic rash. Methimazole, PTU, and, to a lesser extent, carbimazole can cause immune-mediated, dose-related, and age-related agranulocytosis and neutrophil dyscrasias.^{61,66,72,83}

This potentially life-threatening adverse effect can be treated by administration of granulocyte colony-stimulating factor.⁵ Premature withdrawal of thioamides can lead to rebound symptoms and thyrotoxic states.⁵⁵

There are little data regarding overdose with thioamides. A 12-year-old girl with a previous thyroidectomy, who was estimated to have ingested 5000 to 13,000 mg PTU, developed only a transient decreased T₃ concentration and elevated alkaline phosphatase concentration (7350 mU/mL).⁴⁴ The absence of a functioning thyroid gland may have contributed to the benign course in this patient. No other serious sequelae have been associated with acute overdose of thioamides.

Iodides

Prior to the development of thioamides, iodide salt was the principal treatment for hyperthyroidism. Iodides decrease thyroid hormone concentrations by inhibiting formation and release. In thyroid storm, high-dose iodides (>2 g/day) decrease thyroid hormone release and produce substantial improvements by 2 to 7 days. Common sources of iodides include calcium iodide, sodium iodide, KI (pharmaceutical preparations, iopanoic acid, Lugol solution {iodine + KI solution}, oral drops {saturated solution KI}), and methyl iodide (industrial preparations).

The adverse reaction to chronic ingestion of small or excessive amounts of iodide salts, termed iodism, is characterized by cutaneous rash, laryngitis, bronchitis, esophagitis, conjunctivitis, drug fever, metallic taste, “mumps,” salivation, headache, and bleeding diathesis. Immune-mediated hypersensitivity symptoms consisting of urticaria, angioedema, eosinophilia, vasculitis, arthralgia, lymphadenitis, and, rarely, anaphylactoid reactions may occur. Chronic iodide therapy has produced goiters, hypothyroidism, and rarely hyperthyroidism. As much as 10 g sodium iodide has been administered IV without development of signs or symptoms of toxicity.

Iodide (I⁻), unlike iodine (I₂), is not a caustic (Chaps. 104 and 106). KI is added to table salt to form iodized salt for prevention of goiter. It also is used prophylactically after exposure to large amounts of nuclear fallout to prevent uptake of radioactive iodine into the thyroid gland (Antidotes in Depth: A43) and is the most commonly used iodide for thyroid suppression in hyperthyroidism. Iodide mumps is a well-described but rare disorder characterized by severe sialadenitis (or parotitis),⁴⁷ allergic vasculitis, and/or conjunctivitis following administration of ionic and nonionic iodine-containing contrast media and oral iodide salts (Table 56–4).^{12,13,45} Although the mechanism remains unclear, it is thought to be idiosyncratic or secondary to iodide accumulation and subsequent inflammation in the ductal systems of the salivary gland. Clinical effects tend to occur within 12 hours and resolve spontaneously within 48 to 72 hours.¹²

Iodides should be avoided in pregnancy because they readily cross the placenta. Severe fetal complications, such as cretinism and death from respiratory failure secondary to obstructive goiter, are reported.^{21,40,67} Iodide salts are adsorbed to activated charcoal.

Methyl iodide is a methylating agent used in the chemical and pharmaceutical industry, as a reagent in microscopy, as a catalyst in production of organic lead compounds, as an etching agent, as a component in fire extinguishers, and formerly as a soil fumigant. Methyl iodide toxicity from inhalation is associated with early pulmonary congestion, lethargy, and acute kidney injury. It also is associated with delayed cerebellar degeneration, multifocal neuropathies (cranial nerve and spinal), parkinsonian symptoms, and late and persistent psychiatric symptoms (months to years).^{2,41} Chronic repeated overexposures have led to misdiagnoses such as multiple sclerosis. The toxicity is similar to that of the monohalomethanes (Chap. 111).

SUMMARY

- Despite the prevalence of thyroid disorders in the general population and the widespread use of levothyroxine, remarkably little morbidity and mortality associated with overdose from thyroid hormones is reported.
- Most children with unintentional exposures can be observed as outpatients for 5 to 10 days.
- Acute intentional ingestions in adults may result in severe symptoms that require management in an intensive care unit.
- Supportive care with sedation, cooling measures, and β -adrenergic antagonism are adequate in most cases.
- Chronic ingestions may produce more severe symptoms as they may present more insidiously or are complicated by thyroid storm.
- Clinicians should suspect exogenous thyroid hormone exposure in patients with thyrotoxicosis and suppressed TSH concentrations.

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D. ANTIMICROBIALS

57 ANTIBACTERIALS, ANTIFUNGALS, AND ANTIVIRALS

Christine M. Stork

HISTORY AND EPIDEMIOLOGY

Antimicrobials, including antibacterials, antifungals, and antivirals, have significantly improved the clinical care of infected patients since the introduction of penicillin in the 1940s. The development of antimicrobial-resistant strains of these pathogens has continually expanded the number of antimicrobials necessary, and this has increased the overall potential for toxicity after use. Fortunately, toxicity due to acute overdose is limited and chronic therapeutic doses are safe in the majority of patients.

Most adverse effects related to antimicrobials occur as a result of iatrogenic complications rather than intentional overdose. The diverse origins of these complications include dose, route and decision errors, allergic reactions, adverse effects, and interactions. Prevention, in the form of process improvements and information regarding populations at risk for adverse effects, is continually required to minimize these untoward events. Dosing errors are prominent in neonates and infants, necessitating care and constant diligence on the part of health care professionals.

Antimicrobials are more commonly associated with allergic reactions than are other xenobiotics. The reason for this is unclear, but it may be a result of their high frequency of use, repeated intermittent prescriptive use, or environmental contamination. A complete allergy history is essential to minimize these adverse events in patients being considered for antimicrobial therapy.

Many adverse effects attributed to antimicrobials are difficult to predict even when given patient and population specific parameters. In some cases, an excipient is responsible for the adverse effect, as recognized with the adverse effects found in patients after the use of procaine penicillin G. Antimicrobials are involved in many common and severe xenobiotic interactions, primarily through the inhibition of metabolic enzymes. Patients being considered for antimicrobial therapy should be carefully assessed for the use of concomitant therapies, both prescription and nonprescription which may be pharmacokinetically or pharmacodynamically affected by the chosen antimicrobial.

PHARMACOLOGY AND TOXICOLOGY

Antimicrobial pharmacology is aimed at the destruction of microorganisms through the inhibition of cell cycle reproduction or the altering of a critical function within a microorganism. [Table 57–1](#) lists antimicrobials and their associated mechanisms of activity, toxicologic effects, and related toxicologic mechanisms. Often the mechanisms for toxicologic effects following acute overdose differ from the therapeutic mechanisms.

TABLE 57–1. Antimicrobial Pharmacology and Adverse Effects

Antimicrobial	Antimicrobial Mechanism of Action	Acute Overdose	Chronic Administration
Antibacterial			
Aminoglycosides	Inhibit 30s ribosomal subunit	Neuromuscular blockade—inhibit the release of acetylcholine from presynaptic nerve terminals and acts as an antagonist at acetylcholine receptors	Nephrotoxicity/ototoxicity—form an iron complex that inhibits mitochondrial respiration and causes lipid peroxidation
Penicillins, cephalosporins, and other β -lactams	Inhibit cell wall mucopeptide synthesis	Seizures—agonist at picrotoxin-binding site, causing GABA antagonism	Hypersensitivity—immune
Chloramphenicol	Inhibits 50s ribosomal subunit and inhibits protein synthesis in rapidly dividing cells	Cardiovascular collapse	"Gray baby syndrome" Same as mechanism of action
Fluoroquinolones	Inhibit DNA topoisomerase and DNA gyrase	Same as mechanism of action; bind to cations (Mg^{++}), seizures	Not entirely known; bind to cations (Mg^{++}); tendon rupture, hyperglycemia or hypoglycemia
Linezolid	Inhibits bacterial protein synthesis through inhibition of N-formylmethionyl-t RNA	None clinically relevant	MAOI activity; vasopressor response to tyramine; serotonin toxicity with SSRI and possibly meperidine
Macrolides, lincosamides, and ketolides	Inhibit 50s ribosomal subunit in multiplying cells	Prolong QT interval; blocks delayed rectifier potassium channel	Not entirely known; cytotoxic effect; exacerbation of myasthenia gravis
Nitrofurantoin	Bacterial enzymatic inhibitor	Gastritis	Dermatologic, hematologic, pancreatitis, parotitis, hepatitis, crystalluria, pulmonary fibrosis
Sulfonamides	Inhibit paraaminobenzoic acid and/or paraamino glutamic acid in the synthesis of folic acid	None clinically relevant	Hypersensitivity—metabolite acts as hapten leading to hemolysis/methemoglobinemia—exposure to UVB causes free radical formation
Tetracycline	Inhibits 30s and 50s ribosomal subunits; binds to aminacyl transfer RNA	None clinically relevant	Photosensitivity reaction
Vancomycin	Inhibits glycopeptidase polymerase in cell wall synthesis	"Red man syndrome"—anaphylactoid	Unknown
Antifungal			
Amphotericin B	Binds with ergosterol on cytoplasmic membrane to create pores to facilitate organelle leak	Same as mechanism of action	Nephrotoxicity—vehicle deoxycholate may be involved; nephrocalcinosis
Triazoles, imidazoles, and thiazoles	Increase permeability of cell membranes	None clinically relevant	None clinically relevant ?CYP inhibition

GABA = γ -aminobutyric acid; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; UVB = ultraviolet light.

ANTIBACTERIALS

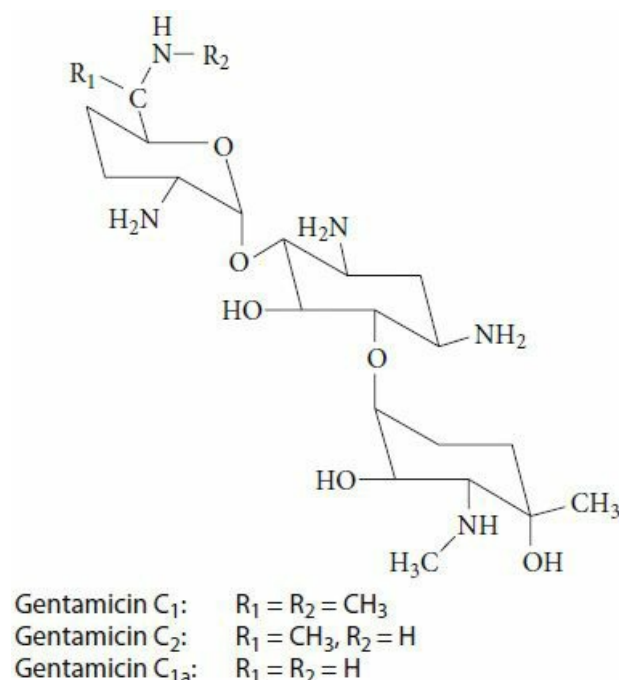
Aminoglycosides

Aminoglycoside that are in current use in the United States include amikacin, gentamicin, kanamycin, neomycin, paromomycin, streptomycin, and tobramycin.

Because aminoglycosides are only available in parenteral, topical, and ophthalmic forms, overdoses are almost exclusively the result of dosing errors. Fortunately, overdoses are rarely life threatening, and most patients can be safely managed with minimal intervention.^{24,121} The adverse effects of aminoglycosides are generally class based, although subtle differences may exist in the potency with which the adverse effects occur (Table 57–2).

TABLE 57–2. Predominant Manifestations of Aminoglycoside Toxicity

<i>Cochlear</i>	<i>Cochlear and Vestibular</i>	<i>Vestibular</i>	<i>Renal</i>
Kanamycin	Amikacin	Gentamicin	Amikacin
Neomycin	Tobramycin	Streptomycin	Gentamicin
			Kanamycin
			Neomycin
			Streptomycin
			Tobramycin



Large intravenous doses of aminoglycosides are both sufficiently safe and effective for use in single daily doses.⁶ Rarely, acute aminoglycoside overdose results in nephrotoxicity, ototoxicity, or vestibular toxicity.^{117,141} In one reported case, postmortem analysis confirmed complete loss of hair cells in the inner and outer cochlear (Chap. 26).

Aminoglycosides can exacerbate concomitant neuromuscular blockade, particularly at times corresponding to high peak serum aminoglycoside concentrations (Chap. 69).¹⁷¹ This is caused by inhibiting presynaptic calcium channels, thereby inhibiting the release of acetylcholine from presynaptic nerve terminals. Risk factors for enhanced neuromuscular blockade include patients with abnormal neuromuscular junction function, such as those with myasthenia gravis and botulism.

Adverse Effects Associated with Therapeutic Use. Adverse effects, including nephrotoxicity and ototoxicity, correlate more closely with elevated trough serum concentrations than with elevated peak concentrations.^{108,149} Less common adverse effects associated with chronic use include electrolyte abnormalities, allergic reactions, hepatotoxicity, anemia, granulocytopenia, thrombocytopenia, eosinophilia, retinal toxicity, reproductive dysfunction, tetany, and psychosis.^{55,112,126,217,233} When aminoglycosides are administered at high doses or during once-daily dosing, sepsislike chills and malaise may occur that can be the result of excipients delivered during the infusion.⁴⁶

Nephrotoxicity. The mechanism of nephrotoxicity and ototoxicity is incompletely understood, but appears to include the formation of reactive oxygen species in the presence of iron. Mitochondrial respiration is inhibited, lipid peroxidation occurs, and stimulation of glutamate activated N-methyl-D-aspartate (NMDA) receptors may play a role.^{96,243} The incidence of nephrotoxicity with aminoglycoside therapy is estimated at 5% to 10%.⁹ Although the aminoglycosides are almost completely excreted prior to biotransformation in the kidney, a small fraction of filtered aminoglycoside is transported by absorptive endocytosis across the apical membrane of proximal tubular cells where it becomes sequestered within lysosomes. The aminoglycoside then binds to and destroys phospholipids contained on brush border membranes in the proximal renal tubule.⁹

When this happens, acute tubular necrosis occurs after 7 to 10 days of standard-dose therapy. Laboratory abnormalities include granular casts, proteinuria, elevated urinary sodium, and increased fractional excretion of sodium. Usually acute kidney injury (AKI) that results is reversible; however, irreversible toxicity has been reported. Functionally, the injury occurs days prior to elevations in serum creatinine concentration, and for this reason a delay in diagnosis is common.²⁰⁴ Risk factors for the development of nephrotoxicity include increasing age, chronic kidney disease (CKD), female sex, previous aminoglycoside therapy, liver dysfunction, large total dose, long duration of therapy, frequent doses, high trough

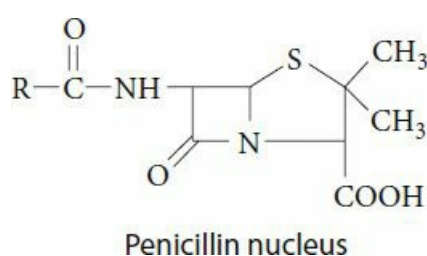
concentrations, the presence of other nephrotoxic xenobiotics, and shock.^{9,152} Because the uptake of aminoglycosides into organs is saturable, appropriate once-daily high-dose regimens are less problematic than several lesser doses given in a single day.

Ototoxicity. Ototoxicity can occur after acute or prolonged exposure to aminoglycosides.²⁰⁶ Both cochlear and vestibular dysfunction occur and injury is thought to result from prolonged contact time with sensory hair cells after bioaccumulation in the endolymph and perilymph spaces.³ Vestibular toxicity, caused by destruction of sensory receptor portions of the inner ear or destruction of hair cells in the utricle and saccule, occurs in 0.4% to 10% of patients. Symptoms include vertigo or tinnitus. Table 57–2 details the relative characteristic toxicity of various aminoglycosides.

Full-tone audiometric testing may first show high-frequency hearing loss, which may subsequently progress. Given the inability of cochlear hair cells to regenerate, all hearing loss that develops is permanent. After early diagnosis of vestibular dysfunction, patients may improve after discontinuation of the xenobiotic. Simultaneous administration of other ototoxic xenobiotics enhances the ototoxicity of aminoglycosides (Chap. 26).

Withdrawal of the offending xenobiotic is indicated in patients with either nephrotoxicity or ototoxicity caused by an aminoglycoside antibiotic. Supportive care is the mainstay of therapy. Experimental treatments in animal models include the use of deferoxamine, glutathione, and NMDA-receptor antagonists in an attempt to chelate and or detoxify a reactive intermediate.^{165,221} The antibiotic ticarcillin forms a renally eliminated complex with aminoglycosides to provide protection against tobramycin-induced AKI. In humans, ticarcillin removes 50% more tobramycin in 48 hours than in two sessions of hemodialysis.⁷² However, ticarcillin therapy is generally of limited value because in most instances the serum concentration of the aminoglycoside has decreased before any therapeutic measures can be used.

Penicillins



Penicillin is derived from the fungus *Penicillium* and many semisynthetic derivatives have clinical utility. Penicillins, as a class, contain a 6-aminopenicillanic acid nucleus, composed of a β -lactam ring fused to a five-member thiazolidine ring. Classic available penicillins include penicillin G, penicillin V, and the antistaphylococcal penicillins (nafcillin, oxacillin, cloxacillin, and dicloxacillin). Penicillins developed to enhance the spectrum of antibiotic efficacy, particularly against Gram-negative bacilli, include the second generation penicillins (ampicillin, amoxicillin, bacampicillin, and mezlocillin), third generation penicillins (carbenicillin and ticarcillin), and fourth-generation penicillins (piperacillin). Table 57–1 lists the pharmacologic mechanism of penicillins.

Acute oral overdoses of penicillin-containing xenobiotics are usually not life threatening.²²⁶ The most frequent complaints following acute overdose are nausea, vomiting, and diarrhea.

Seizures occur in persons given large intravenous or cerebral intraventricular doses of penicillins.^{113,123,147} More than 50 million units intravenously in less than 8 hours are generally required to produce seizures in adults.²⁰⁹ Penicillin induced seizures appear to be mediated through the picrotoxin-binding site on the neuronal chloride channel near the γ -aminobutyric acid (GABA) binding site (Chap. 14). Binding of the penicillin produces an allosteric change in the receptor that prevents GABA from binding, resulting in a relative lack of inhibitory tone.⁵⁸ Penicillin analogs (such as imipenem) also cause seizures, presumably through a similar mechanism.

The treatment of patients who develop penicillin induced seizures include GABA agonists such as the benzodiazepines. Patients who receive an intraventricular overdose may require cerebrospinal fluid exchange or perfusion to attenuate seizure activity (Special Considerations: SC3).¹²³ There are rare reports of hyperkalemia resulting in electrocardiographic abnormalities after the rapid intravenous infusion of potassium penicillin G to patients with CKD and amoxicillin overdose resulting in frank hematuria and AKI.^{32,85}

Adverse Effects Associated with Therapeutic Use. Penicillins are associated with a myriad of adverse effects after therapeutic use, the most common of which are allergic reactions. Penicillins are commonly implicated in immune-related reactions such as bone marrow suppression, cholestasis, hemolysis, interstitial nephritis, and vasculitis.^{7,83,103,220} Rare effects include pemphigus after penicillin use and corneal damage after the use of methicillin.^{20,250}

Acute Allergy. Penicillins are the pharmaceuticals most commonly implicated in the development of acute anaphylactic reactions. Anaphylactic reactions are severe, life-threatening, immune-mediated (immunoglobulin E {IgE}) reactions involving multiple organ systems that typically occur immediately after exposure. Table 57–3 lists the classifications of

anaphylactic reactions. Anaphylaxis to penicillin typically occurs after IgE antibody formation, which requires prior exposure. Life-threatening clinical manifestations include angioedema, tongue and airway edema, bronchospasm, bronchorrhea, dysrhythmias, cardiovascular collapse, and cardiac arrest.⁷³ The pathophysiology of systemic anaphylaxis is complex and involves multiple pathways. IgE antibodies are cross linked on the surface of mast cells and basophils, resulting in local and systemic release of preformed mediators of anaphylactic response, including leukotrienes C₄ and D₄, histamine, eosinophilic chemotactic factor, and other vasoactive substances, such as bradykinin, kallikrein, prostaglandin D₂, and platelet-activating factor (Fig. 57–1).

TABLE 57–3. Classification of Anaphylactic Reactions

Grade	Description
I	Large local contiguous reaction (>15 cm)
II	Pruritus (urticaria) generalized
III	Asthma, angioedema, nausea, vomiting
IV	Airway (asthma, lingual edema, dysphagia, respiratory distress, laryngeal edema) Cardiovascular (hypotension, cardiovascular collapse)

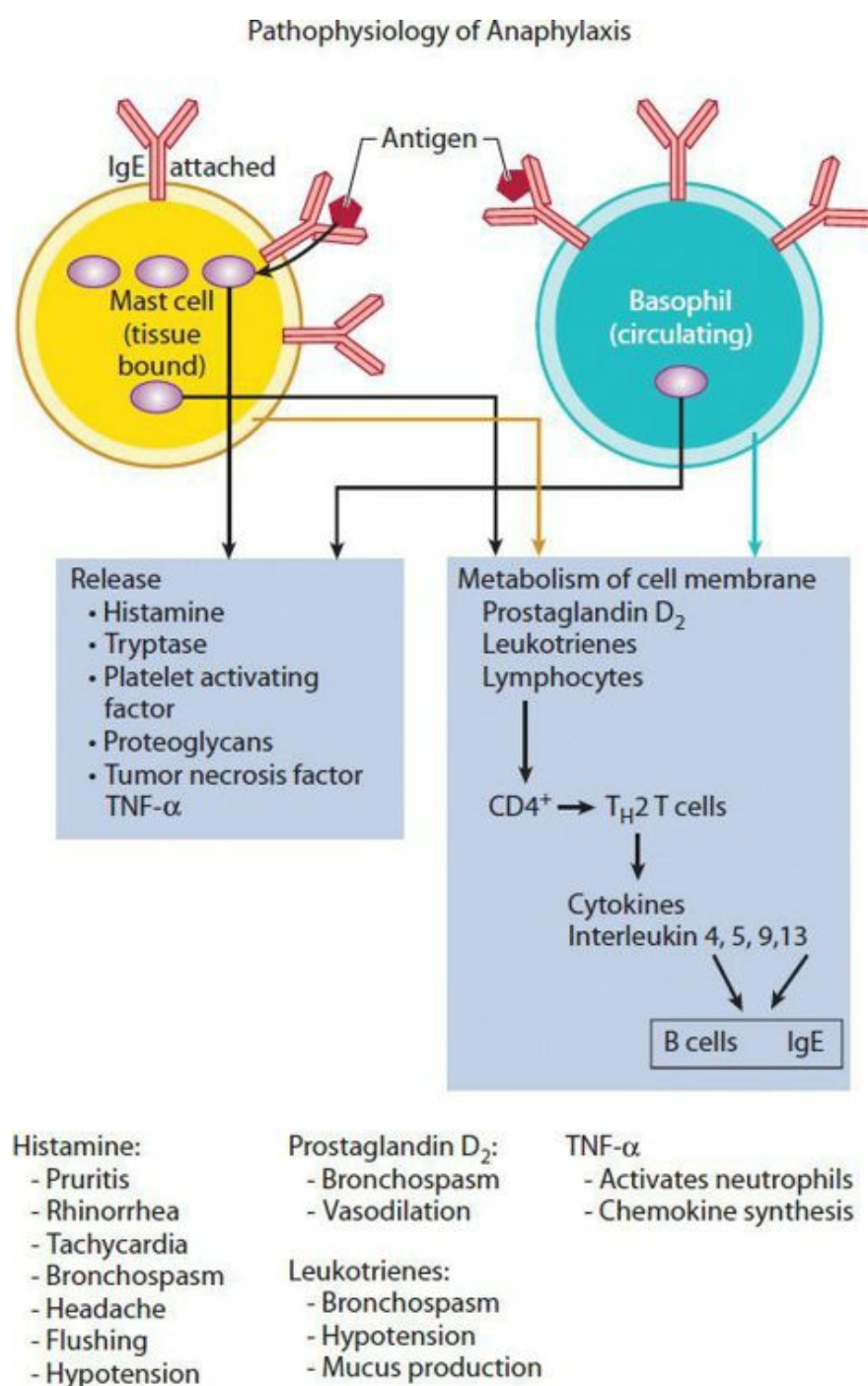


FIGURE 57–1. Description of systemic anaphylaxis.

The incidence of penicillin hypersensitivity is 5% overall, with 1% of penicillin reactions resulting in anaphylaxis. The risk for a fatal hypersensitivity reaction after penicillin administration is two in 100,000 (0.002%) patient exposures.²⁴¹ All routes of penicillin administration can result in anaphylaxis; however, it occurs most commonly after intravenous administration.

Treatment is supportive with careful attention to airway, breathing, and circulation. Initial therapy for anaphylaxis includes epinephrine 0.01 mg/kg (≤ 0.5 mg) given as 1:1000 (1 mg/mL) dilution intramuscularly (IM) every 10 to 20 minutes. Epinephrine bronchodilates and increases cardiac output through β -adrenergic receptor stimulation. In addition, β -adrenergic receptor stimulation results in decreased peripheral vascular tone. Oxygen and inhaled β_2 -adrenergic agonists are warranted in severe cases, as are corticosteroids. H_1 -receptor antagonists may be sufficient in patients with mild allergic reactions who do not have pulmonary manifestations or airway concerns.

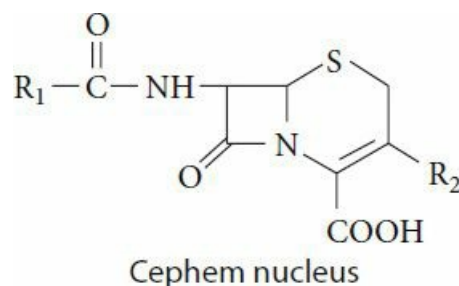
H_2 -receptor antagonism as a treatment for anaphylaxis is controversial. H_2 -receptors, when stimulated in the peripheral vasculature, cause vasodilation; in the heart, they cause positive inotropy, positive chronotropy, and coronary vasodilation; and in the lung, they cause increased mucus production.¹⁹⁹ Theoretically, H_2 -receptor antagonists can lead to a decrease in myocardial function at a time when H_1 -receptor stimulation is causing hypotension, coronary vasoconstriction, and bronchospasm. However, in vitro and animal models demonstrate decreases in coronary circulation and decreases in the overall anaphylactic response following administration of H_1 blockers.¹⁵ All H_2 -receptor antagonists are useful for the treatment of pruritus and flushing after acute allergic reactions involving the skin.^{15,151} Cimetidine use following anaphylaxis may result in clinical improvement, particularly hypotension and tachycardia.^{64,251} Available data indicate that treatment of anaphylaxis using H_2 -receptor antagonists should only be considered when other therapies have failed and the patient is adequately H_1 -receptor antagonized. Finally, glucagon may be of some benefit, particularly in patients who are maintained on β -adrenergic antagonists (Antidotes in Depth: A18).

Amoxicillin-Clavulanic Acid and Hepatitis. If cholestatic hepatitis develops, it occurs 1 to 6 weeks after initiation of therapy with amoxicillin-clavulanate.⁸ The incidence of hepatotoxicity typically is estimated at 1.1 to 2.7 per 100,000 prescriptions.⁸² The mechanism of hepatotoxicity is not clear, but may be related to clavulanate, a β -lactamase inhibitor used to prevent the bacterial destruction of β -lactam antimicrobials, or one of its metabolites. Treatment is supportive and clinical findings typically resolve after the discontinuation of therapy. However, prolonged hepatitis, ductopenia (vanishing bile duct syndrome), and pancreatitis rarely occur.^{48,184} Behavioral disturbances with disorientation, agitation, and visual hallucinations temporally related to use are also reported.¹⁷

Hoigne Syndrome and Jarisch-Herxheimer Reaction. The most common adverse effects occurring after administration of large intramuscular or intravenous doses of procaine penicillin G are the Hoigne syndrome and the Jarisch-Herxheimer reaction.^{110,146} The Hoigne syndrome is characterized by extreme apprehension and fear, illusions, or hallucinations; changes in auditory and visual perception, tachycardia, systolic hypertension, and, occasionally, seizures that begin within minutes of injection.²⁴⁰ These effects occur in the absence of signs or symptoms of anaphylaxis. The cause of this syndrome is unknown. Procaine is implicated as the etiology because of the similarity to events that occur after the administration of other local anesthetics known as the so-called “caine” reaction.^{200,211,236} Hoigne syndrome is six times more common in men than in women.²¹⁴ The reason for this increased prevalence is unclear, but autosomal dominance and influences of prostaglandin and thromboxane A_2 activity in this population may be responsible.¹²

The Jarisch-Herxheimer reaction is a self-limited reaction that develops within a few hours of antibiotic therapy for the treatment of spirochetal diseases such as syphilis or Lyme disease. Myalgias, chills, headache, rash, and fever spontaneously resolve within 18 to 24 hours, even with continued antibiotic therapy.²¹⁰ The pathogenesis of this reaction is likely either endotoxin induced from the lysed spirochete or cytokine elevation.¹⁷⁷ Antiinflammatory medications and immune modulators may offer some relief, but the optimal treatment is still unclear.

CEPHALOSPORINS



Cephalosporins are semisynthetic derivatives of cephalosporin C produced by the fungus *Acremonium*, previously called *Cephalosporium*. Cephalosporins have a ring structure similar to that of penicillins and are generally divided into first, second, third, fourth, and fifth generations based on their antimicrobial spectrum. First generation cephalosporins include cefadroxil, cefazolin, cephalexin, cephradine, and cephadrine. Second generation cephalosporins include cefaclor, cefamandole, cefonicid, cefotetan, cefoxitin, cefprozil, and cefuroxime. Third generation cephalosporins include cefdinir, ceftazidime, cefixime, ceftibuten, cefoperazone, ceftizoxime, cefotaxime, ceftriaxone, and cefpodoxime. The fourth generation cephalosporin is cefepime and the fifth generation cephalosporin is ceftaroline.

Effects occurring after acute overdose of cephalosporins resemble those occurring with penicillins. Some cephalosporins also have epileptogenic potential similar to penicillin.²⁴⁴ Case reports demonstrate seizures after inadvertent intraventricular administration.^{34,129,252} Management of cephalosporin overdose is similar to that of penicillin overdose. Table 57–1 lists the pharmacologic mechanism of cephalosporins.

Adverse Effects Associated with Therapeutic Use. Cephalosporins rarely cause an immune-mediated acute hemolytic crisis.⁷⁰ Cefaclor is the cephalosporin most commonly reported to cause systemic immune complex hypersensitivity or serum sickness, although this can occur with other cephalosporins.^{119,140} Also like penicillins, first-generation cephalosporins are associated with chronic toxicity, including interstitial nephritis and hepatitis.²⁴⁹ Cefepime is reported to cause reversible coma and seizures.^{1,218}

Cross-Hypersensitivity. The cephalosporins contain a six-member dihydrithiazine ring instead of the five-member thiazolidine penicillin ring. The extent of cross-reactivity between penicillins and cephalosporins in an individual patient is largely determined by the type of penicillin allergic response experienced by the patient. The incidence of anaphylaxis to cephalosporins is between 0.0001% and 0.1%, with a threefold increase in patients with previous penicillin allergy.¹²⁰ The overall cross-reactivity rate is approximately 1% between penicillin and a first- or second-generation cephalosporin. Cross-reactivity between penicillin and third-, fourth-, or fifth-generation cephalosporins is likely to be negligible due to a dissimilar antigenic side chain.⁴³ In fact, IgE directed against a methylene substituent linking the side chain to the penicillin molecule is identified.⁹⁵ These determinants are quite distinct among cephalosporins, which cause the pattern of cross-hypersensitivity among cephalosporins to be much less well defined than among the penicillins. Caution should be used when considering first- or second-generation cephalosporins in penicillin- or cephalosporin-allergic patients; however, if a risk-to-benefit analysis demonstrates a clear benefit to the patient without equivalent alternatives, the cephalosporin should be given.

N-methylthiotetrazole Side-Chain Effects. Cephalosporins containing an N-methylthiotetrazole (nMTT) side chain (moxalactam, cefazolin, cefoperazone, cefmetazole, cefamandole, cefotetan) have toxic effects unique to their group structure. As these cephalosporins undergo metabolism, they release free nMTT, which is responsible for their effects (Fig. 57–2).¹⁴⁸ Free nMTT inhibits the enzyme aldehyde dehydrogenase and, in conjunction with ethanol, can cause a disulfiramlike reaction (Chaps. 79 and 80).³⁸

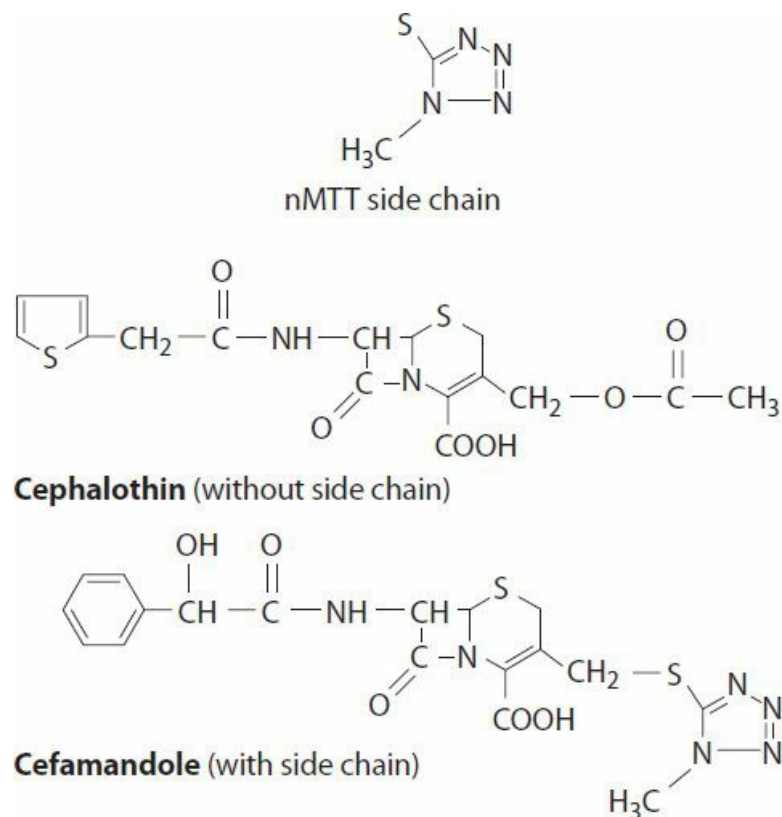
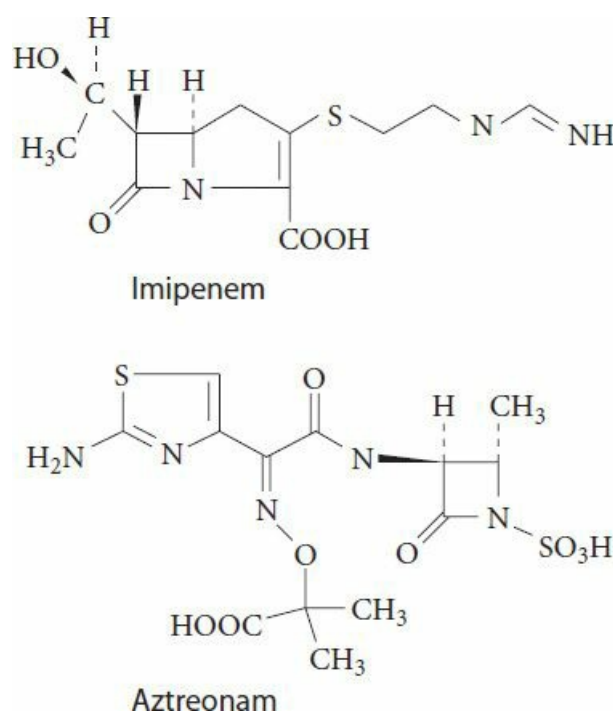


FIGURE 57–2. Characteristic structures of cephalosporins emphasizing the nMTT side chain. nMTT = N-methylthiotetrazole.

The nMTT side chain is also associated with hypoprothrombinemia, although a causal relationship is controversial.⁹¹ It is thought that nMTT depletes vitamin K-dependent clotting factors by inhibition of vitamin K epoxide reductase.¹⁶⁷ In a study of children one month to one year of age who were maintained on a prolonged antibiotic regimen, a significant degree of vitamin K–depletion was found.²² Treatment of patients suspected of hypoprothrombinemia caused by these cephalosporins consists of fresh frozen plasma, if bleeding is evident, and vitamin K₁ in doses required to resynthesize vitamin K cofactors ([Chap. 60](#) and [Antidotes in Depth: A15](#)).

Other β -Lactam Antimicrobials



Included in this group are monobactams such as aztreonam and carbapenems such as imipenem and meropenem. [Table 57–1](#) lists the pharmacologic mechanism of these xenobiotics.

Effects occurring after acute overdose of other β -lactam antimicrobials resemble those occurring after penicillin exposure. Imipenem has epileptogenic potential in both overdose and therapeutic dosing (see [Adverse Effects Associated](#)

With Therapeutic Use).^{42,131} Management guidelines for other β -lactam overdoses are similar to those for penicillin overdoses.

Adverse Effects Associated with Therapeutic Use. The risk factors for imipenem-related seizures include central nervous system disease, prior seizure disorders, and abnormal kidney function.¹⁷³ The mechanism for seizures appears to be GABA antagonism (similar to the penicillins) in conjunction with enhanced activity of excitatory amino acids.^{62,224}

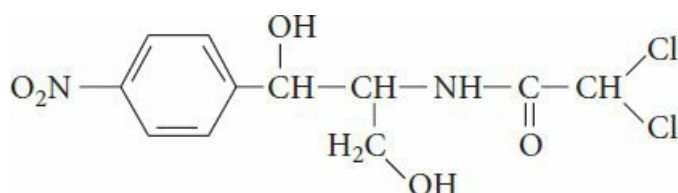
Cross-Hypersensitivity. Aztreonam is a monobactam that does not contain the antigenic components required for cross-allergy with penicillins, and generalized cross-allergenicity is not expected.²⁰² However, aztreonam cross-reacts in vitro with ceftriaxone, thought to be the result of the similarity in their side-chain structure.¹⁷⁵ Skin test manifested cross-allergenicity has also been noted between imipenem and penicillin, although the clinical incidence of adverse reactions is yet to be determined.²⁰¹

Trimethoprim-Sulfamethoxazole

Trimethoprim and sulfamethoxazole work as antibacterials in tandem effectively preventing tetrahydrofolic acid synthesis in bacterial cells. Significant toxicity after acute overdose is not expected; however, a myriad of effects occur after chronic therapeutic use. Hyperkalemia can result due to the ability of trimethoprim to competitively inhibit sodium channels in the distal nephron causing impairment in renal potassium excretion. Clinically significant hyperkalemia is reported in patients concurrently on other xenobiotics that increase potassium and among those with CKD.^{68,164} Other effects commonly reported after use of trimethoprim/sulfamethoxazole combinations include cutaneous allergic reactions, hematologic disorders, methemoglobinemia, hypoglycemia, rhabdomyolysis, and psychosis.

Trimethoprim also inhibits the renal tubular secretion of creatinine resulting in an increase in serum creatinine measurement.⁵⁹ This effect is thought to be dose related and ranges from 13% to 35% in patients with CKD. The rise in creatinine is independent of glomerular filtration rate and resolves upon drug discontinuation.

Chloramphenicol



Chloramphenicol was originally derived from *Streptomyces venezuelae* and is now synthetically produced. Antimicrobial activity is demonstrated against many Gram-positive and Gram-negative aerobes and anaerobes. Table 57–1 lists the pharmacologic mechanism of chloramphenicol.

Acute overdose of chloramphenicol commonly causes nausea and vomiting. Chloramphenicol inhibits protein synthesis in rapidly proliferating cells. Metabolic acidosis occurs as a result of the inhibition of mitochondrial enzymes, oxidative phosphorylation, and mitochondrial biogenesis.⁸¹ Infrequently, sudden cardiovascular collapse can occur 5 to 12 hours after acute overdoses. Cardiovascular compromise is more frequent in patients with serum concentrations higher than 50 $\mu\text{g/mL}$.^{81,154,231} Because concentrations are not readily available, all poisoned patients should be closely observed for at least 12 hours after exposure. Orogastric lavage may be useful for recent ingestions when the patient has not vomited, and activated charcoal 1 g/kg should be orally given.

Extracorporeal means of eliminating chloramphenicol are not usually required because of its rapid metabolism. However, both hemodialysis and charcoal hemoperfusion decrease serum chloramphenicol concentrations and may be of benefit in patients with large overdoses, or in patients with severe hepatic or renal dysfunction.^{80,150,215} Exchange transfusion also lowers serum chloramphenicol concentrations in neonates.²²³ Surviving patients should be closely monitored for signs of bone marrow suppression, which is usually dose dependent.

Adverse Effects Associated with Therapeutic Use. Chronic toxicity of chloramphenicol is similar to that which occurs following acute poisoning. The classic description of chronic chloramphenicol toxicity is the “gray baby syndrome.”¹⁵⁴ Children with this syndrome exhibit vomiting, anorexia, respiratory distress, abdominal distension, green stools, lethargy, cyanosis, ashen color, metabolic acidosis, hypotension, and cardiovascular collapse.

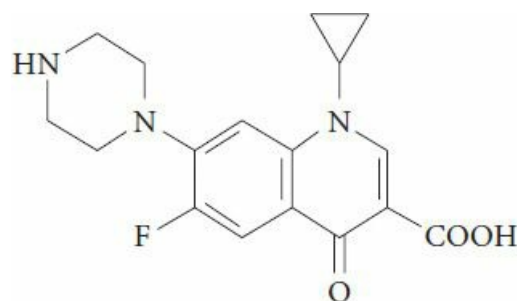
Approximately 90% of systemic chloramphenicol is metabolized via glucuronyl transferase, forming a glucuronide conjugate. The remainder is excreted renally unchanged. Infants, in particular, are predisposed to the gray baby syndrome because they have a limited capacity to form a glucuronide conjugate of chloramphenicol and, concomitantly, a limited ability to excrete unconjugated chloramphenicol in the urine.^{88,248}

There are two types of bone marrow suppression that occur after use of chloramphenicol. The most common type is

dose dependent and occurs with high serum concentrations of chloramphenicol.^{106,107,208} Clinical manifestations usually occur within several weeks of therapy and include anemia, thrombocytopenia, leukopenia, and, very rarely, aplastic anemia. Bone marrow suppression is generally reversible on discontinuation of therapy. A second type occurs through inhibition of protein synthesis in the mitochondria of marrow cell lines.¹⁵⁷ This type causes the development of aplastic anemia, which is not dose related, generally occurs in susceptible patients within 5 months of treatment and has an approximately 50% mortality rate (Chap. 22).^{69,255} The dehydro and nitroso bacterial metabolites of chloramphenicol injure human bone marrow cells through inhibition of myeloid colony growth, inhibition of DNA synthesis, and inhibition of mitochondrial protein synthesis.¹¹⁵

Other adverse effects associated with chloramphenicol include peripheral neuropathy, neurologic abnormalities (eg, confusion, delirium), optic neuritis, nonlymphocytic leukemia, and contact dermatitis.^{52,124,133,180,213}

Fluoroquinolones



Ciprofloxacin

The fluoroquinolones are a structurally similar, synthetically derived group of antimicrobials that have diverse antimicrobial activities. They include balofloxacin, ciprofloxacin, clinafloxacin, enoxacin, fleroxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pefloxacin, rufloxacin, sparfloxacin, temafloxacin, and tosufloxacin. Like other antimicrobials, the fluoroquinolones rarely produce life-threatening effects following acute overdose, and most patients can be safely managed with minimal intervention.¹¹ Table 57–1 lists the pharmacologic mechanism of fluoroquinolones.

Rarely, acute overdose of a fluoroquinolone results in AKI or seizures.¹²⁷ The mechanism of AKI after fluoroquinolone exposure is controversial. In animals, ciprofloxacin and norfloxacin are nephrotoxic, especially in the setting of neutral or alkaline urine.^{54,205} In humans, AKI is reported after both acute and chronic exposure to fluoroquinolones. A hypersensitivity reaction is postulated to explain pathologic changes consistent with interstitial nephritis.^{104,187} Treatment includes discontinuation of the fluoroquinolone and supportive care. Improvement in kidney function usually occurs within several days.

Seizures are reported with ciprofloxacin and may be a result of the inhibition of GABA or elevation of neuronal glutamate.^{2,216,235} Others postulate that seizures result from the ability of fluoroquinolones to bind efficiently to cations, particularly magnesium. This hypothesis is related to the inhibitory role of magnesium at the excitatory NMDA-gated ion channel (Chap. 14).⁶³ Treatment is supportive, using benzodiazepines and, if necessary, barbiturates to increase inhibitory tone.

Adverse Effects Associated with Therapeutic Use. Several fluoroquinolones are substrates and/or inhibitors of cytochrome CYP enzymes. This can result in xenobiotic interactions, which are especially important with xenobiotics that have a narrow therapeutic index.

Serious adverse effects related to fluoroquinolone use consist of central nervous system toxicity, as discussed, cardiovascular toxicity, hepatotoxicity, and notable musculoskeletal toxicity.

Fluoroquinolones cause prolongation of the QT interval, and they may also cause torsade de pointes.¹⁹⁵ Prolongation is due to the ability of fluoroquinolones to block the rapid component of the delayed rectifier potassium current (I_{Kr}). Treatment of patients presenting with QT prolongation is supportive.

Fluoroquinolones also rarely result in potentially fatal hepatotoxicity.¹³⁶ This adverse effect is most notable with trovafloxacin, which was withdrawn from the US market.

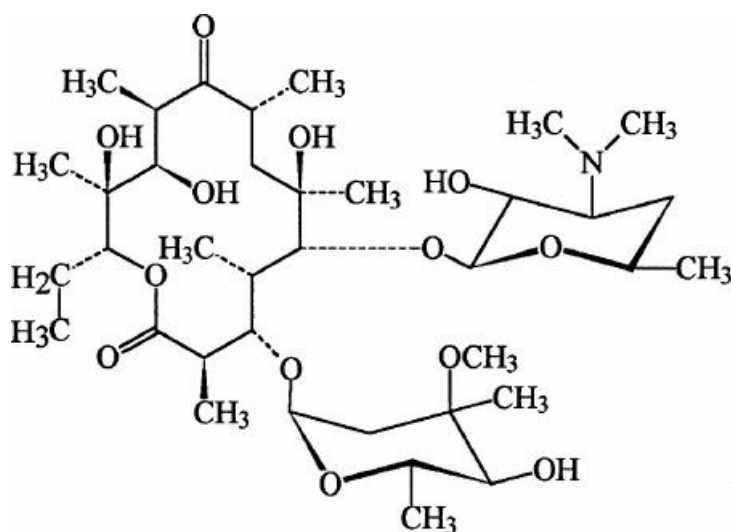
Fluoroquinolones should be used with caution in children and pregnant women because of their potential adverse effects on developing cartilage and bone.¹¹⁸ Damage is more common to fluoroquinolones with fleroxacin, pefloxacin, levofloxacin, and ofloxacin due to a substitution at the R-7 position of the quinolone core structure. There are very limited data regarding damage to articular cartilage as a result of using fluoroquinolones in humans; however, children given ciprofloxacin on a compassionate basis developed complaints of swollen, painful, and stiff joints after 3 weeks of

therapy.¹¹⁴ All signs and symptoms abated within 2 weeks of discontinuation of therapy. However, 29 additional children treated with ofloxacin or ciprofloxacin showed no differences with respect to cartilage thickness, cartilage structure, edema, cartilage-bone borderline, or synovial fluid.⁵⁷ Women who received quinolones during pregnancy had larger babies and more caesarean deliveries because of fetal distress than did controls.¹⁹

Fluoroquinolones are implicated as a cause of tendon rupture, which is reported to occur for months to one year after the start of treatment as well as after the discontinuation of therapy.^{174,219} The fluoroquinolone should be discontinued in patients, particularly in athletes who complain of symptoms consistent with painful and swollen tendons.

Other adverse effects include acute psychosis, hyperglycemia, hypoglycemia, rash, tinnitus, eosinophilia, serum sickness, and photosensitivity.^{39,92,155,172,222}

Macrolides and Ketolides



Erythromycin

The macrolide antimicrobials include various forms of erythromycin (base, ethylsuccinate, gluceptate, lactobionate, stearate), azithromycin, clarithromycin, dirithromycin, fidaxomicin, and troleandomycin. Ketolides are similar in pharmacology to macrolides; telithromycin is the only available agent at this time. [Table 57-1](#) lists the pharmacologic mechanism of macrolides and ketolides.

Acute oral overdoses of macrolide antimicrobials are not life threatening and symptoms, which are generally confined to the gastrointestinal tract, include nausea, vomiting, and diarrhea. However, intravenous overdoses can cause dysrhythmias.²²⁸

Intravenous and oral therapeutic use of macrolides cause QT interval prolongation and dysrhythmias. The QT interval prolongation seen occurs due to blockade of delayed rectifier potassium currents (I_{Kr} ; Chaps. 16 and 64).¹⁹⁴ Erythromycin lactobionate causes QT interval prolongation and torsade de pointes after intravenous use.¹⁶⁸ Oral erythromycin is also implicated in causing prolongation of the QT interval and torsade de pointes, especially in patients concurrently taking cytochrome (CYP3A4) inhibitors, in women, and in those with underlying heart disease.^{66,94,181} Oral use of azithromycin is associated with an increased risk of cardiovascular death with several case reports of QT interval prolongation, torsade de pointes, and polymorphic ventricular tachycardia.¹⁸⁰ In children, intravenous overdoses of azithromycin result in similar findings.

Although there are no acute overdose data regarding ketolide antimicrobials, effects are expected to be similar to macrolide antimicrobials. Therapeutic use of telithromycin is reported to result in QT interval prolongation, hepatotoxicity, toxic epidermal necrolysis, and anaphylaxis.³⁵

Adverse Events Associated with Interactions with Xenobiotics. Erythromycin is the prototypical macrolide and, as such, has received the most attention with respect to potential and documented xenobiotic interactions. Clarithromycin, erythromycin, and troleandomycin are all potent inhibitors of the CYP3A4 enzyme system; azithromycin does not inhibit this enzyme.⁵⁶ Erythromycin inhibits cytochrome P450 after metabolism to a nitroso intermediate, which then forms an inactive complex with the iron (II) of cytochrome P450. The appendix to [Chap. 13](#) lists substrates for the CYP3A4 system. Clinically significant interactions occur with erythromycin and warfarin, carbamazepine, or cyclosporine.^{40,99,178} Inhibition of cisapride metabolism results in increased concentrations of the parent xenobiotic, which is capable of causing prolongation of the QT interval and causing torsade de pointes.²⁹ Cases of carbamazepine toxicity are documented when combined with the use of erythromycin.⁹⁹ Erythromycin also inhibits CYP1A2, producing clinically significant interactions

with clozapine, theophylline, and warfarin.¹⁹⁰

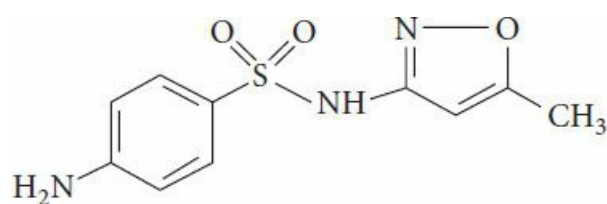
Macrolides may also interact with the absorption and renal excretion of xenobiotics that are amenable to intestinal P-glycoprotein excretion, or interfere with normal gut flora responsible for metabolism. This may be part of the underlying mechanism of cases of macrolide-induced digoxin toxicity (Chap. 65).¹⁶⁶

End-organ effects. The most common toxic effect of macrolides after chronic use is hepatitis, which may be immune mediated.⁴⁴ Erythromycin estolate is the macrolide most frequently implicated in causing cholestatic hepatitis.^{87,111}

Large doses (> 4 g/day) of macrolide antimicrobials are also associated with reversible high-frequency sensorineural hearing loss.³⁶ Renal impairment may be a risk factor.^{198,225} There are rare case reports in which ototoxicity did not resolve following discontinuation of therapy.¹³² Other, rare toxic effects associated with macrolides include cataracts after clarithromycin use in animals and acute pancreatitis in humans.^{75,239} Allergy is rare and reported at a rate of 0.4% to 3%.⁶⁰ Telithromycin contains a carbamate side chain that may interfere with the normal function of neuronal cholinesterase. It should be used cautiously in patients with myasthenia gravis, particularly patients receiving pyridostigmine because of the risk of cholinergic crisis.²²⁹

Clindamycin is a lincosamide with similar structure and clinical effects to macrolides. Clindamycin phosphate is commonly used topically while clindamycin hydrochloride is available for intravenous use. Data regarding acute overdose are limited and most cases of chronic toxicity occur after use of systemic doses of clindamycin phosphate. The most consequential toxicity is gastrointestinal resulting in esophageal ulcers, diarrhea, and *C. difficile* mediated enterocolitis.¹⁸⁸

Sulfonamides



Sulfamethoxazole

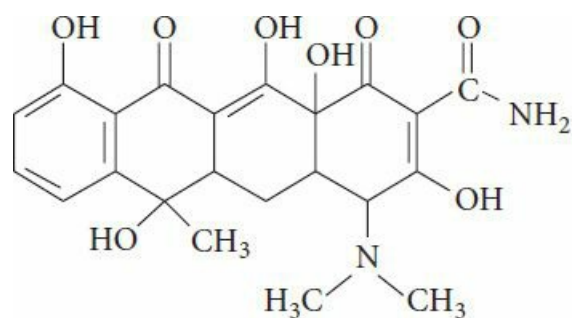
Sulfonamides antagonize para-aminobenzoic acid or paraaminobenzyl glutamic acid, which are required for the biosynthesis of folic acid. Table 57–1 lists the pharmacologic mechanism of sulfonamides. Acute oral overdoses of sulfonamides are usually not life threatening, and symptoms are generally confined to nausea, although allergy and methemoglobinemia occur rarely.⁷⁹ Treatment is similar to acute oral penicillin overdoses.

Adverse Effects Associated with Therapeutic Use. The most common adverse effects associated with sulfonamide therapy are nausea and cutaneous hypersensitivity reactions. Hypersensitivity reactions are thought to be caused by the formation of hapten sulfamethoxazole metabolites, N-hydroxy-sulfamethoxazole and nitroso-sulfamethoxazole. The degree of hapten binding is mitigated in vitro by cysteine and glutathione.¹⁵⁸ The incidence of adverse reactions to sulfonamides, including allergy, is increased in HIV-positive patients and is positively correlated to the number of previous opportunistic infections experienced by the patient.¹³⁰ This may be caused by a decrease in the mechanisms available for detoxification of free radical formation, as cysteine and glutathione concentrations are low in these patients.²⁴⁶ Whether supplementation with a glutathione precursor such as N-acetylcysteine will reduce the incidence of these reactions is unknown.⁴

Methemoglobinemia and hemolysis occur rarely.^{67,159} The mechanism for adverse reactions is not entirely clear. However, when sulfamethoxazole is exposed to ultraviolet B radiation in vitro, free radicals are formed that can participate in the development of tissue peroxidation and hemolysis.²⁵⁵ This finding may be of particular importance in treating patients with glucose-6-phosphate dehydrogenase deficiency associated with decreased in reducing capabilities.⁵

The sulfonamides are associated with many chronic adverse effects. Bone marrow suppression is rare, but the incidence is increased in patients with folic acid or vitamin B₁₂ deficiency, and in children, pregnant women, alcoholics, dialysis patients, and immunocompromised patients, as well as in patients who are receiving other folate antagonists. Other adverse effects include hypersensitivity pneumonitis, stomatitis, aseptic meningitis, hepatotoxicity, renal toxicity, and central nervous system toxicity.²⁵

Tetracyclines

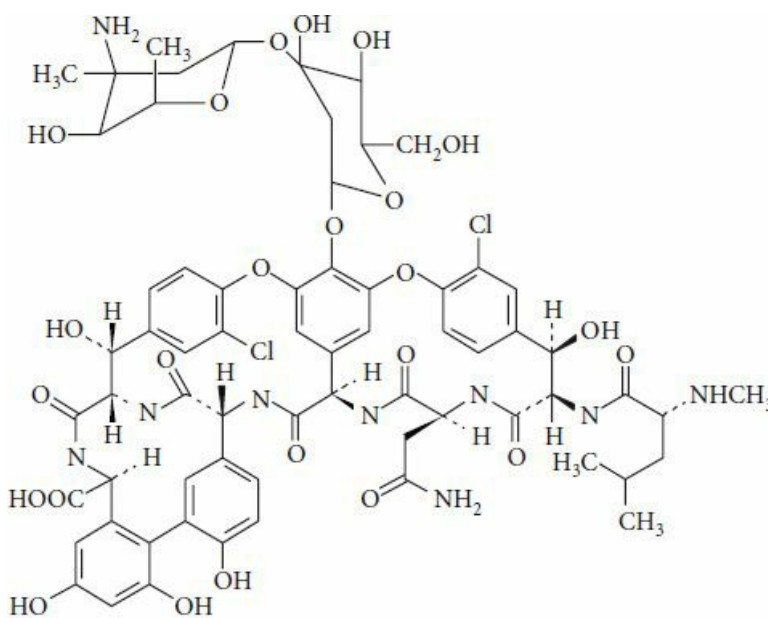


Tetracycline

Tetracyclines are derivatives of *Streptomyces* cultures. Currently available tetracyclines include demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, and tetracycline. Table 57–1 lists the pharmacologic mechanism of tetracyclines. Significant toxicity after acute overdose of tetracyclines is unlikely. Gastrointestinal effects consisting of nausea, vomiting, and epigastric pain have been reported.³⁷

Adverse Effects Associated with Therapeutic Use. Tetracycline should not be used in children during the first 6 to 8 years of life or by pregnant women after the 12th week of pregnancy because of the risk of development of secondary tooth discoloration in children or developing children in utero. Tooth discoloration can be effectively removed using topical application of carbamide peroxide whitening treatments.²³⁴ Other effects associated with tetracyclines include nephrotoxicity, hepatotoxicity, skin hyperpigmentation in sun-exposed areas, and hypersensitivity reactions.^{44,90,109,227} More severe hypersensitivity reactions, xenobiotic-induced lupus, and pneumonitis are reported after minocycline use, as are cases of necrotizing vasculitis of the skin and uterine cervix, and lymphadenopathy with eosinophilia.^{143,207,212} Demeclocycline rarely causes nephrogenic diabetes insipidus (Chaps. 19 and 28).⁴⁵

Vancomycin



Vancomycin

Vancomycin is obtained from cultures of *Nocardia orientalis* and is a tricyclic glycopeptide. Vancomycin is biologically active against numerous Gram-positive organisms. Table 57–1 lists the pharmacologic mechanism of vancomycin.

Acute oral overdoses of vancomycin rarely cause significant toxicity and most cases can be treated with supportive care alone. After large iatrogenic rapidly infused intravenous overdoses, AKI can occur in patients with preexisting kidney disease due to sustained high serum concentrations. In these patients, multiple doses of activated charcoal and potentially high-flux hemodialysis can be considered to enhance clearance.^{125,238}

Adverse Effects Associated with Therapeutic Use. Patients who receive intravenous vancomycin may develop the “red man syndrome” through an anaphylactoid (non-IgE-mediated) mechanism.⁸⁴ Symptoms include chest pain, dyspnea, pruritus, urticaria, flushing, and angioedema.¹⁹³ Signs and symptoms spontaneously resolve, typically within 15 minutes. Other symptoms attributable to “red man syndrome” include hypotension, cardiovascular collapse, and seizures.^{13,162}

The incidence of red man syndrome appears to be related to the rate of infusion and is approximately 14% when 1 g is given over 10 minutes, and falls dramatically to only 3.4% when given over 1 hour.^{162,169} A trial in 11 healthy persons

studied the relationship between intradermal skin hypersensitivity and the development of red man syndrome. Each of the 11 study participants underwent skin testing that was followed one week later by an intravenous dose of vancomycin 15 mg/kg over 60 minutes. Following intravenous vancomycin, all participants developed dermal flare responses and erythema, and 10 of 11 participants developed pruritus within 20 to 45 minutes. After the infusion was terminated, symptoms resolved within 60 minutes.¹⁷⁶

The signs and symptoms of this syndrome are related to the rise and fall of histamine concentrations.^{134,200} Tachyphylaxis occurs in patients given multiple doses of vancomycin.^{97,245} Animal models demonstrated a direct myocardial depressant and vasodilatory effect of vancomycin.⁵³ More serious reactions result when vancomycin is given via intravenous bolus, further supporting a rate-related anaphylactoid mechanism.²¹

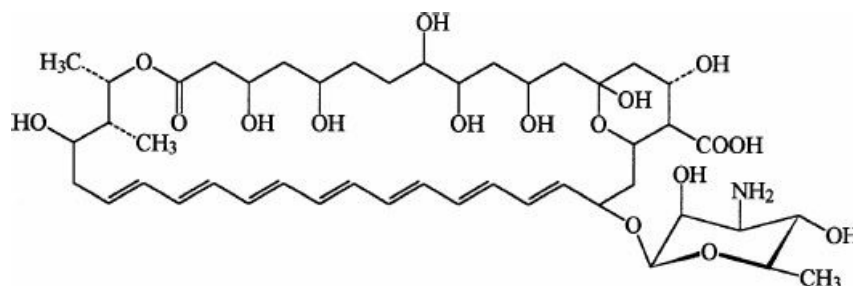
Patients most often experience red man syndrome after vancomycin is administered intravenously. In rare cases, oral administration of vancomycin can also result in the syndrome.¹⁸ Treatment includes increasing the dilution of vancomycin and slowing intravenous administration. Antihistamines may be useful as pretreatment, especially prior to the first dose.¹⁸³ A placebo-controlled trial in adult patients studied the incidence of these symptoms in patients given 1 g of vancomycin over one hour, as well as the effect of diphenhydramine in the prevention of the syndrome.²⁴⁵ There was a 47% incidence of reaction without diphenhydramine and a 0% incidence with diphenhydramine.

Chronic use of vancomycin may cause reversible nephrotoxicity, particularly in patients with prolonged excessive steady-state serum concentrations.^{10,186} Concomitant administration of aminoglycoside antimicrobials may increase the risk of nephrotoxicity.¹⁹⁶ Vancomycin also causes, though rarely, thrombocytopenia and neutropenia.^{50,51,65}

ANTIFUNGALS

Numerous antifungals are available. Toxicity related to the use of antifungals is variable and is based generally on their mechanism of action.

Amphotericin B



Amphotericin B is a potent antifungal derived from *Streptomyces nodosus*. Amphotericin B is generally fungistatic against fungi that contain sterols in their cell membrane. Table 57–1 lists the pharmacologic mechanism of amphotericin B. Development of lipid and colloidal formulations of amphotericin B attenuate the adverse effects associated with amphotericin B.⁹³ In these preparations, the amphotericin B is complexed with either a lipid or cholesteryl sulfate. On contact with a fungus, lipases are released to free the complexed amphotericin B, resulting in focused cell death.¹⁰¹

There are several case reports of amphotericin B overdose in infants and children. Significant clinical findings include hypokalemia, increased aspartate aminotransferase concentrations, and cardiac complications. Dysrhythmias and cardiac arrest have occurred following doses of 5 to 15 mg/kg of amphotericin B.^{31,51,122} Care should be used in the doses of amphotericin B administered according to specific formulation design, as these are not interchangeable. For example, intravenous therapy for fungal infections includes a usual dose of 0.25 to 1 mg/kg/day of amphotericin B or 3 to 4 mg/kg/day of amphotericin B cholesteryl. The potential for significant dosage errors and their sequelae is readily apparent in this comparison.

Adverse Effects Associated with Therapeutic Use. Infusion of amphotericin B results in fever, rigors, headache, nausea, vomiting, hypotension, tachycardia, and dyspnea.¹⁴⁴ Pretreatment with acetaminophen, diphenhydramine, ibuprofen, and hydrocortisone is helpful in alleviating the febrile symptoms, as are slower rates of infusion and lower total daily doses.^{86,237} Doses greater than 1 mg/kg/day and rapid administration in less than 1 hour are not recommended. Infusion concentrations of amphotericin B greater than 0.1 mg/mL can result in localized phlebitis. Slower infusion rates, hot packs, and frequent line flushing with dextrose in water may help to alleviate symptoms.

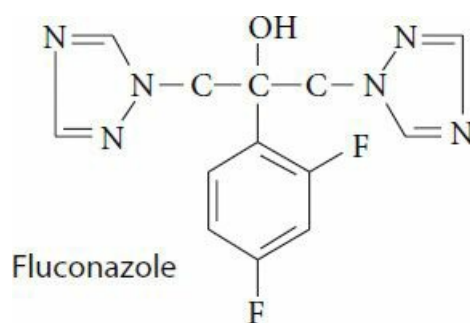
A total of 80% of patients exposed to amphotericin B will sustain some degree of kidney dysfunction (Chap. 28).⁴¹ Initial distal renal tubule damage causes renal artery vasoconstriction ultimately resulting in azotemia.⁷⁶ Studies in animals show depressed renal blood flow and glomerular filtration rate, and increased renal vascular resistance. It is unclear why

this occurs, but at this time, renal nerves, angiotensin II, nitric oxide, and tubuloglomerular feedback are excluded.^{197,203} The toxic effects associated with amphotericin B may also be caused by the deoxycholate vehicle.²⁵⁴ After large total doses of amphotericin B, residual decreases in glomerular filtration rate may occur even after discontinuation of therapy. This is hypothesized to be the result of nephrocalcinosis. Potassium and magnesium wasting, proteinuria, decreased renal concentrating ability, renal tubular acidosis, and hematuria can also occur (Chaps. 19 and 28).^{14,144} Strategies to reduce renal toxicity after amphotericin B include intravenous saline or magnesium and potassium supplementation.^{28,77,100} Liposomal formulations of amphotericin B resulted in fewer patients with breakthrough fungal infections, infusion-related fever, rigors, or nephrotoxicity.²⁴⁷ However, chest pain is uniquely reported after use of the liposomal preparation.¹¹⁶

Other adverse effects reported after treatment with amphotericin B include normochromic, normocytic anemia secondary to decreased erythropoietin release; respiratory insufficiency with infiltrates; and, rarely, dysrhythmias, tinnitus, thrombocytopenia, peripheral neuropathy, and leukopenia.^{135,142,144}

Exchange transfusion may be useful in neonates and infants and should be considered after large intravenous doses. In adults, extracorporeal elimination is not expected to be useful because of the low water solubility and high blood-protein binding of the xenobiotic.

Azole Antifungals: Triazole, Imidazoles, and Thiazoles



Triazole antifungals include fluconazole, fosfluconazole, hexaconazole, itraconazole, posaconazole, terconazole, and voriconazole. Common imidazoles include clotrimazole, econazole, ketoconazole, and miconazole. Abafungin is a thiazole. Triazole antifungals treat an array of fungal pathogens, whereas imidazoles and thiazoles are used almost exclusively in the treatment of superficial mycoses and vaginal candidiasis. Severe toxicity is not expected in the overdose setting. Hepatotoxicity, thrombocytopenia, and neutropenia are uncommon.²⁶ Rare case reports implicate voriconazole in the development of toxic epidermal necrolysis.¹⁰⁵ Most of the toxic effects noted after the use of these xenobiotics result from their xenobiotic interactions. Fluconazole, itraconazole, ketoconazole, and miconazole competitively inhibit CYP3A4, the isoenzyme system responsible for the metabolism of many xenobiotics. Table 57–4 lists other organ system manifestations associated with antifungal agents and other antimicrobials.

TABLE 57–4. Major Organ System Manifestations Associated with Antimicrobial Toxicity

<i>Antimicrobial</i>	<i>System</i>	<i>Signs/Symptoms/Laboratory Findings</i>
Antibacterials		
Bacitracin	Immune	Hypersensitivity reactions
Clindamycin	Immune	Hypersensitivity reactions
	Gastrointestinal	Nausea, vomiting, diarrhea
	Neurologic	Dizziness, headache, vertigo
Colistimethate (colistin sulfate)	Renal	Decreased function, acute tubular necrosis
	Neurologic	Peripheral paresthesias, confusion, coma, seizures, neuromuscular blockade
Metronidazole	Neurologic	Peripheral neuropathy, seizures
	Gastrointestinal	Nausea, vomiting
	Other	Disulfiram reactions
Nitrofurazone	Immune	Hypersensitivity reactions
	Other	Ointment contains polyethylene glycols (renal dysfunction)
Nitrofurantoin	Gastrointestinal	Nausea, vomiting, diarrhea
	Hepatic	Jaundice
	Immune	Rash, acute and chronic pulmonary hypersensitivity
Novobiocin	Neurologic	Peripheral neuropathy
	Immune	Rash
	Gastrointestinal	Nausea, vomiting, diarrhea
	Hematologic	Pancytopenia, hemolytic anemia
Polymyxin B sulfate	Neurologic	Muscle weakness, seizures
	Renal	Azotemia, proteinuria
Selenium sulfide	Cutaneous	Contact dermatitis, alopecia (rare)
Silver sulfadiazine	Cutaneous	Contact dermatitis
	Hematologic	Anemia, aplastic anemia
Spectinomycin	Immune	Rash (rare)
Antifungals		
Benzoic acid	Gastrointestinal	Nausea, vomiting, diarrhea
Carbol-fuchsin solution (phenol/resorcinol/fuchsin)	Gastrointestinal	Nausea, vomiting, diarrhea
Gentian violet	Gastrointestinal	Nausea, vomiting, diarrhea
	Immune	Rash (rare)
Griseofulvin	Renal	Proteinuria, nephrosis
	Hepatic	Increased enzymes
	Gastrointestinal	Nausea, vomiting, diarrhea
	Immune	Neutropenia
	Other	Disulfiram reactions, increased porphyrins
Nystatin	Gastrointestinal	Nausea, vomiting, diarrhea
Salicylic acid	Gastrointestinal and dermal	Higher concentrations are caustic
Undecylenic acid and undecylenate salt	Gastrointestinal	Nausea, vomiting, diarrhea

ANTIPARASITICS

Antiparasitics such as thiabendazole, mebendazole, albendazole, diethylcarbazine, ivermectin, metrifonate, niclosamide, oxfamniquine, piperazine, praziquantel, and pyrantel pamoate generally have limited toxicity in the overdose. Common symptoms after therapeutic use are gastrointestinal in nature and include abdominal pain, nausea, vomiting, and diarrhea. A single case of ivermectin associated hepatic failure is reported one month after a single dose.²⁴²

Antiviral

Acyclovir and valacyclovir are generally well tolerated in therapeutic doses and overdoses. In 105 dogs ingesting 40 to 2195 mg/kg, gastrointestinal symptoms were most common, with one dog developing mild creatinine increases.¹⁸⁵ A single case report describes AKI with crystalluria after ingestion of 30 g of valacyclovir.¹⁸⁹ Depressed mental status and nephrotoxicity are also reported after therapeutic use in humans.²⁷

ANTIMICROBIALS SPECIFIC TO THE TREATMENT OF HIV AND RELATED INFECTIONS

The evaluation and management of patients infected with HIV/AIDS continues to dramatically evolve. Medications used to manage this disorder have increased life expectancy as new, more powerful antivirals and xenobiotic combinations become available. Xenobiotic therapy for HIV commonly consists of a combination of xenobiotics from different classes (nucleoside reverse transcriptase inhibitor {NRTI}, nonnucleoside reverse transcriptase inhibitor, protease inhibitor, integrase inhibitor, fusion inhibitor, and C-C chemokine receptor type 5 {CCR5} antagonist) to utilize the advantages of the unique mechanisms that each xenobiotic offers in inhibiting viral replication and minimizing xenobiotic resistance. Drug and dosage errors, particularly in infants, are of significant concern and have resulted in iatrogenic overdose.^{30,49,138} This section focuses on overdoses and major toxic effects from HIV directed antiviral therapy, as well as from xenobiotics that are specifically used in the management of opportunistic infections.²³⁰ A comprehensive review of these medications and currently recommended use patterns, drug interactions, and end-organ toxicities can be found at <http://aidsinfo.nih.gov/guidelines>. Table 57–5 lists the common antimicrobials used to treat HIV-related opportunistic infections, and Table 57–6 lists common adverse xenobiotic effects and overdose effects, if known, for antimicrobials that are specific in their use for HIV-related infections.

TABLE 57–5. Antimicrobials Used to Treat Common Opportunistic Infections

<i>Antimicrobial</i>	<i>Opportunistic Infection</i>
Albendazole	Microsporidiosis
Amphotericin B	Aspergillosis Candidiasis Coccidioidomycosis Cryptococcosis Histoplasmosis Leishmaniasis Paracoccidioidomycosis Penicilliosis
Antimony (pentavalent)	Leishmaniasis
Atovaquone	<i>Pneumocystis jiroveci</i>
Azithromycin	<i>Mycobacterium avium</i> complex
Clarithromycin	<i>Mycobacterium avium</i> complex
Caspofungin	Aspergillosis
Clindamycin	<i>Pneumocystis jiroveci</i> <i>Toxoplasma gondii</i>
Dapsone	<i>Pneumocystis jiroveci</i>
Ethambutol	<i>Mycobacterium avium</i> complex
Fluconazole	Coccidioidomycosis Histoplasmosis
Flucytosine	Cryptococcosis
Foscarnet	Cytomegalovirus
Fumagillin	Microsporidiosis
Ganciclovir	Cytomegalovirus
Itraconazole	Histoplasmosis
Nitazoxanide	Cryptosporidiosis Microsporidiosis
Paromomycin	Cryptosporidiosis
Pentamidine	<i>Pneumocystis jiroveci</i>
Primaquine	<i>Pneumocystis jiroveci</i>
Pyrimethamine	<i>Toxoplasma gondii</i>
Rifabutin	<i>Mycobacterium avium</i> complex
Sulfadiazine	<i>Toxoplasma gondii</i>
Trimethoprim/sulfamethoxazole	<i>Pneumocystis jiroveci</i> <i>Toxoplasma gondii</i> Isosporiasis
Trimetrexate	<i>Pneumocystis jiroveci</i>
Valganciclovir	Cytomegalovirus
Voriconazole	Aspergillosis

TABLE 57–6. Toxicity of Antimicrobials Used in the Treatment of HIV Related Infections

Antimicrobial	Overdose Effects	Common Adverse Drug Effects
Albendazole	No reported cases	Increased AST/ALT, nausea, vomiting, and diarrhea; hematologic (rare), encephalopathy, AKI, rash
Antimony (pentavalent)	AKI	AKI, multiorgan system failure
Atovaquone	No clinical effects	Rashes, anemia, leukopenia, increased AST/ALT
Caspofungin	No reported cases	Phlebitis, headache, hypokalemia, increased AST/ALT, fever
Flucytosine	No reported cases	Bone marrow suppression, hepatotoxicity, nausea, vomiting, diarrhea, rash
Foscarnet	No reported cases	Azotemia, hypocalcemia, and kidney failure (common); anemia, leukopenia, thrombocytopenia, fever, headache, seizures, genital and oral ulcers, food-drug eruptions, nausea, vomiting, diarrhea, headaches, seizures, coma, diabetes insipidus, hypophosphatemia, hypokalemia, hypomagnesemia
Fumagillin	No reported cases	Neutropenia, thrombocytopenia
Ganciclovir	No clinical effects	Leukopenia, worsening of kidney function; can also cause nausea, vomiting, diarrhea, increased AST/ALT, anemia, thrombocytopenia, headache, dizziness, confusion, seizures
Nitazoxanide	No reported cases	Hypotension, headache, abdominal pain, nausea, vomiting; may cause green-yellow urine discoloration
Pentamidine	40 times dosing error in a 17 month-old child resulted in cardiac arrest	Hypoglycemia (early) followed by hyperglycemia, azotemia; can cause hypotension, torsade de pointes, phlebitis, rash, Stevens-Johnson syndrome, hypocalcemia, hypokalemia, anemia, nausea, vomiting, metallic taste, leukopenia, thrombocytopenia
Primaquine	No reported cases	Neutropenia, hemolytic anemia, methemoglobinemia, leukocytosis, hypertension
Pyrimethamine	No reported cases	Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia
Rifabutin	High doses (> 1 g daily): arthralgia/arthritis	Nausea, vomiting, diarrhea; can cause hepatotoxicity, neutropenia, thrombocytopenia, hypersensitivity reactions
Sulfadiazine	AKI and hypoglycemia	Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme; headaches, depression, hallucinations, ataxia, tremor, crystalluria, hematuria, proteinuria, and nephrolithiasis
Trimethopate	No reported cases; treat similarly to methotrexate (Chap. 51)	Myelosuppression, nausea, vomiting, histaminergic reactions
Valganciclovir	No reported cases; expect to be similar to ganciclovir	Anemia, neutropenia, thrombocytopenia; nausea, vomiting, headache, peripheral neuropathy

AKI = acute kidney injury; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Specific Antiretroviral Classes

Nucleoside Analog Reverse Transcriptase Inhibitors. The nucleoside analog reverse transcriptase inhibitors inhibit the reverse transcription of viral RNA into proviral DNA. Currently available xenobiotics include abacavir, emtricitabine, didanosine (ddI), lamivudine, stavudine, telbivudine, and zidovudine.

Acute overdose effects. Many intentional overdoses of reverse transcriptase inhibitors occur without major toxicologic effect. The most serious adverse effect anticipated after acute overdose of an NRTI is the development of a metabolic acidosis with elevated lactate concentration, which appears to be more common in women.^{47,74,145} Following incorporation of the nucleoside analog into mitochondrial DNA by RNA polymerase, DNA polymerase γ is inhibited. This results in decreased production of mitochondrial DNA electron transport proteins, which ultimately inhibits oxidative phosphorylation (Chaps. 13 and 23). Organ system toxicity follows in addition to the development of acidemia. The reported mortality in patients with NRTI-associated metabolic acidosis associated with elevated lactate is 33% to 57%.⁷⁴ Resolution of symptoms in survivors occurs in 1 to 24 weeks. Patients with NRTI-associated acidemia may recover more quickly after the use of cofactors such as thiamine, riboflavin, L-carnitine, vitamin C, and antioxidants.^{33,61} The indications for the use of these xenobiotics are unclear at this time; however, because of the relative lack of toxicity, they may be considered.

Chronic effects. Development of acidemia is more commonly associated with therapeutic use of reverse transcriptase inhibitors than with acute overdose. The mechanism is likely identical to that described above. Other common adverse

effects are somewhat agent specific and include hematologic toxicity after zidovudine, pancreatitis with didanosine, hypersensitivity after abacavir, and sensory peripheral neuropathy after stavudine and didanosine.^{60,61,89,128,153}

Nonnucleoside Reverse Transcriptase Inhibitors. The nonnucleoside reverse transcriptase inhibitors bind directly to reverse transcriptase enzymes enabling allosteric inhibition of enzymatic function.²³² Delavirdine (Rescriptor), efavirenz (Sustiva), etravirine (Intelence), nevirapine (Viramune), and rilpivirine (Endurant) comprise the currently available xenobiotics.

There are a paucity of acute overdose data on these xenobiotics, although they generally appear to have limited toxicity. An adult male with a reported ingestion of 6 g of nevirapine had a sustained laboratory elevation in γ -glutamyl transferase, but no other reported effects.⁷¹ An infant received a 40 times therapeutic dose of nevirapine with mild neutropenia and metabolic acidosis with elevated lactate concentration.³⁰ Finally, a 12 year-old child reported an ingestion of 3 g of efavirenz resulting in throat burning, visual impairment, peripheral nervous system abnormalities, and nightmares.¹⁶⁰ Treatment should include supportive care until more information is available. The nonnucleoside reverse transcriptase inhibitors are also limited in toxicity after chronic use. Use of nevirapine and delavirdine commonly results in hypersensitivity reactions such as rash. Efavirenz is reported to result in dizziness and dysphoria. Otherwise, toxicity can result from the ability of these xenobiotics to either inhibit or enhance CYP isozymes in the metabolism of other xenobiotics.

Protease Inhibitors. Protease inhibitors inhibit the vital enzyme (proteinase), which is required for viral replication.⁷⁸ Currently available xenobiotics include atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Lexiva), indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), saquinavir mesylate (Invirase), and tipranavir (Aptivus).

Data after protease inhibitor overdose are limited. A review of data submitted to the manufacturer of indinavir found that of 79 reports, the complaints were nausea, vomiting, abdominal pain, and nephrolithiasis. Protease inhibitors as a class commonly result in gastrointestinal symptoms and rash.⁷⁸ Drug interactions can occur due to inhibition of CYP isoenzymes.¹⁷⁰ A unique finding is an altered fat distribution pattern that, over time, results in lymphodystrophy central obesity, “buffalo hump,” breast enlargement, cushingoid appearance, and peripheral wasting.⁷⁸

Fusion Inhibitors. This class of xenobiotics interferes with the binding or entry of the HIV virion into the cell.²³ No acute overdose data are available for this class, but after chronic use, hypersensitivity, hepatotoxicity, and infusion reactions seem to be of greatest concern.^{16,156,163} The currently available drugs include enfuvirtide (Fuzeon) and maraviroc (Selzentry).

Integrase Inhibitor. This class of xenobiotics prevents the activity of the enzyme in HIV to function normally. This enzyme is responsible for the incorporation of the virus into DNA. The currently available xenobiotic is raltegravir (Isentress), although elvitegravir and dolutegravir are in stage 2 and 3 clinical trials, respectively. No information is currently available regarding its toxicity after acute overdose. It appears that these xenobiotics are well tolerated at therapeutic doses with a potential association with myotoxicity.

C-C Chemokine Receptor Type 5 Antagonists. This class of xenobiotics antagonize the receptor by which HIV enters cells. Maraviroc (Selzentry) is the only C-C chemokine receptor type 5 inhibitor currently available. No information is currently available regarding its toxicity after acute overdose.

SUMMARY

- Adverse effects attributable to antimicrobials are largely related to chronic administration, although, rarely, acute toxicity does occur after large exposures.
- Acute toxic effects of antimicrobials are far more common following intravenous administration, xenobiotic interactions, or after iatrogenic overdose.
- Vigilance on the part of the health care professional will prevent the majority of acute toxic manifestations following antimicrobial use.

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58 ANTITUBERCULOUS MEDICATIONS

Christina H. Hernon

HISTORY AND EPIDEMIOLOGY

Approximately one-third of the total population of the world, or 2 billion people, are infected with *Mycobacterium tuberculosis*. An estimated 8.8 million new cases of disease are diagnosed, and 1.6 million persons die from tuberculosis (TB) annually.³ In 2011, the incidence of TB in the United States was the lowest recorded (10,521 new cases) since the inception of national reporting in 1953.²² The introduction of isoniazid (INH) into clinical practice in 1952 produced a steady decline in the number of TB cases in the United States over the subsequent 30 years. However, between 1985 and 1991, there was a resurgence in TB cases in the United States resulting primarily from the effects of human immunodeficiency virus (HIV), homelessness, deterioration in the health care infrastructure, and an increase in immigration. With the initiation and implementation of containment strategies, the spread of the infection slowed by aggressive case identification and patient-centered management, including directly observed therapy, social support, housing, and substance abuse treatment. These methods have decreased the prevalence rate in the United States as well as worldwide. In 2005, the TB incidence was stable or declining worldwide, although the total number of new TB cases continued to increase slowly. Also in that year, extensively drug-resistant tuberculosis (XDR-TB) was recognized.^{7,21,94} In 2010, at least 5% to 10% of multidrug-resistant tuberculosis (MDR-TB) strains were extensively drug-resistant to both INH and rifampin, all fluoroquinolones, and at least one of three injectable drugs (capreomycin, kanamycin, and amikacin).¹³³ At present, populations that remain at risk for TB include HIV-positive patients, homeless people, people with alcoholism, injection drug users, health care workers, prisoners, prison workers, and Native Americans. In addition, the TB rate in foreign born persons is nearly 10 times higher than in US born persons. In the US population, countries of birth generating the highest number of TB cases are Mexico, the Philippines, India, and Vietnam.^{7,21} The use of second-line (reserve) drugs and multidrug antituberculous regimens for MDR-TB and XDR-TB resulted in an incidence of adverse drug effects increasing to 40% to 70% and sometimes requiring discontinuation of the treatment. Hepatotoxicity, peripheral neuropathy, and ocular neuropathy are often irreversible and potentially fatal.

ISONIAZID

Pharmacology

Isoniazid (INH, or isonicotinic hydrazide) is structurally related to nicotinic acid (niacin, or vitamin B₃), nicotinamide adenosine dinucleotide (NAD), and pyridoxine (vitamin B₆) (Fig. 58–1). The pyridine ring is essential for antituberculous activity. INH itself does not have direct antibacterial activity. It is a prodrug that undergoes metabolic activation by KatG, a catalase peroxidase in *M. tuberculosis* that produces a highly reactive intermediate,^{95,135} which in turn interacts with InhA, a mycobacterial enzyme that functions as an enoyl-acyl carrier protein (enoyl-ACP) reductase.^{92,93} InhA is required for the synthesis of very-long-chain lipids, mycolic acids (containing between 40 and 60 carbons) that are important components of mycobacterial cell walls.



FIGURE 58–1. Isoniazid and related compounds.

The activated form of INH is stabilized by the pyridine ring. Enoyl-ACP reductase (InhA) catalyzes the NADH-

dependent reduction of the double bonds in the growing fatty acid chain linked to acyl carrier proteins. This INH metabolite enters the binding site of InhA, where it reacts with the reduced form of nicotinamide adenine dinucleotide (NADH).⁹⁵ The covalently linked INH-NADH complex remains bound to the active site of InhA, irreversibly inhibiting the enzyme.^{76,92}

Pharmacokinetics

When therapeutic doses of 300 mg are administered orally, INH is rapidly absorbed, reaching peak serum concentrations typically within 2 hours.^{60,88,89} INH diffuses into all body fluids with a volume of distribution of approximately 0.6 L/kg and has negligible binding to serum proteins. After the drug penetrates infected tissue, it persists in concentrations well above those generally required for bactericidal activity.⁸⁹

The primary metabolic pathway for INH is via N-acetylation via hepatic acylamine N-acetyltransferase type 2 (NAT2) to acetylisoniazid, which may be (1) excreted by the kidney; (2) oxidized to hydroxylamine, a hepatotoxic metabolite via CYP2E1¹³⁰; (3) directly hydrolyzed to hepatotoxic hydrazine; or (4) further metabolized by NAT2 to (somewhat hepatotoxic) acetylhydrazine, which may be further metabolized by NAT2 to nontoxic diacetylhydrazine. Hydrazine and (to a lesser extent) acetylhydrazine are oxidized by CYP2E1 to reactive metabolites, which induce oxidative stress or alter lipid metabolism, resulting in hepatic apoptosis or steatosis. The mechanisms and circumstances of hepatotoxicity are not clearly elucidated and are of continuing interest in research.¹³⁰ Approximately 75% to 95% of INH is renally eliminated in the form of these hepatic metabolites within 24 hours of administration.⁴⁹ N-acetyltransferase-2 (NAT2) exhibits Michaelis-Menten kinetics but is genotypically polymorphic, and the activity of an individual's enzymes is determined by an autosomal dominant inheritance pattern, with homozygous fast acetylators (FF), heterozygous fast acetylators (FS), and homozygous slow acetylators (SS). Patients are distinguishable phenotypically as fast, intermediate, and slow acetylators. Whereas the fast acetylation isoform is found in 40% to 50% of American whites and African Americans, the fast acetylator isoenzymes are found in 80% to 90% of Asians and Inuits.³⁷ These isoforms are distinguishable by the following characteristics: (1) slow acetylators have less presystemic clearance, or first-pass effect, than do fast acetylators; (2) fast acetylators metabolize INH five to six times faster than slow acetylators; and (3) serum INH concentrations are 30% to 50% lower in fast acetylators than in slow acetylators. The elimination half-life of INH is approximately 70 minutes in fast acetylators, and 180 minutes in slow acetylators. Twenty-seven percent of INH is excreted unchanged in urine by slow acetylators compared with 11% excretion in fast acetylators. Slow acetylators are at increased risk of peripheral neuropathy and may require dose adjustments.¹¹⁷ The clearance of INH averages 46 mL/min.^{10,125} Additionally, a small portion of INH is directly hydrolyzed into isonicotinic acid and hydrazine, and this pathway is of greater quantitative significance in slow acetylators than in rapid acetylators. Although both hepatic microsomal oxidation by CYP2E1 of hydrazine or the acetylhydrazine intermediate into reactive intermediates have been proposed as causes of INH related hepatotoxicity, there is no significant association between variations in genetic polymorphisms and hepatotoxicity.^{44,81,121,130} There is increasing evidence that hydrazine is linked to direct hepatotoxicity as well as causing hepatotoxicity via an immune mediated, idiosyncratic mechanism.⁷⁷ **Figure 58–2** illustrates the metabolism of INH.

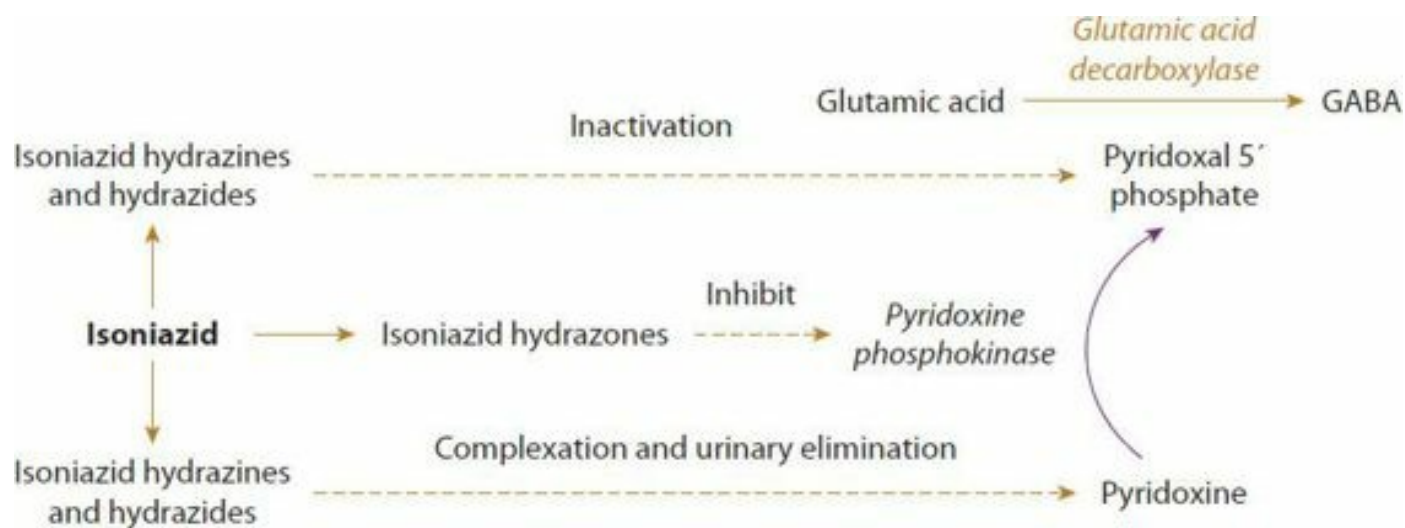


FIGURE 58–3. The effect of isoniazid on γ -aminobutyric acid (GABA) synthesis.

Pyridoxine is converted in vivo to an active form, pyridoxal-5'-phosphate, which serves as an important cofactor in many biotransformation reactions such as transamination, transketolation, and decarboxylation. INH metabolites inhibit the enzyme pyridoxine phosphokinase, which converts pyridoxine (vitamin B₆) to its active form, pyridoxal-5'-phosphate, which is a required cofactor for many pyridoxine dependent enzyme systems in the body, including two enzymes that control GABA metabolism.^{25,59,79} Glutamic acid decarboxylase (GAD) catalyzes GABA synthesis from glutamate, and GABA aminotransferase degrades the inhibitory neurotransmitter. The inhibitory effects are greater on GAD, which leads to both decreased GABA and elevated glutamate concentrations.¹²⁷

Pyridoxine depletion is also involved in a decrease in catecholamine synthesis and interferes with the synthesis of and/or reacts with NAD to form inactive hydrazone adducts, thereby disrupting cellular reduction/oxidation reactions.

Pyridoxine depletion is further compounded when INH directly reacts with pyridoxal phosphate to produce an inactive hydrazone complex that is renally excreted and thereby increases renal losses of this required cofactor.^{79,125} Urinary excretion of pyridoxine and its metabolites increases with increasing INH dose, reflecting the effect of INH on pyridoxine metabolism.

Structurally similar chemicals exert similar acute toxic effects. Monomethylhydrazine, a metabolite produced from gyromitrin isolated from the *Gyromitra* spp (“false morel”) mushroom, and the hydrazines used in liquid rocket fuel have a similar mechanism of action (Chap. 120).

Interactions with Other Drugs and Foods

Drug–drug interactions associated with INH are mediated through alteration of hepatic metabolism of several CYP enzymes. The majority of these interactions are inhibitory, with decreased CYP-mediated transformations, particularly demethylation, oxidation, and hydroxylation (Chap. 13). Clinically relevant adverse effects with elevated concentrations of theophylline (CYP1A2), phenytoin (CYP2C9/CYP2C19), warfarin (CYP2C9/CYP2C19), valproic acid, and carbamazepine (CYP3A4) are caused by decreased hepatic metabolism of these xenobiotics.^{33,106,131} The CYP2E1 cytochrome subtype, however, exhibits a complex response to INH; a therapeutic dose of INH induces expression of CYP2E1, but simultaneously binds, stabilizes, and inhibits its metabolic activity. Eventual dissociation of INH from the enzyme active site creates an increased intracellular concentration of CYP2E1 available to metabolize potential substrates. The formation of the acetaminophen (APAP) metabolite responsible for toxicity, NAPQI (N-acetyl-p-benzoquinoneimine), is catalyzed by CYP2E1. INH mediated effects in APAP-induced hepatotoxicity are uncertain because of differences in acetylator status (fast, slow) and variations in CYP2E1 activity.^{24,106}

INH interacts with numerous foods. INH is a weak monoamine oxidase inhibitor; both tyramine reactions to foods (aged cheeses, wines) and serotonin toxicity from meperidine are reported in patients taking INH. Clinical effects include flushing, tachycardia, and hypertension.^{32,43,69,113} Furthermore, INH inhibits the enzyme histaminase, leading to exacerbated reactions after the ingestion of histamine in scombrototoxic fish.^{55,79,106} Table 58–1 summarizes additional INH drug and food interactions.

TABLE 58–1. Adverse Reactions and Drug Interactions of Antituberculous Drugs

Drug	Major Adverse Reactions	Drug Interactions/Clinical Effect	Monitoring	Comments
Isoniazid (INH)	Acute: seizures, acidosis, coma, hyperthermia, oliguria, anuria Chronic: elevation of liver enzyme concentrations, autoimmune hepatitis, arthritis, anemia, hemolysis, eosinophilia, peripheral neuropathy, optic neuritis, vitamin B ₆ deficiency (pellagra)	Rifampin, PZA, ethanol: hepatic necrosis Acetaminophen: hepatic necrosis Warfarin: increased INR Theophylline: tachycardia, vomiting, seizures, acidosis Phenytoin: increased phenytoin concentrations Carbamazepine: altered mental status Meperidine: serotonin toxicity Lactose: decreased INH absorption Antacids: decreased INH absorption Red wine/soft cheese: tyramine reaction Fish (scombroid): flushing, pruritus	Liver enzymes, ANA, CBC	HIV enteropathy may decrease absorption; INH should not be given with lactose-containing drug formulations because lactose can form hydrazones and lower INH concentrations
Rifampin	Acute: diarrhea, periorbital edema Chronic: hepatitis, reddish discoloration of body fluids	Protease inhibitors: decreased serum concentration of protease inhibitor Delavirdine: increased HIV resistance Cyclosporine: graft rejection Warfarin: decreased INR Oral contraceptives: ineffective contraception Methadone: opioid withdrawal Phenytoin: higher frequency of seizures Theophylline: decreased theophylline concentrations Verapamil: decreased cardiovascular effect	If administered with HIV antiretrovirals, viral titers should be followed. Liver enzymes; monitor serum concentrations of drugs (ie, phenytoin, cyclosporine) or clinical markers of efficacy (ie, INR)	Interactions of rifampin with several HIV medications are very poorly described; changes in dosing or dosing interval for both rifampin and antiretroviral drugs may be required; teratogenic
Ethambutol	Chronic: optic neuritis, loss of red-green discrimination, loss of peripheral vision		Visual acuity, color discrimination	Contraindicated in children too young for formal ophthalmologic examination
Pyrazinamide (PZA)	Chronic: hepatitis, decreased urate excretion	INH: increased rates of hepatotoxicity (when extended courses or high dose pyrazinamide used)	Liver enzymes	Courses of therapy of ≤ 2 months are recommended
Cycloserine	Chronic: depression, paranoia, seizures, megaloblastic anemia	INH: increased frequency of seizures	CBC, psychiatric monitoring	
Ethionamide	Chronic: orthostatic hypotension, depression	Cycloserine: may increase CNS effects	Blood pressure, pulse, orthostasis	
para-Aminosalicylic acid	Chronic: malaise, GI upset, elevated liver enzyme concentrations, hypersensitivity reactions, thrombocytopenia		Liver enzymes, CBC	
Capreomycin	Chronic: hearing loss, tinnitus, proteinuria, sterile abscess at IM injection sites		Audiometry, kidney function tests	

ANA = antinuclear antibodies; CBC = complete blood count; CNS = central nervous system; HIV = human immunodeficiency virus.

Pregnancy

The use of INH in pregnancy is of concern because it is a class C drug, crosses the placenta, and produces umbilical cord serum concentrations comparable to maternal serum concentrations.^{13,14,61} Mammalian teratogen studies suggest that INH is not a human teratogen, although fetal deformities after acute overdose of INH are reported.^{70,125} Administration of INH to pregnant women was not associated with cancer in their offspring. Although INH readily enters breast milk, breastfeeding during therapy is considered acceptable.^{100,125}

Clinical Manifestations of Isoniazid Toxicity

Acute Toxicity. INH produces the triad of seizures refractory to conventional therapy, severe metabolic acidosis, and coma. These clinical manifestations may appear as soon as 30 minutes after ingestion.^{53,57,119} The case fatality rate of a single acute ingestion may be as high as 20%.^{15,18} Although vomiting, slurred speech, dizziness, and tachycardia may represent early manifestations of toxicity, seizures may be the initial sign of acute overdose.⁷² Seizures may occur after the ingestion of greater than 20 mg/kg of INH and invariably occur with ingestions greater than 35 to 40 mg/kg. Patients with underlying seizure disorders may develop seizures at lower doses.¹⁵ Hyperreflexia or hyporeflexia may herald INH induced seizures. Consciousness may return between seizures, or status epilepticus can occur.^{30,84} Because GABA, the primary inhibitory neurotransmitter, is depleted in acute INH toxicity, seizure activity may persist until GABA concentrations are restored even with anticonvulsant therapy.

Acute INH toxicity is often associated with seizures and an anion gap metabolic acidosis associated with a high serum lactate concentration. Typically, arterial pH ranges between 6.80 and 7.30, although survival in the setting of an arterial pH of 6.49 was reported.⁵³ Paralyzed animals poisoned with INH do not develop elevated lactate concentrations, a finding that suggests the lactate arises from intense muscular activity.^{25,85}

In acute severe INH toxicity, coma may last as long as 24 to 36 hours and persist beyond both the termination of seizures and the resolution of acidemia. The cause of coma is unknown.^{11,53} Additional sequelae from acute INH toxicity include rhabdomyolysis, kidney failure, hyperglycemia, glycosuria, ketonuria, hypotension, and hyperthermia.^{4,8,19,86,125,126}

Chronic Toxicity. Chronic therapeutic INH use is associated with a variety of adverse effects. Overall incidence of adverse reactions to INH is estimated to be 5.4%,⁴⁹ the most serious of which is hepatocellular necrosis.³⁹ Although asymptomatic elevation of aminotransferases is common in the first several months of treatment, laboratory testing may reveal the onset of hepatitis up to one year after starting INH therapy. In 1978, after several deaths among patients receiving INH therapy, the US Public Health Service reported the incidence of clinically evident hepatitis as 1% of those taking INH; of that subgroup, 10% died, for an overall mortality rate of 0.1%.^{17,66} Research performed since the resurgence of TB, however, identified a considerably lower rate of hepatotoxicity. Clinically manifest hepatitis occurred in only 11 patients in a population of 11,141 persons receiving INH and close monitoring, yielding an incidence of 0.1%.⁸³ Additional studies suggest that the death rate from INH hepatotoxicity is only 0.001% (two of 202,497 treated patients).⁹⁸ Hepatotoxicity is associated with chronic overdose, increasing age, comorbid conditions such as malnutrition, and combinations of antituberculous drugs that may serve as cytochrome inducers. Overt hepatic failure often occurs if INH therapy is continued after the onset of hepatocellular injury in both adults and children.^{35,36,50,74,110,129} The incidence of hepatitis is two to four times higher in pregnant women than in nonpregnant women.⁴¹

Isoniazid induced hepatitis can arise via two pathways.^{35,132} The first involves an immunologic mechanism resulting in hepatic injury that is thought to be idiopathic.^{103,125} The association of hepatitis with lupus erythematosus, hemolytic anemia, thrombocytopenia, arthritis, vasculitis, and polyserositis supports an immunologic process.^{102,125} However, symptoms commonly found in autoimmune disorders such as fever, rash, and eosinophilia are usually absent with drug induced lupus erythematosus, and rechallenge with INH often fails to provoke recurrence of hepatocellular injury.^{35,102,132} The second, more common mechanism involves direct hepatic injury by INH or its metabolites. The metabolites believed responsible for hepatic injury are acetylhydrazine and hydrazine (Fig. 58–2).^{44,81,120}

Peripheral neuropathy and optic neuritis are known adverse drug effects of chronic INH use. Neurotoxicity is probably caused by pyridoxine deficiency aggravated by the formation of pyridoxine-INH hydrazones.³⁷ Peripheral neuropathy, the most common complication of INH therapy, presents in a stocking-glove distribution that progresses proximally. Although primarily sensory in nature, myalgias and weakness may occur.¹¹¹ Peripheral neuropathy is generally observed in severely malnourished, alcoholic, uremic, or diabetic patients; it is also associated with slow acetylator status, an effect that leads to increased INH concentrations and, consequently, increased pyridoxine depletion.⁴⁶ Optic neuritis may occur with INH therapy, usually concurrent with other medications such as ethambutol or etanercept, and presents as decreased visual acuity, eye pain, and dyschromatopsia; visual field testing may reveal central scotomata and bitemporal hemianopsia.^{47,57,64} INH is also associated with such findings of CNS toxicity as ataxia, psychosis, hallucinations, and coma.^{1,9,45,97}

Diagnostic Testing

Acute INH toxicity is a clinical diagnosis that may be inferred by history and confirmed by measuring serum INH concentrations.¹⁰⁵ Acute toxicity from INH is defined as a serum INH concentration greater than 10 mg/L one hour after ingestion, greater than 3.2 mg/L 2 hours after ingestion, or greater than 0.2 mg/L six hours after the ingestion.⁸⁴ Because serum INH concentration measurements are not widely available, clinicians cannot rely on serum concentrations to confirm the diagnosis or initiate therapy. Because of the risk of hepatitis associated with chronic INH use, hepatic aminotransferases should be regularly monitored after therapy is started. In critically ill patients, serum should be assessed for acidemia, kidney function, creatine phosphokinase (CPK), and urine myoglobin indicating rhabdomyolysis and possible kidney failure.

Management

Acute Toxicity. The antidote for INH induced neurologic dysfunction is pyridoxine (Antidotes in Depth: A14). Pyridoxine rapidly terminates seizures, corrects metabolic acidosis, and reverses coma. The efficacy of pyridoxine is correlated with the administered dose; one study identified recurrent seizures in 60% of patients who received no pyridoxine and in 47% of those who received 10% of the ideal pyridoxine dose, and no seizures in patients who received the full dose of pyridoxine.¹²⁴ To treat acute toxicity, the pyridoxine dose in grams should equal the amount of INH ingested in grams, with a first dose of up to 5 g intravenously in adults. Unknown quantities of ingested INH warrant initial empiric treatment with a pyridoxine dose of no more than 5 g (pediatric dose, 70 mg/kg to a maximum of 5 g). Pyridoxine should be administered at a rate of 1 g every 2 to 3 minutes. Seizures that persist beyond administration of the initial dose should receive an additional similar dose of pyridoxine.⁶

Hospital pharmacies may stock insufficient quantities of intravenous (IV) pyridoxine to treat even a single patient with a large INH ingestion.¹⁰¹ In the event that IV formulations are unavailable in sufficient quantities, pyridoxine tablets may be crushed and administered with fluids via a nasogastric tube.¹⁰¹

Conventional anticonvulsants, although generally used as first line therapy, demonstrate variable effectiveness in terminating INH induced seizures. Benzodiazepines may be used to potentiate the antidotal efficacy of pyridoxine, particularly if optimal doses of the antidote are unavailable. The benzodiazepines act synergistically with pyridoxine, as well as possessing inherent GABA agonist activity, but they may be ineffective as the sole treatment of acute INH poisoning because of their reliance on GABA to exert their activity.^{26,27,57,124} Phenytoin has no intrinsic GABAergic effect and is not recommended as therapy for patients with INH-induced seizures.^{57,84,96} Barbiturates that have potent GABA agonist activity are expected to be as effective as the benzodiazepines, although the risk of respiratory depression is greater with this class of anticonvulsant. The efficacy of propofol in terminating INH induced seizures has not been evaluated in humans.

Although hemodialysis has been used to enhance elimination of INH in acute overdose, with clearance rates reported as high as 120 mL/min, hemodialysis is rarely indicated for initial management unless associated with kidney failure.^{19,125}

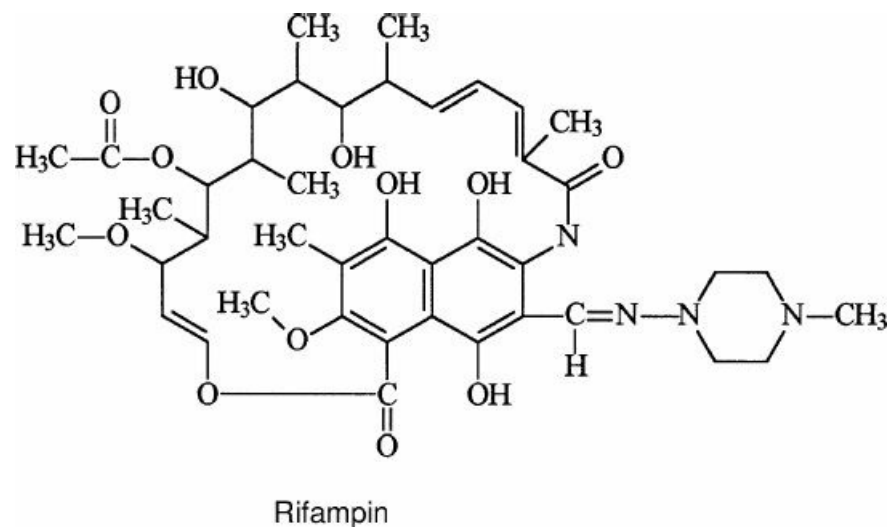
Asymptomatic patients who present to the emergency department within 2 hours of ingestion of toxic amounts of INH should receive prophylactic administration of 5 g of oral or IV pyridoxine. This recommendation is based on the observation that INH reaches its peak serum concentration within 2 hours of ingestion of therapeutic doses. Asymptomatic patients may be observed for a 6 hour period for signs of toxicity. Acute toxicity is unlikely to manifest more than 6 hours beyond ingestion.

Gastrointestinal (GI) decontamination should be performed by administering activated charcoal only in patients who are awake and able to comply with therapy.¹⁰⁹ Late GI decontamination with activated charcoal will probably be ineffective in preventing toxicity because delayed absorption has not been observed.¹⁰⁴ Orogastric lavage is relatively contraindicated unless the patient is intubated because of the risk of seizures.

Chronic Toxicity. Hepatitis (defined as aminotransferase concentrations more than two to three times baseline) resulting from therapeutic INH administration mandates termination of therapy; malnourished patients may require nutritional support. After resolution of liver injury, INH may be restarted, provided aminotransferase concentrations are closely monitored, with reassessment in six weeks or any time the patient experiences nausea, vomiting, or abdominal discomfort.^{35,110} Pyridoxine does not reverse hepatic injury; consequently, surveillance for and recognition of hepatocellular injury remains essential. Cases of hepatitis refractory to medical therapy may require liver transplantation.^{38,54,129}

Isoniazid produces an axonopathy caused by pyridoxine depletion and manifests as peripheral neuropathies, cerebellar findings, and psychosis. Neurotoxicity is commonly treated with as much as 50 mg/d of oral pyridoxine, although doses as low as 6 mg/d appear to be effective.^{1,9,97,114} Because of its effectiveness in preventing neurologic toxicity, pyridoxine is often used concurrently with INH therapy.

RIFAMYCINS



Pharmacology

Rifamycins are a class of macrocyclic antibiotics derived from *Ammycolatopsis mediterranei*. Xenobiotics in this class include rifampin (a semisynthetic derivative), rifabutin, and rifapentine, of which the first two are most commonly used.⁴⁹ Rifampin inhibits the initial steps in RNA chain polymerization through the formation of a stable drug enzyme complex with RNA polymerase. Disruption of RNA synthesis interrupts protein synthesis, leading to cell death. Whereas mycobacterial RNA polymerase is susceptible to rifampin, eukaryotic RNA polymerase is not. High concentrations of rifamycin antibiotics, however, can affect mammalian mitochondrial RNA synthesis, as well as reverse transcriptases and viral DNA dependent RNA polymerases.⁴⁹

Pharmacokinetics and Toxicokinetics

When administered orally, rifampin reaches peak serum concentrations in 0.25 to 4 hours; foods, but not antacids, interfere with absorption.⁸⁹ Rifampin is secreted into the bile and undergoes enterohepatic recirculation. Although the recirculating antibiotic is deacetylated, the metabolite retains antimicrobial activity. The half-life of rifampin, which is normally 1.5 to 5 hours, increases in the setting of hepatic dysfunction. After therapy is started, however, rifampin autoinduces its metabolism to shorten its half-life by approximately 40%. Rifampin is distributed widely into body compartments, and imparts a reddish color to all body fluids, including the cerebrospinal fluid⁴⁹ and in this setting has been erroneously identified as xanthochromia suggesting subarachnoid hemorrhage to the clinician.⁵⁷ Because mycobacteria rapidly develop resistance to rifampin, it should not be used as the sole therapy against TB.⁴⁹

In large overdose, elimination half-life has been observed within the normal range expected after therapeutic dosing. Rifampin may inhibit hepatic excretion of bilirubin, causing transient elevations; however, this may also be caused by interference with the bilirubin assay because of the reddish color imparted to all body fluids, including serum.¹²⁸ Rifampin therapy carries greater teratogenic risk than other antituberculous therapies, with 4.4% incidence of malformation. Anencephaly, hydrocephalus, and congenital limb abnormality and dislocations are reported.^{14,116} Rifampin is associated with hemorrhagic disease of the newborn¹⁴ but is nevertheless compatible with breastfeeding because only minute amounts of rifampin are secreted into breast milk.^{14,115}

Drug–Drug Interactions

Rifamycins are potent inducers of CYP enzymes, which result in numerous drug interactions ([Chap. 13](#)). Of the rifamycins, rifampin has greater activity in inducing CYP3A4 than rifapentine; rifabutin has the least inductive activity of the class.⁷¹ Rifampin also induces CYP1A2, CYP2C9, and CYP2C19.¹³¹ Additionally, the ability of rifampin to induce CYP3A4 is strongly correlated with p-glycoprotein (P-gp) concentrations. P-gp is a transmembrane protein that functions as a cellular efflux pump of endogenous and exogenous xenobiotics; variations in expression of P-gp significantly affects the bioavailability of many xenobiotics and subsequent drug–drug interactions ([Chaps. 9 and 13](#)).⁴⁰ Concurrent administration of rifampin thus affects the metabolism of an array of drugs such as warfarin, cyclosporine, phenytoin, opioids, and oral contraceptives.^{40,108,131} P-gp induction by rifampin therefore may be responsible for a variety of pathophysiologic processes, including insufficient anticoagulation in patients receiving oral anticoagulants, acute graft rejection in transplant patients, graft-versus-host disease, difficulty controlling phenytoin concentrations, methadone withdrawal, and unplanned pregnancy. Effects arising from CYP3A4 induction begin within 5 to 6 days after rifampin is started and persist for up to 7 days after therapy is stopped.⁴⁹

Rifamycins and HIV

Coinfection with both TB and HIV is common, causing approximately 4 million deaths per year worldwide. Approximately one-third of all patients with HIV also have TB, and concurrent highly active antiretroviral therapy (HAART) and antituberculous therapy decrease mortality.¹²³ However, many factors influence the efficacy and feasibility of treating these illnesses. There is decreased absorption of nearly all antituberculous drugs in patients with advanced HIV caused by chronic diarrhea, intestinal pathogens, and general malabsorption. Also, there are many drug–drug interactions between antituberculous and HIV medications caused by alterations in absorption, cytochrome enzymes, P-gp transporters, and noncytochrome metabolism.^{40,51,58,121} This often creates additive toxicities that compromise efficacy as well as compliance. This is particularly true when combining rifamycins and HIV medications. Toxic manifestations of individual xenobiotics may be additive, such as combining nevirapine and rifampin, which both have risk of skin rash and hepatitis. Caution should be exercised when combining these therapies, and individual toxicities should be reviewed to avoid summative effects. [Table 58–1](#) lists common adverse effects and drug–drug interactions.

Clinical Manifestations

Acute Toxicity. The most common side effects of acute rifampin overdose are GI in nature consisting of epigastric pain, nausea, vomiting, and diarrhea.^{35,49} The presence of diarrhea distinguishes rifampin ingestion from overdose of other antituberculous medications. Three reported deaths are described from rifampin or rifampicin ingestion; an autopsy performed on one of these patients demonstrated the presence of pulmonary edema, although no causation was implied.^{12,62,91} Other effects include flushing, angioedema, and obtundation. Overdoses of rifampin in children can result in facial or periorbital edema. Anterior uveitis is occasionally observed, as are neurologic effects consisting of generalized numbness, extremity pain, ataxia, and muscular weakness.⁴⁸ Isolated rifamycin overdose infrequently produces serious acute effects.

Chronic Toxicity. When rifampin was originally introduced as an antituberculous medication, hepatitis was more frequently observed in patients taking combination therapy with INH than in those taking INH alone. These findings potentially arise from the ability of rifampin to induce cytochromes responsible for INH hepatotoxicity and not from direct hepatic injury by rifampin itself. Liver injury, when attributable to rifampin alone, is predominantly cholestatic, suggesting that clinical surveillance for hepatic injury is important as is regular biochemical monitoring.^{35,87} Rifampin alters the metabolism of other xenobiotics, such as INH, pyrazinamide (PZA), and APAP, to increase their potential for hepatotoxicity.^{35,82} Although some reports highlight increased compliance and typically mild and transient hepatotoxicity with combined rifampin and PZA treatment for latent TB infection, other recent studies suggest a significant risk of fatal hepatotoxicity, and the Centers for Disease Control and Prevention recommends generally avoiding this combination of drugs.⁷⁵

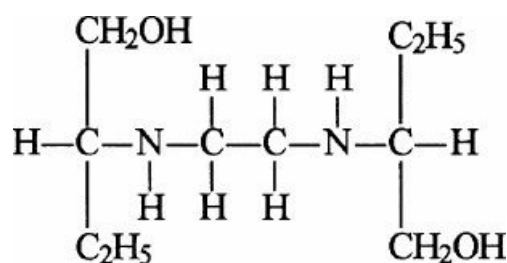
A condition similar to a viral syndrome may result from a hypersensitivity reaction that is associated with rifampin therapy. The syndrome, which occurs in 20% of patients receiving high doses or intermittent (less than twice weekly) dosing, includes fever, chills, and myalgias. Eosinophilia, hemolytic anemia, thrombocytopenia, and interstitial nephritis can develop in severe cases, and acute kidney injury is likely related to hypersensitivity. Acute kidney injury is rarely oliguric and is usually self-limited; patients usually recover with supportive care, although rechallenge with rifampin should be undertaken only with caution.⁸⁷

The concomitant administration of rifampin and protease inhibitors results in increased rates of arthralgias, uveitis, leukopenia, and skin discoloration. Identical side effects occurred during the simultaneous administration of rifampin and CYP3A4 inhibitors such as clarithromycin, suggesting that toxic effects arise from elevated serum rifampin concentrations.¹⁶ Current recommendations are that rifampin not be given with protease inhibitors, except for ritonavir in rare circumstances. In patients already taking protease inhibitors, rifabutin may be used in place of rifampin.⁹⁰

Diagnostic Testing and Management

Management of patients with acute rifampin overdose is primarily observational and proactive. Stabilization of vital signs and administration of activated charcoal are usually adequate, although clinicians should remain vigilant for coingestants. For chronic toxicity, recognition of interactions between rifampin and other xenobiotics is critical. Hepatic function should be monitored because of the ability of rifampin to augment the hepatotoxicity of other xenobiotics. Treatment for hepatic injury involves withholding rifampin therapy and reassessing the appropriateness of other xenobiotics administered to the patient. Supportive care for hepatotoxicity may be required. Influenza-like symptoms and acute kidney injury secondary to rifampin may respond to decreasing the interval between administration of the medication.⁸⁷ Although rifampin interacts with protease inhibitors, the utility of therapeutic drug monitoring is uncertain because the correlation of clinical events with serum concentrations of rifampin and antiretroviral drugs is unknown.¹⁶

ETHAMBUTOL



Pharmacology

Ethambutol is effective against *M. tuberculosis* and *Mycobacterium kansasii* as well as some strains of *Mycobacterium avium* complex; however, it has no effect on other bacteria. Ethambutol inhibits arabinosyl transferases, interfering with biosynthesis of arabinogalactan and liparabinomannan, which are required for polymerization of arabinan within mycobacterial cell walls.^{49,63}

Pharmacokinetics

Only the D(+) isomer is used therapeutically because the L(–) isomer is the major contributor to optic neuritis, but both enantiomers are bactericidal.¹⁰⁷ It is taken up rapidly by growing cells, where bacteriostatic effects appear approximately 24 hours after ethambutol is incorporated by mycobacteria.⁴⁹ About 80% of an oral dose is absorbed, but both foods and antacids decrease absorption.^{16,49} Maximum serum concentrations are reached within 4 hours of oral administration and are proportional to the dose. Ethambutol is approximately 20% to 30% protein bound and has a half-life of 4 to 6 hours.^{49,68} Three-fourths of a standard dose is excreted unchanged in the urine by a combination of glomerular filtration and tubular secretion. Consequently, ethambutol accumulates in patients with impaired glomerular filtration rate (GFR), making adjustments in dosing necessary.⁴⁹ Increasingly, mutations in the *Mycobacterium embB* gene confer resistance to ethambutol, as high as 14.2%, with acquired resistance reaching nearly 40%.⁶³

Ethambutol is considered safe for use during pregnancy as a first-line medication. Although a 2.2% incidence of congenital abnormalities was identified in women undergoing ethambutol therapy, no consistent pattern of abnormalities occurred in their offspring.¹⁴ Although ethambutol is excreted into breast milk in approximately a 1:1 ratio with serum, it is considered to be compatible with breastfeeding.¹⁴

Clinical Manifestations and Management

Acute overdose of ethambutol is generally well tolerated, although a death has been reported.⁶² More commonly, nausea, abdominal pain, confusion, visual hallucinations, and optic neuropathy occur after acute ingestions of greater than 10 g.³⁴ Although stabilization of vital signs and GI decontamination with activated charcoal remain the hallmarks of therapy, clinicians must remain vigilant for coingestants, particularly INH. Hemodialysis is rarely used as treatment for multidrug ingestions including ethambutol.³⁴

Although peripheral neuropathy and cutaneous reactions occur with chronic therapy, the most significant effect of the therapeutic use of ethambutol is unilateral or bilateral ocular toxicity presenting as painless blurring of vision, decreased perception of color, and loss of peripheral vision. These effects are largely dose and duration related and are typically reversible with drug discontinuation.^{23,29,122} Optic neuritis develops in approximately 15% of patients receiving 50 mg/kg/d, 5% of patients receiving 25 mg/kg/d, and fewer than 1% of those receiving 15 mg/kg/d.⁸⁷ Patients may develop subclinical ocular disease within 30 days of starting ethambutol.¹³⁴ The loss of peripheral vision and color discrimination that accompanies the optic neuropathy caused by ethambutol distinguishes this condition from the optic neuropathy secondary to INH.^{57,87}

Management of chronic toxicity from ethambutol involves cessation of therapy, although improvement may be hastened by treatment with hydroxocobalamin.^{49,57} Recovery is less likely in older patients and is related to the degree of visual impairment.¹²⁰

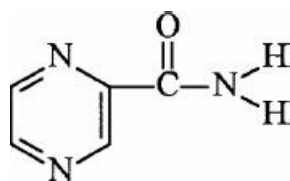
Ethambutol is a strong metal chelator, and inactivation of zinc and copper may be related to its induction of retinal cell vacuoles and enlarged lysosomes, which interfere with membrane permeability, possibly causing abnormal cell function and cell death.^{29,65} The visual abnormalities induced by ethambutol are similar to those caused by a hereditary condition known as Leber optic neuropathy. Both ethambutol and Leber hereditary optic neuropathy can affect oxidative phosphorylation through impairment of mitochondrial function.^{28,65} Ethambutol is suspected of mimicking this condition by binding intracellular copper, altering mitochondrial function, and producing neuronal injury.^{56,65} Alternatively, optic

neuritis may be related to zinc metabolism. Ethambutol chelates intracellular zinc to induce reversible vacuolar degeneration in retinal cultures. Progressive degeneration leads to irreversible neuronal destruction.²⁹ The effect of this injury is a shift in the threshold for wavelength discrimination without changing the absolute sensitivity of the cone system, which leads to a loss of red–green discrimination.¹¹²

Diagnostic Testing and Management

All patients should receive neuroophthalmic testing before ethambutol therapy. The use of visual evoked potentials is especially useful in identifying subclinical optic nerve disease. Furthermore, patients should receive regular visual acuity examinations, and clinicians should encourage patients to report any subjective visual symptoms. The use of ethambutol may be relatively contraindicated in children who are unable to comply with an ophthalmic examination.^{57,87}

PYRAZINAMIDE



Pharmacology and Pharmacokinetics

Pyrazinamide is a structural analog of nicotinamide with a mechanism of action similar to that of INH. Similar to INH, PZA is a prodrug. PZA requires deamidation to anionic pyrazinoic acid by pyrazinamidase, an endogenous cytoplasmic bacterial enzyme. In this form, PZA has no antibacterial activity, but after being exposed to acidic conditions, it becomes protonated to the uncharged, active form, 5-hydroxypyrazinoic acid, which enters the cell, accumulates, and kills the bacteria by disruption of mycolic acid biosynthesis. PZA is effective against both active and dormant bacteria, and its use in antituberculous regimens shortens the course of therapy; however, resistance rapidly develops if it is used as single-agent therapy, and it should therefore only be used with other antituberculous medications.⁴⁹ PZA is synergistic with rifampin and has greatest efficacy if administered during the first 2 months of treatment with both INH and rifampin; this regimen effectively shortens the treatment course to only 6 months.¹³⁶ After oral administration, PZA is rapidly absorbed, with maximum concentrations occurring within 1 to 2 hours of administration, and a half-life of approximately 9 hours. Hepatic metabolism to pyrazinoic acid and 5-hydroxypyrazinoic acid occurs with the metabolites subsequently renally excreted.⁴⁹

When introduced in the 1950s, PZA was administered in doses of 40 to 50 mg/kg for extended periods of time. The dosages produced clinical hepatitis, with manifestations of highly elevated aminotransferase and bilirubin concentrations. Of patients taking high-dose PZA, elevations in aminotransferases were identified in 20%, and symptomatic hepatitis was identified in 10%, with a small number of those who developed hepatitis dying from a fulminant hepatic failure. As a result of these findings, PZA was believed to be highly hepatotoxic, and its use was discouraged. The resurgence of multidrug-resistant mycobacteria, however, has forced clinicians to reassess the role of PZA. Modern dosing regimens of 30 mg/kg for brief courses of 2 months infrequently produce hepatic injury, with some studies suggesting that addition of PZA to multidrug TB regimens confers no additional risk for hepatotoxicity.³⁵

Pyrazinamide is rarely used in pregnancy because the risk of birth defects is poorly defined. Animal studies suggest that PZA has no teratogenicity at therapeutic doses.² PZA is minimally excreted into breast milk and is presumed safe for breastfeeding.¹⁴ It is considered a category C drug in pregnancy.

Diagnostic Testing

Proper dosing of PZA and short courses of therapy are the two most important factors in preventing toxicity. Treatment for hepatotoxicity involves cessation of PZA therapy in conjunction with supportive care.³⁵ PZA inhibits the renal excretion of uric acid, and hyperuricemia is observed. More than 90% of children treated with short courses developed elevated uric acid concentrations.⁹⁹ Most patients, regardless of age, remain asymptomatic and do not develop symptoms of gout. Toxic effects from acute overdose of PZA have not been reported.

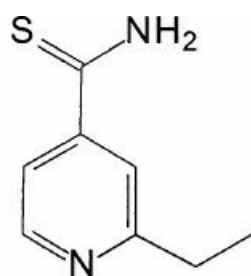
CYCLOSERINE

Cycloserine, previously avoided because of its adverse effects, is being used increasingly as second-line treatment with other tuberculostatic medications when treatment with primary agents (INH, rifampin, ethambutol, and streptomycin) fails or as initial therapy when drug susceptibility testing indicates either MDR-TB or XDR-TB. Cycloserine is a structural

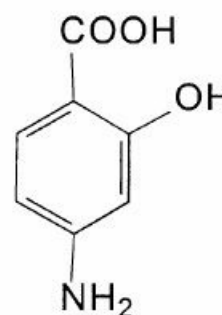
analog of alanine and demonstrates inhibition of D-alanine racemase and D-alanine ligase, which are involved in peptidoglycan cell wall synthesis.⁵² After oral doses, 70% to 90% of the drug is absorbed, and peak concentrations are reached in 3 to 8 hours. Cycloserine is distributed throughout all tissues and body fluids and easily crosses the blood–brain barrier. Less than 35% of the antibiotic is metabolized, and remaining xenobiotic is excreted unchanged in the urine.^{31,49}

Toxicity is dose dependent and occurs in as many as 50% of patients taking cycloserine. Cycloserine is a partial agonist at the NMDA/glycine receptor, which may contribute to neurologic effects such as somnolence, headache, tremor, dysarthria, vertigo, confusion, irritability, and seizures.⁵² Psychiatric manifestations include paranoid reactions, depression, and suicidal ideation. Reversible hypersomnolence and asterixis are reported with cycloserine, suggesting reversible thalamic neurotoxicity, which is corroborated by magnetic resonance imaging.⁶⁷ Cycloserine is contraindicated in patients with a history of either seizures or depression. Whenever this drug is used, serum concentrations must be monitored. Optimal treatment concentrations are between 20 and 35 mg/dL, and adverse effects are more common above 30 mg/dL. Cycloserine should be introduced slowly to avoid CNS toxicity.^{31,57,87} Toxicity, which can be potentiated by alcohol, usually appears within the first 2 weeks of therapy and ceases upon discontinuation. Because cycloserine is renally excreted, patients with impaired GFR may be predisposed to toxicity; it is removed by hemodialysis.³¹ Although no teratogenic effects were noted in three women exposed to cycloserine during the first trimester of pregnancy, cycloserine is not recommended for use during pregnancy. Cord blood concentrations are approximately 70% of serum concentrations, and no adverse effects occurred in breastfed infants. Consequently, cycloserine is considered to be safe in women who are breastfeeding.¹⁴ Reports of overdose are lacking in the English medical literature.

OTHER ANTIMYCOBACTERIALS



Ethionamide



Aminosalicilic acid

ETHIONAMIDE

Ethionamide, a congener of INH, is a prodrug with a mycotoxic intermediary metabolite thought to have a similar mechanism of action as INH, causing cell death from disruption of mycolic acid biosynthesis. Ethionamide is rapidly absorbed, widely distributed, and crosses the blood–brain barrier. Oral doses yield peak serum concentrations within approximately 3 hours of administration. The half-life is approximately 2 hours. The most common adverse symptoms associated with ethionamide are GI irritation and anorexia. Toxic effects such as orthostatic hypotension, depression, and drowsiness are common. Rash, purpura, and gynecomastia are observed, as are tremor, paresthesias, and olfactory disturbances. Approximately 5% of patients receiving ethionamide develop hepatitis; patients using this medication should be screened intermittently for hepatic injury. Treatment for toxicity involves withholding ethionamide therapy.⁴⁹

Birth defects were observed in seven of 23 newborns exposed to ethionamide in utero, although a consistent pattern of anomalies was lacking. Data regarding the presence and safety of breastfeeding on ethionamide also are lacking.¹⁴ Ethionamide is too toxic to be used as first-line therapy, but when needed, it should only be administered with another antituberculous medication because resistance develops rapidly when ethionamide is used alone.⁴⁹ Reports of death from ethionamide overdose are absent from the English literature.

para-AMINOSALICYLIC ACID

para-Aminosalicilic acid (PAS) is a structural analog of para-aminobenzoic acid and is thought to inhibit enzymes responsible for folate biosynthesis in mycobacteria but not in other organisms.⁴⁹ Despite common adverse effects, PAS is being used to a greater extent in the multidrug treatment plans for treating XDR-TB.⁸⁰ PAS is readily absorbed from the gut and is rapidly distributed in all tissues, especially the pleural fluid and caseous material. PAS has a half-life of

approximately one hour and is renally excreted. Adverse effects of PAS occur in 10% to 30% of patients and include anorexia, nausea, vomiting, diarrhea, sore throat, and malaise. Between 5% and 10% of patients receiving PAS develop hypersensitivity reactions characterized by high fever, rash, and arthralgias. Hematologic abnormalities of agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, and acute hemolytic anemia are reported.⁴⁹ PAS may be removed by hemodialysis in patients with kidney failure.⁷³ Adverse effects associated with chronic therapy may be treated by its withdrawal. Data regarding the safety of PAS in pregnancy and breastfeeding are lacking.¹⁴

Capreomycin

Capreomycin is a cyclic polypeptide currently used more frequently because of its antibacterial activity against MDR-TB and intracellular TB bacilli. TB strains resistant to more than one aminoglycoside may be susceptible to this polypeptide. Capreomycin interferes with ribosomes and inhibits protein translation but may also act by other mechanisms such as alterations in topoisomerase or the glyoxylate shunt pathway.⁴² Because of poor absorption after oral dosing, capreomycin must be administered intramuscularly. Toxicity associated with capreomycin use includes tinnitus, hearing loss, proteinuria, and electrolyte disturbances, although severe acute kidney injury is rare. Eosinophilia, leukocytosis, and rashes are described. Pain and sterile abscesses at the site of capreomycin injection are reported.⁴⁹ Data are lacking regarding the safety of capreomycin in pregnancy and breastfeeding.¹⁴

Many other antibiotics and immunomodulators that have been primarily overlooked or rejected for the management of TB are increasingly being used as part of multidrug regimens against resistant strains. Discussed more extensively in [Chap. 57](#), these include fluoroquinolones such as ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, sparfloxacin, macrolides such as clarithromycin, aminoglycosides such as amikacin, streptomycin, kanamycin, interferon, amoxicillin–clavulanate, linezolid, and clofazimine.⁸⁰

SUMMARY

- In overdose, certain antituberculous medications are of significant toxicologic concern.
- Patients acutely poisoned with INH require immediate and appropriate action to reverse seizures, acidemia, and coma beginning with the specific antidote pyridoxine. Pyridoxine is effective therapy, commonly augmented by benzodiazepines.
- Although less common than previously believed, hepatocellular injury resulting from therapeutic dosing of INH requires regularly scheduled, frequent evaluations to prevent fulminant hepatic failure.
- With the increasing prevalence of MDR-TB and XDR-TB strains, antituberculous medications previously avoided or ignored are now being used typically in combination with two or more other antituberculous medications. Despite reduced dosages compared with those previously used, significant adverse effects remain a concern in some cases.
- Rifampin causes numerous drug–drug interactions, some involving several anti-HIV therapies. Because antituberculous therapies are commonly needed in HIV infected patients, potential interactions between rifampin and antiretrovirals should remind clinicians to remain vigilant for unanticipated adverse effects.
- Patients receiving ethambutol, PZA, and other antituberculous medications benefit from careful surveillance for specific adverse effects such as decreased visual acuity, hepatic injury, and psychiatric manifestations. Despite the toxicity of this class of drugs, poisonings are often responsive to intervention when recognized early and treated appropriately.

Acknowledgment

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A14 ANTIDOTES IN DEPTH

Pyridoxine

Mary Ann Howland

INTRODUCTION

Pyridoxine (vitamin B₆), a water-soluble vitamin, is an antidote for overdoses of isonicotinic acid hydrazide (Isoniazid, INH), *Gyromitra esculenta* mushrooms, hydrazine, methylated hydrazines, and ethylene glycol. With the exception of ethylene glycol, all of these xenobiotics produce seizures by the competitive inhibition of pyridoxal-5'-phosphate (PLP). Pyridoxine overcomes this inhibition and may also enhance the less toxic pathway of ethylene glycol metabolism to form benzoic and hippuric acid, instead of oxalic acid.⁶ Hydrazine and methylated hydrazines (1,1-dimethylhydrazine, UDMH; monomethylhydrazine, MMH) are used as rocket fuels, and MMH is also found in *Gyromitra esculenta* mushrooms.³

HISTORY

Pyridoxine deficiency, which is characterized by seborrheic dermatitis, cheilosis, stomatitis, and glossitis, was first identified in 1926 but was mistakenly attributed to the absence of vitamin B₂ (Chap. 47).³¹ Ten years later, the deficiency was fully characterized and correctly recognized as a deficiency of vitamin B₆.³¹ A rare genetic abnormality that produces pyridoxine-responsive seizures in newborns was described in 1954.⁵

PHARMACOLOGY

Chemistry

The active form of pyridoxine is PLP.³¹ The alcohol pyridoxine, the aldehyde pyridoxal, and the aminomethyl pyridoxamine are all naturally occurring, related compounds that are metabolized by the body to its active form PLP.³¹ Pyridoxine was chosen by the Council on Pharmacy and Chemistry to represent vitamin B₆.³¹ Pyridoxine hydrochloride was chosen as the commercial preparation because of its stability.⁵⁵

Mechanism of Action

Pyridoxal-5'-phosphate is an important cofactor in more than 100 enzymatic reactions, including decarboxylation and transamination of amino acids, and the metabolism of tryptophan to 5-hydroxytryptamine (serotonin) and methionine to cysteine.^{23,31} In animals, iatrogenic pyridoxine deficiency produces seizures, resulting from reduced brain concentrations of PLP, glutamic acid decarboxylase, and γ -aminobutyric acid (GABA).¹⁶

Isoniazid and methylated hydrazines such as MMH interfere with the normal function of pyridoxine as a coenzyme. INH produces a syndrome resembling cerebral vitamin B₆ deficiency, which results in seizures.⁴³ Specifically, INH and other hydrazides and hydrazines inhibit the enzyme pyridoxine phosphokinase that converts pyridoxine to PLP (Fig. 58–3).²³ In addition, hydrazides directly combine with PLP, causing inactivation through the production of hydrazones that are rapidly excreted by the kidney.^{23,50} PLP is a coenzyme for L-glutamic acid decarboxylase, which facilitates the synthesis of GABA from L-glutamic acid. Animal studies suggest that interference with PLP limits the formation of GABA,^{23,50,51} which results in increased glutamic acid, thereby reducing cerebral inhibition, which contributes to the INH and methylated hydrazine–induced seizures.^{41,53} The administration of large doses of pyridoxine overcomes the deficiency.

Pharmacokinetics

Whereas pyridoxine is not protein bound, has a volume of distribution of 0.6 L/kg, and easily crosses cell membranes, PLP

is nearly entirely plasma protein bound.⁵⁵ At extrahepatic sites, pyridoxine is rapidly metabolized to pyridoxal, PLP, and 4-pyridoxic acid, with only 7% excreted unchanged in the urine.⁵⁵ After intravenous (IV) infusion of 100 mg of pyridoxine, PLP concentration increases rapidly in serum and in erythrocytes.⁵⁵ PLP rises from 37 to 2183 nmol/L in serum and from undetectable to 5593 nmol/L in erythrocytes.⁵⁵ Oral pyridoxine, in doses of 600 mg, is 50% absorbed within 20 minutes of ingestion by a first-order process, with rapid achievement of peak serum concentrations of pyridoxine, PLP, and pyridoxal.⁵⁴ The concentration of PLP appears to be tightly controlled in the serum and related to alkaline phosphatase activity.^{24,54} Oral doses of pyridoxine from 10 to 800 mg result in PLP concentrations of 518 to 732 nmol/L at 4 hours after ingestion.⁵⁴ Chronic alcoholic patients have lower baseline serum PLP concentrations because acetaldehyde enhances the degradation of PLP in erythrocytes through stimulation of an erythrocyte membrane-bound phosphatase that hydrolyzes phosphate containing B₆ compounds.³⁰

ROLE IN HYDRAZIDE- AND HYDRAZINE-INDUCED SEIZURES

Animal Studies

In a canine model of INH induced toxicity, pyridoxine reduced the severity of seizures, increased the duration of seizure free periods, and prevented death from a previously determined lethal dose of INH in a dose dependent fashion.^{13,14} Lower molar ratios prevented deaths, and higher molar ratios prevented both deaths and seizures.¹⁴ When used as single treatments for INH induced seizures, phenobarbital, pentobarbital, phenytoin, ethanol, and diazepam were ineffective in controlling seizures and death, but when combined with pyridoxine, each protected the animals from seizures and death.¹³ Other small animal experiments have documented the effectiveness of pyridoxine against MMH induced seizures when used without^{23,34,46} and with diazepam.²⁰ Anticonvulsant efficacy is also demonstrated in feline⁴² and primate⁴⁴ models.

Rat studies with intraperitoneal UDMH also demonstrate the protective effects of pyridoxine, which prevented seizures and death in a model that produced 94% mortality and 100% seizures without pyridoxine.¹⁵ Other studies in dogs and monkeys also demonstrate the effectiveness of pyridoxine in preventing seizures and mortality, and in treating seizures.⁴ Intramuscular pyridoxine protected the monkeys from death and stopped the seizures caused by IV exposure to UDMH.

Human Data

Clinical experience with pyridoxine for INH overdose in humans demonstrates favorable results.^{2,11} Rapid seizure control with no morbidity or mortality was achieved when the ratio in grams of pyridoxine administered to INH ingested ranged from 0.14 to 1.3, although in practice, most patients receive approximately gram-for-gram amounts. In five patients, the use of gram-for-gram amounts of pyridoxine resulted in the complete control of seizures and a resolution of the metabolic acidosis.⁴⁹ In eight patients with intentional INH overdoses, basic poison management, intensive supportive care, and a mean dose of 5 g of pyridoxine IV resulted in no fatalities.⁸ Seizures were controlled in a 22 month-old boy given 100 mg of IV pyridoxine after an estimated INH ingestion of 5 g.⁴³ Variable results are reported when lesser amounts of pyridoxine are used.³² Seizures were reported in two patients after ingestion of INH–pyridoxine combination tablets, although the actual amount of pyridoxine ingested was not noted.⁴⁵

In addition to controlling seizures, administration of pyridoxine also appears to restore consciousness. Two patients, who remained obtunded for as long as 72 hours after the apparent resolution of the seizures, were reported to awaken immediately after 3 to 10 g of IV pyridoxine was administered.¹⁰ A third patient who was lethargic awakened with IV pyridoxine. This suggests that mental status abnormalities associated with INH overdose (and possibly hydrazine overdoses) may be responsive to pyridoxine and may also require repetitive dosing.^{11,49} Patients treated with large doses of pyridoxine awaken more rapidly even after experiencing sustained seizure activity or status epilepticus.

Monomethylhydrazine poisoning can be encountered in a variety of clinical situations. In the aerospace industry, where MMH is used as a rocket propellant, percutaneous or inhalational poisoning may occur. Ingestion of the false morel mushroom, *Gyromitra esculenta*, can also produce toxicity when its major toxic compound, gyromitrin, is metabolized to MMH (Chap. 120).^{3,18}

The neurologic effects of MMH poisoning are similar to those of INH toxicity and include seizures and respiratory failure.¹⁶ Severe liver damage similar to INH induced hepatotoxicity is also described.⁹ As in the case of INH induced hepatotoxicity, there is no evidence that MMH induced hepatotoxicity can be treated by administration of pyridoxine.⁹

A patient who was exposed to hydrazine became comatose 14 hours later and remained comatose for 60 hours until treated with 25 mg/kg of pyridoxine.²⁵ A man with an altered consciousness who had ingested an unknown quantity of hydrazine improved after treatment with 10 g of pyridoxine.²² This improvement occurred over 24 hours and may have been unrelated to pyridoxine therapy. A severe sensory peripheral neuropathy lasting for 6 months developed one week after the overdose and was most likely a result of the hydrazine ingestion and not the pyridoxine. Six patients exposed to an

Aerozine-50 (hydrazine and UDMH) spill were effectively treated with pyridoxine after developing twitching, clonic movements, hyperactivity, or gastrointestinal symptoms.¹⁹ A patient exposed to UDMH during an explosion developed extensive burns, diverse neurologic manifestations, and electroencephalographic findings that resolved rapidly after the administration of IV pyridoxine.¹⁷

ROLE IN ETHYLENE GLYCOL

Pyridoxal-5'-phosphate is a cofactor in the conversion of glycolic acid to nonoxalate compounds ([Chap. 109](#)). Patients poisoned with ethylene glycol should receive 100 mg/d of pyridoxine IV in an attempt to shunt metabolism preferentially away from the production of oxalic acid. This approach is supported by an animal model⁶ and the study of primary hyperoxaluria,²¹ although there are no adequate studies of human ethylene glycol poisoning.³⁶

ADVERSE EFFECTS AND SAFETY ISSUES

Pyridoxal-5'-phosphate is neurotoxic to animals and humans when administered chronically in supraphysiologic doses.^{25,27,37} Delayed peripheral neurotoxicity occurred in patients taking daily doses of 200 mg to 6 g of pyridoxine for one month.^{35,40,41} Healthy volunteers given 1 or 3 g/d developed a small and large fiber distal axonopathy, with sensory findings and quantitative sensory threshold abnormalities occurring after 1.5 months at the high dose and 4.5 months at the low dose exposure. When symptoms occurred, the pyridoxine was immediately stopped, but symptoms progressed for 2 to 3 weeks ([Chap. 24](#)).⁷

Pyridoxine may also induce a sensory neuropathy when massive doses are administered, either as a single dose or over several days.^{1,26,48} Ataxia occurred in dogs receiving 1 g/kg of pyridoxine.⁴⁸ Larger doses of pyridoxine result in loss of coordination, ataxia, seizures, and death.⁴⁸ Death after pyridoxine administration was sometimes delayed for 2 to 3 days.⁴⁸

Two patients treated with 2 g/kg of IV pyridoxine (132 and 183 g, respectively) over 3 days developed severe and disabling sensory neuropathies.¹ One year later, both patients were unable to walk. Inadequate information is available to determine the maximal single acute nontoxic dose in humans; however, there appears to be a wide margin of safety. Doses of pyridoxine ranging from 70 to 375 mg/kg or doses equivalent to the milligram-per-kilogram historical dose of ingested INH have been administered without adverse effects.^{28,49}

The 0.5% chlorobutanol preservative in IV pyridoxine equates to doses of 250 to 500 mg of chlorobutanol when 5 and 10 g doses of pyridoxine are administered. Chlorobutanol is a sedative with a long elimination half-life, but doses of 600 mg were given to human volunteers without complication.^{12,47} A dose of 5 g IV pyridoxine administered over 5 minutes to five healthy volunteers produced a transient minor increase in base deficit without any alteration in the level of consciousness.²⁹

PREGNANCY AND LACTATION

Pyridoxine is Food and Drug Administration pregnancy category A. The recommended daily allowance for pyridoxine in pregnancy is 2.2 mg. There has never been a controlled trial in pregnant women of gram doses of pyridoxine, but the benefit of using pyridoxine for INH induced seizures would clearly exceed the theoretical risk to the fetus. Pyridoxine enters breast milk and is considered compatible with breastfeeding. However, concentrations of pyridoxine in breast milk after maternal gram doses of pyridoxine have not been studied.

DOSING AND ADMINISTRATION

A safe and effective pyridoxine regimen for INH overdoses in adults is 1 g of pyridoxine for each gram of INH ingested, or 70 mg/kg in a child both to a maximum of 5 g.⁴⁹ These doses are sufficient in the majority of patients, but the dose can be repeated if necessary. The best way to administer pyridoxine in a patient after an INH overdose has not been established. For a patient who is actively seizing, pyridoxine may be given by slow IV infusion at approximately 0.5 g/min until the seizures stop or the maximum dose has been reached. When the seizures stop, the remainder of the dose should be infused over 4 to 6 hours to maintain pyridoxine availability while the INH is being eliminated. The dose should be repeated if seizures persist or recur or if the patient exhibits mental status depression, which could be an indication of persistent neurotoxicity and electrical status epilepticus. If IV pyridoxine is unavailable, oral pyridoxine should be administered.^{39,52}

For hydrazine and methylated hydrazines (ie, MMH, UDMH) poisoning, there is no established dose.⁵³ Using the same dosage regimen as in the case of INH poisoning is theoretically reasonable and appropriate, although it has never been tested in humans.

FORMULATION

Pyridoxine hydrochloride is available parenterally at a concentration of 100 mg/mL with a 1 mL fill in a 2 mL vial with 0.5% chlorobutanol as the preservative and 1.4 µg/mL aluminum from APP Pharmaceuticals.³⁸ Thus, a 5 g IV dose of pyridoxine requires fifty 100 mg/mL vials. This is an exception to the rule that appropriate doses of medications rarely require multiple vials and certainly not of this magnitude. This quantity also emphasizes the necessity of maintaining an adequate supply in the emergency department as well as in the pharmacy.³³ Oral pyridoxine is available in many tablet strengths from 10 to 500 mg depending on the manufacturer.

SUMMARY

- Pyridoxine and a benzodiazepine should be used to achieve synergistic control of INH or MMH poisoning. An adequate dose of IV pyridoxine is 70 mg/kg to a maximum of 5 g and repeated once as needed.
- Five grams of IV pyridoxine requires administration of fifty 100-mg/mL vials.
- Adequate stocks should be ensured in the ED and pharmacy.
- If IV pyridoxine is unavailable, oral pyridoxine may be used.

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59 ANTIMALARIALS

James David Barry

The malaria parasite has caused untold grief throughout human history. The name originated from Italian *mal aria* (bad air) because the ancient Romans believed the disease was caused by the decay in marshes and swamps and was carried by the malodorous “foul” air emanating from these areas.¹⁰ In the 1880s, both the *Plasmodium* protozoa as well as its mosquito vector were identified.¹⁰ Today, 40% of the world’s population lives in areas where malaria is endemic. More than 500 million people develop acute malaria infection, and an estimated one million die from the infection each year.^{2,10,46} Most of these deaths are from *Plasmodium falciparum* infections of young children in Africa.⁵ To put this into perspective, it is estimated that two children die from malaria every minute worldwide.⁵⁵ Included among those at risk of becoming infected are 50 million travelers from industrialized countries who visit the developing countries each year. Despite using prophylactic medications, 30,000 of these travelers will acquire malaria.¹⁰¹

MALARIA OVERVIEW

Malaria is an infection of protozoan parasites in the *Plasmodium* genus with a unique lifecycle involving the *Anopheles* mosquito as vector. Today malaria is primarily endemic in tropical and subtropical areas worldwide. It was once endemic in temperate areas, including Western Europe and the United States, but economic development and improvements in public health hastened its retreat.⁴⁵ Malaria was fully eradicated from the United States between 1947 and 1951 due in large part to the powerful insecticidal effects of dichloro-diphenyl-trichloroethane (DDT).⁴⁵ The emergence of DDT-resistant *Anopheles* mosquitoes and chloroquine resistant *Plasmodium* spp have impeded eradication in other parts of the world.⁴⁵

Malaria has a unique lifecycle (Fig. 59–1) beginning with inoculation of sporozoites from an infected female *Anopheles* saliva. The sporozoites travel to the liver, where they invade the host’s hepatocytes and undergo asexual division (asexual exoerythrocytic cycle), ultimately causing rupture of the infected hepatocyte (tissue schizont) and release of thousands of merozoites into the blood stream.⁹ The tissue phase is complete at this point with the exception of *Plasmodium vivax* and *Plasmodium ovale*, which can remain dormant in liver cells (hypnozoites), causing recurrent infections years later. The erythrocytic cycle begins when merozoites penetrate erythrocytes (trophozoites), undergoing additional cycles of asexual division (erythrocytic schizont), leading to cell rupture and the release of a new wave of merozoites to infect additional erythrocytes. This erythrocytic cycle is responsible for the clinical manifestations of malaria. Some erythrocytic merozoites differentiate into sexual forms (macrogametocytes, female and microgametocytes, male). Ingestion of both sexual forms by the female *Anopheles* during a blood meal allows fertilization and zygote formation in the mosquito midgut epithelium (sporogonic cycle), ultimately leading to rupture of an oocyst and release of sporozoites that migrate to the salivary glands, awaiting injection into another victim.¹²³

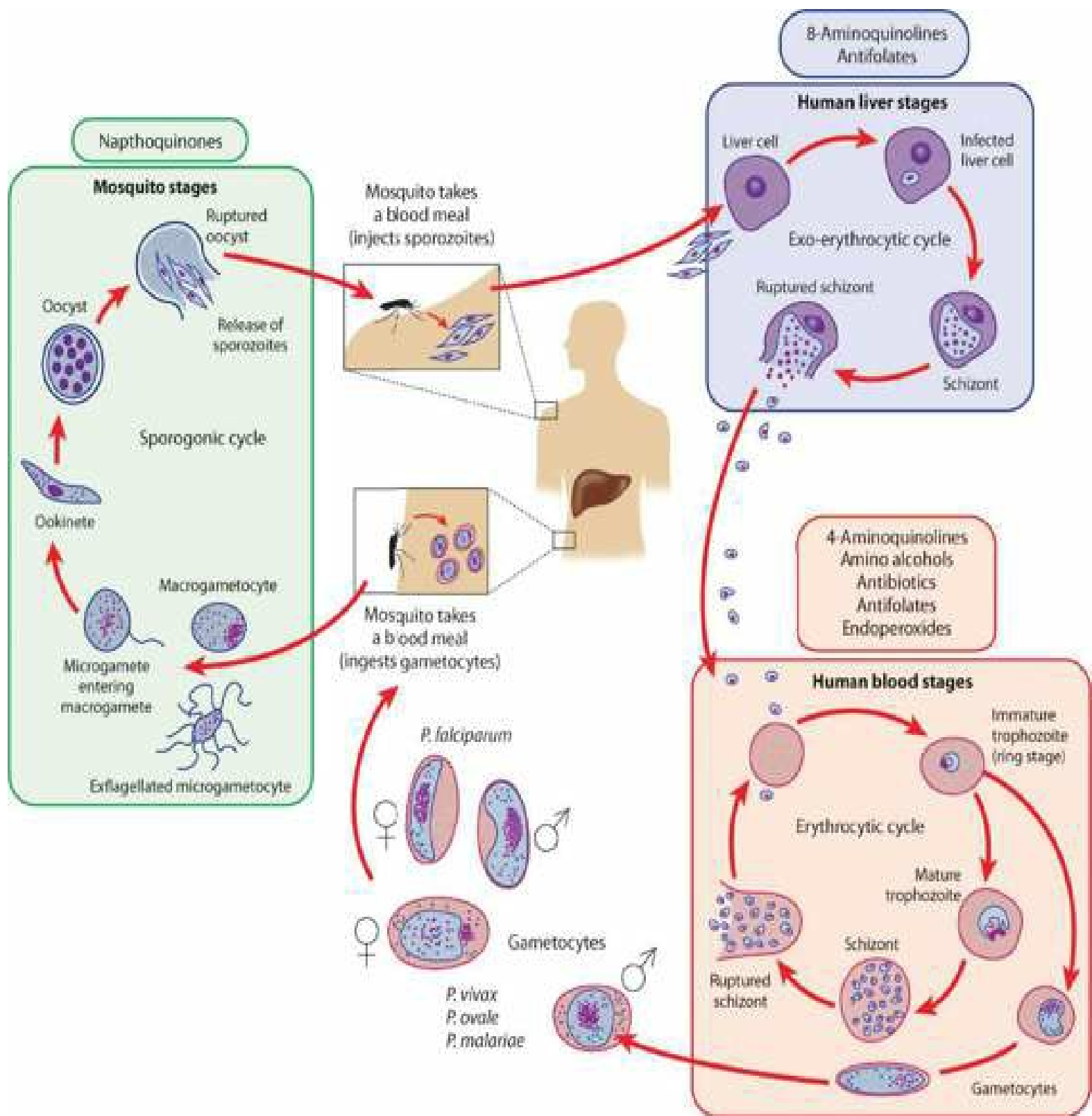


FIGURE 59–1. Life cycle stages during which antimalarials exert their effects.

Five *Plasmodium* spp cause malaria in humans (Table 59–1). The majority of cases worldwide are caused by *P. falciparum* and *P. vivax*, with *P. falciparum* responsible for the overwhelming majority of deaths.⁷⁷ Traditional teaching highlights the synchronization of blood parasite cycles causing a somewhat predictable fever periodicity, described as tertian or quartan fever depending on the causative organism. These classic periodic fevers are rarely observed in Western countries because symptomatic cases are diagnosed earlier than in the past.⁹ The routine use of antipyretics may also contribute to atypical presentations.

TABLE 59–1. *Plasmodium* spp Affecting Humans

Species	Distribution	Fever Cycle (days)	RBC Preference	Parasitemia Levels	Comments
<i>P. falciparum</i>	Widespread throughout tropics	2 or less (sub-tertian)	All ages	Can be high	Most fatalities
<i>P. knowlesi</i>	Malaysia and neighboring countries	1	All ages	Can be high	Zoonosis (primary host Macaque monkey) severe disease
<i>P. malariae</i>	Patchy worldwide	3–4 (quartan)	Old	Low	Chronic infections, late recrudescence
<i>P. ovale</i>	Africa	2–3 (tertian)	Young	Low	Relapses/hepatic hypnozoites
<i>P. vivax</i>	Predominantly Asia	2–3 (tertian)	Young	Low	Relapses/hepatic hypnozoites

Unlike the other forms of human malaria, *Plasmodium knowlesi* is a true zoonosis, the natural host being macaques (*Macaca* spp) and related monkey species. Natural transmission of a nonhuman *Plasmodium* spp to humans was thought to be rare, but increasing numbers of *P. knowlesi* malarial infections have been reported in and around Malaysia, Indonesia, and Southeast Asia, causing scientists to include this agent as a potential human pathogen.⁵⁵

ANTIMALARIAL HISTORY

It is somewhat ironic that despite sophisticated drug development methods and advanced technology of the 21st century, the most widely used old treatments (quinine and its derivatives) and the best new regimens (artemisinins) have both been used for centuries as ancient herbal remedies derived from plants.

The bark of the cinchona tree, the first effective remedy for malaria, was introduced to Europeans more than 350 years ago.¹¹⁷ The toxicity of its active ingredient, quinine, was noted from the inception of its use. Pharmaceutical advances occurred, funded largely by the US military during World War II, yielding 4-aminoquinolines, 8-aminoquinolines, and novel antifolates. To combat emerging strains of drug resistant *P. falciparum* that developed during the Vietnam conflict, alternate quinine derivatives (amino alcohols) were developed.^{112,117} Other drugs used to treat malaria include the folate inhibitors, selected antibiotics, the sulfonamide sulfadoxine, the tetracyclines, and the macrolides ([Chap. 57](#)).

With the introduction of each new drug, resistance developed, particularly in Oceania, Southeast Asia, and Africa.^{112,117} In some places, quinine is again the first-line therapy for malaria.⁶² In the past 2 decades, the search for active xenobiotics has returned to a natural product, the Chinese herb qinghaosu. The active metabolite, dihydroartemisinin, is common to all the endoperoxidases. These drugs are primarily used as part of an artemisinin-based combination therapy (ACT), which is recommended by the World Health Organization (WHO) as the preferred treatment of malaria in drug-resistant areas.^{2,10} With increased leisure travel, a greater number of North Americans are taking prophylactic medications with potential toxicity.

This chapter highlights the toxicity of the most commonly used antimalarials using the structural and mechanistic classification outlined in [Table 59–2](#).

TABLE 59–2. Antimalarial Classification and Mechanisms

<i>Class</i>	<i>Examples</i>	<i>Antimalarial Mechanism</i>	<i>Lifecycle Stage Effect</i>
Amino alcohols	Halofantrine Lumefantrine Mefloquine Quinine	Inhibit heme digestion	Erythrocytic cycle ^a
4-aminoquinolines	Amodiaquine Chloroquine Hydroxychloroquine Piperaquine	Inhibit heme digestion	Erythrocytic cycle ^a
8-aminoquinolines	Diethylprimaquine Primaquine	Oxidant stress	Liver stages hypnozoitocidal
Endoperoxides	Artemether Artesunate Artemisinin Artemisone Dihydroartemisinin	Unknown but oxidant stress likely contributes	Erythrocytic cycle ^a
Antifolates	Cycloguanil Chlorproguanil Dapsone Proguanil Pyrimethamine Trimethoprim	Inhibit dihydro-folate reductase	(All growing stages) Erythrocytic cycle ^a Exo-erythrocytic cycle ^b
Antibiotics	Sulfonamides Sulfadoxine	Inhibit dihydropteroate synthetase	Erythrocytic cycle ^a
	Cyclines Doxycycline Tetracycline	Inhibit protein synthesis	Erythrocytic cycle ^a
	Macrolides Azithromycin Clindamycin	Apicoplast disruption	Erythrocytic cycle ^a
Napthoquinones	Atovaquone	Inhibit mitochondrial respiration	Mosquito sporogonic cycle ^c

^aBlood schizonticidal and blood gametocidal. ^bLiver schizonticidal but not effective against hypnozoites.

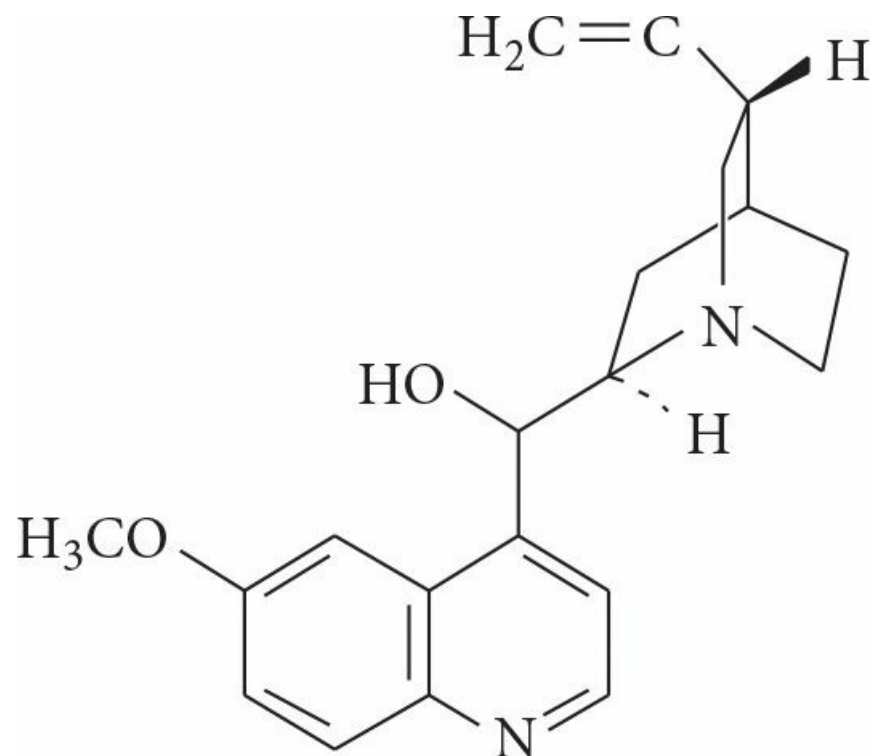
^cAltered oocyst development.

AMINO ALCOHOLS

Antimalarial Mechanism

Unlike humans, who detoxify heme through the use of heme oxygenase producing the bile pigment biliverdin, *Plasmodium* spp convert heme to the nontoxic relatively inert compound hemozoin. Amino alcohols and 4-aminoquinolines concentrate in parasite food vacuoles, where they inhibit the ability of the parasite to detoxify hemozoin, leading to accumulation of toxic heme byproducts and parasite death.^{94,123} In resistant parasites, these antimalarials fail to concentrate in food vacuoles because of increased drug efflux. This resistance is thought to be conferred through amplification of a transmembrane pump. Interestingly, tricyclic antidepressants, phenothiazines, and calcium channel blockers have been shown to reverse resistance in experimental models.⁹⁴

Quinine



The therapeutic benefits of the bark of the cinchona tree have been known for centuries. As early as 1633, cinchona bark was used for its antipyretic and analgesic effects,⁷⁶ and in the 1800s, it was used for the treatment of “rebellious palpitations.”¹¹⁷ Quinine, the primary alkaloid in cinchona bark, was the first effective treatment for malaria. Additionally, because of a reported curarelike action, quinine has also been used as a treatment for muscle cramps. Because of its extremely bitter taste similar to that of heroin, quinine is used as an adulterant in drugs of abuse. Small quantities of quinine can be also found in some tonic waters.

High doses of quinine and other cinchona alkaloids are oxytocic, potentially leading to abortion or premature labor in pregnant women. Because of this, quinine has been used as an abortifacient ([Chap. 21](#)).⁷⁸ Chloroquine continues to be used for this purpose in some parts of the developing world.^{12,95} Neither is safe for this purpose because of their narrow toxic-to-therapeutic ratio.

Pharmacokinetics and Toxicokinetics. See [Table 59–3](#) for the pharmacokinetic properties of quinine. Quinine and quinidine are optical isomers and share similar pharmacologic effects as class IA antidysrhythmics and antimalarials. Both are extensively metabolized in the liver, kidneys, and muscles to a variety of hydroxylated metabolites. Quinine undergoes transplacental distribution and is secreted in breast milk.

TABLE 59–3. Pharmacokinetic Properties of Antimalarials

<i>Antimalarial</i>	<i>Bioavailability (%)</i>	<i>Time to Peak Hours (oral)</i>	<i>Protein Bound (%)</i>	<i>Volume of Distribution (L/kg)</i>	<i>Half-Life</i>	<i>Urinary Excretion (%)</i>	<i>Comments</i>
Artemisinin	Limited	—	Large	—	2–5 h	—	Metabolism largely through cytochrome P450 system.
Chloroquine	80	2–5	50–65	>100	40–55 d	55	—
Dapsone	90	3–6	70–80	0.5–1	21–30 h	20	—
Halofantrine	Low, varies	4–7	—	>100	1–6 d	—	Active metabolite.
Mefloquine	>85	8–24	98	15–40	15–27 d	<1	Hepatic metabolism. Inactive metabolite.
Primaquine	74	1–3	—	2.9	5–7 h	4	Active Metabolites primarily responsible for therapeutic and toxic effects.
Pyrimethamine	>95	2–6	87	3	3–4 d	16–32	—
Quinine	76	1–3	93	1.8–4.6	9–15 h	20	Protein binding increased in alkaline environments. Urinary excretion increased with acidic urine.

— = poorly studied or unknown.

Pathophysiology. Quinine overdose affects multiple organ systems through a number of different pathophysiologic mechanisms. Studies evaluating mechanisms of toxicity have focused on those organ systems primarily affected. Outcomes appear to be most closely related to the degree of cardiovascular dysfunction.⁴²

Quinine and quinidine share anti- and prodysrhythmic effects primarily from an inhibiting effect on the cardiac sodium channels and potassium channels (**Chaps. 16 and 64**).⁴³ Blockade of the sodium channel in the inactivated state decreases inotropy, slows the rate of depolarization, slows conduction, and increases action potential duration. Inhibition of this rapid inward sodium current is increased at higher heart rates (called use-dependent blockade), leading to a rate-dependent widening of the QRS complex.^{117,126}

Inhibition of the potassium channels suppresses the repolarizing delayed rectifier potassium current, particularly the rapidly activating component,¹²⁶ leading to prolongation of the QT interval. The resultant increase in the effective refractory period is also rate dependent, causing greater repolarization delay at slower heart rates and predisposing to torsade de pointes. As a result, syncope and sudden dysrhythmogenic death may occur. An additional α -adrenergic antagonist effect contributes to the syncope and hypotension occurring in quinine toxicity.

Inhibition of the adenosine triphosphate (ATP)–sensitive potassium channels of pancreatic β cells results in the release of insulin, similar to the action of sulfonylureas (**Chap. 53**).³² Patients at increased risk of quinine induced hyperinsulinemia include those patients receiving high dose intravenous (IV) quinine, intentional overdose, and patients with other metabolic stresses (eg, concurrent malaria, pregnancy, malnutrition, and ethanol consumption).^{21,63,86,90,114}

The mechanism of quinine induced inhibition of hearing appears to be multifactorial.¹¹² Microstructural lengthening of the outer hair cells of the cochlea and organ of Corti occurs.⁴⁸ Additionally, vasoconstriction and local prostaglandin inhibition within the organ of Corti may contribute to decreased hearing.¹¹² Inhibition of the potassium channel may impair hearing and produce vertigo because it is known that the homozygous absence of gene products that form part of some potassium channels (Jervell and Lange-Nielson syndrome) causes deafness and prolonged QT intervals (**Chaps. 16 and 26**).¹¹¹

Although older theories suggested that quinine caused retinal ischemia, the preponderance of evidence points to a direct toxic effect on the retina.⁴⁹ Electroretinographic studies demonstrate a rapid and direct effect on the retina (decreased potentials) within minutes after doses of quinine.⁴⁴ These early retinographic changes, as well as histologic lesions in photoreceptor and ganglion cell layers, provide evidence of direct damage.⁴⁴ Changes in the electrooculogram suggest changes in the retinal pigment epithelium and parallel changes in visual acuity. In contrast, no electrophysiologic, angiographic, or morphologic experimental evidence for retinal ischemia has been found.⁴⁹ Quinine may also antagonize cholinergic neurotransmission in the inner synaptic layer.

Quinine has direct irritant effects on the gastrointestinal (GI) tract and stimulates the brainstem center responsible for nausea and emesis.¹¹⁷

Clinical Manifestations. Quinine overdose typically leads to GI complaints, tinnitus, and visual symptoms within hours, but the time course varies with the formulation ingested, coingestants, patient characteristics, and other case-specific

details. Significant overdose is heralded by cardiovascular and central nervous system (CNS) toxicity. Death can occur within hours to days, usually from a combination of shock, ventricular dysrhythmias, respiratory arrest, or acute kidney failure (AKI).

Patients receiving even therapeutic doses often experience a syndrome known as “cinchonism,” which typically includes GI complaints, headache, vasodilation, tinnitus, and decreased hearing acuity.^{76,117} Vertigo, syncope, dystonia, tachycardia, diarrhea, and abdominal pain are also described.^{51,67,86}

Quinine toxicity is closely correlated with total serum concentrations, but only the non protein bound portion is likely responsible for toxic effects. However, because free and total quinine concentrations vary widely from person to person,³⁹ a single quinine concentration may not always correlate with clinical toxicity. In general, serum concentrations greater than 5 µg/mL may cause cinchonism, greater than 10 µg/mL visual impairment, greater than 15 µg/mL cardiac dysrhythmias, and greater than 22 µg/mL death.⁸ Similar concentrations in individuals who are severely ill with malaria do not necessarily result in as severe toxicity because of the increase α_1 -acid glycoprotein and consequent reduction in free fraction of quinine present.^{102,106}

The margin between therapeutic and toxic dosing of quinine is very small. It is not surprising that patients taking therapeutic doses frequently develop toxicity because the recommended range of serum quinine concentrations for treatment of falciparum malaria is 5 to 15 µg/mL, well above the concentration reported to cause cinchonism.

The average oral lethal dose of quinine is 8 g, although a dose as small as 1.5 g is reported to cause death.^{40,51} Delirium, coma, and seizures are less common, usually occurring only after severe overdoses.¹⁷

Cardiovascular manifestations of quinine use are related to myocardial drug concentrations.¹⁵ They manifest on the electrocardiogram (ECG) as prolongation of the PR interval; prolongation of the QRS complex, QT interval, and ST depression with or without T wave inversion also occur.¹¹ Patients may develop complete heart block or dysrhythmias.¹⁵ Patients taking high doses of quinine must be monitored for torsade de pointes, ventricular tachycardia, and ventricular fibrillation. Quinine toxicity can also result in significant hypotension.

Although not commonly reported, mild hyperinsulinemia and resultant hypoglycemia can occur in cases of oral quinine overdose.^{17,21,42,63,105,128,129} Hypoglycemia with elevated serum insulin concentrations after therapeutic dosing was documented in case reports complicated by severe congestive heart failure and significant ethanol consumption. Hypoglycemia is also noted in healthy patients after overdose.⁶³

Eighth cranial nerve dysfunction results in tinnitus and deafness. The decreased acuity is not usually clinically apparent, although the patient recognizes tinnitus.⁹⁹ These findings usually resolve within 48 to 72 hours, and permanent hearing impairment is unlikely.

Ophthalmic presentations include blurred vision, visual field constriction, tunnel vision, diplopia, altered color perception, mydriasis, photophobia, scotomata, and sometimes complete blindness.^{17,36,44} The onset of blindness is invariably delayed and usually follows the onset of other manifestations by at least 6 hours. The pupillary dilation that occurs is usually nonreactive and correlates with the severity of visual loss. Funduscopic examination findings may be normal but usually demonstrate extreme arteriolar constriction associated with retinal edema. Normal arteriolar caliber may be initially present, but funduscopic manifestations such as vessel attenuation and disc pallor may develop as clinical improvement occurs. Improvement in vision can occur rapidly but is usually slow, occurring over a period of months after a severe exposure. Initially, improvement occurs centrally and is followed later by improvement in peripheral vision. The pupils may remain dilated even after return to normal vision.⁴⁰ Patients with the greatest exposure may develop optic atrophy.

Hypokalemia is often described in the setting of quinine poisoning,¹⁰⁵ although the mechanism is unclear. An intracellular shift of potassium rather than a true potassium deficit is the predominant theory behind the hypokalemia associated with chloroquine,^{71,73} and the mechanism may be similar with quinine.

A number of hypersensitivity reactions are described. These are the result of antiquinine or antiquinine-hapten antibodies cross-reacting with a variety of membrane glycoproteins.^{18,57} Asthma and dermatologic manifestations, including urticaria, photosensitivity dermatitis, cutaneous vasculitis, lichen planus, and angioedema, also occur.¹¹⁴

Hematologic manifestations of hypersensitivity are rare, but include thrombocytopenia ([Chap. 22](#)), agranulocytosis, microangiopathic hemolytic anemia, and disseminated intravascular coagulation (DIC), which can lead to jaundice, hemoglobinuria, and renal failure.^{51,57} Hemolysis may also occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immunogenic drug platelet complex interactions can occur even after low doses of quinine, such as those in tonic drinks. This self-limited interaction has previously been termed “cocktail purpura.”^{76,117}

A hepatitis hypersensitivity reaction,³⁸ acute respiratory distress syndrome (ARDS), and a sepsislike syndrome are also reported.⁶⁰

Diagnostic Testing. Urine thin-layer chromatography is sensitive enough to confirm the presence of quinine even after

the ingestion of tonic water.¹²⁹ Quinine immunoassay techniques are also available. Quantitative serum testing is not rapidly or widely available.

Management. Patients frequently vomit spontaneously. Emetics should not be used in the absence of vomiting because seizures, dysrhythmias, and hypotension can occur rapidly. Orogastric lavage should only be considered for patients with recent, substantial (potentially life-threatening) ingestions with no spontaneous emesis. Activated charcoal effectively adsorbs quinine and may additionally decrease serum concentrations by altering enteroenteric circulation.^{3,66}

Expectant treatment should be initiated, including oxygen, cardiac and hemodynamic monitoring, IV fluid resuscitation, and frequent ECG and blood glucose measurements.

Extracorporeal membrane oxygenation was used in one case of severe quinidine poisoning with bradydysrhythmias and refractory hypotension to stabilize the cardiovascular system while a quinidine-activated charcoal bezoar was removed and the patient metabolized the remaining quinidine.¹¹⁵ A similar approach should be considered for intractable quinine toxicity.

Cardiac. A conduction delay manifested by a QRS duration of more than 100 msec should be treated with sodium bicarbonate alkalization to achieve a serum pH of 7.45 to 7.50, as would be done in patients with cardiotoxicity associated with cyclic antidepressant overdoses (Antidotes in Depth: A5). Protein binding is increased in the setting of alkalemia, decreasing the cardiotoxic manifestations of quinine. Thus, serum alkalization with sodium bicarbonate is a logical therapeutic intervention. Sodium bicarbonate therapy is successful in case reports^{15,42,76} but has not been specifically studied. Hypertonic sodium bicarbonate may result in or worsen existing hypokalemia, potentially exacerbating the effect of potassium channel blockade.

Potassium supplementation for quinine-induced hypokalemia is controversial because experimental data from the 1960s suggest that hypokalemia is protective against cardiotoxicity and prolongs survival.^{20,71,105} Because hypokalemia can also lead to lethal dysrhythmias, supplementation for hypokalemia is presently recommended.

The QT interval should be carefully monitored for prolongation. If necessary, interventions for torsade de pointes, including magnesium administration, potassium supplementation, and overdrive pacing, should be initiated (Chap. 17).

Class IA, IC, or III antidysrhythmics and other xenobiotics with sodium channel or potassium channel blocking activity should not be used to treat quinine-overdosed patients because they may exacerbate quinine-induced conduction disturbances or dysrhythmias. The Class IB antidysrhythmics, such as lidocaine, have been used with reported success, but no clinical trials have been performed (Chap. 64).

Hypotension refractory to IV crystalloid boluses should be treated with vasopressors. Although not directly studied, direct acting vasopressors such as epinephrine, norepinephrine, and phenylephrine are recommended. An intraaortic balloon pump was successfully used for the treatment of refractory hypotension in one case report.¹⁰⁵

Ophthalmic. Fundoscopic examination, visual field examination, and color testing may be appropriate bedside diagnostic studies. Electroretinography, electrooculography, visual-evoked potentials, and dark adaptation may be helpful in assessing the injury but are not practical because they require equipment that is not portable or readily available in most clinical settings. There is no specific, effective treatment for quinine retinal toxicity,^{44,47} although hyperbaric oxygen (HBO) was used in three patients who recovered vision, but the role of HBO in that recovery was not established.^{44,129}

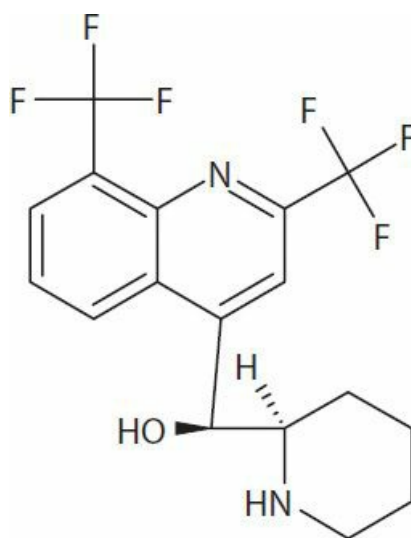
Hypoglycemia. A low serum glucose concentration should be supported with an adequate infusion of dextrose. Serum potassium concentration and the QT interval should be monitored during correction and maintenance. Octreotide was successfully used to correct quinine induced hyperinsulinemia in adult malaria victims.^{89,90} In volunteers, quinine induced hyperinsulinemia was suppressed within 15 minutes after a 100 µg intramuscular dose of octreotide (Antidotes in Depth: A13).⁸⁹ Octreotide should be used for cases of refractory hypoglycemia in a fashion similar to that recommended in sulfonylurea toxicity, which is 50 µg (1 µg/kg in children) subcutaneously every 6 hours (Chap. 53).

Enhanced Elimination. The effect of multiple-dose activated charcoal (MDAC) on quinine elimination was studied in an experimental human model and in symptomatic patients.⁹² In these patients, MDAC decreased the half-life of quinine from approximately 8 hours to about 4.5 hours and increased clearance by 56%.⁹² Although numerous studies show that activated charcoal decreases quinine half-life,^{13,66,92} evidence of clinical benefit is lacking. Nevertheless, because ophthalmic, CNS, and cardiovascular toxicity are related to serum concentration, it is prudent to reduce concentrations as quickly as practicable; thus, activated charcoal (0.5 g/kg) should be administered every 2 to 4 hours for about four doses unless contraindications exist.

There is conflicting evidence about a benefit of urinary acidification in enhancing clearance.^{13,102} But because of the increased potential for cardiotoxicity associated with acidification, this technique is never recommended.

Because quinine has a relatively large volume of distribution and is highly protein bound, hemoperfusion, hemodialysis, and exchange transfusion have only a limited effect on drug removal.^{13,17,102,117} Although the blood compartment can be cleared with these techniques, total body clearance is only marginally altered. After rapid tissue distribution occurs, there is little impact on the total body burden because of the large volume of distribution and extensive protein binding.

Mefloquine



Pharmacokinetics and Toxicodynamics. See Table 59–3 for the pharmacokinetic properties of mefloquine.

Clinical Manifestations. Common side effects with prophylactic and therapeutic dosing include nausea, vomiting, and diarrhea.⁸³ These side effects are noted particularly in the extremes of age and with high therapeutic dosing. Similar symptoms should be expected in acute overdose.^{114,125}

Mefloquine has a mild cardiodepressant effect—less than that of quinine or quinidine—which is not clinically significant in prophylactic dosing or with therapeutic administration. Bradycardia is commonly reported.^{25,67,83} With prophylactic use, neither the PR interval nor the QRS complex is prolonged, but QT prolongation is reported.^{34,67} Reports of torsade de pointes are rare, but the increase in QT and risk of torsade de pointes are increased when mefloquine is used concurrently with quinine; chloroquine; or, most particularly, with halofantrine.^{67,83,84,126} The long half-life of mefloquine means that particular care must be taken with therapeutic use of other antimalarials when breakthrough malaria occurs during mefloquine prophylaxis or within 28 days of mefloquine therapy to avoid potential drug–drug interactions. This risk may increase with acute overdose, although there is little clinical experience.

Mefloquine commonly has neuropsychiatric side effects. During prophylactic use, 10% to 40% of patients experience insomnia and bizarre or vivid dreams and complain of dizziness, headache, fatigue, mood alteration, and vertigo.^{103,122} Only 2% to 10% of these complications necessitate the traveler to seek medical advice or change normal activities.^{25,50,113} Predisposing factors include a past history of neuropsychiatric disorders, recent prior exposure to mefloquine (within 2 months), previous mefloquine-related neuropsychiatric adverse effects, and previous treatment with psychotropics.¹¹⁴ Women appear to be more likely than men to experience neuropsychiatric adverse effects.^{114,122}

The risk of serious neuropsychiatric adverse effects (convulsions, altered mental status, inability to ambulate because of vertigo or ataxia, psychosis, or acute neurosis) during prophylaxis is estimated to be one in 10,600 but is reported to be as high as one in 200 with therapeutic dosing.^{33,114} Seizures occur rarely with prophylaxis and therapeutic use.^{91,100} In many of these cases, there is a history of previous seizures, seizures in a first-degree relative or other seizure risk factors. Other neuropsychiatric symptoms include dysphoria, altered consciousness, encephalopathy, anxiety, depression, giddiness, and agitated delirium with psychosis. Although there is a suggestion that the severity of neuropsychiatric events is dose dependent, there does not seem to be a correlation with serum or tissue concentrations.⁵⁷ In one case report, the severe neuropsychiatric manifestations of mefloquine were reversed with physostigmine, leading the authors to suggest a possible central anticholinergic mechanism.¹¹⁰ Physostigmine is not recommended as a routine treatment for mefloquine neuropsychiatric side effects. A self-resolving postmalaria neurologic syndrome including confusion, seizures, or tremor is associated with therapeutic use of mefloquine for severe malaria.^{81,100}

The effect of mefloquine on the pancreatic potassium channel is much less than that of quinine, resulting in only a mild increase in insulin secretion.^{32,34} Symptomatic hypoglycemia has not been reported as an effect of mefloquine alone in healthy individuals, but has occurred with concomitant use of ethanol and in a severely malnourished patient with acquired immune deficiency syndrome (AIDS).^{11,34,67} In overdose, particularly when accompanied by ethanol use or starvation, hypoglycemia can be severe.

Rare events such as hypersensitivity reactions reported with prophylaxis include urticaria, alopecia, erythema multiforme, toxic epidermal necrolysis, myalgias, mouth ulcers, neutropenia, and thrombocytopenia.^{72,83,103,108} It is unclear which, if any, would be significant after overdose. ARDS was linked to therapeutic dosing in one case.¹¹⁹

In therapeutic use, mefloquine is associated with an increased incidence of stillbirth compared with quinine and a group

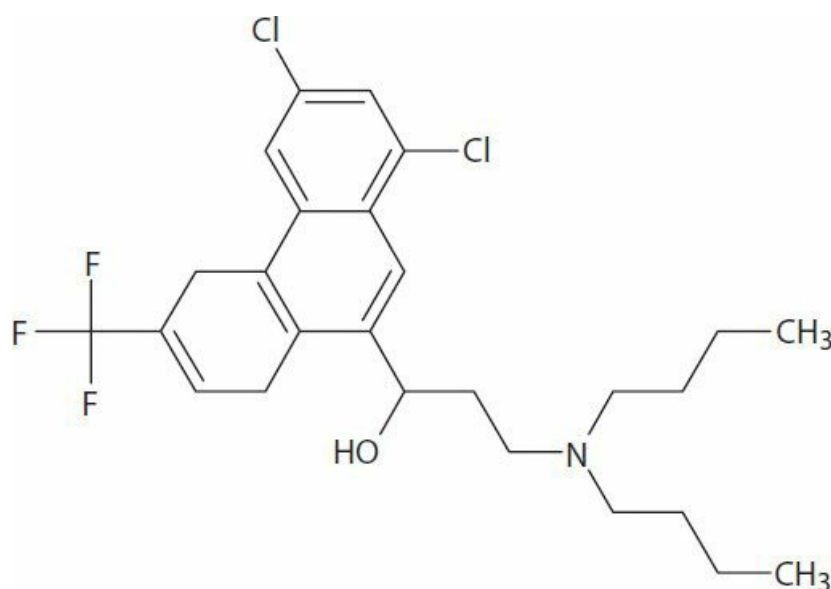
of other antimalarials.⁸⁵ Mefloquine was not, however, linked to an increased incidence of abortion, low birth weight, mental retardation, or congenital malformations. The implications of overdose in the absence of malaria are unknown, but fetal monitoring should be instituted.

The consequences of excessive dosing and overdose are not only severe but also prolonged and potentially permanent. Mefloquine overdose led to acute hearing loss and gradual resolution of acute symptoms over one year in one case and persistent symptoms even after one year in another.⁶⁵ After ingesting 5.25 g of mefloquine over 6 days, a man had prolonged prothrombin time resolving in 5 days and weakness persisting for 2 months after resolution of the acute symptoms.¹⁹ A fourth case involved coingestion of 2.5 times the usual therapeutic doses of mefloquine, chloroquine, and sulfadoxine–pyrimethamine over 3 days. The man had encephalopathy which had not resolved 8 months later.²³

Management. In overdose, treatment is primarily supportive with monitoring for potential adverse effects. Decontamination with activated charcoal is indicated if the patient presents soon after the ingestion. Specific monitoring for ECG abnormalities, hypoglycemia, and liver injury should be provided. Patients should also be followed for CNS and cranial nerve complications.

In two patients with kidney failure who received mefloquine, prophylactic hemodialysis did not remove mefloquine.³⁰ Given the large volume of distribution and high degree of protein binding of mefloquine, extracorporeal elimination techniques are unlikely to be effective.

Halofantrine



Because of erratic absorption, the potential for lethal cardiotoxicity, and concern for cross resistance with mefloquine, halofantrine is not presently recommended for malaria prophylaxis by the WHO.^{2,114}

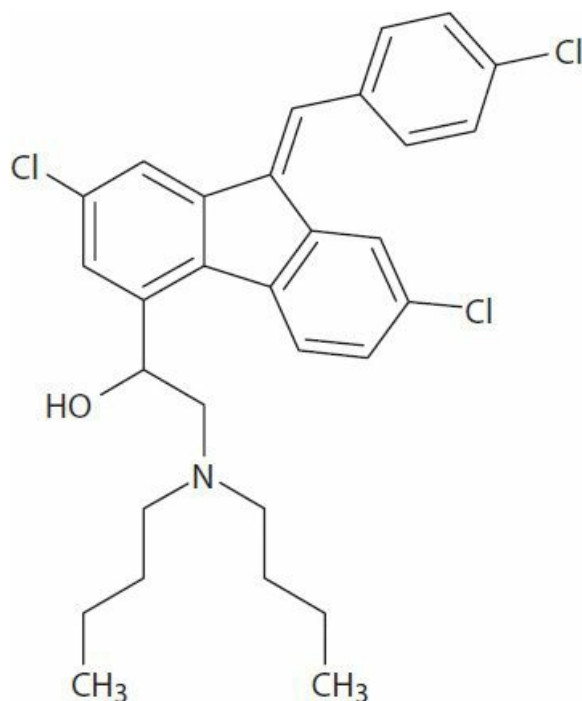
Pharmacokinetics and Toxicodynamics. See Table 59–3 for the pharmacokinetic properties of halofantrine.²²

Clinical Manifestations. The primary toxicity from therapeutic and supratherapeutic doses is prolongation of the QT interval and the risk of torsade de pointes and ventricular fibrillation.^{84,116} Palpitations, hypotension, and syncope may occur. First degree atrioventricular (AV) block is common, but bradycardia is rare.⁸⁴ Dysrhythmias are also likely in the context of combined overdose or combined or serial therapeutic use with other xenobiotics that cause QT interval prolongation, particularly mefloquine.⁵⁶ Because the QT interval duration is directly related to the serum halofantrine concentration, dysrhythmias should be expected in overdose.^{25,84,114} Fifty percent of children receiving a therapeutic course of halofantrine will have a QT interval greater than 440 msec.¹⁰⁹

Other side effects, including nausea, vomiting, diarrhea, abdominal cramps, headache, and lightheadedness, which frequently occur in therapeutic use, are also expected in overdose.⁶⁷ Less frequently described side effects include pruritus, myalgias, and rigors. Seizures, minimal liver enzyme abnormalities, and hemolysis are described.^{67,75,120} Whether these manifestations are related to halofantrine or to the underlying malaria is not clear.

Management. Management of patients with halofantrine overdose should focus on decontamination, supportive care, monitoring for QT interval prolongation, and treatment of any associated dysrhythmias.

Lumefantrine



Lumefantrine is structurally similar to halofantrine. It is primarily used as a partner drug in the artemisinin based combination therapy artemether plus lumefantrine.

Little toxicity of lumefantrine alone or in combination is reported.¹²⁷ Studies do not show QT interval prolongation or evidence of cardiac toxicity related to lumefantrine.³⁷ Cough and angioedema were described in one case.⁶¹ As in the case of all antimalarials, it is difficult to differentiate drug related adverse events from those of malaria, comorbid diseases, or other ingested drugs, which confounds the study of potential complications.

4-AMINOQUINOLINES

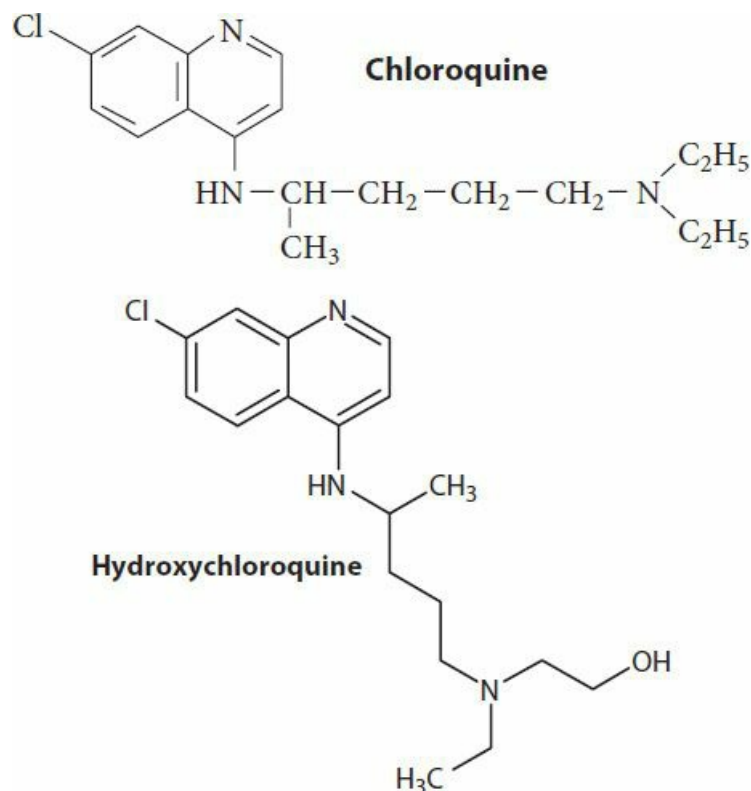
The structurally related compounds chloroquine and amodiaquine were once used extensively for malaria prophylaxis. However, with the development of resistance, they are now used in fewer geographic regions. Amodiaquine is associated with a higher incidence of hepatic toxicity and agranulocytosis. In general, these xenobiotics have low toxicity when used in therapeutic doses. Because of its low toxicity, chloroquine remains the first line drug for malaria prophylaxis and treatment in areas where *Plasmodium* spp remain sensitive.

Hydroxychloroquine is similar to chloroquine in therapeutic, pharmacokinetic, and toxicologic properties.⁷⁰ The side effect profiles of the two are slightly different, favoring chloroquine use for malarial prophylaxis and hydroxychloroquine use as an antiinflammatory agent.^{67,117} Hydroxychloroquine is used in the treatment of rheumatic diseases such as rheumatoid arthritis and lupus erythematosus. In animal studies, chloroquine is two to three times more toxic than hydroxychloroquine.⁵³

Piperaquine is structurally similar to chloroquine but is primarily used in conjunction with artemisinin compounds as a component of an ACT.

Antimalarial Mechanism. The 4-aminoquinolines interfere with the digestion of heme and hemozoin formation in a manner similar to that of the amino alcohols.³⁵

Chloroquine and Hydroxychloroquine



Pharmacokinetics and Toxicodynamics. See Table 59–3 for the pharmacokinetic properties of chloroquine. Oral chloroquine is rapidly and completely absorbed and is ultimately sequestered in many organs, particularly the kidney, liver, lung, and erythrocytes.^{16,48}

Chloroquine is slowly distributed from the blood compartment to the larger central compartment, leading to transiently high whole blood concentrations shortly after ingestion.^{95,107} It is the initial high blood concentrations that are thought to be responsible for the rapid development of profound cardiorespiratory collapse typical of chloroquine toxicity. These whole blood chloroquine concentrations correlate with death.²⁹

Pathophysiology. With structural similarity to quinine, the pathophysiologic mechanisms of chloroquine and hydroxychloroquine are also similar. Most notably, sodium and potassium channel blockade are the proposed primary mechanisms of cardiovascular toxicity.¹²⁶

Although less common in quinine toxicity, hypokalemia is extremely common in chloroquine overdose. The mechanism appears to be a shift of potassium from the extracellular to the intracellular space and not a true potassium deficit.^{71,95,105}

Clinical Manifestations. Similar to quinine, chloroquine has a small toxic-to-therapeutic margin. Severe chloroquine poisoning is usually associated with ingestions of 5 g or more in adults, systolic blood pressure less than 80 mm Hg, QRS duration of more than 120 msec, ventricular fibrillation, hypokalemia, and serum chloroquine concentrations exceeding 25 $\mu\text{mol/L}$ (8 $\mu\text{g/mL}$).^{27,97}

Symptoms usually occur within 1 to 3 hours of ingestion.⁹⁷ The range of symptoms associated with chloroquine toxicity is similar to that of quinine, but the frequencies of various manifestations differ, and other features such as cinchonism are uncommon. Nausea, vomiting, diarrhea, and abdominal pain occur less commonly than with quinine.^{51,67} In contrast, respiratory depression is common, and apnea, hypotension, and cardiovascular compromise can be precipitous.⁵¹

The cardiovascular effects of chloroquine and hydroxychloroquine are similar to those of quinine, including QRS prolongation, AV block, ST and T wave depression, increased U waves, and QT interval prolongation. Hypotension is more prominent in chloroquine toxicity than with quinine.⁵¹

Significant hypokalemia in chloroquine toxicity is invariably associated with cardiac manifestations.^{28,51} In fact, the extent of hypokalemia is a good indicator of the severity of chloroquine overdose.²⁷

Neurologic manifestations include CNS depression, dizziness, headache, and convulsions.⁴⁷ Rarely, dystonic reactions occur.⁸⁷ Transient parkinsonism is also reported after excessive dosing.⁸⁷

Ophthalmic manifestations are infrequent in acute chloroquine toxicity and transient in nature.^{51,67} More severe and irreversible vision and hearing changes are described in association with the chronic use of chloroquine and hydroxychloroquine as antiinflammatory agents.^{67,79} Myopathy, neuropathy, and cardiomyopathy also occur when used for that purpose.^{10,124} Dermatologic findings and hypersensitivity reactions are similar to those associated with quinine.³⁴ Likewise, red blood cell (RBC) oxidant stress from chloroquine may result in hemolysis in patients with G6PD deficiency (Chap. 22).

Acute hydroxychloroquine toxicity is similar to chloroquine toxicity.⁵³ Side effects from therapeutic doses include

nausea and abdominal pain; hemolysis in G6PD deficient patients; and, rarely, retinal damage, sensorineural deafness, and hypoglycemia.^{52,104} Hypersensitivity reactions, including myocarditis and hepatitis, are described.^{41,69}

Management. Aggressive supportive care should be initiated, including oxygen, cardiac and hemodynamic monitoring, and large bore IV access, and serial blood glucose concentrations should be obtained. Orogastric lavage could be considered for life-threatening ingestions presenting early, but there is little evidence of efficacy. Activated charcoal adsorbs chloroquine well, binding 95% to 99% when administered within 5 minutes of ingestion.⁵⁹ The frequent development of precipitous cardiovascular and CNS toxicity should be considered before initiating any type of GI decontamination.

Early aggressive management of severe chloroquine toxicity decreases the mortality rate.⁹⁷ This includes early endotracheal intubation and mechanical ventilation. Evidence suggests that barbiturates may not be desirable for induction in patients with chloroquine overdose. When thiopental was used to facilitate intubation, its use immediately preceded sudden cardiac arrest in seven of 25 patients after chloroquine overdose.²⁹ An adequate FiO_2 , tidal volume, and ventilatory rate should be ensured.

Although theoretically any direct acting vasopressor would be beneficial in the setting of hypotension not responsive to fluid resuscitation, epinephrine is the vasopressor most extensively studied and is considered the vasopressor of choice. High doses of epinephrine were used in the original studies describing the benefits of early mechanical ventilation and the administration of diazepam and epinephrine in chloroquine poisoning.^{97,98} The epinephrine doses used in these studies are still recommended today.^{97,98} The recommended dose is 0.25 $\mu\text{g/kg/min}$, increasing by 0.25 $\mu\text{g/kg/min}$ until an adequate systolic blood pressure (greater than 90 mm Hg) is achieved.^{31,73,97,98} Clinicians should be mindful that high doses of epinephrine could exacerbate preexisting hypokalemia.

The use of diazepam to augment the treatment of dysrhythmias and hypotension is a unique use of this drug. Initial observations with regard to patients with mixed overdoses of chloroquine and diazepam suggested less cardiovascular toxicity and a potential benefit of high dose diazepam.^{27,71} Animal and human studies that followed also showed a potential benefit.^{31,97,98} When early mechanical ventilation was combined with the administration of high-dose diazepam and epinephrine in patients severely poisoned by chloroquine, a dramatic improvement in survival compared with historical control participants (91% versus 9% survival) occurred.⁹⁷ Studies in moderately poisoned patients failed to show similar benefit,²⁷ and a rat model failed to show an inotropic effect. Although the definitive study has yet to be done, high-dose diazepam therapy (2 mg/kg IV over 30 minutes followed by 1 to 2 mg/kg/d for 2–4 days) seems warranted for serious toxicity. Diazepam or an equivalent benzodiazepine should also be used to treat seizures and for sedation.

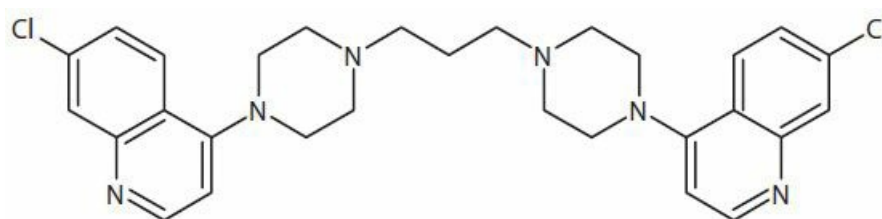
The mechanism for a potential benefit of diazepam is unclear, but multiple theories have been postulated: (1) a central antagonistic effect, (2) an anticonvulsant effect, (3) an antidysrhythmic effect by an electrophysiologic action inverse to chloroquine, (4) a pharmacokinetic interaction between diazepam and chloroquine, and (5) a decrease in chloroquine-induced vasodilation.^{71,95,97,98} (Antidotes in Depth: A23).

The use of sodium bicarbonate for correction of QRS prolongation is also controversial. Although alkalization would be expected to counteract the effects of sodium channel blockade, it could also exacerbate preexisting hypokalemia. Although case reports describe the successful use of sodium bicarbonate in conjunction with xenobiotics for massive hydroxychloroquine overdose, no clinical trials have been performed.^{64,130} Before using sodium bicarbonate in the setting of chloroquine toxicity, clinicians should consider the overall clinical status of the patient, including the suspected degree of cardiac toxicity and severity of hypokalemia.

Hypokalemia in the setting of chloroquine overdose correlates with the severity of the toxicity.^{27,71} Potassium replacement in this setting is, again, controversial because it has not been shown that potassium supplementation will improve cardiac toxicity. In fact, several reports suggest a possible protective effect of hypokalemia in acute chloroquine toxicity.^{27,71,95} This should be balanced against the fact that severe hypokalemia can itself result in lethal dysrhythmias and data suggesting severe hypokalemia (less than 1.9 mEq/L) is associated with severe, life-threatening ingestion.^{25,51,71,107} Hypokalemia could not be directly attributed as the cause of death in most cases, however.²⁷ Based on the available evidence, potassium replacement for significant hypokalemia seems warranted, but it is essential to anticipate rebound hyperkalemia as chloroquine toxicity resolves and redistribution of intracellular potassium occurs. Cases of hyperkalemia related complications are reported after aggressive potassium supplementation.^{53,64,71}

Because chloroquine and hydroxychloroquine have high volumes of distribution and significant protein binding, enhanced elimination procedures are not beneficial.^{16,51}

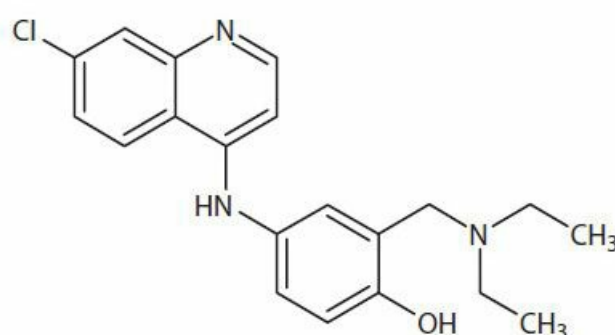
Piperaquine



Piperaquine was used extensively in China and Indonesia as an antimalarial until the development of piperaquine resistant strains led to the use of better alternatives. Piperaquine has since undergone a rediscovery as a viable combination with artemisinin derivatives in ACT DP (dihydroartemisinin-piperaquine) therapy. Animal studies show piperaquine to be substantially less toxic than chloroquine. Cardiovascular toxicity with piperaquine requires cumulative doses five times higher than that of chloroquine. Hepatotoxicity occurs after chronic exposure in animals. In a human study, no significant changes in ECG or in serum glucose concentration, and no postural hypotension occurred after therapeutic doses of DP.

Management. Patients with overdose should be managed with supportive measures and expectant observation, including cardiovascular and CNS monitoring.

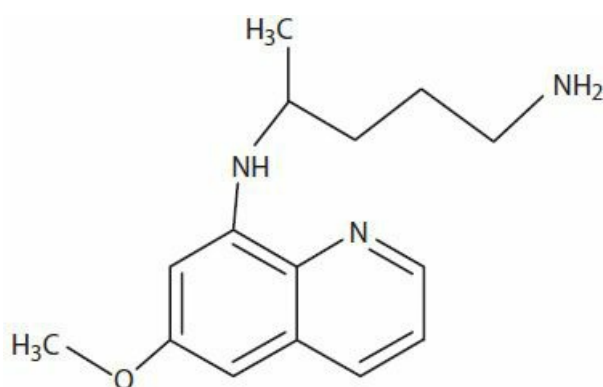
Amodiaquine



Reports of amodiaquine toxicity suggest that involuntary movements, muscle stiffness, dysarthria, syncope, and seizures may occur.^{6,51} Amodiaquine is associated with hypersensitivity hepatitis and neutropenia in prophylactic use but not therapeutic use.²¹ There is no overdose experience reported.

8-AMINOQUINOLINES

Primaquine



Primaquine and its related compounds are the only drugs licensed for the prevention of *P. ovale* and *P. vivax* relapse caused by hepatic hypnozoites.⁷⁷ Studies using primaquine in the early 1950s led to the discovery of G6PD deficiency after those with the disease developed hemolysis when administered the drug.¹⁴ G6PD deficiency actually offers some protection against malaria because the erythrocytes of those with the disease rupture under the increased oxidative stress of the parasite's metabolism before completion of the erythrocytic cycle.

Antimalarial Mechanism. The antimalarial action of primaquine is poorly understood but thought to be related to increasing the oxidative stress of erythrocytes,¹²³ obstructing proper parasitic development.

Pharmacokinetics and Toxicodynamics. See Table 59–3 for the pharmacokinetic properties of primaquine.

Pathophysiology. Primaquine blocks sodium channels both in vitro and animal models.^{51,126} Significant cardiovascular toxicity has not been reported, although experience with primaquine overdose is limited primarily to case reports.

The predominant clinical toxicity of primaquine relates to its ability to cause RBC oxidant stress and resultant hemolysis or methemoglobinemia. Methemoglobinemia and hemolysis can even occur in normal individuals given high doses as well as those with G6PD deficiency.^{67,114}

The major complication of primaquine in therapeutic use is hemolysis in G6PD deficient individuals.³² Primaquine is contraindicated in pregnant women because of the risk of methemoglobinemia or hemolysis in the fetus. Reversible bone marrow suppression can occur.

Clinical Manifestations. Gastrointestinal irritation is common and dose related.

The extent of hemolysis in G6PD deficient individuals depends on the extent of enzyme activity, those with greater enzyme activity having less severe hemolysis than those with less enzyme activity ([Chap. 22](#)). Other variables include the dose of primaquine and comorbid conditions, such as infection, liver disease, and administration of other drugs with hemolytic activity.

Overdose with primaquine is rarely reported, and unintentional overdoses have led to methemoglobinemia requiring IV methylene blue.¹¹⁴ Acute liver failure has occurred after unintentional overdose, and fatal hepatotoxicity is described in animal models.⁶⁵

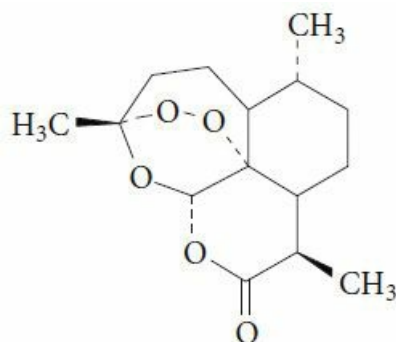
Management. Therapy should be directed at minimizing absorption with appropriate decontamination and diagnosing and then treating significant methemoglobinemia or hemolysis. Because of structural similarities with other quinolone antimalarials and animal model evidence of sodium channel blockade, cardiovascular toxicity should be anticipated with continuous monitoring and resuscitative interventions initiated as needed.

Activated charcoal would be expected to bind primaquine quite successfully if given early ([Antidotes in Depth: A1](#)). Methylene blue ([Chap. 127](#) and [Antidotes in Depth: A42](#)) should be administered for patients who are symptomatic with methemoglobinemia. Treatment of hemolysis necessitates avoiding further exposure to primaquine and possibly exchange transfusion in severe cases. Adequate hydration should be ensured to protect against hemoglobin-induced AKI. Urinary alkalization with sodium bicarbonate is controversial in this setting but may have some benefit ([Antidotes in Depth: A5](#)).

Although no clinical studies have been performed, the large volume of distribution of primaquine makes it an unlikely candidate for benefit from extracorporeal removal.

ENDOPEROXIDES

Artemisinin and Derivatives



The medicinal value of natural artemisinin, the active ingredient of *Artemisia annua* (sweet wormwood or qinghao), has been known for thousands of years. Its antimalarial properties were first recognized by Chinese herbalists in 340 A.D., but the primary active component of qinghaosu, now known as artemisinin, was not isolated until 1974.^{10,117} Artemisinin and its semisynthetic derivatives, artesunate, artemether, arteether, and dihydroartemisinin, are the most potent and rapidly acting of all antimalarials. They were introduced in the 1980s in China for the treatment of malaria, and since then millions of doses have been used in Asia and Africa. Because of their extremely short half-lives, the artemisinins are now used in combination with drugs with longer half-lives to delay or prevent the emergence of resistance. ACTs are currently recommended by the WHO for the treatment of uncomplicated malaria^{1,10} but have not been licensed for use in the United States. Only four ACTs are currently recommended by the WHO. These include artesunate plus mefloquine, artesunate plus pyrimethamine-sulfadoxine, artesunate plus amodiaquine, and artemether plus lumefantrine.

Antimalarial Mechanism. The artemesinins have a unique structure containing a 1,2,4-trioxane ring. The endoperoxide linkage within this ring is cleaved when it comes into contact with ferrous iron, releasing free radicals that destroy the parasite.⁴ Artemisinin is the only known natural product to contain a 1,2,4-trioxane ring, and although chemical synthesis is possible, thus far it has not been financially advantageous.

Pharmacokinetics and Toxicodynamics. See [Table 59–3](#) for the pharmacokinetic properties of artemisinin. Similar to its proposed efficacy, the toxicity of artemisinin is thought to be a result of the ability of the trioxane molecular core to form

intracellular free radicals, particularly in the presence of heme. In animals, damage to brainstem nuclei is consistently produced after prolonged, high-dose, and parenteral administration.¹¹⁴ Sustained CNS exposure from slowly absorbed or eliminated artemisinins is considered markedly more neurotoxic than intermittent brief exposure that occurs after oral dosing.¹¹⁴ Embryonic loss is also observed in animals.¹¹⁴

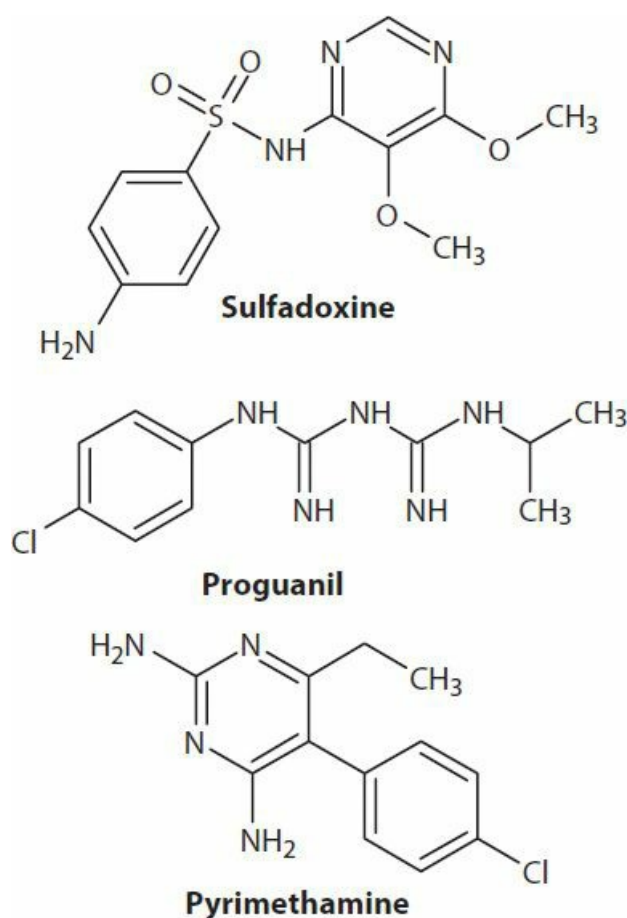
Clinical Manifestations. In contrast to the experience with animals, the experience of more than 8000 human study participants shows that these drugs have a very low incidence of side effects.¹¹⁴ Uncommon side effects include nausea, vomiting, abdominal pain, diarrhea, and dizziness.

Prospective studies have failed to identify adverse neurologic outcomes.^{58,114} Rare reports of adverse CNS effects during therapeutic use suggest the possibility of CNS depression, seizures, or cerebellar symptoms after intentional self poisoning. In children with cerebral malaria, a higher incidence of seizures and a delay to recovery from coma were noted in a comparison with quinine.¹²¹ No neurologic difference was noted in long-term follow up. In an artemether–quinine comparative trial of adults with severe malaria, recovery from coma was also prolonged in the artemether group.¹¹⁸ Rare patients receiving an artemisinin derivative in two other studies experienced transient dizziness or cerebellar signs.^{74,93} Most recovered within days. One patient in each study had prolonged symptoms lasting 1 month and 4 months, respectively, but both ultimately recovered.^{74,93}

When serial ECGs were obtained, a small but statistically significant decrease in heart rate was noted coincident with peak drug concentrations.⁷⁴ In one therapeutic trial, 7% of adult patients receiving artemether had an asymptomatic QT interval prolongation of at least 25%.¹¹⁸ Changes in the QRS are not reported.

Although uncommon, neutropenia, reticulocytopenia, anemia, eosinophilia, and elevated aminotransferases are reported.¹¹⁴ Acute ACT overdose is rarely reported outside large population-based studies. Morbidity and mortality of overdose are frequently difficult to differentiate from those of the underlying malarial disease and coingestants.

ANTIFOLATES AND ANTIBIOTICS



Antimalarial Mechanism

Proguanil, pyrimethamine, and the antibiotic trimethoprim interfere with malarial folate metabolism by inhibiting dihydrofolate reductase at concentrations far lower than that required to produce comparable inhibition of mammalian enzymes.¹¹⁷ Dapsone and sulfonamide antibiotics also disrupt malarial folate metabolism, but by inhibiting a different enzymatic reaction; dihydropteroate synthase. Slow onset of action and concerns for the development of resistance have led to the use of these antibiotics in synergistic combinations leading to inhibition of folate metabolism at two different sites.

Pharmacokinetics and Toxicodynamics

See Table 59–3 for the pharmacokinetic properties of pyrimethamine and dapsone.

Genetic polymorphism is described in the metabolism of proguanil and dapsone.^{54,96} This may be the cause of the significant hypersensitivity reactions noted with dapsone.⁹⁶

Clinical Manifestations

The side effects of proguanil during prophylaxis include nausea, diarrhea, and mouth ulcers.⁶⁷ Because of the interference with folate metabolism, megaloblastic anemia is a rare complication. Megaloblastic bone marrow toxicity is reported in patients with chronic kidney disease (CKD).¹¹⁴ Folate supplementation may be required in pregnancy and CKD to avoid this complication.³³ Rarely, neutropenia, thrombocytopenia, rash, and alopecia are also noted.³³ In a single case report, hypersensitivity hepatitis was described.³³ When used to treat malaria, atovaquone–proguanil causes vomiting, sometimes severe, in a significant portion of patients (15%–45%).¹¹⁴ This combination is also associated with elevated aminotransferases.⁹⁴ Unintentional or deliberate overdose has caused little serious toxicity.¹¹⁴

Overdose of pyrimethamine alone is rare. In children, it results in nausea, vomiting, a rapid onset of seizures, fever, and tachycardia.^{7,51} Blindness, deafness, and mental retardation have followed.^{7,51} Seizures were attributed to sulfadoxine–pyrimethamine in an overdose of 12 tablets over 2 days (the usual dose is three tablets taken once).⁸² It is unclear whether the chronic neurologic deficits described in case reports are attributable to direct toxicity of pyrimethamine on the CNS or to complications of toxicity such as status epilepticus.^{7,51} Chronic high dose use may be associated with a megaloblastic anemia, requiring folate replacement.⁷

The sulfonamides, including the sulfone dapsone, have a long history of causing idiosyncratic reactions, including neutropenia, thrombocytopenia, eosinophilic pneumonia, aplastic anemia, neuropathy, and hepatitis.^{67,114} The rare occurrence of life-threatening erythema multiforme major and toxic epidermal necrolysis, associated with pyrimethamine–sulfadoxine prophylaxis, has limited the use of this combination for prophylaxis.

Acute ingestion of dapsone may result in nausea, vomiting, and abdominal pain.⁵¹ After overdose, dapsone produces RBC oxidant stress, leading to methemoglobinemia and, to a much lesser extent, sulfhemoglobinemia through formation of an active metabolite (Chap. 127).^{24,68} The onset of hemolysis may be either immediate or delayed. Dapsone, in particular, is known for its tendency to cause prolonged methemoglobinemia. Other symptoms, particularly tachycardia, dyspnea, dizziness, visual hallucinations, seizure, syncope, and coma resulting from end-organ hypoxia, can occur.^{24,51} Additional effects described in overdose include hepatitis and peripheral neuropathy.⁵¹

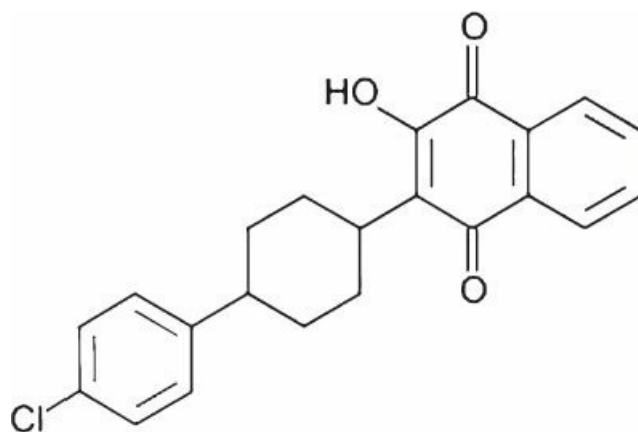
Management

Folate supplementation should be considered after an overdose of proguanil or pyrimethamine (Antidotes in Depth: A10). Other efforts should include supportive care.

After dapsone ingestion, clinically significant methemoglobinemia should be treated with methylene blue and possibly cimetidine (Chap. 127 and Antidotes in Depth: A42). There is no antidote for sulfhemoglobinemia, but it constitutes an insignificant portion of total hemoglobin. Both hemodialysis and MDAC enhance elimination of dapsone during therapy.⁸⁰ MDAC is routinely recommended in the treatment of dapsone overdose.⁶⁸ Required support may include RBC transfusion and urinary alkalinization if hemolysis is extensive (Antidotes in Depth: A5).

NAPTHOQUINONES

Atovaquone



Atovaquone inhibits the de novo pyrimidine synthesis that is necessary for protozoal survival and replication but is unnecessary in mammalian cells. Based on its beneficial side effect profile, many North American physicians are switching from mefloquine to atovaquone–proguanil for routine antimalarial prophylaxis for travelers. Atovaquone and proguanil may now be the most common antimalarials used in North America. The price of this combination previously limited its use mainly to travelers from affluent countries.²⁵ The availability to patients from other countries may increase because the generic form of this combination became available in late 2011.

Atovaquone alone, primarily used to treat *Pneumocystis jiroveci* in patients with AIDS, is relatively well tolerated.⁸⁸ Side effects include maculopapular rash, erythema multiforme (rarely), GI complaints, and mild aminotransferase elevations. Three cases of 3 to 42 fold overdose or excess dosing have been reported.²⁶ No symptoms occurred in one case (at three times therapeutic serum concentration). Rash occurred in another, and in the third case, methemoglobinemia was attributed to a simultaneous overdose of dapsone.

SUMMARY

- Malaria is a parasitic infection of human erythrocytes caused by protozoan parasites in the *Plasmodium* genus with a unique lifecycle involving the *Anopheles* mosquito as the vector. It is primarily endemic in tropical and subtropical areas worldwide.
- The antimalarial properties of quinine have been known for centuries. Therapeutic dosing can result in a unique symptom complex known as “cinchonism.” Significant overdose is heralded by cardiovascular and CNS toxicity.
- The development of resistance has limited the use of chloroquine to specific geographic regions harboring susceptible malarial strains. Rapid development of cardiorespiratory collapse is typical of chloroquine toxicity. High dose epinephrine and valium are recommended for the treatment of serious chloroquine toxicity.
- Primaquine and dapsone produce significant oxidant stress, resulting in methemoglobinemia and often hemolysis.
- Because of their extremely short half-lives, artemisinins are used in combination with drugs with longer half-lives to delay or prevent the emergence of resistance. Little is known of the acute toxicity after overdose of the newest artemisinin based medications.

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E. CARDIOPULMONARY MEDICATIONS

CASE STUDY 4

History A 48 year-old woman was brought to the hospital by emergency medical services (EMS). According to the paramedics, they were called to the house after the patient sent a text message to a friend saying that she no longer wanted to live. The friend went to the patient's house and called 911 to have the police break down the door when no one answered. The patient was found on her bed with a suicide note. The friend related that the patient had migraine headaches, but did not know what medications she took.

EMS personnel reported that on the scene the patient was lethargic with the following vital signs: blood pressure, 70/40 mm Hg; pulse, 25 beats/min; and respiratory rate, 8 breaths/min. EMS started the patient on oxygen via nasal cannula, inserted an intravenous catheter, started 0.9% sodium chloride running wide open, and administered 0.5 mg of atropine before arrival to the hospital.

Physical Examination On arrival to the hospital, the patient had the following vital signs: blood pressure, 76/42 mm Hg; pulse, 35 beats/min; respiratory rate, 10 breaths/min; temperature, 98.3°F; O₂ saturation, 99% on room air; end-tidal CO₂, 38 mm Hg; and rapid reagent bedside glucose, 58 mg/dL. Physical examination was notable for pupils that were 2 to 3 mm and sluggishly reactive to light. Gag reflex was intact, and there were no secretions, pills, or blood in the mouth. The patient's chest was clear, and other than bradycardia, her cardiac examination was normal. The abdomen was soft with normal bowel sounds, and her skin was without diaphoresis or pallor. The patient responded to sternal rub and opened her eyes but mumbled incoherently. She moved all four extremities and was able to localize pain.

Initial Management Dextrose (50 g IV) and naloxone (0.04 mg followed by 0.08 mg and 0.4 mg IV) were given with no clinical response. Blood samples were sent for a complete blood count, electrolytes, ethanol, and acetaminophen (APAP), and an electrocardiogram (ECG) was ordered.

What Is the Differential Diagnosis?

Many xenobiotics cause bradycardia (Table 17–2), but this patient has the combined features of hypotension and bradycardia. Here, the differential diagnosis is more narrow, with the most common causes listed in Table CS4–1.

TABLE CS4–1. Differential Diagnosis

Most Common Toxicologic Causes of Combined Hypotension and Bradycardia

α_2 -Adrenergic agonists	Calcium channel blockers
β -Adrenergic antagonists	Cardioactive steroids
Antidysrhythmics (Class I)	Opioids
Baclofen	

What Clinical Factors Help Narrow the Differential Diagnosis? Often, the physical examination provides significant insight into the diagnosis. Patients who overdose with either opioids or α_2 -adrenergic agonists may present with the classic opioid toxic syndrome (Chaps. 3, 38, and 63) that is predominated by miosis and depression of the central nervous system and respiratory drive. Although this patient has many features consistent with that toxic syndrome, the normal oxygen saturation on room air, normal end-tidal CO₂, and failure to respond to naloxone largely exclude the diagnosis of an opioid. Also, most other etiologies for hypotension and bradycardia will decrease the mental status except for calcium channel blockers, which tend to preserve the level of consciousness.

An ECG should subsequently be evaluated (Fig. CS4–1). Although all of the etiologies listed in Table CS4–1 can present with sinus bradycardia, certain features may be suggestive of the etiology. When bradycardia is associated with traditional Class I antidysrhythmics, the QRS complex is usually significantly widened as a result of sodium channel blockade (Chap. 64). Patients who take cardioactive steroids often have underlying atrial fibrillation or demonstrate a digoxin effect (Fig. 65–2) or have ventricular premature beats, high degrees of atrioventricular blockade, or delayed after depolarizations on their ECGs (Chaps. 16 and 65). Finally, although a prolongation of the QT interval is nonspecific, it is expected with Class IA and IC antidysrhythmics and some opioids, most notably methadone.

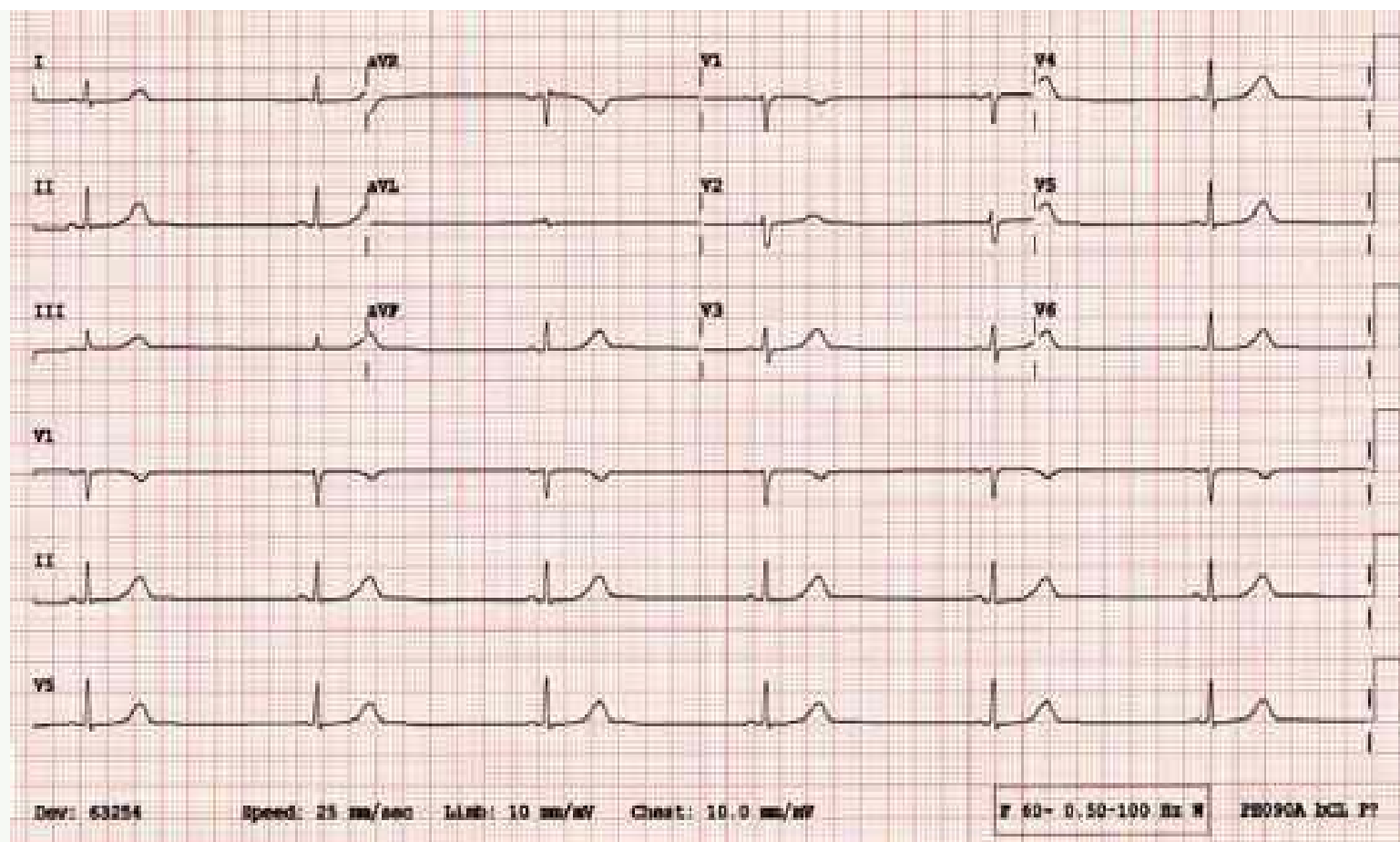


FIGURE CS4–1. Electrocardiogram on presentation showing profound sinus bradycardia with a heart rate of 36 beats/min. The axis is normal, as are the PR interval of 120 msec and the QRS duration of 80 msec. The QT interval is slightly prolonged at 510 msec and there is no evidence of ischemia or infarction.

Rapid laboratory testing may also be of some utility. With acute toxicity from cardioactive steroids, the serum potassium concentration rises, and this increase has prognostic implications ([Chap. 65](#)). Less dramatic rises occur with β -adrenergic antagonist overdose but have unclear prognostic value. This patient's serum potassium was 5.2 mEq/L. β -Adrenergic antagonists also tend to cause hypoglycemia; in contradistinction hyperglycemia while not only common with calcium channel blockers, has prognostic implications.

Treatment A clinical decision was made to forgo attempts at gastrointestinal decontamination given the patient's mental status. She was given a second liter of 0.9% sodium chloride intravenously, and the decision was made to start with glucagon for a presumed β -adrenergic antagonist overdose. This diagnosis was suspected given the history of migraines, the ECG, the serum potassium concentration, and the blood glucose concentration. After 3 mg of glucagon IV, the patient's blood pressure rose to 102/62 mm Hg with a pulse of 60 beats/min, and this dose was repeated in 15 minutes when her blood pressure fell again (*Antidotes in Depth: A18*). Her anion gap was normal, and both APAP and ethanol concentrations were negative. By the next day, she was awake, and her vital signs remained normal. During a subsequent psychiatric evaluation, she admitted to taking an unspecified amount of propranolol. She was voluntarily admitted for psychiatric care.

60 ANTITHROMBOTICS

Betty C. Chen and Mark Su

HISTORY AND EPIDEMIOLOGY

Antithrombotics have numerous clinical applications, including in the treatment of coronary artery disease, cerebrovascular events, hypercoagulable states, deep venous thrombosis, and pulmonary embolism. The antithrombotics are a diverse group of xenobiotics that are widely studied and constantly in the process of therapeutic evolution.

The origins and discovery of antithrombotics are extraordinary.^{4,22,119,207} The discovery of modern-day oral anticoagulants originated following investigations of a hemorrhagic disorder in Wisconsin cattle in the early 20th century that resulted from the ingestion of spoiled sweet clover silage. The hemorrhagic agent, eventually identified as bishydroxycoumarin, would be the precursor to its synthetic congener warfarin (named after the Wisconsin Alumni Research Foundation). Warfarin was rapidly marketed as both a medicine and a rodenticide. “Superwarfarins” were subsequently developed for the increasing rat population that had developed genetic resistance to warfarin.

The origins of the anticoagulant heparin are equally fascinating. A medical student initially attempting to study ether soluble procoagulants derived from porcine intestines serendipitously found that, over time, these apparent “procoagulants” actually prevented normal blood coagulation. The phospholipid anticoagulant responsible for this effect would later be identified as a variant form of heparin. Shortly thereafter, the water-soluble mucopolysaccharide termed heparin (because of its abundance in the liver) was discovered. Unfractionated heparin is a mixture of polysaccharide chains with varying molecular weights. Following the identification of the active pentasaccharide segment of heparin in the 1970s, multiple low molecular-weight heparins were isolated and synthetic forms were created.

Hirudin, a 65 amino acid polypeptide, was produced by the salivary glands of the medicinal leech (*Hirudo medicinalis*).²⁵⁶ Antistasin and antistasinlike proteins are naturally secreted by the Mexican leech, *Haementeria officinalis*, and the earthworm.^{82,289} These xenobiotics have not been used therapeutically; however, they inspired the development of the synthetic factor inhibitors, such as direct thrombin inhibitors and factor Xa inhibitors.

In the late 19th century, human urine was noted to have proteolytic activity with specificity for fibrin. A substance found to be an activator of endogenous plasminogen leading to the consumption of fibrin, fibrinogen, and other coagulation proteins was isolated and purified and given the name urokinase. Streptokinase, a protein produced by β -hemolytic streptococci, tissue plasminogen activator (t-PA), and other synthetic thrombolytics were later discovered. Although known to exist for many years, anicrod, a purified derivative of Malayan pit viper, only recently gained therapeutic attention as a naturally occurring antithrombotic.

In the early 20th century, antithrombotic properties of aspirin were noted in anecdotal reports of patients having a predisposition to bleeding while taking aspirin. Clinicians also noted lower rates of myocardial infarction, and studies to elucidate the effects of aspirin on coagulation soon followed with further research exposing the role of platelet aggregation in thrombosis.²⁰¹ These discoveries led to the development of the antiplatelet xenobiotics.

The diversity of these antithrombotics has led to ever-increasing use in many fields of medicine. Although warfarin is the most common oral anticoagulant in use today because of its utility in patients with cerebrovascular disease, cardiac dysrhythmias, and thromboembolic disease, the emergence of newly developed oral antithrombotics has changed the landscape of modern medicine. During the period from 2009 to 2011, the total number of cases of reported antithrombotic exposures to the American Association of Poison Control Centers was 17,622 with 16 deaths ([Chap. 136](#)). Throughout this time, there was a general trend toward an increasing number of reports. In 2011, dabigatran and warfarin led the US Food and Drug Administration (FDA) Safety Information and Adverse Event Reporting Program’s list of adverse drug events, with 3781 reports of serious adverse events associated with dabigatran, including 542 patient deaths. In comparison, warfarin alone accounted for 1106 reports with 72 deaths.²⁰⁴

PHYSIOLOGY

Balance between Coagulation and Anticoagulation

An understanding of the normal function of the coagulation pathways is essential to appreciate the etiology of a

coagulopathy. This section summarizes the critical steps of the coagulation cascade. For additional details, the reader is referred to [Chap. 22](#) and several reviews.^{104,202,206,238}

Coagulation consists of a series of events that prevent blood loss and assist in the restoration of blood vessel integrity. Although the traditional understanding of the events that occur in the coagulation cascade,^{71,184} as discussed below, adequately describe *in vitro* events, the current understanding emphasizes some distinct differences that occur *in vivo*.^{104,206,238} Despite these differences, an understanding of the traditional model is most useful for interpreting the results of diagnostic tests of coagulation.

Within the cascade, coagulation factors exist as inert precursors and are transformed into enzymes when activated. Activation of the cascade occurs through one of two distinct pathways, the intrinsic and extrinsic systems (Fig. 60–1).^{71,184} Once activated, these enzymes catalyze a series of reactions that ultimately converge to generate thrombin with the subsequent formation of a fibrin clot.

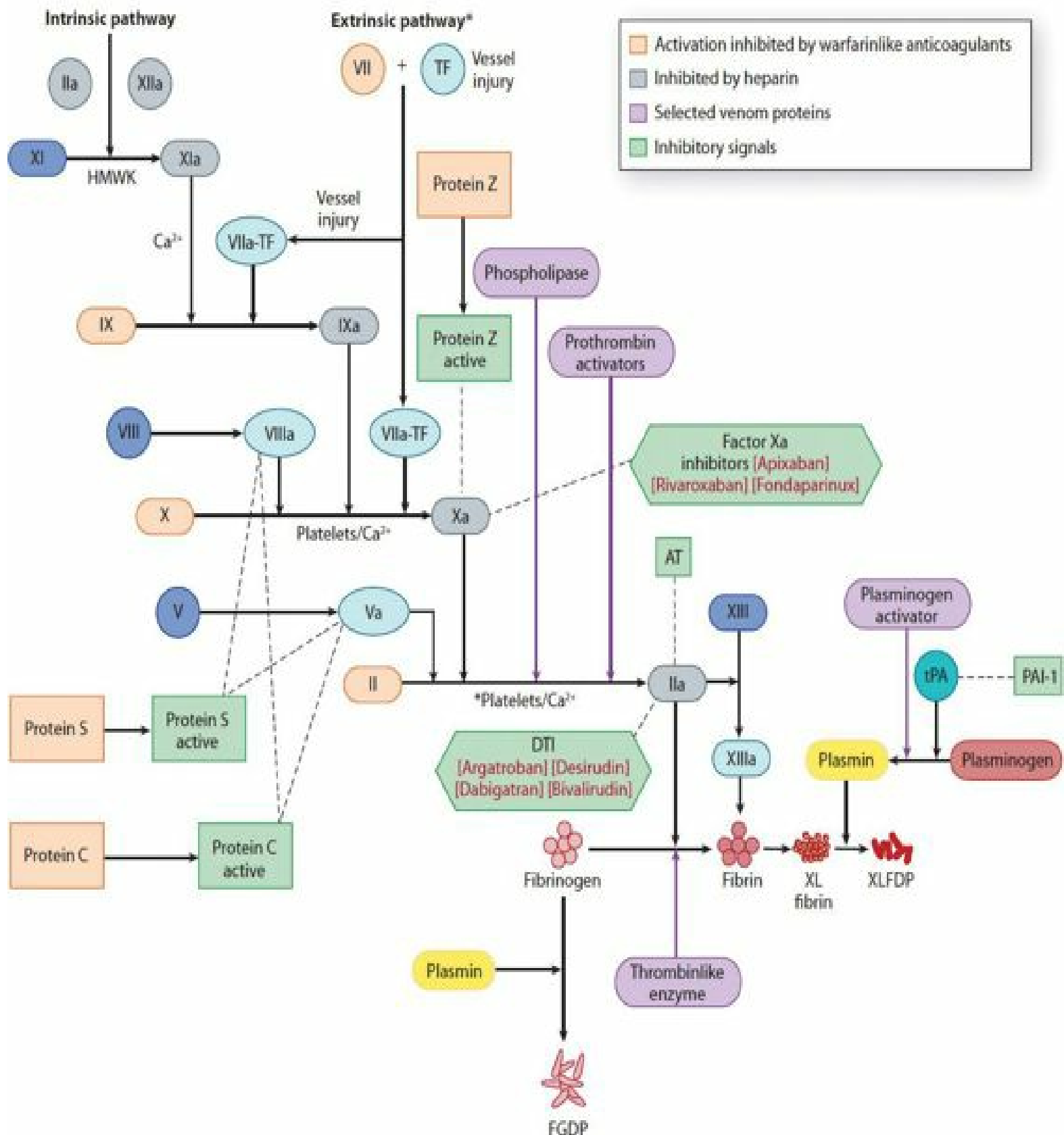


FIGURE 60–1. A schematic overview of the coagulation, platelet activation, and fibrinolytic pathways indicating where phospholipids on the platelet surface interact with the coagulation pathway intermediates. Arrows are not shown from platelets to phospholipids involved in the tissue factor VIIa and the factor IX to VIIIa interactions to avoid confusion. Interactions of selected venom proteins are indicated in the purple boxes. The diagram is not complete with reference to the multiple sites of interaction of the serine protease inhibitors (SERPINs) to avoid overcrowding. Dashed lines indicate inhibitory effects. *Refer to Figs. 60–4 and 60–5 for platelet activation pathway. DTI = direct thrombin inhibitor; FDP = fibrin degradation products; FGDP = fibrinogen degradation products; HMWK = high molecular weight kininogen; TF = tissue factor; XL = cross-linked.

The intrinsic pathway is activated by the complexation of factor XII (Hageman factor) with high-molecular-weight kininogen (HMWK) and prekallikrein, or vascular subendothelial collagen. This results in sequential activation of factor XII, active kallikrein, active factors IX to XI, and prothrombin (factor II) (Fig. 60–1). Prothrombin is converted to thrombin in the presence of factor V, calcium, and phospholipid. The integrity of this system is usually evaluated by determining the partial thromboplastin time (PTT).

In the extrinsic or tissue factor dependent pathway, a complex is formed between factor VII, calcium, and tissue factor, which is released following injury. A calcium and lipid dependent complex is then created between factors VII and X. The factor VII–X complex subsequently converts prothrombin to thrombin, which promotes the formation of fibrin from fibrinogen (Fig. 60–1). The integrity of this pathway is usually assessed by determining the prothrombin time (PT or international normalized ratio {INR}). The distinction between PT and INR is discussed in Chap. 22.

Activation of factor X provides the important link between the intrinsic and extrinsic coagulation pathways. Additional evidence that tissue factors can activate both factors IX and X suggests that there are more interrelations between the two pathways.²¹⁸ Furthermore, cell surfaces facilitate the process of clotting. Platelets are also known to interact with proteins of the coagulation cascade through surface receptors for factors V, VIII, IX, and X.^{109,188,263} As a final step, factor XIII assists in the cross-linking of fibrin to form a stable thrombus.

Antithrombin (AT), and proteins C, S, and Z serve as inhibitors, maintaining the homeostasis that is required to prevent spontaneous clotting and keep blood fluid. Protein C, when aided by protein S, inactivates two plasma factors, V and VIII.^{34,56,104} Protein Z is a glycoprotein molecule that forms a complex with the protein Z dependent protease inhibitor (ZPI) which, in turn, inhibits the activated factor X (Xa).²⁹⁷ AT complexes with all the serine protease coagulation factors (factor Xa, factor IXa, and contact factors, including XIIa, kallikrein, and HMWK), except factor VII.^{34,104,238}

Thrombolytics such as streptokinase, urokinase, anistreplase, and recombinant tissue plasminogen activator (rt-PA) enhance the normal processes that lead to clot degradation.²⁰⁶

Thrombosis is initiated when exposed endothelium or released tissue factors lead to platelet adherence and aggregation, the formation of thrombin, and cross-linking of fibrinogen to form fibrin strands.^{104,206,238} This results in a hemostatic plug or thrombus formation. Thrombus formation, in turn, leads to generation of plasmin from plasminogen, which causes fibrinolysis and eventual dissolution of the hemostatic plug.^{57,58} Thus the fibrinolytic system may be thought of as a natural balance against unregulated coagulation. Thrombolytic therapy increases fibrinolytic activity by accelerating the conversion of plasminogen to plasmin, which actively degrades fibrin.^{57,58} Following the administration of thrombolytics, a drug-induced coagulopathy ensues, and fibrin degradation products are elevated secondary to the rapid turnover of clot.

DEVELOPMENT OF COAGULOPATHY

Impaired coagulation results from decreased production or enhanced consumption of coagulation factors, the presence of inhibitors of coagulation, activation of the fibrinolytic system, or abnormalities in platelet number or function. Platelets are involved in the initial phases of clotting following blood vessel injury by assisting in the formation of the fibrin plug.

Decreased production of coagulation factors results from congenital and acquired etiologies. Although congenital disorders of factor VIII (hemophilia), factor IX (Christmas factor), factor XI, and factor XII (Hageman factor) are all reported, their overall incidence is still quite low. Clinical conditions that result in acquired factor deficiencies are much more common and result from either a decrease in synthesis or activation. Factors II, V, VII, and X are entirely synthesized in the liver,^{104,206,238} making hepatic dysfunction a common cause of acquired coagulopathy. In addition, factors II, VII, IX, and X also require postsynthetic modification by an enzyme that uses vitamin K as a cofactor,^{273,278,279} such that vitamin K deficiency (from malnutrition, changes in gut flora secondary to xenobiotics, or malabsorption), or inhibition of vitamin K cycling (from warfarin) are all capable of impairing coagulation.

Excessive consumption of coagulation factors usually results from massive activation of the coagulation cascade. Massive activation occurs during severe bleeding or disseminated intravascular coagulation. The latter results from infection, such as sepsis, and from conditions that introduce tissue factor into the blood, such as neoplasms, snake envenomations, stagnant blood flow, diffuse endothelial injury secondary to hyperthermia, ruptured aortic aneurysm, or

aortic dissection. The hallmark of a consumptive coagulopathy is a depressed concentration of fibrinogen with an elevation of fibrin degradation products. This combination suggests the rapid turnover of fibrin in the coagulation process. In the other coagulopathic conditions, the failure to activate the coagulation cascade is associated with normal or high fibrin concentrations and low fibrin degradation products because of limited clot formation.

Hypothermia is a well known cause of disseminated intravascular coagulation leading to death.²⁸⁴ Canine studies show decreased fibrinogen, factor II, and factor VII concentrations when cooled to 68°F (20°C) while a simultaneous rise in factor V concentration occurs.¹⁴⁰ In vitro studies show increased coagulation time, clot formation time, and maximum clot strength in hypothermic whole blood samples from healthy volunteers.^{80,242} In addition, thrombocytopenia occurs secondary to sequestration in the spleen, liver, and splanchnic circulation.^{236,275} Infants with hypothermia have an increased risk for intracranial and pulmonary hemorrhage.⁴⁷

Inhibitors of the coagulation cascade (circulating anticoagulants) are of two types: immunoglobulins to coagulation factors or antibodies to phospholipid membrane surfaces. Immunoglobulins may occur without obvious cause, be part of a systemic autoimmune disorder, or be the result of repeated transfusions with exogenous factors (as occurs in patients with hemophilia).^{125,167,257} Antibodies to factors V, VII to XI, and XIII are described.^{26,257} The clinical syndromes associated with antibody inhibitors are similar to those associated with deficiencies of the particular coagulation factors involved. Antiphospholipid antibodies are directed against phospholipid membrane surfaces and β_2 -glycoprotein I, also known as apolipoprotein H. This protein is essential in preventing hemostasis by inhibiting ADP-induced platelet aggregation, inhibiting activation of the intrinsic pathway of the coagulation cascade, and inhibiting both platelet-mediated factor Xa and factor VII activation. Therefore, destroying β_2 -glycoprotein I creates a prothrombotic clinical status.^{252,253,260} Paradoxically, this antibody creates a prolonged PTT because the antibody also binds to most phospholipid containing PTT reagents. This reduction in amount of active reagent results in a falsely elevated PTT.^{125,167}

GENERAL MANAGEMENT

Gastrointestinal decontamination should be performed on patients who are believed to have potentially significant life threatening ingestions unless they already present with significant bleeding. For patients who present after a few hours of ingestion, gastric emptying is not indicated (**Chap. 8**). Although convincing data on the efficacy of either single- or multiple-dose activated charcoal (AC; possible enterohepatic circulation) are lacking, a single dose of AC seems appropriate unless it is contraindicated. Oral cholestyramine can also be used to enhance warfarin elimination,²³⁵ but no studies are available that compare these two therapies or evaluate the role of combined AC and cholestyramine therapy. In addition to general supportive measures, the patient should be placed in a supervised medical and psychiatric environment that offers protection against external or self-induced trauma and permits observation for the onset of coagulopathy.

Blood transfusion is required for any patient with a history of blood loss or active bleeding who is hemodynamically unstable, has impaired oxygen transport, or is expected to become unstable. Although a transfusion of packed red blood cells is ideal for replacing lost blood, it cannot correct a coagulopathy, and thus patients will continue to bleed. Whole blood contains both the cellular elements and necessary coagulation factors to reverse the coagulopathy. Transfusion of whole blood may be considered in severe cases because whole blood contains many components, including platelets, white blood cells, and non-vitamin K-dependent factors.

VITAMIN K ANTAGONISTS

Warfarin and “Warfarinlike” Anticoagulants

The vitamin K antagonist (VKA) anticoagulants can be divided into two groups: (a) hydroxycoumarins, including warfarin (commonly called by its trade name Coumadin), difenacoum, coumafuryl, fumasol, prolin, ethyl biscoumacetate, phenprocoumon, dicumarol, bishydroxycoumarin, and acenocoumarin; and (b) indanediones, including chlorophacinone, diphacinone, diphenadione, phenindione, and anisindione. Regardless of the classification, their mechanism of action involves inhibition of the vitamin K cycle. Vitamin K is a cofactor in the postribosomal synthesis of clotting factors II, VII, IX, and X (**Fig. 60–2**). The vitamin K-sensitive enzymatic step that occurs in the liver involves the γ -carboxylation of 10 or more glutamic acid residues at the amino terminal end of the precursor proteins, to form a unique amino acid γ -carboxyglutamate.^{81,273,278,279} These amino acids chelate calcium in vivo, which allows the binding of the four vitamin K-dependent clotting factors to phospholipid membranes during activation of the coagulation cascade.³¹⁷

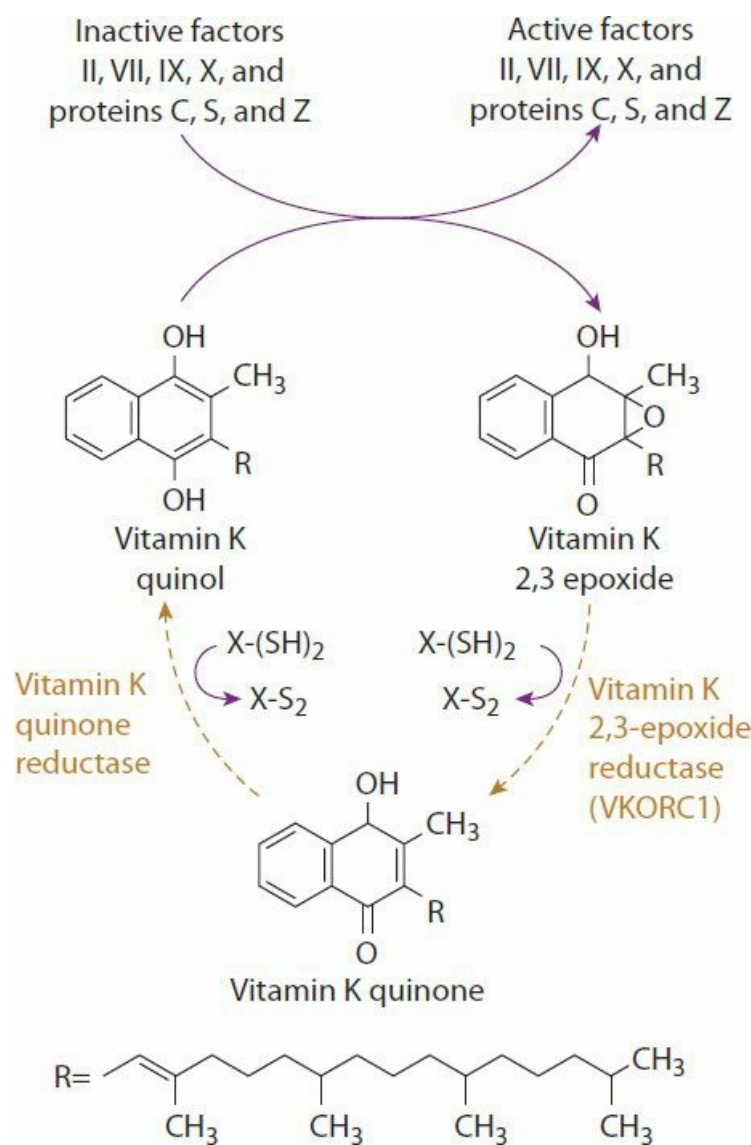


FIGURE 60–2. The vitamin K cycle. Dotted lines represent pathways that can be blocked with warfarin and warfarinlike anticoagulants. The aliphatic side chain (R) of vitamin K is shown below the metabolic pathway. VKORC1 = vitamin K reductase complex 1.

Vitamin K is inactive until it is reduced from its quinone form to a quinol (or hydroquinone) form in hepatic microsomes. This reduction of vitamin K must precede the carboxylation of the precursor factors. The carboxylation activity is coupled to an epoxidase activity for vitamin K, whereby vitamin K is oxidized simultaneously to vitamin K 2,3-epoxide (Fig. 60–2).^{278,316} This inactive form of the vitamin is converted back to the active form by two successive reductions.^{81,186,220,311} In the first step, an epoxide reductase (known as vitamin K 2,3-epoxide reductase) uses reduced nicotinamide adenine dinucleotide (NADH) as a cofactor to convert vitamin K 2,3-epoxide to a quinone form.^{214,215,278} Subsequently, the quinone is reduced to the active vitamin K quinol form (Antidotes in Depth: A15).

Warfarin is a racemic mixture of R warfarin and S warfarin enantiomers. In humans, S warfarin is approximately 2.7 to 3.8 times more potent than R warfarin.³⁷ Warfarin and all warfarinlike compounds inhibit the activity of vitamin K 2,3-epoxide reductase, as can be demonstrated by the observation of elevated concentrations of vitamin K 2,3-epoxide.^{53,320} Additional evidence suggests that vitamin K quinone reductase is also inhibited by warfarin and its related compounds (Fig. 60–2).^{81,95} This reduction in the cyclic activation of vitamin K subsequently inhibits the formation of activated clotting factors.

Pharmacology of Vitamin K Antagonists

Oral warfarin is well absorbed, and peak serum concentrations occur approximately 3 hours after administration.²⁷⁷ Because only the free warfarin is therapeutically active, concurrent administration of xenobiotics that alter the concentration of free warfarin, either by competing for binding to albumin or by inhibiting warfarin metabolism, may markedly influence the anticoagulant effect.^{17,100,277} The pharmacologic response to warfarin is a polygenic trait with approximately 30 genes contributing to its therapeutic effects.¹⁵³ The reader is referred to a review of xenobiotics and foods that potentiate warfarin's effects.³¹⁴ Although vitamin K regeneration is altered almost immediately, the anticoagulant effect of warfarin and other warfarin-like anticoagulants is delayed until the existing stores of vitamin K are depleted and

the active coagulation factors are removed from circulation. Because vitamin K turnover is rapid, this effect is largely dependent on factor half-life ($t_{1/2}$), with factor VII ($t_{1/2} \sim 5$ hours) depleted most rapidly.¹⁰⁰ For a prolongation of the INR to occur, factor concentrations must fall to approximately 25% to 30% of normal values.⁵⁵ Assuming complete inhibition of the vitamin K cycle, this suggests that most patients require at least 15 hours (three factor VII half-lives) before the effect of warfarin is evident on the INR.⁹⁷ In fact, since complete inhibition does not occur, the onset of coagulation is delayed even further.

Because the half-life of warfarin in humans is 35 hours, its duration of action may be as long as 5 days.^{36,277} On average, it takes approximately 6 days of warfarin administration to reach a steady-state anticoagulant effect.

R warfarin is metabolized by enzymes CYP1A2 and CYP3A4, and S warfarin is metabolized by CYP2C9 of the hepatic microsomal P450 enzyme system. R warfarin is metabolized by side-chain reduction to secondary alcohols that are subsequently excreted by the kidney, whereas S warfarin is metabolized by hydroxylation to 7-hydroxy warfarin, which is excreted into the bile.²⁷⁷ The elimination of S warfarin is more rapid than that of R warfarin.³⁷

Dosing of warfarin and other VKAs is problematic in many patients. In one study, genetic polymorphisms of the vitamin K epoxide reductase complex 1 (VKORC1) and CYP2C9 genes appear to be the strongest predictors of interindividual variability in the anticoagulant effect of warfarin.¹⁵³ Pharmacogenomic research with complex xenobiotics, such as warfarin, may improve the treatment of patients and predict or prevent interactions with other xenobiotics. While the FDA has approved a commercially available test to identify variants within these genes,¹⁵¹ current guidelines do not advocate genetic testing to guide VKA dosing.¹¹⁷

Within the coumarin group are two 4-hydroxycoumarin derivatives, difenacoum and brodifacoum, that differ from warfarin by their longer, higher molecular weight polycyclic hydrocarbon side chains. Together with chlorophacinone, an indandione derivative, they are known as superwarfarins or long-acting VKAs.

Long-acting VKAs were designed to be effective rodenticides in warfarin-resistant rodents.¹⁸³ Their mechanism of action is identical to that of the traditional warfarinlike anticoagulants, as demonstrated by increased concentrations of vitamin K 2,3-epoxide after administration.^{35,38,41,168,220} The ability of these xenobiotics to perform as superior rodenticides is attributed to their high lipid solubility and concentration in the liver.^{168,183,220} They also may saturate hepatic enzymes at very low concentrations, as demonstrated by zero-order elimination following overdose.⁴¹ These factors make them about 100 times more potent than warfarin on a molar basis.^{168,183,220} In addition, they have a longer duration of action than the traditional warfarins.^{168,183,220} For example, to obtain 100% lethality in a mouse, more than 21 days of feeding with a warfarin-containing rodenticide (0.025% anticoagulant by weight of bait) is required.¹⁸³ Similar efficacy can be achieved with a single ingestion of brodifacoum (0.005% anticoagulant by weight of bait).¹⁸³ Furthermore, more concentrated liquid formulations, such as brodifacoum (0.5% anticoagulant), are available through illegal vendors and have been implicated in prolonged coagulopathy.¹⁰⁷ It should also be noted that although ingestion of these xenobiotics is the most common route of exposure and subsequent cause of toxicity, dermal absorption of liquid preparations can occur, also resulting in a coagulopathy.²⁶⁸

Clinical Manifestations

Although intentional ingestions of warfarin-containing products are uncommon, adverse drug events resulting in excessive anticoagulation and bleeding frequently occur. The risk of bleeding during VKA therapy depends on a myriad of factors, including the intensity of anticoagulation, patient characteristics, and comorbid conditions. Clearly, the most serious complication of excessive anticoagulation is intracranial bleeding, which is reported to occur in as many as 2% of patients on long term therapy, which is an 8 to 10 fold increase in risk when compared to patients who are not anticoagulated.^{99,100,322} Overall risk of major bleeding in patients can be estimated using tools such as the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly (HAS-BLED) score, which has been prospectively validated in patients with atrial fibrillation.^{179,226} Bleeding can range between 1 and 12.5 episodes per 100 patient-years, with a higher risk in patients with multiple risk factors.²²⁶ Another study showed that patients over the age of 80 have a cumulative incidence of major bleeding at 13.1 per 100 person-years with major bleeding defined as bleeding at serious sites (eg, intracranial, retroperitoneal, intraspinal, or pericardial) or bleeding that results in blood transfusion or death. Patients between the ages of 65 and 80 have a lower risk of 4.7 major episodes of bleeding per 100 person-years.¹³⁵ Major bleeding complications are associated with a fatality rate as high as 77%.¹⁹¹ A recent study of patients with intracranial bleeding found that decreased level of consciousness and increased size of hematoma were predictors of poor prognosis.³³¹ Somewhat surprisingly, the degree of INR elevation was not associated with worse outcome.³³¹

Many cases of intentional overdose of long-acting VKAs in humans are described in the literature. The clinical courses of these patients are characterized by a severe coagulopathy that may last weeks to months, often accompanied by consequential blood loss. Most patients do not seek medical care until bruising or bleeding is evident,^{14,41,42,94,129,152} which

often occurs many days after ingestion. The most common sites of bleeding are the gastrointestinal and genitourinary tracts. In one study describing 12 patients with surreptitious ingestion of oral anticoagulants, nine were health care professionals.²¹⁵ These patients presented with bruising, hematuria, hematochezia, and menorrhagia. Bleeding into the neck with resultant airway compromise is a rare but life-threatening complication that has occurred.³¹

Patients with unintentional ingestions must be distinguished from those with intentional ingestions, because the former demonstrate a low likelihood of developing a coagulopathy and have rare morbidity or mortality. Most patients (usually children) are entirely asymptomatic and have a normal coagulation profile following an acute unintentional exposure. Typical warfarinlike rodenticides contain only small concentrations of anticoagulant, 0.005% (or 5 mg of brodifacoum per 100 g of product). A 10 kg child would require an initial dose of 10 g of rodenticide (8 pellets, each of which is approximately 25 mm in size). These quantities are far greater than those that occur in typical “tastes.” Thus, single small unintentional ingestions of warfarin-containing rodenticides pose a minimal threat to normal patients.¹⁴⁷ Prolongation of the INR is unlikely with a single small ingestion of a long-acting VKA rodenticide. Clinically significant anticoagulation is even rarer. In a combined pediatric case series, prolongation of the INR occurred in only 8 of 142 children (5.6%) reported with single small ingestions of long-acting VKAs.^{21,146,147,266} Only one child in this group was reported to have “abnormal prolonged bleeding,” but this required no medical attention.²⁶⁶ In a single case report, a 36 month-old child developed a coagulopathy manifested by epistaxis and hematuria, with anticoagulation persisting for more than 100 days after a presumed, but unwitnessed, single unintentional ingestion of brodifacoum.²⁸⁵ Clinically significant coagulopathy can result, however, following small repeated ingestions. Two children reportedly became poisoned by repeated ingestions of a long-acting anticoagulant. One child presented with a neck hematoma that compromised his airway, and the other with a hemarthrosis.¹¹⁵ Similarly, a 7 year-old girl required multiple hospitalizations over a 20 month period following repeated unintentional ingestions of brodifacoum.²⁴ Finally, a 24 month-old child who presented with unexplained bruising and a PT greater than 125 seconds was the victim of brodifacoum poisoning secondary to Munchausen syndrome by proxy.¹⁰

Laboratory Assessment

Although warfarin concentrations may be useful to confirm the diagnosis in unknown cases and to study drug kinetics,^{118,212} the routine use of simple and inexpensive measures such as INR determination seems more appropriate (Table 60–1). When blood loss is evident, serial determinations of hemoglobin concentration are indicated.

TABLE 60–1. Antithrombotics: Laboratory Testing, Antidotes, and Treatment Strategies

	Laboratory Testing	Antidotes and Treatment Strategies
Antiplatelet Agents Cyclooxygenase inhibitors Phosphodiesterase inhibitors Adenosine uptake inhibitors Adenosine diphosphate receptor inhibitors Glycoprotein IIb/IIIa inhibitors	Bleeding time prolonged; platelet function assays abnormal	Desmopressin 0.3 µg/kg IV for life-threatening bleeding; platelet administration is controversial
Antithrombin Agents Unfractionated heparin	PTT prolonged; TT abnormal; ACT elevated; fibrinogen normal; anti-factor Xa activity decreased	1 mg protamine per 100 units of heparin. In overdose, if unknown quantity of heparin administered, treat based on ACT*, or empirically with 25–50 mg ACT < 150 sec: no protamine needed ACT 200–300 sec: 0.6 mg/kg protamine ACT 300–400 sec: 1.2 mg/kg protamine
Low-molecular-weight heparin (eg, enoxaparin, dalteparin)	Anti-factor Xa activity decreased; PTT is insensitive	For partial reversal, 1 mg protamine per 100 anti-factor Xa units (or 1 mg of enoxaparin) given in the last 8 hours. May administer an additional 0.5 mg protamine per 100 anti-factor Xa units if bleeding continues
Direct Thrombin Inhibitors Dabigatran Bivalirudin Argatroban	PTT prolonged; TT prolonged; ECT prolonged; anti-factor Xa activity elevated (at low concentrations, PT and PTT may be normal); dTT prolonged ^{†‡§}	Activated charcoal in acute overdose PCC administration with up to 100 units/kg in repeated 50 units/kg doses as needed. If bleeding continues 30 minutes after PCC, give FEIBA. [¶] Consider hemodialysis FFP 15 mL/kg
Factor Xa Inhibitors Rivaroxaban Apixaban	PT and PTT normal or prolonged (can vary with reagents); anti-factor Xa elevated; specific modified chromogenic antifactor Xa [¶]	Activated charcoal in acute overdose only PCC administration with up to 50 units/kg in repeated 25 units/kg doses as needed
Fibrinolytics	PT and PTT prolonged; TT abnormal; fibrinogen abnormal	Cryoprecipitate Factor replacement with 15 mL/kg of FFP or 50 units/kg of PCC For life-threatening bleeding, consider tranexamic acid at 1 g intravenously over 10 minutes, followed by 1 g over 8 hours. If tranexamic acid is unavailable, IV aminocaproic acid can be given as a loading dose of 5 g over 1 hour, followed by an infusion at 1 g/h for 23 hours. Stop infusion if bleeding ceases.
Pentasaccharides Fondaparinux	Fondaparinux-specific anti-Xa assay PTT is insensitive	PCC administration with up to 50 units/kg in repeated 25 units/kg doses as needed.
Vitamin K Antagonists Warfarin	Early (PT prolonged; PTT normal) Late (PT and PTT prolonged; TT and fibrinogen normal)	Vitamin K Factor replacement (FFP or PCC) See Table 40–7 for detailed management recommendations

*May need to repeat in 2–4 hours due to potential heparin rebound. †Size of ACT is only validated in the operative setting following cardiopulmonary bypass. ‡In patients with a history of heparin-induced thrombocytopenia, avoid PCC (except proline) and use FEIBA or rFVIIa. §No readily available method to assess extent of anticoagulation at this time.

ACT = activated clotting time; ECT = ecarin clotting time; FFP = fresh frozen plasma; PCC = prothrombin complex concentrate; PT = prothrombin time; PTT = partial thromboplastin time; TT = thrombin time; FEIBA = factor eight inhibitor bypassing activity.

For patients with an acute and significant long acting VKA overdose, daily INR evaluations for 2 days should be adequate to identify most patients at risk for coagulopathy. Earlier detection through direct coagulation factor analysis may be preferred,^{118,129} and concentrations of long acting VKAs can now be measured, although they are usually only performed in reference laboratories.^{157,212} Children with possibly significant exposures should be followed up with at least a single INR at least 48 hours after the exposure. Despite the fact that significant toxicity from long acting VKAs is rare, it should be recognized that the reported benign courses of exposures in children may be misleading. Multiple retrospective studies suggest that children with unintentional acute exposures do not require any follow-up coagulation studies.^{205,208,222,258} However, this conclusion and approach to management may be an unjustified attempt to decrease the cost of “unnecessary” coagulation studies. There are clearly insufficient data to justify this conclusion, as many of these “exposed” children were never documented to have ingested long-acting VKAs (Chap. 136). We recommend that clinicians continue to manage these children as possibly significant exposures and that all children be followed up with at least a single INR at a minimum of 2 days after the exposure. A baseline INR is usually unnecessary but may be performed if there is a suspicion of an antecedent ingestion. A baseline INR is also helpful when chronic exposure is suspected.

Treatment of Vitamin K Antagonist Induced Coagulopathy

Life threatening bleeding secondary to VKA toxicity should be immediately reversed with factor replacement, followed by vitamin K₁ (Table 60–1). The American College of Chest Physicians recommends factor replacement with four-factor prothrombin complex concentrate (PCC) as a first-line treatment.¹³⁰ While four-factor PCC has recently become available in the United States, three-factor PCC was more commonly stocked by hospitals. There are no trials that directly compare four-factor PCC against three-factor PCC. Both formulations contain concentrated factors II, VII, IX, X, C, and S. However, the factor VII concentration is significantly decreased to limit thrombosis potential in three-factor PCC. Most countries use traditional four-factor PCC, which contains factor VII in its formulation. Most forms of PCC, contain small amounts of heparin. These heparin-containing PCCs are contraindicated in patients with heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis syndrome (HITT). In those cases, factor eight inhibitor bypassing activity (FEIBA), an activated prothrombin complex concentrate (aPCC), should be used. FEIBA does not contain heparin, and is, therefore, acceptable to use in patients with HIT or HITT. Despite its increased cost, the rationale for using PCC instead of fresh-frozen plasma (FFP) includes less risk of infection transmission.¹³⁰ In addition, small-volume factor replacement may be preferable in patients at risk of volume overload, such as patients with heart failure, chronic kidney disease (CKD), or intracranial bleeding.¹ Unfortunately, there are only a few studies comparing PCC with FFP in reversing coagulopathy. These studies show that PCC safely produces complete INR reversal faster than FFP with more consistent factor IX replacement.^{74,143,187} However, unequal factor replacement in these small studies favors more factor replacement in patients receiving PCC,²⁴⁷ and the use of four-factor PCC currently limits the generalizability of these studies to clinical practice in the United States. FFP is rich in active vitamin K–dependent coagulation factors and will reverse oral anticoagulant-induced coagulopathy in most patients. In general, approximately 15 mL/kg of FFP should be adequate to reverse any VKA-induced coagulopathy.⁶⁸ However, the specific factor quantities and volume of each unit may be varied, leading to an unpredictable response.¹⁸⁷ In addition, delay to FFP administration may be accentuated by requirements for blood type matching and thawing.

rfVIIa is approved for patients with hemophilia or various factor inhibitors and has been successfully used to reverse VKA toxicity. The safety of off-label rFVIIa to reverse VKA coagulopathy is unclear. Preliminary data using rFVIIa suggested its utility for bleeding secondary to warfarin induced excessive anticoagulation, and a case series showing beneficial effects in four patients with long acting VKA toxicity.³³² However, adverse outcomes such as arterial thrombotic events may occur at higher than acceptable rates. Initial concerns for thromboembolic adverse events were raised when review of the FDA’s Adverse Event Reporting System database found that the majority of these complications arose in patients who received rFVIIa for off-label purposes. Cerebrovascular accident, acute myocardial infarction, pulmonary embolism, venous thrombosis, and clotted devices all occurred at higher rates in off-label applications.²¹³ The Factor Seven for Acute Hemorrhagic Stroke Trial (FAST) showed that arterial thromboembolic adverse events increased in a dose dependent fashion with the administration of rFVIIa.⁷⁹ A subsequent meta-analysis confirmed that an increased rate of arterial thrombosis occurs in patients who receive rFVIIa.¹⁷⁵ The risk of continued bleeding versus the benefit of rapid reversal of coagulopathy with rFVIIa is unknown, and further experience with rFVIIa is necessary to determine its safety and efficacy in anticoagulant-induced bleeding. It should also be noted that if rFVIIa is used, assays based on PT may be inaccurate and should be avoided when administering rFVIIa.¹⁴⁸

Treatment with vitamin K₁ takes several hours to activate enough factors to reverse the patient’s coagulopathy,^{187,221} and this delay may be potentially fatal. Repetitive, large doses of vitamin K₁ (on the order of 60 mg/d or greater) may be required in some patients.^{118,215} If complete reversal of INR prolongation occurs or is desirable (as in most cases of life-threatening bleeding), and the underlying medical condition of the patient still requires some degree of anticoagulation, the patient can then receive anticoagulation with heparin once the bleeding is controlled and clinical stability restored. Heparin

anticoagulation was used without apparent bleeding complications in 25% of patients in one cross-sectional study.³¹⁹

Vitamin K₁ is preferable over the other forms of vitamin K; the other forms are ineffective^{141,209,214,291} and are potentially toxic.¹² Other forms, such as vitamin K₃ (menadione) and vitamin K₄ (menadiol sodium diphosphate), can cause oxidative stress on neonatal erythrocytes and produce hemolysis, hyperbilirubinemia, and kernicterus. They are not available in the United States. Parenteral administration of vitamin K₁ (phytonadione) is traditionally preferred as initial therapy by many authors, but success can also be achieved with early oral therapy, especially when the coagulopathy is not severe.⁴¹ In most cases, the patient can be switched to oral vitamin K₁ for long-term care. Vitamin K₁ can be administered intramuscularly, subcutaneously, intradermally, or intravenously. Although intravenous therapy has the most rapid onset of action of all routes of delivery, its use as the sole therapeutic is still associated with a delay of several hours^{221,311} and carries the added risk of anaphylactoid reactions.²³⁷ The use of low doses and slow rate of administration reduces this risk²⁶¹ (Antidotes in Depth: A15). In cases where oral administration is undesirable, for example, with significant gastrointestinal bleeding, the subcutaneous route may be used, realizing that absorption may be erratic. Furthermore, if a patient is anticoagulated or overanticoagulated, administration of vitamin K₁ by the intramuscular route may result in a large hematoma. Caution should be exercised if this route of administration is chosen.

For patients with non-life-threatening bleeding, the clinician must consider whether anticoagulation is required for long-term care. In patients not requiring chronic anticoagulation, even small elevations of the INR may be treated with vitamin K₁ alone to prevent deterioration in coagulation status and reduce the risk of bleeding. Because most cases of warfarin-induced coagulopathy only last several days, there may be a rationale for prophylactic vitamin K₁ administration in known warfarin-like anticoagulant ingestions in patients not requiring anticoagulation. In contrast to ingestions of warfarin, prophylactic vitamin K₁ should not be given to asymptomatic patients with unintentional ingestions of long-acting warfarinlike anticoagulants because (a) if the patient develops a coagulopathy, it will last for weeks, and the one or two doses of vitamin K₁ given will not prevent complications; (b) a gradual decline in coagulation factors occurs over the first day of anticoagulation, so an individual would not be expected to develop a life-threatening coagulopathy in 1 or 2 days; and (c) after vitamin K₁ is administered, the onset of an INR abnormality will be delayed, which could impair the ability of the clinician to recognize a coagulation abnormality, possibly requiring the patient to undergo an unnecessarily prolonged observation period.

For patients requiring chronic anticoagulation, the American College of Chest Physicians has issued guidelines for the management of patients with elevated INRs (Table 60–2). Moreover, the use of a regression formula may assist in calculating the amount of oral vitamin K₁ necessary to partially correct the INR, without completely discontinuing the oral anticoagulant. Although this formula remains unvalidated, it may be useful prior to minor surgery or dental procedures in patients requiring chronic anticoagulation, while theoretically decreasing the likelihood of thromboembolism.^{67,315} It should also be noted that low-dose vitamin K may be safely administered to patients with mildly elevated INRs (4 to 10) to decrease the INR more rapidly; however, one study did not demonstrate decreased bleeding in the treatment group.⁶⁷ Furthermore, simply omitting warfarin doses may be adequate for the patient without active bleeding who has an INR between 4 and 9.⁶⁷

TABLE 60–2. Recommendations for Management of Elevated INRs or Bleeding in Patients Receiving Vitamin K Antagonists

<i>INR</i>	<i>Recommendations^a</i>
<4.5; no significant bleeding	Lower or omit the next dose of warfarin
≥4.5–10; no significant bleeding	Omit warfarin for the next one or two doses
>10; no evidence of bleeding	Give oral vitamin K ₁ (1–2.5 mg). If more rapid reversal is necessary, give oral vitamin K ₁ (≤5 mg) and wait 24 hours. Give additional vitamin K ₁ orally (1–2 mg) as needed
Serious bleeding at any INR concentration or life-threatening bleeding	Hold warfarin therapy and give FFP or PCC supplemented with vitamin K ₁ (5–10 mg by slow intravenous ^b infusion). Vitamin K ₁ administration may need to be repeated q12h

^aData from Reference 130. ^bIntravenous infusion of vitamin K₁ rarely may cause severe anaphylactoid reactions.

FFP = fresh frozen plasma; INR = international normalized ratio; PCC = prothrombin complex concentrate.

It is often unclear why patients with consistent therapeutic dosing have seemingly random elevations in their INR. A

case-control study identified the following risk factors associated with overanticoagulation from VKAs: previous medical history of increased INR, antibiotic therapy, fever, and concomitant use of amiodarone and proton pump inhibitors.⁴⁵ Clinicians should pay particular attention to patients with these conditions and close monitoring of coagulation profiles should be performed.⁴⁵

Treatment of Long-Acting Vitamin K Antagonist Overdoses

In patients with unintentional, small ingestions of long-acting VKAs, the risk of coagulopathy is low. Because it takes days to develop coagulopathy, most authors recommend supportive care only, although administration of activated charcoal is reasonable.^{147,266}

Treatment of a patient with a coagulopathy resulting from a long-acting anticoagulant overdose is essentially the same as the treatment of oral anticoagulant toxicity with certain exceptions. Although initial parenteral vitamin K₁ doses as high as 400 mg have been required for reversal,⁴² daily oral vitamin K₁ requirements may be in the range of 50 to 200 mg. Recent experience in both animals and humans suggests that parenteral vitamin K₁ therapy might not be required after initial stabilization (Antidotes in Depth: A15).^{41,327}

Long-acting VKAs are metabolized by the cytochrome P450 system.^{11,214} In a rat model, the duration of coagulopathy was shortened by administering phenobarbital, a CYP3A4 inducer.¹¹ Although phenobarbital has never been systematically studied in humans, this approach was used by several authors in isolated human cases of long-acting anticoagulant toxicity.^{42,141,180,285,309} These anecdotal reports suggest some improvement with phenobarbital therapy, but the risk of sedation in a patient who might be prone to bleeding complications would argue against this approach.

Patients with long-acting VKA overdose should be followed until their coagulation studies remain normal without treatment for several days. This usually requires daily or even twice-daily INR measurements until the INR is at the lower limit of the therapeutic range. Monitoring of serial INR measurements should allow for a gradual decrease in vitamin K₁ requirement over time. Periodic coagulation factor analysis (particularly factor VII), however, may provide an early clue to the resolution of toxicity.¹²⁹ The patient may require weeks to months of close observation for both psychiatric and medical management. Emphasis has been placed on determining a critical superwarfarin concentration below which anticoagulation does not occur.⁴² In one case report, brodifacoum was observed to follow zero-order elimination kinetics.⁴¹ If this type of toxicokinetics is consistent in the analysis of other long-acting VKAs, these laboratory measurements may prove more reliable than the current empiric end points of therapy.

Nonbleeding Complications of Vitamin K Antagonists

Warfarin therapy is associated with three nonhemorrhagic lesions of the skin: urticaria,²⁵¹ purple toe syndrome,⁹⁶ and warfarin skin necrosis.^{59,151,160,193,301} Although warfarin skin necrosis was once thought to be a rare and idiosyncratic reaction,^{151,160} more recent evidence suggests a link between this disorder and protein C deficiency.^{160,301} Protein C activation is also dependent on vitamin K.⁵⁶ Patients who are homozygotes for protein C deficiency have an increased incidence of thrombosis and embolic events, such that they often require long-term anticoagulant therapy.⁵⁶ Because the half-life of protein C is shorter than that of many of the vitamin K–dependent coagulation factors, protein C concentrations fall rapidly during the first hours of warfarin therapy. This results in an imbalance that actually favors coagulation, and skin necrosis results due to microvascular thrombosis in dermal vessels.^{193,301} Although warfarin skin necrosis is more common in patients with protein C deficiency, this disorder is also described in patients with protein S and AT deficiencies.⁵⁹ Unfortunately, these deficiencies are neither necessary nor sufficient to account for the incidence of warfarin necrosis.⁵⁹ If necrosis occurs, warfarin should be discontinued and heparin should be initiated to decrease thrombosis of postcapillary venules. Some patients may also require surgical débridement.²⁴⁶

The purple toe syndrome, in contrast to warfarin-induced skin necrosis, is presumed to result from small atheroemboli that are no longer adherent to their plaques by clot (Fig. 18–10).

A recently recognized form of warfarin toxicity is warfarin-related nephropathy (WRN). In patients with CKD an acute increase in the INR above 3 was associated with an increase in serum creatinine and accelerated reduction in kidney function. The etiology of the WRN has been attributed to acute tubular injury and glomerular bleeding, demonstrated by the finding of red blood cells filling Bowman's capsule and red blood cells casts obstructing glomeruli on specimens from kidney biopsies.^{39,40} Further studies that retrospectively reviewed kidney function in patients on long-term warfarin anticoagulation showed 33% of patients with CKD and 16.5% of patients without CKD developed WRN. WRN is associated with a mortality rate of 31.1%, a significant increase in risk compared to 18.9% in patients without WRN.³⁹

An additional major nonhemorrhagic complication of warfarin therapy is warfarin embryopathy. Most warfarin-induced fetal abnormalities occur during weeks 6 to 12 of gestation, but central nervous system (CNS) and ocular abnormalities can develop at any time during gestation (Chap. 31).^{121,274}

ANTITHROMBIN AGONISTS

Heparin

Conventional or unfractionated heparin is a heterogeneous group of molecules within the class of glycosaminoglycans.¹³⁸ The heparin precursor molecule is composed of long chains of mucopolysaccharides, a polypeptide, and carbohydrates. The main carbohydrate components of heparin molecules include uronic acids and amino sugars in polysaccharide chains. Heparin for pharmaceutical use is extracted from bovine lung tissue and porcine intestines.²⁵⁵

Heparin inhibits thrombosis by accelerating the binding of AT to thrombin (activated factor II) and other serine proteases involved in coagulation.^{185,241} Thus, factors IX to XII, kallikrein, and thrombin are inhibited. Heparin also affects plasminogen activator inhibitor, protein C inhibitor, and other components of coagulation. The therapeutic effect of heparin is usually measured through the activated PTT. The activated clotting time (ACT) may be more useful for monitoring large therapeutic doses or in the overdose situation.¹⁵⁹

Low-molecular-weight heparins (LMWHs) are 4000- to 6000-Da fractions obtained from conventional (unfractionated) heparin.¹⁰² As such, they share many of the pharmacologic and toxicologic properties of conventional heparin.³³ The various LMWHs (eg, nadroparin, enoxaparin, dalteparin) are prepared by different methods of depolymerization of heparin; consequently, they each differ to a certain extent regarding their pharmacokinetic properties and anticoagulant profiles. The major differences between LMWHs and conventional heparin are greater bioavailability, longer half-life, more predictable anticoagulation with fixed dosing, targeted activity against activated factor X, and less targeted activity against thrombin.^{33,102} As a result of this targeted factor X activity, LMWHs have minimal effect on the activated PTT, thereby eliminating either the need for, or the usefulness of monitoring. They are therefore administered on a fixed dose schedule. However, in certain instances (eg, patients with CKD, pregnancy, etc), monitoring of anti-factor Xa activity may be performed to assess adequacy of anticoagulation and to prevent the risk of bleeding.¹²² Controversy exists as to whether such testing is clinically necessary.³²

LMWHs have been investigated for prevention of thromboembolic disease after hip surgery and trauma, in patients with stroke or deep venous thrombosis, in pregnancy, and in other conditions where anticoagulation with heparin would otherwise be indicated (eg, at the onset of oral anticoagulation therapy). They have a minimal risk in pregnancy¹⁹⁷ because they do not cross the placenta,^{98,276} and they are therefore preferred for the treatment or prophylaxis of thromboembolic disease in pregnancy.²⁴⁰ Most studies demonstrate a lower incidence of embolization; however, there is still a trend toward increased bleeding.^{23,116,176} The PROTECT trial, which compared dalteparin and unfractionated heparin in terms of rates of proximal leg deep vein thrombosis, pulmonary emboli, and major bleeding in critically ill patients, found that patients randomized to the dalteparin group had statistically fewer pulmonary emboli. This particular study found no statistically significant differences in proximal DVT and major bleeding rates.²³²

Pharmacology

Because of the large size of heparin and negative charge, the molecule is unable to cross cellular membranes. These factors prevent oral administration, and heparin must be administered parenterally. Following parenteral administration, heparin remains in the intravascular compartment, in part bound to globulins, fibrinogen, and low-density lipoproteins, resulting in a volume of distribution of 0.06 L/kg in humans.^{93,216} Because of its rapid metabolism in the liver by a heparinase, heparin has a short duration of effect.¹⁸⁵ Although the half-life of elimination is dose dependent and ranges from 1 to 2.5 hours,^{185,192,216} the duration of anticoagulant effect is usually reported as 1 to 3 hours.¹⁸⁵ Dosing errors or drug interactions with thrombolytics, antiplatelet drugs, or nonsteroidal antiinflammatory drugs may increase the risk of bleeding.¹²⁴ LMWHs are nearly 90% bioavailable following subcutaneous administration and have an elimination half-life of 3 to 6 hours.¹⁰⁶ Anti-factor Xa activity peaks between 3 and 5 hours after dosing.¹⁰⁶ LMWHs are renally eliminated and patients with stage 4 or 5 CKD are at increased risk of toxicity.³⁰² Although there are insufficient data guiding therapeutic LMWH dosing in patients with severe CKD, some advocate dose reduction to decrease the risk of bleeding. However, no dosage regimens are provided.¹¹⁷

Clinical Manifestations

Intentional overdoses with heparin are rare.¹⁹⁰ Most reported cases involve iatrogenic toxicity in hospitalized patients.^{105,110,190,219,254} These cases have involved the administration of large amounts of heparin as a consequence of misidentification of heparin vials, during the process of flushing intravenous lines, and secondary to intravenous pump malfunction. Significant bleeding complications occurred in several cases, including at least one fatality.¹⁰⁵ However, intentional overdoses of LMWHs are reported, although none of them have been fatal.^{43,203}

Similar adverse effects to unfractionated heparin are also reported with LMWHs and include epidural/spinal hematoma, intrahepatic bleeding,¹³² abdominal wall hematomas,⁷ psoas hematoma after lumbar plexus block,¹⁵⁰ and

intracranial bleeding in patients with CNS malignancy.⁷⁷ While the above complications were all reported in patients who received the LMWH enoxaparin, there are no data to suggest differing toxicities among LMWHs.

Diagnostic Testing

For therapeutic anticoagulation, the effect of heparin is usually monitored with aPTT. Most hospitals have heparin nomograms that recommend heparin dose alterations based on aPTT, although these nomograms need to be individualized by each hospital due to the variation expected from the particular aPTT reagent and laboratory technology employed. For patients undergoing cardiovascular procedures, activated clotting time may be used to monitor these patients since they require higher-dose heparin.¹⁰⁶ More recently, an anti-Xa assay specific for heparin has been FDA approved.

In patients with heparin resistance, where extremely high doses of heparin are required to accomplish a therapeutic aPTT, anti-Xa levels may be used to guide heparin dosing. Despite lower heparin dosing and subtherapeutic aPTTs, patients monitored with anti-Xa activity had similar rates of recurrent thromboembolism and bleeding when compared to the patients who were given high-dose heparin to maintain therapeutic aPTTs in a prospectively collected randomized control trial.¹⁷⁷

LMWHs are usually administered at fixed doses for VTE prophylaxis or at weight-based doses for VTE treatment. Laboratory monitoring is not done unless patients are pregnant, have CKD, or are obese. In these cases, anti-factor Xa activity is measured, with target ranges varying based on agent and dosing regimen.¹⁰⁶ In patients without the aforementioned risk factors, monitoring and dose adjustment are of no benefit when compared to fixed-dose regimens of LMWH.³ In addition, several studies have shown no correlation between anti-factor Xa level activity and bleeding propensity.^{13,171,305}

Treatment

After stabilization of the airway and breathing and circulation are assured, the physician should be prepared to replace blood loss and reverse the coagulopathy, if indicated. Because of the relatively short duration of action of heparin, observation alone might be indicated if significant bleeding has not occurred. For the patient requiring anticoagulation, serial aPTT determinations will indicate when it is safe to resume therapy. If significant bleeding occurs, either removal of the heparin or reversal of its anticoagulant effect is indicated. Because heparin has a very small volume of distribution, it can be effectively removed by exchange transfusion.²⁵⁴ Although this technique has been used successfully in neonates, it is not generally applicable to older children and adults.

When severe bleeding occurs, unfractionated heparin may be effectively neutralized by protamine sulfate⁵ (Table 60–1). Protamine is a low-molecular-weight protein found in the sperm and testes of salmon, which forms ionic bonds with heparin and renders it devoid of anticoagulant activity.¹⁸⁵ One milligram of protamine sulfate injected intravenously neutralizes 100 units of unfractionated heparin.¹⁸⁵ The dose of protamine should be calculated from the dose of heparin administered if known and assuming the approximate half-life of heparin to be 60 to 90 minutes; the amount of protamine should not exceed the amount of heparin expected to be found intravascularly at the time of infusion. As with other foreign proteins, protamine administration is associated with numerous adverse effects such as hypotension, bradycardia, and allergic reactions. Because approximately 0.2% of patients receiving protamine experience anaphylaxis, a complication that carries a 30% mortality rate, most authors recommend that protamine be reserved for patients with life-threatening bleeding (Antidotes in Depth: A16).¹³² It should also be noted that excess protamine administration may result in paradoxical anticoagulation.

Because of the severe adverse effects associated with protamine, research has focused on safer methods to reverse heparin anticoagulation. These agents include heparinase,¹⁹⁹ synthetic protamine variants,^{303,304} and platelet factor 4. These therapies are not widely available, and their efficacy and safety have not been established.

If life-threatening bleeding occurs following LMWH administration, patients should also be treated with protamine. Several studies suggest that protamine partially reverses LMWHs such as enoxaparin, dalteparin, and tinzaparin. In one case report of a 10-fold dosing error of enoxaparin, protamine effectively reversed the anticoagulant effects.³²¹ In a series of 14 bleeding patients given protamine to reverse LMWH, bleeding ceased in two-thirds of the patients. These data, however, are complicated by repeat dosing of protamine as well as administration of other procoagulant antidotes such as clotting factors and vitamin K in a subset of patients. In addition, patients received protamine between 30 minutes and 48 hours after their last dose of LMWH.²⁹⁶ Current recommendations are to administer 1 mg protamine per 100 anti-factor Xa units, where 1 mg enoxaparin equals 100 anti-factor Xa units if within 8 hours of the LMWH administration.⁷⁹ A second dose of 0.5 mg protamine per 100 anti-factor Xa units should be administered if bleeding continues. If more than 8 hours has elapsed, a smaller dose of protamine can be administered.¹⁰⁶ The appropriate dosages for protamine are described in detail in the Antidotes in Depth: A16. The newer experimental protamine variants appear to be effective against LMWHs but are not yet available.^{303,304} Interestingly, there is one case report of recombinant activated factor VII (rfVIIa) reversing

the effects of LMWH in the setting of postoperative acute kidney injury (AKI),^{75,200,210} and there is also a single case report demonstrating efficacy at reversing severe bleeding caused by enoxaparin.¹³⁴

NONBLEEDING COMPLICATIONS

Postoperative thrombocytopenia that occurs in the first 1 or 2 days following surgery usually results from platelet consumption. This early fall in platelet count tends to cause concern for a drug-induced thrombocytopenia called heparin-induced thrombocytopenia (HIT) because postoperative venous thromboembolism (VTE) prophylaxis with heparin is usually started simultaneously.³⁰⁸ However, postoperative thrombocytopenia usually improves by the third postoperative day, distinguishing itself from HIT, which typically occurs between days 5 and 10 following heparin initiation. In patients who were previously treated with heparin, HIT-related events can occur within 24 hours post reexposure.¹⁷⁸

HIT affects up to 5% of patients receiving heparin.^{178,308} Heparin stimulates platelets to release platelet factor 4, which subsequently complexes with heparin to provoke an IgG response, causing platelet aggregation and thrombocytopenia.^{9,329} A more severe form of thrombocytopenia, heparin-induced thrombocytopenia and thrombosis syndrome (HITT; formerly known as HIT-2 or the white clot syndrome), occurs in up to 55% of patients with untreated HIT.¹⁷⁸ The antibodies against the heparin–platelet factor 4 complex activate platelets, which may lead to platelet–fibrin thrombotic events.^{9,329}

Patients may present with either hemorrhagic or thromboembolic complications. LMWH is also associated with thrombocytopenia (isolated HIT), and less frequently with HITT.¹⁷⁸ Consequently, once HITT occurs, LMWH is contraindicated.¹⁷⁸ Treatment of HIT includes discontinuation of heparin or LMWH and immediate use of alternative anticoagulant such as lepirudin, argatroban, or danaparoid.^{52,178} In addition to HIT and HITT, necrotizing skin lesions²²⁷ and hyperkalemia from aldosterone suppression²¹⁷ also rarely occur in patients receiving heparin therapy. These patients should not receive heparin or LMWH again, not even in low doses to maintain venous patency.

Some additional complications of heparin use include osteoporosis, which mostly occurs in patients on long-term therapy with unfractionated heparin.¹³³ A small percentage of these patients may develop bone fractures if treated continuously for more than 3 months. Data for LMWHs are limited, and the incidence of osteoporosis may be less compared with unfractionated heparin.¹³³ In 2008, an outbreak of adverse events was linked to heparin contaminated with over sulfated chondroitin sulfate.¹⁸¹ The contaminated heparin, which was found in at least 10 countries, originated in China.²⁹ Many patients developed anaphylactoid-type reactions with at least 100 reported deaths.¹⁸¹

DIRECT THROMBIN INHIBITORS

Hirudin and its congeners (lepirudin and desirudin) are used in acute coronary syndrome, the prevention of thromboembolic disease, and in patients with HIT(T).^{27,250,256} Desirudin appears to be at least as effective as unfractionated heparin and without an increased risk of bleeding or thrombocytopenia. However, in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb study of patients with unstable angina/non-Q wave myocardial infarction, there was an increase in the number of blood transfusions in patients who received desirudin as compared with those who received heparin.²⁶² This increased risk of bleeding as compared to heparin has caused desirudin to fall out of favor. Instead bivalirudin and argatroban tend to be used more often, especially in the setting of HIT(T). In fact, initial studies using bivalirudin during coronary artery angioplasty for unstable or postinfarction angina showed that it is a safe substitute for heparin with lower bleeding rates.²⁷ Unfortunately, all of these thrombin inhibitors are short acting and require parenteral administration.

Because of the potential therapeutic limitations of warfarin (eg, dosing, risk of bleeding, narrow therapeutic window), novel oral anticoagulants have been developed with directed activity against specific clotting factors. The proposed benefits of these medications include the convenience of fixed dosing and avoidance of close therapeutic monitoring. Ximelagatran was one of the first direct thrombin inhibitors that appeared to be as effective as warfarin in the treatment of stroke prevention, nonvalvular atrial fibrillation, and deep venous thrombosis.¹²⁸ Ximelagatran had many advantages over warfarin, including rapidity of onset, fixed dosing, stable absorption, decreased risk of drug interactions, and lack of necessity for therapeutic monitoring.¹²⁸ However, in 2006, drug manufacturers abandoned ximelagatran after noticing a high rate of hepatic failure. Countries that had approved ximelagatran withdrew the medication from the market.

Subsequently, dabigatran was approved for systemic anticoagulation in patients with nonvalvular atrial fibrillation in the United States and many other countries. Some countries also label an indication for dabigatran use in VTE prophylaxis following elective knee or hip surgery. The Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial demonstrated that dabigatran administration was associated with lower rates of systemic embolic events, with similar rates of bleeding, when compared to anticoagulation with warfarin.⁶³ However, subsequent evaluation of the data acquired from the RE-LY trial demonstrates that patients 75 years of age and older may have an increased risk of extracranial bleeding

when compared to those on warfarin.⁸⁶ In multiple noninferiority trials, dabigatran is as effective as enoxaparin in reducing VTE without increasing bleeding risk after select joint replacement.^{89,90}

Pharmacology

Thrombin has four separate binding sites, each of which is specific for substrate, inhibitor, or cofactors.²⁸⁷ Bivalent direct thrombin inhibitors, such as hirudin and bivalirudin, bind the active site and one of two exosites (binding sites outside of the active site), whereas univalent direct thrombin inhibitors, such as dabigatran, bind just the active site⁷⁶ (Fig. 60–3). By directly inhibiting thrombin, anticoagulation is possible without the need for antithrombin.²⁵⁶ In addition, inhibiting thrombin also inhibits platelet activation because thrombin is a potent and direct-acting platelet activator. Unlike heparin, direct thrombin inhibitors are able to enter clots and inhibit clot-bound thrombin due to their small size, offering the distinct advantage of restricting further thrombus formation.

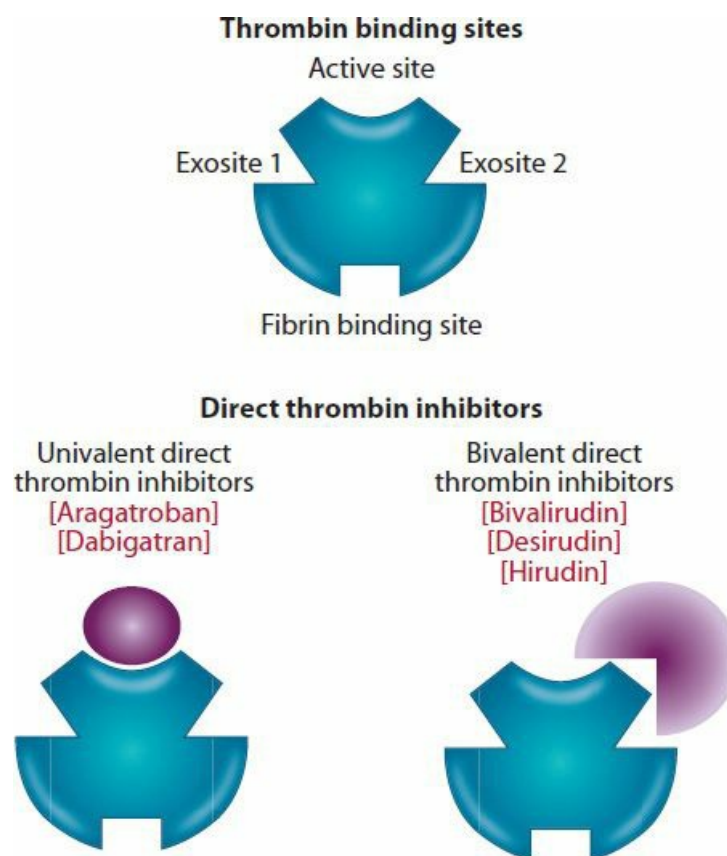


FIGURE 60–3. Thrombin has four separate binding sites. Each site is specific for substrate, inhibitor, or cofactors. Bivalent direct thrombin inhibitors, such as hirudin and bivalirudin, bind the active site and one of two exosites. Univalent direct thrombin inhibitors, such as dabigatran, bind only the active site.

Desirudin, bivalirudin, and argatroban are all administered parenterally. Desirudin is given as subcutaneous injections for VTE prophylaxis. While the dosing for desirudin is 15 mg as a subcutaneous injection every 12 hours, this dose may need to be decreased or stopped in patients with stage 3 or greater CKD. In addition, patients who have been treated with the hirudins may develop antibodies, creating the potential for anaphylaxis with repeat dosing.¹⁰⁶ Bivalirudin is also an analogue of hirudin. It is used in patients with HIT(T) who require cardiac catheterization or cardiopulmonary bypass surgery.¹⁰⁶ Argatroban binds noncovalently to the active site of thrombin to function as a competitive inhibitor.¹⁰⁶ It is metabolized by CYP3A4/5 in the liver and is particularly useful in patients with CKD.¹⁰⁶

Dabigatran is orally administered as dabigatran etexilate. This prodrug has no anticoagulant properties, and serum esterase converts it to dabigatran, the active drug.²⁶⁹ At therapeutic doses, peak concentrations occur in 2 hours (Table 60–3). Approximately 35% of dabigatran is protein bound; 85% is eliminated renally, with 78% of it eliminated within the first 24 hours. Its mean terminal half-life is approximately 8 to 12 hours.²⁸ Contraindications to dabigatran are active pathological bleeding or a hypersensitivity reaction to dabigatran. While there are theoretical interactions with other drugs that are p-glycoprotein inducers or inhibitors, the package insert does not recommend any dose adjustment for patients taking medications that are known p-glycoprotein inducers or inhibitors.

TABLE 60–3. Pharmacology of Oral Antithrombotics^a

	<i>Warfarin</i>	<i>Dabigatran (Pradaxa)</i>	<i>Rivaroxaban (Xarelto)</i>	<i>Apixaban (Eliquis)</i>
T _{max} (hours)	3	2	3	1–3
t _{1/2} (hours) ^a	35	8–12	5–13	8–15
Protein binding	97%	35%	>90%	87%
Metabolism and elimination	Hepatic metabolites (primarily CYP1A2, CYP3A4, and CYP2C9) excreted via renal and biliary systems	80%–85% renal; 15%–20% biliary	33% renal (unchanged); 33% renal metabolite; 33% hepatic metabolite	25% renal; 55% fecal, 15% hepatic metabolite

^aAntithrombotic metabolism and t_{1/2} may be altered by a number of factors such as diet, genetic polymorphisms, and kidney disease.

Clinical Manifestations

Intentional overdoses with the direct thrombin inhibitors are rare events. Although there are reports of patients who develop significant coagulopathy following unintentional ingestion of excess dabigatran,^{49,326} the more common scenario is that patients become overanticoagulated due to improper dosing in patients with CKD or failure to adjust dosing in patients who develop AKI. In general, the parenterally administered medications have short elimination half-lives, and iatrogenic medication administration errors, if recognized, may be less risky than those that are longer acting.

Dabigatran, the newest of the direct thrombin inhibitors, is orally administered with a longer duration of action. Since its approval in 2010, bleeding as a complication of therapy remains a serious risk, there is no specific reversal xenobiotic. In 2011, the FDA released an advisory announcing that they were reviewing postmarketing reports of serious bleeding associated with dabigatran use. In addition, dabigatran has led the list of fatalities reported to the MedWatch system. There are many published case reports of patients bleeding while anticoagulated with dabigatran. Patients may have been subjected to increased risk of bleeding with risk factors such as increased age or CKD. In New Zealand and Australia, a significant number of bleeding events, including intracranial bleeding, gastrointestinal bleeding, hematuria, and hemoptysis, were reported in the period immediately following the approval of the medication. Up to 25% of the reports in this series involved errors in prescribing practices.¹²³ In particular, off-label use of dabigatran for anticoagulation in the setting of mechanical heart valves has led to valve thrombosis.^{54,231} Cardiac tamponade from hemopericardium, fatal epistaxis, serious gastrointestinal bleeding, postoperative bleeding complications, and intracranial bleeding are all reported.^{19,50,83,264,286} In addition, clinicians have expressed difficulties in treating traumatized patients with bleeding while anticoagulated with dabigatran.⁶⁶

Furthermore, several questions regarding other adverse effects related to dabigatran use have been raised. A meta-analysis comparing patients anticoagulated with dabigatran versus warfarin, enoxaparin, or placebo showed higher rates of myocardial infarction or acute coronary syndrome.²⁹⁰ In addition, though prior trials have implied that discontinuation of dabigatran does not cause rebound thrombosis, the authors of anecdotal reports of thrombotic events after cessation of dabigatran anticoagulation have questioned whether thrombosis is due to rebound or just sequelae from underlying hypercoagulability or illness.²⁸³

Laboratory Assessment

Monitoring the anticoagulant effect in the setting of direct thrombin inhibitor use is complex. For bivalirudin and argatroban, serial aPTT measurements are commonly used to estimate the degree of anticoagulation.¹⁰⁶ Admittedly, the aPTT is not a good test, since the degree of anticoagulation does not follow a linear relationship. This is particularly emphasized with dabigatran, the most recently developed direct thrombin inhibitor. For example, the aPTT increases at higher dabigatran concentrations, but relationship is nonlinear, with the aPTT plateauing at dabigatran concentrations greater than 200 ng/mL.²⁹⁵ Furthermore, the PT and INR may be elevated, but they do not correlate with the anticoagulant effect of dabigatran.^{270,295} Dilute thrombin time (dTT) and ecarin clotting time (ECT) are proposed as more accurate reflections of the anticoagulation effect.²⁹⁵ ECT is a laboratory assay that uses ecarin, a derivative of saw-scaled viper venom, as the reagent to activate prothrombin. Although some hospitals are able to obtain a TT in a clinically relevant time, the dTT and the ECT are usually unavailable.

Treatment of Direct Thrombin Inhibitor–Induced Coagulopathy

The direct thrombin inhibitors currently have no reversal agent. Limited data are available regarding toxicity of these xenobiotics. Although overdose of argatroban was successfully treated with FFP in one case report,³²⁸ the orally administered dabigatran has a significantly longer half-life compared to the older parenteral direct thrombin inhibitors. In the event of an acute ingestion of dabigatran, AC is indicated based on data from an in vitro model.²⁹⁴ The manufacturer suggests several strategies to treat patients with significant bleeding while anticoagulated with dabigatran. Transfusion of red blood cells and FFP along with supportive care is the mainstay of treatment (Table 60–1). Use of rFVIIa, PCC, and hemodialysis should be considered, but this is incompletely studied. In a murine study of dabigatran, collagenase-induced intracranial hematoma expansion was inhibited in a dose-dependent fashion by PCC with the best results at 100 units/kg, the equivalent of 200% factor replacement. In the same study, high-dose PCC decreased but did not normalize the tail vein bleeding time. rFVIIa was ineffective in limiting intracranial hematoma volume, while FFP limited intracranial hematoma size in the mice that were given a lower dose of dabigatran.³³⁰

However, conclusions drawn from murine studies should be limited when treating humans. First, the hemostatic therapies used in these murine experiments are human-derived, and cross-species effects cannot be predicted. Second, these mice had prolongation of their tail vein bleeding times, but dabigatran at therapeutic doses does not change bleeding time in humans.¹⁴⁴ Another study done in healthy humans found that aPTT, endogenous thrombin potential lag time, thrombin time, and ECT did not decrease with the administration of four-factor PCC.⁸⁴

Activated prothrombin complex concentrates (aPCC) contain factors II, VII, IX, and X in inactive and activated forms. The only product available in the United States is factor eight inhibitor bypassing activity (FEIBA). One ex-vivo study showed that after a single dose of dabigatran in healthy volunteers, FEIBA decreased endogenous thrombin potential and lag time while thrombin generation increased in a dose dependent fashion. In a murine study, aPCC reduced bleeding time at low doses. Unfortunately, at high doses, this effect was reduced.³³⁵

Hemodialysis remains a controversial intervention. A single study showed that after a subtherapeutic dose of dabigatran in patients with stage 5 CKD, the extraction ratios were 62% and 68% at 2 and 4 hours after the initiation of hemodialysis.²⁷¹ Although this suggests that dabigatran can be removed from the serum, it is unclear if hemodialysis can be safely performed in patients actively bleeding. The degree of anticoagulation in relation to a serum dabigatran concentration is unknown. Additionally, the possibility of rebound concentrations from redistribution following hemodialysis was not investigated and is a concern due to its high mean apparent volume of distribution (1160–5040 L) during the terminal phase.^{270,271} Several published case reports demonstrated significant drug rebound following hemodialysis in bleeding patients, sometimes up to 87% of the initial dabigatran concentration within 2 hours after the cessation of hemodialysis.^{48,49,264} In one case, posthemodialysis drug rebound was incompletely evaluated in an overdosed patient with pulmonary hemorrhage. Dabigatran concentrations at the beginning of hemodialysis (1100 ng/mL) were more than eight times the peak serum concentrations expected for patients taking the maximum daily dose. Although hemodialysis was able to decrease the serum dabigatran concentration to 18 ng/mL over 4 hours, it rebounded to 100 ng/mL just 20 minutes after cessation of dialysis. However, during hemodialysis, the patient's bleeding ceased, and he survived to discharge.⁴⁹ In other case reports, hemodialysis was not effective in stopping bleeding, and despite massive transfusion of red blood cells, FFP, and platelets, deaths from exsanguination occurred. In some cases, a repeat hemodialysis session or continuous venovenous hemodiafiltration was performed in anticipation of posthemodialysis rebound. While they were successful in decreasing serum dabigatran concentrations, they did not normalize the aPTT or the TT.²⁶⁴

A monoclonal antibody targeting dabigatran is being developed for use in patients requiring rapid reversal of anticoagulation.^{292,293} Its structure has an affinity for dabigatran that is over 350 times that for thrombin.²⁴⁹ Rat studies show that administration of this dabigatran-specific monoclonal antibody rapidly normalizes the aPTT and TT in rats pre-treated with dabigatran.²⁴⁹ In addition, in vitro studies using human and rat plasma show that the antidote reverses the effect of dabigatran as measured by a battery of functional clotting assays, including clotting time.²⁴⁹

Until approval of a definitive antidote, reversal of coagulopathy should be attempted with PCC at an initial dose of 25 units/kg. The effect of PCC should be maximal immediately after administration. Repeat dosing up to a total of 100 units/kg may be necessary in cases of life-threatening bleeding, with the understanding that the risk of thrombosis is unknown but real. Hemodialysis should be attempted in patients suspected of having extremely supratherapeutic serum dabigatran concentrations, if placement of a large bore catheter and hemodialysis is not prohibitive of definitive treatments such as operative intervention.

FACTOR Xa INHIBITORS

Rivaroxaban is the first orally active direct factor Xa inhibitor approved for VTE and stroke prophylaxis and treatment. Development of this class of drugs started in the 1980s after the discovery of antistasin, a naturally occurring factor Xa inhibitor from leeches. After screening a library of more than 200,000 compounds, a pharmaceutical company was able to

identify structures that inhibit factor Xa. After structure optimization, rivaroxaban was created for clinical trials.²²⁶

Numerous clinical trials have investigated the efficacy and safety of rivaroxaban. Initial studies evaluated efficacy for VTE prophylaxis following orthopedic joint replacements in noninferiority studies in comparison with LMWH.⁸⁷ After proving noninferiority, numerous trials compared rivaroxaban with either warfarin or LMWH for VTE prophylaxis and treatment, stroke prevention in nonvalvular atrial fibrillation, and prevention of cardiac events in acute coronary syndrome. Overall, rivaroxaban appears to have a lower associated rate of VTE. Although bleeding rates were higher in patients on rivaroxaban, the difference was not statistically significant.^{16,88,145,161,288} When compared to warfarin, rivaroxaban prevented more strokes or systemic thromboembolic events and significantly reduced the number of intracranial bleeds in patients with nonvalvular atrial fibrillation.²²⁴ The most recent published trial compared the use of rivaroxaban to placebo in patients with acute coronary syndrome. There was a significant risk reduction in death caused by any cardiac cause or stroke. However, rivaroxaban-treated patients had statistically significant increased rates of major and intracranial bleeding.¹⁹⁴

Apixaban is another oral factor Xa inhibitor that was recently approved by the FDA. Apixaban is approved for VTE prophylaxis in patients with atrial fibrillation. In Europe, it is used for the treatment of venous thromboembolic disease as well. Initial trials found that apixaban decreased the rate of VTE and all cause mortality following total knee replacement when compared to those patients anticoagulated with enoxaparin or warfarin. However, the overall bleeding rates were higher in those patients treated with apixaban.¹⁶² Subsequent studies evaluating the use of apixaban for VTE prophylaxis after hip or knee replacement showed lower rates of VTE and lower rates of bleeding when compared to anticoagulation with enoxaparin.^{163,164} Further studies show that in patients with atrial fibrillation unsuitable for anticoagulation with VKAs, apixaban significantly decreased the rate of stroke or systemic embolism when compared to anticoagulation with aspirin. In this study group, the rates of bleeding, intracranial bleeding, and mortality were all lower in the apixaban treated group.⁶² Similarly, patients anticoagulated with apixaban for atrial fibrillation had decreased rates of stroke, decreased bleeding rates, and lower mortality rates compared to those treated with warfarin.¹¹⁴ However, concomitant use of apixaban with aspirin or aspirin plus ADP-receptor antagonists (eg, clopidogrel) demonstrated increased rates of major bleeding without any reduction in ischemic events. Fatal bleeding and intracranial bleeding were significantly higher in the group that received apixaban.²

In trials comparing apixaban with enoxaparin, apixaban had similar or superior efficacy in preventing VTE following knee and hip surgeries. In addition, bleeding rates were lower in the group receiving apixaban.^{161,163,164} On the other hand, a trial comparing treatments for VTE prophylaxis in medical patients found lower DVT rates in patients treated with apixaban when compared to those treated with enoxaparin. However, rates of major bleeding were significantly higher in the apixaban group.¹¹² In trials investigating the use of apixaban in patients with recent acute coronary syndrome, excess bleeding caused early cessation of trials; however, most patients were concurrently treated with dual antiplatelet therapy.^{2,8}

There is an ever-growing list of factor Xa inhibitors on the horizon. Betrixaban, edoxaban, otamixaban, and TAK-442 are examples of synthetic factor Xa inhibitors in various stages of evaluation for therapeutic use.^{61,198,243,312}

Pharmacology

The factor Xa inhibitors are ideal anticoagulants as their site of action is the intersection of the intrinsic and extrinsic pathways, preventing thrombin activation.⁴⁴ These synthetic drugs reversibly inhibit factor Xa without any cofactor requirements. Some believe that this class of anticoagulants is safer than the direct thrombin inhibitors since they do not completely neutralize thrombin.

Rivaroxaban and apixaban selectively bind free and clot-bound factor Xa without inhibiting related serine proteases, including thrombin, trypsin, plasmin, or other activated clotting factors.⁹¹ In addition, rivaroxaban and apixaban inhibit tissue factor or collagen-induced thrombin formation. In vitro, the factor Xa inhibitors hinder tissue factor–induced platelet aggregation.^{91,325} Rivaroxaban does not directly inhibit platelet aggregation, and concomitant aspirin use does not affect the pharmacokinetics or safety of rivaroxaban in healthy human studies.^{44,91,154}

Rivaroxaban has an oral bioavailability of approximately 80%.³¹³ Inhibition of factor Xa peaks approximately 3 hours after administration of the rivaroxaban. This inhibition lasts for approximately 12 hours.¹⁵⁶ However, kidney or liver disease may lengthen its duration of action (Table 60–3). Dosing varies by indication and kidney function. Postorthopedic prophylaxis starts at 10 mg daily, while treatment of deep venous thrombosis or pulmonary embolus is between 15 and 20 mg twice daily. For VTE prophylaxis for nonvalvular atrial fibrillation, the dose is 20 mg daily. The manufacturer provides recommended dose adjustments for each indication based on kidney function.

Approximately one-third of rivaroxaban is eliminated unchanged by the kidneys while one-third is metabolized to inactive form and excreted by the kidney. The remaining one-third is metabolized by the CYP3A4-dependent and –independent pathways in the liver and then excreted fecally. Concomitant use of CYP3A4 inhibitors or p-glycoprotein inhibitors is contraindicated due to increased risk of serum drug accumulation of up to 160%.^{127,313}

In addition, rivaroxaban may be a suitable anticoagulant alternative in patients with HIT(T) because in vitro studies do not show platelet aggregation or activation in the presence of HIT(T) antibodies or release of PF4 from platelets.³⁰⁶ Future studies proving efficacy and safety are needed before these xenobiotics can be recommended for use in patients with HIT(T).

In preclinical studies, the oral bioavailability of apixaban is approximately 66%. Apixaban is primarily distributed to the blood compartment and is approximately 87% protein bound.⁹¹ Peak serum concentrations occur between 1 and 3 hours postingestion. There are multiple elimination pathways, suggesting that patients with either renal or hepatic impairment may be able to tolerate apixaban well. Approximately 25% of apixaban is excreted in the urine, with the majority being excreted up to 24 hours after a single dose. The majority of apixaban is excreted fecally between 24 to 48 hours after ingestion.^{91,233} Simultaneous administration of strong CYP3A4 inhibitors is contraindicated with apixaban.

Apixaban was recently approved in the United States for stroke prevention in patients with nonvalvular atrial fibrillation. Dosing in clinical trials varied based on indication. For stroke prevention in patients with atrial fibrillation, apixaban is dosed at 5 mg twice daily. Clinical trials show favorable efficacy in comparison to warfarin and aspirin, with reduced stroke rates and similar occurrences of bleeding.^{62,114} In other countries, apixaban is approved for VTE prophylaxis, where it is dosed at 2.5 mg twice daily.

Clinical Manifestations

Bleeding is the most concerning consequence of the factor Xa inhibitors, even at therapeutic doses. A case report describes a 21 month-old girl who developed an INR of 3.5 approximately 12 hours after ingesting an unknown quantity of rivaroxaban. She did not suffer any hemorrhagic consequences.¹⁹⁶ Another case report describes a 58 year-old man taking 10 mg of rivaroxaban per day who developed prolonged rectal bleeding 31 days after initiating treatment for prophylaxis following hip replacement.³⁰

Diagnostic Testing

Some studies done in healthy volunteers show that rivaroxaban inhibits factor Xa activity and prolongs PT, aPTT, and LMWH activity in a dose-dependent fashion.^{155,156} Unfortunately, PT and aPTT are not reliable measures of the anticoagulant effect of rivaroxaban because results can widely vary depending on the reagent used. Thrombin generation assays are prolonged and endogenous thrombin potential is decreased. Unfortunately, these assays are not readily available in most medical centers. Chromogenic anti-factor Xa activity, on the other hand, has been shown to reliably measure rivaroxaban concentrations over a large range of concentrations.³³³

Studies investigating the effect of apixaban on hematologic laboratory studies are limited, but multiple in vitro studies show that aPTT and PT increase in a dose-dependent fashion. The HepTest, a newly developed clotting assay that measures anti-Xa and anti-IIa activity, correlates best with the antithrombotic effect of apixaban. Unfortunately, it is not widely available since it is not yet FDA approved.^{91,324}

Treatment of Factor Xa Inhibitor–Induced Coagulopathy

The factor Xa inhibitors have no definitive reversal agent. The factor Xa inhibitors are not well studied, and there are no trials that evaluate the efficacy of gastrointestinal decontamination. However, the administration of AC after an acute overdose is prudent because of the lack of a definitive reversal agent once coagulopathy develops (Table 60–1). A single human study evaluated the use of four-factor PCC in reversing patients given rivaroxaban 20 mg twice daily for 2.5 days. PT and endogenous thrombin rapidly normalized after administration of 50 units/kg of PCC.⁸⁴ Rivaroxaban-anticoagulated rabbits showed improvements in coagulation assays after treatment with PCC and rFVIIa. However, these agents were clinically ineffective in achieving hemostasis.¹¹¹ Due to its high protein binding, hemodialysis is unlikely to be an effective adjunct method to accelerate rivaroxaban removal.

Preliminary in vitro studies show that four-factor PCC may improve thrombin generation and coagulation parameters in blood aliquots treated with apixaban.⁹² However, there are no human studies with clinically relevant outcomes to support the use of PCC in factor Xa–associated bleeding.

While the half-lives of the factor Xa inhibitor are substantially shorter than that of warfarin, normalization of hemostasis due to drug clearance can still require more than 24 hours without intervention. During this time, supportive measures such as restoration of intravascular volume are helpful but do not correct the xenobiotic-induced coagulopathy. PCC at a starting dose of 25 units/kg appears to be the only antidote that may improve laboratory parameters immediately following infusion, but its effect on hemostasis is unknown. Regardless, in case of life threatening bleeding, PCC can be administered to attempt hemostasis, although further studies are needed to support this recommendation. Its peak effect should occur immediately after administration. In severe cases, repeat doses may need to be administered. The risk of thrombosis is unknown and should be weighed when administering PCC.

PENTASACCHARIDES

Pentasaccharides are synthetic anticoagulants that possess activity against factor Xa and are used for the prevention and treatment of VTE. Although other xenobiotics have been studied, fondaparinux is the only pentasaccharide currently available for clinical use.¹⁷³ The pentasaccharide binds to AT with an affinity higher than that of heparin facilitating the formation of the AT–factor Xa complex. Once this complex forms, the pentasaccharide dissociates and repeats the process.¹⁰⁶ Routine measurements of coagulation are not generally performed. When degree of anticoagulation needs to be assessed, the fondaparinux-specific anti-Xa assay is the most helpful. The pentasaccharides have long half-lives and have no reliable antidote if bleeding occurs; they do not bind to protamine.¹⁰⁶ Patients with stage 3 CKD should have their dose reduced 50%; fondaparinux is contraindicated in patients with stages 4 and 5 CKD.¹⁰⁶ No controlled trials are available yet, but rfVIIa may be effective for reversal, as demonstrated in one study of healthy volunteers.²⁵ In a case series of eight patients who received 90 µg/kg of rfVIIa for unstable bleeding, only 50% of patients had favorable outcomes. Anti-Xa activity remained unchanged, and none of the patients suffered any thrombotic complications. However, many of these patients were on other antithrombotics, including antiplatelet drugs.

ANTICOAGULANT APTAMERS

Aptamer anticoagulants are small nucleic acid molecules that are currently under development to target specific blood coagulation proteins.²¹¹ They are direct protein inhibitors and function similarly to monoclonal antibodies.²¹¹ Specific aptamers that are currently being studied include the anti–factor IX aptamer, the anti–activated protein C aptamer, and the anti–factor VIIa aptamer.¹¹³ These xenobiotics may have future clinical utility since their anticoagulant effects appear to be easier to control, and consequently safer, compared with the currently most used anticoagulants.

Although not yet approved, pegnivacogin is an RNA aptamer that inhibits factor IX and is undergoing human trials to evaluate its efficacy and safety. Numerous phase I trials are being conducted in healthy volunteers and patients with coronary artery disease.^{229,230} The effects of pegnivacogin mimic hemophilia B, also known as Christmas disease, which results in a tendency to bleed. By inhibiting factor IX, the conversion of factor X to factor Xa is inhibited.²⁹⁹ Previous studies have shown that approximately 1 mg/kg of pegnivacogin inhibits more than 99% of factor IX. Pharmacokinetic studies demonstrate a half-life of pegnivacogin to be approximately 100 hours and stable antithrombotic effects for 30 hours.^{228,229} While anticoagulated with pegnivacogin, the degree of anticoagulation can be monitored with aPTT as previous studies have demonstrated that the degree of factor IX inhibition correlates well with aPTT.²²⁹ Because this aptamer is a synthetically tailored nucleic acid sequence, its antidote is easily manufactured. By creating a complementary aptamer that possesses a nucleic acid sequence that binds to pegnivacogin through Watson-Crick base pairing, it can effectively neutralize the original xenobiotic by creating an inactive complex. In fact, pegnivacogin is being studied in conjunction with anivamersen, the complementary aptamer to pegnivacogin.²⁹⁸

FIBRINOLYTICS

The fibrinolytic system is designed to remove unwanted clots, while leaving those clots protecting sites of vascular injury intact. Plasminogen exists as a proenzyme that is converted to the active form, plasmin, by plasminogen activators.^{57,58} The actions of plasmin are nonspecific in that it degrades fibrin clots and also, some plasma proteins and coagulation factors.³¹¹ Inhibition of plasmin occurs through α_2 -antiplasmin.³¹¹ Tissue plasminogen activator (t-PA) is released from the endothelium and is under the inhibitory control of two inactivators known as tissue plasminogen activator inhibitors 1 and 2 (t-PAI-1 and t-PAI-2).^{57,58,206,311} Under physiological conditions, endogenous t-PA does not induce a lytic state because there is no fibrin to initiate the conversion of plasminogen to plasmin. However, exogenous t-PA administration results in supraphysiological concentrations that promote a lytic state.³¹¹

With their diverse indications in acute myocardial infarction, unstable angina, arterial and venous thrombosis and embolism, and cerebrovascular disease, the thrombolytics are commonly used.²⁰ The reader is referred to a number of reviews for specific indications and dosing regimens.^{65,166,223,265,311,318} Although all fibrinolytics enhance fibrinolysis, they differ in their specific sites of action and duration of effect. t-PA is produced by recombinant DNA technology, and it is clot-specific (ie, it does not increase fibrinolysis in the absence of a thrombus). Newer thrombolytics include reteplase and tenecteplase; they possess longer half-lives that facilitate administration via bolus dosing rather than infusion.³¹¹ On the other hand, streptokinase, urokinase, and anistreplase are not clot-specific. t-PA has the shortest half-life and duration of effect (5 minutes and 2 hours, respectively) and anistreplase the longest (90 minutes and 18 hours, respectively).^{223,265} Streptokinase has the additional risk of potential severe allergic reaction on rechallenge, limiting its use to once in a lifetime. In fact, streptokinase is no longer used in the United States.

Newer thrombolytics such as alteplase, tenecteplase, and desmoteplase are used in other countries or are

currently being evaluated for therapeutic use.¹⁸² These fibrinolytics have a longer half-life and may be administered via single or repeated bolus injections. They also have increased fibrin selectivity but no apparent improvement in mortality when compared to t-PA.¹⁴²

A number of contraindications preclude the use of fibrinolytics in order to decrease the risk of bleeding. Undesired bleeding occurs due to clot destruction at vascular compromised sites and destruction of coagulation factors from plasmin generation.³¹¹ As a result, patients with risk factors for bleeding, such as recent surgery or bleeding, known vascular lesions, or prior intracranial bleeding, are contraindications for fibrinolytic administration.

Clinical Manifestations

Although the incidence of bleeding requiring transfusion may be as high as 7.7% following high-dose (150 mg) t-PA and 4.4% following low-dose t-PA,⁶⁵ the incidence of intracranial bleeding with t-PA appears to be similar to the newer agents (alteplase, tenecteplase, reteplase, and lanoteplase).³⁰⁰ The addition of heparin to thrombolytic therapy increases the risk of bleeding. Reviews of multiple trials suggest that life-threatening events such as intracranial bleeding occur in 0.30% to 0.58% of patients receiving anistreplase, 0.42% to 0.73% of patients receiving alteplase, and 0.08% to 0.30% of patients receiving streptokinase.³¹⁸ Regardless of the thrombolytic used, the frequency of bleeding events is similar, with the exception that lanoteplase may have a decreased incidence of significant bleeding.⁷³

Treatment

Supportive care is indicated for patients with minor bleeding complications. However, for patients with significant bleeding, fibrinogen and coagulation factor replacement with cryoprecipitate, FFP, or PCC should be administered.²⁴⁸ If fibrinogen and factor replacement are ineffective, then antifibrinolytics such as aminocaproic acid and tranexamic acid should be considered (Table 60–1). These fibrinolytics prevent activation of plasmin by competing with fibrin to bind to plasminogen and plasmin. While a significant amount of fibrinolysis has already occurred, competitive inhibition of further plasmin-activated fibrinolysis may be helpful in cases of life-threatening bleeding. Aminocaproic acid is also able to prevent the binding of t-PA to fibrin. Not only can these agents prevent fibrinolysis, but they can also reverse excessive fibrinolysis,^{248,311} although it is not well studied in the setting of fibrinolytic therapy.

Aminocaproic acid can be given orally or intravenously. When administered intravenously, a loading dose of 4 to 5 g over one hour is followed by an infusion of 1–1.25 g/h with a maximum of 30 g given in 24 hours. The infusion should be stopped before 24 hours if the bleeding has ceased. Aminocaproic acid should not be given to patients with hematuria. These patients are at risk for developing obstructive AKI from ureteral clots that cannot be lysed. There are also rare reports of myopathy and muscle necrosis.³¹¹ Theoretically, aminocaproic acid could reverse bleeding following fibrinolytic therapy. However, there are no case reports or studies supporting its use in this situation.

Tranexamic acid can also be administered orally or intravenously. It is currently approved for the treatment of menorrhagia and is dosed at 1 g orally four times a day for four days.³¹¹ It is also used in hemophiliac patients undergoing cardiac surgery. However, recent studies have garnered significant attention for the use of tranexamic acid in patients with traumatic bleeding. The CRASH-2 study, a multicentered randomized controlled trial evaluating outcomes of patients receiving tranexamic acid with traumatic bleeding, found that infusion of 1 g over 10 minutes, followed by 1 g over 8 hours, resulted in a significant reduction in mortality. In addition, the risk of arterial thrombosis, as well as fatal and nonfatal thrombosis, was significantly reduced when compared to controls who received placebo.²³⁹ A case report describes the successful use of tranexamic acid in a patient who developed an intracranial bleeding following thrombolytic therapy. After receiving 1.675 g of intravenous tranexamic acid, repeat computed tomography and magnetic resonance imaging of his brain revealed no hematoma expansion, and he did not develop any thrombotic complications.¹⁰¹

Unfortunately aminocaproic acid and tranexamic acid are associated with generalized tonic-clonic seizures in up to 7.6% of patients. The precise mechanism of seizures is not known. In murine studies, competitive antagonism of glycine receptors is suggested. When the mice were treated with isoflurane and propofol, seizure activity ceased.¹⁶⁹

ANTIPLATELET DRUGS

Under normal conditions, vascular endothelium provides thromboregulators that prevent thrombus formation. When the endothelium becomes compromised, exposed collagen triggers two cascades of events to promote platelet aggregation. First, a tissue factor–mediated pathway indirectly activates platelets. Tissue factor, either from the damaged vessel wall or carried in the blood, complexes with factor VIIa and activates factor IX and the extrinsic pathway of the coagulation cascade. Thrombin then directly stimulates further platelet adhesion.¹⁰³ Secondly, when von Willebrand factor (vWF) adheres to the exposed endothelium, platelet glycoprotein Ib-V-IX binds to the vWF and anchors platelets to the site of vascular injury. In addition, platelet glycoprotein VI and Ia tether the platelets to exposed collagen^{70,103,158} (Fig. 60–4).

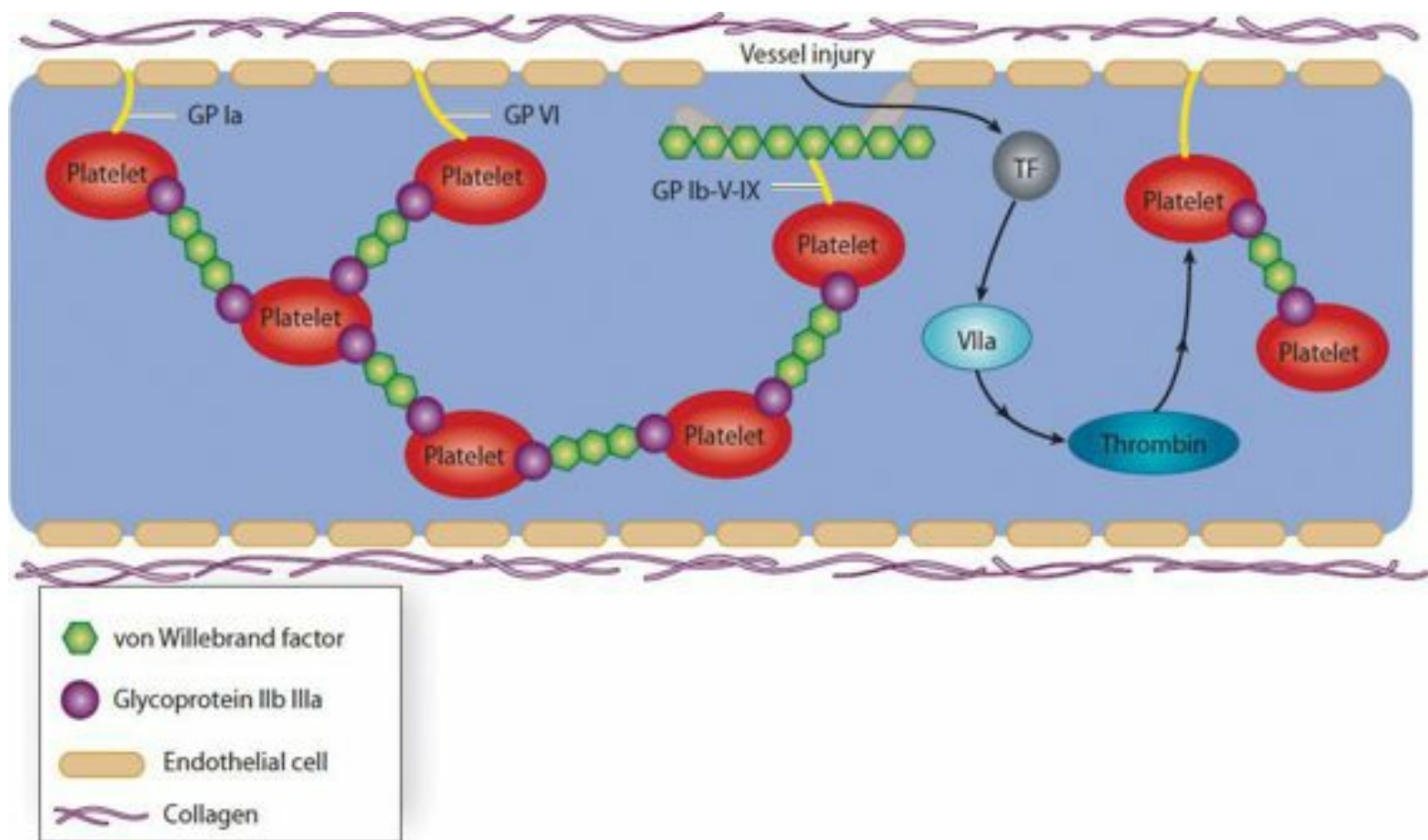


FIGURE 60–4. A schematic diagram of platelet aggregation. An injury to the endothelium results in initial platelet tethering by means of von Willebrand factor (vWF) and glycoprotein (GP) Ib-V-IX. Platelet GP VI and Ia tether the platelets to exposed collagen. GP IIb-IIIa is expressed on the surface of the platelets and allows platelet cross-linking with vWF bridging. TF = tissue factor.

After platelet adhesion, modulators such as adenosine diphosphate (ADP) and thromboxane A₂ (TXA₂) maintain platelet activation.^{70,103,311} Intracellular signaling results in the release of arachidonic acid (AA) via phospholipase A₂. Next, AA is converted into prostacyclin via cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2). This stimulates the production of TXA₂, which further propagates platelet activation and aggregation^{70,139} (Fig. 60–5).

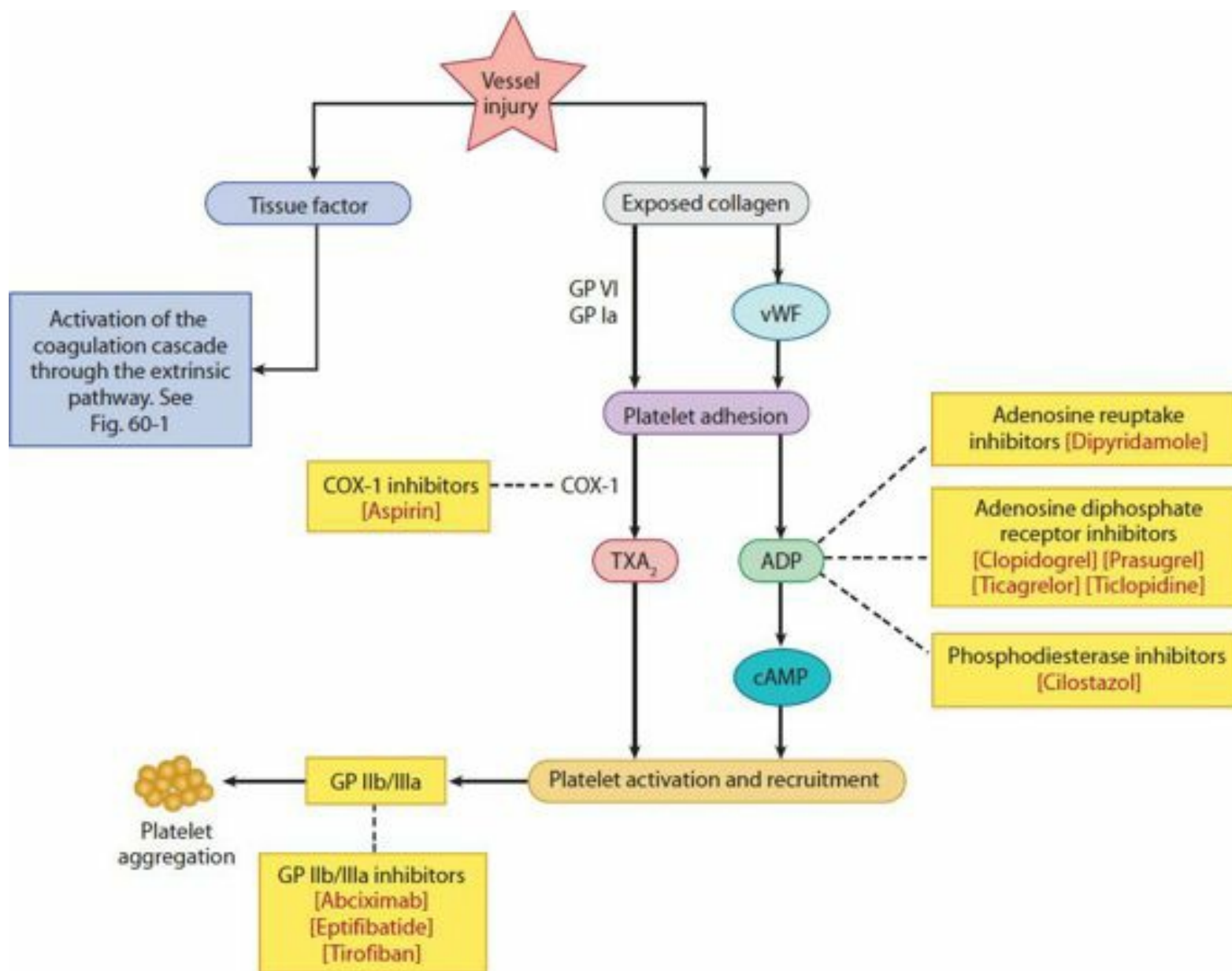


FIGURE 60–5. The antiplatelet drugs act in various stages of platelet aggregation. ADP = adenosine diphosphate; cAMP = cyclic adenosine monophosphate; COX-1 = cyclooxygenase 1; GP = glycoprotein; TXA₂ = thromboxane A₂; vWF = von Willebrand factor.

These mediators recruit more platelets to the area of vessel injury. Glycoprotein IIb-IIIa is expressed on the surface of the platelets and allows platelet cross-linking via this receptor with vWF acting as a bridge.^{70,103}

Thrombus formation perpetuates platelet aggregation and adhesion to the vessel wall. Platelet glycoprotein IIb-IIIa activation results in further thrombus formation by binding fibrinogen and vWF, essential to the linking of platelets.⁷⁰

Antiplatelet therapies aim to decrease platelet activation or aggregation by inhibiting one of the steps in the many pathways leading to glycoprotein IIb-IIIa activation of platelets.

CYCLOOXYGENASE INHIBITORS

Widespread use of aspirin as an antiplatelet drug is associated with significantly decreased vascular events. Aspirin acetylates the COX-1 enzyme, prevents substrate binding to the enzyme, and results in irreversible inhibition of TXA₂ generation. Daily low-dose aspirin can fully inhibit COX-1 function and subsequent platelet aggregation because platelets are unable to regenerate COX-1.⁸⁵ However, while aspirin irreversibly inhibits COX-2, larger doses of aspirin are required to decrease COX-2 mediated processes due to rapid synthesis of new COX-2.⁸⁵

Aspirin dosed between 75 and 150 mg showed the best odds reduction in preventing myocardial infarction and stroke when compared to other doses.^{6,85} In fact, high-dose aspirin may cause inhibition of other down regulators of platelet adhesion such as endothelium-derived prostacyclin. While effective in preventing vascular events, the risk of bleeding and gastrointestinal irritation must be considered. A randomized trial comparing low dose (70–150 mg/d) and standard-dose (300–325 mg/d) aspirin in patients with acute coronary syndrome, standard-dose aspirin conferred an increased risk of gastrointestinal bleeding without significant additional cardiovascular benefit.⁶⁹ However, even daily low-dose aspirin

resulted in a significantly increased risk of gastrointestinal bleeding when compared to nonaspirin use, but this risk is outweighed by the benefits of cardiovascular disease and stroke prevention.³¹⁰

CYCLIC ADENOSINE MONOPHOSPHATE MODULATORS

Phosphodiesterase Inhibitors

Cilostazol is a phosphodiesterase inhibitor marketed for the treatment of intermittent claudication secondary to peripheral vascular disease (PVD). By increasing cyclic adenosine monophosphate (cAMP), vasodilation is achieved by inhibiting myosin light-chain kinase, essential for smooth muscle contraction. Additionally, cAMP inhibits platelet aggregation. Small trials demonstrate that cilostazol improves walking distances, decreases arterial thrombosis, and improves rethrombosis rates in patients with PVD. In the Cilostazol for Prevention of Secondary Stroke (CSPS) study, cilostazol was not inferior to aspirin in preventing secondary stroke. However, due to its common gastrointestinal adverse effects and headache, a high rate of discontinuation precludes this xenobiotic from being more widely used.⁸⁵

Adenosine Reuptake Inhibitors

Dipyridamole has antiplatelet properties, although its mechanism of action is not completely known. Evidence suggests that by inhibiting degradation of cAMP and by blocking adenosine reuptake, intracellular cAMP accumulates and inhibits platelet aggregation.^{85,311} Dipyridamole may also have antiinflammatory properties by decreasing monocyte gene expression of chemokines.³¹⁷ Dipyridamole 200 mg is marketed alone or in combination with 25 mg of aspirin (Aggrenox).

Randomized studies demonstrate a significant reduction in stroke in high-risk patients taking dipyridamole with aspirin when compared with patients taking aspirin alone. However, many patients discontinue dipyridamole due to headache.^{78,120} Unfortunately, when compared to clopidogrel, dipyridamole and aspirin offer no improvement in stroke prevention and an increase in the risk of major bleeding.²⁴⁵

ADENOSINE DIPHOSPHATE RECEPTOR INHIBITORS

Platelets require stimulation of P2Y1 and P2Y12, adenosine diphosphate (ADP) receptors, to inhibit adenylyl cyclase. cAMP formation decreases as a result of the inhibition of adenylyl cyclase, and the platelet loses its ability to activate. Clopidogrel, prasugrel, ticagrelor, and ticlopidine are ADP receptor inhibitors. By increasing cAMP concentrations through inhibition of the P2Y12 receptor, these xenobiotics are able to inhibit platelet activation.^{85,311}

Ticlopidine is a first-generation ADP receptor inhibitor. It is typically taken orally at 250 mg twice daily. Despite its rapid absorption with peak plasma concentrations between 1 and 3 hours, peak platelet inhibition occurs one week after initiation. Two of the many metabolites are noted to have significantly stronger ADP receptor inhibitor activity than the parent drug. Ticlopidine does not confer an overall reduction of cardiovascular death, stroke, or myocardial infarction risk,¹⁰⁸ but coadministration with aspirin decreases stent thrombosis in some situations.¹⁷²

The relatively high risk of neutropenia as well as the risks of agranulocytosis, thrombocytopenia, and thrombocytopenic purpura–hemolytic uremic syndrome and the development of newer generation ADP receptor inhibitors has rendered ticlopidine nearly obsolete.^{85,311}

Clopidogrel irreversibly binds and inhibits ADP receptors. Maximal platelet inhibition is achieved between day 4 and 7 after initiation of maintenance doses but occurs 2 to 4 hours after a 600 mg loading dose.⁸⁵ Clopidogrel requires conversion via CYP2C19 to form its active metabolite. Up to one-third of patients are resistant to clopidogrel. Many of these patients possess a CYP2C19 genetic polymorphism that results in loss of function, and these patients have an increased risk of major cardiovascular adverse events, especially following coronary artery stenting.^{85,195} Similarly, concomitant administration of medications that inhibit numerous CYP enzymes may result in decreased efficacy. Further studies are required to determine if dosing modification may improve efficacy in preventing adverse vascular events.⁸⁵

Clopidogrel is dosed at 75 mg daily. It is commonly administered with aspirin as numerous studies, such as the CREDO, COMMIT, and CLARITY trials, have shown dual antiplatelet therapy to be beneficial in the reduction of vascular events.^{51,244,272} However, in the ACTIVE trials, warfarin was superior to dual antiplatelet therapy with aspirin and clopidogrel in preventing major vascular events.⁶⁰

The risk of bleeding remains a major concern associated with the use of clopidogrel, particularly in dual antiplatelet regimens. The ACTIVE A trials found an increased risk of major bleeding in patients with atrial fibrillation on clopidogrel and aspirin when compared to patients on aspirin alone.⁶⁴ In contrast, the COMMIT trial demonstrated no difference in major bleeding rates between study groups treated with and without clopidogrel.⁵¹

Another ADP receptor inhibitor, prasugrel similarly requires conversion to an active metabolite, which occurs within 30 minutes of dosing. CYP2C19 inhibition or concomitant proton pump inhibitor administration does not affect efficacy. A

head-to-head comparison of prasugrel and clopidogrel in patients undergoing coronary artery intervention found a decreased incidence of overall vascular adverse outcomes and death and stent thrombosis in patients on prasugrel but no improvement in overall morbidity, mortality, or bleeding events.^{85,323}

Ticagrelor is the newest of the ADP receptor inhibitors that exerts its effects by allosterically and reversibly inhibiting the ADP receptor. Absorption is rapid with peak plasma concentrations in approximately 2.5 hours.²⁸² Dosing of ticagrelor includes a loading dose of 180 mg, followed by a maintenance dose of 90 mg twice daily.

The PLATO trial demonstrated patients with acute coronary syndrome had a lower mortality rate from myocardial infarction and stroke when treated with ticagrelor versus clopidogrel. While overall bleeding rates were equivalent, nonprocedure bleeding, including fatal intracranial bleeding, was higher in the ticagrelor-treated group.³⁰⁸

GLYCOPROTEIN IIb-IIIa Inhibitors

Three glycoprotein IIb-IIIa inhibitors are available for use with patients with acute coronary syndromes. Abciximab is a monoclonal Fab antibody that binds the glycoprotein IIb-IIIa receptor. When administered with heparin and aspirin in patients undergoing coronary artery intervention, stent thrombosis, myocardial infarction, and mortality all decrease. Abciximab is administered as an intravenous bolus dose of 0.25 mg/kg is followed by an infusion on 0.125 mg/kg/min. The plasma half-life is short, with plasma concentrations becoming negligible approximately 30 minutes following cessation of the infusion. However, the Fab fragments bind to the platelets and inhibit platelet function for up to 24 hours.³¹¹

Eptifibatide is a synthetic glycoprotein IIb-IIIa inhibitor used in patients with acute coronary syndrome undergoing coronary artery interventions. Its molecular structure is based on snake venom disintegrin. An intravenous loading dose of 180 µg/kg is followed by an infusion of 2 µg/kg/min.³¹¹ Dosing in patients with CKD is unstudied, but there is a demonstrable increase in rates of bleeding in patients with a creatinine clearance less than 60 mL/min.²³⁴ Tirofiban also inhibits the glycoprotein IIb-IIIa receptor, and has similar clinical efficacy compared to eptifibatide.³¹¹

Up to 10% of patients treated with glycoprotein IIb-IIIa inhibitors have major bleeding events. Thrombocytopenia can also occur as a result of antigenic recognition of the xenobiotic-bound platelets.⁸⁵

A number of trials examining the efficacy and safety of the glycoprotein IIb-IIIa inhibitors have noted positive trends in decreasing predefined end points such as 30-day mortality, stent rethrombosis, and myocardial infarction. After evaluation of the combined data from multiple trials, the benefits of glycoprotein IIb-IIIa inhibitor therapy without early coronary artery revascularization are unclear when weighing the risks of bleeding. However, with early coronary artery revascularization, it is accepted that adding a glycoprotein IIb-IIIa inhibitor may be beneficial despite some concerns that the highest-risk patients truly benefit from this adjunctive therapy.^{72,85}

DEVELOPMENT OF NOVEL RECEPTOR AND ENZYME INHIBITORS

Recent pharmaceutical development has focused on inhibition of several key enzymes or receptors in platelet activation and aggregation. Thromboxane A₂ function can be inhibited by thromboxane A₂ synthase inhibitors or by antagonizing the thromboxane A₂ receptor. Clinical trials are currently underway to evaluate the efficacy of inhibiting protease-activated receptors, also called thrombin receptors.²⁸¹

Laboratory Assessment

Bleeding time is traditionally the most useful and widely available used to assess platelet function. However, its popularity has decreased because of its insensitivity, invasiveness, scarring, and high coefficient of variation. A variety of platelet function assays exist, but few are widely available. The gold standard assay, light transmission aggregometry is commonly used in specialty laboratories, but it does not reflect physiologic platelet adhesion or aggregation. Furthermore, this test is time-consuming and expensive. Several widely used tests to assess platelet function, such as flow cytometry and serum thromboxane B₂ assay, are available. Each of these tests has significant disadvantages such as being artifact-prone, expensive, nonspecific, or insensitive to select antiplatelet agents. In addition, extrapolating these results to determine a patient's risk of bleeding or thrombosis is not possible.¹²⁶

Management

When managing bleeding in patients taking antiplatelet xenobiotics, blood transfusion should be employed in patients with significant blood loss. However, transfusion of packed red blood cells will not increase platelet adhesion or aggregation. Unfortunately, the published literature that assesses interventions on bleeding patients maintained on antiplatelet xenobiotics is conflicting, and there is no clear consensus on appropriate reversal strategies and agents. The most widely evaluated intervention is platelet transfusion. The existing studies are small and mostly retrospective. Prospective studies

are biased by nonrandomization, specifically by the clinician ultimately deciding whether to transfuse the platelets. Many of these studies show that platelet transfusion is harmful and independently predict increased mortality and bleeding^{15,46} (Table 60–1).

Desmopressin is approved for the treatment of inherited defects of hemostasis and potentiates thrombosis by releasing vWF and factor VIII from the endothelium into the plasma. In these patients, complications such as arterial thrombosis and myocardial infarction have been reported after desmopressin administration.^{165,174} However, some proposed protocols for reversing antiplatelet xenobiotics in the setting of life-threatening bleeding include desmopressin. Most of these protocols are based on case reports since the majority of the studies have evaluated prophylactic desmopressin prior to surgery to prevent blood loss. A single study evaluated the administration of desmopressin on platelet aggregation and platelet activity in healthy volunteers given a single dose of clopidogrel. They found that platelet reactivity and platelet aggregation increased after desmopressin administration. There was no mention of adverse outcomes in any of the study subjects.¹⁷⁰ The risk of desmopressin-induced thrombosis in patients on antiplatelet xenobiotics is unknown; in patients taking antiplatelet medications for atherosclerosis, the risk of thrombosis may be greater.¹⁷⁰

In the case of abciximab, cessation of the infusion results in a rapid decrease in circulating antibodies. If severe bleeding occurs, platelet transfusion after discontinuation of the infusion is effective in restoring platelet activation and aggregation.³¹¹

In most cases, discontinuation of eptifibatide and tirofiban results in restoration of normal platelet function within hours. However, patients with renal dysfunction may suffer from prolonged platelet inhibition. Both of these xenobiotics are renally cleared, and some have suggested hemodialysis as a means to enhance clearance.²⁸⁰ While not formally studied, case reports of patients with protracted platelet inhibition in the setting of eptifibatide use and end stage CKD suggest that hemodialysis restores platelet aggregation capacity.²⁶⁷ Unlike abciximab, transfusion of platelets to these patients is believed to be ineffective in restoring platelet function. At therapeutic concentrations, the amount of these xenobiotics far outnumber the inhibited glycoprotein IIb-IIIa receptors by several orders of magnitude.²⁸⁰ Further studies are required to produce recommendations or guidelines for emergent reversal of antiplatelet xenobiotics to determine if any interventions are effective and offer a favorable risk to benefit profile.

SNAKE VENOMS

A detailed discussion of snake envenomations is found in Chap. 122 and Special Considerations: SC8; only a few specific issues are discussed here. Snake venoms may be composed of a vast number of complex proteins and peptides that interact with components of the human hemostatic system. In general, their functions may be thought of as being procoagulant, anticoagulant, fibrinolytic, vessel wall interactive, platelet active, or as protein inactivators. Additionally, they may more specifically also be classified based on their specific biologic activity; some of the various mechanisms include individual factor activation, inhibition of protein C and thrombin, fibrinogen degradation, platelet aggregation, and inhibition of serine protease inhibitors (SERPINS). Currently, there are more than 100 different snake venoms that affect the hemostatic system.^{136,137} Figure 60–1 is an overview of their multiple interactions with the coagulation and fibrinolytic systems.¹⁸⁹

Some of these venom proteins are being used as therapeutic agents for human diseases. Ancrod, a purified derivative of the Malayan pit viper, *Calloselasma rhodostoma* (formerly known as *Agkistrodon rhodostoma*), is therapeutically used because of its defibrinogenating property.¹⁸ The mechanism of action of ancrod and other similar agents is to link fibrinogen end-to-end and subsequently prevent cross-linking. It has been investigated in the treatment of deep venous thrombosis, myocardial infarction, pulmonary embolus, acute cerebrovascular thrombosis, HIT(T), and warfarin-related vascular complications. In a multicenter study of 500 patients with acute or progressing ischemic neurologic events, ancrod showed a favorable benefit-to-risk ratio compared with placebo.²⁵⁹ As expected, an increased risk of bleeding is observed; however, the risk appears to be less than that with thrombolytics.²⁵⁹ Monitoring of fibrinogen concentrations is essential to avoid potential complications, because no specific antidote exists. For envenomation of other snake venoms (such as from the Crotalinae family) that induce bleeding, antivenin treatment may be required.

SUMMARY

- The development of new antithrombotics and the increasing frequency of antithrombotic therapeutic use are associated with complications and adverse outcomes.
- A complete understanding of the normal mechanisms of coagulation, anticoagulation, and thrombolysis, combined with an understanding of the pharmacology of the xenobiotic and the clinical needs of the patient will allow the clinician to better choose among the complex therapies currently available.
- Supportive care is often adequate for certain complications associated with these therapies.
- More aggressive interventions and specific antidotes are necessary depending on the specific xenobiotic, particularly the newer factor inhibitors, and medical condition of the patient.

- Ongoing development of new antithrombotics will raise new challenges for clinicians as adverse outcomes and bleeding complications arise, and new antidotes will be developed to address these issues.

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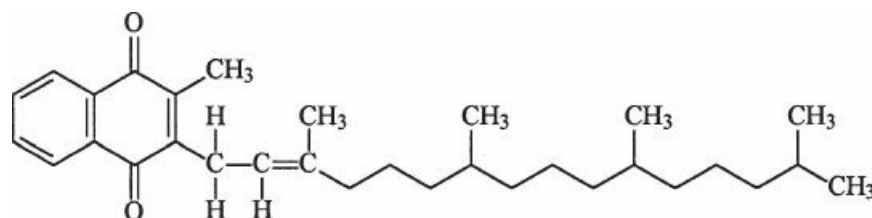
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A15 ANTIDOTES IN DEPTH

Vitamin K₁

Mary Ann Howland



Vitamin K₁ (phytonadione) is the commercial preparation of the natural form of vitamin K (phylloquinone) that is indicated for the reversal of an elevated prothrombin time (PT) or an international normalized ratio (INR) in patients with xenobiotic induced vitamin K deficiency. Acquired vitamin K deficiency typically results from the therapeutic administration of warfarin, or following the overdose of warfarin or a long-acting anticoagulant rodenticide (LAARs), such as brodifacoum. The optimal dosage regimen of vitamin K₁ to treat patients who develop an elevated INR while receiving warfarin is given in the 2012 American College of Chest Physicians consensus guidelines.¹ Oral administration of vitamin K₁ is safe and effective. Because intravenous (IV) administration of vitamin K₁ may be associated with anaphylactoid reactions, it should be avoided unless serious or life-threatening bleeding is present. Subcutaneous administration should only be considered when a patient is unable to tolerate oral vitamin K therapy and is not clinically compromised enough to necessitate IV vitamin K₁.⁸

HISTORY

It was noted in 1929 that chickens fed a poor diet developed spontaneous bleeding. In 1935, Dam and coworkers discovered that incorporating a fat soluble substance, defined as a “koagulation factor,” into the diet could correct the bleeding, leading to the name vitamin K.^{19,32,37}

PHARMACOLOGY

Chemistry

Vitamin K is an essential fat-soluble vitamin that encompasses at least two distinct natural forms. Vitamin K₁ (phytonadione, phylloquinone) is the only form synthesized by plants and algae. Vitamin K₂ (menaquinones) is actually a series of compounds with the same 2-methyl-1, 4-naphthoquinone ring structure as phylloquinone, but with a variable number (1–13) of repeating five-carbon units on the side chain. Bacteria synthesize vitamin K₂ (menaquinones). Most of the vitamin K ingested in the diet is phylloquinone (vitamin K₁).

Related Vitamin K Compounds

Vitamin K₁ (phytonadione) is the only vitamin K preparation that should be used to reverse anticoagulant induced vitamin K deficiency or to treat infants or pregnant women. In addition, patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency have an increased risk of hemolysis with other vitamin K preparations. Vitamin K₁ is superior to the other previously commercially available vitamin K preparations because it is more active, requires smaller doses, and has fewer associated risks.^{15,34}

Vitamins K₃ (menadione) and K₄ (menadiol sodium diphosphate) are no longer approved by the US Food and Drug Administration, (FDA) because they can produce hemolysis, hyperbilirubinemia, and kernicterus in neonates, as well as hemolysis in G6PD-deficient patients. The only advantage that menadione and menadiol sodium diphosphate have is that

these preparations are absorbed directly from the intestine by a passive process that does not require the presence of bile salts. Theoretically, they are advantageous for patients with cholestasis or severe pancreatic insufficiency. However, they are neither interchangeable with vitamin K₁, nor a substitute for vitamin K₁, when anticoagulants such as warfarin or a LAAR are responsible for coagulation deficits. Therefore, for a patient deficient in bile salts who requires vitamin K₁, exogenous bile salts, such as ox bile extract 300 mg or dehydrocholic acid 500 mg, should be given with each dose of oral vitamin K₁.²⁷

Mechanism of Action

Activation of coagulation factors II, VII, IX, and X, and proteins S, C and Z require γ -carboxylation of the glutamate residues in a vitamin K-dependent process. Only the reduced (K₁H₂, hydroquinone) form of vitamin K manifests biologic activity. During the carboxylation step, the active reduced vitamin K₁ is converted to an epoxide. This 2,3-epoxide is reduced and recycled to the active K₁H₂ in a process that is inhibited by warfarin (Fig. 60–2). For further details, the reader is referred to an in-depth model of the chemical basis of this reaction.^{10,42} The phytonadione form of vitamin K can be activated to the reduced, vitamin K₁H₂ form directly by nicotinamide adenine dinucleotide (phosphate) (NAD(P)H)-dehydrogenase (DT-diaphorase) enzymes that can use both NADH and NADPH in a pathway that is relatively insensitive to warfarin, while the vitamin K 2,3-epoxide form cannot be activated through this pathway.^{32,36,37,39}

Daily Requirement

The human daily requirement for vitamin K is small; the Food and Nutrition Board set the recommended daily allowance at 1 μ g/kg/d of phyloquinone for adults, although 10 times that amount is required for infants to maintain normal hemostasis.³¹ Vitamin K dependent extrahepatic enzymatic reactions relate to carboxylation of proteins in the bone, kidney, placenta, lung, pancreas, and spleen, and include the synthesis of osteocalcin, matrix Gla protein, plaque Gla protein, and one or more renal Gla proteins.^{31,32,36} Variations in dietary vitamin K intake while receiving therapeutic oral anticoagulation can result in significant over or under anticoagulation.^{1,14}

Pharmacokinetics of Dietary Vitamin K

Dietary vitamin K in the forms of phyloquinone and menaquinones is solubilized in the presence of the bile salts, free fatty acids, and monoglycerides, which enhance absorption. Vitamin K is incorporated into chylomicrons, entering the circulation through the lymphatic system in transit to the liver.³² In the plasma, vitamin K is primarily in the phyloquinone form, whereas liver stores are 90% menaquinones and 10% phyloquinone.³² Within 3 days of a low vitamin K diet, a group of surgical patients showed a fourfold decrease of liver vitamin K concentrations, without an effect on their PT.³⁵ Rats given a vitamin K deficient diet develop severe bleeding within 2 to 3 weeks.

Pharmacokinetics of Administered Vitamin K₁

There are only a limited number of pharmacokinetic studies of vitamin K₁.^{7,16,26,43} One study evaluated the pharmacokinetics of vitamin K₁ in healthy volunteers, brodifacoum anticoagulated rabbits, and a patient poisoned with brodifacoum.²⁶ In the volunteers and the poisoned patient, a 10 mg IV dose of vitamin K₁ had a half-life of 1.7 hours. After oral administration of doses of 10 and 50 mg of vitamin K₁, peak concentrations of 100 to 400 ng/mL and 200 to 2000 ng/mL, respectively, occurred at 3 to 5 hours. Bioavailability varied significantly among patients (10%–65%) for both doses and in individual patients with the 50 mg dose. Oral vitamin K₁ is absorbed in an energy dependent saturable process in the proximal small intestine, which likely contributes to the variability.²⁶ In maximally brodifacoum anticoagulated rabbits, IV vitamin K₁ (10 mg/kg) increased prothrombin complex activity from 14% to 50% by 4 hours and to 100% by 9 hours, after which it declined with a half-life of 6 hours.²⁶ Similarly, high doses of oral vitamin K₁ were effectively used to treat a patient anticoagulated with brodifacoum.⁷

The pharmacokinetics of oral and intramuscular (IM) vitamin K₁ were compared in eight healthy female volunteers. Baseline serum vitamin K₁ concentrations were 0.23 ng/mL. Following the oral administration of 5 mg of vitamin K₁ peak serum concentrations of 90 ng/mL were achieved between 4 and 6 hours. These concentrations dropped to a steady state of 3.8 ng/mL, and exhibited a half-life of about 4 hours.

The pharmacokinetics were distinctly different and quite variable after IM administration. IM administration of 5 mg of vitamin K resulted in peak serum concentrations of only 50 ng/mL, with delays from 2 to 30 hours following administration and with the maintenance of a plateau for about 30 hours.¹⁶ Consequently, IM administration is not recommended; either oral or IV administration is more appropriate, and the route will be defined by the severity of bleeding. Only in the case of

acute gastrointestinal disease in a patient without life-threatening over anticoagulation is the subcutaneous route an appropriate alternative to the oral route (Table 60–3).

Pharmacodynamics of Administered Vitamin K₁

The time necessary for the INR to return to a safe or normal range is variable and dependent on the rate of absorption of vitamin K₁, the serum concentration achieved, and the time necessary for the synthesis of activated clotting factors. A decrease in the INR can often occur within several hours, although it may take 8 to 24 hours to reach target values.^{1,6,12,23,28} Maintenance of a normal INR depends on the half-life of the vitamin K₁, maintenance of an effective serum concentration, and the half-life of the anticoagulant involved. The IV route is unpredictably faster than the oral route in restoring the INR to the chosen target range.^{1,16,21} A comparison of oral versus IV vitamin K₁ therapy for excessive anticoagulation, without major bleeding, demonstrated that individuals with INRs of 6 to 10 had similarly improved INRs at 24 hours.²¹ The onset of action began at 2 hours with IV compared to 6 hours with oral.²¹ The IV group was more often overcorrected to an INR of less than two.²¹ In a randomized controlled trial in asymptomatic patients on warfarin with an INR between 4.5 and 10, the administration of 1 mg of vitamin K orally was associated with a faster return to a therapeutic INR than with 1 mg administered subcutaneously.⁸

Vitamin K Deficiency and Monitoring

Vitamin K deficiency can result from inadequate intake, malabsorption, or interference with the vitamin K cycle. Malnourishment and any condition in which bile salts or fatty acids are inadequate, such as extrahepatic cholestasis or severe pancreatic insufficiency, can lead to vitamin K deficiency. Additionally, multifactorial etiologies place newborns at risk for hemorrhage. Phylloquinone does not readily cross the placenta, and breast milk contains less phylloquinone than vitamin K fortified formula. Fetal hepatic stores of phylloquinone are low, and treatments such as maternal anticonvulsant therapy may lead to increased vitamin K metabolism.^{32,36} Although menaquinones are produced in the colon by bacteria, it is unlikely that enteric production contributes significantly to vitamin K stores or that eradication of the bacteria with antibiotics, without a coexistent dietary deficiency of vitamin K, results in deficiency.³² Determination of vitamin K deficiency is usually established on the basis of a prolonged PT or INR, which are surrogate markers of specific coagulation factors. Measurement of the vitamin K dependent factors, II, VII, IX, and X, appears to be an effective way to determine the adequacy of vitamin K₁ dosing.¹⁷ Serial measurements of factor VII, the factor with the shortest half-life, allow for the early detection of inadequate vitamin K in the diet or a therapeutic regimen.⁷ Direct measurement of serum vitamin K concentrations is done by high-performance liquid chromatography analysis. The human serum vitamin K concentration required for adequate production of activated clotting factors in the presence of LAARs is still unclear. A single study in a patient who overdosed on brodifacoum suggested that a serum vitamin K concentration of 0.2 to 0.4 µg/mL was sufficient to achieve a normal coagulation profile. Prior studies suggested 1.0 µg/mL was necessary in rabbits.^{7,26}

ROLE IN XENOBIOTIC INDUCED VITAMIN K DEFICIENCY

Oral anticoagulants are vitamin K antagonists that interfere with the vitamin K cycle, causing the accumulation of vitamin K 2,3-epoxide, an inactive metabolite. Warfarin is a strong irreversible inhibitor of the vitamin K 2,3 epoxide reductase, which regenerates vitamin K into its active (K₁H₂, hydroquinone) form.³ The superwarfarins are even more potent vitamin K reductase inhibitors. Without exogenous interference, vitamin K is recycled and only 1 µg/kg/d is required in adults to maintain adequate coagulation. DT-diaphorases are warfarin insensitive enzymes capable of reducing vitamin K₁ to its active hydroquinone form, but they are incapable of regenerating vitamin K from vitamin K 2,3-epoxide following carboxylation of the coagulation factor (Fig. 60–2).³ Thus, in the presence of warfarin or superwarfarin, additional vitamin K₁ must be administered to supply this active cofactor for each and every carboxylation step, because it can no longer be recycled.⁷ The minimum vitamin K₁ requirement in the presence of a LAAR is unknown. Other compounds have varying degrees of vitamin K antagonistic activity and include the N-methyl-thiotetrazole side-chaincontaining antibiotics such as moxalactam and cefamandole (Chap. 57), as well as salicylates (Chap. 39).³²

ADVERSE EFFECTS AND SAFETY ISSUES

Although vitamin K₁ can be administered orally, subcutaneously, intramuscularly, or intravenously, the oral route is preferred for maintenance therapy. When administered orally, vitamin K₁ is virtually free of adverse effects, except for overcorrection of the INR for a patient requiring maintenance anticoagulation. The preparations available for IV administration are rarely associated with anaphylactoid reactions. Because of the lipid solubility of vitamin K, these

preparations are not available in solution but rather as an aqueous colloidal suspension of a polyoxyethylated castor oil derivative, dextrose, and benzyl alcohol. IV administration has resulted in death secondary to anaphylactoid reactions, probably as a result of the colloidal formulation of the preparation.^{4,9,22} Numerous anaphylactoid reactions are reported, even when the preparation is properly diluted and administered slowly.^{13,25,29,41} In a 5 year retrospective study, two patients experienced “clinical anaphylaxis” shortly after initiation of 0.5 to 1 mg IV vitamin K₁ diluted in 50 mL D₅W to be infused over one hour. Based on the total number of 6572 administered doses of vitamin K₁ infused according to this protocol, the estimated incidence of “clinical anaphylaxis” was 3 in 10,000. Rarely, subcutaneous and IM routes of administration may also result in an anaphylactoid reaction.¹³ Liposomal preparations, which may become safer alternatives, are in development.

PREGNANCY AND LACTATION

Vitamin K₁ is listed as FDA pregnancy category C. There are no reproductive studies in animals. However, Briggs⁵ suggests that vitamin K is compatible with human pregnancy and is the treatment of choice for vitamin K deficiency during pregnancy and to prevent hemorrhagic disease in the newborn. Briggs also states that vitamin K is compatible with breastfeeding. However, the amount of vitamin K transferred in mother’s milk is not usually enough to prevent hemorrhagic disease in the newborn without supplementing the newborn directly.

DOSING AND ADMINISTRATION

The optimal regimen for vitamin K₁ remains unclear. Variables include the vitamin K₁ pharmacokinetics and the amount and type of anticoagulant ingested.³⁰ Reported cases of LAAR poisoning have required as much as 50 to 250 mg of vitamin K₁ daily for weeks to months.^{2,7,11,18,20,33,40} A reasonable starting approach for a patient who has overdosed on LAAR is 25 to 50 mg of vitamin K₁ orally three to four times a day for 1 to 2 days. For usually large oral vitamin K doses the IV formulation can be given orally.⁸ The INR should be monitored, and the vitamin K₁ dose adjusted accordingly. Once the INR is less than 2, a downward titration in the dose of vitamin K₁ can be made on the basis of factor VII analysis. For an ingestion of brodifacoum, serial serum concentrations of brodifacoum may be helpful in determining the ultimate duration of treatment.^{7,24}

The management of patients with elevated INRs secondary to excessive warfarin is described in [Table 60–2](#). IV administration of vitamin K₁ should be reserved for life threatening bleeding and serious bleeding at any elevation of INR.¹ Under these circumstances, patients may be supplemented with prothrombin complex concentrate and fresh frozen plasma (FFP), based on a risk-to-benefit analysis. A starting dose of 10 mg of vitamin K₁ is recommended. To minimize the risk of an anaphylactoid reaction, the preparation should be diluted with preservative-free 5% dextrose, 0.9% sodium chloride, or 5% dextrose in 0.9% sodium chloride, and administered slowly, using an infusion pump, over a minimum of 20 minutes according to the 2012 American College of Chest Physicians guidelines.¹ The package insert recommends administration at a rate not to exceed 1 mg/min in adults.³⁸ Precautions should be anticipated in the event of an anaphylactoid reaction.

Because the duration of action of vitamin K₁ is short-lived, the dose must be repeated two to four times daily. The onset of the effect of vitamin K₁ is not immediate, regardless of the route of administration.

FORMULATION AND ACQUISITION

Vitamin K₁ is available for IV and subcutaneous administration as phytonadione injection emulsion in 2 mg/mL and 10 mg/mL concentrations. These preparations contain benzyl alcohol (0.9%) as a preservative. Oral vitamin K₁ is available as Mephyton in 5 mg tablets.

SUMMARY

- Vitamin K₁ (phytonadione) is indicated for the reversal of an elevated PT or INR in patients with xenobiotic induced vitamin K deficiency.
- IV administration is reserved for patients with serious or life-threatening bleeding. The intravenous route is rarely associated with consequential adverse reactions.
- Vitamin K₁ is administered with other therapies such as prothrombin complex and FFP that have rapid onsets of action.

- The onset of action of vitamin K₁ is delayed for several hours regardless of the route of administration.

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A16 ANTIDOTES IN DEPTH

Protamine

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Protamine is a rapidly acting antidote that is used primarily to reverse the anticoagulant effects of unfractionated heparin (UFH). It neutralizes the anti-IIa activity of low-molecular-weight heparin (LMWH) and incompletely neutralizes the anti-Xa activity of LMWH, which may normalize activated partial thromboplastin time (aPTT) and the thrombin time, but variably resolves clinical bleeding. Protamine has no effect on heparin pentasaccharide fragments or analogs such as fondaparinux.

HISTORY

The antidotal properties of protamine were recognized in the late 1930s, leading to its approval as an antidote for heparin overdose in 1968.⁶⁹ However, the largest body of literature pertaining to protamine originates from its use in neutralizing heparin following cardiopulmonary bypass and dialysis procedures.

PHARMACOLOGY

Chemistry

The protamines are a group of simple basic cationic proteins found in fish sperm that bind to heparin to form a stable neutral salt, rapidly inactivating heparin and reversing its anticoagulant effects.⁷⁶ Commercially available protamine sulfate is derived from the sperm of mature testes of salmon and related species. Upon hydrolysis, protamine yields basic amino acids, particularly arginine, proline, serine, and valine, but not tyrosine and tryptophan.

Related Protamine Variants

In animal studies, synthetic protamine variants, not available for clinical use, were effective in reversing the anticoagulant effects of LMWH and are reported to be less toxic than protamine.^{11,41,85,86} The effects of protamine sulfate and protamine chloride appear to be comparable.⁵³

Mechanism of Action

Heparins are large electronegative xenobiotics that are rapidly complexed by the electropositive protamine, forming an inactive salt. Heparin is an indirect anticoagulant, requiring a cofactor. This cofactor, AT, was formerly called antithrombin III. Heparin alters the stereochemistry of AT, thereby catalyzing the subsequent inactivation of thrombin and other clotting factors.³² Only about one-third of an administered dose of unfractionated heparin binds to AT, and this fraction is responsible for most of its anticoagulant effect.^{3,55} LMWH has a reduced ability to inactivate thrombin as a result of lesser AT binding, but the smaller fragments of LMWH inactivate factor Xa almost as well as the larger molecules of UFH, allowing for equivalent efficacy. Immuno-electrophoretic studies demonstrate that because of the net positive charge of protamine, it has a greater affinity for heparin than heparin for AT, producing a dissociation of the heparin-AT complex and favoring a protamine-heparin complex.⁷³ This complex is removed by the reticuloendothelial system.²

PHARMACOKINETICS AND PHARMACODYNAMICS

Normal volunteers, free of cardiovascular disease and heparin-free, received 0.5 mg/kg protamine intravenously over 10 min. In this study, the protamine plasma half-life was 7.4 minutes, and it was undetectable within 20 minutes.

Pharmacokinetic modeling did not fit a typical pattern.⁸ The same investigators administered 250 mg of protamine intravenously over 5 minutes at the end of cardiopulmonary bypass for heparin reversal revealing a total protamine half-life

(free plus bound to heparin) of 4.5 minutes and this study, a two-compartment model best explained the data.

ROLE IN REVERSING HEPARINS

Protamine is indicated to reverse anticoagulant effects of heparin.²⁸ It is commonly used during coronary artery bypass graft (CABG) and cardiac valve surgeries, abdominal aortic aneurysm and other open abdominal surgeries, in fistula placement and noncardiac vascular surgeries, during catheterization for cardiac or electrophysiologic procedures, and in hemodialysis.^{9,37,61,92} Multiple controlled human trials substantiate the effectiveness of protamine in terminating the effects of heparin.^{33,37,92} Protamine can be used in heparin overdose.

ROLE IN REVERSING LOW-MOLECULAR-WEIGHT HEPARIN

In contrast to the case of heparin, there is no proven method for completely neutralizing LMWH. Protamine neutralizes the anti-IIa activity of LMWH and a variable portion of the anti-Xa activity of LMWH.²⁸ Because the interaction of protamine and heparin is dependent on the MW of heparin, LMWH (mean MW, 4500 Da) has reduced protamine binding. The protamine resistant fraction in LMWH is an ultra-low-molecular-weight fraction with low sulfide charge.²¹ No human studies offer convincing evidence either demonstrating or disputing a beneficial effect of protamine as treatment for hemorrhage following LMWH use.²⁸ Case studies and case reviews report both success and failure of protamine administration to reverse LMWH-associated bleeding.^{5,10,11,16,41,62,64,84–86,95}

ADVERSE EFFECTS AND SAFETY ISSUES

Protamine is routinely used in the neutralization of heparin at the completion of CABG surgery. More than a million coronary revascularizations are performed each year in the United States. However, unlike previous years, only one-fourth of those cases are now CABGs and routinely expose patients to protamine. Since the advent of CABG surgery, there have been approximately 100 deaths reported in total with the use of protamine in these circumstances. It is largely in this setting that the adverse effects of protamine are also documented and studied.^{38,39,59,72} It is often difficult to separate the adverse effects caused by protamine from those of the protamine–heparin complex or those actually related to heparin. Adverse effects associated with protamine include both administration rate- and non-rate-related hypotension,^{18,24–26,29,31,43,46,79,81} anaphylaxis,^{42,58} anaphylactoid reactions,^{45,65,67} bradycardia,¹ thrombocytopenia,⁹⁰ thrombogenicity,²⁰ leukopenia, decreased oxygen consumption,^{87,89} acute respiratory distress syndrome (ARDS),^{7,83} pulmonary hypertension and pulmonary vasoconstriction,^{13,35} cardiovascular collapse,^{56,77} and dose dependent paradoxical anticoagulation with protamine excess.^{2,6,47,70,71}

Mechanisms for these adverse effects are multifactorial. Some contribution may result from significant electropositivity of protamine. The protamine–heparin complex activates the arachidonic acid pathway, and the production of thromboxane A₂ is at least partly responsible for some of the hemodynamic changes, including pulmonary hypertension.^{13,19,36,66,91}

Pretreatment with indomethacin limits these effects.^{19,36,66,91} Free protamine or protamine complexed with heparin can convert L-arginine to nitric oxide (formerly called endothelium-derived relaxing factor), which in turn causes vasodilation and inhibits platelet aggregation and adhesion, potentially increasing bleeding risks.⁷⁴ Methylene blue, via reduction in the amount and effect of nitric oxide, has been used with success to treat the vasoplegia secondary to a severe protamine reaction. Protamine in excess of heparin can enter the myocardium and decrease cyclic adenosine monophosphate (cAMP), causing myocardial depression.^{13,80} Protamine and protamine–heparin complexes can activate the complement pathway and contribute to vasoactive events.^{13,75} Protamine stimulates mast cells in the human heart and skin to release histamine.^{13,60} Protamine administered in the absence of heparin, or in an amount exceeding that necessary for heparin neutralization, can act as an anticoagulant through several mechanisms. Protamine can impair ADP induced platelet aggregation, clot initiation, clot kinetics, and platelet function, resulting in weaker clot formation.^{44,47,87} Additionally, protamine reduces factor V activation by both thrombin and factor Xa, decreases factor VII^{6,70,71} activation by tissue factor, and enhances tissue-type plasminogen activator mediated fibrinolysis. A trial of patients undergoing CABG reported higher rates of microvascular bleeding and coagulation factor replacement in patients receiving excess protamine.⁵²

Risk factors for protamine induced adverse reactions include prior exposure to protamine in insulin, exposure during previous surgery with protamine reversal, vasectomy, fish allergy, or a rapid of protamine infusion rate.^{56,75} A prospective study reported a 0.06% incidence of anaphylactic reactions to protamine in all patients undergoing CABG, but a 2% incidence in diabetics using neutral protamine Hagedorn (NPH) insulin.¹² A recent systematic review of the literature revealed an anaphylaxis incidence of 1%, but the authors were cautious in interpreting the results because of study heterogeneity.⁷² The resultant elevation of histamine concentrations, the activation of complement, and elevated IgE, IgA,

and IgG concentrations are also suggested as possible mechanisms for the adverse effects.^{54,82,93,94} Diabetic patients receiving daily subcutaneous injections of a protamine containing insulin (NPH) have a 40% to 50% increased risk of immune-mediated adverse reactions, including anaphylaxis.^{28,30,34,42,51,81}

Occasionally, patients manifesting a protamine allergy are incorrectly presumed to have insulin allergy.⁵⁰ In diabetic patients receiving protamine insulin injections, the presence of serum antiprotamine IgE antibody is a significant risk factor for acute protamine reactions. Only patients with previous exposure to protamine insulin injections had serum antiprotamine IgE antibodies. However, in the group without previous protamine insulin exposure, antiprotamine IgG antibody was noted as a risk factor for protamine reactions.⁹⁴ Either naturally occurring cross-reacting antibodies, or perhaps previously unrecognized protamine exposure, was responsible for the generation of these IgG antibodies.

ALTERNATIVES TO PROTAMINE IN PATIENTS AT RISK FOR ADVERSE DRUG REACTIONS

There are limited options to replace protamine for the reversal of heparin in patients who have previously experienced “clinical anaphylaxis” following protamine therapy or in patients who are suspected of being at high risk. Possible strategies include clotting factor replenishment, exchange transfusion in neonates, protamine avoidance, or protamine administration with expectant management of anaphylaxis. Several investigational alternatives include heparin removal devices in the coronary artery bypass extracorporeal circuit, as well as the use of hexadimethrine, methylene blue, platelet factor 4, and heparinase antidotes.^{12,49} Pretreatment with antihistamines and corticosteroids may be sufficient for immune-mediated mechanisms but will probably not be beneficial for pulmonary vasoconstriction and non-immune-mediated anaphylactoid reactions.⁴⁰

PREGNANCY AND LACTATION

Protamine is FDA pregnancy category C. No animal studies have been done on reproduction. Taking into consideration the benefit-risk assessment, protamine may be used to reverse or partially reverse the bleeding in a pregnant woman considered secondary to UFH or LMWH, respectively.⁴ Excretion in breast milk is unknown.

DOSING AND ADMINISTRATION

Dosing in Cardiopulmonary Bypass

Protamine is most frequently used at the conclusion of cardiopulmonary bypass operations to reverse the effects of heparin. Many regimens are used for protamine dosing. These include using arbitrary amounts of protamine and dosing on the basis of the total amount of heparin used, often using a ratio of 0.3 to 1 mg of protamine to 100 units of heparin and subsequently titrating based on activating clotting time (ACT) point-of-care testing.^{22,33,44,57,96}

Dosing in Heparin Rebound and Redosing of Protamine

A heparin anticoagulant rebound effect is noted after cardiopulmonary bypass and is attributed to the presence of detectable circulating heparin several hours after apparently adequate heparin neutralization with protamine. The incidence of heparin rebound and the need for additional protamine range from 4% to 42%, depending on the neutralization protocol.^{32,63,78} It is likely that larger heparin doses may prolong the heparin clearance, contributing to higher than expected heparin concentrations.⁷⁸ When 300 units/kg of body weight doses of heparin were reversed with 3 mg/kg of protamine at the conclusion of cardiopulmonary bypass, a 14% incidence of small but detectable concentrations of circulating heparin was noted at 2 hours, which lasted less than one hour in all but one case.⁶³ A prolonged prothrombin time and thrombocytopenia occurred without increase in hemorrhage.

Dosing for Heparin and Low-Molecular-Weight Heparin

Approximately 1 mg of protamine will neutralize about 100 units (1 mg) of heparin (UFH). In the case of unintentional overdose, the half-life of heparin should be considered, because half of the administered dose of heparin is eliminated within 60 to 90 minutes under normal dosing conditions. In the case of an unintentional overdose without hemorrhage, the short half-life of heparin and the potential risks of protamine diminish the benefit from protamine administration. If protamine is necessary to reverse active hemorrhage, it must be administered very slowly intravenously either undiluted or diluted in D₅W or 0.9% sodium chloride over 10 to 15 minutes to limit the incidence of rate-related hypotension.^{48,76,88}

Several studies suggest incomplete protamine neutralization of the LMWHs enoxaparin, dalteparin, and tinzaparin. Current recommendations are to administer 1 mg of protamine per 100 anti-factor Xa units, where 1 mg enoxaparin equals

100 anti-factor Xa units if administered within 8 hours of the LMWH. A second dose of 0.5 of mg protamine should be administered per 100 anti-factor Xa units if bleeding continues.²³ If more than 8 hours have elapsed, then a smaller dose of protamine can be administered.

A number of tests directly measure heparin concentrations or indirectly measure the effect of heparin on the clotting cascade.^{14,17,22} These tests may be helpful in determining the appropriate protamine dosing. Because excessive protamine can act as an anticoagulant, the dose chosen should be an underestimation of that which is needed.

Dosing in the Overdose Setting

When a patient is believed to have received an overdose of an unknown quantity of heparin, the decision to use protamine should be determined by the presence of a prolonged aPTT and the presence of persistent hemorrhage. The risks of protamine use, especially in those who have had a prior life-threatening reaction to protamine, as well as in a diabetic receiving protamine-containing insulin, and the risks of continued heparin anticoagulation must be weighed. A baseline ACT, thrombin time, heparinneutralized thrombin time, heparin activity, platelets, prothrombin time, partial thromboplastin time, hemoglobin, and hematocrit ideally should be obtained. Because of the routine nature of heparin reversal following cardiopulmonary bypass, consultation with members of the bypass team may be helpful. An empiric dose of protamine may be suggested by the baseline ACT: (a) an ACT of <200 seconds necessitates no protamine, (b) an ACT of 200 to 300 seconds necessitates 0.6 mg/kg, and (c) an ACT of 300 to 400 seconds necessitates 1.2 mg/kg. These doses have not been validated outside of the operative setting. The ACT should be repeated 5 to 15 minutes following protamine administration and in 2 to 8 hours to evaluate for potential heparin rebound. Further dosing should be based on these values.²⁷

When an ACT is unavailable, protamine 25 mg to a maximum of 50 mg can be administered to an adult and adjusted accordingly.⁷⁶ Repeat dosing in several hours may be necessary with heparin rebound. The dose should be administered slowly intravenously over 15 minutes with resuscitative equipment immediately available. Neonates should not receive protamine that has been diluted with bacteriostatic water containing benzyl alcohol.^{6,68,71}

AVAILABILITY

Protamine is available as a parenteral solution ready for injection in a concentration of 10 mg/mL in either a 5 mL or 25 mL vial containing totals of 50 mg and 250 mg, respectively.⁶²

SUMMARY

- Protamine effectively and rapidly reverses the anticoagulant effect of unfractionated heparin.
- Protamine variably reverses the anticoagulant effects of LMWH.
- Protamine has no effect on heparin pentasaccharide fragments or analogs.
- Protamine should only be used for a prolonged aPTT in the presence of active hemorrhage, given the risks of hypotension, anaphylaxis, dysrhythmias, leukopenia, thrombocytopenia, and ARDS.

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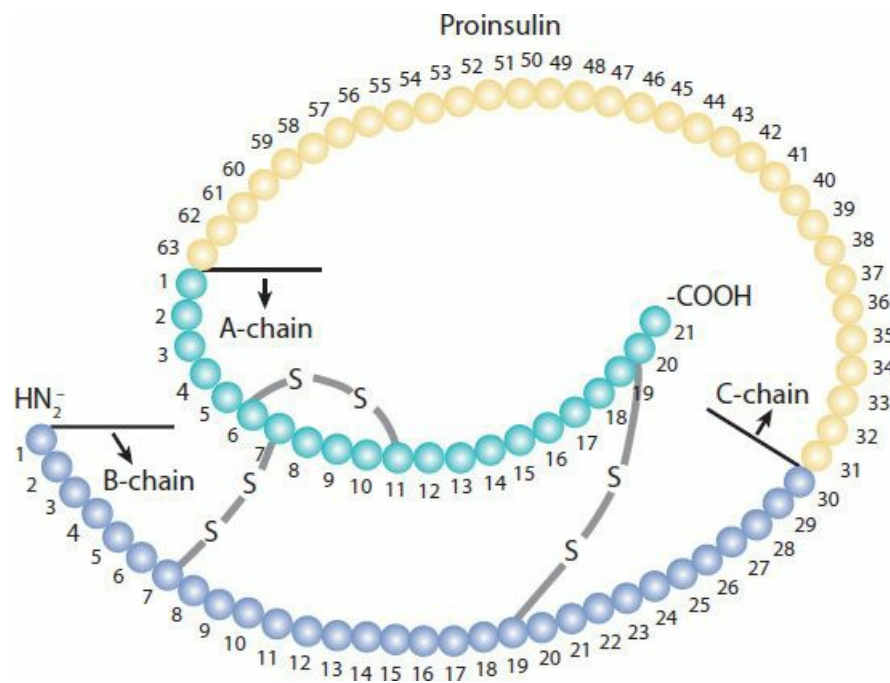
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A17 ANTIDOTES IN DEPTH

High-Dose Insulin Euglycemia

Samuel J. Stellpflug and William Kerns, II



HISTORY

Insulin was discovered and named in 1922, although its existence had been previously surmised. Clinicians at Toronto General Hospital successfully achieved glycemic control in a 14 year-old boy with diabetes by injecting him with pancreatic extract, and this success was the culmination of more than 30 years of research.⁶⁵ In the last two decades, insulin has gained increased attention and importance in the management of a spectrum of critical illnesses, including sepsis, heart failure, and cardiac drug toxicity. The benefits of insulin go well beyond simple control of hyperglycemia. In xenobiotic induced myocardial depression, the use of high dose insulin euglycemia (HIE) of HIE along with sufficient dextrose, can restore normal hemodynamics status.

PHARMACOLOGY

Chemistry/Physiology

To understand the role of insulin specifically for resuscitating patients with cardiac drug toxicity, the altered myocardial physiology that occurs during drug induced shock is briefly reviewed. The hallmarks of severe β -adrenergic antagonist (BAA) and calcium channel blocker (CCB) toxicity are bradycardia and decreased inotropy that compromise cardiac output and produce cardiogenic shock.¹⁵ This is due to direct β -adrenergic receptor antagonism and calcium channel blockade. Peripheral vasodilation can occur as well, especially in the context of dihydropyridine CCB ingestions.^{20,64} In addition to direct receptor and ion channel effects, metabolic derangements may occur that closely resemble diabetes with hyperglycemia, insulin deficiency, insulin resistance, and acidemia.

In the nonstressed state, the heart primarily catabolizes free fatty acids for its energy needs. On the other hand, the stressed myocardium switches its preferred energy substrate to carbohydrates, as demonstrated in models of both BAA and CCB toxicity.^{19,37,61} The greater the degree of shock, the greater the carbohydrate demand.³⁸ The liver responds to stress by making more glucose available via glycogenolysis. As a result, blood glucose concentrations increase. Hyperglycemia is noted both in animal models and in human cases of some cardiac drug overdoses; it can be especially evident with CCB

toxicity.^{9,21,40,62} CCBs interfere with carbohydrate processing by inhibiting pancreatic insulin release, which is necessary to transport glucose across cell membranes. Insulin release from islet cells requires functioning L-type or voltage-gated calcium channels similar to those found in myocardial and vascular tissue. CCBs directly inhibit pancreatic calcium channels (Figs. A17-1A and A17-1B).¹⁴ In vitro models of verapamil infusion confirm this toxicity; circulating glucose concentrations increase without an associated increase in insulin.³⁸ CCBs also create a state of insulin resistance by interfering with glucose transporter 1 (GLUT-1) and phosphatidyl inositol 3-kinase (PI3K) glucose transport (Figs. A17-2A and A17-2B).^{4,42} As a result of diminished circulating insulin and inhibited enzymatic glucose uptake, glucose movement into cells becomes concentration dependent and may not sufficiently support myocardial demand. CCBs further contribute to metabolic abnormalities by inhibiting lactate oxidation.^{37,41} This likely occurs through inhibition of pyruvate dehydrogenase, the enzyme responsible for conversion of pyruvate to acetylcoenzyme A (acetyl-CoA). As a result, pyruvate is preferentially converted to lactate, rather than the acetyl-CoA that would ordinarily enter the Krebs cycle; lactate then accumulates. Lactate accumulation and acidemia are consistent manifestations of CCB toxicity^{15,41} and are also observed in BAA models.¹⁰

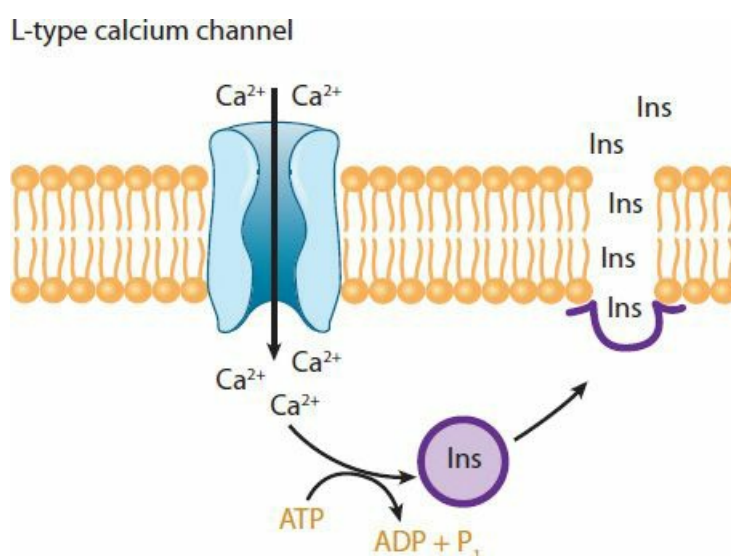


FIGURE A17-1A. Insulin (INS) release from the β -pancreatic islet cell is mediated via influx of calcium through voltage-gated (L-type) calcium channels and requires adenosine triphosphate (ATP).

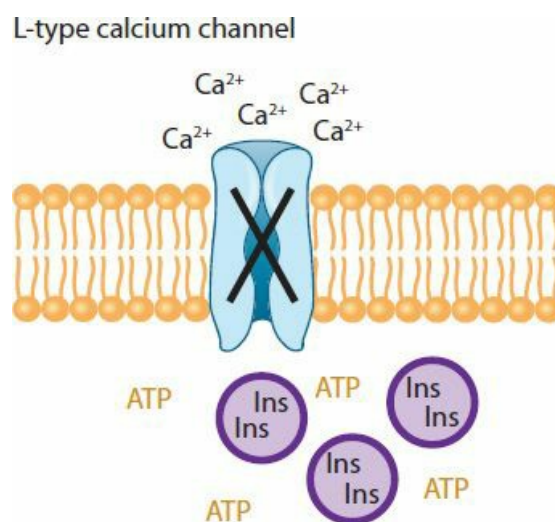


FIGURE A17-1B. CCBs inhibit pancreatic insulin release by antagonizing calcium entry via L-type calcium channel. This results in insufficient insulin to support the glucose demands of the stressed heart and also contributes to hyperglycemia that occurs with CCB toxicity.

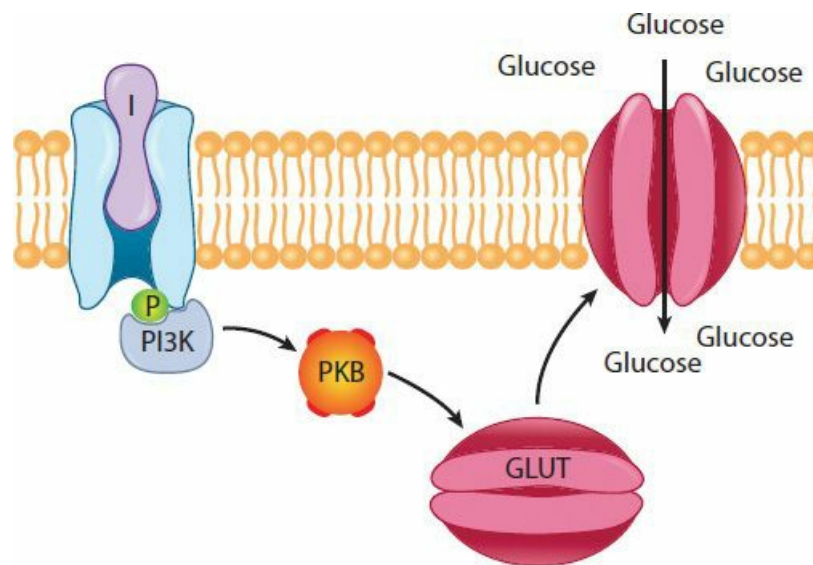


FIGURE A17-2A. The binding of insulin (I) to its receptor stimulates glucose entry into cells via a series of phosphorylation reactions involving phosphatidylinositol-3 kinase (PI3K) and protein kinase B (PKB). Ultimately, glucose transporters (GLUTs) are recruited from the cytosol into the cell membrane to facilitate glucose entry.

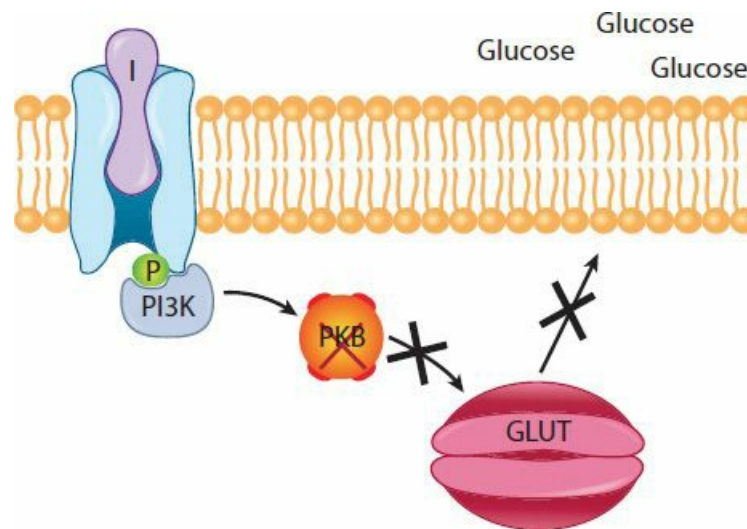


FIGURE A17-2B. CCBs interfere with the phosphatidylinositol-3 kinase (PI3K) pathway for glucose entry by inhibiting protein kinase B (PKB). Inhibition of this pathway creates a state of insulin resistance and provides one plausible explanation for the need for high doses of insulin (I) to treat drug-induced myocardial depression.

Mechanism of Action

HIE therapy supports the metabolic demands associated with cardiogenic shock and augments calcium processing, thereby increasing myocardial contractility and improving tissue perfusion.

Insulin mediated improved contractility appears to be a critical factor leading to survival from cardiogenic shock. In studies comparing insulin to more traditional therapies such as epinephrine and glucagon, insulin improves cardiac function and work efficiency.^{28,39} Epinephrine and glucagon performed less well, possibly because they promoted free fatty acid utilization. As such, epinephrine and glucagon afforded limited increases in contractility at the expense of less efficient work, increased oxygen demand, and ultimately higher mortality. Interestingly, in BAA and CCB studies using HIE, survival occurs without dramatic improvement in hypotension or bradycardia.^{20,28,37,41} The lack of effect on drug induced hypotension in animal studies and human cases may be due to the vasodilatory properties of insulin.¹⁹ The vasodilatory effects occur in the systemic, coronary, and pulmonary vasculature; this contradicts the occasionally published idea that insulin is a vasopressor. The mechanism is likely due to activation of the PI3K pathway enhancing endothelial nitric oxide synthase (eNOS) activity (Fig. A17-3).^{4,29} Vasodilation in concert with improved cardiac contractility allows for improved tissue perfusion. Improved tissue perfusion may also explain why insulin is associated with superior survival effect as compared with vasopressor adrenergic xenobiotics such as epinephrine.²⁸

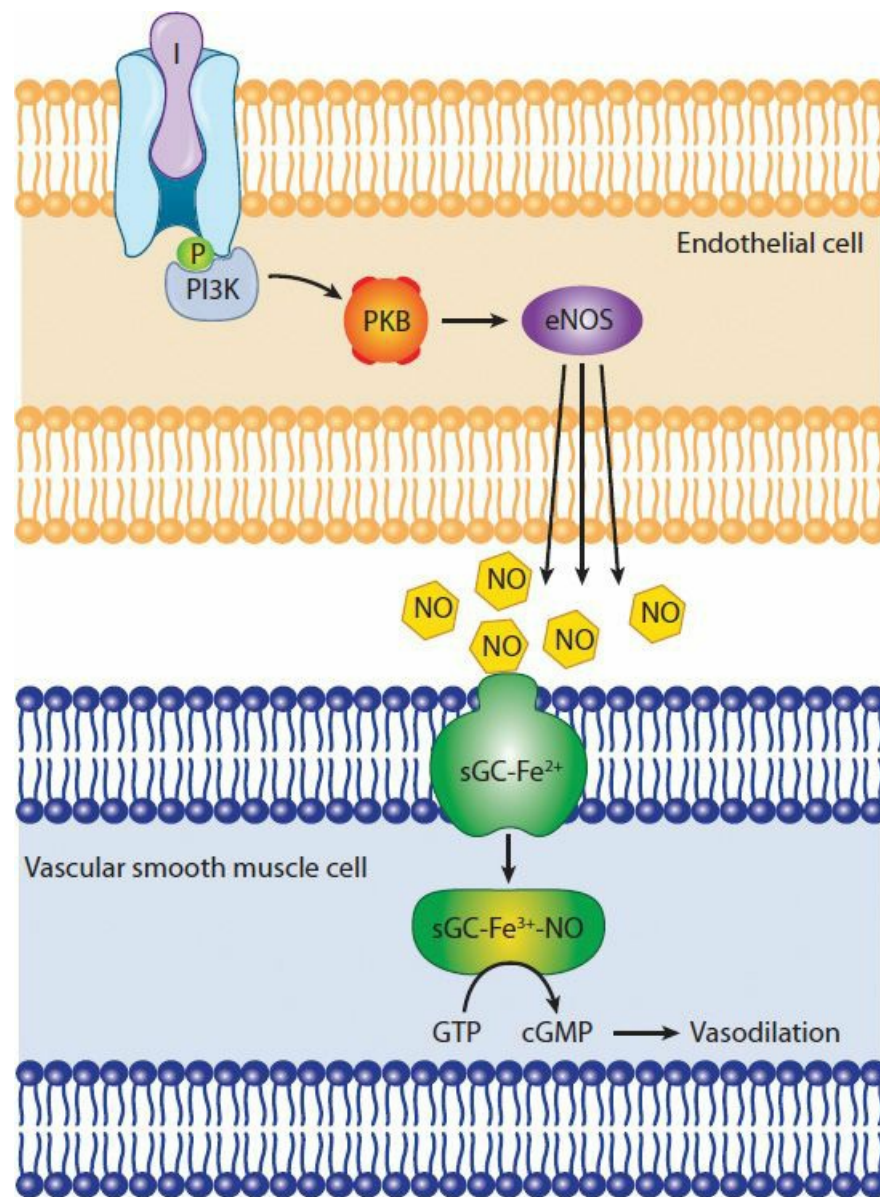


FIGURE A17-3. Nitric oxide (NO) is released from endothelial cells in response to insulin. This process involves two kinases: phosphatidylinositol-3 kinase (PI3K) and protein kinase B (PKB). NO diffuses into adjoining vascular smooth muscle cells and binds at a ferric site on the enzyme soluble guanylyl cyclase (sGC). Activation of sGC produces cyclic guanosine monophosphate (cGMP) a signaler of cell relaxation, ultimately leading to vasodilation.

Initially, the ability of insulin to improve cardiac function was attributed to increased catecholamine release. However, evidence does not support this explanation. For example, β -receptor antagonism did not prevent improved contractility that followed insulin administration.^{43,61} In a CCB toxic model, insulin therapy improved cardiac function and survival without increasing circulating catecholamine concentrations.⁴⁰ The preponderance of evidence demonstrates that the positive inotropic effects of insulin occur because of metabolic support of the heart during hypodynamic shock. As alluded to above, during drug-induced shock the heart switches preferred energy precursors from fatty acids to carbohydrates and insulin facilitates this demand.³⁷ Studies demonstrate a direct correlation between carbohydrate metabolism and the improved indices of cardiac function that occur with insulin therapy. Despite β -adrenergic antagonism by propranolol, insulin increased myocardial glucose uptake with subsequent increased contractility.⁶¹ In a model of verapamil toxicity, insulin increased glucose uptake with resultant improved contractility.³⁷ Insulin therapy also increased lactate uptake, most likely by restoring pyruvate dehydrogenase activity.³⁹ In this way, lactate serves as a carbohydrate energy source following conversion to pyruvate and ultimately acetyl-CoA, which can then enter the Krebs cycle.

There is also evidence that insulin may have an effect beyond enhanced carbohydrate usage via direct effects on calcium and, to a lesser extent, potassium and sodium ion homeostasis.^{17,43} It appears that insulin may increase available intracellular calcium by enhancing reverse mode sodium/calcium exchange, with a resultant increase in the sarcoplasmic reticulum (SR) calcium load, thus causing increased contractility.^{31,74} Additionally, there is some support for the idea that this insulin mediated increase in SR calcium availability may not only be due to the reverse mode sodium calcium exchange but also further activation of sodium/hydrogen exchange³¹ (Fig. 61-2).

Pharmacokinetics and Pharmacodynamics

Regular insulin administered as HIE therapy is intravenously given, so gastrointestinal absorption is not an issue. The peak plasma concentration is essentially immediate. The onset and peak of the cardiovascular effect of insulin is roughly 15 to 40 minutes.^{10,28,29,36,41} Insulin is slightly soluble in water, has a volume of distribution of roughly 21 L in an adult human, and demonstrates protein binding of roughly 5%, which can increase in a diabetic patient with insulin antibodies.^{46,63} More than one-half of insulin metabolism occurs in the liver, but there is also a sizable degree that occurs in adipose tissue, muscle, and in the kidneys.⁵⁷ The elimination half-life of intravenously administered insulin is roughly 5 to 10 minutes, and it is partially eliminated in both the kidneys and the bile.^{60,63}

ROLE IN DRUG INDUCED CARDIOVASCULAR TOXICITY

As mentioned above, the positive inotropic effects of insulin were recognized in 1927; however, HIE therapy for drug-induced shock in human was first reported in 1999.^{72,75} This case series included four patients who overdosed on verapamil and one with a combined amlodipine-atenolol overdose. All patients failed traditional antidote therapy but responded to rescue insulin therapy. Since this initial case series, more than 90 cases have been published reporting use of insulin therapy for treatment of isolated or mixed drug induced cardiac drug toxicity.^{1-3,5-8,11-13,16,18,22-27,34,44,45,47-50,52,53,55,56,58,59,62,66-71} Various regimens of classic antidotes were used prior to insulin therapy in many of these cases. No direct outcome comparisons can be made between insulin and these other therapies once thought to be standard care. That being said and recognizing the inherent reporting bias, overall survival was very good when insulin was included in resuscitation. Further review of these cases and animal models yields important clinical information that can be used to guide HIE therapy.

Experimental models suggest that large doses of regular insulin (2.5–10 units/kg/h) may be necessary to provide inotropic support.^{4,10,36,39,41} The most recent human case series utilized 10 units/kg/h as the standard dose.³⁰ In one case, 22 units/kg/h was used with survival after cardiac arrest from nebivolol.⁶⁷ However, humans may respond to less insulin. Most patients in the early reports were treated with HIE ranging between 0.5 and 2 units/kg/h. Many of the literature reported patients received an initial insulin bolus (between 0.1 and 1 unit/kg) prior to continuous infusion. The theoretical advantage to giving an initial insulin bolus is to rapidly saturate insulin receptors to speed the physiological response. Interestingly, one report noted that patients receiving an insulin bolus prior to the infusion showed a better blood pressure response than patients who received only a continuous infusion.²² Three patients received bolus insulin without continuous infusion, including a patient who inadvertently received 1000 units.⁵⁹ In this case, hemodynamics improved and there was no adverse event related to the extreme insulin dose. The typical reported duration of insulin infusion is 24 to 48 hours, with a range of 0.75 to 96 hours. The need for prolonged infusion likely reflects the prolonged toxicokinetics of cardiovascular drugs typically observed following severe overdose.

The predominant clinical effect of insulin was increased cardiac contractility with subsequent improvement in perfusion, often without initial increase in blood pressure. Contractility typically increased within 15 to 40 minutes after initiating insulin and often allowed a decrease in concurrent vasopressor use, sparing the toxicity of those agents. The timing of increased contractility is consistent with the observed response times in animal models.^{10,28,29,36,41} Other salutary effects were observed during insulin therapy. In one case of a combined amlodipine and valsartan overdose, blood pressure increased directly because of increased vascular resistance rather than increased cardiac function.⁶⁶ Two patients converted from third-degree heart block to normal sinus rhythm with increased pulse in temporal relationship to insulin.⁷⁵ Except for these two patients, insulin therapy did not significantly affect heart rate in other reports. One reported case, technically a high-dose insulin failure, strongly supports the idea of insulin as an inotrope.⁶⁸ A patient with baseline hypertrophic cardiomyopathy but no baseline obstructive pathophysiology ingested diltiazem, metoprolol, and amiodarone. With insulin dosing quickly escalated to 10 units/kg/h, there was increased cardiac contractility documented by ultrasonography to the point of inducing hemodynamically significant obstructive outflow. The patient's clinical course ultimately improved following intravenous fat emulsion administration. There have been other cases in which authors reported a lack of response to insulin. Reasons for no response in three of these reports may include inadequate dosing and excessive delay to insulin therapy.¹²

Based on the sum of experimental and clinical experience, we suggest using “off label” HIE (bolus of regular insulin 1 unit/kg followed by 1 to 10 units/kg/h continuous infusion) early in the resuscitation of severe BAA and CCB-induced myocardial depression, simultaneous with traditional pharmacologic and supportive therapies.

ADVERSE EVENTS AND SAFETY ISSUES

The major anticipated adverse event associated with the use of large amounts of insulin, especially in patients naïve to insulin, is hypoglycemia, defined as blood glucose less than 60 mg/dL (3.3 mmol/L) regardless of the presence or absence of symptoms. Because of potential hypoglycemia, all experimental animals received sufficient dextrose during insulin infusion to maintain euglycemia. In the aggregate human cases, patients typically received empiric supplemental dextrose

based on frequent glucose monitoring. The typical dextrose dose was 25 g/h, but requirements varied widely from 0.5 to 75 g/h. The duration of exogenous dextrose supplementation was roughly 2 days, but also varied significantly from 9 to 100 hours. Dextrose supplementation was necessary beyond cessation of insulin for a majority of the documented cases. Despite empiric dextrose and blood glucose monitoring (albeit with no standard frequency of testing), hypoglycemia occurred in some patients. In one retrospective series, hypoglycemia occurred in 5 out of 37 patients and resulted in HIE cessation.⁴⁸ In a prospective evaluation of seven separate CCB overdoses, there was one clinically insignificant episode.²² In another retrospective 12-patient case series, there were 6 patients with a total of 19 hypoglycemic events (8 in one patient), all of uncertain but unlikely clinical significance.³⁰ Of note, dextrose requirement does not directly correlate well with insulin dose or severity of shock. Patients with severe shock and marked hyperglycemia may not need any supplemental dextrose during the initial hours of insulin therapy due to insulin deficiency and insulin resistance. Additionally, there may be a ceiling requirement for dextrose. One animal model demonstrated that dextrose need was greater for animals treated with 5 versus 1 unit/kg/h insulin, but not between groups treated with 5 versus 10 units/kg/h.¹⁰ Overall, hypoglycemia is a potential consequence of HIE therapy, but clinically significant hypoglycemia is rare. A combination of rigorous glucose monitoring and dextrose administration can prevent hypoglycemia and avoid unnecessary cessation of insulin treatment.

Another anticipated consequence of insulin treatment is hypokalemia. Although serum potassium concentrations may fall below normal laboratory ranges, HIE does not typically cause profound hypokalemia. The observed decrease reflects a shifting of potassium from the extracellular to intracellular space that occurs as a result of the action of insulin. Patients maintain normal total body potassium stores and do not experience true deficiency unless they have other reasons for potassium loss. In the initial case series, three patients had a nadir of potassium ranging from 2.2 to 2.8 mEq/L without sequelae.⁷³ In two case series of seven and twelve patients, there were 2/7 and 7/12 patients, respectively, who demonstrated clinically insignificant hypokalemia.^{22,30} There is a theoretical risk of excessive potassium replacement in the instance of lowered serum potassium, but normal total body stores. Hyperkalemia may also worsen verapamil induced myocardial depression.^{33,51}

Other observed ion changes during insulin therapy include hypomagnesemia and hypophosphatemia. Similar to action on potassium, insulin causes an intracellular shift of both phosphorus and magnesium.^{35,54} In the initial series of drug-induced shock treated with insulin, four patients had lowered magnesium (0.4–0.6 mmol/L; normal, 0.8–1.2 mmol/L) and phosphorus (0.2–0.5 mmol/L; normal, 1–1.4 mmol/L) concentrations. No symptoms were attributed to these lowered serum concentrations, but three patients received supplementation of both electrolytes. No other insulin-treated CCB cases address these two electrolytes. Insulin (0.1 units/kg/h) for diabetic ketoacidosis is likewise associated with similar effects on magnesium and phosphorus, so it is unlikely that alterations of magnesium and phosphorus are dose related.³²

PREGNANCY AND LACTATION

Regular insulin is pregnancy category B and is compatible with breastfeeding.

DOSING AND ADMINISTRATION

Based on the experimental studies and aggregate human cases, HIE will most likely benefit patients with cardiac drug induced myocardial depression. Insulin therapy may also be considered for those patients with refractory hypotension due to poor vascular resistance without associated poor contractility. The experimental evidence and human case experience are strongest for CCB toxicity. Animal studies and growing human experience also support its use for BAA intoxication.

Myocardial function can be estimated via emergency department focused cardiac ultrasonography or through machine estimated cardiac output utilizing pulse contour analysis attached to a standard arterial catheter. This can be done less accessibly or more invasively via formal echocardiography or placement of a pulmonary artery catheter. When decreased myocardial function is present, insulin therapy can be used by first administering a 1 unit/kg bolus of regular human insulin along with 0.5 g/kg bolus of dextrose. Patients with markedly elevated blood glucose may not require dextrose support at the initiation of insulin therapy. If blood glucose is greater than 300 mg/dL (16.7 mmol/L), then the dextrose bolus is not necessary. An infusion of regular insulin should immediately follow the bolus starting at 1 unit/kg/h. Ideally, this insulin infusion should be concentrated to prevent fluid overload that may occur with large doses. The authors' institutions concentrate the infusion at 10 unit/mL compared with the typical insulin infusion concentration of 1 unit/mL used for diabetic ketoacidosis. This unusual pharmacy formulation requires close collaboration with hospital pharmacists. A continuous dextrose infusion, beginning at 0.5 g/kg/h, should be concurrently initiated. Dextrose can be started as D₁₀, especially without central venous access and while determining the dextrose need, but it is ultimately best delivered as D₂₅ or D₅₀ via central venous access, also with the intent to lessen large fluid volumes that would otherwise be necessary with administration of more dilute dextrose solutions.

If possible, cardiac function should be reassessed every 10 to 15 minutes after starting HIE therapy. If cardiac function remains depressed, then the insulin dose should be increased. Dosing recommendations typically range up to 10 units/kg/h;

however, doses up to 22 units/kg/h have been used, and the maximum dose is not established.^{10,67} The blood glucose should be monitored every 15 to 30 minutes until stable, and then every 1 to 2 hours. The dextrose infusion should be increased to maintain blood glucose concentrations between 100 and 250 mg/dL (5.5–14 mmol/L) rather than reducing the insulin.

The serum potassium concentration should be measured during HIE therapy. If it is low, especially when potassium loss is suspected, then supplementation is indicated to maintain the concentration in the “mildly hypokalemic” range (2.8–3.2 mEq/L). A reasonable time frame is to evaluate serum potassium hourly while actively titrating the insulin infusion, and every 6 hours once the infusion rate is stabilized. Magnesium and phosphorus can also be measured and supplemented as medically indicated. However, unless there is reason for loss of these three electrolytes, lowered serum concentrations likely reflect compartmental shifts, not depletion.

The ultimate goal of HIE is improvement in organ perfusion as demonstrated by increased cardiac output, improved mental status, adequate urine output, and reversal of metabolic abnormalities, as indicated by serum lactate, bicarbonate, pH, and base excess. This improvement is often, but not always, accompanied by an improvement in mean arterial blood pressure. Because insulin improves both cardiac function and perfusion while slightly vasodilating, treatment goals should focus more on organ perfusion and outcome as opposed to simply the numerical blood pressure. An increase in the rate of dextrose infusion to maintain euglycemia often accompanies hemodynamic and metabolic improvements. This increase in dextrose demand is due, in part, to increased CCB or BAA metabolism and loss of the CCB-induced diabetogenic influences, and can be regarded as a favorable prognostic indicator.

Typical duration of therapy has been 1 to 2 days, although HIE has been used for up to 4 days. We recommend reducing the insulin infusion rate by 1 unit/kg/h once the patient has stabilized, and reassessing hourly for additional infusion reduction while maintaining adequate perfusion. Recognize that the dextrose infusion may be necessary after the insulin is reduced and ultimately eliminated. The reduction of insulin and dextrose may cause potassium shifting which should also be monitored.

SUMMARY

- High-dose insulin euglycemia can be used to augment cardiac function and perfusion in the context of cardiogenic shock due to calcium channel blockers and β -adrenergic antagonists.
- This therapy supports the metabolic demands associated with the cardiogenic shock and augments calcium processing, thereby increasing myocardial contractility and improving tissue perfusion.
- High doses of concentrated regular insulin are intravenously given, along with appropriate amounts of dextrose, and monitoring is required of serum glucose and potassium, in addition to surrogate markers of tissue perfusion, such as cardiac output, urine output, bicarbonate, pH, and lactate.

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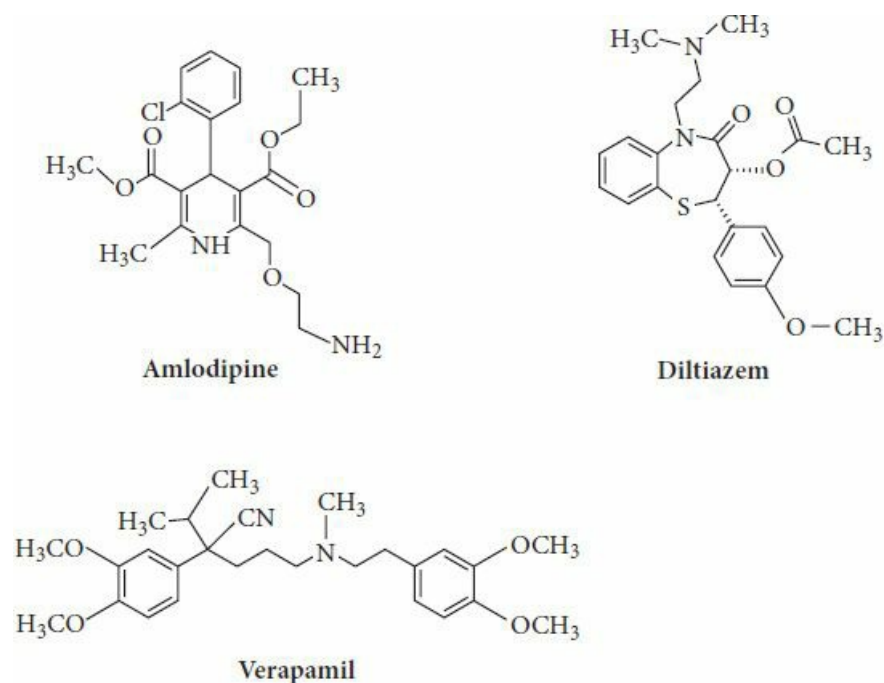
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61 CALCIUM CHANNEL BLOCKERS

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HISTORY AND EPIDEMIOLOGY

In 1964, Albrect Fleckenstein described an inhibitory action of verapamil and prenylamine on excitation-contraction coupling that was similar to calcium depletion.³ By the late 1970s, the clinical use of calcium channel blockers (CCBs) was widely accepted for variety of cardiovascular indications, including hypertension, dysrhythmias, and angina. Later indications, including Raynaud phenomenon, migraine headaches, and subarachnoid hemorrhage, have been adopted. There are currently 10 individual CCBs marketed in the United States that are available as immediate or sustained-release formulations and as combination products with other antihypertensives.

The cardiovascular drug class is one of the leading classes of drugs associated with poisoning fatality. Over the past 5 years of available data, there were more than 12 million poisonings with more than 7000 poisoning-related deaths reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System. Cardiovascular drugs were involved in more than 474,000 of the reported poisonings and accounted for nearly 18% of the overall poisoning fatalities. Within this class, CCBs were the most common cardiovascular drugs involved in poisoning fatalities. CCBs accounted for more than 50,000 cases reported over the past 5 years, with 289 cases resulting in major effects and more than 100 deaths (Chap. 136).

PHARMACOLOGY

Calcium (Ca^{2+}) ion channels exist as either voltage-dependent or ligandgated channels. There are many types of voltage-gated Ca^{2+} channels that include P, N, R, T, Q, and L-type channels (Table 61–1). Ligand-gated Ca^{2+} channels include IP_3 and ryanodine receptors, which are found intracellularly and play a critical role in cell signaling. Voltage-gated Ca^{2+} channels are located throughout the body in the heart, nervous system, pancreas, and muscles.⁹⁰ The structure of voltage-dependent Ca^{2+} channels is composed of several components that include α_2 , β , δ , and the ion-conducting α_1 -subunit. The α_1 -subunit is the most important component of the Ca^{2+} channel as it contains the actual pore through which Ca^{2+} ions pass and also serves as the binding site of all CCBs. The other subunits such as β and δ act to modulate the function of the α_1 -subunit.^{65,104}

TABLE 61–1. Voltage-Sensitive Calcium Channel Subtypes

Type	Distribution	Function	Blocked By
T (transient)	Polysynaptic nerve terminals and cardiac nodal tissue	Pacemaker activity	Mibefradil
R	Neural tissue	Neurotransmitter release	Cadmium
Q	Presynaptic nerve terminals	Neurotransmitter release	Agatoxin
P (Purkinje)	Cerebellar Purkinje neurons	Neurotransmitter release	Agatoxin
N (neuronal)	Presynaptic nerve terminals	Catecholamine release	ω -Conotoxin
L (long-acting)	Myocardium and smooth muscle	Muscular contraction	Calcium channel blockers

The primary action of all CCBs available in the United States is antagonism of the L-type or “long-acting” voltage-gated Ca^{2+} channels. CCBs are often classified into three groups based on their chemical structure (Table 61–2).^{34,59,65} A fourth class, the tetraols, were developed and included mibefradil, but this drug was withdrawn because of significant adverse drug interactions.⁹⁸ Each group binds a slightly different region of the α_{1c} subunit of the Ca^{2+} channel and thus has different affinities for the various L-type Ca^{2+} channels, both in the myocardium and the vascular smooth muscle. It is often more logical to classify them as nondihydropyridine versus dihydropyridine CCBs. The former includes verapamil and diltiazem, whereas the latter includes many drugs, the chemical names of which all currently end in–pine, such as nifedipine and amlodipine. Verapamil and diltiazem have inhibitory effects on both the sinoatrial (SA) and atrioventricular (AV) nodal tissue and thus are commonly used for the treatment of hypertension, to reduce myocardial oxygen demand, and also to achieve rate control in a variety of tachydysrhythmias.¹ In contrast, the dihydropyridines have very little direct effect on the myocardium at therapeutic doses and act primarily as peripheral vasodilators.¹⁰⁴ They are therefore commonly used as vasodilators for conditions with increased vascular tone such as hypertension, migraine headaches, and postintracranial hemorrhage–associated vasospasm.

TABLE 61–2. Classification of Calcium Channel Blockers Available in the United States

Class	Specific Compounds
Phenylalkylamine	Verapamil (Calan, Isoptin, Verelan)
Benzothiazepine	Diltiazem (Cardizem, Dilacor, Tiazac)
Dihydropyridines	Amlodipine (Norvasc) Clevipine (Cleviprex) Felodipine (Plendil) Isradipine (DynaCirc) Nicardipine (Cardene) Nifedipine (Adalat, Procardia) Nimodipine (Nimotop) Nisoldipine (Sular)
Diarylaminopropylamine ether	Bepidil (Vascor) (withdrawn—QT prolongation)
T-channel blocker	Mibefradil (Posicor) (withdrawn—drug interactions)

Experimental studies suggest an additional vasodilatory effect of some CCBs due to stimulation of nitric oxide release.

Amlodipine and other dihydropyridine CCBs release nitric oxide in a dose-dependent fashion from canine coronary microvessels.^{109,111} Although the exact mechanism is uncertain, it is hypothesized that this amlodipine-induced nitric oxide production results from increasing endothelial nitric oxide synthase activity through phosphorylation of this enzyme. Bradykinin B₂ receptors may also be contributory.¹¹⁰

PHARMACOKINETICS AND TOXICOKINETICS

Absorption. All CCBs are well absorbed orally, but many exhibit low bioavailability due to extensive hepatic first-pass metabolism. Once the CCBs reach the liver, they undergo hepatic oxidative metabolism predominantly via the CYP3A4 subgroup of the cytochrome P450 (CYP) enzyme system.⁶⁴

Distribution. All CCBs are highly protein bound. Volumes of distribution are large for amlodipine (21 L/kg), verapamil (5.5 L/kg), and diltiazem (5.3 L/kg), and somewhat smaller for nifedipine (0.8 L/kg).^{38,69}

Metabolism. Norverapamil, formed by N-demethylation of verapamil, is the only active metabolite and retains 20% of the activity of the parent compound. Diltiazem is predominantly deacetylated into minimally active deacetyldiltiazem, which is then eliminated via the biliary tract.^{39,46} After repeated doses, as well as following overdose, these hepatic enzymes become saturated, reducing the potential of the first-pass effect and increasing the quantity of active drug absorbed systemically.¹⁰⁶ Saturation of metabolism as well as the modified release dosage form contribute to the prolongation of the apparent half-lives reported following overdose of various CCBs.⁷⁹

Excretion. The majority of CCBs undergo a significant amount of renal excretion after metabolism with a small percentage eliminated in the urine unchanged. This varies depending on the CCB. For example, amlodipine undergoes 60% renal excretion after metabolism to inactive metabolites compared with 70% for verapamil (3.4% as unchanged drug) and 90% for nifedipine as inactive metabolites.^{27,66}

One interesting aspect of the pharmacology of CCBs is their potential for drug–drug interactions. CYP3A4, which metabolizes most CCBs, is also responsible for the initial oxidation of numerous other xenobiotics. Verapamil and diltiazem specifically compete for this enzyme and can decrease the clearance of many drugs including carbamazepine, cisapride, quinidine, various β -hydroxy- β -methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, cyclosporine, tacrolimus, most human immunodeficiency virus–protease inhibitors, and theophylline (Chap. 13, Appendix).^{32,76} In June 1998, mibefradil, a structurally unique CCB, was voluntarily withdrawn following several reports of serious adverse drug interactions caused in part by its potent inhibition of CYP3A4.⁵⁵ Other inhibitors of CYP3A4, such as cimetidine, fluoxetine, some antifungals, macrolide antibiotics, and even the flavonoids in grapefruit juice, raise serum concentrations of several CCBs and may result in toxicity.^{31,86}

In addition to affecting CYP3A4, verapamil and diltiazem also inhibit P-glycoprotein–mediated drug transport into peripheral tissue—an inhibition that results in elevated serum concentrations of xenobiotics such as cyclosporine and digoxin that use this transport system (Chap. 13, Appendix). Unlike diltiazem and verapamil, nifedipine and the other dihydropyridines do not appear to affect the clearance of other xenobiotics via CYP3A4 or P-glycoprotein–mediated transport. Similarly, inhibition of P-glycoprotein–mediated transport by certain xenobiotics such as statins result in increased oral bioavailability of CCBs, which may require enhanced monitoring of appropriate patients.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Ca²⁺ plays an essential role in many cellular processes throughout the body as many types of cells depend on the maintenance of a Ca²⁺ concentration gradient across cell membranes in order to function. The extracellular Ca²⁺ concentration is approximately 10,000 times greater than the intracellular concentration. This concentration gradient is important for contraction and relaxation of muscle cells (Fig. 61–1). Ca²⁺ channels located on the cell membrane play a key role to maintain this concentration gradient within muscle cells.^{48,67}

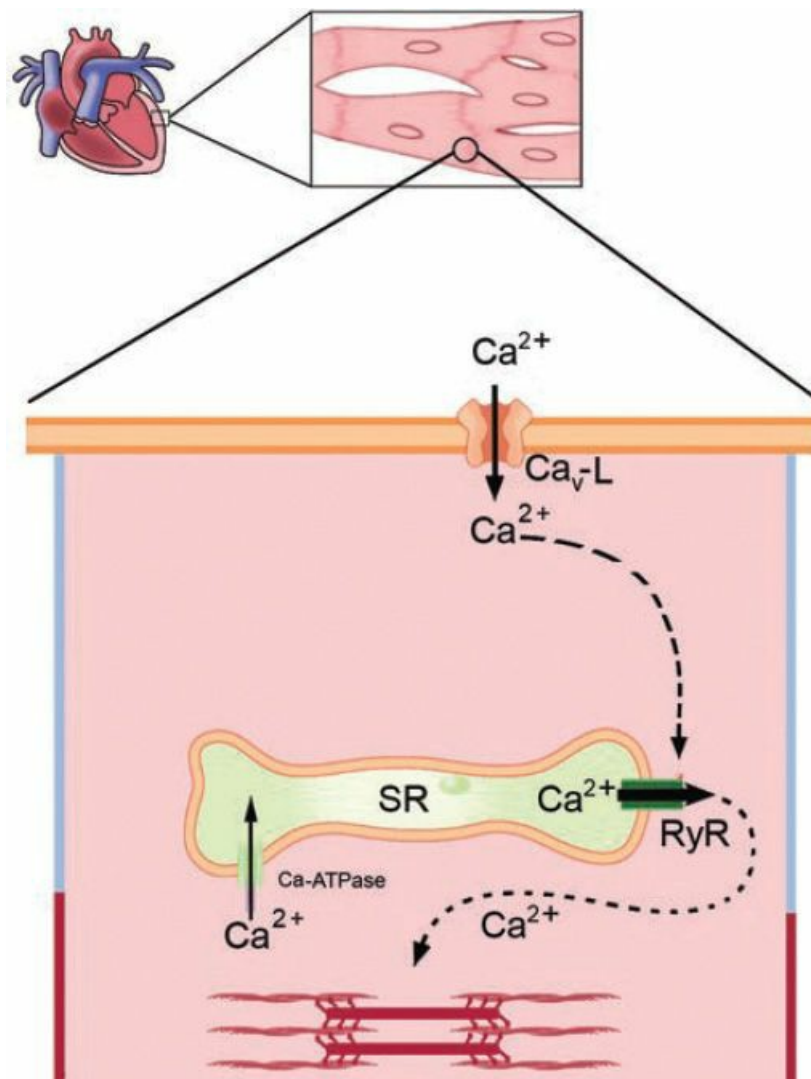


FIGURE 61–1. Normal contraction of myocardial cells. The L-type voltage sensitive calcium channels ($\text{Ca}_v\text{-L}$) open to allow calcium ion influx during myocyte depolarization. This causes the concentration-dependent release of more calcium ions from the ryanodine receptor (RyR) of the sarcoplasmic reticulum (SR).

Ca^{2+} is driven down a large electrical and concentration gradient through L-type Ca^{2+} channels located in all muscle cell types (cardiac, striated, and smooth). This influx of Ca^{2+} is critical for the function of both cardiac and smooth muscle cells; however, skeletal muscle depends primarily on intracellular Ca^{2+} stores for excitation-contraction coupling and not the intracellular influx of Ca^{2+} . In smooth muscle, the rapid influx of Ca^{2+} binds calmodulin, and the resulting complex stimulates myosin light chain kinase activity. The myosin light chain kinase phosphorylates, and thus activates, myosin, which subsequently binds actin, causing a contraction.⁶²

Ca^{2+} plays a similarly important role in myocardial contractility. In myocardial cells, Ca^{2+} influx is slower relative to the initial sodium influx that initiates cellular depolarization, and prolongs this depolarization, creating the plateau phase (phase 2) of the action potential (Chap. 16). The Ca^{2+} subsequently stimulates a receptor operated Ca^{2+} channel on the sarcoplasmic reticulum, known as the ryanodine receptor, releasing Ca^{2+} from the vast stores of the sarcoplasmic reticulum into the cytosol.⁷¹ This is often termed Ca^{2+} -dependent Ca^{2+} release. Ca^{2+} then binds troponin C, which causes a conformational change that displaces troponin and tropomyosin from actin, allowing actin and myosin to bind, resulting in a contraction.^{16,21} Ca^{2+} influx also plays an important role in the spontaneous depolarization (phase 4) of the action potential in the sinoatrial (SA) node. This Ca^{2+} influx also allows normal propagation of electrical impulses via the specialized myocardial conduction tissues, particularly the atrioventricular (AV) node. After opening, the rates of recovery of these slow Ca^{2+} channels, in both the SA and AV nodal tissue, determine the rate of conduction.

The nondihydropyridine CCBs such as verapamil and diltiazem have the greatest affinity for the myocardium, with verapamil considered the most potent. In addition, not only do verapamil and, to a lesser extent, diltiazem impede Ca^{2+} influx and channel recovery in the myocardium, but their blockade is potentiated as the frequency of channel opening increases.^{35,73} Therefore, in a frequently contracting tissue, such as the myocardium, the blockade of verapamil and diltiazem would be augmented.

At therapeutic doses, the dihydropyridine CCBs such as nifedipine have little effect at the myocardium and have most of their effect at the peripheral vascular tissue; thus, they have the most potent vasodilatory effects when compared to the

nondihydropyridine CCBs. Dihydropyridines bind the Ca^{2+} channel best at less-negative membrane potentials. Because the resting potential for myocardial muscle (-90 mV) is lower than that of vascular smooth muscle (-70 mV), dihydropyridines bind preferentially in the peripheral vascular tissue.⁷³

The toxicity of CCBs in poisoning is largely an extension of their therapeutic effects within the cardiovascular system. Inhibition of the L-type Ca^{2+} channels within both the myocardium and peripheral vascular smooth muscle results in a combination of decreased inotropy, heart rate, and arterial vasodilation. Because dihydropyridines have limited myocardial effect at therapeutic concentrations, the baroreceptor reflex remains intact and a slight increase in heart rate and cardiac output may occur. Isradipine is the only dihydropyridine whose inhibitory effect on the SA node is significant enough to blunt any reflex tachycardia. CCB poisoning can also result in blockade of L-type Ca^{2+} channels located in the pancreas. This results in decreased insulin release resulting in hyperglycemia.

CLINICAL MANIFESTATIONS

The hallmark of the CCB poisoning is hypotension and bradycardia, which results from depression of myocardial contraction and peripheral vasodilation.⁸⁴ Myocardial conduction may also be impaired, producing AV conduction abnormalities, idioventricular rhythms, and complete heart block. Junctional escape rhythms frequently occur in patients with significant poisonings.^{13,36,42,75,107} The negative inotropic effects may be so profound, particularly with verapamil, that ventricular contraction may be completely ablated.^{5,10,11,19}

Hypotension is the most common and life-threatening finding in an acute CCB poisoning, typically caused by a combination of decreased inotropy, bradycardia, and peripheral vasodilation.⁷⁸ Patients may also present asymptomatic early following ingestion and subsequently deteriorate rapidly to severe cardiogenic shock.^{5,10,44} The associated clinical findings reflect the degree of cardiovascular compromise and hypoperfusion, particularly to the central nervous system. Early symptoms include fatigue, dizziness, and lightheadedness. Alteration in mentation in the absence of hypotension should prompt the clinician to consider other causes and ingestions. Severely poisoned patients may manifest syncope, altered mental status, coma, and sudden death.^{81,85} Gastrointestinal (GI) effects, such as nausea and vomiting, are not a typical feature of CCB poisoning. Acute respiratory distress syndrome (ARDS) may also occur with severe CCB poisoning. This may be due to precapillary vasodilation with a subsequent increase in transcapillary pressure. The elevated pressure gradient results in increased capillary transudates and possible interstitial edema.^{26,43}

In mild to moderate overdose of dihydropyridine CCBs, the predominantly peripheral effect may induce a reflex tachycardia. However, severe poisoning with any CCBs can result in loss of receptor selectivity resulting in bradycardia. A prospective poison center study noted AV nodal block to occur more frequently with verapamil poisoning.⁷⁸ While deaths are attributed mainly to the nondihydropyridines, a significant number of dihydropyridine-related deaths are also reported.^{58,91} This may reflect the wider use of this latter class of CCBs.

There are several factors that ultimately determine CCB toxicity. These include medication formulation, dose, and coingestion with other cardioactive medications such as β -adrenergic antagonists, underlying comorbidities, and age. Elderly patients and those with underlying cardiovascular disease such as congestive heart failure are more sensitive to CCBs.⁶³ Even at therapeutic doses, these patients are more susceptible to the cardioactive effects of these medications and may develop symptomatic hypotension.

Pediatric cases of CCB are commonly from medication errors or unintentional ingestions of pills found at home.^{12,33} Children with CCB poisoning may develop nonspecific clinical effects such as lethargy, emesis, and confusion. While CCB exposure in children is uncommon, there are reported cases of severe poisoning and death.⁹¹

DIAGNOSTIC TESTING

Any patients with suspected CCB poisoning should be considered at risk for cardiovascular collapse and be evaluated with a 12 lead electrocardiogram (ECG), followed by continuous cardiac and hemodynamic monitoring. A chest radiograph, pulse oximetry, and serum chemistry should also be obtained if any degree of hypoperfusion is suspected. Assessment of electrolytes, including magnesium, and a serum digoxin concentration may be useful in a bradycardic patient with unknown exposure history, although a careful history, if possible, may narrow down the etiology. Cardioactive steroids should be a consideration in the setting of hyperkalemia with normal kidney function. Assays for CCB serum concentrations are not routinely available and therefore have no role in the management of patients poisoned with CCBs.

Hyperglycemia is considered a prognostic sign in cases of severe CCB poisoning. The release of insulin from the β -islet cells in the pancreas is dependent on Ca^{2+} influx through the L-type Ca^{2+} channel. CCB poisoning reduces insulin release with resultant hyperglycemia. An additional mechanism may be dysregulation of the insulin dependent phosphatidylinositol 3-kinase pathway.¹¹ It should be noted that hyperglycemia might also be the result of diabetes or the administration of glucagon for suspected β -adrenergic antagonist poisoning.

A retrospective study suggests that serum glucose concentration correlate with the severity of CCB poisoning. The initial mean serum glucose concentration was 188 mg/dL in patients who met a composite end point of requiring vasopressors, a pacemaker, or death, versus 122 mg/dL in those not requiring intervention. Peak serum glucose concentrations were also significantly different.⁵⁷ This finding may become a useful early sign of severity and an indicator for when to initiate hyperinsulinemia-euglycemia therapy.

MANAGEMENT

General Approach

All patients with suspected CCB poisoning should undergo prompt evaluation even when the initial vital signs are normal. This urgency is due to the potential to initiate early GI decontamination and pharmacologic therapies before patients manifest severe poisoning. This is particularly important with ingestions involving sustained-release formulations. Intravenous access should be obtained and initial treatment should be directed toward aggressive GI decontamination of patients with large recent ingestions. All patients who become hypotensive should receive a fluid bolus of 10 to 20 mL/kg of crystalloid which should be repeated as needed. Caution is required, as aggressive fluid resuscitation should not be given to patients with congestive heart failure, evidence of ARDS, or chronic kidney disease (CKD).

Pharmacotherapy should focus on maintenance or improvement of both cardiac output and peripheral vascular tone. Although atropine, calcium, insulin, glucagon, isoproterenol, dopamine, epinephrine, norepinephrine, and phosphodiesterase inhibitors have been used with reported success in CCB-poisoned patients, no single intervention has consistently demonstrated efficacy. It is also important to be aware that certain treatment such as vasopressors may be detrimental with long-term use, so these should be avoided when there are more effective and safer treatment options.

Although therapy for hypotension and bradycardia should begin with crystalloids and atropine, most critically poisoned patients will not respond to these initial efforts and will require further pharmacotherapy. While it would be ideal to initiate each therapy individually and monitor the patient's hemodynamic response, in the most critically ill patients, multiple therapies should be administered simultaneously. A reasonable treatment sequence based on existing data and clinical experience should initially consist of isotonic fluids, atropine, glucagon, and calcium. If the patient does not respond to these initial treatments, hyperinsulinemia-euglycemic therapy should be initiated. In cases of refractory shock or in cardiac arrest, the use of 20% intravenous fat emulsion should be considered. The use of vasopressors such as norepinephrine or dopamine can result in tissue ischemia with long-term use and thus should be avoided. Phosphodiesterase inhibitors such as inamrinone, milrinone, and enoximone have been used to treat CCB poisoning.^{54,82,103} These xenobiotics inhibit the breakdown of cAMP by phosphodiesterase, thereby increasing intracellular cAMP concentrations, resulting in increased cardiac output. Despite some reported success, phosphodiesterase inhibitors are not readily available, and there are other xenobiotics that are more effective and easier to utilize (Fig. 61–2).

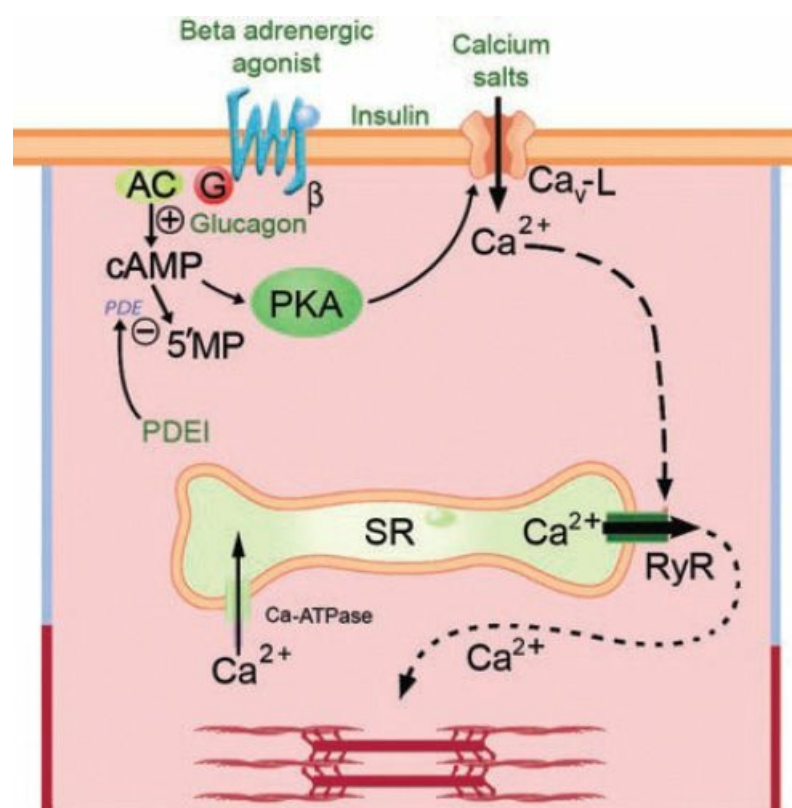


FIGURE 61–2. Myocardial toxicity of calcium channel blockers and use of antidotal therapies. Calcium channel blockers

reduce calcium ion influx through the L-type calcium channel ($\text{Ca}_v\text{-L}$) and thus reduce contractility. The entry of calcium via voltage-sensitive channels ($\text{Ca}_v\text{-L}$) initiates a cascade of events that result in actin-myosin coupling and contractions. Mechanisms to increase intracellular calcium include recruitment of new or dormant calcium channels by increasing cyclic adenosine monophosphate (cAMP) by stimulating its formation by adenylyl cyclase (AC) with glucagon (see text). The use of calcium salts may increase the calcium concentration gradient across the cellular membrane to further its influx and improve contractility. The mechanism by which insulin therapy enhances inotropy is not fully known. $5'\text{MP} = 5'$ -monophosphate; PDEI = phosphodiesterase inhibitor; PKA = protein kinase A; RyR = ryanodine receptor; SR = sarcoplasmic reticulum.

Gastrointestinal Decontamination

Because CCB poisoning is a leading cause of poisoning fatality, attempts to prevent absorption from the GI tract should be strongly considered, assuming there are no contraindications for the described techniques below. This is particularly important if sustained-release CCBs are suspected. Patients who present early with minimal or no symptoms can have delayed cardiovascular toxicity, which can be profound and refractory to conventional treatment, making early GI decontamination a cornerstone in CCB management.

Induced emesis is contraindicated because CCB-poisoned patients can rapidly deteriorate. Orogastric lavage should be considered for all patients who present early (1–2 hours postingestion) after large ingestions and for those who are critically ill and require immediate endotracheal intubation. Although the effects of orogastric lavage following overdose of a sustained-release CCB have not been specifically studied, given the toxicity of CCB poisoning, orogastric lavage should still be strongly considered. When performing orogastric lavage in a CCB-poisoned patient, it is important to remember that lavage may increase vagal tone and potentially exacerbate any bradydysrhythmias.⁹⁴ Pretreatment with a therapeutic dose of atropine may therefore be desirable.

All patients with CCB ingestions should receive 1 g/kg of activated charcoal orally or via nasogastric tube as long as the airway is stable or protected. Multiple-dose activated charcoal (MDAC) (0.5 g/kg every 4–6 hours) without a cathartic should be administered for nearly all patients with either sustained-release pill ingestions or signs of continuing absorption. Although data are limited, there is no evidence that MDAC increases CCB clearance from the serum.⁷⁹ Rather, its efficacy may be a result of the continuous presence of activated charcoal throughout the GI tract, which adsorbs any active xenobiotic from its slow-release formulation. MDAC should not be administered to a patient with inadequate GI function (eg, hypotension, diminished peristalsis sounds (Antidotes in Depth: A1)).

WBI with polyethylene glycol solution (1–2 L/h orally or via nasogastric tube in adults, up to 500 mL/h in children) should be initiated for patients who ingest sustained-release products and for whom there are no contraindications.¹⁵ Administration should be continued until the rectal effluent is clear (Antidotes in Depth: A2).

Atropine

Atropine is often first-line medication for patients with symptomatic bradycardia from xenobiotic poisoning such as organic phosphorus compounds, β -adrenergic antagonists, and calcium channel blockers. While the use of atropine improved both heart rate and cardiac output in an early dog model of verapamil poisoning and a few patients with bradycardia from CCB poisoning,^{30,77} reports of patients with severe CCB poisoning demonstrate atropine to be largely ineffective.^{45,74,89} The decreased effectiveness may be largely due to the negative inotropic effects and/or peripheral vasodilation of CCBs. Given its availability, familiarity, efficacy in mild poisonings, and safety profile, atropine should be considered as initial therapy in patients with symptomatic bradycardia.

Dose. The dosing of atropine for xenobiotic induced bradycardia is similar to the dose used for Advanced Cardiac Life Support. Dosing should begin with 0.5 to 1.0 mg (minimum of 0.1 mg; 0.02 mg/kg in children) intravenously every 2 or 3 minutes up to a maximum dose of 3 mg in all patients with symptomatic bradycardia. However, treatment failures should be anticipated in severely poisoned patients. In patients in whom whole-bowel irrigation (WBI) or MDAC will be used, the use of atropine must be carefully considered, weighing the potential benefits of improved heart rate, and thus cardiac output, against the anticholinergic effects with potential decreased GI motility.

Calcium

Ca^{2+} is another treatment often utilized for CCB poisoning to increase in extracellular Ca^{2+} concentration with an increase in transmembrane concentration gradient. Pretreatment with intravenous Ca^{2+} prevents hypotension without diminishing the antidysrhythmic efficacy prior to therapeutic verapamil use in reentrant supraventricular tachydysrhythmias.^{22,88} This also is observed with CCB poisoning where Ca^{2+} tends to improve blood pressure more than heart rate. Experimental models have also demonstrated the utility of Ca^{2+} salts with CCB poisoning. In verapamil-poisoned dogs, improvement in inotropy and blood pressure was demonstrated after increasing the serum Ca^{2+} concentration by 2 mEq/L with an intravenous infusion of

10% calcium chloride (CaCl_2) at 3 mg/kg/min.^{30,36}

Clinical experience demonstrates that Ca^{2+} reverses the negative inotropy, impaired conduction, and hypotension in many humans poisoned by CCBs.^{56,60,79} Unfortunately, this effect is often short lived, and more severely poisoned patients may not improve significantly with Ca^{2+} administration alone.^{18,45,83} Although some authors believe that these failures might represent inadequate dosing, optimal effective dosing of Ca^{2+} is unclear and they recommend repeat doses of Ca^{2+} to markedly increase the serum ionized Ca^{2+} concentrations.^{42,56} The excessive use of Ca^{2+} can result in significant complications, particularly if a Ca^{2+} infusion is used.⁸⁷ Caution should be exercised in the administration of Ca^{2+} in patients who may have suspected acute cardioactive steroid poisoning as a cause of their bradycardia.¹⁴ The use of Ca^{2+} in the setting of cardioactive steroid poisoning may result in cardiac complications such as asystole (Chap. 65).

Dose. Recommendations for poisoned adults include an initial intravenous infusion of approximately 13 to 25 mEq of Ca^{2+} (10–20 mL of 10% CaCl_2 or 30–60 mL of 10% Ca^{2+} gluconate) followed by either repeat boluses every 15 to 20 minutes up to three to four doses or a continuous infusion of 0.5 mEq/kg/h of Ca^{2+} (0.2–0.4 mL/kg/h of 10% CaCl_2 chloride or 0.6–1.2 mL/kg/h of 10% Ca^{2+} gluconate) (Antidotes in Depth: A29). Careful selection and attention to the type of Ca^{2+} used is critical for dosing. Although there is no difference in efficacy of CaCl_2 or calcium gluconate, 1 g of CaCl_2 contains 13.4 mEq of Ca^{2+} , which is about three times the 4.65 mEq found in 1 g of calcium gluconate. Thus, in order to administer equal doses of Ca^{2+} , three times the volume of calcium gluconate compared with that of CaCl_2 is required. The main limitation of using CaCl_2 , however, is that it has significant potential for causing tissue injury if extravasated, so administration should ideally be via central venous access. Adverse effects of intravenous Ca^{2+} include nausea, vomiting, flushing, constipation, confusion, hypercalcemia, and hypophosphatemia.

Glucagon

Glucagon is an endogenous polypeptide hormone secreted by the pancreatic alpha-cells in response to hypoglycemia and catecholamines. In addition, it has significant inotropic and chronotropic effects (Antidotes in Depth: A18).^{17,92,108} Glucagon is a therapy of choice for β -adrenergic antagonist poisoning (Chap. 62) because of its ability to bypass the β -adrenergic receptor and activate adenylate cyclase via a G_s protein in the myocardium.¹⁰⁵ Thus, glucagon is unique in that it is functionally a “pure” β_1 agonist, with no peripheral vasodilatory effects (Fig. 61–2). There are reports of both successes and failures of glucagon in CCB-poisoned patients who failed to respond to fluids, Ca^{2+} , or dopamine and dobutamine.^{19,23,37,45}

Dose. Dosing for glucagon is not well established.⁶ An initial dose of 3 to 5 mg IV, slowly over 1 to 2 minutes, is reasonable in adults, and if there is no hemodynamic improvement within 5 minutes, retreatment with a dose of 4 to 10 mg may be effective. The initial pediatric dose is 50 $\mu\text{g/kg}$. Because of the short half-life of glucagon, repeat doses may be useful. A maintenance infusion should be initiated once a desired effect is achieved. Adverse effects include vomiting and hyperglycemia, particularly in diabetics or during continuous infusion. In addition, patients who receive repeat administration develop tachyphylaxis, which is an acute decrease in response to a drug after repeated administration.

Insulin-Euglycemia Therapy

Insulin-euglycemia or high-dose insulin-euglycemia (HIE) therapy has become the treatment of choice for patients who are severely poisoned by CCBs. Healthy myocardial tissue relies predominantly on free fatty acids for its metabolic needs, and CCB poisoning forces it to become more carbohydrate dependent.^{49,50,52,53} At the same time, CCBs inhibit Ca^{2+} -mediated insulin secretion from the β -islet cells in the pancreas, making glucose uptake in myocardial cells dependent on passive diffusion down a concentration gradient rather than insulin-mediated active transport.²⁰ In addition, there is evidence that the CCB-poisoned myocardium also becomes insulin resistant, possibly by dysregulation of the phosphatidylinositol 3 kinase pathway (Antidotes in Depth: A17). This may prevent normal recruitment of insulin-responsive glucose transporter proteins. The combination of inhibited insulin secretion and impaired glucose utilization may explain why severe CCB toxicity often produces significant hyperglycemia.^{51,52}

Many CCB-poisoned patients have been successfully treated with HIE therapy as demonstrated by improved hemodynamic function, mainly resulting from improved contractility, with little effect on heart rate. There are also reports of the failure of this treatment, but this may represent initiation of therapy in terminally ill patients with multiple organ failure.^{28,45}

Dose. Although the dose of insulin is not definitively established, therapy typically begins with a bolus of 1 unit/kg of regular human insulin along with 0.5 g/kg of dextrose. If blood glucose is greater than 300 mg/dL (16.65 mmol/L), the dextrose bolus is unnecessary. An infusion of regular insulin should follow the bolus starting at 1.0 units/kg/h titrated up to 2 units/kg/h if no improvement after 30 minutes. Some authors advocate the use of even higher doses (10 units/kg) of

insulin.²⁵ A continuous dextrose infusion, beginning at 0.5 g/kg/h, should also be started. Glucose should be monitored every 30 minutes for the first 4 hours and titrated to maintain euglycemia. The response to insulin is typically delayed for 15 to 60 minutes, so the use of HIE should be considered very early in the patient's course if severe CCB poisoning is suspected. Primary complications of HIE include hypoglycemia and hypokalemia from intracellular shifting of potassium. It is essential to note that the development of hypoglycemia is an indication to increase glucose delivery rather than decrease the insulin infusion rate.

Intravenous Fat Emulsion

Intravenous fat emulsion (IFE) has been used as a source of parenteral nutrition and as a diluent for intravenous drug delivery of highly lipophilic medications such as propofol and liposomal amphotericin.²⁴ The use of IFE as an antidote is most extensively studied for the treatment of local anesthetic toxicity, specifically from bupivacaine, but has been utilized in overdoses from other lipophilic drugs such as psychiatric medication, calcium channel blockers, and β -adrenergic antagonists.

IFE is a white, milky liquid composed of two types of lipids, triglycerides and phospholipids. It is sterile and nonpyrogenic with a pH of about 8 (range, 6–9). IFEs are isotonic solutions (260–310 mOsm/L) and are available in 5%, 10%, 20%, and 30% solutions.⁹⁷ There are three proposed mechanisms of action for IFE: activation of ion channels (calcium); enhancement of intracellular metabolism⁹⁵; and acting as a lipid sink to sequester lipid-soluble drugs. The latter mechanism is the most likely explanation based on existing literature.

An important property of medications that may determine the effectiveness of IFE is lipophilicity. Lipophilicity means the tendency of a drug to partition between lipophilic organic phase and the polar aqueous phase, and value of lipophilicity most commonly refers to logarithm of partition coefficient P (logP) between these two phases. For ionizable compounds, the partition is changed as a function of pH; this relationship is called a distribution constant (logD) or sometimes also as an apparent partition coefficient. Drugs that are highly lipophilic may benefit more from the use of IFE in severe poisoning. Table 61–3 lists major CCBs with their logD and logP values.

TABLE 61–3. LogP and LogD of Commonly Available Calcium Channel Blockers

<i>Calcium Channel Blocker</i>	<i>LogP</i>	<i>LogD at pH 7</i>
Amlodipine	3.72	2.00
Bepridil	6.43	4.27
Diltiazem	4.53	2.64
Felodipine	4.92	4.92
Isradipine	3.68	3.67
Nicardipine	5.22	4.68
Nimodipine	3.94	3.94
Verapamil	4.91	2.91

Existing experimental evidence supports that IFE decreases the toxicity of a few lipid-soluble drugs, most notably bupivacaine.^{100,101} Pretreatment with IFE also increased the dose of certain medications to cause toxicity.¹⁰² Other models suggest that IFE is an effective therapy for CCB-poisoned patients. In a controlled study of rodents that were poisoned with

verapamil, the use of IFE resulted in both increased survival and heart rate when compared to the control groups.^{9,70,93} IFE was also used on a patient with severe verapamil poisoning who failed Ca^{2+} and HIE but when given IFE showed improvement and survival. Serum verapamil concentrations were measured before and after IFE treatment. There was a decrease in verapamil after IFE administration once the lipid was removed from the samples, which demonstrate sequestration of verapamil²⁸ (Antidotes in Depth: A20).

Dose. The recommended dose of IFE is a 1.5 mL/kg bolus. The bolus can be repeated several times for persistent asystole followed by an infusion of 0.25 mL/kg/min or 15 mL/kg/h to run for 30 to 60 minutes. IFE has only traditionally been given to patients in extremis from an overdose, but at this time IFE should be considered in patients who are persistently unstable despite the use of other therapies such as HIE.

Adjunctive Pharmacologic Treatment

Other pharmacotherapies have been studied in the setting of CCB poisoning. There are limited data with these therapies, and they should be considered only when all of the above treatments have failed. Digoxin has been experimentally evaluated in CCB poisoning since it raises the intracellular Ca^{2+} concentration.^{7,8} In a canine model of verapamil poisoning, digoxin, in conjunction with atropine or Ca^{2+} , improved both systolic blood pressure and myocardial inotropy.⁷ However, because digoxin requires a significant amount of time to distribute into tissue, and because limited efficacy data and no safety data have yet been collected, more evaluation is needed before digoxin is administered to patients with CCB poisoning. Another xenobiotic that has been utilized as a treatment for CCB poisoning is levosimendan. Levosimendan is a Ca^{2+} sensitizer used in the management of acutely decompensated congestive heart failure. While there are reported cases of success with the use of this drug, there is also existing experimental evidence that does not support its use.^{2,68,96}

Most recently, methylene blue was reported in a confirmed ingestion of amlodipine poisoning in a patient that failed conventional therapy, including HIE treatment. A Swan-Ganz catheter confirmed pure vasodilatory shock, which responded to methylene blue (2 mg/kg).⁴⁵ Methylene blue is also reported with success in a case of a mixed β -blocker and CCB overdose,⁴ and it is used in other states of refractory vasodilatory shock such as anaphylaxis and sepsis due to inhibition of methylene blue along the nitric oxide–cyclic guanosine monophosphate pathway. There is some evidence to suggest certain dihydropyridines such as amlodipine mediate its vasodilatory effects via nitric oxide, but the importance of this pathway in acute poisoning is unclear. Further investigation is required before methylene blue can routinely be recommended in patients with CCB poisoning.

Inotropes and Vasopressors

Catecholamines are often administered once first-line therapy such as atropine, Ca^{2+} , glucagon, and isotonic fluids fail. There are numerous cases that describe either success or failure with various agents, including epinephrine, norepinephrine, dopamine, isoproterenol, dobutamine, and vasopressin.^{18,37,41,61} Based on experimental and clinical data, no single xenobiotic is consistently effective. The variability in response is from the differences of CCB involved, coingestants with other cardioactive medications, and patient response. CCB poisoning may involve the myocardium (verapamil and diltiazem) mediated by β_1 -adrenergic receptors, resulting in negative chronotrophy/inotrophy and/or peripheral smooth muscle relaxation (dihydropyridines) with vasodilation mediated by α_1 -adrenergic receptors. Despite variable success in CCB poisoning, the existing data described previously show that all vasopressors are generally inferior with significantly more adverse effects such as tissue ischemia with long-term use.

Adjunctive Hemodynamic Support

The most severely CCB-poisoned patients may not respond to any pharmacologic intervention. Transthoracic or intravenous cardiac pacing may be required to improve heart rate, as several case reports demonstrate.^{89,99} However, in a prospective cohort of CCB poisonings, two of four patients with significant bradycardia requiring electrical pacing had no electrical capture.⁷⁷ In addition, even if electrical pacing is effective in increasing the heart rate, blood pressure often remains unchanged.^{40,41}

Intraaortic balloon counterpulsation is another invasive supportive option to be considered in CCB poisoning refractory to pharmacologic therapy.⁴⁷ Intraaortic balloon counterpulsation was used successfully to improve cardiac output and blood pressure in a patient with a mixed verapamil and atenolol overdose.²⁹

Severely CCB-poisoned patients have also been supported for days and subsequently recovered fully with much more invasive and technologically demanding extracorporeal membrane oxygenation (ECMO) and emergent open and percutaneous cardiopulmonary bypass.^{40,80} The major limitation of all these technologies, however, is that they are available only at tertiary care facilities.

Molecular adsorbents recirculating system (MARS) therapy is a specific extracorporeal albumin dialysis that is reported in the treatment of severe CCB poisoning. MARS therapy has the unique ability to selectively remove from

circulation protein-bound xenobiotics that are not cleared by conventional hemodialysis. The use of MARS therapy is under current investigation with *Amanita* poisoning but reportedly was successfully utilized in three patients with severe nondihydropyridine CCB poisoning.⁷²

DISPOSITION

Patients who manifest signs or symptoms of toxicity should be admitted to an intensive care setting. Because of the potential for delayed toxicity, patients who ingest sustained-release products should be admitted for 24 hours to a monitored setting, even if asymptomatic. This precautionary approach is particularly important for toddlers and small children in whom even one or a few tablets may produce significant toxicity. Criteria for safe discharge or medical clearance apply only to patients with a reliable history of an ingestion of an “immediate-release” preparation who have received adequate GI decontamination, had serial ECGs over 6 to 8 hours that have remained unchanged, and are asymptomatic.

SUMMARY

- The hallmarks of CCB toxicity include bradydysrhythmias and hypotension, which are an extension of their pharmacologic effects.
- Although most patients develop symptoms of hypoperfusion, such as lightheadedness, nausea, or fatigue, within hours of a significant ingestion, ingestion of sustained-release formulations may result in significant delays in any hemodynamic consequences and may prolong toxicity.
- Aggressive decontamination of patients with exposures to sustained-release products should begin as soon as possible and should not be delayed while awaiting signs of toxicity.
- The early use of high-dose insulin therapy should be instituted with attempts to avoid the use of vasopressors as it requires time for the effects to occur. In cases of severe toxicity, the use of intravenous fat emulsion therapy should be considered.
- Patients who fail to respond to all pharmaceutical interventions should be considered for adjunctive hemodynamic support whenever available.

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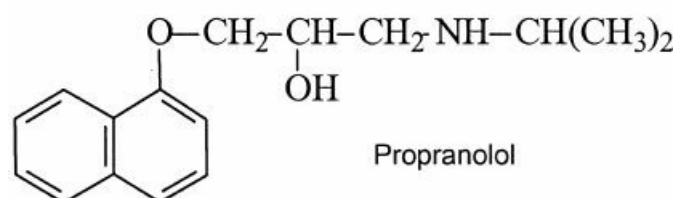
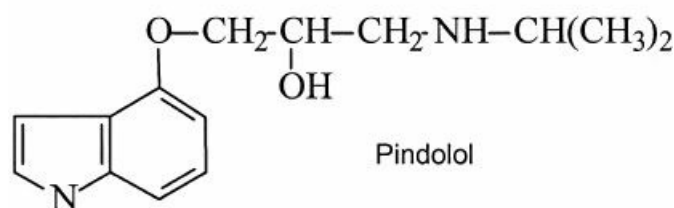
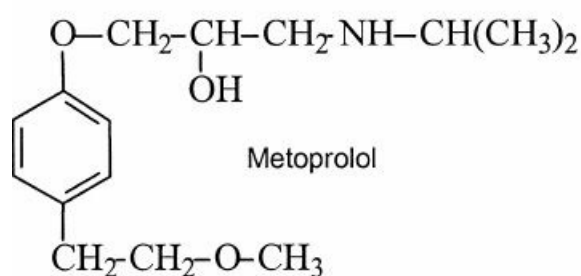
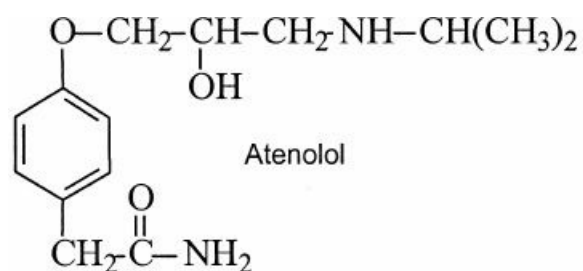
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62 β -ADRENERGIC ANTAGONISTS

Jeffrey R. Brubacher



HISTORY

In 1948, Raymond Alquist postulated that the cardiovascular actions of epinephrine, hypertension and tachycardia, were best explained by the existence of two distinct sets of receptors that he generically named α and β receptors. At that time, the contemporary “antiepinephrine” xenobiotics such as phenoxybenzamine reversed the hypertension but not the tachycardia associated with epinephrine. According to Alquist’s theory these xenobiotics acted at the α receptors. The β receptors, in his schema, mediated catecholamine induced tachycardia. The British pharmacist, Sir James Black was influenced by Alquist’s work and recognized the potential clinical benefit of a β -adrenergic antagonist. In 1958, Black synthesized the first β -adrenergic antagonist, pronethalol. This drug was briefly marketed as Alderlin, named after Alderly Park, the research headquarters of ICI Pharmaceuticals. Pronethalol was discontinued because it produced thymic tumors in mice. Propranolol was soon developed and marketed as Inderal (an incomplete anagram of Alderlin) in the United Kingdom in 1964.^{22,199} and in the United States in 1973. Prior to the introduction of β -adrenergic antagonists, the management of angina was limited to medications such as nitrates, which reduced preload through dilation of the venous capacitance vessels and increased myocardial oxygen delivery by vasodilation of the coronary arteries. Propranolol gave clinicians the ability to decrease myocardial oxygen utilization. This new approach proved to decrease morbidity and mortality in patients with ischemic heart disease.¹¹² New drugs soon followed and by 1979 there were ten β -adrenergic antagonists available in the United States.⁵⁴ Unfortunately it soon became apparent that these medications were dangerous

when taken in overdose and by 1979 cases of severe toxicity and death from β -adrenergic overdose were reported.⁵⁴ Today there are nineteen β -adrenergic antagonists approved by the US Food and Drug Administration, and other β -adrenergic antagonists are available worldwide (Table 62–1). The pharmacology, toxicology, and poison management issues discussed in this chapter are applicable to all of these drugs. They are commonly used in the treatment of cardiovascular disease: hypertension, coronary artery disease, and tachydysrhythmias. Additional indications for β -adrenergic antagonists include congestive heart failure, migraine headaches, benign essential tremor, panic attack, stage fright, and hyperthyroidism. Ophthalmic preparations containing β -adrenergic antagonists are used in the treatment of glaucoma.⁸⁰

TABLE 62–1. Pharmacologic Properties of the β -Adrenergic Antagonists

	Adrenergic Blocking Activity	Partial Agonist Activity (ISA)	Membrane Stabilizing Activity	Vasodilating Property	Log <i>P</i> ^a	Protein Binding (%)	Oral Bioavailability (%)	Half-Life (hours)	Metabolism	Volume of Distribution (L/kg)
Acetazolol	β ₁	Yes	Yes	No	0.53	25	40	2–4	Hepatic/renal	1.2
Atenolol	β ₁	No	No	No	–2.03	<5	40–50	5–9	Renal	1
Betasolol (tablets and ocular drops)	β ₁	No	Yes	Yes (calcium channel blockade)	0.56	50	30–90	14–22	Hepatic/renal	4.9–8.8
Bisoprolol	β ₁	No	No	No	0.11	30	80	9–12	Hepatic/renal	3.2
Bucindolol	α, β ₁ , β ₂	β ₁ agonism		Yes (β ₁ agonism and α ₁ blockade)	—		30	8 ± 4.5	Hepatic	//
Carteolol ophthalmic	β ₁ , β ₂	Yes	No	Yes, partial (β ₁ agonism and nitric oxide mediated)	–0.42	30	35	5–6	Renal	//
Carvedilol (long acting form available)	α, β ₁ , β ₂	No	Yes	Yes (α ₁ blockade, calcium channel blockade)	3.16	–98	25–35	6–10	Hepatic	115
Celiprolol	α, β ₁	β ₁ agonism		Yes (β ₁ agonism, nitric oxide mediated)	—	22–24	30–70	5	Hepatic	//
Esmolol	β ₁	No	No	No	–0.22	50	//	– 8 minutes	RBC esterases	2
Labetalol	α, β ₁ , β ₂	β ₁	Low	Yes (α ₁ blockade, β ₁ agonism)	0.99	50	20–33	4–8	Hepatic	9
Levobundolol ophthalmic	β ₁ , β ₂	No	No	No	0.56	//	//	6	//	//
Metipranolol ophthalmic	β ₁ , β ₂	No	No	No	0.53	//	//	3–4	//	//
Metoprolol (long acting form available)	β ₁	No	Low	No	–0.34	10	40–50	3–4	Hepatic	4
Nadolol	β ₁ , β ₂	No	No	No	–0.84	20–30	30–35	10–24	Renal	2
Nebivolol	β ₁	No		Yes (nitric oxide mediated)	—	98	12–96	8–32	Hepatic	10–40
Oxprenolol	β ₁ , β ₂	Yes	Yes	No	—	80	20–70	1–3	Hepatic	1.3
Pembolol	β ₁ , β ₂	Yes	No	No	2.05	90	– 100	5	Hepatic/renal	//
Pindolol	β ₁ , β ₂	Yes	Low	No	–0.19	50	75–90	3–4	Hepatic/renal	2
Propranolol (long acting form available)	β ₁ , β ₂	No	Yes	No	0.99	90	25	3–5	Hepatic	4
Sotalol	β ₁ , β ₂	No	No	No	–1.82	0	90	9–12	Renal	2
Timolol (tablets and ophthalmic)	β ₁ , β ₂	No	No	No	–1.99	60	75	3–5	Hepatic/renal	2

Agents in italics are not FDA approved. Information from References 35, 57, 75, 140, 146, 148, 152, 270, 273. The symbol “//” indicates that information is not available.

^aLog *P* is the octanol/water partition coefficient at pH 7.

EPIDEMIOLOGY

Intentional β -adrenergic antagonist overdose, although relatively uncommon, continues to account for a number of deaths annually. From 1985 to 1995, there were 52,156 β -adrenergic antagonist exposures reported to the American Association of Poison Control Centers (AAPCC; Chap. 136). These exposures accounted for 164 deaths of which β -adrenergic antagonists were implicated as the primary cause of death in 38. The other fatalities could not be clearly ascribed to β -adrenergic antagonists due to cardioactive coingestants such as calcium channel blockers or other factors. Children under the age of 6 accounted for 19,388 exposures, but no fatalities were reported in this age group. The youngest fatality reported in this series was aged 7 years. It is interesting to note that more than one-half of the fatalities developed cardiac arrest after reaching health care personnel.¹³³ The number of exposures to β -adrenergic antagonists reported to the AAPCC has increased annually from 9500 in 1999 to more than 23,000 in 2010. Just under one-half of these exposures were single substance ingestions. Each year since 2006, single substance exposures to β -adrenergic antagonists have resulted in between 54 and 70 cases with major morbidity and three to six fatalities (Chap. 136).

Compared with the other β -adrenergic antagonists, propranolol accounts for a disproportionate number of cases of self-poisoning^{36,167} and deaths.^{109,133} This may be explained by the fact that propranolol is frequently prescribed to patients with diagnoses, such as anxiety, stress, hyperthyroidism, and migraine, who may be more prone to suicide attempts.¹⁶⁷ Propranolol is also more lethal due to its lipophilic and membrane stabilizing properties.^{75,167}

PHARMACOLOGY

Cardiac Cycle

Normal cardiac electrical activity involves a complex series of ion fluxes that result in myocyte depolarization and repolarization. Cardiac electrical activity is coupled to myocyte contraction and relaxation respectively by increases and decreases in intracellular calcium concentrations. Cardiac electrical and mechanical activity is closely regulated by the autonomic nervous system.

Under normal conditions, heart rate is determined by the rate of spontaneous discharge of specialized pacemaker cells that comprise the sinoatrial (SA) node (Fig. 62–1). Pacemaker cells are also found in the atrioventricular (AV) node and in Purkinje fibers. Spontaneous pacemaker cell depolarization has traditionally been ascribed to inward cation current through “pacemaker channels.”^{2,43} Recent research suggests that spontaneous depolarization of pacemaker cells involves several mechanisms including a “membrane clock,” consisting of “pacemaker channels” and other inward cation channels located on the cell membrane, and a “calcium clock,” which is driven by rhythmic release of calcium from the sarcoplasmic reticulum.^{35,111,117,140} β -Adrenergic stimulation significantly increases the rate of pacemaker cell depolarization by phosphorylating proteins within the sarcoplasmic reticulum, thereby increasing the rate of the “calcium clock.” There is also a direct, phosphorylation-independent action of cyclic adenosine monophosphate (cAMP) at the pacemaker channels, which increases the rate of the “membrane clock.”³⁵ Depolarization of cells in the SA node spreads to surrounding atrial cells where it triggers the opening of fast sodium channels. This initiates an electric current that spreads from cell to cell along specialized pathways to depolarize the entire heart. This depolarization, referred to as cardiac excitation, is linked to mechanical activity of the heart by the process of electrical–mechanical coupling described below (Chap. 16).

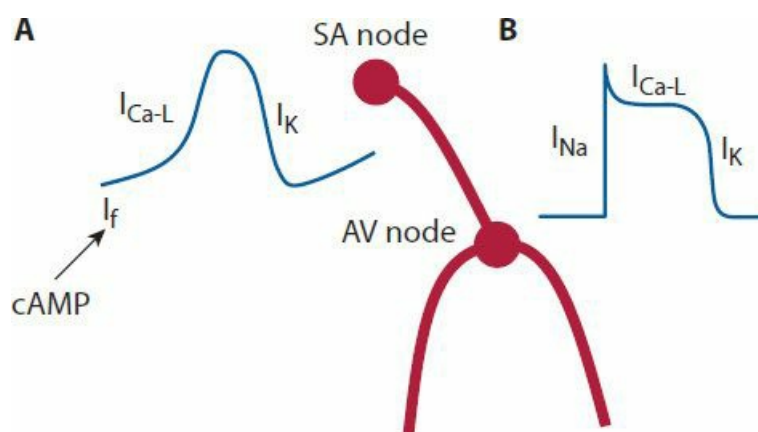


FIGURE 62–1. Cardiac conduction system: A. The cardiac cycle begins when pacemaker cells in the sinoatrial node depolarize spontaneously. Traditionally, this depolarization has been attributed to inward “pacemaker” currents (I_f). There is recent evidence that that pacemaker cell depolarization may also be driven by cyclical calcium release from a “calcium clock” in the sarcoplasmic reticulum (SR). β -Adrenergic stimulation increases both the frequency of the “calcium clock” by a phosphokinase A (PKA) mediated effect and the magnitude of the pacemaker current secondary to a direct effect of cAMP. These effects both increase the heart rate. Cholinergic stimulation has the opposite effects and results in

bradycardia. Pacemaker cells lack fast sodium channels. Pacemaker cell depolarization triggers the opening of voltage sensitive L-type calcium channels (I_{Ca-L}) and the impulse is transmitted to surrounding cells. B. Coordinated SA nodal depolarization generates an impulse sufficient to open fast sodium channels in surrounding atrial tissue and the impulse spreads along specialized pathways to depolarize the atria and ventricles.

Myocyte Calcium Flow and Contractility

During systole, voltage sensitive slow calcium channels (L-type channels) on the myocyte membrane open in response to cell depolarization allowing calcium to flow down its concentration gradient into the myocyte (Fig. 62–2). Invaginations of the myocyte membrane, known as T-tubules, place L-type calcium channels in close approximation to calcium release channels (ryanodine receptors {RyRs}) on the sarcoplasmic reticulum (SR). The local increase in calcium concentration that follows the opening of a single L-type calcium channel on the cell membrane triggers the opening of the associated RyR channels, resulting in a large release of calcium from the SR, a phenomenon known as calcium-induced calcium release.^{67,224} Myocytes contain tens of thousands of couplons, clusters of L-type calcium channels and RyR channels. The calcium released from one couplon is not sufficient to trigger firing of neighboring couplons.³⁰ Organized myocyte contraction requires synchronized release of calcium from numerous couplons throughout the myocyte. This process depends on membrane depolarization to synchronize opening of L-type channels and subsequent calcium release. This occurs rapidly throughout an extensive network of T-tubules that spans the myocyte.⁸⁶ Following release from the sarcoplasmic reticulum, cytosolic calcium binds to troponin C and allows actin myosin interaction and subsequent myocyte contraction. The strength of contraction is proportional to the amount of calcium release from the SR during depolarization, which depends, in part, on the magnitude of SR calcium stores. Actin–myosin interaction is also modulated by β -adrenergic-mediated troponin phosphorylation, ischemia, intracellular pH, and myofilament stretch.^{9,17,19,209}

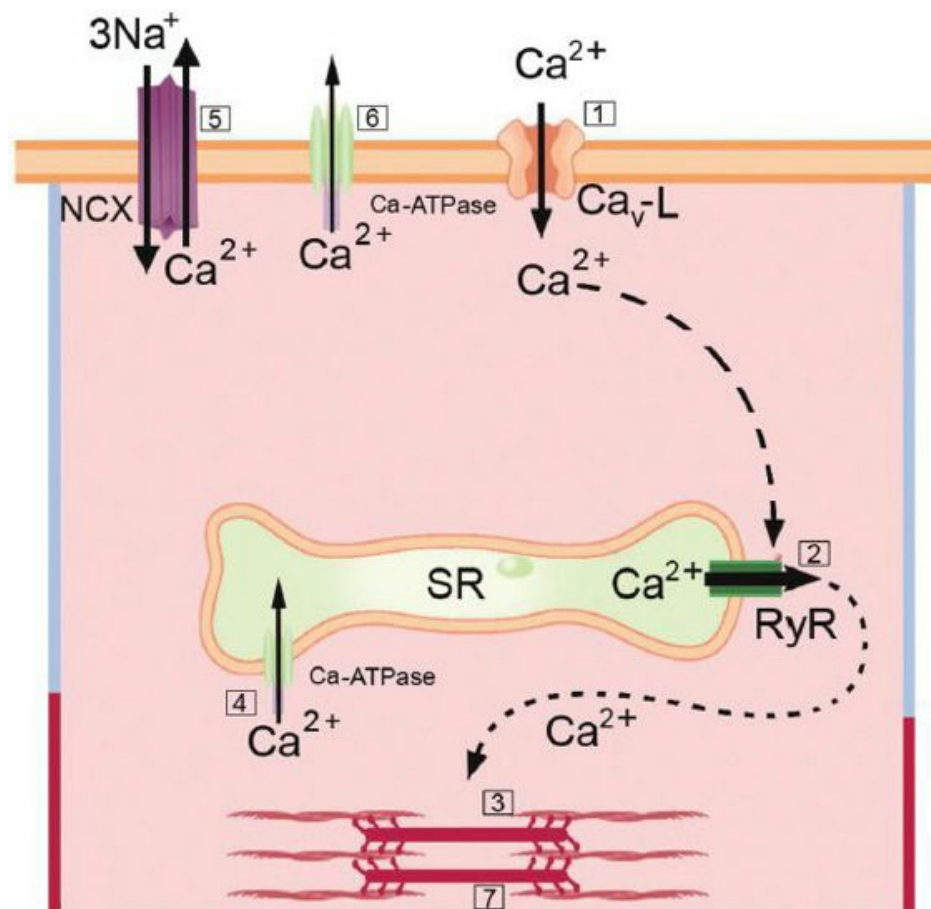


FIGURE 62–2. Fluctuations in calcium concentrations couple myocyte depolarization with contraction and myocyte repolarization with relaxation. [1] Depolarization causes voltage sensitive calcium channels to open and calcium to flow down its concentration gradient into the myocyte. [2] This calcium current triggers the opening of calcium release channels in the sarcoplasmic reticulum and calcium pours out of the sarcoplasmic reticulum (SR). The amount of calcium released from the SR is proportional to the initial inward calcium current and to the amount of calcium stored in the SR. [3] At rest, actin–myosin interaction is prevented by troponin. When calcium binds to troponin, this inhibition is removed, actin and myosin slide relative to each other, and the cell contracts. Following contraction, calcium is actively removed from the myocyte to allow relaxation. [4] Most calcium is actively pumped into the SR where it is bound to calsequestrin. Calcium stored in the SR is thus available for release during subsequent depolarizations. The sarcoplasmic calcium ATPase is inhibited by phospholamban (Fig. 62–3). [5] The calcium sodium antiporter couples the flow of three molecules of sodium flow in one direction to that of a single molecule of calcium in the opposite direction. This transporter is passively driven

by electrochemical gradients which usually favor the inward flow of sodium coupled to the extrusion of calcium. Extrusion of calcium is inhibited by high intracellular sodium or extracellular calcium concentrations and by cell depolarization. Under these conditions, the pump may “run in reverse.” [6] Some calcium is actively pumped from the cell by a calcium ATPase. [7] As myocyte calcium concentrations fall, calcium is released from troponin and the myocyte relaxes.

During diastole, several ion pumps actively remove calcium from the cytoplasm (Fig. 62–2). The most important of these are the sarcoplasmic reticulum calcium ATPase that pumps cytosolic calcium into the SR, and the calcium–sodium transporter that exchanges one calcium ion for three sodium ions with the extracellular fluid. The SR calcium ATPase is important for maintaining SR calcium stores and is modulated by β -adrenergic stimulation (see below). When calcium concentrations drop during diastole, calcium dissociates from troponin and relaxation occurs.^{15,17,18,19,187}

β -Adrenergic Receptors and the Heart

β -Adrenergic receptors are divided into β_1 , β_2 , and β_3 subtypes. In the healthy heart, approximately 80% of human cardiac β -adrenergic receptors are β_1 and 20% are β_2 . Human hearts may also contain a small number of β_3 -adrenergic receptors.^{28,60,61,150,177} The relative density of cardiac β_2 -adrenergic receptors increases with heart failure.^{28,200} β_1 -Adrenergic receptors mediate increased inotropy by a well-described pathway involving cyclic AMP and protein kinases (Fig. 62–3). β_1 -Adrenergic receptors are coupled to G_s proteins that activate adenylate cyclase when the receptor is stimulated. This increases intracellular production of cAMP, which binds to and activates protein kinase A and other cAMP-dependent protein kinases.¹²² Protein kinase A, in turn, phosphorylates important myocyte proteins, including phospholamban, the voltage sensitive calcium channels, the calcium release (RyR) channels, and troponin.^{17,28,70,187,204,209} Phosphorylation of the L-type calcium channel increases contractility by increasing the influx of calcium during each cell depolarization triggering greater release of calcium from the sarcoplasmic reticulum.^{169,190,197} Phospholamban inhibits the SR calcium ATPase. Phosphorylation of phospholamban removes this inhibition and increases the activity of the sarcoplasmic calcium ATPase, resulting in increased SR calcium stores and hence enhanced contractility.^{40,204} Improved activity of the SR calcium ATPase will also result in more rapid removal of cytoplasmic calcium during diastole and aid in myocyte relaxation. Phosphorylation of the RyR channels results in more rapid release of calcium from SR stores.^{17,187,209} Troponin phosphorylation facilitates calcium unbinding and thus improves cardiac performance by enhancing myocyte relaxation.^{3,15,123,204} β_1 -Adrenergic receptors increase chronotropy by an incompletely understood mechanism that may involve phosphorylation of SR proteins, resulting in an increased rate of calcium discharge from the SR^{140–142} in addition to direct cAMP interaction with membrane bound pacemaker channels.^{2,26} Although β -adrenergic stimulation acutely improves cardiac function, chronic β -adrenergic stimulation, acting through β_1 -adrenergic receptors, results in a number of detrimental effects, including calcium overload, increased risk of dysrhythmias, impaired excitation-contraction coupling, and myocyte apoptosis.^{17,28,230}

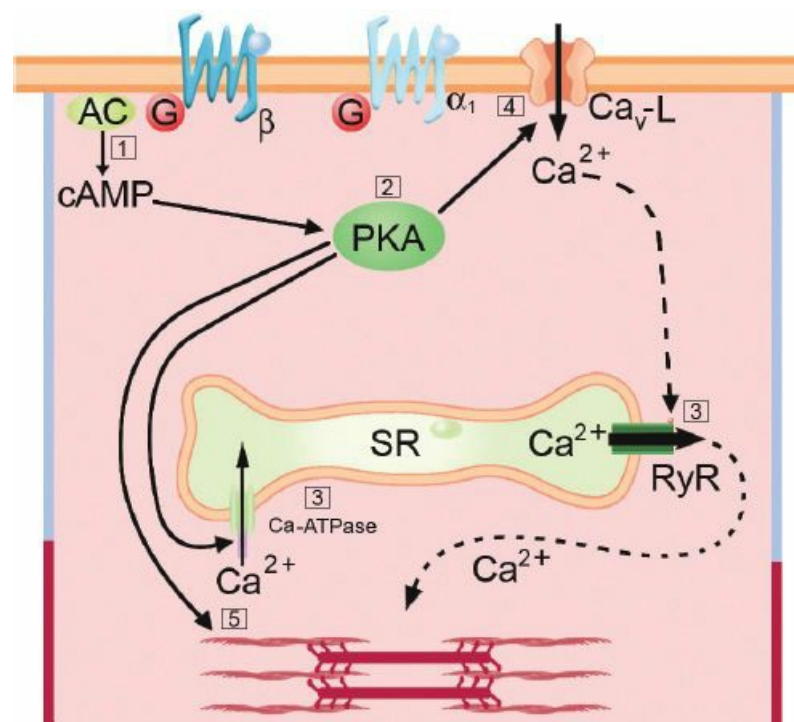


FIGURE 62–3. β_1 -adrenergic agonists are positive inotropes by virtue of their ability to activate protein kinase A (PKA). [1] β_1 -adrenergic receptors are coupled to G_s proteins, which activate adenyl cyclase when catecholamines bind to the

receptor. This causes increased formation of cAMP from ATP. [2] Increased cAMP concentrations activate PKA, which mediates the ultimate effects of β -adrenergic receptor stimulation by phosphorylating key intracellular proteins. [3] Phosphorylation of phospholamban disinhibits the sarcoplasmic reticulum (SR) calcium ATPase resulting in increased SR calcium stores available for release during subsequent depolarizations and phosphorylation of SR calcium release channels enhances calcium release from SR stores during contraction. [4] Phosphorylation of voltage sensitive calcium channels increases calcium influx through these channels during systole. [5] Troponin phosphorylation improves cardiac performance by facilitating calcium unbinding during diastole. β_2 Receptors are also coupled to G_s proteins and mediate positive inotropy through a cAMP mechanism. Increased cAMP directly increases heart rate (Fig. 62–1).

Cardiac β_2 -adrenergic receptors are dually linked to both excitatory G_s proteins and inhibitory G_i proteins.^{101,175,231} Under normal conditions, the G_s pathway predominates in human cardiac β_2 -adrenergic receptors and β_2 -adrenergic stimulation increases contractility, relaxation, and chronotropy through the protein kinase A pathway described above. However, in the failing heart, the inhibitory G_i protein pathway becomes dominant and β_2 -adrenergic stimulation inhibits cardiac function.^{28,73,187} Chronic β_2 -adrenergic stimulation may prevent myocyte apoptosis.²³⁰

Noncardiac Effects of β -Adrenergic Receptor Activation

β -Adrenergic agonists have important noncardiac effects. β -Adrenergic receptors mediate smooth muscle relaxation in several organs. Relaxation of arteriolar smooth muscle predominately by β_2 -adrenergic stimulation reduces peripheral vascular resistance and decreases blood pressure. This counteracts α -adrenergic-mediated arteriolar constriction. In the lungs, β_2 -adrenergic receptors mediate bronchodilation. Unfortunately, chronic β -adrenergic stimulation may cause adverse pulmonary effects, including mucous cell proliferation, hyperreactive airways, and inflammation.³⁷ Third-trimester uterine tone and contractions are inhibited by β_2 -adrenergic agonists, and gut motility is decreased by both β_1 - and β_2 -adrenergic stimulation. Chronic, high-dose β_2 -adrenergic stimulation causes skeletal muscle hypertrophy.¹⁰⁴

β -Adrenergic receptors play a role in the immune system. Mast cell degranulation is inhibited by β_2 -adrenergic stimulation, explaining the role of epinephrine in aborting and treating severe allergic reactions. Polymorphonuclear leukocytes demarginate in response to β -adrenergic stimulation, resulting in the increased white blood cell counts with catecholamine infusions or with increased endogenous release of epinephrine that occurs with pain or physiologic stress.

β -Adrenergic agonists also have important metabolic effects. Insulin secretion is increased by β_2 -adrenergic receptor stimulation. Despite increased insulin concentrations, the net effect of β_2 -adrenergic receptor stimulation is to increase glucose due to increased skeletal muscle glycogenolysis and hepatic gluconeogenesis and glycogenolysis. β_2 -Adrenergic receptors also cause glucagon secretion from pancreatic α cells.¹¹⁰ β -Adrenergic agonists act at fat cells to cause lipolysis and thermogenesis. Stimulation of adipocyte β -adrenergic receptors results in breakdown of triglycerides and release of free fatty acids. Skeletal muscle potassium uptake is increased by β_2 -adrenergic stimulation resulting in hypokalemia, explaining the role of β_2 -adrenergic agonists in the treatment of hyperkalemia. Finally, renin secretion is increased by β_1 -adrenergic stimulation, resulting in increased blood pressure.²²³

Effects of β -Adrenergic Antagonists

β -Adrenergic antagonists competitively antagonize the effects of catecholamines at β -adrenergic receptors and blunt the chronotropic and inotropic response to catecholamines. Bradycardia and hypotension may be severe in patients who take additional medications that impair cardiac conduction or contractility or in those with underlying cardiac or medical conditions that make them reliant on sympathetic stimulation. In addition to slowing the rate of SA node discharge, β -adrenergic antagonists inhibit ectopic pacemakers and slow conduction through atrial and AV nodal tissue. β -Adrenergic antagonists block the detrimental effects of chronic adrenergic overstimulation and have become standard of care for patients with all stages of compensated chronic heart failure, including patients with stable NYHA (New York Heart Association) class III or IV disease.^{1,66,226} β -Adrenergic blockade may exacerbate symptoms in patients with decompensated congestive heart failure but, in the absence of cardiogenic shock or symptomatic bradycardia, β -adrenergic antagonists should not be routinely discontinued in heart failure patients admitted to hospital.²²⁹ β -Adrenergic antagonists prevent adverse cardiac events in patients with recent myocardial infarctions but may be ineffective in patients with prior myocardial infarction, stable coronary artery disease, or risk factors for coronary artery disease.¹³

The antihypertensive effect of β -adrenergic antagonists is counteracted by a reflex increase in peripheral vascular resistance. This effect is augmented by the β_2 -adrenergic antagonism of nonselective β -adrenergic antagonists. By causing increased peripheral vascular resistance, β_2 -adrenergic antagonists may rarely worsen peripheral vascular disease.

Patients with reactive airways disease may suffer severe bronchospasm after using β -adrenergic antagonists due to loss of β_2 -adrenergic-mediated bronchodilation. Catecholamines inhibit mast cell degranulation through a β_2 -adrenergic

mechanism. Interference with this may predispose to life-threatening effects following anaphylactic reactions in atopic individuals.⁸⁹ β_2 -Adrenergic antagonists impair the ability to recover from hypoglycemia and may mask the sympathetic discharge that serves to warn of hypoglycemia. This combination of effects is dangerous for patients with diabetes at risk for hypoglycemic episodes.²²³

β_2 -Adrenergic antagonism inhibits catecholamine-mediated potassium uptake at skeletal muscle. This may cause slight elevations in serum potassium especially after exercise. Although β_2 -adrenergic stimulation augments insulin release, β -adrenergic antagonists seldom lower insulin concentrations and may actually cause hypoglycemia by interference with glycogenolysis and gluconeogenesis. These effects are important in patients with diabetes at risk for hypoglycemia. β -Adrenergic antagonists also alter lipid metabolism. Although the release of free fatty acids from adipose tissue is inhibited, patients taking nonselective β -adrenergic antagonists typically have increased plasma concentrations of triglycerides and decreases in high-density lipoproteins.²²³

PHARMACOKINETICS

The pharmacokinetic properties of the β -adrenergic antagonists depend in large part on their lipophilicity. Propranolol is the most lipid soluble of the β -adrenergic antagonists and atenolol is the most water soluble. The oral bioavailability of the β -adrenergic antagonists ranges from approximately 25% for propranolol to almost 100% for pindolol and penbutolol.

The highly lipid-soluble drugs cross lipid membranes rapidly and concentrate in adipose tissue. These properties allow rapid entry into the central nervous system (CNS), and typically result in large volumes of distribution. In contrast, highly water-soluble drugs, cross lipid membranes slowly, distribute in total body water, and tend to have less CNS toxicity. Volumes of distribution range from about 1 L/kg for atenolol to more than 100 L/kg for carvedilol.

The highly lipid soluble β -adrenergic antagonists are highly protein bound and poorly excreted by the kidneys. They require hepatic biotransformation before they can be eliminated and accumulate in patients with liver failure. By contrast, the water-soluble β -adrenergic antagonists tend to be slowly absorbed, poorly protein bound, and renally eliminated. They accumulate in patients with kidney failure. Esmolol, although water-soluble, is rapidly metabolized by red blood cell esterases and does not accumulate in patients with kidney failure. The half-life of esmolol is about 8 minutes. Half-lives of the other β -adrenergic antagonists range from about 2 hours for oxprenolol to as much as 32 hours for nebivolol. The β -adrenergic antagonists also differ in their β_1 -adrenergic selectivity, intrinsic sympathomimetic activity, and vasodilatory properties (Table 62–1).^{157,166,170,206,223}

β_1 Selectivity (Acebutolol, Atenolol, Betaxolol, Bisoprolol, Celiprolol, Esmolol, Metoprolol, Nebivolol)

β_1 -Selective antagonists may avoid some of the adverse effects of the non-selective antagonists. Short-term use of β_1 -adrenergic selective antagonists appears to be safe in patients with mild to moderately severe reactive airways.¹⁸¹ These drugs may be safer for patients with diabetes mellitus or peripheral vascular disease and may be more effective antihypertensives. Their β_1 -adrenergic selectivity, however, is incomplete, and adverse reactions secondary to β_2 -adrenergic antagonism may occur with therapeutic dosage as well as in overdose.^{124,223}

Membrane Stabilizing Effects (Acebutolol, Betaxolol, Carvedilol, Oxprenolol, Propranolol)

β -Adrenergic antagonists that inhibit fast sodium channels (also known as type I antidysrhythmic activity) are said to possess membrane-stabilizing activity. No significant membrane stabilization occurs with therapeutic use of β -adrenergic antagonists, but this property can contribute to toxicity in overdose.

Intrinsic Sympathomimetic Activity (Acebutolol, Carteolol, Oxprenolol, Penbutolol, Pindolol)

These medications act as partial agonists at β -adrenergic receptors and are said to have intrinsic sympathomimetic activity (ISA). This property is unrelated to β_1 -adrenergic selectivity. These drugs may avoid the dramatic decrease in resting heart rate that occurs with β -adrenergic antagonism in susceptible patients, but their clinical benefit is not demonstrated in controlled trials.^{50,57}

Potassium Channel Blockade (Acebutolol, Sotalol)

Sotalol is a nonselective β -adrenergic antagonist with low lipophilicity, no membrane stabilizing effect, and no ISA.

Sotalol is unique because of its ability to block the delayed rectifier potassium current responsible for repolarization. This prolongs the action potential duration and is manifested on the electrocardiogram (ECG) by a prolonged QT interval.⁸¹ The prolonged QT interval predisposes to torsade de pointes and ventricular dysrhythmias may complicate the therapeutic use of sotalol.¹⁰⁸ In patients taking sotalol therapeutically, torsade de pointes is most common in those who have kidney failure, use other drugs that prolong the QT interval, or have predisposing factors for QT prolongation such as hypokalemia, hypomagnesemia, bradycardia, or congenital QT prolongation.^{38,81} Some authors suggest that QT dispersion is a better predictor of sotalol induced torsade de pointes than QT prolongation alone (Chap. 17). A difference between the longest and shortest QT interval on 12-lead ECG of more than 100 milliseconds indicates an increased risk of torsade de pointes.³⁸ Acebutolol also prolongs the QT interval presumably secondary to blockade of outward potassium channels.¹²⁵

Vasodilation (Betaxolol, Bucindolol, Carteolol, Carvedilol, Celiprolol, Labetalol, Nebivolol)

Labetalol and the newer “third-generation” β -adrenergic antagonists (betaxolol, bucindolol, carteolol, carvedilol, celiprolol, nebivolol) are also vasodilators. Labetalol and carvedilol are nonselective β -adrenergic antagonists that also possess α -adrenergic antagonist activity. Nebivolol is a selective β_1 -adrenergic antagonist that causes vasodilation by release of nitric oxide.¹⁴³ Bucindolol, carteolol, and celiprolol vasodilate because they are agonists at β_2 -adrenergic receptors. Celiprolol and carteolol also vasodilate because of nitric oxide mediated effects. Bucindolol and celiprolol are not FDA approved. Carteolol is currently available as an ocular preparation. Betaxolol and carvedilol also have calcium channel blocking properties that result in vasodilation (Table 62–1). β -Adrenergic antagonists with vasodilating properties may be particularly beneficial for patients with congestive heart failure.¹⁶⁴ These drugs may also have a role in managing patients with coronary artery disease or peripheral vascular disease. Those drugs with β_2 -adrenergic agonist activity may prove useful for patients with reactive airways.

β -Adrenergic antagonists should not be given without appropriate α -adrenergic blockade in situations of catecholamine excess such as pheochromocytoma. In these conditions, β_2 -adrenergic-mediated vasodilation is essential to counteract α -adrenergic-mediated vasoconstriction. β -Adrenergic antagonists would result in “unopposed α ” adrenergic effect causing dangerous increases in vascular resistance. Even agents with combined α - and β -adrenergic antagonist properties can cause this problem. Labetalol, for example, is five to ten-fold more potent as a β -adrenergic antagonist than as an α -adrenergic antagonist. Theoretically, xenobiotics with β_2 -adrenergic agonist properties may avoid the “unopposed α ” effect, but their use in this situation has not yet been investigated.^{48,63,143,210,223}

Other Preparations (Ophthalmic Preparations, Sustained Release, Combined Products)

Therapeutic use of ophthalmic solutions containing β -adrenergic antagonists may cause systemic adverse effects such as bradycardia, high-grade AV block, heart failure, and bronchospasm.^{24,56,151,189,191,216,223}

An extended-release tablet containing a combination of the calcium channel blocker, felodipine, and metoprolol has been studied as an antihypertensive medication.^{69,85} This medication (Logimax, AstraZeneca) is marketed in more than 35 countries worldwide but is not available in the United States or Canada. Another combined β -adrenergic and calcium channel antagonist containing atenolol and nifedipine (Nif-Ten, AstraZeneca) is also used as an antihypertensive.⁴⁵

PATHOPHYSIOLOGY

Most of the toxicity of β -adrenergic antagonists is due to their ability to competitively antagonize the action of catecholamines at cardiac β -adrenergic receptors. The peripheral vascular effects of β -adrenergic antagonism are less prominent in overdose. β -Adrenergic antagonists also appear to have toxic effects independent of their action at catecholamine receptors. In catecholamine depleted, spontaneously beating isolated rat hearts, propranolol, timolol and sotalol all decreased heart rate and contractility.⁴² Surprisingly, these effects were similar in catecholamine depleted and nondepleted hearts.¹¹⁴ A membrane depressant effect likely contributes to the cardiac depressant effects of propranolol but not to that of timolol or sotalol. It may be concluded that β -adrenergic antagonists cause myocardial depression at least in part by an action independent of catecholamine antagonism or membrane depressant activity.¹¹⁴ This effect may be mediated by interference with calcium handling in the sarcoplasmic reticulum.

Other investigators studied the role of extracellular ions and cardiac membrane potential in modulating β -adrenergic antagonist toxicity. β -Adrenergic antagonists interfere with calcium uptake into intracellular organelles. This interference with cytosolic calcium handling may stimulate calcium sensitive outward potassium channels and result in myocyte hyperpolarization and subsequent refractory bradycardia. Lowering extracellular potassium or raising extracellular sodium

concentrations was conjectured to counteract this effect and, in fact, partially reversed propranolol and atenolol toxicity in isolated rat hearts.⁹⁷ In another series of experiments with isolated rat hearts, calcium improved the function of rat hearts poisoned with β -adrenergic antagonists. This may have been due to a nonspecific positive inotropic action of calcium.¹¹⁴

Although cardiovascular effects are most prominent in overdose, β -adrenergic antagonists also cause respiratory depression.¹¹⁵ This effect is centrally mediated and appears to be an important cause of death in spontaneously breathing animal models of β -adrenergic antagonism toxicity.¹¹⁶ There is evidence that propranolol is concentrated in synaptic vessels and may impair synaptic function by inhibition of membrane ion pumps, including the sodium-potassium ATPase, the calcium ATPase, and the magnesium ATPase. These actions may explain some of the CNS effects noted in propranolol overdose.⁶⁴

CLINICAL MANIFESTATIONS

Symptoms of toxicity generally occur within hours after β -adrenergic antagonist overdose. Propranolol overdose, in particular, may be complicated by the rapid development of hypoglycemia, seizures, coma, and dysrhythmias. In a retrospective review of published reports of adult β -adrenergic antagonist overdose there were 39 symptomatic patients with well documented times from ingestion to symptom onset. Only one patient had ingested a sustained release product. Thirty-one patients were symptomatic at 2 hours, all but one developed symptoms at 4 hours, and everyone developed symptoms within the first 6 hours. The authors conclude that there have been no well documented reports of immediate release β -adrenergic antagonist overdose resulting in toxicity delayed more than 6 hours after ingestion.¹²⁶ The authors of an Australian series also noted that, in their 58 patients with β -adrenergic antagonist overdose, all major symptoms began within 6 hours of ingestion.¹⁶⁷ These observations do not apply to sotalol, which is well known to cause delayed toxicity in overdose, or to sustained-release preparations.

Isolated β -adrenergic antagonist overdose in healthy people is often benign. In several series, one-third or more of patients reporting a β -adrenergic overdose remained asymptomatic.^{46,51,127,206} This is partially explained by the fact that β -adrenergic antagonism is often well tolerated in healthy persons who do not rely on sympathetic stimulation to maintain cardiac output. In particular, unintentional ingestions in children rarely result in significant toxicity.¹⁶ In fact, a review of published cases found a few reports of hypoglycemia but no deaths or serious cardiovascular morbidity following β -adrenergic antagonist ingestion in children younger than 6 years of age.¹³⁵

β -Adrenergic antagonists severely impair the ability of the heart to respond to peripheral vasodilation, bradycardia, or decreased contractility caused by other xenobiotics. Therefore even relatively benign vasoactive xenobiotics may cause catastrophic toxicity when coingested with β -adrenergic antagonists.⁵⁸ According to one author, the most important predictor of toxicity in β -adrenergic antagonist overdose is likely to be the presence of a cardioactive coingestant.¹²⁹ Isolated β -adrenergic antagonist overdose is most likely to cause symptoms in persons with congestive heart failure, sick sinus syndrome, or impaired AV conduction who rely on sympathetic stimulation to maintain heart rate or cardiac output. Nevertheless, severe toxicity and death may still occur in healthy persons who have ingested β -adrenergic antagonists alone.^{54,167,198} This may be explained by an increased susceptibility of certain persons to β -adrenergic antagonism or by special properties that increase the toxicity of certain β -adrenergic antagonists (see below). In patients without a coingestant, toxicity is most likely to occur in those who ingest a β -adrenergic antagonist with membrane stabilizing activity.¹²⁹

Patients with symptomatic β -adrenergic antagonist overdose will most often be hypotensive and bradycardic. Decreased SA node function results in sinus bradycardia, sinus pauses, or sinus arrest. Impaired atrioventricular conduction manifested as prolonged PR interval or high-grade AV block occurs rarely. Prolonged QRS and QT intervals may occur and severe poisonings may result in asystole. Congestive heart failure often complicates β -adrenergic antagonist overdose. Delirium, coma, and seizures occur most commonly in the setting of severe hypotension but may also occur with normal blood pressure, especially with exposure to the more lipophilic xenobiotics such as propranolol.^{54,167} Respiratory depression and apnea may have an additional role in toxicity.⁶ In a review of reported cases, 18% of patients with propranolol toxicity and 6% of those with atenolol toxicity had a respiratory rate fewer than 12 breaths/min.¹⁶⁷ Respiratory depression following β -adrenergic antagonist overdose typically occurs in patients who are hypotensive and comatose but is reported in awake patients.¹⁵³ Hypoglycemia may complicate β -adrenergic antagonist poisoning in children^{77,135} but is uncommon in acutely poisoned adults. In a series of 15 cases of β -adrenergic antagonist overdose, none of the 13 adults were hypoglycemic whereas both of the two children had symptomatic hypoglycemia.⁵⁴ Bronchospasm is relatively uncommon following β -adrenergic antagonist overdose and appears to occur only in susceptible patients. In the series mentioned above, only two of the 15 patients developed bronchospasm⁵⁴ and in a recent review of 39 cases of symptomatic adults with β -adrenergic antagonist overdose, only one patient developed bronchospasm.¹²⁶ Clinical use of β -adrenergic antagonists slightly increases serum potassium¹³⁶; however, significant hyperkalemia is rare.

β₁ Selectivity (Acebutolol, Atenolol, Betaxolol, Bisoprolol, Esmolol, Metoprolol, Nebivolol)

In overdose, cardioselectivity is largely lost and deaths due to the β₁-adrenergic selective agents including acebutolol,⁷⁵ atenolol,¹³³ betaxolol,²⁰ and metoprolol^{172,198} are reported. There have been single reports of minor toxicity following overdose with bisoprolol²¹² and nebivolol.⁷⁴

Membrane-Stabilizing Effects (Acebutolol, Betaxolol, Carvedilol, Oxprenolol, Propranolol)

Propranolol possesses the most membrane stabilizing activity of this class and propranolol poisoning is characterized by coma, seizures, hypotension, bradycardia, impaired atrioventricular conduction, and widened QRS interval. A Brugada-pattern on ECG may occur following propranolol overdose (Chap. 16).¹⁶⁸ Ventricular tachydysrhythmias may also occur.^{4,133} Hypotension may be out of proportion to bradycardia and deaths from propranolol overdose are well reported.^{54,75,133} Acebutolol, betaxolol and oxprenolol also possess significant membrane stabilizing activity and have caused fatalities when taken in overdose.^{20,75,100,157,165}

Lipid Solubility

In overdose, the more lipophilic β-adrenergic antagonists may cause delirium, coma, and seizures even in the absence of hypotension.^{54,167} Atenolol, the least lipid soluble of β-adrenergic antagonists, appears to be one of the safer β-adrenergic antagonists when taken in overdose.⁷⁵ In fact, in one series of β-adrenergic antagonist overdoses, none of the 18 patients with atenolol overdose had seizures compared with eight out of 28 patients with propranolol overdose.¹⁶⁷ Nevertheless, atenolol overdose may result in severe toxicity and cardiovascular death.^{133,161,202}

Intrinsic Sympathomimetic Activity (Acebutolol, Carteolol, Oxprenolol, Penbutolol, Pindolol)

There is little experience with overdose of these agents, but ISA would theoretically make these drugs safer than the other β-adrenergic antagonists. Sympathetic stimulation with mild tachycardia or hypertension often predominates in pindolol overdose, and this class of medications appears to be relatively safe in overdose.^{54,109,166} In addition to ISA, acebutolol and oxprenolol have significant membrane-stabilizing activity, making them dangerous in overdose, and deaths due to acute toxicity from these β-adrenergic antagonists are reported.^{54,75,125,165} Overdose with carteolol or penbutolol has not been reported.

Potassium Channel Blockade (Acebutolol, Sotalol)

In six patients with sotalol overdose, the average QT interval was 172% of normal and five patients had ventricular dysrhythmias, including multifocal ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation.¹⁵⁶ Sotalol overdose may also be complicated by hypotension, bradycardia, and asystole,^{5,156} and fatalities are well documented.^{152,160}

Sotalol overdose may cause delayed and prolonged toxicity although ECG changes appear to occur early. In a series of six patients with sotalol overdose, all had prolonged QT interval noted on the initial ECG taken 30 minutes to 4.5 hours after ingestion. It is not clear whether these patients were taking sotalol therapeutically prior to the overdose so it is possible that the prolonged QT on the initial ECG was present prior to the overdose. The greatest QT prolongation occurred 4 to 15 hours after ingestion, and the risk of ventricular dysrhythmias was highest between 4 and 20 hours. All four patients who developed ventricular tachycardia did so after 4 hours, and in two patients ventricular dysrhythmias first occurred 9 hours after ingestion. One patient continued to have ventricular dysrhythmias at 48 hours, and abnormally prolonged QT intervals were noted as long as 100 hours after ingestion. In this series the average sotalol half-life was 13 hours, and the average time until normalization of the QT interval was 82 hours.¹⁵⁶ Acebutolol-induced QT interval prolongation may partially explain the ventricular tachydysrhythmias that occur with severe acebutolol toxicity.^{44,125,133}

Vasodilation (Betaxolol, Bucindolol, Carteolol, Carvedilol, Celiprolol, Labetolol, Nebivolol)

The vasodilatory properties of these drugs would theoretically act in synergy with β-adrenergic antagonism to increase toxicity. Conversely, the low membrane-stabilizing effect of these drugs may make them relatively safe in overdose. Betaxolol is the sole drug in this class with membrane stabilizing properties. Overdose with labetalol appears to be similar to that of other β-adrenergic antagonists with hypotension and bradycardia as prominent features.^{103,105,194} Experience with

overdose of the newer vasodilating β -adrenergic antagonists is limited. Similar to conventional β -adrenergic antagonists, carvedilol overdose causes hypotension and bradycardia.^{23,68,205} In a case report from Germany, nebivolol overdose was complicated by bradycardia, lethargy, and hypoglycemia. The patient received standard treatment and had a benign outcome.⁷⁴ Another patient became hypotensive and bradycardic and then experienced cardiac arrest following nebivolol overdose. That person was successfully resuscitated with lipid emulsion and high-dose insulin.²⁰¹ Severe toxicity and death have occurred following betaxolol^{20,21} and celiprolol¹⁷⁶ poisoning. Overdoses with bucindolol or carteolol have not been reported.

Other Preparations (Ophthalmic Preparations, Sustained Release, Combined Products)

There is very little published experience with overdoses of the sustained release β -adrenergic antagonists, but it is reasonable to expect that overdose with these agents will result in both a delayed onset and prolonged duration of toxicity. Acute overdose of ophthalmic β -adrenergic antagonists has not been reported. Patients who take mixed overdoses with calcium channel antagonists and β -adrenergic antagonists are difficult to manage because of synergistic toxicity.^{180,188,195} Overdoses with combined β -adrenergic antagonist and calcium channel blocker preparations such as felodipine and metoprolol or atenolol and nifedipine have not been reported, but these combinations would be expected to be quite dangerous in overdose.

DIAGNOSTIC TESTING

All patients with an intentional overdose of a β -adrenergic antagonist should have a 12-lead ECG and continuous cardiac monitoring. Serum glucose should be measured regardless of mental status because β -adrenergic antagonists can cause hypoglycemia. A chest radiograph and assessment of oxygen saturation should be obtained if the patient is at risk for or suffering symptoms of congestive heart failure. For patients with bradycardia of uncertain etiology, measurement of thyroid function, potassium, kidney function, cardiac enzymes, and digoxin concentration may prove helpful. Serum concentrations of β -adrenergic antagonists are not readily available for routine clinical use but may prove helpful in making a retrospective diagnosis in selected cases. Lactate concentrations may be elevated in patients with β -adrenergic antagonist poisoning but are poor predictors of survival.¹⁴⁷

MANAGEMENT

Airway and ventilation should be maintained with endotracheal intubation if necessary. Because laryngoscopy may induce a vagal response, it is reasonable to give atropine prior to intubation of the bradycardic patient. This is particularly true for children who are more susceptible to this complication. The initial treatment of bradycardia and hypotension consists of atropine and intravenous fluids. These measures will likely be insufficient in patients with severe toxicity but may suffice in patients with mild poisoning or other etiologies for bradycardia.

Gastrointestinal decontamination is warranted for all persons who have ingested significant amounts of a β -adrenergic antagonist. Induction of emesis is contraindicated because of the potential for catastrophic deterioration of mental status and vital signs in these patients, and since vomiting increases vagal stimulation and may worsen bradycardia.¹⁹⁶ Orogastric lavage is recommended for patients with significant effects such as seizures, hypotension, or bradycardia if the patient presents in a time frame when the drug is still expected to be in the stomach. Orogastric lavage is also recommended for all patients who present shortly after ingestion of large (gram amount) ingestions of propranolol or one of the other more toxic β -adrenergic antagonists (ie, acebutolol, betaxolol, metoprolol, oxprenolol, sotalol). Orogastric lavage causes vagal stimulation and carries the risk of worsening bradycardia so it is reasonable to pretreat patients with standard doses of atropine. We recommend activated charcoal alone for persons with minor symptoms following an overdose with one of the more water-soluble β -adrenergic antagonists who present later than one hour following ingestion. Whole bowel irrigation with polyethylene glycol should be considered in patients who have ingested sustained release preparations (Antidotes in Depth: A2).

Seizures or coma associated with cardiovascular collapse is treated by attempting to restore circulation. Seizures in the patient with relatively normal vital signs should be treated with benzodiazepines followed by barbiturates if benzodiazepines fail. Refractory seizures are rare in β -adrenergic antagonist overdose.

Specific Management

Patients who fail to respond to atropine and fluids require management with the inotropics discussed below (Fig. 62–4). When time permits, it is preferable to introduce new medications sequentially so that the effects of each may be assessed. We recommend glucagon followed by calcium, and high-dose insulin euglycemia therapy. In the critically ill patient, there

may not be enough time for this approach and multiple treatments may be started simultaneously. If these therapies fail, we suggest starting a catecholamine pressor and phosphodiesterase inhibitors. Advanced hemodynamic monitoring, when available, is advisable to guide therapy for all patients receiving catecholamine pressors or phosphodiesterase inhibitors. Lipid emulsion therapy should be given to patients with severe toxicity or cardiac arrest. Mechanical life support with intra-aortic balloon pump or extracorporeal circulation may be lifesaving when medical management fails and is most effective when started early.

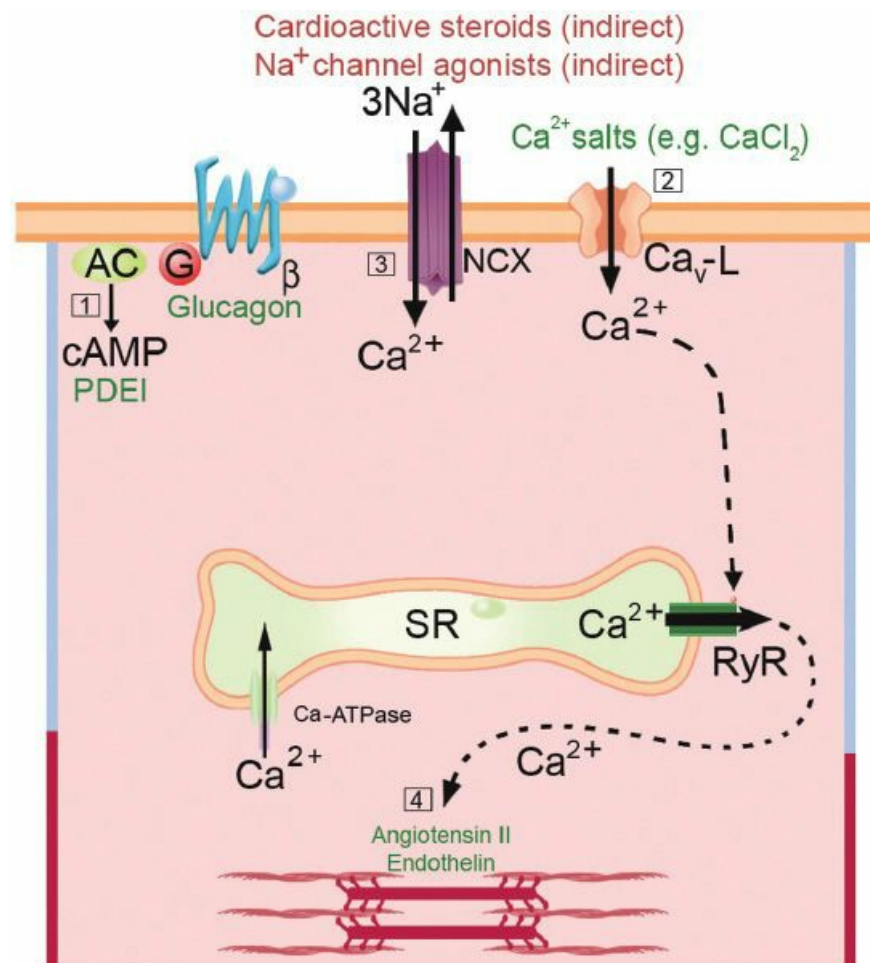


FIGURE 62–4. Positive inotropes improve cardiac function by a number of mechanisms, which usually result in increased intracellular calcium. Xenobiotics that [1] increase cAMP: Glucagon receptors and β -adrenergic receptors are coupled to G_s proteins so that receptor binding increases cAMP by activation of adenylyl cyclase. Phosphodiesterase inhibitors increase cAMP by inhibiting its breakdown. [2] increase calcium influx: Calcium salts increase calcium influx through L-type calcium channels by a direct mass effect. [3] inhibit extrusion of calcium via the sodium-calcium exchange pump: Those that increase intracellular sodium such as digoxin and sodium channel agonists (eg, aconitine) and those such as 4-aminopyridine that prolong the action potential duration alter the electrochemical gradients in a way that hinders the extrusion of calcium. [4] increase the sensitivity of the contractile elements to calcium: Angiotensin II and endothelin do this by inducing an intracellular alkalosis. The calcium sensitizers, levosimendan and pimobendan are used to treat heart failure in some countries.

Glucagon

Cardiac glucagon receptors,²²⁰ like β -adrenergic receptors, are coupled to G_s proteins. Glucagon binding increases adenylyl cyclase activity independent of β -adrenergic receptor binding.²²⁷ The inotropic effect of glucagon is enhanced by its ability to inhibit phosphodiesterase and thereby prevent cAMP breakdown.¹⁴⁹

There are no controlled trials of glucagon in humans with β -adrenergic antagonist poisoning.^{12,25} Nevertheless, with more than 30 years of clinical use,^{107,217} glucagon is still recognized as a useful treatment of choice for severe β -adrenergic antagonist toxicity.^{96,163,206,222} This is supported by animal models,^{62,106,132} and a case series suggesting that glucagon is also effective in correcting symptomatic bradycardia and hypotension secondary to therapeutic β -adrenergic antagonist use.¹³⁴ Glucagon is a vasodilator, and in animal models of propranolol poisoning it is more effective in restoring contractility, cardiac output, and heart rate than in restoring blood pressure.^{12,132}

The initial adult dose of glucagon for β -adrenergic antagonist toxicity is 3 to 5 mg given slowly over 1 to 2 minutes. The initial pediatric dose is 50 μ g/kg. If there is no response to the initial dose, higher doses up to a total of 10 mg may be

used. Once a response occurs, a glucagon infusion is started. Most authors recommend using an infusion of 2 to 5 mg/h, although many authorities recommend glucagon infusions as high as 10 mg/h. We suggest that the glucagon infusion be started at the “response dose” per hour. Thus, for example, if the patient receives 7 mg of glucagon before a response occurs, the glucagon infusion should be started at 7 mg/h. When a full 10 mg dose of glucagon fails to restore blood pressure and heart rate and the diagnosis of β -adrenergic antagonist toxicity is probable, we still recommend starting an infusion of glucagon at 10 mg/h as glucagon will have synergistic effects with subsequent antidotes. Glucagon may cause vomiting with risk of aspiration. Other adverse events of glucagon in this setting include hyperglycemia and mild hypocalcemia⁸⁷ and these should be treated appropriately if they develop. Patients also develop rapid tachyphylaxis to glucagon, and the need for increasing doses and additional therapies should be expected, even when patients initially respond (Antidotes in Depth: A18).

Calcium

Calcium salts effectively treat hypotension but not heart rate in animal models of β -adrenergic antagonist toxicity.^{114,128} Calcium chloride successfully reverses hypotension in patients with β -adrenergic antagonist overdose^{27,161} and in combined calcium channel blocker and β -adrenergic antagonist toxicity.⁷⁶ The adult starting dose of calcium gluconate is 3 g of the 10% solution given intravenously. We recommend using up to 9 g of calcium gluconate if needed. The initial dose of calcium gluconate in children is 60 mg/kg up to 3 g. This may be repeated up to a total of 180 mg/kg (Antidotes in Depth: A29).

Insulin and Glucose

High-dose insulin, euglycemia therapy improves cardiac function following cardiac surgery⁶⁵ and survival following myocardial infarction.^{49,137-139} There is evidence that high-dose insulin combined with sufficient glucose to maintain euglycemia is beneficial in β -adrenergic antagonist poisoning. In a canine model of propranolol toxicity, all six animals treated with insulin and glucose survived compared with four out of six in the glucagon group, one of six in the epinephrine group, and no survivors in the sham treatment group.⁹⁹ Insulin plus glucose was markedly more effective than vasopressin plus epinephrine in a porcine model of propranolol toxicity. In that experiment, all five animals in the insulin group survived the 4-hour protocol and all five in the vasopressin plus epinephrine group died within 90 minutes.⁸² In a rabbit model of severe propranolol toxicity, high-dose insulin was more effective than lipid emulsion in restoring blood pressure and heart rate, but there was no difference in survival.⁷¹ Clinical experience with high-dose insulin for β -adrenergic antagonist poisoning is increasing but still limited to case reports and case series.⁴⁷ Improvements in heart rate and blood pressure following high-dose insulin are reported in patients with isolated overdoses of metoprolol, nebivolol, and propranolol.^{84,158,201} High-dose insulin was also effective in combined poisoning with β -adrenergic antagonists and calcium channel blockers.^{84,228}

High-dose insulin is simple to use, safe (with appropriate monitoring of glucose and potassium), and does not require invasive monitoring. For these reasons, we recommend using high-dose insulin and glucose infusions for patients with β -adrenergic antagonist toxicity who have not responded to fluids, atropine, and glucagon. Although the dose of insulin is not definitively established, therapy typically begins with a bolus of 1 unit/kg of regular human insulin along with 0.5 g/kg of dextrose. If blood glucose is greater than 300 mg/dL (16.7 mmol/L), the dextrose bolus is not necessary. An infusion of regular insulin should follow the bolus starting at 1 unit/kg/h. A continuous dextrose infusion, beginning at 0.5 g/kg/h should also be started. Glucose should be monitored every 15 to 30 minutes until stable and then every 1 to 2 hours and titrated to maintain the blood glucose between 100 and 250 mg/dL. Cardiac function should also be reassessed every 10 to 15 minutes, and if it remains depressed, the insulin infusion can be increased up to 10 units/kg/h as required (rarely higher). The goal of therapy includes improved organ perfusion with improvements in cardiac output, mental status, urine output, and acid-base abnormalities. The response to insulin is typically delayed for 15 to 60 minutes so it will usually be necessary to start a catecholamine infusion before the full effects of insulin are apparent. It is important to continue monitoring glucose and electrolytes for several hours after insulin is discontinued (Antidotes in Depth: A17).

Catecholamines

Patients who do not respond to the preceding therapies usually require a catecholamine infusion. The choice of catecholamine is somewhat controversial. Theoretically, the pure β -adrenergic agonist isoproterenol would seem to be the ideal agent because it can overcome β -adrenergic blockade without causing any α -adrenergic effects. Unfortunately, this therapy has several potential drawbacks, which limit its efficacy. In the presence of β -adrenergic antagonism, extraordinarily high doses of isoproterenol and other catecholamines are frequently required.^{36,165,171,206,215} Individual case reports document isoproterenol infusions as high as 800 μ g/min.¹⁶⁶ At these high doses, the β_2 -adrenergic effects of isoproterenol cause peripheral vasodilation and may actually lower blood pressure.¹⁷¹ Nevertheless, in some animal models, isoproterenol is the most effective catecholamine and is even more effective than glucagon in reversing β -

adrenergic antagonist toxicity.^{203,219} However, clinical experience has not shown this to be the case. In a review of reported cases, glucagon increased heart rate 67% of the time and blood pressure 50% of the time. In contrast, isoproterenol was effective in increasing heart rate only 11% of the time and blood pressure only 22% of the time. Epinephrine was more effective than isoproterenol.²²² The selective β_1 -adrenergic agonist prenalterol may avoid some of the problems associated with isoproterenol and was used successfully to treat β -adrenergic antagonist overdose.^{52,109} Prenalterol would be expected to be especially effective following overdose of the cardioselective β -adrenergic antagonists.⁵² Prenalterol is not FDA approved and prenalterol therapy is limited as its relatively long half-life (~ 2 hours) makes titration difficult.¹⁷³ Dobutamine is a β_1 -adrenergic agonist with relatively little effect on vascular resistance that may be useful in this setting. However, experience is limited and dobutamine is not always effective in patients with β -adrenergic antagonist overdose.^{165,193} In the setting of β -adrenergic antagonism, catecholamines with substantial α -adrenergic agonist properties may increase peripheral vascular resistance without improving contractility, resulting in acute cardiac failure. Severe hypertension due to lack of β_2 -adrenergic-mediated vasodilation is another potential adverse reaction from this so-called “unopposed α -adrenergic” effect.⁵⁹ Because of these potential problems, we recommend that catecholamine use be guided by hemodynamic monitoring using noninvasive techniques such as bioimpedance or echocardiographic monitoring or direct invasive measures of determining cardiac performance. Catecholamine infusions should be started at the usual rates and then increased rapidly until a clinical effect is obtained. If advanced monitoring is impossible and the diagnosis of β -adrenergic antagonist overdose is fairly certain, it is reasonable to begin an isoproterenol or epinephrine infusion with careful monitoring of the patient’s blood pressure and clinical status. The infusion should be stopped immediately if the patient becomes more hypotensive or develops congestive heart failure.

Lipid Emulsion

Lipid emulsion is a promising antidote that has a role in selected cases of severe β -adrenergic antagonist overdose. Intravenous administration of lipid emulsion is hypothesized to reduce the toxicity of lipid-soluble xenobiotics by lowering free serum concentrations of these compounds, because they partition into the lipemic component of blood and improve the bioenergetics of the heart. Lipid emulsion has proven effective in animal models of poisoning with propranolol, a highly lipid soluble β -adrenergic antagonist, but not those that are water-soluble such as atenolol or metoprolol.^{29,31,32,34} Lipid emulsion was less effective than high-dose insulin in restoring heart rate and blood pressure in a rabbit model of propranolol poisoning.⁷¹ Human experience with the use of lipid emulsion in β -adrenergic antagonist overdose is limited, but cases of dramatic recovery from cardiac arrest have been reported.^{33,90,182,201,205} It is reasonable to administer intravenous lipid emulsion in patients with severe toxicity from a lipid-soluble β -adrenergic antagonist that does not respond to usual therapy.^{34,72} The optimal dose and formulation of lipid emulsion for this purpose is unknown. One protocol calls for a 1.5 mL/kg of 20% Intralipid followed by an infusion of 0.25 mL/kg/min. The bolus can be repeated in 3 to 5 minutes if necessary. The total dose should be less than 8 mL/kg²²¹ (Antidotes in Depth: A20).

Phosphodiesterase Inhibitors

The phosphodiesterase inhibitors amrinone, milrinone, and enoximone are theoretically beneficial in β -adrenergic antagonist overdose since they inhibit the breakdown of cAMP by phosphodiesterase and hence increase cAMP independently of β -adrenergic receptor stimulation. Phosphodiesterase inhibitors increase inotropy in the presence of β -adrenergic antagonism in both animal models¹¹⁸ and in humans.²¹³ Although these agents appear to be as effective as glucagon in animal models of β -adrenergic antagonist toxicity,^{132,185} controlled dog models were unable to demonstrate an additional benefit of these agents over glucagon.^{131,186} Phosphodiesterase inhibitors might be useful in selected patients who fail glucagon therapy, and have been used clinically to treat β -adrenergic antagonist poisoned patients.^{79,103,183,184} Therapy with phosphodiesterase inhibitors is often limited by hypotension secondary to peripheral vasodilation. Furthermore, these drugs are difficult to titrate because of relatively long half-lives (30–60 minutes for milrinone, 2–4 hours for amrinone, and ~ 2 hours for enoximone).^{94,154} For these reasons the phosphodiesterase inhibitors should generally only be considered for patients who have arterial and pulmonary artery pressure monitoring.

Ventricular Pacing

Ventricular pacing is not a particularly useful intervention in patients with β -adrenergic antagonist toxicity, but it will increase the heart rate in some patients.⁹⁵ Unfortunately, there will frequently be failure to capture or pacing may increase the heart rate with no increase in cardiac output or blood pressure.^{4,109,113,206} In fact, some authors have noticed that ventricular pacing occasionally decreases blood pressure perhaps secondary to loss of organized atrial contraction or due to impaired ventricular relaxation.²⁰⁶

Extracorporeal Removal

Extracorporeal removal is ineffective for the lipid-soluble β -adrenergic antagonists due to their large volumes of distribution. Hemodialysis may remove water-soluble renally eliminated β -adrenergic antagonists such as atenolol¹⁷⁹ and acebutolol.¹⁷⁴ Because hemodialysis is often technically difficult in poisoned patients due to hypotension and bradycardia, it is rarely utilized in patients with β -adrenergic antagonist overdose but may be considered in selected cases.

Mechanical Life Support

It is important to remember that the patient with circulatory failure from an acute overdose will typically recover without sequelae if ventilation and circulation are maintained until the xenobiotic is eliminated. When the preceding medical treatment fails, it is appropriate to consider the use of an intra-aortic balloon pump or extracorporeal life support (ECLS). Several case reports describe remarkable recoveries following the use of these therapies for refractory β -adrenergic antagonist toxicity^{21,113,146} or combined β -adrenergic antagonist and calcium channel blocker overdose.^{53,88,102,162,178,225} In one report, a neonate who developed refractory circulatory collapse from an iatrogenic overdose of propranolol was supported with extracorporeal membrane oxygenation (ECMO) for 5 days and survived neurologically intact.⁴¹ A case series documents experience with ECMO for patients with cardiac arrest caused by cardiovascular drug poisoning. In this series of six patients, two deaths were attributed to delayed institution of ECMO. The other four patients survived without sequelae.¹¹ In another series, ECLS was used in 17 patients with circulatory failure following a drug overdose. Eight patients had taken β -adrenergic antagonists either alone or in combination with other cardiovascular toxins. Thirteen of the 17 patients had long-term survival. The authors conclude that ECLS is efficient and relatively safe as a last resort treatment for patients with cardiac arrest or refractory shock following a drug overdose.³⁹ More recently, researchers compared survival with ECLS versus conventional therapy in poisoned patients with circulatory failure. Six patients in the ECLS group and ten in the conventional therapy group had ingested β -adrenergic antagonists. In this series, 12 out of 14 (86%) of the ECLS patients survived compared with 23 out of 48 (48%) in the conventional therapy group. The authors concluded that ECLS is helpful in critically ill poisoned patients who do not respond to conventional therapy.¹⁴⁴

Experimental Treatment

Vasopressin is a hypothalamic hormone that acts at G protein-coupled receptors to mediate vasoconstriction (at V_1 receptors), water retention (at V_2 receptors), and corticotropin secretion (at V_3 receptors), and may also increase the response to catecholamines. Vasopressin analogues have been used as vasopressors clinically in shock states and for patients in cardiopulmonary arrest.^{14,214} Vasopressin was as effective as glucagon but less effective than high-dose insulin in a porcine model of propranolol toxicity.^{82,83} There are no reports of vasopressin use for human β -adrenergic antagonist toxicity.

The calcium sensitizers, levosimendan and pimobendan, interact with the contractile proteins to improve cardiac function and are used clinically to treat heart failure.^{7,119,120,159} Levosimendan is both a positive inotrope and a vasodilator and has a better safety profile than pimobendan. It is approved in Europe for use in heart failure patients and is as effective as dobutamine in increasing contractility. Levosimendan infusions allow up titration of β -adrenergic antagonists in patients with severe heart failure.²²⁹ Levosimendan improved survival in a porcine model of propranolol toxicity¹²¹ and improved cardiac output in a murine model of metoprolol toxicity⁹³ but was not beneficial in a murine model of propranolol toxicity.⁹² Calcium sensitizers are not available in the United States or Canada. They may prove to have a role in managing patients poisoned with β -adrenergic antagonists.

Fructose 1,6-diphosphate (FDP) is an intermediate in the glycolytic pathway. FDP is able to cross cell membranes and it increases cardiac contractility.^{155,208} Compared with glucose infusion, FDP infusion resulted in improved survival in murine models of propranolol toxicity and verapamil toxicity.⁹¹ FDP may prove to have a role in the management of β -adrenergic antagonist poisoning, but it cannot be recommended at this time.

Special Circumstances

The preceding discussion applies to the generic management of β -adrenergic antagonists. Certain β -adrenergic antagonists have unique properties that modify their toxicity. The management considerations for these unique agents are discussed as follows.

Sotalol

In addition to bradycardia and hypotension, sotalol toxicity may result in a prolonged QT interval and ventricular dysrhythmias including torsade de pointes. Sotalol induced bradycardia and hypotension should be managed as with other β -adrenergic antagonists. Specific management of patients with sotalol overdose includes correction of hypokalemia and

hypomagnesemia. Overdrive pacing and magnesium infusions may be effective for sotalol-induced torsade de pointes.^{8,211} Lidocaine is also effective for sotalol-induced torsade de pointes.¹⁰ In the future, potassium channel openers such as the cardioprotective drug nicorandil may prove effective for sotalol-induced torsade de pointes.^{192,207,218}

Peripheral Vasodilation (Betaxolol, Bucindolol, Carteolol, Carvedilol, Celiprolol, Labetalol, Nebivolol)

Treatment of patients who have overdosed with one of the vasodilating β -adrenergic antagonists is similar to that for patients who ingest other β -adrenergic antagonists. Decisions about the need for vasopressors should be guided by clinical findings. If vasodilation is a prominent feature, high doses of vasopressors with α -adrenergic agonist properties (eg, norepinephrine or phenylephrine) may be required.⁷⁸ Conversely, if β -adrenergic antagonism is prominent, xenobiotics that act to increase intracellular cAMP, like glucagon, may be needed.^{74,103}

Membrane Stabilizing Effects (Acebutolol, Betaxolol, Carvedilol, Oxprenolol, Propranolol)

It might be expected that hypertonic sodium bicarbonate would be beneficial in treating the ventricular dysrhythmias that occur with these β -adrenergic antagonist. Unfortunately there is limited experience with the use of sodium bicarbonate in this situation, and the experimental data are mixed. Sodium bicarbonate was not beneficial in a canine model of propranolol toxicity, although there was a trend toward QRS interval narrowing in the sodium bicarbonate group.¹³⁰ In models with propranolol poisoned isolated rat hearts, however, hypertonic sodium chloride proved beneficial.^{97,98} Perhaps most compelling is the fact that sodium bicarbonate appeared to reverse ventricular tachycardia in a human case of acebutolol poisoning.⁴⁴ Because sodium bicarbonate is a relatively safe and simple intervention, we would recommend that it be used in addition to standard therapy for β -adrenergic antagonist poisoned patients with QRS widening, ventricular dysrhythmias, or severe hypotension. Sodium bicarbonate would not be expected to be beneficial in sotalol induced ventricular dysrhythmias and, by causing hypokalemia, may actually increase the risk of torsade de pointes. The usual dose of hypertonic sodium bicarbonate is 1 to 2 mEq/kg given as an intravenous bolus. This may be followed by an infusion or repeated boluses may be given as needed. Care should be taken to avoid severe alkalosis or hypokalemia (Antidotes in Depth: A5).

Observation

All patients who have bradycardia, hypotension, abnormal ECG findings, or CNS toxicity following a β -adrenergic antagonist overdose should be observed in an intensive care setting until these findings resolve. Toxicity from regular release β -adrenergic antagonist poisoning other than with sotalol almost always occurs within the first 6 hours.^{126,129,167} Therefore patients without any findings of toxicity following an overdose of a regular release β -adrenergic antagonist other than sotalol may be discharged from medical care after an observation time of 6 to 8 hours if they remain asymptomatic with normal vital signs and normal ECG and have had gastrointestinal decontamination with activated charcoal. Ingestion of extended-release preparations may be associated with delayed toxicity, and these patients should be observed for 24 hours in an intensive care unit. Patients who may have delayed absorption because of a mixed overdose or underlying gastrointestinal disease may also require longer observation. Sotalol toxicity may also be delayed with ventricular dysrhythmias first occurring as late as 9 hours after ingestion.¹⁵⁶ We recommend that all patients with sotalol overdose be monitored for at least 12 hours. Patients who remain stable without QT prolongation may then be discharged from a monitored setting.

SUMMARY

- β -Adrenergic antagonists are commonly used to treat hypertension, angina, tachydysrhythmias, tremor, migraine, and panic attacks.
- Overdoses of β -adrenergic antagonists are relatively uncommon but continue to cause deaths worldwide.
- Patients who develop symptoms after ingesting regular release β -adrenergic antagonists do so within the first 6 hours. Sotalol ingestions are an exception to this and may cause delayed and prolonged toxicity. Extended release formulations may also result in delayed toxicity and require 24 hour observation.
- Patients with consequential β -adrenergic antagonist overdose typically develop bradycardia and hypotension.
- Propranolol and other β -adrenergic antagonists with membrane-stabilizing properties and high lipid solubility are the most toxic in overdose. These xenobiotics cause prolongation of the QRS interval, severe hypotension, coma, seizures, and apnea.
- Sotalol is unique in its ability to prolong the QT interval and its toxicity often results in refractory ventricular

dysrhythmias, which may respond to overdrive pacing or to magnesium infusions.

- In addition to supportive care, the most important therapy for β -adrenergic antagonist toxicity is glucagon. High doses of insulin together with glucose provide a promising new treatment modality. Catecholamine infusions may also be helpful but should be closely monitored and large doses are typically required. Patients who fail treatment with glucagon, insulin, and catecholamines are critically ill and may respond to intravenous fat emulsion therapy, phosphodiesterase inhibitors, or mechanical support of circulation. Fortunately, most patients respond to simpler measures and this aggressive therapy is rarely required.

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A18 ANTIDOTES IN DEPTH

Glucagon

Mary Ann Howland

INTRODUCTION

The traditional role of glucagon was to reverse life-threatening hypoglycemia in patients with diabetes unable to receive dextrose in the outpatient setting. However, in medical toxicology, glucagon is used “off label” early in the management of β -adrenergic antagonist and calcium channel blocker toxicity to increase heart rate, contractility, and blood pressure by increasing myocardial cyclic adenosine monophosphate (cAMP) via a non- β -adrenergic receptor mechanism of action. The use of glucagon is based primarily on animal studies and as well as human case series and case reports. The effects of glucagon are often transient.

HISTORY

Glucagon was discovered in 1923, just 2 years after the discovery of insulin.¹⁰ The positive inotropic and chronotropic effects have been known since the 1960s.^{12,15}

PHARMACOLOGY

Chemistry/Preparation

Glucagon is a polypeptide counterregulatory hormone with a molecular weight of 3500 Da, secreted by the α cells of the pancreas. Previously animal derived, and possibly contaminated with insulin, the form approved by the US Food and Drug Administration (FDA) has been synthesized by recombinant DNA technology since 1998; therefore, it no longer contains any insulin.²⁵

Mechanism of Action

In both animals and humans, glucagon receptors can be found in the heart, brain, and pancreas.^{22,33,64} Binding of glucagon to cardiac receptors is closely correlated with activation of cardiac adenylate cyclase (AC).⁵² A large number of glucagon binding sites are demonstrated, and as little as 10% occupancy produces near maximal stimulation of adenylate cyclase. Binding of glucagon to its receptor results in coupling with two isoforms of the G_s protein and catalyzes the exchange of guanosine triphosphate (GTP) for guanosine diphosphate on the α subunit of the G_s protein.^{21,51,69} One isoform is coupled to β agonists, while both isoforms are coupled to glucagon.⁶⁹ The GTP- G_s units stimulate adenylate cyclase to convert adenosine triphosphate (ATP) to cAMP.^{32,40} In animal hearts, glucagon inhibits the phosphodiesterase PDE-3.^{5,43} Selective inhibition of PDE-4 potentiated the cAMP response to glucagon in adult rat ventricular myocytes.⁵⁰ Glucagon, along with β_2 agonists, histamine, and serotonin (but not β_1 agonists), also activates G_i , which inhibits cAMP formation in human atrial heart tissue.²⁷

Evidence now suggests an additional mechanism of action for glucagon, independent of cAMP, and dependent on arachidonic acid.⁵⁷ Cardiac tissue metabolizes glucagon, liberating mini-glucagon, an apparently active smaller terminal fragment.^{57,66} Mini-glucagon stimulates phospholipase A_2 , releasing arachidonic acid. Arachidonic acid acts to increase cardiac contractility through an effect on calcium. The effect of arachidonic acid—and therefore of mini-glucagon—is synergistic with the effect of glucagon and cAMP.⁵⁸

Stimulation of glucagon receptors in the liver and adipose tissue increases cAMP synthesis, resulting in glycogenolysis, gluconeogenesis, and ketogenesis.³² Other properties of glucagon include relaxation of smooth muscle in the lower esophageal sphincter, stomach, small and large intestines, common bile duct, and ureters.^{18,21,30}

Cardiovascular Effects

Investigations of the mechanism of action of glucagon on the heart have been performed on cardiac tissue obtained from patients during surgical procedures and in a variety of in vivo and ex vivo animal studies. The results are often species specific and are affected by the presence or absence of congestive heart failure. The inotropic action of glucagon is likely related to an increase in cardiac cAMP concentrations.^{12,32,40} Both the positive inotropic^{3,15,38,45} and chronotropic^{3,12,15,30,38,40,45,67} actions of glucagon are very similar to those of the β -adrenergic agonists, except that they are not blocked by β -adrenergic antagonists.⁶⁹ Although in some canine experiments glucagon caused ventricular tachycardia, glucagon is not dysrhythmogenic in patients with severe chronic congestive heart failure, myocardial infarction-related acute congestive heart failure, or in postoperative patients with myocardial depression.^{26,34,39,42} The effects of glucagon diminish markedly as the severity and chronicity of congestive heart failure increases.⁴⁵

Volunteer Studies

Cardiovascular effects were extensively studied in 21 patients with heart failure who were given varied doses and durations of glucagon therapy.⁴⁶ Eleven patients who received 3 to 5 mg via intravenous (IV) bolus had increases in the force of contraction, as measured by maximum dP/dT (upstroke pattern on apex cardiogram), heart rate, cardiac index, blood pressure, and stroke work. There was no change in systemic vascular resistance, left ventricular end-diastolic pressure, or stroke index. Additionally, glucose concentrations increased by 50% and the potassium concentrations fell. A study of nine patients demonstrated a 30% increase in coronary blood flow following a 50 μ g/kg IV dose.⁴² Patients who received 1 mg via IV bolus also had an increase in cardiac index, but systemic vascular resistance fell, probably secondary to splanchnic and hepatic vascular smooth muscle relaxation.⁴⁶ Patients who received an infusion of 2 to 3 mg/min for 10 to 15 minutes responded similarly to those who received the 3 to 5 mg IV boluses, but patients receiving boluses experienced significant dose limiting nausea and vomiting.⁴⁶

Pharmacokinetics and Pharmacodynamics

The volume of distribution of glucagon is 0.25 L/kg.¹⁶ The plasma, liver, and kidney extensively metabolize glucagon with an elimination half-life of 8 to 18 minutes.¹⁶ In human volunteers following a single IV bolus, the cardiac effects of glucagon begin within 1 to 3 minutes, are maximal within 5 to 7 minutes, and persist for 10 to 15 minutes.⁴⁵ The time to maximal glucose concentration is 5 to 20 minutes, with a duration of action of 60 to 90 minutes.¹⁶ Smooth muscle relaxation begins within 1 minute and lasts 10 to 20 minutes.¹⁶ The onset of action following intramuscular and subcutaneous administration occurs in about 10 minutes, with a peak at about 30 minutes.¹⁶

Activation of AC in adipose, myocardial, and hepatic tissue and myocardial contractility requires pharmacologic levels of glucagon, exceeding 0.1 nM.⁵² At physiologic concentrations of glucagon below 0.1 nM, it appears to duplicate the cardiac metabolic effects of insulin by activating a phosphatidylinositol-3 kinase (PI3K)-dependent signal without stimulating AC.⁵² Tachyphylaxis or desensitization of receptors may occur with repetitive dosing. Experimental heart preparations exposed to glucagon for varying lengths of time demonstrated a decrease in the amount of generated cAMP.^{24,70} Possible explanations for tachyphylaxis include uncoupling from the glucagon receptor, increased PDE hydrolysis of cAMP, or both.^{24,66,70,73} Other experiments demonstrated a transient effect of glucagon on contractility and hyperglycemia, also suggesting tachyphylaxis.^{20,26}

ROLE IN THE MANAGEMENT OF OVERDOSES WITH β -ADRENERGIC ANTAGONISTS

Overdoses with β -adrenergic antagonists are particularly dangerous and are manifested by hypotension, bradycardia, prolonged atrioventricular conduction times, depressed cardiac output, and cardiac failure. Other noncardiovascular effects include alterations in consciousness, seizures, and, rarely, hypoglycemia.^{1,14,19,65} Management is often complicated, and many therapies, including atropine, isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, and various combinations, are used with variable success.^{13,14} Recently high dose insulin with dextrose (Antidotes in Depth: A17), and in the event of a cardiac arrest, IV fat emulsion (Antidotes in Depth: A20), have been added to the armamentarium. Animal studies document the ability of glucagon to increase contractility, restore the sinus node function after sinus node arrest, increase atrioventricular conduction, and rarely improve survival.^{2,36,45,55} In canine studies, high-dose insulin euglycemia (HIE) therapy has a more sustained effect on hemodynamic parameters and an improved survival rate compared with glucagon.²⁶ Glucagon has successfully reversed bradydysrhythmias and hypotension in patients unresponsive to the aforementioned traditional xenobiotics, and should be administered early in the management of patients with severe overdoses.^{54,63} By increasing myocardial cAMP concentrations independent of the β receptor,^{36,44} glucagon is able to

increase inotropy^{3,15,38,45} and chronotropy.^{3,15,38,45,67}

Glucagon successfully reversed the bradycardia, low-output heart failure, and hypotension that developed in a premature newborn, presumably as a result of an inappropriately large prenatal dose of labetalol given to the mother. This neonate, delivered at 32 weeks' gestation and weighing 1.8 kg, received 0.3 mg/kg glucagon IV initially and five additional doses of 0.3 to 0.6 mg/kg over the next 5 hours, with improvement in heart rate, blood pressure, and perfusion. Epinephrine and diuretics were also used.⁵⁹

Combined Effects with Phosphodiesterase Inhibitors and Calcium

Strategies for enhancing the effects of glucagon have involved combining it with the PDE-3 inhibitor amrinone (inamrinone), its derivative milrinone, and most recently rolipram, a selective PDE-4 inhibitor. In a canine model of propranolol toxicity, both amrinone (inamrinone) and milrinone, alone were comparable with glucagon,^{36,56} but the combination of amrinone and glucagon resulted in a decrease in mean arterial pressure.³⁵ Tachycardia occurred when milrinone was used with glucagon.⁵⁵ In an ex vivo model using strips of rat ventricular heart, rolipram enhanced the inotropic effect of glucagon and limited glucagon tachyphylaxis.²⁴ However, because the evidence for the effectiveness of HIE was demonstrated in animal models and human case reports, combining glucagon with a phosphodiesterase inhibitor is no longer recommended.

The relationship between calcium and the chronotropic effects of glucagon was demonstrated in rats.⁸ Maximal chronotropic effects of glucagon are dependent on a normal circulating ionized calcium. Both hypocalcemia and hypercalcemia blunt the maximal chronotropic response.^{7,8}

ROLE IN CALCIUM CHANNEL BLOCKER OVERDOSE

Calcium channel blocker overdoses produce a constellation of clinical findings similar to those recognized with β -adrenergic antagonist overdoses, including hypotension, bradycardia, conduction block, and myocardial depression. Animal studies^{2,23,53,60,61,71,72} demonstrate the ability of glucagon to improve heart rate, atrioventricular conduction, and reverse the myocardial depression produced by nifedipine, diltiazem, and verapamil. However, there was no survival benefit attributed to glucagon in these studies, while a canine model of verapamil overdose comparing glucagon to HIE only revealed a survival benefit for HIE.^{2,28} Human case reports demonstrate improved hemodynamics.^{11,41,44,62}

ROLE IN REVERSAL OF HYPOGLYCEMIA

Glucagon was once proposed as part of the initial treatment for all comatose patients because it stimulates glycogenolysis in the liver.⁴⁹ The theoretical rationale for this approach is only partially sound in that glucagon requires time to act and may be ineffective in a patient with already depleted glycogen stores. Patients with type 2 diabetes are more likely to respond than are patients with type 1 diabetes. The IV administration of 0.5 to 1.0 g/kg of 50% dextrose in adults rapidly reverses hypoglycemia and does not rely on glycogen stores for its effect. Therefore, IV dextrose is preferred over glucagon as the initial substrate to be given to all patients with an altered mental status presumed to be related to hypoglycemia (Antidotes in Depth: A12). Glucagon may retain some role as a temporizing measure, until medical help can be obtained, in settings such as in the home where IV dextrose is not an option, or when IV access is not rapidly available.

In patients with insulinoma, after an initial hyperglycemic response glucagon may actually worsen hypoglycemia, as the result of a feedback increase in insulin.

ADVERSE EFFECTS AND SAFETY ISSUES

Side effects associated with glucagon include dose-dependent nausea, vomiting,³⁹ hyperglycemia, hypoglycemia, and hypokalemia; relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon; and, rarely, urticaria, respiratory distress, and hypotension.^{16,39} Hypotension is reported up to 2 hours after administration in patients receiving glucagon as premedication for upper gastrointestinal endoscopy procedures.¹⁶ The hyperglycemia is followed by an immediate rise in insulin, which causes an intracellular shift in potassium, resulting in hypokalemia.^{20,39,45} It is unclear whether stimulation of the Na^+ - K^+ -ATPase in skeletal muscle also contributes to the hypokalemia as occurs with β -adrenergic agonists.^{29,48} Glucagon may increase the anticoagulant effect of warfarin.¹⁶

Glucagon can also increase the release of catecholamines in a patient with a pheochromocytoma, resulting in a hypertensive crisis,²⁰ which can be treated with phentolamine.¹⁶ Continuous prolonged treatment with glucagon might lead to a dilated cardiomyopathy, as was reported in a patient with a glucagonoma.⁶

PREGNANCY AND LACTATION

Glucagon is FDA pregnancy category B. It is presumed that benefit exceeds risk. There are no reports of glucagon use during lactation. However, the size and peptide nature of glucagon suggest that the exposure to a lactating infant would be limited.

DOSAGE AND ADMINISTRATION

An initial IV bolus of 50 µg/kg, infused over 1 to 2 minutes, is recommended (3–5 mg in a 70-kg person).¹⁴ If clinically acceptable, then a longer duration of infusion may be used to minimize vomiting. Higher doses may be necessary if the initial bolus is ineffective, and up to 10 mg can be used in an adult.²² Using too small a dose can potentially decrease systemic vascular resistance.⁴⁶ In some cases, the bolus dose should be followed by a continuous infusion of 2 to 5 mg/h (≤ 10 mg/h) in 5% dextrose in water, which can be tapered as the patient improves.^{1,21,22,47,54,65} This dosing regimen has never been studied and is based on case reports. Experimental heart preparations clearly demonstrate tachyphylaxis with continuous administration. Whether this occurs in humans is unclear, but might argue for repeated bolus infusions over 1 to 5 minutes rather than continuous infusion.^{24,70} In addition, the smooth muscle relaxation associated with a continuous infusion would be assumed to impede attempts at gastrointestinal decontamination with multiple-dose activated charcoal or whole-bowel irrigation.

FORMULATION AND ACQUISITION

Glucagon [rDNA origin] for injection is available as a sterile, lyophilized white powder in a vial, alone, or accompanied by Sterile Water for Reconstitution, also in a vial. It is also supplied in the form of a kit for treatment of hypoglycemia with one vial containing 1 mg (1 unit) of glucagon [rDNA origin] for injection with a disposable prefilled syringe containing Sterile Water for Reconstitution, as well as a “10-pack” with 10 vials, each containing 1 mg (1 unit) GlucaGen (glucagon [rDNA origin] for injection). The glucagon powder should be reconstituted with 1 mL of sterile water for injection, after which the vial should be shaken gently until the powder completely dissolves. The final solution should be clear, without visible particles.¹⁶ The reconstituted glucagon should be used immediately after reconstitution, and any unused part discarded. Concentrations greater than 1 mg/mL should not be used. An adequate supply of glucagon in the emergency department is at least 20 1-mg vials, with assurance of another 30 mg in the pharmacy.^{9,37}

SUMMARY

- Glucagon can produce positive inotropic and chronotropic effects despite β-adrenergic antagonism and calcium channel blockade.
- Glucagon is often beneficial in the treatment of patients with severe overdoses of β-adrenergic antagonists and calcium channel blockers.
- The effects of glucagon may not persist and other therapies, such as insulin and dextrose, should also be considered (Chaps. 61 and 62).
- The relatively benign character of an IV bolus of glucagon in the patient with a serious overdose of a β-adrenergic antagonist or calcium channel blocker should lead the clinician to use glucagon early in patient management.
- Nausea and vomiting should be anticipated and managed.

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63 MISCELLANEOUS ANTIHYPERTENSIVES AND PHARMACOLOGICALLY RELATED AGENTS

Francis Jerome DeRoos

Hypertension is one of the commonest chronic medical problems and one of the most readily amenable to pharmacotherapy. Beginning in the 1960s, when asymptomatic hypertension was linked to significant adverse effects such as stroke, myocardial infarction, and sudden death, antihypertensive pharmacotherapeutics began being used. The first generation included centrally acting, sympatholytics, direct vasodilators, sodium nitroprusside, and diuretics. Unfortunately, these often had significant adverse events, leading to the development of β -adrenergic antagonists, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and, more recently, direct renin inhibitors (DRIs). This chapter reviews the first-generation antihypertensives, as well ACEIs, ARBs, and DRIs. In general, the majority of antihypertensives manifest clinical signs and symptoms in terms of the degree of hypotension produced. Particular attention will be placed on mechanisms of action and unique toxicologic considerations for each of these xenobiotics.

CLONIDINE AND OTHER CENTRALLY ACTING ANTIHYPERTENSIVES

Clonidine is an imidazoline compound that was synthesized in the early 1960s. Because of its potent peripheral α_2 -adrenergic agonist effects, it was initially studied as a potential topical nasal decongestant. However, hypotension was a common adverse event, which redirected its consideration for other therapeutic applications.¹⁰⁵ Clonidine is the best understood and the most commonly used of all the centrally acting antihypertensives, a group that includes methyldopa, guanfacine, and guanabenz. Although these drugs differ chemically and structurally, they all decrease blood pressure in a similar manner. The imidazoline compounds oxymetazoline and tetrahydrozoline, which are used as ophthalmic topical vasoconstrictors and nasal decongestants, produce similar systemic effects when ingested.¹⁰⁵

Since 1985, the increased efficacy and improved adverse event profiles of the newer antihypertensives have diminished the use of the α_2 -adrenergic agonists in routine hypertension management. However, their use is increasing as a result of a wide variety of applications, including attention-deficit/hyperactivity disorder (ADHD), peripheral nerve and spinal anesthesia, and as an adjunct in the management of opioid, ethanol, and nicotine withdrawal.^{120,127,130,224} In addition, abuse of clonidine may be a growing problem in opioid dependent patients, and it has been used in criminal acts of chemical submission.^{20,145}

Although centrally acting α_2 -adrenergic agonist exposure is relatively uncommon, it may cause significant toxicity, particularly in children. One report from two large pediatric hospitals identified 47 children requiring hospitalization for unintentional clonidine ingestions over a 5-year period.²⁶⁶ Significant clonidine poisoning has also resulted from formulation and dosing errors in children.^{211,241} Imidazolines used as ocular vasoconstrictors have resulted in significant systemic toxicity, especially when ingested.^{109,150,137,202}

Pharmacology

Clonidine and the other centrally acting antihypertensives exert their hypotensive effects primarily via stimulation of presynaptic α_2 -adrenergic receptors in the brain.^{78,194,218,257} This central α_2 -adrenergic receptor agonism enhances the activity of inhibitory neurons in the vasoregulatory regions of the central nervous system (CNS), notably the nucleus tractus solitarius in the medulla, resulting in decreased norepinephrine release.²¹⁷ This results in decreased sympathetic outflow from the intermediolateral cell columns of the thoracolumbar spinal tracts into the periphery^{2,256} and reduces the heart rate, vascular tone, and, ultimately, arterial blood pressure.^{186,256} This centrally mediated sympatholytic effect is modulated by nitric oxide and γ -aminobutyric acid (GABA), which may explain some of the clinical variability that occurs among patients who have overdosed with clonidine.^{37,87,234,260}

Pharmacokinetics

Clonidine is well absorbed from the gastrointestinal (GI) tract (~ 75%) with an onset of action within 30 to 60 minutes. The peak serum concentration occurs at 2 to 3 hours and lasts as long as 8 hours.⁵⁹ Clonidine has 20% to 40% protein binding and an apparent volume of distribution of 3.2 to 5.6 L/kg.¹³⁸ The majority of clonidine is eliminated unchanged via the kidneys.¹⁴³

Clonidine is available in both oral and patch form. The patch, referred to as the clonidine transdermal therapeutic system, allows slow, continuous delivery of drug over a prolonged period of time, typically one week. This formulation, however, offers unique clinical challenges. Each patch contains significantly more drug than is typically delivered during the prescribed duration of use. For example, while a patch that delivers 0.1 mg/day of clonidine contains a total of 2.5 mg, the product that delivers 0.3 mg/day and contains a total of 7.5 mg.³⁶ Even after one week of use, between 35% and 50% and, in some instances, as much as 70%, of the drug remains in the patch.^{36,98} Puncturing the outer membrane layer or backing opens the drug reservoir and allows a significant amount of the drug to be released rapidly. In addition, patients do not perceive this delivery system as a medication, and they may not exercise appropriate precautions. For example, discarding a used patch in an open wastebasket provides toddlers, who often are fascinated with stickers and other adhesive objects, an opportunity to remove the patch and apply, taste, or ingest it. Numerous reports of toxicity in both adults and children have resulted from dermal exposure, mouthing, or ingesting one clonidine patch, emphasizing this concern.^{36,47,98,102,124,204,205}

Guanabenz and guanfacine are structurally and pharmacologically very similar to each other. They are well absorbed orally, achieving peak concentrations within 3 to 5 hours, and both have large volumes of distribution (4–6 L/kg for guanfacine, 7–17 L/kg for guanabenz).^{109,237} Whereas guanabenz is metabolized predominantly in the liver and undergoes extensive first-pass effect, guanfacine is eliminated equally by the liver and kidney.^{109,237} The metabolism of neither drug results in the production of significant active metabolites.

Whereas clonidine, guanabenz, and guanfacine are all active drugs with direct α_2 -adrenergic agonist effects, methyl dopa is a prodrug. It enters the CNS, probably by an active transport mechanism, before it is converted into its pharmacologically active degradation products.²² α -Methylnorepinephrine is the most significant of its metabolites, although α -methyl dopamine and α -methylepinephrine may also be important.^{75,101,210} These metabolites are direct α_2 -adrenergic agonists and impart their hypotensive effect as do the other centrally acting antihypertensives. Approximately 50% of an oral dose of methyl dopa is absorbed, and peak serum concentrations are achieved in 2 to 3 hours.¹⁷⁰ However, because methyl dopa requires metabolism into its active form, these concentrations have little correlation with its clinical effects. Methyl dopa has a small volume of distribution (0.24 L/kg) and little protein binding (15%).¹⁷⁰ It is eliminated in the urine, both as parent compound and after hepatic sulfation.¹⁷⁹

Pathophysiology

In therapeutic oral dosing, clonidine and the other centrally acting antihypertensives have little effect on the peripheral α_2 receptors, the peripheral sympathetic nervous system, or the normal circulatory responses that occur with exercise or the Valsalva maneuver.^{169,183} However, when serum concentrations increase above 2 ng/mL, as in the setting of intravenous (IV) administration or oral overdose, peripheral postsynaptic α_2 -adrenergic stimulation may occur, causing increased norepinephrine release and producing vasoconstriction and hypertension.^{44,53,173,243} This hypertension is short lived, however, because the potent centrally mediated sympathetic inhibition becomes the predominant effect, and hypotension ensues.^{4,154,168,210} Imidazoline specific binding sites are identified both in the rostral ventrolateral medulla and in coronary artery vascular smooth muscle and may be important in the clinical effects of these xenobiotics although their exact function has not been elucidated.^{210,248} Direct stimulation of these imidazoline binding sites appears to lower blood pressure independent of central α_2 -adrenergic effects.^{24,62} Therefore, although their precise physiologic relationship has not been clearly elucidated, more evidence supports the concept that both imidazoline and α_2 -adrenergic receptors modulate the ability of clonidine, and presumably other centrally acting antihypertensives, to inhibit central norepinephrine release and the cardiovascular effects.^{25,62,99,163}

Clinical Manifestations

Although the majority of the published cases involve clonidine, the signs and symptoms of poisoning with any centrally acting antihypertensive are similar. The CNS and cardiovascular toxicity reflect an exaggeration of their pharmacologic action. Common signs include CNS depression, bradycardia, hypotension, and (occasionally) hypothermia.^{6,192,227,253} Most patients who ingest clonidine or the other similarly acting drugs manifest symptoms rapidly, typically within 30 to 90 minutes.²⁶⁶ The exception may be methyl dopa, a prodrug, which requires metabolism to be activated, possibly delaying toxicity for hours.^{227,270}

CNS depression is the most frequent clinical finding and may vary from mild lethargy to coma.^{149,154,182,203} In addition,

severely obtunded patients may experience decreased ventilatory effort and hypoxia.⁴ Respirations may be slow and shallow, with intermittent deep, sighing breaths. Various other terms are used to describe this phenomenon, including gasping, Cheyne-Stokes respirations, and periodic apnea.^{6,10,124,154} This hypoventilation is characteristically responsive to tactile stimuli in children, although mechanical ventilation may be required in severe cases.^{4,6,103,124} The associated CNS depression typically resolves over 12 to 36 hours.^{10,182} Other manifestations of this CNS depression include hypotonia, hyporeflexia, and irritability.^{44,154,239} The cranial nerve examination often demonstrates miotic pupils that may remain reactive to light.^{4,6,245} Two unusual case reports describe seizures in the setting of clonidine poisoning,^{44,146} the mechanism of which is unclear.

Hypothermia is associated with overdoses involving centrally acting antihypertensives.^{6,154,192,210} This is thought to be a consequence of α -adrenergic effects within the thermoregulatory center, although other authors suggest that these drugs activate central serotonergic pathways that alter normal thermoregulation.^{138,161} Although this phenomenon may last several hours, it rarely requires treatment and responds well to passive rewarming.^{44,192}

Sinus bradycardia may occur in up to 50% of patients who ingest clonidine and it results from the combination of an exaggerated centrally mediated sympatholytic effect, a centrally mediated increase in vagal tone, or a direct stimulation of α_2 -adrenergic receptors on the myocardium.^{55,132,239,256,266,267}

Other conduction abnormalities, including first degree heart block, type 1 and 2 Mobitz atrioventricular block, and complete heart block, are described both in overdose and after therapeutic dosing.^{123,182,218,220,254,267} It appears that very young patients and patients who have underlying sinus node dysfunction, concurrent sympatholytic drug therapy, or chronic kidney disease (CKD) are at particular risk of developing bradydysrhythmia after central antihypertensive ingestion.^{31,239,247}

Hypotension is the major cardiovascular manifestation of central antihypertensive toxicity.^{6,36,182,222,239,266} While studies have suggested a doseresponse relationship between the history of the quantity of the centrally acting antihypertensive ingested and the severity of the clinical manifestations, clonidine ingestions as small as 0.2 mg have resulted in clinically severe poisoning, mandating the necessity to individually assess each exposure; the presence of any symptoms should prompt immediate medical evaluation.^{18,182} Fatalities from any of these xenobiotics are rare, with few published reports from the American Association of Poison Control Centers (AAPCC) database²⁹ (Chap. 136).

After deaths of four children who were prescribed clonidine were reported, concerns that there was a causal association between combination clonidine–methylphenidate therapy and sudden death were raised.^{35,71} Fortunately, closer scrutiny of these cases revealed significant confounders, and a formal investigation by the US Food and Drug Administration (FDA) concluded that there was inadequate evidence to confirm this association.^{71,199,242,266}

Withdrawal

Abrupt cessation of central antihypertensive therapy may result in withdrawal that is characterized by excessive sympathetic activity. Symptoms include agitation, insomnia, tremor, palpitations, tachycardia, and hypertension, that begin between 16 and 48 hours after cessation of therapy.^{95,206} Ventricular tachycardia and myocardial infarction may occur in patients with clonidine withdrawal.^{19,172,193} The frequency and severity of symptoms appear to be greater in patients treated with higher doses for several months and in those with the most severe pretreatment hypertension.²⁰⁶ Shorter-acting drugs such as clonidine and guanabenz are more frequently associated with withdrawal.^{30,82,201,269} Due to the prolonged and continuous exposures, children being treated with extended release guanfacine formulations and transdermal patches, may be placed at greater risk of developing withdrawal upon cessation. The mechanism for this hyperadrenergic phenomenon appears to involve an increase in CNS noradrenergic activity in the setting of decreased α_2 -receptor sensitivity.⁶⁵ Reasonable treatment strategies include administering clonidine or benzodiazepines, via either the oral or IV route, followed by a closely monitored tapering of the dosing over several weeks. Animal and human data suggest that β -adrenergic antagonists, including labetalol, are contraindicated in clonidine withdrawal.^{9,117} Esmolol exacerbates this paradoxical hypertension in a manner similar to that which occurs when these xenobiotics are used in cocaine toxicity by inducing unopposed α_1 -receptor stimulation (Chap. 78).

Diagnostic Testing

Clonidine and other centrally acting antihypertensives are not routinely included in serum or urine toxicologic assays. Consequently, management decisions should be based on clinical parameters. No electrolyte or hematologic abnormalities are associated with this exposure. Because of the potential for bradydysrhythmia and hypoventilation, 12-lead electrocardiography (ECG) and continuous cardiac and pulse oximetry monitoring are recommended.

Management

Appropriate therapy begins with particular focus on the patient's respiratory and hemodynamic status. Administration of activated charcoal (AC) is the primary mode of GI decontamination in most cases of ingestion. Patients often present after the onset of symptoms rather than immediately after ingestion, and patients respond well to supportive care. In cases involving clonidine patch ingestions, whole-bowel irrigation appears to be an effective intervention.¹⁰²

All patients with CNS depression should be evaluated for hypoxia and hypoglycemia. Those with respiratory compromise, including apnea, often respond well to simple auditory or tactile stimulation.^{4,6,103,124} Significant arousal during preparation for intubation often precludes the need for mechanical ventilation.⁴ Endotracheal intubation should be performed if clinically indicated.

Patients with isolated hypotension should initially be treated with IV boluses of crystalloid: 20 mL/kg in children and 500 to 1000 mL in adults. Bradycardia is typically mild and usually does not require any therapy if adequate peripheral perfusion exists. If the symptomatic bradycardia occurs, then atropine is often effective and redosing may be required.^{4,6,149,239}

It is likely that naloxone was first used in clonidine-poisoned patients because of their clinical findings of CNS and respiratory depression and miosis is similar to opioid-poisoned patients.¹⁷⁴ Clonidine-poisoned patients, particularly children, may have increased arousal, respiratory effort, heart rate, and blood pressure after naloxone administration.^{10,129,174,245} The mechanism for this may relate to modulation of CNS sympathetic outflow by endogenous CNS opioids.^{26,70,116,222}

This concept is supported by a clinical study in which clonidine administration to hypertensive patients for 3 days resulted in a significant decrease in blood pressure. Subsequent administration of 0.4 mg of naloxone parenterally reversed the decrease in blood pressure and heart rate in almost 60% of the patients.⁶⁹ Because of the short duration of effects of naloxone (20–60 minutes) redosing or continuous infusion may be required. As with some synthetic opioids, such as propoxyphene and fentanyl, clinical improvement may occur only after high doses (4–10 mg) of naloxone,^{124,152} and some patients have no response regardless of dose used.^{149,266}

Early onset hypertension is typically self limited and therapy should be cautiously undertaken. If hypertension is severe or prolonged, then treatment with a short acting and titratable antihypertensive such as IV nicardipine and sodium nitroprusside is appropriate.¹⁵⁴ Esmolol may exacerbate this paradoxical hypertension in a manner similar to that which occurs when these xenobiotics are used in cocaine toxicity by inducing unopposed α_1 -receptor stimulation ([Chap. 78](#)). Although oral nifedipine has been used,⁵⁸ its inability to titrate and its unpredictable efficacy make its use inappropriate as well.

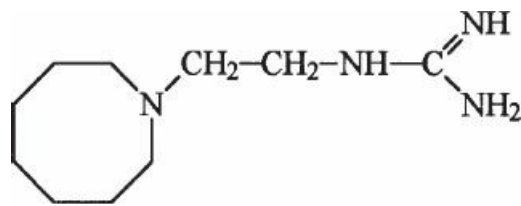
CENTRAL IMIDAZOLINE AGONISTS

Moxonidine and related rilmenidine are also known as second-generation centrally acting antihypertensives and are the newest class of antihypertensives available in the United States.⁶² They are structurally similar to clonidine, but selectively attach at I_1 -imidazoline binding sites which are found predominantly in the rostral ventrolateral medulla, and they have much less affinity for the α_2 -adrenergic receptor.⁶⁶ The exact molecular structure of these imidazoline binding sites has not been determined nor has the exact physiologic cascade or effect of ligand binding at these sites. Therefore these sites are not currently termed “receptors.” Although the exact mechanism of action is still being investigated, binding at these I_1 -imidazoline specific sites ultimately leads to sympathetic outflow from the medulla, vasodilation, and reduction in blood pressure. Nitric oxide or GABA mechanisms may be involved in their central effects.^{190,191} Therapeutically, moxonidine is used both as monotherapy or in combination with the antihypertensives. Patients with diabetes or metabolic syndrome may particularly benefit from moxonidine because of its positive effects on insulin resistance, impaired glucose tolerance, and hyperlipidemia.^{62,72} There is one published overdose resulted in initial hypertension and somnolence suggesting that weak α_2 -adrenergic receptor affinity is overwhelmed in overdose.¹⁴⁸ This patient subsequently had two seizures that were responsive to benzodiazepines however never developed any hypotension.¹⁴⁸

OTHER SYMPATHOLYTIC ANTIHYPERTENSIVES

Several other xenobiotics also exert their antihypertensive effect by decreasing the effects of the sympathetic nervous system. Often termed sympatholytics, they can be classified as ganglionic blockers, presynaptic adrenergic blockers, or α_1 -adrenergic antagonists, depending on their mechanism of action. These drugs are rarely used clinically, and little is known about their effects in overdose.

Presynaptic Adrenergic Antagonists



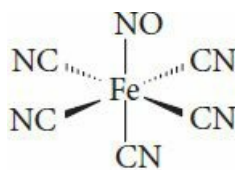
Guanethidine

These xenobiotics exert their sympatholytic action by decreasing norepinephrine release from presynaptic nerve terminals. Whereas guanethidine and guanadrel interfere with the action potential that triggers norepinephrine release,²²⁴ reserpine depletes norepinephrine, serotonin, and other catecholamines from the presynaptic nerve terminals, probably by direct binding and inactivation of catecholamine storage vesicles.⁸⁴ Adverse events limit their clinical usefulness. These effects include a high incidence of orthostatic and exercise-induced hypotension, diarrhea, increased gastric secretions, and impotence.¹⁷⁹ In addition, this hypotensive effect may be prolonged for as long as one week.^{119,225} Because of its ability to cross the blood–brain barrier, reserpine may also deplete central catecholamines and produce drowsiness, extrapyramidal symptoms, hallucinations, migraine headaches, or depression.¹⁴² In overdose, an extension of their pharmacologic effects is expected. Patients with severe orthostatic hypotension should be anticipated and treated with IV crystalloid boluses and a direct-acting vasopressor. If reserpine is involved, significant CNS depression should also be anticipated.¹⁴²

Peripheral α_1 -Adrenergic Antagonists

The selective α_1 -adrenergic antagonists include prazosin, terazosin, and doxazosin. The α_1 receptor is a postsynaptic receptor primarily located on vascular smooth muscle, although they are also found in the eye and in the GI and genitourinary tracts.^{49,107} In fact, these xenobiotics provide first line pharmacologic therapy for patients with urinary dysfunction secondary to benign prostatic hyperplasia.¹³⁶ They produce arterial smooth muscle relaxation, vasodilation, and a reduction of the blood pressure. Although better tolerated than ganglionic blockers and peripheral adrenergic neuron blockers, they may still produce significant symptoms of postural hypotension, including lightheadedness, syncope, or palpitations, particularly after the first dose or if the dosing is rapidly increased.¹⁷ Hypotension and CNS depression ranging from lethargy to coma are reported in overdose.^{135,140,216} In addition, priapism may occur.^{140,208} Treatment includes supportive care, IV crystalloid boluses, and a vasopressor, with phenylephrine being a logical initial choice.

Direct Vasodilators



Nitroprusside

Hydralazine, Minoxidil, and Diazoxide. These xenobiotics produce vascular smooth muscle relaxation independent of innervation or known pharmacologic receptors.^{60,118,126} This vasodilatory effect has been attributed to stimulation of nitric oxide release from vascular endothelial cells. The nitric oxide then diffuses into the underlying smooth muscle cells, stimulating guanylate cyclase to produce cyclic guanosine monophosphate (cGMP). This second messenger indirectly inhibits calcium entry into the smooth muscle cells, producing vasodilation.²¹⁵ Minoxidil, however, also has direct potassium channel activation effects.^{128,176} It has been proposed that the opening of these adenosine triphosphate linked potassium channels results in potassium influx and cell depolarization, thereby reducing calcium influx and ultimately relaxing vascular smooth muscle.³³

As this vasodilation occurs, the baroreceptor reflexes, which remain intact, produce an increased sympathetic outflow to the myocardium, resulting in an increase in heart rate and contractile force. Typically, these xenobiotics are used therapeutically in patients with severe, refractory hypertension and in conjunction with a β -adrenergic antagonist to diminish reflex tachycardia. Hydralazine, minoxidil, and diazoxide are effective orally, but sodium nitroprusside is only used IV. Minoxidil is also used topically in a 2% solution to promote hair growth, and significant poisoning has occurred in suicidal adults who have ingested this formulation.^{68,160} Diazoxide, although previously used to rapidly reduce blood pressure in hypertensive emergencies, is rarely used for this indication now as a consequence of its poor ability to titrate and its variable, and occasionally profound, hypotensive effect.¹²⁵

Adverse effects associated with daily hydralazine use include several immunologic phenomena such as hemolytic

anemia, vasculitis, acute glomerulonephritis, and most notably a lupuslike syndrome.¹⁹⁶ Minoxidil may cause changes on ECG, both in therapeutic doses and in overdose. Sinus tachycardia, ST segment depression, and T-wave inversion are all reported.^{94,198,232} There also appears to be an association with supratherapeutic doses of minoxidil and left ventricular multifocal, subacute necrosis, and subsequent fibrosis.^{96,97} The significance of either of these changes is unknown; they typically resolve with either continued therapy or as other toxic manifestations resolve.^{94,97,232}

The common toxic manifestations of these xenobiotics in overdose are an extension of their pharmacologic action. Symptoms may include lightheadedness, syncope, palpitations, and nausea.^{3,147} Signs may be isolated to tachycardia alone,^{198,232} flushing, or alterations in mental status, which is related to the degree of hypotension.¹⁶⁰ Based on AAPCC annual poison data, in recent years, the majority of reported exposures to this class of drugs may have involved the topical formulation of minoxidil²⁹ (Chap. 136).

After appropriate GI decontamination, routine supportive care should be performed with special consideration to maintaining adequate mean arterial pressure. If IV crystalloid boluses are insufficient, then a peripherally acting α -adrenergic agonist, such as norepinephrine or phenylephrine, is an appropriate next therapy. Dopamine and epinephrine should be avoided to prevent an exaggerated myocardial response and tachycardia from β -adrenergic stimulation.

Nitroprusside. Sodium nitroprusside is effectively a prodrug, exerting its vasodilatory effects only after its breakdown and the release of nitric oxide. The nitroprusside molecule also contains five cyanide radicals that, although gradually released, occasionally produce cyanide or thiocyanate toxicity.^{178,219} Physiologic methemoglobin can bind the liberated cyanide. The binding capacity of physiologic methemoglobin is about 175 $\mu\text{g/kg}$ of cyanide, corresponding to a little less than 500 $\mu\text{g/kg}$ of infused sodium nitroprusside. These cyanide moieties are rapidly cleared, both by interacting with various sulfhydryl groups in the surrounding tissues and blood and enzymatically in the liver by rhodanese, which couples them to thiosulfate-producing thiocyanate.⁷⁶ This cyanide detoxification process in healthy adults occurs at a rate of about 1 $\mu\text{g/kg/min}$, which corresponds to a sodium nitroprusside infusion rate of 2 $\mu\text{g/kg/min}$.^{51,219} It is limited by the sulfur donor availability, so factors that reduce these stores, such as poor nutrition in infants and toddlers, critical illness, surgery, and diuretic use, place patients at risk for developing cyanide toxicity.^{40,51} The hemolysis associated with cardiopulmonary bypass may place the patient at particular risk because the elevated free hemoglobin may accelerate the release of cyanide from the sodium nitroprusside moiety.⁴⁰ Therefore, depending on the balance of cyanide release (eg, rate of sodium nitroprusside infusion) and the rate of cyanide detoxification (eg, sulfur donor stores), cyanide toxicity may develop within hours. Infusion rates greater than 4 $\mu\text{g/kg/min}$ of nitroprusside for greater than 12 hours may overwhelm the capacity of rhodanese for detoxifying cyanide.²⁰⁷ Signs and symptoms of cyanide toxicity include alteration in mental status; anion gap metabolic acidosis; and in late stages, hemodynamic instability. If cyanide poisoning does occur, then hydroxycobalamin is the current treatment of choice for treatment (Chap. 126).

One method of preventing cyanide toxicity from sodium nitroprusside is to expand the thiosulfate pool available for detoxification by the concomitant administration of sodium thiosulfate.^{51,92,164,219} Dosing of 1 g sodium thiosulfate for every 100 mg of nitroprusside is typically sufficient to prevent cyanide accumulation.²⁰⁷ Unfortunately, the thiocyanate formed may accumulate, particularly in patients with renal insufficiency, and produce thiocyanate toxicity.^{76,219} Simultaneous infusion of thiosulfate does not interfere with the vasodilatory effects of sodium nitroprusside.¹⁰⁴ Needless to say, the potential of sodium nitroprusside to produce cyanide poisoning, in addition to the introduction of other equally effective and rapidly titratable antihypertensives, has greatly reduced its use.

Thiocyanate is almost exclusively renally eliminated, with an elimination half-life of 3 to 7 days. It is postulated that a continuous sodium nitroprusside infusion of 2.5 $\mu\text{g/kg/min}$ in patients with normal renal function could produce thiocyanate toxicity within 7 to 14 days, although it may be as short as 3 to 6 days or as little as 1 $\mu\text{g/kg/min}$ in patients with CKD who are not receiving hemodialysis.²¹⁹ The symptoms of thiocyanate toxicity begin to appear at serum concentrations of 60 $\mu\text{g/mL}$ (1 mmol/L); are very nonspecific; and they may include nausea, vomiting, fatigue, dizziness, confusion, delirium, and seizures.⁷⁶ Thiocyanate toxicity may produce life-threatening effects, such as hemodynamic and intracranial pressure elevation, when serum concentrations are above 200 $\mu\text{g/mL}$.^{51,76,92,249} Anion gap metabolic acidosis and hemodynamic instability do not occur with thiocyanate toxicity. Although cyanide or thiocyanate concentrations are not typically useful in the management of patients with cyanide toxicity, they may be beneficial for monitoring critically ill patients who are at risk of thiocyanate poisoning. Hemodialysis clears thiocyanate from the serum and should be strongly considered in patients with significant clinical manifestations of thiocyanate toxicity.^{64,153,166}

Another therapy used to prevent cyanide toxicity from sodium nitroprusside is a simultaneous infusion of hydroxocobalamin.¹²⁸ Dosing of 25 mg/h has successfully reduced cyanide poisoning in humans.^{48,270} As with thiosulfate, simultaneous infusion of hydroxocobalamin does not interfere with the vasodilatory effects of sodium nitroprusside.¹⁰⁴ Because of the relative higher cost of hydroxocobalamin as well its interactions with some laboratory tests, thiosulfate should remain the mainstay of prophylaxis against sodium nitroprusside-induced cyanide toxicity (Antidotes in Depth: A40 and A41).

Diuretics

Diuretics can be divided into three main groups: (1) the thiazides and related compounds, including hydrochlorothiazide and chlorthalidone, (2) the loop diuretics, including furosemide, bumetanide, and ethacrynic acid, and (3) the potassium-sparing diuretics, including amiloride, triamterene, and spironolactone. Two other groups of diuretics—the carbonic anhydrase inhibitors, such as acetazolamide, and osmotic diuretics (eg, mannitol)—are not used as antihypertensive agents.

The thiazides produce their diuretic effect by inhibition of sodium and chloride reabsorption in the distal convoluted tubule. Loop diuretics, in contrast, inhibit the coupled transport of sodium, potassium, and chloride in the thick ascending limb of the loop of Henle. Although their exact antihypertensive mechanism is unclear, an increased urinary excretion of sodium, potassium, and magnesium results from the use of loop diuretics. Potassium-sparing diuretics act either as aldosterone antagonists, such as spironolactone, or as renal epithelial sodium channel antagonists, such as triamterene, in the late distal tubule and collecting duct.¹¹⁴

The majority of toxicity associated with diuretics is metabolic and occurs during chronic therapy or overuse.²⁶⁴ Hyponatremia develops within the first 2 weeks of initiation of diuretic therapy in more than 67% of susceptible patients, and female sex, old age, and malnourishment are the greatest risk factors.^{8,235} Symptoms of severe hyponatremia (< 120 mEq/L) may include headache, nausea, vomiting, confusion, seizures, or coma (Chap. 19). The osmotic demyelination syndrome, formally known as central pontine myelinolysis, is reported during rapid correction of severe hyponatremia secondary to diuretic abuse.⁴⁶

Other electrolyte abnormalities associated with diuretic use include hypokalemia and hypomagnesemia, which may precipitate ventricular dysrhythmias such as torsade de pointes and sudden death. This is an extremely controversial topic, with several excellent studies providing conflicting results.^{21,77,185,228,230} Although it is unclear how great a risk, if any, diuretic use may be, it remains prudent to monitor and correct the patient's potassium concentration.^{108,228,262} This is particularly important in elderly patients and for those patients who concomitantly use digoxin, in which setting hypokalemia is clearly associated with dysrhythmias (Chap. 65).^{28,240} Potassium-sparing diuretics may cause hyperkalemia, particularly in the setting of renal insufficiency or when combined with other hyperkalemia-producing drugs such as ACEIs.¹¹⁸

Thiazide diuretics are associated with inducing hyperglycemia, particularly in patients with diabetes mellitus. This is a result of depletion of total body potassium stores. Because insulin secretion is dependent on transmembrane potassium fluxes, this decrease in potassium concentration reduces the amount of insulin secreted.¹⁴⁴ This effect is dose dependent and reversible either by potassium supplementation or discontinuation of the thiazide diuretic.^{39,100} This association has led to significant work and discussion about the routine use of thiazide diuretics as first-line antihypertensives in the treatment of uncomplicated patients.^{52,90,166} In addition, thiazides are less well tolerated than any other antihypertensive drug class leading to significant noncompliance.¹⁶⁵

Thiazide diuretics are also associated with inducing hyperuricemia, renal calculi, and gout.^{34,91,93} This is because the renal elimination of uric acid is extremely dependent on intravascular and urinary volume so diuretic-induced volume depletion reduces uric acid filtration and increases its proximal tubule resorption.^{226,238}

Several unusual reactions are associated with thiazide diuretic use, including pancreatitis; cholecystitis; and hematologic abnormalities, such as hypercoagulability, thrombocytopenia, and hemolytic anemia.^{61,63,212,214,252,261}

Despite the widespread use of these xenobiotics, acute overdoses are distinctly rare.¹³⁹ Major signs and symptoms include GI distress, brisk diuresis, possible hypovolemia and electrolyte abnormalities, and altered mental status.¹³⁹ Typically, the diuresis is short lived because of the limited duration of effect and the rapid clearance of the majority of diuretics. Assessment should focus on fluid and electrolyte status, which should be corrected as needed. If hyperkalemia is unexpectedly discovered, either the ingestion of a potassium-sparing xenobiotic or, more likely, an overdose of potassium supplements, which are frequently prescribed in conjunction with thiazide and loop diuretics, should be considered.^{111,112} Altered mental status, including coma, may result from diuretic overdose without evidence of any fluid or electrolyte abnormalities.^{17,18,139,213} Postulated mechanisms include a direct drug effect and induction of transient cerebral ischemia due to hypotension.¹⁸⁰

Angiotensin-Converting Enzyme Inhibitors

ACEIs are among the most widely prescribed antihypertensives. At the time of this writing, there are 10 ACEIs approved by the US FDA for the treatment of hypertension (Table 63–1). In general, they are well absorbed from the GI tract, reaching peak serum concentrations within 1 to 4 hours. Enalapril and ramipril are prodrugs and require hepatic metabolism to produce their active forms. Elimination is primarily via the kidneys.

TABLE 63–1. Antihypertensives and Pharmacologically Related Agents

β -Adrenergic antagonists ([Chap. 62](#))

Calcium channel blockers ([Chap. 61](#))

Sympatholytics (antagonize α -adrenergic vasoconstriction)

Central α_2 -adrenergic agonists

Clonidine, dexmedetomidine, guanabenz,^a guanfacine,^a methyldopa,^a tizanidine

Central imidazoline agonists

Moxonidine, rilmenidine

Ganglionic blockers

Trimethaphana

Peripheral adrenergic neuron antagonists

Guanadrel,^a metyrosine,^a reserpine^a

Peripheral α_1 -adrenergic antagonists

Doxazosin, prazosin, silodosin, terazosin

Diuretics

Thiazides

Bendroflumethiazide,^a chlorthalidone,^a chlorothiazide, hydrochlorothiazide, hydroflumethiazide,^a indapamide, methyclothiazide,^a metolazone, polythiazide,^a trichlormethiazide^a

Loop diuretics

Bumetanide, ethacrynic acid, furosemide, torsemide

Potassium-sparing diuretics

Amiloride, eplerenone, spironolactone, triamterene

Vasodilators

Diazoxide,^a hydralazine, minoxidil,^a nitroprusside

Angiotensin-converting enzyme inhibitor

Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril,trandolapril

Angiotensin II receptor blockers

Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan

Direct renin inhibitors

Aliskiren

^aIncluded for historical reference; use as antihypertensive limited in the United States.

All ACEIs have a common core structure of a 2-methylpropanolol-L-proline moiety.⁸¹ This structure binds directly to the active site of ACE, which is found in the lung and vascular endothelium, preventing the conversion of angiotensin I to angiotensin II. Because angiotensin II is a potent vasoconstrictor and stimulant of aldosterone secretion, vasodilation;

decreased peripheral vascular resistance; decreased blood pressure; increased cardiac output; and a relative increase in renal, cerebral, and coronary blood flow occur.⁸¹ This hypotensive response may be severe in select patients after their initial dose, resulting in syncope and cardiac ischemia.^{42,106} Patients with renovascular-induced hypertension and patients who are hypovolemic from concomitant diuretic use appear to be at greatest risk.¹⁰⁶ Overall, however, these drugs are well tolerated and have a very low incidence of side effects. Some reported adverse effects include rash, dysgeusia, neutropenia, hyperkalemia, chronic cough, and angioedema.^{56,81,246} Because of their interference with the renin–angiotensin system, ACEIs are potential teratogens and should never be used by pregnant women or women of childbearing age.¹³

ACEI-Induced Angioedema. Angioedema is an inflammatory reaction in which there is increased capillary blood flow and permeability, resulting in an increase in interstitial fluid. If this process is confined to the superficial dermis, urticaria develops; if the deeper layers of the dermis or subcutaneous tissue are involved, angioedema results. Angioedema most commonly involves the periorbital, perioral, or oropharyngeal tissues.¹⁹⁹ This swelling may progress rapidly over minutes and result in complete airway obstruction and death.^{80,85,223} The pathogenesis of acquired angioedema involves multiple vasoactive substances, including histamine, prostaglandin D₂, leukotrienes, and bradykinin.¹¹⁰ Because ACE also inactivates bradykinin and substance P, ACE inhibition results in elevations in bradykinin concentrations that appear to be the primary cause of both ACEI angioedema and cough (Fig. 63–1).^{5,113} There is no evidence that the ACEI angioedema phenomenon is immunoglobulin E (IgE) mediated.⁵

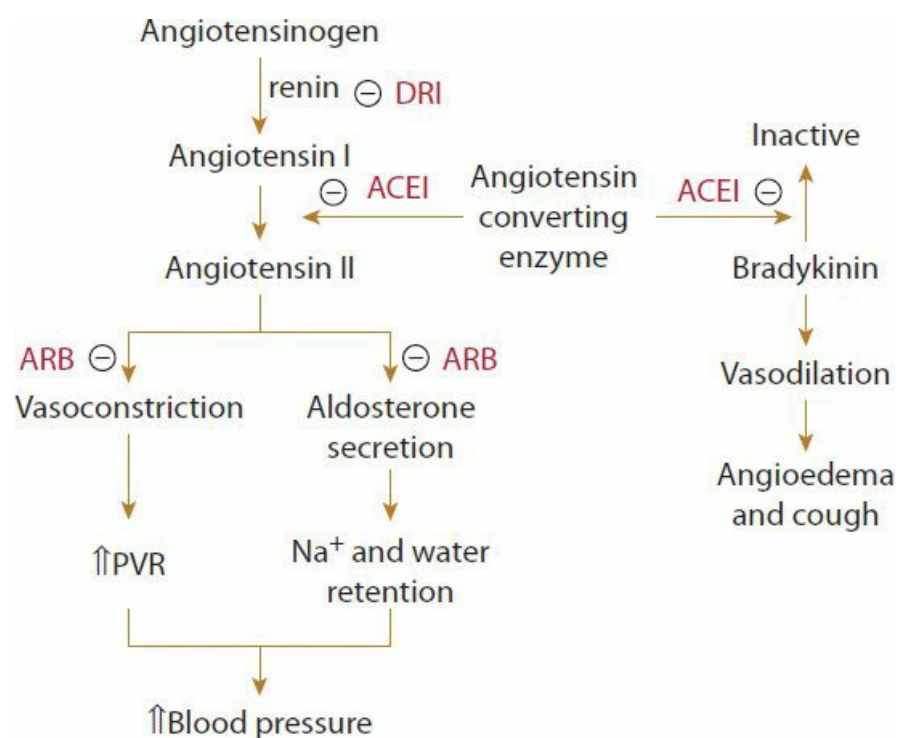


FIGURE 63–1. An overview of the normal function of the renin-angiotensin-aldosterone system (RAAS) and the mechanisms of action of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and direct renin inhibitors (DRIs) on that system. PVR = peripheral vascular resistance.

Although the literature is replete with reports of ACEI angioedema, the overall incidence is only approximately 0.1%, and it is idiosyncratic.^{73,113,231} One-third of these reactions occur within hours of the first dose and another third occur within the first week.^{151,231} It is important to remember that the remaining third of cases may occur at any time during therapy, even after years.⁴¹ Women, African Americans, and patients with a history of idiopathic angioedema appear to be at greater risk.^{151,184} In addition, there is evidence that patients who develop ACEI angioedema are at increased subsequent risk of developing angioedema from any etiology.¹⁶

Treatment varies depending on the severity and rapidity of the swelling. Because of its propensity to involve the tongue, face, and oropharynx, the airway must remain the primary focus of management. A nasopharyngeal airway is often helpful. If there is any potential for or suggestion of airway compromise, then endotracheal intubation should be performed. Severe tongue and oropharyngeal swelling may make orotracheal or nasotracheal intubation extremely difficult, if not impossible. If this is a concern, then fiberoptic nasal intubation may be an attractive option, provided that the resources are available. Other techniques, including retrograde intubation over a guidewire that was passed through the cricothyroid membrane and emergent cricothyrotomy, may also be considered.²⁰⁷ However, the most important aspect of airway management in patients experiencing ACEI angioedema is early risk assessment for airway obstruction and rapid intervention before the development of severe and obstructive swelling.²

Because ACEI angioedema is not an IgE-mediated phenomenon pharmacologic therapy targeting an allergic cascade, such as epinephrine, diphenhydramine, and corticosteroids, should not be expected to be effective. However, when the history is unclear, these medications should not be withheld in order to ensure providing life-saving therapy to someone having a severe IgE-mediated allergic reaction.

Newer treatment modalities developed to target various points along the cascade of events associated with hereditary angioedema may be beneficial in the treatment of ACEI angioedema. Hereditary angioedema results from a genetically mediated defect in C1 inhibitor resulting in limited activity of this enzyme and an increase in kallikrein concentrations. Kallikrein is a protease that cleaves kininogen into bradykinin. The end result is very similar to the cause of ACEI angioedema, namely an activation of vascular bradykinin B2 receptors.¹³ Several new treatments have been developed to target specific steps in the development of hereditary angioedema, including Berinert, a C1 esterase inhibitor, ecallantide, a kallikrein inhibitor, and icatibant, a bradykinin B2 receptor antagonist. Case reports of successful treatment of ACEI angioedema with these xenobiotics are few.^{14,79,177} However, one case series of eight patients with ACEI angioedema who were treated with 30 mg subcutaneous icatibant had more rapid improvement in their signs and symptoms as well as no need for subsequent steroid or diphenhydramine use.¹⁴ While further evidence is needed, icatibant may be a reasonable treatment for ACEI angioedema; however, its significant cost should limit its use only in patients with rapidly progressive or severe angioedema.

Fresh frozen plasma (FFP) which contains ACE has also been proposed as treatment for ACEI angioedema. FFP infusion will elevate ACE concentrations and lead to the degradation of accumulated bradykinin. Clinical use of FFP for the successful treatment of both hereditary and ACEI angioedema is reported.^{122,189,200,263} In these case reports, doses range from 1 to 5 units of FFP (200–250 mL/unit) with most using an infusion of 2 units of FFP as initial, and typically definitive, treatment.²⁰⁰

All patients with mild or rapidly resolving angioedema should be observed for several hours to ensure that the swelling does not progress or return. Outpatient therapy with a short course of oral antihistamines and corticosteroids should be considered if there is any question as to whether ACEI therapy produced the angioedema because allergic-mediated angioedema will benefit from this treatment. Patients developing angioedema from ACEI therapy should be instructed to discontinue them permanently and to consult their primary care physicians about other antihypertensive options. Because this is a mechanistic and not allergic adverse effect, the use of any other ACEIs is contraindicated.

Angiotensin-Converting Enzyme Inhibitor Overdose. The toxicity of ACEIs in overdose appears to be limited.^{43,141} Although several reports of overdoses involving ACEIs are published, the majority of the cases reported manifested toxicity of a coingestant.^{54,89,262} Hypotension may occur in select patients,^{11,12,131} but deaths are rarely reported in isolated ACEI ingestions.^{187,235} Other patients may remain asymptomatic despite high serum drug concentrations.¹³¹

Treatment should focus on supportive care and on identifying any coingestants that may be more toxic, particularly other antihypertensives such as β -adrenergic antagonists and calcium channel blockers. In most cases, AC alone is sufficient GI decontamination. IV crystalloid boluses are often effective in correcting hypotension, although in rare cases, catecholamines may be required.^{7,83} Naloxone may also be effective in reversing the hypotensive effects of ACEIs. ACEIs may inhibit the metabolism of enkephalins and potentiate their opioid effects, which include lowering blood pressure.^{57,167} In a controlled human volunteer study, continuous naloxone infusion effectively blunted the hypotensive response of captopril.¹ In one case report, naloxone appeared to be effective in reversing symptomatic hypotension secondary to a captopril overdose.²⁵⁸ In another published case, naloxone was ineffective.¹¹ Although its role in the setting of ACEI overdose remains unclear, naloxone may obviate the need for large quantities of crystalloid or vasopressors and should therefore be considered.

Angiotensin II Receptor Blockers

ARBs were first introduced in 1995, and currently, six members of this class are marketed in the United States. These xenobiotics are rapidly absorbed from the GI tract, reaching peak serum concentrations in 1 to 4 hours, and then are eliminated either unchanged in the feces or after undergoing hepatic metabolism via the mixed function oxidase system eliminated in the bile.^{156–159,181}

Although these xenobiotics are similar to ACEIs in that they decrease the effects of angiotensin II rather than decrease the formation of angiotensin II, they act by antagonizing angiotensin II at the type 1 angiotensin (AT-1) receptor (Fig. 63–1).¹²³ This allows the drugs to inhibit the vasoconstrictive and aldosterone-promoting effects of angiotensin II and reduce blood pressure by blunting both the sympathetic as well as the renin–angiotensin systems.¹⁵⁶ Despite the mechanistic evidence that ARBs do not affect bradykinin degradation and therefore should have a much lower incidence of angioedema when compared to ACEIs, serious cases of angioedema associated with ARB therapy have been reported.^{38,151,255} In addition, there is a significantly higher incidence of angioedema associated with ARBs when compared to other antihypertensives, such as β -adrenergic antagonists.²⁵⁰

Similar to ACEIs, ARBs should never be used by pregnant patients because of their teratogenic potential.^{13,229} In

addition, when initiating the xenobiotic, up to 1% develop of patients first-dose orthostatic hypotension.⁸⁶

There have been few published reports of overdoses involving ARBs. Adverse signs and symptoms reflect orthostatic or absolute hypotension and include palpitations, diaphoresis, dizziness, lethargy, or confusion.^{74,162,233} Hypotension should be treated with crystalloid boluses and catecholamine therapy.^{162,233} Patients who are chronically taking ARBs may exhibit significant hypotension during induction of general anesthesia that has been refractory to traditional vasoconstrictor therapy, such as norepinephrine, ephedrine, and phenylephrine, but appear to respond to vasopressin.^{23,27,67}

One promising new treatment for hypotension produced by ARBs and ACEIs is methylene blue.^{155,171,251} This treatment was first explored in patients placed on cardiopulmonary bypass (CPB).^{186,236,251} During CPB systemic blood pressure and peripheral vascular resistance decrease due to a number of factors, including acute hemodilution, citrate use in the cardioplegia, a poorly defined inflammatory response that results in nitric oxide release, and an increase in circulating bradykinin.^{45,50,268} This increase in bradykinin, which also mediates its vasodilatory effects via nitric oxide, occurs because bradykinin metabolism is primarily in pulmonary tissue and CPB mechanically bypasses the pulmonary system.^{45,50} ACEIs and ARBs exacerbate this vasodilation by inhibiting bradykinin metabolism.¹⁹⁷ In a double blinded placebo controlled study of 30 patients taking ACEIs who were undergoing elective cardiac surgery requiring CPB, administration of methylene blue at the onset of CPB resulted in an increase in mean arterial pressure and systemic vascular resistance and less use of phenylephrine and norepinephrine.¹⁵⁵ A reasonable starting dose of methylene blue, when used as a vasopressor, appears to be 2 mg/kg with subsequent intermittent boluses or possibly continuous infusions starting at 0.5 mg/kg/h.^{115,155}

DIRECT RENIN INHIBITORS

Direct renin inhibitors (DRIs) such as aliskiren exert their antihypertensive effects via the renin-angiotensin-aldosterone system (RAAS) by directly inhibiting circulating renin.²⁶⁵ Unfortunately, all RAAS acting antihypertensives such as ACEIs, ARBs, and DRIs induce a compensatory increase in serum renin concentrations; however, only DRIs are able to blunt the physiologic effects of this rise.^{32,221,265} Aliskiren is well tolerated and is an effective antihypertensive both as monotherapy and in combination with other antihypertensives, including hydrochlorothiazide, calcium channel blockers, and β -adrenergic antagonists.¹⁴⁴ However, significant controversy surrounds aliskiren use when combined ARBs or ACEIs after a clinical trial was halted due to an increased incidence of ischemic stroke, acute kidney injury, hyperkalemia, and hypotension was noted in patients with diabetes and CKD.¹⁸⁸ There are no reported cases of poisoning or overdose; however, hypotension should be anticipated and treatment that includes supportive care, including IV crystalloid and catecholamines, seems reasonable.

SUMMARY

- These xenobiotics are not often associated with severe poisonings, either because of limited use, as with most of the sympatholytics and direct vasodilators, or because of limited toxicity, as with diuretics, ACEIs, ARBs, and DRIs.
- Severe clonidine poisoning classically presents as the opioid toxidrome producing profound CNS depression and bradycardia.
- Clonidine withdrawal manifests as CNS agitation, tachycardia, and hypertension and should be treated with clonidine or benzodiazepines.
- Nitroprusside infusions greater than 4 $\mu\text{g/kg/min}$ may result in cyanide poisoning which can be prevented with coadministration of thiosulfate or hydroxycobalamin.
- Because of the pathogenesis of ACEI-induced angioedema, it is unlikely to respond to “typical” allergic treatment such as antihistamines, epinephrine, and steroids. Rather, focus should be on definitive airway management in patients with rapidly progressing swelling or symptoms.

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64 ANTIDYSRHYTHMICS

Lewis S. Nelson

HISTORY AND EPIDEMIOLOGY

The term dysrhythmia encompasses an array of abnormal cardiac rhythms that range in clinical significance from merely annoying to instantly life threatening. Antidysrhythmics include all medications that are used to treat any of these various dysrhythmias. The importance of dysrhythmia management in the modern practice of medicine cannot be overstated, as dysrhythmias are among the most common causes of preventable sudden cardiac death.⁴²

For a long time antidysrhythmics were considered among the most rational of the available cardiac medications. This well-earned reputation related to their high efficacy at reducing the incidence of malignant dysrhythmias. Similarly, they are effective at controlling discomforting rhythm disorders. However, this approach changed dramatically following publication of the Cardiac Arrhythmia Suppression Trials (CAST and CAST II),²³ and, more recently, with the rise of mechanical interventions, such as ablation therapy and implantable defibrillators. CAST assessed the ability of three antidysrhythmics to suppress asymptomatic ventricular dysrhythmias known to be harbingers of sudden death. The original CAST was discontinued in 1989 before completion, when encainide and flecainide, two of the study medications, not only failed to prevent sudden death but actually increased overall mortality. CAST II noted similar problems with moricizine.⁹² It has since become clear that the enhanced mortality associated with many antidysrhythmics is a result of their prodysrhythmogenic effects and that virtually all medications of this group carry such risk. Since patients with atrial fibrillation do not benefit from rhythm conversion compared to control of the ventricular response rate, the use of antidysrhythmics for this indication is now uncommon.⁸⁰

In addition to the predictable, mechanism-based adverse effect of each medication, unique and often unanticipated effects also occur.⁷⁵ Experience with overdose of many of these medications is limited, and management is generally based on the underlying pharmacologic principles, existing case reports, and the experimental literature. This chapter focuses on the medications that serve primarily as antidysrhythmics and, with the exception of lidocaine ([Chap. 67](#)), have few other medicinal indications. [Chapter 16](#) provides a more detailed description of the electrophysiology of dysrhythmias and a discussion of their genesis. In addition, the toxicities from Ca^{2+} channel blockers and β -adrenergic antagonists, which have indications in addition to dysrhythmia control, are discussed separately in [Chaps. 61 and 62](#).

CLASSIFICATION OF ANTIDYSRHYTHMICS

Despite an incomplete understanding of the underlying mechanisms of dysrhythmia formation, an abundance of antidysrhythmics have been developed, each attempting to alter specific electrophysiologic components of the cardiac impulse generating or conducting system.

Antidysrhythmics modify impulse generation and conduction by interacting with various membrane Na^+ , K^+ , and Ca^{2+} channels. Generally, antidysrhythmics manifest electrophysiologic effects either through alteration of the channel pore or, more commonly, by modification of its gating mechanism ([Fig. 62–1](#)). Unfortunately, given their exceedingly complex mechanisms of action, the descriptive terms used to explain their molecular actions are not always completely accurate. For example, the description of an antidysrhythmic as a specific “channel blocker,” although representative of the conceptual action of that medication, is inaccurate because in most cases the molecule does not actually block the channel but rather prevents the channel from opening or closing properly. Furthermore, many of these medications are active nonspecifically at other channels or on other cells, resulting in divergent clinical actions of similarly classified medications.

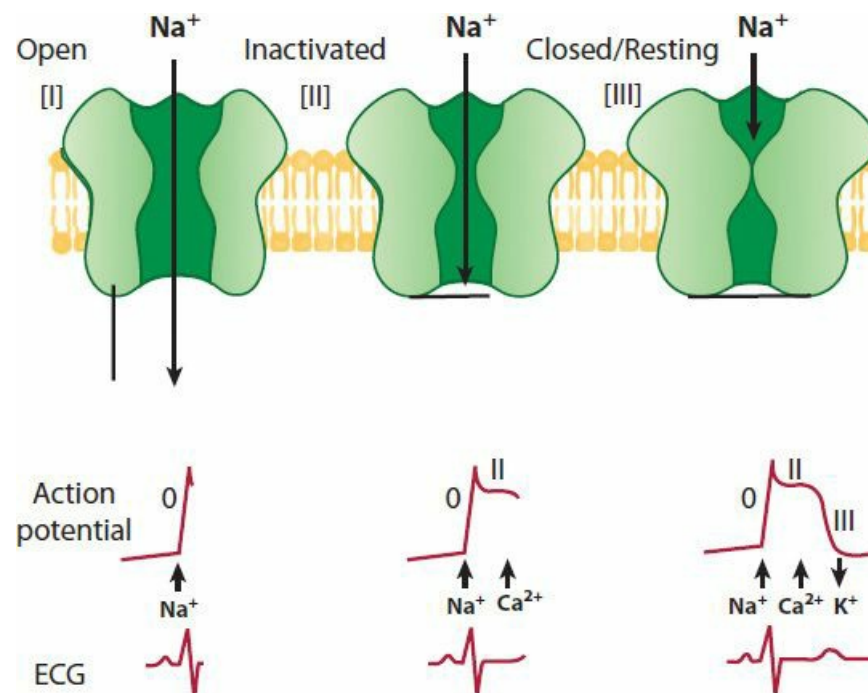


FIGURE 64–1. Sodium channel blockade. On appropriate signal, Na^+ channel activation occurs, at which time the sodium channel converts from the resting [III] state to the open state [I]. This allows sodium ion influx to initiate phase 0 of the action potential, or cellular depolarization. The sodium channels subsequently assume the inactivated state by closure of an inactivation gate; this is a voltage-dependent phenomena and occurs concomitantly with—although more slowly than—channel activation. Cellular depolarization is maintained for a period of time by other ion channels that form the plateau of the action potential. Prior to reactivating, sodium channels must convert back to the resting state, which also occurs in a voltage-dependent fashion. Many antidysrhythmics stabilize the inactivated state of the channel and, by slowing conversion to the resting state, prevent its reopening, reducing the excitability of the cell. As this is a population phenomena, there are dose-dependent effects on channel blockade; thus, more medication interferes with more channels. Interestingly, certain xenobiotics, such as ciguatoxin and aconitine, stabilize the open state of the sodium channel and produce persistent depolarization.

The Vaughan-Williams classification of antidysrhythmics by electrophysiologic properties emphasizes the connection between the basic electrophysiologic actions and the antidysrhythmic effects.⁹³ Although initially proposed as a descriptive model for electrophysiologic actions and not for clinical effects, the Vaughan-Williams classification is commonly invoked as a user friendly guide to clinical therapy. In 1991, a competing system known as “the Sicilian Gambit” was constructed by a task force of European cardiologists based on the mechanisms by which antidysrhythmics modify dysrhythmogenic mechanisms.⁷⁸ Although perhaps more contemporary in theory, this latter classification system is complex and was therefore never widely implemented. An even more rational classification would match the electrophysiologic effects of the antidysrhythmics with their molecular interactions on different regions of the various ion channels, such as channel gating and pore conductance.

This discussion of antidysrhythmics uses the Vaughan-Williams classification, recognizing the shortcomings delineated above.⁹⁷ The pharmacokinetic properties of the various medications are summarized in [Table 64–1](#).

TABLE 64–1. Antidysrhythmics: Pharmacology, Pharmacokinetics, and Adverse Effects

<i>Antidysrhythmic</i>	<i>Route</i>	<i>Primary Route of Elimination</i>	<i>Elimination $t_{1/2}$</i>	<i>Channel Blockade</i>	<i>Volume Distribution L/Kg</i>	<i>Protein Binding (%)</i>	<i>Adverse Effects and Complicating Factors</i>	<i>Other</i>
Class IA								
Disopyramide	PO	Liver, kidney	5–10 hours	Na ⁺ ($\tau = 9s$), K ⁺ , Ca ²⁺	0.59 ± 0.15	35–95 depending on plasma concentration	CHF, negative inotropic effects, anticholinergic, torsade de pointes, heart block, hypoglycemia	
Procainamide	IV, PO	50%–60% unchanged in kidney; active hepatic metabolite (NAPA)	PA: 3–4 hours ↑ CKD NAPA: 6–10 hours ↑ CKD	Na ⁺ ($\tau = 1.8s$), K ⁺	1.9 ± 0.3	16 ± 9	Hypotension (ganglionic blockade), QRS widening, fever, Lupus-like syndrome, torsade de pointes	NAPA: active metabolite, renally eliminated, K ⁺ channel blocker; $t_{1/2}$ 6–10 hours; sustained-release PA preparation is available
Quinidine	PO	Liver, kidney, 10%–20% unchanged	6–8 hours ↑ liver disease (to >50 hours) and renal failure (to 9–12 hours)	Na ⁺ ($\tau = 3s$), K ⁺ , Ca ²⁺	2.7 ± 1.2	87 ± 3	Heart block, sinus node dysfunction, prolonged QT, hypotension, hypoglycemia, torsade de pointes, thrombocytopenia, ↑ (digoxin)	
Class IB								
Lidocaine	SC, IV, PO (30% BA)	Liver, active metabolite (MEGX, CYP3A4)	8 minutes after bolus 2-hour terminal	Na ⁺ ($\tau = 0.1s$)	1.1 ± 0.4	70 ± 5	Fatigue, agitation, paresthesias, seizures, hallucinations, rarely bundle branch block	Metabolites: GX and MEGX, are less potent as Na ⁺ channel blockers than lidocaine
Mexiletine	IV, PO	Liver (CYP2D6)	10–24 hours	Na ⁺ ($\tau = 0.3s$)	4.9 ± 0.5	63 ± 3	See lidocaine	
Phenytoin	IV, PO	Liver		Na ⁺ ($\tau = 0.2s$)	0.64 ± 0.04	89 ± 23	Hypotension and asystole related to IV propylene glycol infusion, nystagmus, ataxia	
Tocainide	IV, PO	Kidney, liver	9–14 hours	Na ⁺ ($\tau = 0.4s$)	3.0 ± 0.2	10 ± 15	See lidocaine, aplastic anemia, interstitial pneumonia	
Class IC								
Flecainide	IV, PO	Liver (CYP2D6) 75%, kidney 25%	20 hours	Na ⁺ ($\tau = 11s$), Ca ²⁺ , K ⁺	4.9 ± 0.4	61 ± 10	Negative inotropic effects, bradycardia, heart block, ventricular fibrillation, ventricular tachycardia, neutropenia	Two metabolites, one active
Moricizine	PO	Liver	2–4 hours	Na ⁺ ($\tau = 10s$)	?	95	↑ Mortality after myocardial infarction, bradycardia, CHF, ventricular fibrillation, ventricular tachycardia	
Propafenone	IV, PO	Liver (CYP2D6) [extensive first pass]	2–10 hours	Na ⁺ ($\tau = 1s$), K ⁺	3.6 ± 2.1	85 ± 95	Asthma, CHF, hypoglycemia, AV block, QRS prolongation, bradycardia, ventricular fibrillation, ventricular tachycardia	Active metabolite 5-OH-propafenone
Class II								
β-Adrenergic antagonists	IV, PO	Variable	Variable	β-Adrenergic receptor	Variable	Variable	CHF, asthma, hypoglycemia, Raynaud disease	

Class III								
Amiodarone	IV, PO	Liver (100%) (CYP3A4)	2 months	Na ⁺ , K ⁺ , Ca ²⁺	66 ± 44	99.98 ± 0.01	Negative inotropic effects, pulmonary fibrosis, corneal microdeposits, thyroid abnormalities, hepatitis photosensitivity, ↑ diltiazem, quinidine, procainamide, flecainide, digoxin concentrations	Desethylamiodarone has comparable activity to the parent compound
Dofetilide	IV, PO	Kidney	7.5 hours	K ⁺	3.6 ± 0.8	64	Torsade de pointes	Active N-dibutyl metabolite (10%–33% potency)
Dronedarone	PO	Liver (CYP3A4)	13–19 hours	Na ⁺ , K ⁺ , Ca ²⁺	20	>98	Contraindicated in decompensated heart failure, atrial fibrillation that cannot be converted. Liver, thyroid, and pulmonary toxicity (less than amiodarone)	
Ibutilide	IV	Kidney	2–12, average 6 hours	K ⁺ , Na ⁺ opener	11	40	Torsade de pointes, heart block	
Class IV								
Ca ²⁺ channel blockers	IV, PO	Variable	Variable	Ca ²⁺	Variable	Variable	Asystole (if used IV with IV β-adrenergic receptor antagonists), AV block, hypotension, congestive heart failure, constipation, ↑ [digoxin]	
Not classified								
Adenosine	IV	All cells (intracellular adenosine deaminase)	Seconds	Nucleoside-specific G protein-coupled adenosine receptors, ↑ Ca ²⁺ currents activates ACh-sensitive K ⁺ current			Transient asystole < 5 s, chest pain, dyspnea, atrial fibrillation, ↓ BP, effects potentiated by dipyridamole and in heart transplant patients, ↑ dose needed with methylxanthine use	

$\tau_{1/2, \text{Na}^+}$ describes the time it takes for the Na⁺ channel to recover from blockade

AV = antivenetricular; BA = bioavailable; BP = blood pressure; CHF = congestive heart failure; CKD = chronic kidney disease; GI = glycine xylidide; IV = intravenous; NAPA = N-acetylprocainamide; MEGX = monoethylglycidyl ether; PO = oral; SC = subcutaneous.

CLASS I ANTIDYSRHYTHMICS

All antidysrhythmics in Vaughan-Williams class I (A, B, and C) alter Na⁺ conductance through cardiac voltage-gated, fast inward Na⁺ channels (Table 64–1). These medications bind to the Na⁺ channels and slow their recovery from the open or inactivated state to the resting state (Fig. 64–1). This conversion must occur before the channel can reopen and participate in another depolarization. Consequently, as the proportion of medication bound Na⁺ channels increases, fewer of these channels are capable of reactivation on the arrival of the next depolarizing impulse. As a result, by reducing the excitability of the myocardium, abnormal rhythms are both prevented and terminated.

Blockade of these Na⁺ channels slows the rise of phase 0 of the cellular action potential, which correlates with a reduction in the rate of depolarization of the myocardial cell (or V_{max}). Similarly, conduction through the myocardium is slowed, producing a measurable prolongation of the QRS complex on the surface electrocardiogram. Correspondingly, slowed intra-myocardial conduction is associated with reduced contractility, manifesting as negative inotropy. Myocardial depression also results from effects of reduced intracellular Na⁺ on Na⁺-Ca²⁺ exchange.⁶¹ This, in turn, reduces the intracellular Ca²⁺ concentration, which is required for adequate contractility.

The differences among class I antidysrhythmics are directly related to their pharmacologic relationships with the Na⁺

channel. However, it is noteworthy that the original subdivision of class I antidysrhythmics was based on clinical observations, not current pharmacologic awareness, accounting for the somewhat illogical ordering of the class I subdivisions.⁹⁷ Type IB antidysrhythmics have their highest affinity for inactivated Na⁺ channels. This occurs at the end of depolarization, during early repolarization, and during periods of myocardial ischemia, all situations in which the myocardium is partially depolarized. These medications also have rapid “on–off” binding kinetics (rapid τ_{recovery}) and are thus bound only briefly, during late electrical systole, the period during which the Na⁺ channels are predominantly in the inactivated form. They are almost exclusively unbound during electrical diastole, which is the major portion of the cardiac cycle at normal heart rates. However, the degree of binding increases as the heart rate accelerates, because the duration of diastole decreases and the relative proportion of time spent in systole increases; this is termed use dependence. Because all IB antidysrhythmics do not bind to activated Na⁺ channels, in therapeutic doses they do not affect the rate of rise of phase 0 of the action potential, or V_{max} , and have no effect on the electrocardiogram. Alternatively, the class IC antidysrhythmics preferentially act on activated Na⁺ channels or they release from the Na⁺ channels very slowly (slow τ_{recovery}), and, thus, are still bound during the next cardiac cycle. This prolonged channel blockade and reduced channel reactivation result in both greater pharmacologic effects and toxicity, even at slow heart rates. These medications reduce V_{max} and prolong the QRS complex. Class IA antidysrhythmics fall between the other two subclasses.

Although in the Vaughan-Williams classification all class I antidysrhythmics are considered primarily Na⁺ channel blockers, many, particularly those in class IA, have important effects on cardiac K⁺ channels. These channels are critical to maintenance of the cardiac action potential and repolarization of the myocardial cell. Slowing of K⁺ efflux prolongs the duration of the action potential and accounts for the persistence of refractoriness, or the time during which the cell is incapable of repolarization. This effect produces QT prolongation and predisposes to the triggering of polymorphic ventricular tachycardia.⁴³ Because class IB antidysrhythmics have no effect on myocardial K⁺ channels, they do not alter refractoriness or the QT interval. In fact, class IB antidysrhythmics often reduce the action potential duration, shortening refractoriness. Further discussion of K⁺ channel blockade is found in [Chap. 16](#) and in the discussion of class III antidysrhythmics below.

See [Table 64–1](#) for a description of the pharmacokinetics and clinical properties of the various antidysrhythmics.

Class IA Antidysrhythmics: Procainamide, Quinidine, and Disopyramide

Procainamide. Procainamide can be used to suppress either atrial or ventricular tachydysrhythmias. Importantly, procainamide undergoes hepatic biotransformation by acetylation to N-acetylprocainamide (NAPA), the rate of which is genetically determined.⁶⁴ Although NAPA lacks the Na⁺ channel-blocking activity of procainamide, it prolongs the action potential duration through blockade of the K⁺ rectifier currents, and for this reason is available as the class III antidysrhythmic acecainide.³⁸

Rapid intravenous dosing of procainamide is potentially dangerous because its initial volume of distribution is smaller than its final volume of distribution. Because this initial compartment includes the heart, adverse myocardial effects may be unexpectedly pronounced. Thus, to prevent toxicity during medication infusion, the intravenous loading dose is generally administered by slow infusion with electrocardiographic monitoring. Both procainamide and NAPA are renally eliminated and may accumulate in patients with chronic kidney disease (CKD).⁵⁵

Although the chronic use of procainamide is commonly accompanied by the development of antinuclear antibodies or medication-induced systemic lupus erythematosus,³⁹ this syndrome is not associated with acute poisoning. Furthermore, NAPA has less propensity than procainamide to produce this syndrome.³⁸ Other reported adverse effects include seizures and antimuscarinic effects with acute overdose and myopathic pain, thrombocytopenia, and agranulocytosis following long-term use.

Serum concentrations of both procainamide and NAPA serum concentrations should be determined as part of therapeutic drug monitoring (therapeutic: 5–20 $\mu\text{g/mL}$) and in patients with procainamide overdose. Because the elimination half-life of procainamide is 3 to 4 hours, which is substantially shorter than that of NAPA (6–10 hours), chronic overdosing typically results in NAPA toxicity.⁴ In this situation, the QT interval, a reflection of K⁺ channel blockade, correlates directly, and blood pressure correlates inversely, with the degree of poisoning. Severe effects usually do not occur until total (procainamide plus NAPA) serum concentrations are greater than 60 $\mu\text{g/mL}$. Because of its structural similarity with amphetamine, patients with procainamide overdose may have a false-positive urine enzyme-multiplied immunoassay test (EMIT) for amphetamines.⁹⁸

Quinidine. Quinidine, the d-isomer of quinine, is derived from the bark of the cinchona tree. Because it is a weak base, it is typically formulated as the sulfate or gluconate salt. Quinidine undergoes hydroxylation by the liver, and both active and inactive metabolites are renally eliminated.

Quinidine was once widely used for the management of atrial or ventricular dysrhythmias, but has largely fallen out of favor due to its adverse effects. Quinidine has substantial cardiotoxicity that includes intraventricular conduction

abnormalities and an increased QT interval. “Quinidine syncope,” in which patients on therapeutic doses of quinidine experience paroxysmal, transient loss of consciousness, is most frequently a result of torsade de pointes.⁴¹

Because quinidine shares many pharmacologic properties with quinine (Chap. 59), patients may occasionally experience cinchonism following either chronic or acute quinidine overdose. This syndrome includes abdominal symptoms, tinnitus, and altered mental status. Quinidine also produces both peripheral and cardiac antimuscarinic effects, which enhance conduction via the atrioventricular (AV) node. Furthermore, as with quinine, quinidine-induced blockade of K⁺ channels in pancreatic islet cells may cause uncontrolled insulin release, leading to hypoglycemia.⁶⁹

Serum quinidine concentrations greater than 14 µg/mL are associated with cardiotoxicity,⁴⁷ as evidenced by a 50% increase in either the QRS or QT interval.

Disopyramide. Disopyramide (Fig. 64–2) is more likely than other class IA antidysrhythmics to produce negative inotropy and congestive heart failure. This effect may be noted both in patients receiving therapeutic dosing,⁸⁸ and in those who overdose, and may be related to the blockade of myocardial Ca⁺⁺ channels caused by disopyramide. The current use of disopyramide for the treatment of patients with hypertrophic cardiomyopathy capitalize on this clinical effect.²⁵ The mono-N-dealkylated metabolite of disopyramide produces the most pronounced anticholinergic effects of the class,⁹⁵ accounting for the occasional, though unproven, use of disopyramide to treat neurocardiogenic syncope.⁷⁷ Lethargy, confusion, or hallucinations may be prominent in overdose.

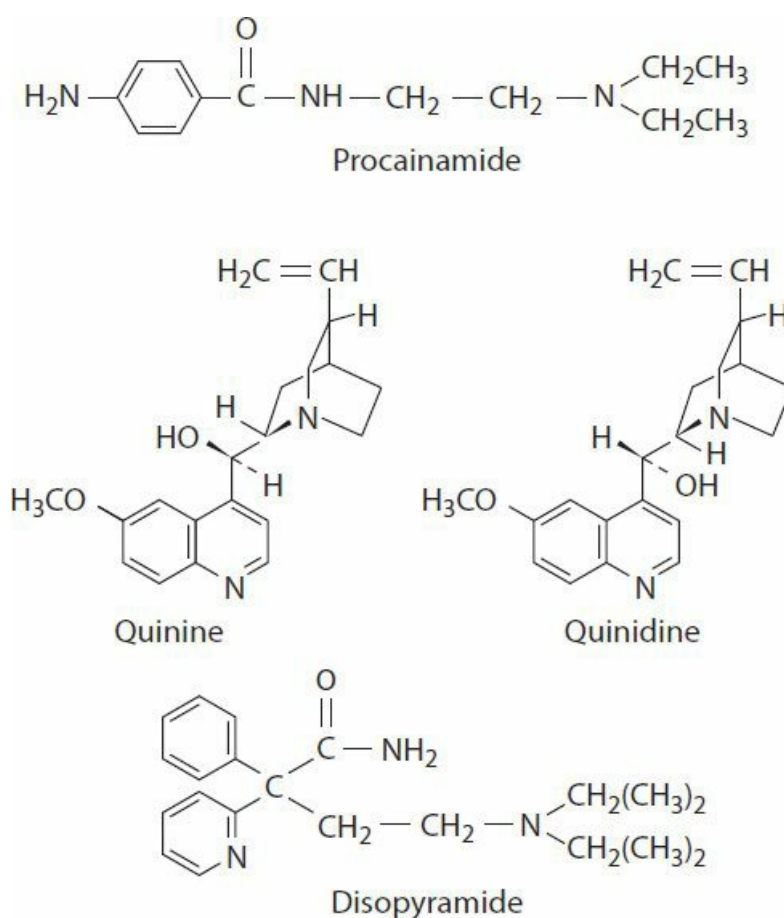


FIGURE 64–2. Structures of class IA antidysrhythmics and quinine.

Electrophysiologic abnormalities similar to those associated with poisoning from other class IA antidysrhythmics can occur, including intraventricular conduction abnormalities, torsade de pointes, and other ventricular dysrhythmias. Disopyramide may cause hyperinsulinemic hypoglycemia through its antagonism of K⁺ channels in the pancreatic islet cells.¹

Management of Class IA Antidysrhythmic Toxicity. Management concentrates on assessment and correction of cardiovascular dysfunction. Following airway evaluation and intravenous line placement, 12-lead electrocardiography (ECG) and continuous ECG monitoring are of paramount importance. Appropriate gastrointestinal decontamination is recommended when the patient is sufficiently stabilized and should include whole-bowel irrigation if a sustained-release preparation is involved (Chap. 8 and Antidotes in Depth: A2).

For patients who have widening of the QRS complex duration, bolus administration of intravenous hypertonic sodium bicarbonate is indicated (Antidotes in Depth: A5). Depolarization is accelerated and the QRS complex duration is reduced, by enhancing rapid Na⁺ ion influx through the myocardial Na⁺ channels.⁸ However, hypokalemia from the use of sodium bicarbonate may further prolong the QT interval, requiring careful monitoring of the serum K⁺ and ECG. Class IA

antidysrhythmic-induced hypotension is treated primarily with rapid infusion of 0.9% NaCl to expand intravascular volume and to simultaneously increase myocardial contractility by enhancing the Starling force. Hypotension in the setting of QRS complex duration prolongation may respond favorably to hypertonic sodium bicarbonate, which enhances inotropy by both accelerating depolarization and raising intravascular volume. Dobutamine (an inotrope) or norepinephrine (an inotrope and pressor), and intraaortic balloon pump insertion may also be required, but their use has not been systematically evaluated. Because disopyramide also blocks Ca^{2+} channels, Ca^{2+} administration is reportedly beneficial,² although evidence to support this antidotal effect is lacking. Glucagon effectively reversed myocardial depression in canine models, but it has not been evaluated in humans.⁶³

Patients with stable ventricular dysrhythmias occurring in the setting of class IA antidysrhythmic poisoning are usually treated with hypertonic sodium bicarbonate or lidocaine. Although it may seem counterintuitive to administer another class I antidysrhythmic to a patient already poisoned by a class I antidysrhythmic, there is sound theoretical and experimental literature to support the use of lidocaine in this setting.⁹⁹ Because lidocaine is a class IB antidysrhythmic with rapid on-off receptor kinetics, it may displace the “slower” class IA antidysrhythmic from the binding site on the Na^+ channel, effectively reducing channel blockade. Sodium bicarbonate enhances conduction through the myocardium, promoting spontaneous termination of the ventricular dysrhythmia. Magnesium sulfate and overdrive pacing may be helpful in preventing recurrent torsade de pointes. Medications that must be avoided in treating patients with dysrhythmias associated with class IA poisoning include other class IA and IC antidysrhythmics, as well as the β -adrenergic antagonists and Ca^{2+} channel blockers, all of which may exacerbate conduction abnormalities or produce hypotension.

The roles of charcoal hemoperfusion, hemofiltration, and continuous arteriovenous hemodiafiltration are inadequately defined, but may be most beneficial for removing NAPA.⁵⁵ There is no clinical evidence to support the use of hemodialysis or hemoperfusion for quinidine or disopyramide poisoning.¹

Class IB Antidysrhythmics: Lidocaine, Tocainide, Mexiletine, and Moricizine

Lidocaine. Lidocaine (Fig. 64–3) is an aminoacyl amide that is a synthetic derivative of cocaine. Its predominant clinical uses are as a local anesthetic and, for mechanistically similar reasons, to control ventricular dysrhythmias. The high frequency of lidocaine-related medication errors relates in part to its wide use in the past as well as the availability of “amps” of varying quantities, designed for specific uses such as preparation of intravenous infusions or for local anesthesia.⁴⁴ Lidocaine may prevent myocardial reentry and subsequent dysrhythmia (Chap. 16) by preferentially suppressing conduction in compromised tissue.⁸⁹ Following an intravenous bolus, lidocaine rapidly enters the central nervous system but quickly redistributes into the peripheral tissue with a distribution half-life of approximately 8 minutes.⁹ Lidocaine is 95% dealkylated by hepatic CYP3A4 to an active metabolite, monoethylglycylxylidide (MEGX) and, subsequently, to the inactive glycine xylidide (GX). GX is further metabolized to monoethylglycine and xylidide. MEGX, although less potent as a Na^+ channel blocker than lidocaine, may bioaccumulate because of its substantially longer half-life.⁶

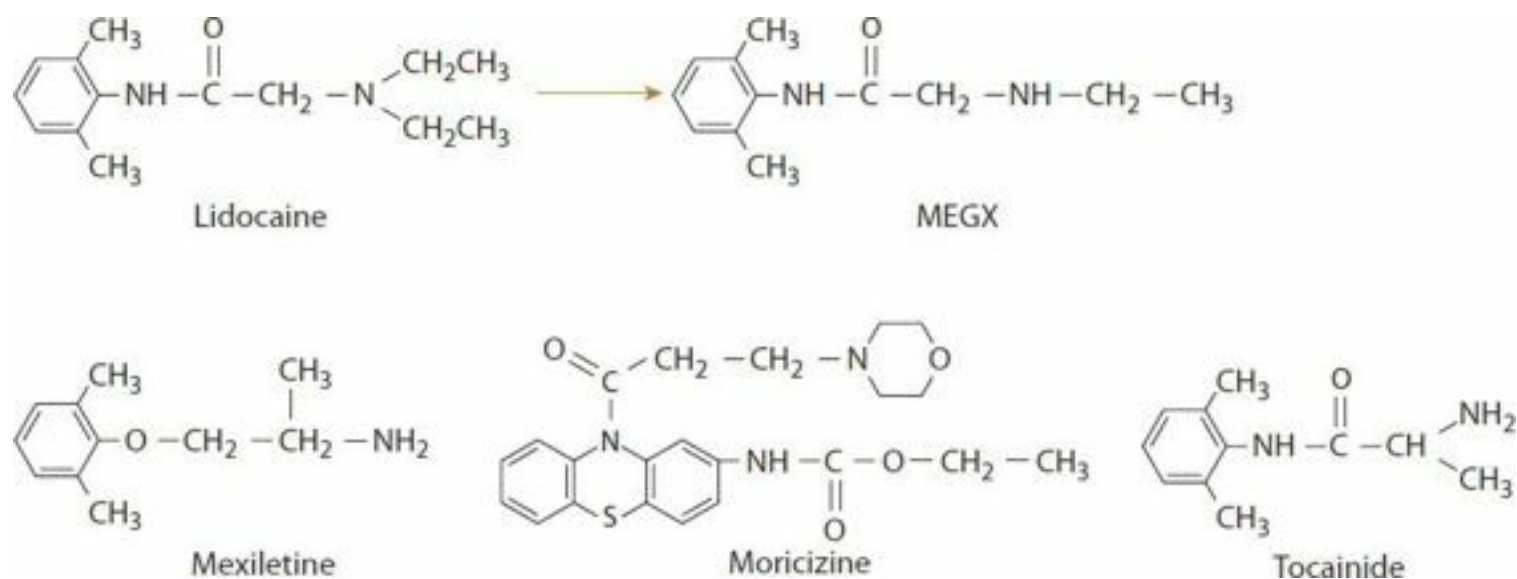


FIGURE 64–3. Structures of the class IB antidysrhythmics lidocaine (and metabolite monoethylglycylxylidide), tocainide, mexiletine, and moricizine.

Patients with massive lidocaine toxicity develop both central nervous system and cardiovascular effects, generally in that order. Because of its rapid entry into the brain, acute lidocaine poisoning typically produces central nervous system dysfunction, with paresthesias or convulsion, as the initial manifestation.^{28,74,84} Concomitant respiratory arrest generally

occurs. Shortly following the central nervous system effects, depression in the intrinsic cardiac pacemakers leads to sinus arrest, AV block, intraventricular conduction delay, hypotension, and/or cardiac arrest. If the patient is supported through this period, then the medication rapidly distributes away from the heart, and spontaneous cardiac function returns.

Acute submassive lidocaine toxicity is generally related to excessive or inappropriate parenteral therapeutic dosing. Common settings include inadvertent intravenous administration instead of the intended route and excessive subcutaneous administration during laceration repair. Acute lidocaine toxicity may occur also with topical tracheal application of lidocaine used for bronchoscopy,¹⁰¹ during circumcision,⁷⁴ as well as ureteral application during ureteroscopic stone extraction.⁶⁶ The typical central nervous system (CNS) manifestations of submassive lidocaine poisoning include drowsiness, weakness, a sensation of “drifting away,” euphoria, diplopia, decreased hearing, paresthesias, muscle fasciculations, and seizures. The more severe of these effects develop when serum lidocaine concentrations exceed 5 µg/mL and are often preceded by paresthesias or somnolence. Therefore, any of these symptoms should prompt the health care professional to examine the patient’s medication administration history or medication-infusion rate. Apnea and seizures, as well as hypotonia in neonates, are reported to result from submassive acute lidocaine toxicity.⁷³

A related form of toxicity and death results from subcutaneous and adipose administration of lidocaine during tumescent liposuction.⁷¹ In this technique, a large volume of dilute lidocaine is used to distend subcutaneous fat prior to liposuction.⁷ Although in some reports the cause of death was controversial,⁷⁰ postmortem lidocaine concentrations were commonly elevated, and it is likely that lidocaine metabolites were also involved in the adverse events.⁴⁵ Interestingly, proponents of this procedure suggest that lidocaine doses up to a maximum of 55 mg/kg are safe,⁷ whereas the conventional recommended limit for subcutaneous lidocaine with epinephrine is only 5 to 7 mg/kg. Of significant concern is that the recommended doses used for liposuction procedures do not consider the ability of lidocaine to saturate the CYP3A4 enzymes. When saturation occurs, elimination lags behind absorption and lidocaine toxicity may result.

Numerous publications unequivocally demonstrate the toxicity associated with orally administered lidocaine despite its poor bioavailability.^{16,102} Some of the toxicity may be due to MEGX. Because of the relatively high concentration of viscous lidocaine (typically 4%), this preparation is overrepresented in reports of oral lidocaine poisoning.¹⁰² As little as 15 mL of 2% viscous lidocaine in a 3 year-old child (estimate, 300 mg or 21.4 mg/kg/dose) may cause seizures.

Chronic lidocaine toxicity most commonly occurs as a result of therapeutic misadventure in patients on lidocaine infusions, generally in a critical care unit. Toxicity following appropriate dosing is most likely to occur in patients with reduced hepatic blood flow as occurs with congestive heart failure, liver disease, or concomitant therapy with CYP3A4 and CYP1A2 inhibitors ([Chap.9](#)).⁹⁴ Adverse reactions to lidocaine also increase with advancing age, decreasing body weight, and increasing infusion rate. Chronic lidocaine toxicity occurs in 6% to 15% of patients receiving infusions at 3 mg/min for several days.⁸² Partly for this reason, lidocaine is no longer routinely used to prevent dysrhythmias in the immediate postmyocardial infarction period. The clearance of lidocaine falls after approximately 24 hours of the start of an infusion, and this effect may be due to competition for hepatic metabolism between lidocaine and its metabolites.

Mexiletine. Mexiletine, originally developed as an anorectic, was found to have antidysrhythmic, local anesthetic, and anticonvulsant activity.¹³ It is currently available in oral form for the management of ventricular dysrhythmias and is also used for the management of chronic neuropathic pain. Its chemical structure and electrophysiologic properties are similar to those of lidocaine. Mexiletine, a base, is absorbed in the small intestine; therefore, its absorption is increased when the gastric contents are alkalinized. Congestive heart failure and cirrhosis, as well as therapy with cimetidine or disulfiram, decrease the clearance of mexiletine.⁵¹ Its metabolism, predominantly through CYP2D6, is accelerated by concomitant use of phenobarbital, rifampin, and phenytoin.

Adverse therapeutic effects are primarily neurologic and are similar to those that occur with lidocaine. The few reported cases of mexiletine overdose describe prominent cardiovascular effects such as complete heart block, torsade de pointes, and asystole.^{18,31} Neurotoxicity resulting from overdose includes self-limited seizures, generally in the setting of cardiotoxicity. Moreover, a single case report described a patient with mexiletine poisoning who experienced status epilepticus without any hemodynamic or electrocardiographic abnormalities.⁶⁰ Mexiletine may produce a false-positive result on the amphetamine immunoassay of the urine.^{18,48}

Moricizine. Moricizine possesses the general qualities of class I antidysrhythmics, but is difficult to specifically subclassify as it has properties that place it in both classes IB or IC.¹⁷ Historically it is discussed as a class IB antidysrhythmic, as it is here. The parent medication undergoes extensive and rapid metabolism. Dose-related lengthening of PR and QRS intervals are expected, as are hemiblocks, bundle blocks, and sustained ventricular tachydysrhythmias. Experience in the setting of myocardial infarction during CAST II suggests that it is a prodysrhythmic.⁹² Clinical experience with overdose is limited, but is expected to be similar to that of other class I antidysrhythmics.

Management of Class IB Antidysrhythmic Toxicity. The focus of the initial management for intravenous lidocaine-induced cardiac arrest is continuous cardiopulmonary resuscitation to allow lidocaine to redistribute away from the heart. Apart from this setting, management of hemodynamic compromise includes fluid replacement and other conventional strategies. Resistant hypotension may require norepinephrine administration, insertion of an intraaortic balloon assist pump,

or bypass.³³ Cardiopulmonary bypass, which does not directly enhance elimination, maintains hepatic perfusion, thereby allowing the lidocaine to be metabolized.³³ Bradydysrhythmias typically do not respond to atropine, requiring the administration of a chronotrope such as norepinephrine or isoproterenol. External pacing or insertion of a transvenous pacemaker may be useful, but the myocardium is often refractory to electrical capture. Lidocaine-induced seizures, and those related to lidocaine analogs, are generally brief in nature and do not require specific therapy. For patients requiring treatment, an intravenous benzodiazepine generally suffices; rarely, a barbiturate is required. Similarly, although intravenous fat emulsion is often described as useful for the resuscitation of patients with life threatening local anesthetic overdose, its use for lidocaine poisoned patients is limited to case reports and likely unnecessary given the rapid time course of recovery (Antidotes in Depth: A20). Enhanced elimination techniques are limited following intravenous poisoning because of the rapid time course of poisoning.³³

Following oral poisoning by a class IB antidysrhythmic, activated charcoal should be administered as appropriate. Lidocaine and its metabolites are not well cleared by hemodialysis,²² and there are no adequate data to support the use of extracorporeal removal for mexiletine or moricizine.

Class IC Antidysrhythmics: Flecainide and Propafenone

Flecainide. Flecainide, a derivative of procainamide, is orally administered to maintain sinus rhythm in patients with structurally normal hearts who have atrial fibrillation or supraventricular tachycardia.⁹⁰ Kidney disease, medication interactions, and congestive heart failure all decrease the clearance of flecainide and its active metabolite. Additionally, alkaluria reduces its clearance, presumably by enhanced tubular reuptake of nonionized medication. Therapeutic doses may produce left ventricular dysfunction with worsening congestive heart failure. This is presumably a result of the negative inotropic effect of flecainide, which itself may relate to its antagonistic effects on Ca^{2+} channels. Furthermore, sudden dysrhythmic death may occur, particularly in patients with underlying ischemic heart disease.⁹⁰

A 50% increase in QRS complex duration, a 30% prolongation of the PR interval, or a 15% prolongation of the QT interval occurs with flecainide toxicity.⁸⁷ The expected consequences of these electrophysiologic disturbances include bradycardia, premature ventricular contractions, and ventricular fibrillation. The combination of marked QRS and PR interval changes, associated with minimal QT interval prolongation, is characteristic of flecainide toxicity and contrasts with those described with other antidysrhythmics.

Propafenone. Propafenone bears a structural resemblance to propranolol,³⁰ as well as similar qualitative, but not quantitative, electrophysiologic properties.²⁷ Propafenone blocks fast inward Na^+ channels, is a weak β -adrenergic antagonist, and is an L-type Ca^{2+} channel blocker.²⁷ Its long half-life allows the accumulation of parent compound, particularly in patients with the slow metabolizer pharmacogenetic variant of CYP2D6, which may cause excessive β -adrenergic antagonism.⁵² Propafenone overdose produces sinus bradycardia, ventricular dysrhythmias, and negative inotropy. The electrocardiogram often shows right bundle-branch block, first-degree AV block, and prolongation of the QT interval. Generalized seizures may also occur.⁶⁵

Management of Class IC Antidysrhythmic Toxicity. Initial stabilization should include standard management strategies for hypotension and seizures. Additionally, therapy for hypotension, and the electrocardiographic manifestations of class IC poisoning, includes intravenous hypertonic sodium bicarbonate to overcome the Na^+ channel blockade.⁶⁰ Several reports of overdose in humans verify QRS complex narrowing in response to hypertonic sodium bicarbonate administration for flecainide^{10,40,54} and propafenone.⁶⁵ Although sodium loading with hypertonic saline may be similarly effective, it remains unproven. The renal elimination of flecainide is reduced by urinary alkalization, suggesting that sodium chloride, in equimolar doses, may ultimately prove superior to sodium bicarbonate.⁵⁸ The administration of other class IC or IA antidysrhythmics is contraindicated because of their additive blockade of the Na^+ channel. Similarly, the administration of phenytoin to a child with propafenone poisoning was associated with a prolongation of the QRS interval, which initially responded to sodium bicarbonate, but the patient subsequently developed bradyasystolic arrest.⁵⁷ However, amiodarone was successful in the setting of flecainide-induced ventricular fibrillation refractory to other therapy.⁸⁵ As with β -adrenergic antagonists, an animal model suggests that hyperinsulinemic euglycemic therapy may be beneficial following propafenone poisoning.¹⁰³ The efficacy of an external or internal pacemaker may be limited because of the medication-induced increased electrical pacing threshold of the ventricle. Successful therapy with cardiopulmonary bypass or extracorporeal membrane oxygenation is reported and should be considered if available.^{5,20} Intravenous fat therapy was reportedly successful in patients with severe flecainide poisoning²⁴ and propafenone poisoning,⁹⁶ although the safety and efficacy of this therapy remain undefined.

Extracorporeal removal is not expected to be beneficial for patients with flecainide poisoning. Although hemodialysis was successful in removing propafenone following overdose, additional studies are needed to determine its clinical benefit.¹¹

CLASS III ANTIDYSRHYTHMICS

Amiodarone, Dofetilide, Dronedarone, and Ibutilide

The class III antidysrhythmics prevent and terminate reentrant dysrhythmias by prolonging the action potential duration and effective refractory period without slowing conduction velocity during phase 0 or 1 of the action potential. This effect on the action potential is generally caused by blockade of the rapidly activating component of the delayed rectifier K^+ current, which is responsible for repolarization.

The class III antidysrhythmics currently used today help prolong repolarization of both the atria and ventricles. Thus, common electrocardiographic effects at therapeutic doses include prolongation of the PR and QT intervals and abnormal T and U waves. Chapter 16 contains a detailed discussion of the pharmacologic mechanisms of class III antidysrhythmics, and Chaps. 16 and 62 discuss sotalol.

Amiodarone and Dronedarone. Amiodarone (Fig. 64–4) is an iodinated benzofuran derivative that is structurally similar to both thyroxine and procainamide. Forty percent of its molecular weight is iodine. Dronedarone is an analog of amiodarone that does not contain iodine.⁴⁹ The 2005 revision of the ACLS guidelines placed tremendous emphasis on the early intravenous administration of amiodarone, and it has retained its prominence in subsequent revisions. Both medications are primarily used to terminate or prevent atrial fibrillation, and, although dronedarone is less effective and has safety issues,¹⁹ it is not associated with many of the potentially severe adverse effects of amiodarone.⁸¹

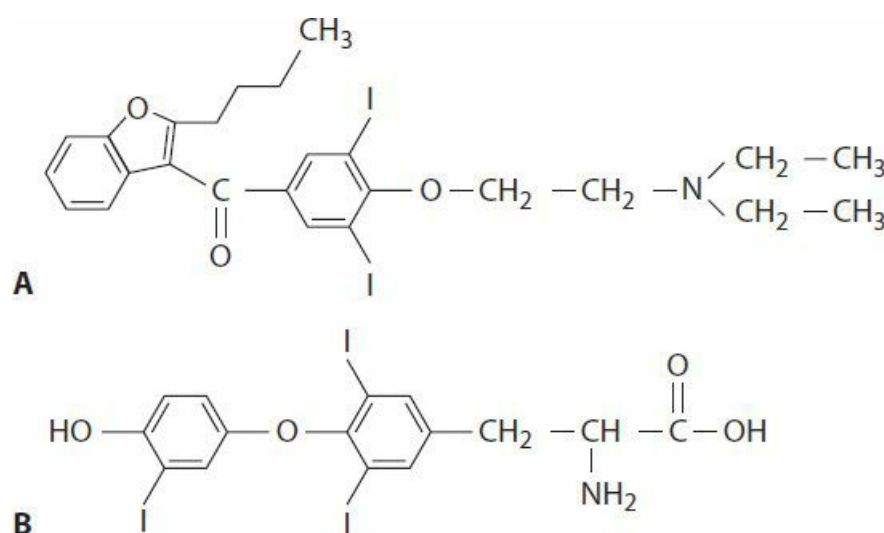


FIGURE 64–4. Structures of amiodarone (A) compared with triiodothyronine (T₃) (B). Note that amiodarone is nearly 40% iodine by weight.

Although amiodarone and dronedarone have multiple pharmacologic effects, their efficacy is primarily the result of their class III antidysrhythmic effects. They also have weak α - and β -adrenergic antagonist activity and can block both L-type Ca^{2+} channels and inactivated Na^+ channels. Amiodarone is slowly absorbed by the oral route and is concentrated in the liver, lung, and adipose tissue. It has a very long elimination half-life, measured in weeks, and steady-state pharmacokinetics may not occur until after a month of use. Dronedarone has a half-life of about 24 hours and a smaller volume of distribution.

The electrocardiographic effects of amiodarone differ, based on the route of medication administration. Therapeutic oral doses prolong the PR and QT intervals but does not alter the QRS complex. Intravenous dosing may prolong the PR interval, but has few other electrocardiographic manifestations. Ventricular dysrhythmias and sinus bradycardia are the most serious cardiac complications of therapeutic doses of amiodarone. Monomorphic and polymorphic ventricular tachycardias may be resistant to cardioversion and pharmacologic interventions,²⁹ but are surprisingly uncommon given the frequency and extent to which the QT interval prolongation occurs. The ability of amiodarone to compete for P-glycoprotein is responsible for several consequential drug effects, including elevated digoxin and cyclosporin concentrations and enhanced anticoagulation effectiveness of warfarin⁵⁰ (Chap. 9).

The diverse complications associated with long-term amiodarone therapy do not occur following short-term intravenous use. Chronic therapy with oral amiodarone is associated with substantial pulmonary, thyroid, corneal, hepatic, and cutaneous toxicities due to bioaccumulation in these organs. Dronedarone may rarely cause hepatic or pulmonary toxicity.²¹ Many of these effects appear to be dose related, but because of the wide range of bioavailabilities and metabolic patterns among different patients, as well as the overlap between therapeutic and toxic serum concentrations, therapeutic drug monitoring is of limited benefit.³⁵ Pneumonitis, the most consequential extracardiac adverse effect, occurs in up to 5% of patients taking the medication therapeutically. Amiodarone pneumonitis may develop within days of initiating therapy, but typically occurs only after years of therapy. Its occurrence may be dose related: a daily dose of more than 400 mg is a

risk factor, and pneumonitis is rare in those taking less than 200 mg daily. The recent focus on using the minimal effective dose has reduced the incidence of pneumonitis.²⁶ Oxygen supplementation may speed the development of pneumonitis, which may explain the initial belief that patients with chronic lung disease are at increased risk for amiodarone pneumonitis. Manifestations of pneumonitis include dyspnea, cough, hemoptysis, crackles, hypoxia, and radiographic changes.¹⁴ Computed tomography is the most helpful initial diagnostic test for pneumonitis, but is not useful for monitoring purposes, which is often done with diffusing capacity of CO.³⁵ Bronchoalveolar lavage typically reveals interstitial pneumonitis with many macrophages and a characteristic finely vacuolated foamy cytoplasm, but confirmation of the diagnosis requires open lung biopsy.

Thyroid dysfunction, either amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH), occurs in approximately 4% of patients.¹⁵ AIH is more common than AIT when iodine intake is sufficient.³⁵ AIH is likely caused by an exaggerated Wolff-Chaikoff effect, in which iodine, in this case from amiodarone, inhibits the organification and release of thyroid hormone. AIT appears to exist in two distinct forms: type I AIT, which occurs in patients with abnormal thyroid glands and iodine-induced excessive thyroid hormone synthesis and release, and type II AIT, in which destructive thyroiditis leads to release of thyroid hormone from the damaged follicular cells. The relative prevalence of the two forms of AIT is unknown, but it may depend on the ambient iodine intake. Amiodarone may also reduce the effect of thyroid hormone on peripheral tissue. The diagnosis is confirmed with standard thyroid function testing⁹¹ (Chap. 56).

Corneal microdeposits are extremely common during chronic therapy and may lead to vision loss.⁵⁶ Abnormal elevation of hepatic enzymes occurs in more than 30% of those on long-term therapy, and the hepatotoxicity may be associated with progression to cirrhosis. Periodic monitoring of aminotransferases is typically recommended.³⁵ Hepatotoxicity may occur after initial loading of amiodarone.⁷² Slate gray or bluish discoloration of the skin is common, particularly in sun-exposed portions of the body.⁷⁶

Dofetilide. Dofetilide is approved for conversion of atrial fibrillation or atrial flutter to a normal sinus rhythm. Dofetilide increases the effective refractory period more substantially in atrial tissue than in ventricular fibers, accounting for this clinical indication.⁷⁹ Unlike many of the other antidysrhythmics, it may reduce the morbidity of atrial fibrillation in patients with congestive heart failure and is still used despite the emphasis on rate control instead of rhythm control in treating atrial fibrillation. Dofetilide has no known effect on Ca²⁺ or Na⁺ channels, nor does it result in β -adrenergic antagonism. Dofetilide increases the QT interval, but does not change either the PR interval or QRS complex in humans. Heart rate and blood pressure are also not appreciably affected.

Although limited data are available, the expected and reported adverse cardiac events include ventricular tachycardia, particularly torsade de pointes.¹⁰⁰ The approximate incidence of torsade de pointes in patients receiving high therapeutic doses of the medication is 3%.³ For this reason, the US Food and Drug Administration has in place strict requirements for the use of dofetilide, such as an individualized dose initiation algorithm and mandatory hospitalization for initial therapy.⁴⁶

Overdose data reported by the manufacturer include two cases. One patient reportedly ingested 28 capsules and experienced no events, whereas a second patient inadvertently received two supratherapeutic doses one hour apart and experienced fatal ventricular fibrillation after the second dose.⁶⁸ A 33 year-old man ingested 5 mg (20 capsules) and developed QT prolongation within one hour of ingestion, but had no dysrhythmia during his 4-day hospital stay.

Ibutilide. Ibutilide is an antidysrhythmic with predominant class III activity used for the rapid conversion of atrial fibrillation and flutter to normal sinus rhythm. Because of its extensive first-pass metabolism, ibutilide can only be administered parenterally. Its metabolic pathways are not well understood, but do not involve CYP3A4 or CYP2D6. Pharmacokinetic data thus far do not indicate that age, sex, hepatic, or CKD necessitates adjustment of recommended dosage of ibutilide. In addition to its effects on the delayed rectifier current, ibutilide activates a slow inward Na⁺ current.⁵⁹

Ibutilide can increase the QT interval and cause torsade de pointes, especially in patients with congenital long-QT syndrome and in women.³⁶ Although ibutilide can enhance the efficacy of transthoracic cardioversion for atrial fibrillation, its use in patients with ejection fractions below 20% is associated with an increased incidence of sustained polymorphic ventricular tachycardia. Acute kidney injury, including biopsy-identified crystals, is reported in association with ibutilide cardioversion, but a causal relationship is not yet definitive.³² Acute overdose information, only available in limited form (four patients) through the manufacturer, suggests that ventricular dysrhythmias and high-degree AV conduction abnormalities should be expected.⁶⁷

Management of Class III Antidysrhythmic Toxicity

Treatment experience with class III antidysrhythmic overdose is limited. Isoproterenol and overdrive pacing have been used successfully to prevent recurrent torsade de pointes after initial spontaneous resolution or defibrillation.⁸³ Administration of class IB antidysrhythmics or propranolol for the control of monomorphic ventricular tachycardia cannot be recommended on theoretical grounds. Paradoxically, amiodarone may reduce the “torsadogenic” effects of the other

class III antidysrhythmics.⁸⁶ This effect is likely mediated by the beneficial effects of amiodarone on the dispersion of myocardial repolarization and its Ca^{2+} channel-blocking activity.

Multiple-dose activated charcoal may be helpful if used shortly following overdose. Hemodialysis is not expected to be beneficial in general, either because of extensive protein binding or because of large volumes of distribution (Table 64–1). A neonate survived cardiovascular collapse with the use of extracorporeal membrane oxygenation (ECMO) following an iatrogenic intravenous amiodarone overdose.³⁷ Fat emulsion sequesters amiodarone, which may be beneficial in amiodarone toxicity,⁶² but caution should be taken when amiodarone is utilized as a treatment for another poisoning requiring lipid emulsion therapy.

UNCLASSIFIED: ADENOSINE

Adenosine, a nucleoside found in all cells, is released from myocardial cells under physiologic and pathophysiologic conditions. It is administered as a rapid IV bolus to terminate reentrant supraventricular tachycardia. The effects of adenosine are mediated by its interaction with specific G protein-coupled adenosine (A_1) receptors that activate acetylcholine-sensitive outward K^+ current in the atrium, sinus nodes, and AV nodes. The resultant hyperpolarization reduces the rate of cellular firing. Adenosine also reduces the Ca^{2+} currents, and its antidysrhythmic activity results from its effect in increasing AV nodal refractoriness and from inhibiting delayed after depolarizations elicited by sympathetic stimulation.⁵³

Adverse effects of adenosine administration are very common and include transient asystole, dyspnea, chest tightness, flushing, hypotension, and atrial fibrillation. Although bronchospasm occurs following pulmonary vascular administration, it is not reported following routine intravenous use. Dyspnea, and probably chest tightness, is related to adenosine stimulation of the pulmonary vagal C fibers.¹² Fortunately, most of the adverse effects of adenosine are transient because of its rapid metabolism to inosine by both extracellular and intracellular deaminases. The clinical effects are potentiated by dipyridamole, an adenosine uptake inhibitor,³⁴ and by denervation hypersensitivity in cardiac transplant recipients. Methylxanthines may produce adenosine receptor blockade (Chap. 66). In this setting, larger-than-usual doses of adenosine are required to produce an antidysrhythmic effect. Overdose of adenosine is not reported. Treatment is supportive because of the rapid elimination of the medication.

SUMMARY

- In the overdose setting, classes IA, IB, and C antidysrhythmics are all associated with Na^+ channel blockade, which can cause profound wide complex cardiac dysrhythmias and morbidity if not judiciously treated.
- Class IC antidysrhythmics are considerably more toxic than the other class I antidysrhythmics, although even class IB antidysrhythmics may be lethal in overdose. Dysrhythmias are their primary toxicologic effect.
- Class III antidysrhythmics in overdose can cause malignant dysrhythmias, particularly torsade de pointes. Amiodarone has many noncardiac effects, particularly pneumonitis and thyroid effects, which limit its therapeutic usefulness.
- Proper management of both adverse effects and overdose can be accomplished only by understanding the pharmacokinetics and toxicokinetics of these medications.

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Neal A. Lewin, MD, Mary Ann Howland, PharmD, and Harold Osborn, MD, contributed to this chapter in previous editions.

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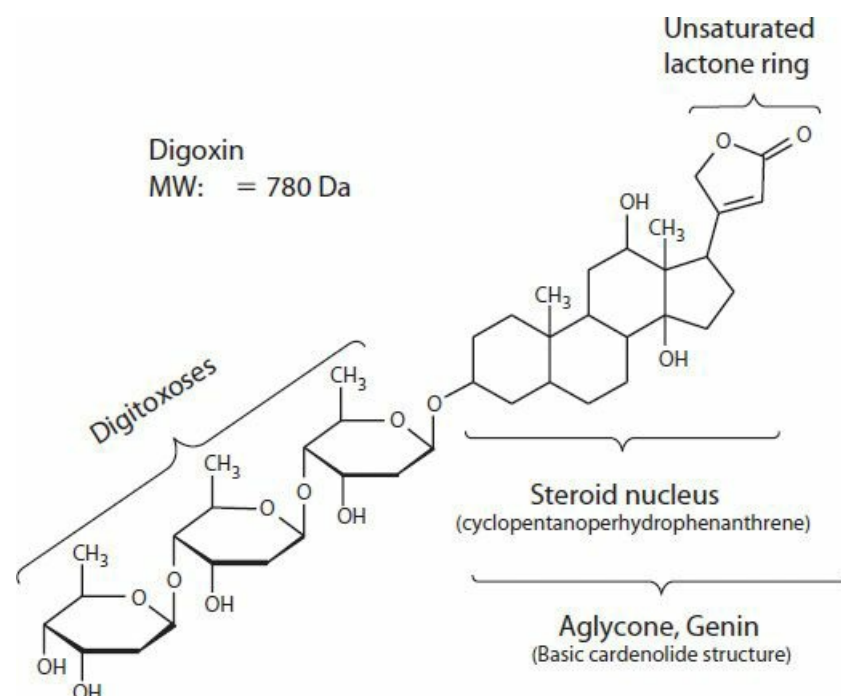
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65 CARDIOACTIVE STEROIDS

Jason B. Hack



HISTORY AND EPIDEMIOLOGY

The Ebers Papyrus provides evidence that the Egyptians used plants containing cardioactive steroids (CASs) at least 3000 years ago. However, it was not until 1785, when William Withering wrote the first systemic account about the effects of the foxglove plant, that the use of CASs was more widely accepted into the Western apothecary. Foxglove, the most common source of plant CAS, was initially used as a diuretic and for the treatment of “dropsy” (edema), and Withering eloquently described its “power over the motion of the heart, to a degree yet unobserved in any other medicine.”¹²⁴

Subsequently, CASs became the mainstay of treatment for congestive heart failure and to control the ventricular response rate in atrial tachydysrhythmias. Because of their narrow therapeutic index and widespread use, both acute and chronic toxicities remain important problems.⁸⁴ According to the American Association of Poison Control Centers data, between the years 2006 and 2011, there were approximately 8000 exposures to CAS-containing plants with one attributable deaths and about 14,500 exposures to CAS-containing xenobiotics resulting in more than 100 deaths (Chap. 136).

Pharmaceutically induced CAS toxicity is typically encountered in the United States from digoxin; other internationally available but much less commonly used preparations are digitoxin, ouabain, lanatoside C, deslanoside, and gitalin. Digoxin toxicity most commonly occurs in patients at the extremes of age or those with chronic kidney disease (CKD). In children, most acute overdoses are unintentional by mistakenly ingesting an adult’s medication, or iatrogenic resulting from decimal point dosing errors (digoxin is prescribed in submilligrams, inviting 10-fold dosing calculation errors), or the elderly who are at risk for digoxin toxicity, most commonly from interactions with another medication in their chronic regimen or indirectly as a consequence of an alteration in the absorption or elimination kinetics. These include drug–drug interactions from an adult’s polypharmacy or from additional acute care xenobiotics that change CAS clearance in the liver or kidney, may alter protein binding and may result in increased bioavailability.

CAS toxicity may also result from exposure to certain plants or animals, including oleander (*Nerium oleander*), yellow oleander (*Thevetia peruviana*), which has been implicated in the suicidal deaths of thousands of patients in Southeast Asia,²⁶ foxglove (*Digitalis* spp), lily of the valley (*Convallaria majalis*), dogbane (*Apocynum cannabinum*), and red squill (*Urginea maritima*). CAS poisoning may result from teas containing seeds of these plants and water and herbal products contaminated with plant CASs (Chap. 45).^{16,19,52,79,90,97,116} Toxicity has resulted from ingestion, instead of the intended topical application, of a purported aphrodisiac derived from the dried secretion of toads from the *Bufo* species, which

contains a bufadienolide-class CAS.^{10,12,13} Although there have been no reported human exposures, fireflies of the Photinus species (*P. ignitus*, *P. marginellus*, and *P. pyralis*) contain the CAS lucibufagin that is structurally a bufadienolides (see Chemistry).^{30,65}

CHEMISTRY

Cardioactive steroids contain an aglycone or “genin” nucleus structure with a steroid core and an unsaturated lactone ring attached at C-17. Cardioactive glycosides contain additional sugar groups attached to C-3. The sugar residues confer increased water solubility and enhance the ability of the molecule to enter cells. Cardenolides are primarily plant-derived aglycons with a five-membered unsaturated lactone ring. The bufadienolide and lucibufagin groups of CAS molecules are mainly animal derived and contain a six-membered unsaturated lactone ring (a plant derived exception is scillaren from red squill). Thus when the aglycone digoxigenin is linked to one or more hydrophilic sugar (digitoxoses) moieties at C-3, it forms digoxin, a cardiac glycoside. The aglycone of digitoxin differs from that of digoxin by the absence of a hydroxyl group on C-12, and ouabain differs from digoxin by both the absence of a hydroxyl group on C-12 and the addition of hydroxyl groups on C-1, C-5, C-10, and C-11. The cardioactive components in toad secretions are genins and lack sugar moieties.

PHARMACOKINETICS

The correlation between clinical effects and serum concentrations is based on steady-state concentrations, which are dependent on absorption, distribution, and elimination (Table 65–1). Although not proven, other CASs likely follow the absorption and distribution pattern of digoxin or digitoxin such that obtaining a serum concentration before 6 hours after ingestion (the time at which tissue concentrations plateau) gives a misleadingly high (predistribution) serum concentration. After therapeutic dosing, the intravascular distribution and elimination of digoxin from the plasma are best described using a two-compartment model that is achieved over approximately 36 to 48 hours in patients with normal kidney function. The distribution or α -phase represents the decrease in intravascular drug concentration and is dependent on whether the route of exposure was intravenous (IV) or oral (PO). Blood concentrations decline exponentially with a distribution half-life of 30 minutes as the drug moves from the blood to the peripheral tissues. Most of the intravascular CAS leaves the blood and distributes to the tissues, resulting in a large volume of distribution (Vd) (eg, the Vd of digoxin is 5–7 L/kg with therapeutic use). The β or elimination phase for digoxin has a half-life of approximately 36 hours and represents the total-body clearance of the drug, which is achieved primarily by the kidneys (70% of its clearance in a person with normal kidney function).^{17,46}

TABLE 65–1. Pharmacology of Selected Cardioactive Steroids

Myocardial irritability causing dysrhythmias

Atrial flutter and atrial fibrillation with atrioventricular (AV) block

Bidirectional ventricular tachycardia

Delayed after-depolarizations

Nonparoxysmal atrial tachydysrhythmias with AV block

Nonsustained ventricular tachycardia

Premature and sustained ventricular contractions

Ventricular bigeminy

Ventricular fibrillation

Primary conduction system dysfunction causing dysrhythmias

Junctional tachycardia

AV dissociation

High degree AV block

Sinus bradycardia

Exit blocks

His-Purkinje dysfunction

Sinoatrial nodal arrest

After a massive acute digoxin overdose, the apparent half-life may be shortened to as little as 13 to 15 hours because elevated serum concentrations result in greater renal clearance before distribution to the tissues.^{51,111} Even with therapeutic administration of CAS, adjustments to the dosing regimen must be made to avert toxicity caused by the physiologic changes associated with aging, including hypothyroidism, chronic hypoxemia with alkalosis, and decreased glomerular filtration rate (GFR). Physiologic changes in CAS kinetics occur with functional decline of the liver, kidney, and heart and dynamics with electrolyte abnormalities, including hypomagnesemia, hypercalcemia, hypernatremia, and commonly hypokalemia. Therefore, serum concentrations should be monitored to avoid inadvertent toxicity. Hypokalemia resulting from a variety of mechanisms, such as the use of loop diuretics, poor dietary intake, diarrhea, and the administration of potassium-binding resins, enhances the effects of CASs on the myocardium and is associated with toxicity at lower serum CAS concentrations. Chronic hypokalemia reduces the number of Na^+ - K^+ -adenosine triphosphatase (ATPase) units in skeletal muscle, which may also alter drug effects.⁶³

Drug interactions between digoxin and quinidine, verapamil, diltiazem, carvedilol, amiodarone, and spironolactone are common.^{20,23,45,68,93} These interactions occur because of a reduction in the protein binding of the CAS, increasing availability to the tissues; a reduction in excretion as a consequence of a decrease in renal perfusion; or, as a result of interference with secretion by the kidneys and intestines, because of inactivation of P-glycoproteins. Also, in approximately 10% to 15% of patients receiving digoxin, a significant amount of digoxin is inactivated in the gastrointestinal (GI) tract by enteric bacterium, primarily *Eubacterium lentum*. Inhibition of this inactivation by the alteration of the GI flora by many antibiotics, particularly macrolides, results in increased bioavailability⁷³ and increased serum CAS concentrations.⁹²

MECHANISMS OF ACTION AND PATHOPHYSIOLOGY

Electrophysiologic Effects on Inotropy

It is currently believed that CASs increase the force of contraction of the heart (positive inotropic effect) by increasing cytosolic Ca^{2+} during systole. Both Na^+ and Ca^{2+} ions enter and exit cardiac muscle cells during each cycle of depolarization and contraction–repolarization and relaxation. Sodium entry heralds the start of the action potential (phase 0) and carries the inward, depolarizing positive charge. Calcium subsequently enters the cardiac myocyte through L-type calcium channels during late phase 0 and the plateau phase of the action potential, and this Ca^{2+} entry triggers the release of Ca^{2+} into the cytosol from the sarcoplasmic reticulum. During repolarization and relaxation (diastole), Ca^{2+} is both pumped back into the sarcoplasmic reticulum by a local Ca^{2+} -ATPase and is moved extracellularly by an Na^+ - Ca^{2+} antiporter (Fig. 65–1; Chap. 17).⁷⁸

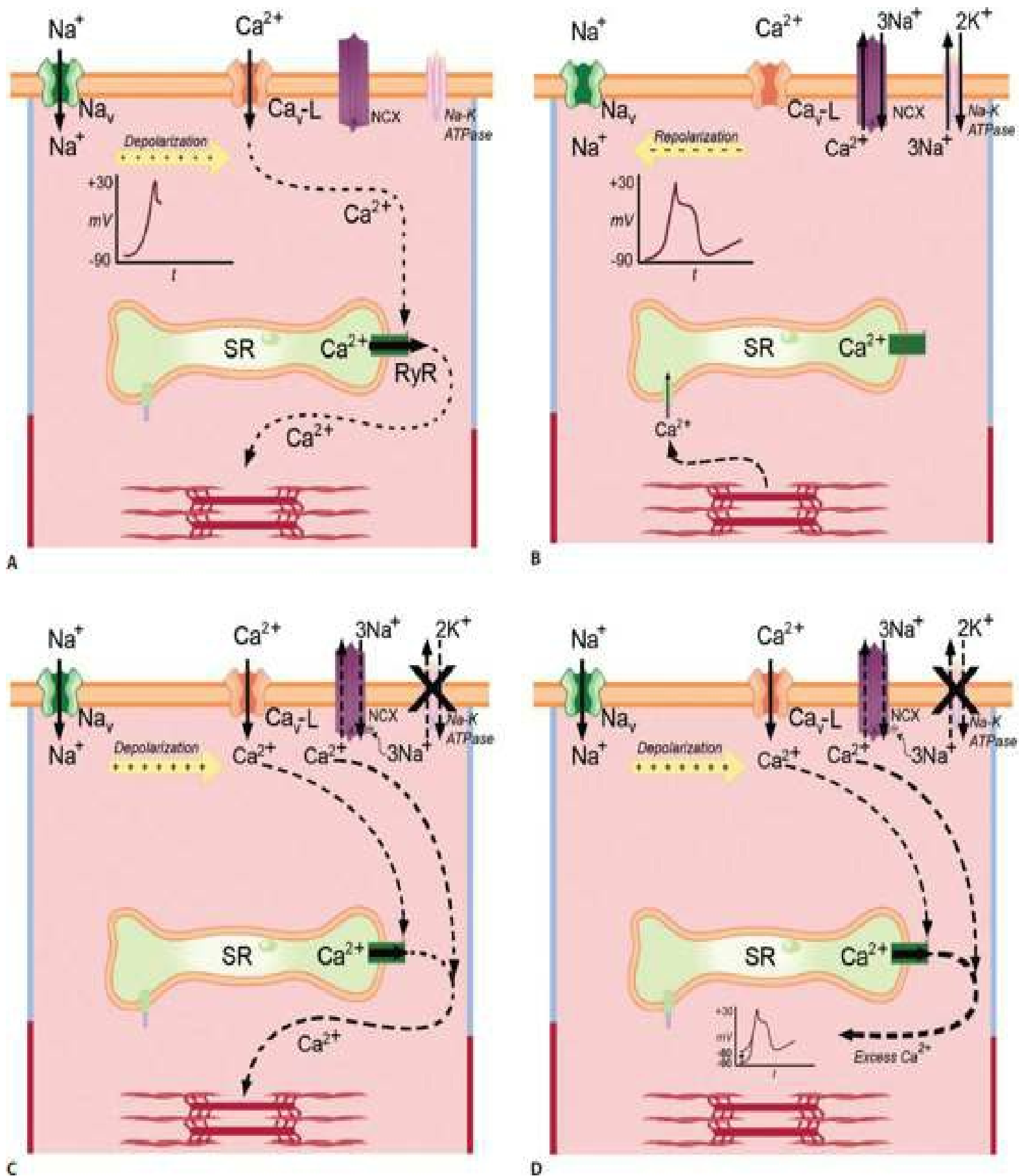


FIGURE 65–1. Pharmacology and toxicology of the cardioactive steroids (CASs). (A) Normal depolarization. Depolarization occurs after the opening of fast Na^+ channels; the increase in intracellular potential opens voltage-dependent Ca^{2+} channels, and the influx of Ca^{2+} induces the massive release of Ca^{2+} from the sarcoplasmic reticulum, producing contraction. (B) Normal repolarization. Repolarization begins with active expulsion of 3Na^+ ions in exchange for 2K^+ ions using an ATPase. This electrogenic (3Na^+ for 2K^+) pump creates a Na^+ gradient used to expel Ca^{2+} via an antiporter (NCX). The sarcoplasmic reticulum resequesters its Ca^{2+} load via a separate ATPase. (C) Pharmacologic CAS. Digitalis inhibition of the $\text{Na}^+-\text{K}^+-\text{ATPase}$ raises the intracellular Na^+ content, preventing the antiporter from expelling 1Ca^{2+} in exchange for 3Na^+ . The net result is an elevated intracellular Ca^{2+} , resulting in enhanced inotropy through enhanced SR calcium release. (D) Toxicologic CAS. Excessive elevation of the intracellular Ca^{2+} elevates the resting potential,

producing myocardial sensitization and predisposing to dysrhythmias.

CASs inhibit active transport of Na^+ and K^+ across the cell membrane during repolarization by binding to a specific site on the extracellular face of the α -subunit of the membrane $\text{Na}^+-\text{K}^+-\text{ATPase}$. This inhibits the cellular Na^+ pump activity, which decreases Na^+ extrusion and increases Na^+ in the cytosol, thereby decreasing the transmembrane Na^+ gradient. Because the $\text{Na}^+-\text{Ca}^{2+}$ antiporter derives its power not from adenosine triphosphate (ATP) but rather from the Na^+ gradient generated by the Na^+-K^+ transport mechanism (the antiporter extrudes 1 calcium ion from the cell in exchange for 3 sodium ions moving into the cell down a concentration gradient),²⁹ the dysfunction of the $\text{Na}^+-\text{K}^+-\text{ATPase}$ pump reduces Ca^{2+} extrusion from the cell. The additional cytoplasmic Ca^{2+} enhances the Ca^{2+} -induced Ca^{2+} release from the sarcoplasmic reticulum during systole and by this mechanism increases the force of contraction of the cardiac muscle. Additional mechanisms of action are being explored and include creation of transmembrane calcium channels by cardioactive glycosides.¹

Effects on Cardiac Electrophysiology

At therapeutic serum concentrations, CASs increase automaticity and shorten the repolarization intervals of the atria and ventricles (Table 65–2). There is a concurrent decrease in the rate of depolarization and conduction through the sinoatrial (SA) and atrioventricular (AV) nodes, respectively. This is mediated both indirectly via an enhancement in vagally mediated parasympathetic tone and directly by depression of myocardial tissue. These changes in nodal conduction are reflected on electrocardiography (ECG) by a decrease in ventricular response rate to suprajunctional rhythms and by PR interval prolongation (the latter is part of digitalis effect). The effects of CASs on ventricular repolarization are related to the elevated intracellular resting potential caused by the enhanced availability of Ca^{2+} that manifests on the ECG as QT interval shortening and ST segment and T-wave forces opposite in direction to the major QRS forces. The last effect results in the characteristic scooping of the ST segments (referred to as the digitalis effect; Fig. 65–2).

TABLE 65–2. Electrophysiologic Effects of Cardioactive Steroids on the Myocardium

Any digoxin related life threatening dysrhythmias, regardless of serum digoxin concentration (SDC)

—Includes ventricular tachycardia or ventricular fibrillation, or progressive bradydysrhythmias such as atropine resistant symptomatic sinus bradycardia, or second or third degree heart block.

Potassium concentration > 5 mEq/L in setting of acute digoxin poisoning

Chronic elevation of SDC associated with dysrhythmias, significant gastrointestinal symptoms, or altered mental status

SDC \geq 15 ng/mL at any time or \geq 10 ng/mL 6 hours postingestion, regardless of clinical effects

Acute ingestion of 10 mg of digoxin in an adult

Acute ingestion of 4 mg of digoxin in a child

Poisoning with a nondigoxin cardioactive steroid

Digoxin-specific Fab dosing (round up to number of whole vials in calculation)

$$\begin{aligned}\text{No. of vials} &= \frac{\text{SDC (ng/mL)} \times \text{Patient weight (kg)}}{100} \\ \text{No. of vials} &= \frac{\text{Amount ingested (mg)}}{0.5 \text{ (mg/vial)}} \times 80\% \text{ bioavailability}\end{aligned}$$

Empiric therapy for acute poisoning:

10–20 vials (adult or pediatric {must watch for volume overload})

Empiric therapy for chronic poisoning:

Adults: 3–6 vials

Children: 1–2 vials



FIGURE 65–2. Digitalis effect noted in the lateral precordial lead, V6. Note the prolonged PR interval (long arrow) and the repolarization abnormality (scooping of the ST segment) (short arrow).

Excessive increases in intracellular Ca^{2+} caused by CAS toxicity result in delayed after-depolarizations. These are fluxes in membrane potential caused by spontaneous Ca^{2+} -induced Ca^{2+} release, which is caused by the excess intracellular Ca^{2+} and appear on the ECG as U waves. Occasionally, these may initiate a cellular depolarization that manifests as a premature ventricular contraction (Chap. 16).^{28,60}

Hypokalemia inhibits Na^+ - K^+ -ATPase activity and contributes to the pump inhibition induced by CASs, enhances myocardial automaticity, and increases myocardial susceptibility to CAS-related dysrhythmias. This may be partly a result of decreased competitive inhibition between the CAS and potassium at the Na^+ - K^+ -ATPase exchanger.⁹⁵ Severe hypokalemia (< 2.5 mEq/L) reduces the efficacy of sodium-potassium pump function, slowing the pump and exacerbating concomitant Na^+ - K^+ pump inhibition by CASs.⁶⁰

Effects of Cardioactive Steroids on the Autonomic Nervous System

CASs affect the parasympathetic system by increasing the release of acetylcholine from vagal fibers,^{75,114} possibly through augmentation of intracellular Ca^{2+} . CASs affect the sympathetic system by increasing efferent sympathetic discharge,^{85,109} which may exacerbate dysrhythmias.

CLINICAL MANIFESTATIONS

Although there are differences in the signs and symptoms of acute versus chronic CAS poisoning, adults and children have similar manifestations when poisoned.

Noncardiac Manifestations

Acute Toxicity. An asymptomatic period of several minutes to several hours may follow a single administered toxic dose of CAS. The first effects are typically nausea, vomiting, or abdominal pain. Central nervous system effects of acute toxicity may include lethargy, confusion, and weakness that are not caused by hemodynamic changes.¹⁶ The absence of nausea and vomiting within several hours following exposure makes severe acute CAS poisoning unlikely.

Chronic Toxicity. Chronic toxicity is often difficult to diagnose as a result of its insidious development and protean manifestations, including weakness, anhedonia, and loss of appetite. Symptoms may also include those that occur with acute poisonings; however, they are often less obvious. GI findings include anorexia, nausea, vomiting, abdominal pain, and weight loss. Neuropsychiatric disorders include delirium, confusion, drowsiness, headache, hallucinations, and, rarely, seizures.^{16,38,40} Visual disturbances include transient amblyopia, photophobia, blurring, scotomata, photopsia, decreased visual activity, and aberrations of color vision (chromatopsia), such as yellow halos (xanthopsia) around lights.^{69,70}

Electrolyte Abnormalities. Elevated serum potassium concentrations frequently occur in patients with acute CAS poisoning.^{60,63} Hyperkalemia has important prognostic implications because the serum potassium concentration is a better predictor of lethality than either the initial ECG changes or the serum CAS concentration.^{5,6} In a study of 91 acutely digitoxin poisoned patients conducted before digoxin-specific Fab was available, approximately 50% of the patients with serum potassium concentrations of 5.0 to 5.5 mEq/L died. Although a serum potassium concentration lower than 5.0 mEq/L was associated with no deaths, all 10 patients with serum potassium concentrations above 5.5 mEq/L died.⁵ Elevation of the serum potassium concentration after administration of CASs is a result of CAS inhibition of the Na^+ - K^+ -ATPase pump, which results in the inhibition of potassium uptake in exchange for Na^+ by skeletal muscle (the largest potassium reservoir). Hyperkalemia probably causes further hyperpolarization of myocardial conduction tissue, increasing AV nodal block, thereby exacerbating CAS-induced bradydysrhythmias and conduction delays.⁶⁰ However, correction of the hyperkalemia alone does not increase patient survival⁵; it is a marker for, but not the cause of, the morbidity and mortality associated with

CAS poisoning. Hyperkalemia may also be marker of increased morbidity and subsequent mortality with chronic digoxin overdose.¹²⁶ The interrelationships between intracellular and extracellular potassium and CAS therapy are complex and incompletely understood.

Cardiac Manifestations

General. With therapeutic use, CASs slow tachydysrhythmias without causing hypotension. With poisoning, the alterations in cardiac rate and rhythm may result in nearly any dysrhythmia with the exception of a rapidly conducted supraventricular tachydysrhythmia due to the prominent AV nodal depressive effect of CASs. In 10% to 15% of cases, the first sign of toxicity is the appearance of an ectopic ventricular rhythm.⁹⁴ Although no single dysrhythmia is pathognomonic of CAS toxicity, toxicity should be suspected when there is evidence of increased automaticity in combination with impaired conduction through the SA and AV nodes.⁶⁰ Bidirectional ventricular tachycardia is nearly diagnostic, although it may also occur with poisoning by aconitine and other uncommon xenobiotics¹⁰⁵ (Fig. 16–19). Dysrhythmias, including atrial tachycardia with high-degree AV block, result from the complex electrophysiologic influences on both the myocardium and conduction system of the heart that stem from direct, vagotonic, and other autonomic actions of the CASs.

The effects of digoxin vary with dose and the type of cardiac tissue involved. The atrial and ventricular myocardial tissues exhibit increased automaticity and excitability, resulting in tachydysrhythmias and extrasystoles. In atrial and nodal conducting system tissues, signal velocity is reduced, resulting in an increased PR interval and AV nodal block. AV junctional blocks of varying degrees associated with increased ventricular automaticity are the most common cardiac manifestations, occurring in 30% to 40% of patients with CAS toxicity.⁷⁶ AV dissociation may result from suppression of the dominant pacemaker with escape of a secondary pacemaker or from inappropriate acceleration of a ventricular pacemaker. Hypotension, shock, and cardiovascular collapse may ensue. Table 65–3 summarizes these findings.

TABLE 65–3. Cardiac Dysrhythmias Associated with Cardioactive Steroid Poisoning

Myocardial irritability causing dysrhythmias

Atrial flutter and atrial fibrillation with atrioventricular (AV) block

Bidirectional ventricular tachycardia

Delayed after-depolarizations

Nonparoxysmal atrial tachydysrhythmias with AV block

Nonsustained ventricular tachycardia

Premature and sustained ventricular contractions

Ventricular bigeminy

Ventricular fibrillation

Primary conduction system dysfunction causing dysrhythmias

Junctional tachycardia

AV dissociation

High degree AV block

Sinus bradycardia

Exit blocks

His-Purkinje dysfunction

Sinoatrial nodal arrest

Acute Toxicity. Many cardiac dysrhythmias are associated with CAS toxicity. These dysrhythmias are unified by a sensitized myocardium and a depressed AV node (Table 65–3). The initial bradydysrhythmia results from increased vagal tone at the SA and AV nodes and is often responsive to atropine.

Chronic Toxicity. Bradydysrhythmias that appear later in acute poisonings and with chronic CAS toxicity occur by direct actions on the heart and often are minimally responsive to atropine, if at all. Ventricular tachydysrhythmias are more common in patients with chronic or late acute poisoning.

DIAGNOSTIC TESTING

Properly obtained and interpreted serum digoxin concentrations aid significantly in the management of patients with suspected digoxin toxicity, as well as in the management of patients poisoned by several other CAS. Although most institutions report a therapeutic range for serum digoxin concentration from 0.5 to 2.0 ng/mL (SI units, 1.0–2.6 nmol/mL), current understanding suggests lowering the upper limit to 1.0 ng/mL maintains benefit while decreasing the risk of toxicity.^{98,107} In addition to determining a serum CAS concentration, care must be taken to interpret the concentration as a correlate with the clinical condition of the patient; the interval between the last dose and the time the blood sample was taken; and the presence of other metabolic abnormalities, including hypokalemia, hypomagnesemia, hypercalcemia, hypernatremia, alkalosis, hypothyroidism, and hypoxemia, and the use of xenobiotics such as amiodarone, calcium channel blockers, catecholamines, quinidine, and diuretics.

CAS poisoning is multifactorial and using the upper limit of the therapeutic range of digoxin as the sole indicator of toxicity may be misleading,¹⁰¹ as there is an overlap in serum digoxin concentrations between toxic and nontoxic patients.

In general, a patient's clinical condition and serum concentration correlate well; the significance of a serum concentration depends on when the value is obtained after an acute ingestion to account for the distribution phase of the drug. Asymptomatic patients with CAS concentrations obtained prior to completion of the α distribution, found to be above the therapeutic range, are less often toxic but require close observation and retesting. Patients with mean pharmaceutical CAS serum concentrations above 2 ng/mL for digoxin and above 40 ng/mL for digitoxin measured 6 hours after the last dose often are clinically toxic.⁵⁹ A patient with a markedly elevated CAS concentration at any point after ingestion (eg, ≥ 15 mg/mL) requires definitive therapy.

In most hospitals, "digoxin levels" are the only estimation available to physicians in the acute setting when evaluating a patient for presumed non-digoxin CAS poisoning. The assays typically used in most institutions frequently, but unpredictably, cross-react with other plant- or animal-derived CASs. Although a monoclonal digoxin immunoassay accurately quantifies the serum digoxin concentration, an elevated digoxin concentration in the correct clinical setting may qualitatively assist in making a presumptive diagnosis of nondigoxin CAS exposure (Chaps. 45 and 121).^{14,88} For example, using various techniques, including high-performance liquid chromatography and monoclonal and polyclonal antibody analysis, "digoxin" concentrations were determined from serum to which oleandrin and oleandrogenin from Nerium oleander was added or from patients exposed to Thevetia peruviana (yellow oleander) or toad-secreted bufadienolides.^{10,26,54} Patients with CAS poisoning from plant- or animal-derived CASs may have a positive detection of CAS when using a polyclonal digoxin assay and a low or negative finding when using a monoclonal assay (Chaps. 45 and 121).

Serum concentrations of digoxin are measured in one of two ways: free digoxin and total digoxin. The most common method of quantifying total digoxin in the serum is by fluorescence polarization immunoassay. Under normal circumstances, measuring total digoxin in the serum is sufficient because serum concentrations are predictive of cardiac concentrations.²⁴ However, after the use of digoxin-specific Fab (which remains almost entirely within the intravascular space {Vd, 0.40 L/kg}), there is a large elevation in total CAS concentrations because the CAS is drawn from the tissues and complexes with the antibody fragment, thus trapping the CAS in the intravascular space. When this bulk movement is achieved by binding with Fab fragments, a tremendous increase in total serum digoxin concentrations occurs—representing free plus bound (inactivated) CAS. In this situation, requesting a "free digoxin level" will avoid this spurious increase and reflect clinically relevant unbound digoxin concentration. Paradoxically, excess digoxin Fab may cause a false elevation in digoxin concentration (Chap. 6).

ENDOGENOUS DIGOXINLIKE IMMUNOREACTIVE SUBSTANCE

Some patients have a positive digoxin assay resulting from an endogenous digoxinlike immunoreactive substance (EDLIS) that is structurally and functionally similar to prescribed CASs.⁴⁵ This substance has been found in patients with increased inotropic need or reduced renal clearance, including neonates,¹¹⁷ patients with endstage kidney disease,^{11,41,53} liver disease,⁸¹ subarachnoid hemorrhage,¹²³ congestive heart failure,^{39,102} insulin-dependent diabetes,³⁵ stress,^{40,118} acromegaly,²⁶ or hypothermia,¹¹⁷ after strenuous exercise¹¹⁸ and in pregnancy.^{32,42,50} An endogenous Na⁺-K⁺-ATPase inhibiting dihydropyrone-substituted bufadienolide CAS has been isolated from human placenta.³³ It differs from the toad bufadienolides solely by a single double-bond pyrone ring. Because bufadienolides are not normally found in either healthy humans or edible plants, a synthetic pathway to produce dihydropyrone-substituted steroids in humans may be responsible for EDLIS. Further research is necessary to confirm this pathway.⁵⁰ The clinician suspecting this problem should consult the clinical laboratory.³⁴ Clinical observations indicate that the serum digoxin concentration contributed by EDLIS is usually less than 2 ng/mL. Other endogenous substances, such as bilirubin,⁸¹ and xenobiotics, such as spironolactone,¹⁰³ may also cross-react with the digoxin assay and cause a false-positive result.

THERAPY

Acute Management Overview

Initial treatment of a patient with acute CAS poisoning includes providing general care, (eg, GI decontamination, monitoring for dysrhythmias, measuring electrolyte and digoxin concentrations) and definitive care (eg, administering digoxin-specific antibody fragments). Secondary care includes treating complications such as dysrhythmias and electrolyte abnormalities.

Gastrointestinal Decontamination

The initial treatment should be directed toward prevention of further GI absorption. Rarely, if ever, should emesis or lavage be considered because efficacy is limited due to rapid absorption from the gut and to the emetic effects of the drug itself. Patients with chronic ingestion also do not benefit from these GI decontamination techniques. Because many

CASs, such as digitoxin and digoxin, are recirculated enterohepatically, both late and repeated activated charcoal administration (1 g/kg of body weight every 2–4 hours for up to 4 doses) are beneficial in reducing serum concentrations.^{17,21,67,71,86,121} Activated charcoal prevents reabsorption of CAS from the GI tract and reduces the serum half-life. It should be administered in CAS toxic patients if definitive therapy with digoxin-specific Fab is not immediately available or when renal function is inadequate.²¹

Advanced Management

Digoxin-Specific Antibody Fragments. The definitive therapy for patients with life-threatening dysrhythmias from CAS toxicity (in descending order of associated mortality: ventricular tachycardia, AV junctional tachycardia, AV block¹²⁷) is to administer digoxin-specific antibody fragments.^{2,34,36,87,90,97,106,112,125} Purified digoxin-specific Fab causes a sharp decrease in free serum digoxin concentrations; a concomitant, but clinically unimportant, massive increase in total serum digoxin concentration; an increase in renal clearance of CAS (as a bound drug); and a decrease in the serum potassium concentration.² In addition, the administration of digoxin-specific Fab is pharmacoeconomically advantageous.²² Although the antidote itself is relatively expensive, its expense is far outweighed by obviating the need, risk, and expense of long-term intensive care unit stays and of repetitive evaluation of potassium and digoxin concentrations. [Table 65–4](#) lists the indications for administering digoxin-specific Fab. Extensive discussion is found in Antidotes in Depth: A19.

TABLE 65–4. Indications for Administration of Digoxin-Specific Antibody Fragments (DSFab)

Any digoxin related life threatening dysrhythmias, regardless of serum digoxin concentration (SDC)

—Includes ventricular tachycardia or ventricular fibrillation, or progressive bradydysrhythmias such as atropine resistant symptomatic sinus bradycardia, or second or third degree heart block.

Potassium concentration > 5 mEq/L in setting of acute digoxin poisoning

Chronic elevation of SDC associated with dysrhythmias, significant gastrointestinal symptoms, or altered mental status

SDC ≥ 15 ng/mL at any time or ≥ 10 ng/mL 6 hours postingestion, regardless of clinical effects

Acute ingestion of 10 mg of digoxin in an adult

Acute ingestion of 4 mg of digoxin in a child

Poisoning with a nondigoxin cardioactive steroid

Digoxin-specific Fab dosing (round up to number of whole vials in calculation)

$$\text{No. of vials} = \frac{\text{SDC (ng/mL)} \times \text{Patient weight (kg)}}{100}$$

$$\text{No. of vials} = \frac{\text{Amount ingested (mg)}}{0.5 \text{ (mg/vial)}} \times 80\% \text{ bioavailability}$$

Empiric therapy for acute poisoning:

10–20 vials (adult or pediatric {must watch for volume overload})

Empiric therapy for chronic poisoning:

Adults: 3–6 vials

Children: 1–2 vials

Other Cardiac Therapeutics. Secondary treatments used in patients with symptomatic CAS exposures include the use of atropine for supraventricular bradydysrhythmias or high degrees of AV block. Atropine dosing is 0.5 mg administered IV to an adult or 0.02 mg/kg with a minimum of 0.1 mg to a child. Atropine should be titrated to block the vagotonic effects of CASs. The dose may be repeated at 5-minute intervals if necessary. Therapeutic success is unpredictable because the depressant actions of CASs are mediated only partly through the vagus nerve.

Phenytoin and lidocaine are rarely used (secondary to Fab fragments obviating their utility) for the management of

CAS-induced ventricular tachydysrhythmias and ventricular irritability. These xenobiotics depress the enhanced ventricular automaticity without significantly slowing, and perhaps enhancing, AV nodal conduction.⁹⁶ In fact, phenytoin may reverse digitalis-induced prolongation of AV nodal conduction while suppressing digitalis-induced ectopic tachydysrhythmia without diminishing myocardial contractile forces.⁴⁸ In addition, phenytoin may terminate supraventricular dysrhythmias induced by digitalis more effectively than lidocaine.⁹⁶ Underlying atrial fibrillation and flutter typically do not convert to a normal sinus rhythm with administration of phenytoin or lidocaine. When used, phenytoin should be slowly IV infused (~ 50 mg/min) or in boluses of 100 mg repeated every 5 minutes until control of the dysrhythmias is achieved or a maximum of 1000 mg has been given in adults or 15 to 20 mg/kg in children.^{9,80} Fosphenytoin has not been evaluated in this setting. Maintenance PO doses of phenytoin (300–400 mg/day in adults and 6–10 mg/kg/day in children) should be continued until digoxin toxicity is resolved. Lidocaine is given as a 1- to 1.5-mg/kg IV bolus followed by continuous infusion at 1 to 4 mg/min in adults, or as a 1- to 1.5-mg/kg IV bolus followed by 30 to 50 µg/kg/min in children as required to control the rhythm disturbance ([Chap. 64](#)).

Class IA antidysrhythmics are contraindicated in the setting of CAS poisoning because they may induce or worsen AV nodal block and decrease His-Purkinje conduction at slow heart rates and because their α -adrenergic receptor blockade and vagal inhibition may induce significant hypotension and tachycardia. Class IA antidysrhythmics are also pro-dysrhythmogenic, and their safety in the setting of CAS poisoning is unstudied. Additionally, quinidine reduces renal clearance of digoxin and digitoxin. The use of isoproterenol should be avoided in CAS-induced conduction disturbances because there may be an increased incidence of ventricular ectopic activity in the presence of toxic concentrations of CAS.

Pacemakers and Cardioversion

External or transvenous pacemakers have had limited indications in the management of patients with CAS poisoning. In one retrospective study of 92 digitalis-poisoned patients, 51 patients were treated with cardiac pacing, digoxin-specific Fab, or both; the overall mortality rate was 13%.¹¹³ Prevention of life-threatening dysrhythmias failed in 8% of patients treated with immunotherapy and 23% of patients treated with internal pacemakers. The main reasons for failure of digoxin-specific Fab were pacing-induced dysrhythmias and delayed or insufficient doses of digoxin-specific Fab. Iatrogenic complications of pacing occurred in 36% of patients. Thus, overdrive suppression with a temporary transvenous pacemaker should not be used in the presence of CAS poisoning.^{6,113} In the setting of digoxin poisoning, administration of transthoracic electrical cardioversion for atrial tachydysrhythmias is associated with the development of potentially lethal ventricular dysrhythmias. The dysrhythmias were related to the degree of toxicity and the amount of administered current in cardioversion.⁹⁹ Transthoracic pacing may be attempted for atropine unresponsive bradydysrhythmias in settings where definitive care (digoxin-specific Fab fragments) are delayed or unavailable. In CAS-poisoned patients with unstable rhythms, such as unstable ventricular tachycardia or ventricular fibrillation, cardioversion, and defibrillation, respectively, are indicated.

Electrolyte Therapy

Potassium. Hypokalemia and hyperkalemia may exacerbate CAS cardiotoxicity even at “therapeutic” digoxin concentrations. When hypokalemia is noted in conjunction with tachydysrhythmias or bradydysrhythmias, potassium replacement should be administered with serial monitoring of the serum potassium concentration. Digoxin-specific Fab administration generally should be withheld until the hypokalemia is corrected as the life-threatening manifestations of CAS cardiotoxicity may resolve.

Hyperkalemia may also exacerbate CAS-induced cardiotoxicity, at “therapeutic” digoxin concentrations. Reduction in potassium concentrations should be judiciously initiated with care to avoid hypokalemia. Any exacerbation of CAS cardiotoxicity despite this correction should be treated immediately with Fab fragments.

In acute CAS toxicity, if potassium is at least 5 mEq/L, digoxin-specific antibody fragments are indicated. If digoxin-specific Fab is not available immediately, and ECG evidence of a dysrhythmia suggestive of hyperkalemia is present, an attempt should be made to lower the serum potassium with IV insulin, dextrose, sodium bicarbonate, and PO administration of the ion-exchange resin sodium polystyrene sulfonate as indicated. Caution should be applied to the subsequent administration of digoxin-specific Fab because of concern for profound hypokalemia.

Although calcium is beneficial in most hyperkalemic patients, in the setting of CAS poisoning, administration of calcium salts is considered to be potentially dangerous. A number of experimental studies cite the additive or synergistic actions of calcium and CAS on the heart (because intracellular hypercalcemia is already present), resulting in dysrhythmias,^{37,83,104} cardiac dysfunction⁶¹ (eg, hypercontractility, so-called “stone heart,” hypocontractility), and cardiac arrest.^{72,104,119} Although a 2004 study was unable to show an adverse effect,⁴³ there exist three case reports^{8,64} of CAS-poisoned patients who died at various intervals after calcium administration, which supports the withholding of calcium administration in the setting of hyperkalemia induced by CAS poisoning.

The purported mechanism is augmented intracellular cytoplasmic Ca^{2+} , which results from an increased transmembrane

concentration gradient that further inhibits calcium extrusion through the Na^+ - Ca^{2+} exchange or increased intracytoplasmic stores.⁵⁹ This additional cytoplasmic calcium may result in altered contraction of myofibril organelles,⁶¹ less negative intracellular resting potential that allows delayed afterdepolarizations to reach firing threshold,^{47,59,83} altered function of the sarcoplasmic reticulum,^{61,95} or increased calcium interfering with myocardial mitochondrial function (Chaps. 16 and 17).⁶¹ Although some investigators suspect that the rate of administration of the calcium may be a factor in the subsequent cardiac toxicity,^{72,83} calcium administration should be avoided because better, safer, alternative treatments, such as digoxin-specific Fab, insulin, and sodium bicarbonate, are available for CAS-induced hyperkalemia.^{8,37,64,83,104}

Magnesium. Hypomagnesemia may also occur in CAS-poisoned patients secondary to the contributory factors mentioned with hypokalemia, such as long-term diuretic use to treat congestive heart failure. The theoretical benefits of magnesium therapy in the setting of hypomagnesemia include blockade of the transient inward calcium current, antagonism of calcium at intracellular binding sites, decreased CAS-related ventricular irritability, and blockade of potassium egress from CAS-poisoned cells.^{4,31,55,89,100,110,122} Although hypomagnesemia increases myocardial digoxin uptake and decreases cellular Na^+ - K^+ -ATPase activity, there is conflicting evidence as whether magnesium “reactivates” the CAS-bound Na^+ - K^+ -ATPase activity.^{81,100,110}

A common regimen uses 2 g of magnesium sulfate IV over 20 minutes in adults (25–50 mg/kg/dose to a maximum of 2 g in children). After stabilization, adult patients with severe hypomagnesemia may require a magnesium infusion of 1 to 2 g/h (25–50 mg/kg/h to a maximum of 2 g in children), with serial monitoring of serum magnesium concentrations, telemetry, respiratory rate (observing for bradypnea), deep tendon reflexes (observing for hyporeflexia), and monitoring of blood pressure. Magnesium is contraindicated in the setting of bradycardia or AV block, preexisting hypermagnesemia, and renal insufficiency or failure.

Extracorporeal Removal of Cardioactive Steroids

Forced diuresis,⁶⁶ hemoperfusion,^{77,79,120} and hemodialysis¹²⁰ are ineffective in enhancing the elimination of digoxin because of its large volume of distribution (4–10 L/kg), which makes it relatively inaccessible to these techniques. Because of its high affinity for tissue proteins, approximately 10% of the amount of digoxin is found in the serum than is found at the tissue level, and of that amount, approximately 20% to 40% is protein bound.⁵⁷

SUMMARY

- Digoxin and digitoxin are the most commonly prescribed members of the drugs classified as CASs and they have a narrow therapeutic index.
- Both cardiac and noncardiac effects occur after CAS poisoning, including nausea, vomiting, headache, weakness, altered mental status bradycardia, atrial and ventricular ectopy with block, or hyperkalemia.
- CAS overdose mimics include dysrhythmias from electrolyte abnormalities, primarily hypokalemia, or hypomagnesemia which can be corrected by repletion of potassium or magnesium.
- Definitive therapy for CAS poisoning is the early administration of digoxin-specific Fab immunotherapy coupled with both decontamination techniques including activated charcoal and supportive therapy.

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A19 ANTIDOTES IN DEPTH

Digoxin-Specific Antibody Fragments

Mary Ann Howland

INTRODUCTION

Digoxin-specific antibody fragments (DSFab) are indicated for the management of patients with toxicity related to digoxin and digitoxin, as well as oleander, squill, and toad venom, which contain other cardioactive steroids. DSFab have an excellent record of efficacy and safety, and they should be administered early in both established and suspected cardioactive steroid poisoning.

HISTORY

The production of antibody fragments to treat patients poisoned with digoxin followed the development of digoxin antibodies for measuring serum digoxin concentrations by radioimmunoassay (RIA).¹³ This RIA technique permitted the correlation between serum digoxin concentration and clinical digoxin toxicity.^{5,21,27,60}

In 1967, Butler and Chen suggested that purified antidigoxin antibodies with a high affinity and specificity should be developed to treat digoxin toxicity in humans.¹³ The digoxin molecule alone, with a molecular weight of 780 Da, was too small to be immunogenic. But digoxin could function as a hapten when joined to an immunogenic protein carrier such as albumin. These investigators immunized sheep with this conjugate to generate antibodies.^{80,82} The immunized sheep subsequently produced a mixture of antibodies that included antialbumin antibodies and antidigoxin antibodies. The antibodies were separated and highly purified to retain the digoxin antibodies, while removing the antibodies to the albumin and all other extraneous proteins. The antibodies that were developed had a high affinity for digoxin as well as sufficient cross-reactivity with digitoxin and other cardioactive steroids to be clinically useful for the treatment of all cardioactive steroid poisonings.^{15,72,73}

Intact IgG antidigoxin antibodies reversed digoxin toxicity in dogs.¹⁴ Unfortunately, the urinary excretion of digoxin was delayed, and free digoxin was released after antibody degradation occurred. Furthermore, there was significant concern with regard to the development of hypersensitivity reactions. To make such antibodies both safe and effective in humans, whole IgG antidigoxin antibodies were cleaved with papain, yielding two antigen-binding fragments (Fab), with a molecular weight of 50,000 Da each, and one Fc fragment of 50,000 Da.¹⁴ Affinity chromatography is used to isolate and purify the DSFab following papain digestion. Since the Fc fragment does not bind antigen and increases the potential for hypersensitivity reactions, it was eliminated. When compared with whole IgG antibodies, the advantages of DSFab included a larger volume of distribution (Vd), more rapid onset of action, diminished risk of adverse immunologic effects, and more rapid elimination.^{14,48,51,53} In 1976, Digibind was used with clinical success,⁸¹ and it became commercially available in 1986 before being discontinued in 2011.²⁵ Another commercial product, DigiFab, approved by the US Food and Drug Administration (FDA) in 2001, is currently available.²⁶ It is very similar to Digibind, except that it is prepared using a digoxin derivative (digoxin-dicarboxymethoxylamine) as the hapten.

PHARMACOLOGY

Mechanism of Action

Immediately following intravenous (IV) administration, DSFab bind intravascular free digoxin. Uncomplexed antibodies then diffuse into the interstitial space, binding free digoxin there. A concentration gradient is then established, which facilitates movement into the interstitial or intravascular spaces of both the free intracellular digoxin and digoxin that is dissociated from its binding sites on (the external surface of Na⁺-K⁺-adenosine triphosphatase {ATPase} enzyme) in the heart and in skeletal muscle.⁷¹ The dissociation rate constant of digoxin for Na⁺-K⁺-ATPase, therefore, affects the time course for binding to DSFab and, consequently, the onset of action.^{55,75}

The binding affinities of DSFab for digoxin and digitoxin are about 10^9 to 10^{10} M⁻¹ and 10^8 to 10^9 M⁻¹, respectively. They are greater than the affinities of digoxin or digitoxin for the Na⁺-K⁺-ATPase pump receptor.²⁶

Pharmacokinetics

The pharmacokinetics of Digibind and DigiFab (previously named DigiTab) were compared in human volunteers.⁹² Each subject received 1 mg of digoxin intravenously as a 5-minute bolus, followed 2 hours later by a 30-minute IV infusion of 76 mg (an equimolar neutralizing dose) of either Digibind or DigiFab. Free and total digoxin (free plus DSFab bound) were assayed using an ultrafiltration method over 48 hours. At 30 minutes after infusion of either DSFab, the serum free digoxin concentration was below the level of assay detection and remained so for several hours. A few patients in both groups had free digoxin concentrations rebound to peak concentrations of 0.5 ng/mL at approximately 18 hours and the area under the serum drug concentration versus time curve (AUC) for 2 to 48 hours, for free digoxin, was similar for both treatment groups. The elimination half-life of total digoxin averaged 18 hours for DigiFab and 21 hours for Digibind, while the distribution half-life was one hour for each. The volumes of distribution were 0.3 L/kg for DigiFab versus 0.4 L/kg for Digibind.^{25,26} The systemic clearance of DigiFab was higher than Digibind, accounting for the shorter elimination half-life of DigiFab (15 hours versus 23 hours).⁹² Urine sampling over the first 24 hours demonstrated mostly free digoxin and very little free DSFab for both groups. The authors postulated that during renal excretion, the DSFab digoxin complex is metabolized in the kidney by the proximal tubular cells, releasing free digoxin and unmeasured DSFab metabolites.⁹²

Similar findings were described, following the first clinical use of Digibind in a patient who gave a history of ingesting 90 (0.25 mg) digoxin tablets.⁸¹ Total serum digoxin concentration, which was 17.6 ng/mL at the time Digibind infusion was initiated, rose to 226 ng/mL at one hour and remained there for 11 hours, before falling off the next 44 hours, with a half-life of 20 hours.⁸¹ Fab concentrations peaked at the end of the infusion and then apparently exhibited a biphasic or triphasic decline, probably reflecting distribution into different compartments, as well as excretion and catabolism. Free serum digoxin concentrations were undetectable for the first 9 hours, then rose to a peak of 2 ng/mL at 16 hours, and fell to 1.5 ng/mL at both 36 hours and 56 hours, at which time sampling stopped. An analysis of renal elimination based on an incomplete collection suggested that digoxin was excreted only in the bound form during the first 6 hours, but by 30 hours after Fab administration all digoxin in the urine was free digoxin.

A study designed to measure efficacy of DSFab delivery compared a loading dose of DSFab followed by an infusion to the DSFab dose infused over a short amount of time.⁷¹ The former strategy increased the ratio of digoxin bound to uncomplexed DSFab in the serum from 50% to 70%.⁷¹ The authors hypothesized that a very rapid infusion regimen would result in the elimination of DSFab before the fragments could optimally bind the digoxin redistributing from tissue sites.⁷¹

Digoxin takes several hours to distribute from the blood to the tissue compartment. As expected, a rodent model demonstrated that DSFab was more effective when administered prior to complete distribution of digoxin.⁶⁸ Once distribution is complete, increasing the dose of DSFab improved efficacy, as measured by comparing the AUC of digoxin to that of the Fab-digoxin complex.⁶⁸

Pharmacokinetic studies in patients with kidney failure demonstrate that the half-life of DSFab is prolonged 10-fold, with no change in the apparent Vd.⁸⁵ In this situation serum DSFab concentrations remain detectable for 2 to 3 weeks. Total serum digoxin concentrations generally follow DSFab serum concentrations. Case reports demonstrate that free digoxin concentrations reappear up to 10 days following administration of DSFab to patients with severe kidney failure, as compared with 12 to 24 hours in patients with normal kidney function.^{19,28,31,46,57,58,77,79,85–87,93} In one series of patients with end-stage kidney disease, the maximum average concentration of free digoxin was 1.30 ± 0.7 ng/mL and occurred at 127 ± 40 hours.⁸⁷ The mechanism for this rebound is unclear. Following the peak, there is a slow decline that parallels the elimination of DSFab.

Pharmacodynamics

In the multicenter study of 150 patients, the mean time to initial response from the completion of the Digibind infusion (accomplished over 15 minutes to 2 hours) was 19 minutes (range, 0–60 minutes), and the time to complete response was 88 minutes (range, 30–360 minutes).²⁰ Time to response was not affected by age, concurrent cardiac disease, or presence of chronic or acute ingestion.¹

ROLE IN DIGOXIN TOXICITY

A large study evaluating adults and children with acute and chronic digoxin toxicity established the efficacy of Digibind.¹ Of the 150 patients treated, 148 were evaluated for cardiovascular manifestations of toxicity prior to treatment: 79 patients (55%) had high grade atrioventricular block, 68 (46%) had refractory ventricular tachycardia, 49 (33%) had ventricular fibrillation, and 56 (37%) had hyperkalemia. Ninety percent of patients responded within minutes to several hours of

Digibind administration. Complete resolution of all signs and symptoms of digoxin toxicity occurred in 80% of cases. Partial response was observed in 10% of patients, and of the 15 patients who did not respond, 14 were moribund prior to initiation of therapy or later found to not be digoxin toxic. The spectacular success of DSFab is demonstrated by the fact that of the 56 patients who had cardiac arrest caused by digoxin, 54% survived to discharge, as compared with 100% mortality prior to the availability of DSFab.^{1,6} Newborns, infants, and children have all been successfully treated with Digibind.^{6,32,44,76}

ROLE OF DIGOXIN-SPECIFIC ANTIBODY FRAGMENTS WITH OTHER CARDIOACTIVE STEROIDS

DSFab were designed to have high-affinity binding for digoxin and digitoxin. There are structural similarities, however, among all cardioactive steroids. In fact, RIA-determined digoxin concentrations have been reported in patients following poisoning with many nondigoxin cardioactive steroids,^{31,52,61,67} suggesting that there is also cross-reactivity between DSFab and other cardioactive steroids. Thus, DSFab may have variable efficacy for all natural cardioactive steroid poisonings, including those unique cardioactive steroids in oleander, yellow oleander, squill, and toad venom.^{3,11,12,18,30,33,69} In vitro studies also suggest the binding affinity of Digibind for cardioactive steroids.^{22,23,63} However one in vitro study demonstrated cross-reactivity of steroidal alkaloidal compounds in *Veratrum viride* (false hellebore) with the digoxin assay but no binding to DigiFab.⁴ An in vitro study demonstrated that although both Digibind and DigiFab bound digoxin equally well, a small difference in the amount of ouabain binding to Fab subpopulations was identified with twice as much bound to Digibind as DigiFab.⁶⁴

The successful reversal, by Digibind, of cardiotoxicity resulting from ingestion of *Nerium oleander* and *Thevetia peruviana* are reported.^{16,78} One adult and one child each responded to five vials (200 mg) of Fab, but larger doses may be required in other cardioactive steroid poisonings because of the lower affinity binding of Digibind for these toxins. DigiFab is expected to have similar affinity binding toward cardioactive steroids. Both products are polyclonal, contributing to their broad spectrum of affinity for nondigoxin cardioactive steroids. Treatment decisions should be based on empirical grounds, with initial therapy consisting of 10 to 20 vials. Subsequent doses can be based on clinical response.

INDICATIONS FOR DIGOXIN-SPECIFIC ANTIBODY FRAGMENTS

DSFab are indicated for life-threatening, or potentially life-threatening, toxicity from any cardioactive steroid, although the package insert for DigiFab only mentions digoxin.^{25,26} Patients with known or suggestive cardioactive steroid exposure with progressive bradydysrhythmias, including symptomatic sinus bradycardia or second- or third-degree heart block unresponsive to atropine, and patients with severe ventricular dysrhythmias, such as ventricular tachycardia or ventricular fibrillation, should also be treated with DSFab. Ventricular tachycardia with a fascicular block is likely to be a digoxin-toxic rhythm.^{29,52} Any patient with a potassium concentration exceeding 5 mEq/L that is attributable to a cardioactive steroid in the presence of other manifestations of acute or chronic digoxin toxicity should be treated.⁷ Acute ingestions greater than 4 mg in a healthy child (or >0.1 mg/kg), or 10 mg in a healthy adult, may require DSFab, with a lower threshold in compromised patients. Serum digoxin concentrations do not correlate with myocardial concentrations until 4 to 6 hours after ingestion, when an equilibrium from the serum to the myocardium is achieved. Serum concentrations of greater than or equal to 10 ng/mL soon after an acute ingestion may predict the need for treatment with DSFab. Because the elderly are to be at greatest risk of lethality, the threshold for treating patients older than 60 years of age should be lower.⁸ Before the advent of DSFab, mortality in patients older than 60 years of age was 58%, as compared to 8% in patients younger than 40 years of age and 34% in patients between 40 and 50 years of age.⁸ A rapid progression of clinical signs and symptoms, such as cardiac and gastrointestinal toxicity and an elevated or rising potassium concentration, in the presence of an acute overdose, suggests a potentially life-threatening exposure and the need for DSFab.

Cardioactive steroid toxicity causes an increase in intracellular calcium, and the administration of exogenous calcium may further exacerbate conduction abnormalities and potentially result in cardiac arrest, unresponsive to further resuscitation. Thus, in a patient with an unknown exposure who is clinically ill with characteristics suggestive of poisoning by a cardioactive steroid, DSFab should be administered early in the management and always prior to administration of calcium gluconate or chloride. The cardioactive steroid effects can be reversed, obviating the risk associated with the administration of calcium. It may also be difficult to distinguish clinically between digoxin poisoning and intrinsic cardiac disease, which the administration of DSFab can resolve.

A computer-based simulation model compared the treatment of non-life-threatening digoxin toxicity with standard therapy. The authors concluded that treatment with DSFab could decrease length of hospitalization by 1.5 days, a major cost containment benefit.²⁴

ADVERSE EFFECTS AND SAFETY ISSUES

DSFab are generally safe and effective. Reported adverse effects include hypokalemia as a consequence of reactivation of the Na⁺-K⁺-ATPase; withdrawal of the inotropic or atrioventricular nodal blocking effects of digoxin, leading to congestive heart failure or a rapid ventricular rate in patients with atrial fibrillation; and, rarely, allergic reactions.^{25,26} In the multicenter study of 150 patients treated with Digibind, the only acute adverse clinical manifestations were hypokalemia in six patients (4%), worsening of congestive heart failure in four patients (3%), and transient apnea in a neonate who was several hours old.¹ There were no other reactions reported in any of the patients in this series. In a postmarketing surveillance study of Digibind that included 451 patients, two patients with a prior history of allergy to antibiotics reportedly developed rashes.⁶² One of these patients developed a total body rash, facial swelling, and a flush during the infusion. The other experienced a pruritic rash. Two other reported adverse reactions were thrombocytopenia and rigors, and were probably unrelated to the use of Digibind.⁶² One patient received Digibind on three separate occasions over the course of one year for multiple suicide attempts, with no adverse effects.⁹

During the clinical trials with DigiFab, one patient developed pulmonary edema, bilateral pleural effusions, and kidney failure, most likely caused by the loss of the inotropic and chronotropic digoxin effects.²⁶ Phlebitis and postural hypotension were related to the infusion of DigiFab in two healthy volunteers.²⁶

Patients with allergies to papain, chymopapain, or other papaya extracts, or the pineapple enzyme bromelain may be at risk for allergic reactions because trace residues of papaya may remain in the DSFab.^{26,53} Patients with an allergy to sheep protein or those who have previously received ovine antibodies or ovine Fab may also be at risk for allergic reactions, although this is not reported.

PREGNANCY AND LACTATION

DSFab is FDA pregnancy category C. Reproduction studies have not been done, and human case reports are limited. However, considering the maternal benefit of DSFab, it should be used as clinically indicated to protect the maternal fetal dyad. DSFab use should not be withheld because of pregnancy.¹⁰ It is unknown whether DSFab is excreted into breast milk.

DOSING AND ADMINISTRATION

The dose of DSFab depends on the total body load (TBL) of digoxin. Adults and children receiving digoxin therapeutically who develop chronic digoxin toxicity require small doses of DSFab because their total body burden of digoxin is usually small. Children with acute overdoses require DSFab doses based on the amount of digoxin ingested, as in adults.

Estimates of digoxin TBL can be made in three ways: (1) estimate the quantity of digoxin acutely ingested and assume 80% bioavailability (milligrams ingested × 0.8 equals TBL); (2) obtain a serum digoxin concentration and, using a pharmacokinetic formula, incorporate the apparent Vd of digoxin and the patient's body weight (in kilograms); or (3) use an empiric dose based on the average requirements for an acute or chronic overdose in an adult or child.

Each of these methods of estimating the dose of DSFab has limitations. History of ingestion is often unreliable, and empiric doses based on averages may overestimate or underestimate Fab requirements. Using the pharmacokinetic formula assumes a steady-state Vd of 5 L/kg.²⁶ This is not accurate in the acute setting. In addition, the 5 L/kg Vd is a population average that varies with the individual and kidney diseases and hypothyroidism.^{17,94}

Sample calculations for each of these methods are shown in [Tables A19–1, A19–2, and A19–3](#). Each vial contains 40 mg (DigiFab) of purified DSFab that will bind approximately 0.5 mg of digoxin or digitoxin. If the quantity of ingestion cannot be reliably estimated, it is safest to use the largest calculated estimate. The clinician should always be prepared to increase the dose, should symptom resolution be incomplete.

TABLE A19–1. Sample Calculation Based on History of Acute Digoxin Ingestion

Adult

Weight: 70 kg

Ingestion: 50 (0.25-mg) digoxin tablets

Calculation:

$0.25 \text{ mg} \times 50 = 12.5 \text{ mg}$ ingested dose

$12.5 \text{ mg} \times 0.80$ (assume 80% bioavailability) =

10 mg (absorbed dose)

$$\frac{10 \text{ mg}}{0.5 \text{ mg / vial}} = 20 \text{ vials}$$

Child

Weight: 10 kg

Ingestion: 50 (0.25-mg) digoxin tablets

Calculation: Same as for adult. Child will require 20 vials.

TABLE A19-2. Sample Calculations Based on the Serum Digoxin Concentration (SDC)

Adult	Child	Quick Estimation (for Adults and Children)
Weight: 70 kg	Weight: 10 kg	$\text{No. of vials} = \frac{\text{SDC (ng/mL)} \times \text{Patient wt (kg)}}{100} \text{ (Roundup)}$
SDC = 10 ng/mL	SDC: 10 ng/mL	
Volume of distribution = 5 L/kg	Volume of distribution: 5 L/kg	
Calculation*:	Calculation*:	
$\text{No. of vials} = \frac{\text{Total body load (mg)}}{0.5 \text{ mg/vial}}$ $= \frac{\text{SDC} \times V_d \times \text{Patient wt (kg)}}{1000 \times 0.5 \text{ mg/vial}}$	$\text{No. of vials} = \frac{10 \text{ ng/mL} \times 5 \text{ L/kg} \times 10 \text{ kg}}{1000 \times 0.5 \text{ mg/vial}} \text{ (Roundup)}$ $\text{No. of vials} = 1$	
$\text{No. of vials} = \frac{10 \text{ ng/mL} \times 5 \text{ L/kg} \times 70 \text{ kg}}{1000 \times 0.5 \text{ mg/vial}} \text{ (Roundup)}$		
No. of vials = 7		

*1000 is a conversion factor to change ng/mL to mg/L. (Round up) to calculate the number of vials indicated.

TABLE A19-3. Empiric Dosing Recommendations

<i>Acute Ingestion</i>	<i>Chronic Toxicity</i>
Adult: 10–20 vials	Adult: 3–6 vials
Child ^a : 10–20 vials	Child ^b : 1–2 vials

^aMonitor for volume overload in very small children. ^bThe prescribing information contains a table for infants and children, with corresponding serum concentrations.

Each 40 mg vial of DigiFab (which binds 0.5 mg digoxin) should be reconstituted with 4 mL of sterile water for IV injection and gently mixed to provide a solution containing 10 mg/mL of DSFab.²⁶ The reconstituted product should be used promptly or, if refrigerated, it should be used within 4 hours. This preparation can be further diluted with sterile isotonic saline for injection. DigiFab should be administered slowly as an IV infusion over at least 30 minutes unless the patient is critically ill, in which case the DigiFab can be given by IV bolus. If a rate related infusion reaction occurs, the infusion should be stopped, the patient stabilized, and restarted at a slower rate. For infants and small children, the manufacturer recommends diluting the 40-mg vial with 4 mL of sterile water for IV injection and administering the dose undiluted using a tuberculin syringe. For very small doses, this preparation can be further diluted with an additional 36 mL of sterile 0.9% sodium chloride for injection (for a total of 40 mL) to achieve a 1 mg/mL concentration.

MEASUREMENT OF SERUM DIGOXIN CONCENTRATION AFTER DIGOXIN-SPECIFIC ANTIBODY FRAGMENT ADMINISTRATION

Many laboratories are unequipped to determine free serum digoxin concentrations. This is relevant because following DSFab administration, total serum digoxin concentrations are clinically meaningless, as they represent free plus bound digoxin.^{2,25,36,41,49,83} The type of test for total digoxin concentrations used can either result in falsely high or falsely low serum concentrations, depending on which phase (solid or supernatant) is sampled.^{40,54} If the correct dose of DSFab is administered, the free serum digoxin concentrations should be near zero. Free digoxin concentrations begin to reappear 5 to 24 hours or longer after Fab administration, depending on the antibody dose, infusion technique, and the patient's renal function. Newer commercial methods, using ultrafiltration or immunoassays, make free digoxin concentration measurements easier to perform and, therefore, more clinically useful, but they remain associated with errors in the underestimation or overestimation of the free digoxin concentration.^{35,42,59,66,84,88} Free digoxin concentrations are particularly useful in patients with severe kidney dysfunction. Independent of the availability of these data, the patient's cardiac status must be carefully monitored for signs of recurrent toxicity.

Other pitfalls in the measurement and utility of serum digoxin concentrations include endogenous and exogenous factors. Endogenous digoxin-like immunoreactive substances (EDLISs) have been described in infants, in women in the third trimester of pregnancy, and in patients with renal and liver failure.^{34,37,39,43,45,55,89,90} When EDLISs are free or weakly bound, as in these circumstances, they are measurable by the typical RIA and can account for factitiously high reported serum digoxin concentrations in the absence of digoxin treatment. The role of EDLISs in the body has not been fully elucidated, but they have an effect on both the Na⁺-K⁺-ATPase pump and the cardioactive steroid receptor site.³⁸ EDLISs are implicated as a causative factor in hypertension and kidney disease.⁵⁶ Exogenous factors relate primarily to measurement techniques and interpretation.⁴⁷ Digoxin metabolites have varying degrees of cardioactivity.⁵⁰ Some metabolites cross-react and are measured by RIA, while others are not. The in vivo production of these metabolites varies in patients, and may depend on intestinal metabolism by gut flora as well as renal and liver clearance.⁹¹

FORMULATION AND ACQUISITION

DSFab is available as DigiFab. Vials contain 40 mg of purified lyophilized digoxin-immune ovine immunoglobulin fragments 75 mg (approximately) of mannitol USP and 2 mg (approximately) sodium acetate USP as a buffering agent. The diluent is not included. The product contains no preservatives and is intended for IV administration after reconstitution with 4 mL of sterile water for injection USP. Each vial binds 0.5 mg digoxin.

SUMMARY

- Digoxin-specific antibody fragments have dramatically advanced the care and have been lifesaving in patients poisoned with cardioactive steroids.
- In the more than 30 years since the release of DSFab, a potentially lethal overdose of a cardioactive steroid has become manageable, allowing clinicians ease in treatment with minimal risks to patients.

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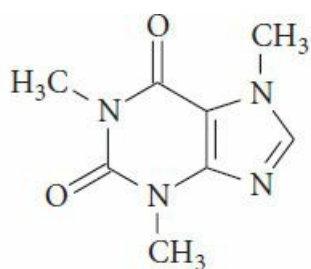
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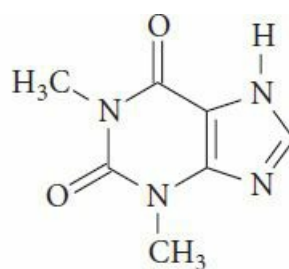
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66 METHYLXANTHINES AND SELECTIVE β_2 -ADRENERGIC AGONISTS

Robert J. Hoffman



Caffeine
(1,3,7-trimethylxanthine)



Theophylline
(1,3-dimethylxanthine)

Caffeine

Molecular weight = 194.19 Da
Therapeutic serum concentration = 1–10 $\mu\text{g/mL}$

Theophylline

Molecular weight = 180.17 Da
Therapeutic serum concentration = 5–15 $\mu\text{g/mL}$
= 28–83 $\mu\text{mol/L}$

HISTORY AND EPIDEMIOLOGY

Methylxanthines are plant-derived alkaloids that include caffeine (1,3,7-trimethylxanthine), theobromine (3,7-dimethylxanthine), and theophylline (1,3-dimethylxanthine). They are so named because they are methylated derivatives of xanthine. Members of this group have very similar pharmacologic properties and clinical effects. Methylxanthines are used ubiquitously throughout the world, most commonly in beverages imbibed for their stimulant, mood-elevating, and fatigue-abating effects. *Coffea arabica* and related species are used to make coffee, a beverage rich in caffeine. Cocoa and chocolate are derived from the seeds of *Theobroma cacao*, which contains theobromine and to a lesser extent caffeine. *Thea sinensis*, a bush native to China but now cultivated worldwide, produces leaves from which various teas, rich in caffeine and containing small amounts of theophylline and theobromine, are brewed. *Paullinia* spp, commonly known as guarana, is a South American plant that produces berries with caffeine content much greater than that of coffee beans.

Selective β_2 -adrenergic agonists have been developed for the treatment of bronchoconstriction. Their selectivity has improved therapy for bronchoconstriction, allowing avoidance of the adverse effects of the previously used therapies: epinephrine, an α - and β -adrenergic agonist, as well as isoproterenol, a β_1 - and β_2 -adrenergic agonist. All β_2 -adrenergic agonists have nearly identical clinical effects; the principal differences are their pharmacokinetics. This chapter does not examine each β_2 -adrenergic agonist individually but instead discusses them as a class. The β_2 -adrenergic agonists include albuterol, clenbuterol, bitolterol, formoterol, pirbuterol, salmeterol, terbutaline, and ritodrine.

The American Association of Poison Control Centers (AAPCC) reported the following trends in methylxanthine exposures. Theophylline exposures, which previously caused thousands of poisonings and dozens of deaths annually, have remained rare. From 2007 to 2011, there were 300 to 400 exposures annually, representing how infrequently theophylline is now used therapeutically. Caffeine exposures continue to decrease at a slow and steady rate. In 1998, there were 7390 reported caffeine exposures. This number has steadily declined: from 2007, with 5448 caffeine exposures, to 2011, with

3667 exposures. Caffeine, as a component of energy drinks, has only recently been added to the National Poisoning Data System (NPDS) of the AAPCC. Included as subcategory of poisoning in 2010, there were 308 reported exposures. The following year, the number of reported exposures to caffeine-containing energy drinks increased to 1610 and exposures to caffeine-containing alcoholic beverages was 131.

It is impossible to know the precise reasons, which may be related to underlying patient health as well as differences in toxicity, but the disparity between theophylline deaths and caffeine deaths is notable. The number of deaths resulting from theophylline remains at approximately one or two per year, and even though caffeine poisoning occurred much more frequently, during this same 5-year time period, there was only a single death attributed to caffeine toxicity in the United States.

The number of β_2 -adrenergic agonist exposures has remained stable during the past 5 years, with approximately 8000 to 9000 reports annually and no reported deaths from these substances (Chap. 136).

The overwhelming preponderance of caffeine consumed is in beverages, and a lesser portion is consumed in foods and tablets or capsules. Users typically seek the stimulant effects of caffeine. Caffeine, particularly in herbal forms such as guarana or cola nut, is also increasingly advocated for various health effects.^{15,81} The use of guarana, a plant with very high caffeine content, for weight loss and athletic performance enhancement has become common in recent years. With some scientific evidence demonstrating benefit in athletic performance, caffeine is advocated as a concentration^{110,172} and “energy” booster and as an athletic performance enhancer.^{35,108} High caffeine content products are widely available as dietary supplements, which are not regulated by the Food and Drug Administration (FDA). These include tablets as well as liquid energy “shots.” Energy drinks, which are FDA regulated, typically containing caffeine and other stimulant ingredients are increasingly popular, particularly with adolescents and athletes (Table 66–1).¹³¹

TABLE 66–1. Caffeine and Stimulant Content of Commonly Used Products

Product	Caffeine Content in Typical Single Serving (mg)	Volume of Typical Single Serving (mL)	Other Relevant Beverage Ingredients	Category
Arizona AZ RX Energy Shot	110	240	Niacin, vitamin B ₁₂	Dietary supplement
Caffeine pill (Vivarin, No-Doz)	200	—	—	Medication
Chocolate (Hershey Kiss)	1	—	—	Food
Chocolate milk	10–15	240	Theobromine	Beverage
Coffee (regular)	115–175	330		Beverage
Cola	30	330		Beverage
Espresso	55	30		Beverage
Five-Hour Energy	207	60	Niacin, taurine, vitamin B ₆ , vitamin B ₁₂	Dietary supplement
Hot chocolate	8	240	Theobromine	Beverage
Red Bull	110	250	Taurine	Beverage
Tea (black)	40–100	240	Theobromine, theophylline	Beverage

These drinks have only recently been recognized as having significant adverse side effects.⁸⁵ Although these adverse effects do not routinely result in severe toxicity, major morbidity and mortality have resulted from their use and misuse.⁴ Between 30% and 50% of adolescents and young adults in the United States regularly consume energy drinks.¹⁷³ Surveys of parents in the United States reveal that children as young as 5 years commonly drink caffeinated beverages daily.²⁰¹

Beverages that combine alcohol with relatively large doses of caffeine have rapidly gained popularity, particularly among young adults and underage drinkers. Toxicity from use of such drinks became apparent very soon after these were introduced to the United States.⁴⁵ In some instances, the incidence of toxicity and adverse events associated with such drinks was so significant that some have been legally banned because they are considered exceptionally dangerous. Caffeine has also been recently discovered as a very common adulterant in drug products sold by Internet vendors.⁵⁶ The quantity of caffeine in such products places users at risk for toxicity, although reports of such have not yet surfaced.

Caffeine, theophylline and aminophylline are used in neonates to treat the apnea and bradycardia syndrome of prematurity. The result of such treatment is an increased respiratory rate, decreased apnea, increased cardiac chronotropy and inotropy, and increased cardiac output.³³

Caffeine is used as an analgesic adjuvant, particularly when combined with analgesics such as acetaminophen, aspirin, and ibuprofen.⁵⁹

Theophylline or its water-soluble salt, aminophylline, is used to treat varied respiratory conditions but is most well studied for its use in reversible bronchospastic airway disease, particularly asthma. Theophylline was once the mainstay of therapy for such diseases, but albuterol and other selective β_2 -adrenergic agonists with fewer adverse effects are now used.

Caffeine toxicity is generally classified as acute, acute on chronic, or chronic in nature. Neonates receiving caffeine therapy may develop acute or chronic caffeine toxicity.^{7,17}

Chronic toxicity from caffeine is most typically results from frequent self-administration of excessive caffeine. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision, notes five distinct caffeine-related disorders, acute toxicity, withdrawal, caffeine-related anxiety disorder, insomnia, and effects not otherwise specified.⁶³ Classically, a syndrome associated with chronic caffeine use consisting of headache, palpitations, tachycardia, insomnia, and delirium has been termed caffeinism.

Theophylline toxicity results from the use of theophylline as a medicinal and may develop as acute, chronic, or acute-on-chronic toxicity.

Acute-on-chronic toxicity may occur with caffeine or theophylline and is the circumstance of acute overdose in a patient already receiving chronic therapy.

Most reported cases of theobromine poisoning occur in the veterinary literature and typically result from small animals ingesting cocoa or chocolate.^{61,90} Theobromine has become an ingredient of numerous “energy” drinks used for stimulation and athletic enhancement, but human toxicity has not yet been reported.

Use of β_2 -adrenergic agonists is widespread. Adverse effects are associated with both therapeutic dosing and overdose. Excessive use of β_2 -adrenergic agonists may result in tachyphylaxis, a phenomenon in which downregulation of receptors occurs and the effects of the drug diminish as a result of excessive use.^{48,104} Consequently, patients may require higher doses to achieve the same clinical effects previously experienced at lower doses, resulting in consequential adverse effects. The most common selective β_2 -adrenergic agonist toxicity results from children ingesting albuterol syrup. The toxicity associated with terbutaline and ritodrine is infrequently reported. Clenbuterol, a long-acting β_2 agonist adrenergic, used for the purpose of treating bronchoconstriction in countries outside the United States, has in recent years emerged as an abused anabolic xenobiotic as well as additive in street drugs. Epidemic clenbuterol exposures have occurred in recent years, as a result of both its admixture with illicit xenobiotics and its intentional use for bodybuilding purposes in the United States.⁵⁵ Food poisoning by consumption of animal meat from livestock treated with clenbuterol has occurred in Europe.¹⁸

PHARMACOLOGY

Methylxanthines

Methylxanthines cause the release of endogenous catecholamines, resulting in stimulation of β_1 and β_2 receptors.¹⁹⁷

Endogenous catecholamine concentrations are extremely elevated in patients with methylxanthine poisoning.²²

Methylxanthines are structural analogs of adenosine and function pharmacologically as adenosine antagonists. Adenosine modulates histamine release and causes bronchoconstriction, which may explain the primary therapeutic efficacy of adenosine antagonists in the treatment of bronchospasm. Additionally, adenosine antagonism results in release of norepinephrine, and to a lesser extent epinephrine, through blockade of presynaptic A_2 receptors. The additional methyl group possessed by caffeine (1,3,7-trimethylxanthine) permits greater central nervous system (CNS) penetration relative to theophylline and theobromine, which are dimethylxanthines. Caffeine is an effective analgesic adjuvant, possibly because of the stimulant properties of the drug.^{138,140,170,171}

Methylxanthines also inhibit phosphodiesterase, the enzyme responsible for degradation of intracellular cyclic AMP (cAMP), which has many effects, including an increase in intracellular calcium concentrations. Phosphodiesterase inhibition was long considered to be the primary therapeutic mechanism of the methylxanthines, but clinically significant elevations in cAMP concentrations are not achieved until serum methylxanthine concentrations are well above the therapeutic range. This likely occurs as a result of the structural similarity of the adenosine moiety of cAMP and the methylxanthines. cAMP is involved in the postsynaptic second messenger system of β -adrenergic stimulation. Thus, elevated cAMP concentrations cause clinical effects similar to adrenergic stimulation, including smooth muscle relaxation, peripheral vasodilation, myocardial stimulation, skeletal muscle contractility, and CNS excitation.

Selective β_2 -Adrenergic Agonists

Selective β_2 -adrenergic agonists act very specifically at β_2 -adrenergic receptors, resulting in an increase in intracellular

cAMP. Effects of β_2 agonism include relaxation of vascular, bronchial, and uterine smooth muscle; glycogenolysis in skeletal muscle; and hepatic glycogenolysis and gluconeogenesis. Selective β_2 -adrenergic agonists have been characterized as directly activating the β_2 receptor, such as albuterol; being taken up into a membrane depot, such as formoterol; or interacting with a receptor-specific auxiliary binding site, such as salmeterol. These differences do not appear to be relevant in acute toxicity.⁹⁹ However, emerging evidence suggests that prolonged overuse of long-acting β_2 -adrenergic agonists may have severe or fatal adverse effects.¹⁶⁸

PHARMACOKINETICS AND TOXICOKINETICS

Caffeine Pharmacokinetics

Caffeine is bioavailable by oral (PO), intravenous (IV), subcutaneous, intramuscular, and rectal routes of administration. PO administration, which is by far the most common route of exposure, results in nearly 100% bioavailability. The presence of food in the gut does little to affect peak concentration. However, food in the gut delays the time until the peak serum concentration is reached, which is typically 30 to 60 minutes in the absence of food. Caffeine rapidly diffuses into the total body water and all tissues and readily crosses the blood–brain barrier and into the placenta. The volume of distribution (Vd) is 0.6 L/kg, and 36% is protein bound. Caffeine is secreted in breast milk with concentrations of 2 to 4 $\mu\text{g/mL}$ in breast milk after 100 mg PO dosing in a breastfeeding mother.¹⁹⁰ Consumption of caffeine does not result in clinically relevant breast milk caffeine concentrations in lactating women or toxicity in their breastfeeding children. Breast milk caffeine concentrations are lower than maternal serum caffeine concentrations, with breast milk having 0.006% to 1.5% of the quantity of maternal serum.²³

When taken in amounts that produce serum caffeine concentrations exceeding a therapeutic range, or approximately 20 mg/kg, caffeine exhibits Michaelis-Menten kinetics and is metabolized, primarily by CYP1A2. The major pathway involves demethylation to 1,7-dimethylxanthine (paraxanthine) followed by hydroxylation or repeated demethylation followed by hydroxylation. To a lesser extent, caffeine is also metabolized to theobromine and theophylline. Neonates demethylate caffeine, producing theophylline, and possess the unique ability to convert theophylline to caffeine by methylation.^{1,76} By 4 to 7 months of age, infants metabolize and eliminate caffeine in a manner similar to adults.¹⁰ All patients demethylate some quantity of caffeine to active metabolites, including theophylline and theobromine. The degree to which this occurs depends on the patient's age, CYP1A2 induction status, and other factors.

Less than 5% of caffeine is excreted in the urine unchanged. The half-life of caffeine is highly variable and dependent on several factors. Generally speaking, younger patients, particularly infants as well as patients with CYP1A2 inhibition, such as pregnant patients and patients with cirrhosis, have longer caffeine half-lives than the 4.5-hour half-life in healthy, adult, nonsmoking patients.^{34,52,57,89}

Caffeine Toxicokinetics. Caffeine toxicity is a dose dependent phenomenon. The range of toxic concentrations reported in different references varies greatly, and no definite conclusions can be drawn regarding the relationship between serum concentrations and symptomatology in overdose. Therapeutic dosing in neonates is typically a loading dose of 20 mg/kg, with daily maintenance dosing of 5 mg/kg. Based on case reports and series, lethal dosing in adults is estimated at 150 to 200 mg/kg, and death may occur with serum concentrations above 80 $\mu\text{g/mL}$. Numerous fatalities are reported with serum concentrations under 200 $\mu\text{g/mL}$; and survival is reported of a patient with an acute caffeine overdose and a serum concentration over 400 $\mu\text{g/mL}$.¹⁹⁴ Infants tolerate greater serum concentrations of caffeine than do children and adults.

Theophylline Pharmacokinetics

Theophylline is approximately 100% bioavailable by the PO and IV routes. Many of the available PO preparations are sustained release designed to provide stable serum concentrations over a prolonged period of time with less frequent dosing. Peak absorption for immediate-release preparations is 60 to 90 minutes; peak absorption of sustained-release preparations generally occurs 6 to 10 hours after ingestion.

Similar to caffeine, theophylline rapidly diffuses into the total body water and all tissues, readily crosses the blood–brain barrier, and crosses into the placenta and breast milk.¹⁴ The Vd of theophylline is 0.5 L/kg, and 56% of it is protein bound at therapeutic concentrations.

Theophylline is metabolized primarily by CYP1A2. The major pathway is demethylation to 3-methylxanthine in addition to being demethylated or oxidized to other metabolites. Less than 10% of theophylline is excreted in the urine unchanged.

Similar to caffeine, the half-life of theophylline is highly variable and depends on several factors. In healthy, adult, nonsmoking patients, the half-life is 4.5 hours. Infants and elderly adults as well as patients with CYP1A2 inhibition, pregnant patients, and those with cirrhosis may have theophylline half-lives twice as long as healthy children and nonsmoking adults.^{100,132,188} Factors that induce CYP1A2, such as cigarette smoking, or others that inhibit CYP1A2, such as

exposure to cimetidine, macrolides, and oral contraceptives, can significantly alter theophylline clearance.^{84,130,146,147,162,199} Cessation of smoking, such as when a patient with chronic obstructive pulmonary disease develops bronchitis, leads to a reversal of CYP1A2 induction and predisposes to the development of chronic toxicity.

Theophylline Toxicokinetics. As in the case of caffeine, theophylline exhibits Michaelis-Menten kinetics, presumably when greater than a single therapeutic dose is taken.¹⁵² At higher doses and in overdose, it undergoes zero-order elimination, and only a fixed amount of the drug can be eliminated in a given time because of saturation of metabolic enzymes.¹⁵⁹

Therapeutic serum concentrations of theophylline are 5 to 15 µg/mL. Although morbidity and mortality are not always predictable based on serum concentrations, life-threatening toxicity is associated with serum concentrations of 80 to 100 µg/mL in acute overdoses and of 40 to 60 µg/mL in chronic overdoses.

Theobromine Toxicokinetics and Pharmacokinetics

Similar to the other methylxanthines, theobromine is well absorbed from the gastrointestinal (GI) tract and is 80% bioavailable when administered in solution. It is completely bioavailable orally and rectally. Theobromine has 21% protein binding, a Vd of 0.62 L/kg, and a serum half-life of 6 to 10 hours.^{62,156} Theobromine undergoes hepatic metabolism by CYP1A2 and CYP2E1.³¹ Theobromine is excreted in breast milk. Toxic concentrations of theobromine in animals are known, but comparable human data are lacking.

Selective β_2 -Adrenergic Agonist Pharmacokinetics

The β_2 -adrenergic agonists are bioavailable by both inhalation and ingestion, and much of “inhaled” β_2 -adrenergic agonists may actually be swallowed and absorbed from the GI tract. Absorption, distribution, and elimination are quite variable. The half-life of albuterol is approximately 4 hours, less than 5% crosses the blood–brain barrier, it is metabolized extensively in the liver, and it is excreted in urine and feces as albuterol and metabolites.³

Terbutaline is partially metabolized in the liver, mainly to inactive conjugates. With parenteral administration, 60% of a given dose is excreted in the urine unchanged.²

Clenbuterol has a terminal half-life of approximately 22 hours and a prolonged duration of action. It is more potent than other β_2 -adrenergic agonist, with a typical therapeutic dose of 20 to 40 µg, as opposed to milligram doses for other β_2 -adrenergic agonists.

Selective β_2 -Adrenergic Agonist Toxicokinetics. Overdose of albuterol, which happens predominantly in young children treated with oral albuterol preparations, may cause significant effects.¹¹⁵ For oral albuterol poisoning 1 mg/kg appears to be the dose threshold for developing clinically significant toxicity.²⁰⁵

Clenbuterol toxicity occurs following illicit drug use by ingestion, intranasal, and IV use of clenbuterol or clenbuterol-tainted street drugs.⁹⁶

Methylxanthine and β_2 -Adrenergic Agonist Toxicity

Caffeine, theobromine, and theophylline affect the same organ systems and cause qualitatively similar effects. There are distinct differences in the activity and effects of the various methylxanthines, particularly in therapeutic dose. Toxicity affects the GI, cardiovascular, central nervous, and musculoskeletal systems in addition to causing a constellation of metabolic derangements. A putative cause for toxicity involves the increase in metabolism that occurs with methylxanthine toxicity, particularly in the setting of a decreased tissue perfusion.

Concomitant poisoning with other xenobiotics that result in adrenergic stimulation, such as pseudoephedrine, ephedrine, amphetamines, or cocaine, may be particularly severe.^{58,203}

Gastrointestinal. In overdose, methylxanthines cause nausea, and most significant acute overdoses result in severe and protracted emesis. Whereas emesis occurs in 75% of cases of acute theophylline poisoning, only 30% of cases of chronically poisoned patients have emesis.¹⁸¹ When it occurs, the emesis may be difficult to control despite the use of potent antiemetics. This is especially evident with sustained-release theophylline preparations.⁴ Emesis is less common with β_2 -adrenergic agonists, than with methylxanthine overdose.

Methylxanthines cause an increase in gastric acid secretion and smooth muscle relaxation. These factors contribute to the gastritis and esophagitis reported in chronic methylxanthine users.⁴⁶ Gastritis is noted in drinkers of decaffeinated coffee, indicating that some adverse gastric effects associated with coffee drinking may be caused by ingredients other than caffeine or even the pH of the beverage.

Cardiovascular. Methylxanthines are cardiac stimulants and result in positive inotropy and chronotropy even with therapeutic dosing. Dysrhythmias, particularly tachydysrhythmias, are common in patients with methylxanthine overdose.

Tachydysrhythmias, particularly ventricular extrasystoles, are more common after overdose of methylxanthines.^{42,139,174} Cardiac dysrhythmias, although described with β_2 -adrenergic agonist poisoning, are most frequently supraventricular in origin and clinically inconsequential. Dysrhythmias other than sinus tachycardia associated with β_2 -adrenergic agonist toxicity are not routinely noted with toxicity from other β_2 -adrenergic agonists, but clenbuterol may result in atrial fibrillation.⁵⁵ Palpitations, tachycardia, and chest pain are common presenting complaints for patients with clenbuterol toxicity.

In the setting of acute poisoning, generally benign sinus tachycardia is nearly universal in patients without antecedent cardiac disease. In any patient, particularly those with underlying cardiac disease, sinus tachycardia may degenerate to a more severe rhythm disturbance, and these represent the most common causes of fatality associated with methylxanthine poisoning. Both atrial and ventricular dysrhythmias, including supraventricular tachycardia (SVT), multifocal atrial tachycardia, atrial fibrillation, premature ventricular contractions, and ventricular tachycardia, may all result from methylxanthine toxicity.^{21,178} Electrolyte disturbances, particularly hypokalemia, may be a contributing factor in the development of dysrhythmias. Dysrhythmias occur more commonly and at lower serum concentrations in cases of chronic poisoning with methylxanthines. Consequential dysrhythmias occur in 35% of patients with chronic theophylline poisoning but in only 10% of acute poisoning.¹⁷⁸ Ventricular dysrhythmias occur at serum concentrations of 40 to 80 $\mu\text{g/mL}$ in patients with chronic theophylline overdoses and most commonly at serum concentrations greater than 80 $\mu\text{g/mL}$ in patients with acute overdoses. Neonates born to mothers who consumed more than 500 mg/day of caffeine are more likely to have dysrhythmias compared with cohorts born to mothers consuming less than 250 mg/day of caffeine.⁸⁶ See [Table 66–1](#) for the caffeine content of other popular products.

Myocardial ischemia and myocardial infarction (MI) may result from acute caffeine or theophylline poisoning.^{69,91,134} MI is associated with albuterol⁶⁶ and more recently clenbuterol.¹¹⁴ Isoproterenol, once a common asthma therapy before widespread use of selective β_2 -adrenergic agonists, has both β_1 - and β_2 -adrenergic agonist activity and is a well-reported cause of MI. Given the frequency of use of selective β_2 -adrenergic agonists as well as toxicity and adverse effects reported from them, MI should be considered unlikely to occur. The same cannot be presumed about clenbuterol because the toxicity profile for this drug is still emerging. Clenbuterol is clearly documented to cause myocardial ischemia and MI in young otherwise healthy patients without coronary artery disease.¹¹⁴

Elevation of troponin, muscle creatine phosphokinase (CK-MM) and cardiac (CK-MB) fractions after large doses of β_2 -adrenergic agonist, particularly terbutaline infusions and continuous albuterol nebulization, is described.^{49,50,109,193} In the absence of electrocardiographic (ECG) changes suggestive of ischemia, the clinical significance of increased CPK-MB and cardiac troponins in patients receiving terbutaline infusions, particularly children, is unclear and has not been demonstrated to correlate with clinically adverse effects.⁴⁴

In therapeutic doses, methylxanthines cause cerebral vasoconstriction, which is a desirable effect when caffeine is used to treat a migraine headache. However, in overdose, this effect likely exacerbates CNS toxicity by diminishing cerebral perfusion.¹³⁴ Tolerance to the vasopressor effects of methylxanthines develops after several days of use and rapidly disappears after relatively brief periods of abstinence.

Dietary caffeine use is associated with a significant increase in blood pressure that may contribute to population levels of morbidity and mortality.¹⁰³ At elevated serum concentrations, patients with methylxanthine or β_2 -adrenergic agonist poisoning often develop a characteristic widened pulse pressure. This is caused by enhanced inotropy (β_1) and may result in increases in systolic blood pressure combined with peripheral vasodilation (β_2), which may result in diastolic hypotension. In cases of acute theophylline overdose, serum concentrations greater than 100 $\mu\text{g/mL}$ are usually associated with significant hypotension.

Methylxanthines cause renal vasodilation that, in addition to the increased cardiac output, results in a mild diuresis.¹⁴⁸

Pulmonary. Methylxanthines stimulate the CNS respiratory center, causing an increase in respiratory rate. For this reason, caffeine and theophylline are used to treat neonatal apnea syndromes. Caffeine and theophylline overdose may cause hyperventilation, respiratory alkalosis, respiratory failure, respiratory arrest, and acute respiratory distress syndrome.

Neuropsychiatric. The stimulant and psychoactive properties of methylxanthines, particularly caffeine, elevate mood and improve performance of manual tasks.^{26,36,102} These stimulant effects are some of the reasons caffeine is so widely used. CNS stimulation is an effect sought by users of coffee, tea, cocoa, and chocolate, but CNS stimulation resulting from therapeutic use of theophylline is generally considered to be an undesirable side effect. Although at low doses methylxanthines have beneficial effects, with increasing doses, they result in adverse effects. Headache, anxiety, agitation, insomnia, tremor, irritability, hallucinations, and seizures may result from caffeine or theophylline poisoning. In adults, caffeine doses of 50 to 200 mg result in increased alertness, decreased drowsiness, and lessened fatigue, and caffeine doses of 200 to 500 mg produce adverse effects such as tremor, anxiety, diaphoresis, and palpitations. Children tend to develop CNS symptoms at lower serum theophylline concentrations than adults, and such excitation is a significant clinical

disadvantage of theophylline use.

Seizures are a major complication of methylxanthine poisoning. The ability of caffeine to both promote and prolong seizures is well recognized. Caffeine has been used to prolong therapeutically induced seizures in electroconvulsive therapy.^{54,112} Seizures resulting from methylxanthine overdose tend to be severe and recurrent and may be refractory to conventional treatment. Antagonism of adenosine, the endogenous neurotransmitter responsible for halting seizures, contributes to the profound seizures associated with methylxanthine overdose.^{64,70,179,209} When studied prospectively, chronic theophylline toxicity results in seizures in 14% of patients, but 5% of acutely poisoned patients experience seizures. In cases of chronic and acute-on-chronic toxicity, seizures are more likely to occur, and they occur at lower serum concentrations.¹⁵⁰ Patients at extremes of age—those younger than age 3 years and older than age 60 years—are more likely to experience seizures with overdose.

Musculoskeletal. Methylxanthines increase striated muscle contractility, secondarily decreasing muscle fatigue. They also increase muscle oxygen consumption and increase the basal metabolic rate. These effects are sought by users to enhance or improve athletic performance or weight loss.^{9,19,46,65,79,80} All methylxanthines cause smooth muscle relaxation.

Tremor is the most common adverse effect of methylxanthines. Skeletal muscle excitation, which may include fasciculation, hypertonicity, myoclonus, or even rhabdomyolysis, may occur with methylxanthine overdose.^{119,129,164,208} Mechanisms by which rhabdomyolysis may result include increased muscle activity, particularly from seizures, and direct cytotoxicity from excessive sequestered intracytoplasmic calcium. Interestingly, multiple case reports associate atraumatic compartment syndrome with rhabdomyolysis with theophylline overdose.^{128,195}

Metabolic. Numerous metabolic derangements result from acute methylxanthine toxicity and are similar to those in other hyperadrenergic situations.^{84,88,168,180}

Severe hypokalemia may result from β_2 -adrenergic stimulation.¹⁹⁶ This results from influx of extracellular potassium into the intracellular compartment despite normal total body potassium content. Both ECG and neuromuscular complications of hypokalemia may develop. Other metabolic effects of methylxanthine and β_2 -adrenergic agonist poisoning include hypomagnesemia and hypophosphatemia.^{30,115,202}

Transient hypokalemia resulting from β -adrenergic agonism occurs in 85% of patients with acute theophylline overdose, and typically the serum potassium decreases to approximately 3 mEq/L.^{5,183} Stimulation of Na^+K^+ -ATPase results in a shift of serum potassium to the intracellular compartment of skeletal muscle. Total body potassium stores are unchanged. The significance of hypokalemia in patients with methylxanthine overdose is unclear. Vomiting and renal losses do not contribute significantly to hypokalemia, but these may result in fluid loss. Hyperkalemia may result from rhabdomyolysis and overly aggressive repletion of potassium.

Metabolic acidosis with increased serum lactate concentration is commonly noted as a complication of theophylline overdose.^{25,124} Tachypnea and respiratory alkalosis secondary to stimulation of the respiratory center are also common. Clenbuterol excess demonstrates significant β_2 -adrenergic agonists toxicity associated with an anion gap metabolic acidosis in some cases.⁹⁶

Hyperglycemia with serum glucose of approximately 200 mg/dL in those without diabetes is common and occurs in 75% of patients with acute theophylline overdose. Hyperthermia caused by increased metabolic activity and increased muscle activity may result from caffeine and theophylline overdose. Leukocytosis, probably secondary to the high concentrations of circulating catecholamines, results from acute methylxanthine overdose. This phenomenon apparently lacks clinical significance. In the absence of seizures or protracted emesis, chronic methylxanthine poisoning does not typically lead to metabolic derangements because such toxicity is an ongoing, compensated process.

Chronic Methylxanthine Toxicity

The distinction between acute and chronic toxicity is based on the duration of exposure to the xenobiotic. Patients with chronic toxicity may manifest subtle signs such as anorexia, nausea, palpitations, or emesis, although they may also present with seizures or dysrhythmias.

Patients chronically receiving theophylline or caffeine have higher total body stores and often underlying medical disorders, and they may develop toxicity with a smaller amount of additional theophylline or caffeine. Chronic methylxanthine poisoning typically occurs in the setting of therapeutic use of theophylline and may occur with iatrogenic administration of caffeine or from frequent, chronic consumption of caffeinated products. Patients often manifest subtle signs of illness, such as anorexia, nausea, palpitations, or emesis. However, the initial presentation in these patients, even with serum concentrations in the 40 to 60 $\mu\text{g/mL}$ range, may be a seizure. In children chronically overdosed with theophylline, the peak serum theophylline concentration may fail to identify those who will progress to life-threatening toxicity. In the absence of protracted emesis or seizures, the initial electrolytes and blood gases are expected to be normal in patients with chronic methylxanthine toxicity.

Chronic Methylxanthine Use

Data on the effect of caffeine on many chronic health issues are mixed and highly contradictory. Studies show inconclusive links to cancer, heart disease, osteoporosis, hyperlipidemia, and hypercholesterolemia associated with caffeine use.^{68,71,83,160,206} Excessive consumption of caffeine-containing beverages may cause hypokalemia.¹⁶³

Caffeine Withdrawal

Caffeine induces tolerance, and a withdrawal syndrome, including headache, yawning, nausea, drowsiness, rhinorrhea, lethargy, irritability, nervousness, a disinclination to work, and depression, may result upon abstinence.¹⁹² Caffeine withdrawal symptoms are described in neonates born to mothers with consequential caffeine use.¹³⁶ The onset of caffeine withdrawal symptoms begins 12 to 24 hours after cessation and lasts up to one week.⁸² In a double-blind trial, 52% of adults with low to moderate caffeine intake, defined as 2.5 cups of coffee daily, developed a withdrawal syndrome upon caffeine abstinence.¹⁸⁶

Reproduction

Massive doses of methylxanthines are teratogenic, but the doses of typical use are not associated with birth defects. Decreased fecundity and adverse fetal outcome are noted in animals with chronic exposure to methylxanthines.^{72,77,135} Human studies of fertility, fetal loss, and fetal outcome produce divergent results, and the effects of methylxanthines use during gestation are unclear.^{99,106,141,144}

Diagnostic Testing

An ECG, serum electrolytes, and serum caffeine or theophylline concentrations are indicated as appropriate in cases of suspected methylxanthine toxicity. Because toxicity is dose related in acute overdose, serum concentrations of caffeine and theophylline may be loosely applied as a correlate with toxicity.

Hospitals in which caffeine is used therapeutically typically have the capability to assay serum caffeine concentration within the institution, and likewise hospitals in which theophylline is used therapeutically typically are able to assay serum theophylline concentrations. Overdose of caffeine may result in a spuriously elevated serum theophylline concentration.^{67,107}

Theophylline concentrations, and to a lesser extent, caffeine concentrations, may be used prognostically to guide management of poisoning. Proper interpretation requires knowledge of whether the poisoning is acute, chronic, or acute on chronic. In the setting of toxicity, serum methylxanthine concentrations should be obtained immediately and then serially every 1 to 2 hours until a downward trend is evident.

Likewise, serum electrolytes, particularly potassium, should be monitored serially as long as the poisoned patient remains symptomatic and such values are in a range that may warrant treatment. Cardiac monitoring should continue until the patient is free of dysrhythmias other than sinus tachycardia, has a falling serum methylxanthine concentration, and is clinically stable. In patients with systemic illness, hyperthermia, or increased muscle tone, assessing serum CK and urinalysis to detect rhabdomyolysis is also indicated.

MANAGEMENT

General Principles and Gastrointestinal Decontamination

After assuring adequacy of airway, breathing, and circulation, supportive care and maintenance of vital signs within acceptable limits are the mainstays of therapy for patients with methylxanthine and selective β_2 -adrenergic agonist toxicity. Decisions regarding GI decontamination, including orogastric lavage, administration of activated charcoal (AC), or whole-bowel irrigation (WBI), depend on the dosage and type of preparation involved, the time since exposure, and the patient's physical condition ([Chap. 8](#)). AC is the only GI decontamination that should be routinely considered for selective β_2 -adrenergic agonist ingestion.

Emesis. Induced emesis is not indicated for selective β_2 -adrenergic agonist ingestion or methylxanthine ingestion. A simulated overdose controlled volunteer study with sustained-release theophylline was unable to demonstrate reduction of absorption of theophylline in patients treated with syrup of ipecac.¹⁴² Seizures are possible with any significant methylxanthine poisoning, and induced emesis in a patient with potential to experience a seizure is contraindicated. Because the benefits of emetics are undemonstrated and emesis interferes with administration of AC, induced emesis is rarely considered for those with methylxanthine poisoning.^{6,175}

Orogastric Lavage. Orogastric lavage may be considered for patients with potentially toxic methylxanthine ingestions who reach medical care shortly after ingestion. Selective β_2 -adrenergic agonist liquid ingestion that occurs within one hour

before treatment may warrant aspiration through a small nasogastric tube.

Ingestion of sustained-release theophylline tablets is associated with the formation of bezoars that may be difficult to remove or dislodge. Treatment in such cases has included endoscopic removal.⁴⁰

Activated Charcoal. AC is essential in the treatment of methylxanthine poisoning. AC can adsorb methylxanthines and selective β_2 -adrenergic agonist present in the GI tract and limit their absorption. Multiple-dose activated charcoal (MDAC) is helpful to enhance the elimination of methylxanthine toxicity but is not indicated for selective β_2 -adrenergic agonist ingestion. MDAC may be useful for any sustained-release methylxanthine preparation. Additionally, MDAC enhances elimination of theophylline by “gut dialysis” (Antidotes in Depth: A1). Such enhanced elimination by gut dialysis is not demonstrated experimentally or otherwise for caffeine or theobromine toxicity. Because caffeine is to some extent metabolized to theophylline, in cases of caffeine poisoning, MDAC would at the very least enhance elimination of theophylline metabolites. The pharmacologic similarity of the methylxanthines and the relative safety of MDAC therapy warrant the use of such treatment for patients with any methylxanthine toxicity. MDAC is used for enhanced elimination.

Whole-Bowel Irrigation. Treatment of patients with significant ingestions of sustained-release pills may include WBI with a balanced electrolyte solution to enhance GI elimination (Antidotes in Depth: A2). Polyethylene glycol electrolyte lavage solution used for WBI may displace theophylline already bound to activated charcoal.⁹⁵ This may be a particular problem in patients who have taken several doses of AC before WBI, in which desorption of methylxanthines from AC may result in a bolus of methylxanthines available for GI absorption. Also, WBI is experimentally demonstrated to provide no additional benefit to AC in treatment of sustained-released theophylline ingestion.³⁸ Despite these data, WBI with MDAC remains the preferred and recommended treatment of a patient with ingestion of sustained-release theophylline.

Selecting a Method of Decontamination. The use of decontamination methods that involve more than minimal risk, specifically orogastric lavage, should only occur after careful consideration of the indications. Patients with potentially life-threatening acute ingestions occurring approximately one hour previously may be treated with orogastric lavage (Chap. 8).

Treatment

Gastrointestinal Toxicity. Phenothiazine antiemetics are contraindicated in those with methylxanthine poisoning because they are typically ineffective and may lower the seizure threshold. The preferred antiemetic is ondansetron, although metoclopramide may be used also.^{53,157,167} Ondansetron dosing in the upper end of the therapeutic dosing range, or even chemotherapeutic doses may be used if necessary. Histamine (H_2) blockers or proton pump inhibitors may be administered to any patient with hematemesis. Cimetidine is contraindicated because it inhibits multiple CYP enzymes, delaying clearance of methylxanthines.

Cardiovascular Toxicity. Patients with hypotension should initially be treated by administration of isotonic IV fluid, such as 0.9% sodium chloride or lactated Ringer solution, in bolus volumes of 20 mL/kg. If acceptable blood pressure cannot be maintained despite several fluid boluses or if there are contraindications to fluid bolus, vasopressor therapy should be considered.

Methylxanthine and selective β_2 -adrenergic agonist toxicity may cause hypotension via β -adrenergic agonism; therefore, administration of vasopressors with β -adrenergic agonist effects, such as epinephrine, dobutamine, or isoproterenol, is suboptimal. An α -adrenergic agonist such as phenylephrine is the first-line pressor of choice in such a situation, although norepinephrine is also acceptable (Table 66–2).

TABLE 66–2. Therapeutic Interventions for Methylxanthines and Selective β_2 -Adrenergic Agonist Poisoning

System	Indication	Therapeutic Agent	Comments
Cardiovascular	Hypotension	Vasopressors	Relatively contraindicated in asthmatic patients Requires hemodynamic monitoring Hypotension unresponsive to IV fluid
		Phenylephrine	
		Norepinephrine	
		β-Adrenergic antagonists	
	Supraventricular dysrhythmias	Esmolol	Relatively contraindicated in asthmatic patients Requires hemodynamic monitoring
		Metoprolol	
		Propranolol	
		Calcium channel blockers	
		Diltiazem	
		Verapamil	
	Ventricular dysrhythmias	β-Adrenergic antagonists	Relatively contraindicated in asthmatic patients Requires hemodynamic monitoring
		Esmolol	
		Metoprolol	
		Propranolol	
		Antidysrhythmics	
		Lidocaine	
		β-Adrenergic antagonists	
		Esmolol	
		Metoprolol	
		Propranolol	
Gastrointestinal	Emesis	Antiemetics	Cimetidine is not recommended as it may decrease clearance of methylxanthines and prolong toxicity
		Metoclopramide	
		Ondansetron	
	Hematemesis	Granisetron	
		Proton pump inhibitors	
		Esomeprazole or others	
		H ₂ antagonists	
Central nervous system	Agitation	Ranitidine	
		Famotidine	
	Anxiety	Benzodiazepines	
		Diazepam	
		Lorazepam	
	Seizures	Benzodiazepines	
		Diazepam	
		Lorazepam	
		Midazolam	
		Barbiturates	
		Phenobarbital	
		Pentobarbital	
		Propofol	
Metabolic	Metabolic acidosis	Sodium bicarbonate (controversial)	Not routinely recommended for this purpose
	Hypokalemia	Potassium chloride	Relatively contraindicated in asthmatic patients Requires hemodynamic monitoring
		β-Adrenergic antagonists	
		Esmolol	
		Metoprolol	
		Propranolol	

In rare cases of refractory hypotension, the administration of an adrenergic antagonist may be warranted.⁶⁰

Administration of an adrenergic antagonist to a hypotensive patient may seem counterintuitive, but it may reverse β_2 -adrenergic-mediated vasodilation. In addition, β_1 -adrenergic blockade treats tachycardia and any associated decreased cardiac output. In dogs with aminophylline-induced tachycardia and hypotension, administration of esmolol results in a return to normal heart rate and blood pressure, and it does not exacerbate hypotension.⁷³ Propranolol, esmolol, and metoprolol have been used successfully to treat methylxanthine-induced hypotension.^{27,154} It is most appropriate to use a β -adrenergic antagonist with a brief duration of action, such as esmolol, at least initially, in such circumstances. In the event of an adverse reaction or side effect such as hypotension or bronchospasm were to occur, the duration of such will be relatively brief. Any β -adrenergic antagonist therapy should ideally be preceded and accompanied by assessment of cardiac output and central venous pressure, either directly or noninvasively.¹¹³

Because of its long half-life and possibly potency, toxicity from clenbuterol exposure appears more likely to require treatment with β -adrenergic antagonist medications.⁹⁴

When drug toxicity is not in question, adenosine or electrical cardioversion are the preferred treatment for SVT, but this is not so for SVT resulting from methylxanthine toxicity. Because of the antagonist effects at the adenosine receptor, administration of adenosine should not be expected to convert a methylxanthine-induced SVT. However, even if adenosine is successfully used to convert an SVT, the effect is likely to be transient. Because methylxanthine toxicity has a global effect on the myocardium and methylxanthine concentrations do not change rapidly, cardioversion, which is effective in electrically “reorganizing” depolarization, is unlikely to result in a sustained normal rhythm.

The primary treatment for methylxanthine-induced SVT includes administration of benzodiazepines, which work to abate CNS stimulation and concomitant release of catecholamines. More focused pharmacologic therapy to treat SVT would be through cautious administration of a conduction-attenuating calcium channel blocker such as diltiazem or verapamil.

In animal models, treatment of acute theophylline toxicity with the calcium channel blockers diltiazem, verapamil, and nifedipine each results in decreased cardiac-related deaths and prevention of dysrhythmias, hypotension, myocardial necrosis, and seizures.²⁰⁴ In addition to the cardiovascular benefit of calcium channel blockers, they may also afford neurologic protection and prevention of seizure. In patients without asthma, methylxanthine-induced SVT and other tachydysrhythmias may be treated by administration of an adrenergic antagonist.

Central Nervous System Toxicity. Administration of a benzodiazepine, such as diazepam, lorazepam, or midazolam, is appropriate treatment for anxiety, agitation, or seizure. Seizures associated with methylxanthine toxicity are severe and often refractory to treatment. Seizures not controlled with one or two therapeutic doses of a benzodiazepine should be treated with a barbiturate such as phenobarbital or pentobarbital or another suitable sedative-hypnotic such as propofol. No delay should occur before administering such medications. Unsuccessful treatment of methylxanthine-induced seizures with any particular antiepileptic should quickly be abandoned in favor of treatment with an additional or more potent and efficacious anticonvulsant. The administration of barbiturates may result in or exacerbate hypotension. Treatment of agitation or seizure with benzodiazepines, barbiturates, or other sedative-hypnotic may require repeated dosing until clinical effect is achieved.

Administration of phenobarbital to prevent seizures in theophylline-poisoned rabbits and mice increases survival by decreasing the incidence of seizures.^{51,78} Although historically, phenobarbital was the recommended drug for such prophylaxis, use of a benzodiazepine such as lorazepam seems preferable based on pharmacokinetic and practical considerations. Patients at risk for seizure include those identified earlier in this chapter—patients older than age 60 years or younger than age 3 years, those with chronic overdose and a serum concentration above 40 $\mu\text{g/mL}$, and acutely overdosed patients with serum concentrations greater than 100 $\mu\text{g/mL}$.

Phenytoin and fosphenytoin are of no benefit in controlling methylxanthine-induced seizures, and they have no role in such treatment.^{93,133} Retrospective review of human cases demonstrated phenytoin to be ineffective in treating seizures in 21 of 22 cases.¹⁰¹ Phenytoin results in the occurrence of seizures at an earlier time after overdose and results in higher mortality when administered to theophylline-poisoned mice.²⁸

Metabolic Derangements. Patients with symptomatic hypocalcemia should be treated with electrolyte repletion. Most cases of mild hypokalemia are well tolerated, but any patient with symptomatic hypokalemia, particularly those associated with ECG changes of T waves or QT interval prolongation, should be treated. The frequency of ventricular dysrhythmias in methylxanthine poisoning is exacerbated by hypokalemia coupled with increased intrinsic catecholamine release. Correction of hypokalemia may be crucial in methylxanthine poisoning associated with ventricular dysrhythmias.

There is no specific degree of hypokalemia that absolutely necessitates treatment. In the absence of associated dysrhythmia, the clinical significance of such hypokalemia is unclear. Although correction is generally performed with the administration of IV or PO potassium, hypokalemia experimentally responds to treatment with β -adrenergic antagonists.

Cautious administration of potassium to treat symptomatic hypokalemia may be indicated, but this is distinct from higher doses of potassium used in total body potassium repletion. In cases of hypokalemia secondary to β -adrenergic agonism, after the β -adrenergic agonism returns to baseline level, an efflux of potassium from the intracellular compartment occurs. A concomitant increase in the serum potassium concentration occurs at that time. Overly aggressive attempts to correct

hypokalemia may result in hyperkalemia after the β -adrenergic agonist effects abate. Acute methylxanthine-induced hypokalemia may be treated with potassium supplementation, but because of the nature of the problem with excess β -adrenergic agonism, potassium supplementation is typically unnecessary and poorly effective.

Experimentally, administration of propranolol to theophylline-poisoned dogs prevented or partially reversed hypokalemia, hypophosphatemia, hyperglycemia, and metabolic acidosis as well as hypotension.¹¹¹ Prevention or correction of the metabolic derangements associated with theophylline toxicity by administration of β -adrenergic antagonists is congruent with the fact that these derangements, particularly hypokalemia, are the consequence of β -adrenergic agonism. The efficacy of β -adrenergic antagonists as therapy for hypokalemia resulting from acute methylxanthine poisoning in humans is unstudied.

Hypomagnesemia, hypophosphatemia, and hypocalcemia should be treated as they would for other patients. As with hypokalemia, QT interval prolongation is an absolute indication to treat these derangements.

Hyperglycemia, likely resulting from increased circulating catecholamines, is common. This hyperglycemia does not necessitate treatment, both because it is a transient effect and because in other situations of hyperglycemia resulting from adrenergic agonism, rebound hypoglycemia may occur.

Musculoskeletal Toxicity. The use of benzodiazepines is appropriate treatment for fasciculations, hypertonicity, myoclonus, and rhabdomyolysis. Rhabdomyolysis necessitates aggressive IV fluid therapy, possibly with sodium bicarbonate (Antidotes in Depth: A5).

Enhanced Elimination. Fortunately, methylxanthine toxicity lends itself well to several methods of enhanced elimination, including GI dialysis with MDAC, charcoal hemoperfusion, and hemodialysis, as well as lesser used methods such as continuous arteriovenous hemoperfusion, continuous venovenous hemoperfusion, and plasmapheresis.^{16,120,126}

Infants with methylxanthine poisoning may be too ill, unstable, or small to be treated with hemodialysis or hemoperfusion. Both MDAC and exchange blood transfusion are effective methods of enhanced elimination in infants and may be the preferred method of treatment in these patients if hemodialysis is unavailable.^{151,153,182,184}

The therapeutic effects of AC in such cases are much greater than simply limiting absorption of ingested methylxanthines. AC, particularly MDAC, allows elimination of theophylline through GI dialysis.¹³ MDAC is extremely effective at enhancing elimination of theophylline.^{24,74,125,149} Experimentally in dogs, rabbits, and human volunteers, AC administered after IV aminophylline administration results in increased systemic clearance and decreased half-life of theophylline.^{98,117,137,155} The pharmacologic similarity of the methylxanthines suggests that MDAC may be effective in caffeine or theobromine poisoning, and MDAC certainly is effective in eliminating theophylline generated from metabolism of caffeine or theobromine. The efficacy of MDAC combined with the safety and ease with which this therapy can be administered makes MDAC the mainstay of enhanced elimination in methylxanthine toxicity. Severe emesis associated with methylxanthine poisoning may result in intolerance of MDAC¹⁷⁶ (Antidotes in Depth: A1).

Charcoal hemoperfusion was once considered the most effective method of enhanced elimination of methylxanthines, decreasing theophylline's half-life to 2 hours and increasing its clearance up to sixfold.^{37,144,165,207} Variations of charcoal hemoperfusion, including albumin colloid hemoperfusion, resin hemoperfusion, and charcoal hemoperfusion in series with hemodialysis, are reported.^{41,97,121,158,191} If hemoperfusion is available, it is preferable, but when charcoal hemoperfusion is unavailable,¹⁷⁷ hemodialysis is excellent and has become routine therapy.

Hemodialysis is slightly less efficient than hemoperfusion in the extracorporeal removal of methylxanthines.^{8,122,124,187} The ability of hemodialysis to correct fluid and electrolyte imbalances, the greater availability of hemodialysis in many regions, greater technical ease, and lower complication rates have resulted in a paradigm shift from considering charcoal hemoperfusion to be the definitive treatment for significant methylxanthine toxicity to one in which charcoal hemoperfusion and hemodialysis are considered equivalent treatment options.¹⁸⁵

The specific indications for hemodialysis are not agreed upon. In the treatment of patients with methylxanthine poisoning. Several studies and clinical experience are the basis for the following suggested indications for extracorporeal elimination by charcoal hemoperfusion, hemodialysis, combined charcoal hemoperfusion and hemodialysis, or combined hemodialysis and MDAC.

Many recommendations regarding hemoperfusion and hemodialysis for theophylline toxicity use serum theophylline concentration as a guideline. Serum concentrations may not be available in instances of caffeine poisoning and do not exist for theobromine poisoning. Thus, the clinical aspects of theophylline management guidelines can be generalized to all methylxanthine toxicities.

When indicated, hemodialysis preferably should be initiated while the patient is still hemodynamically stable. Hemodialysis therapy should be used for patients with clinically significant chronic theophylline poisoning associated with a serum theophylline concentration above 40 to 60 $\mu\text{g/mL}$ or with a deteriorating clinical status.

Hemodialysis should be strongly considered any time a methylxanthine exposure results in a serum theophylline or caffeine concentration of greater than 90 $\mu\text{g/mL}$ and symptoms regardless of clinical stability (Table 66–3). Any patient with a symptomatic methylxanthine poisoning that is associated with ventricular dysrhythmias, seizures, hypotension

unresponsive to fluids, or emesis unresponsive to antiemetics should also be treated with charcoal hemoperfusion, hemodialysis, or both.

TABLE 66-3. Methylxanthine Poisoning: Indications for Charcoal Hemoperfusion or Hemodialysis

1. Acute serum theophylline or caffeine concentration $>90\text{ }\mu\text{g/mL}$ and any symptom
2. Serum theophylline or caffeine concentration $>40\text{ }\mu\text{g/mL}$ and
 - A. Seizures
 - B. Hypotension unresponsive to intravenous fluid or
 - C. Ventricular dysrhythmias

The fact that a patient experiences seizure or dysrhythmias or becomes extremely ill is not a contraindication for extracorporeal drug removal. To the contrary, these events make administration of such therapy more critical to ensure survival of the patient.

Treatment of Chronic Methylxanthine Toxicity

Treatment of chronic methylxanthine toxicity is determined by the patient's clinical status and by the efficacy of MDAC. The precise serum theophylline or caffeine concentration at which patients with chronic theophylline or caffeine toxicity should receive hemodialysis is controversial. For a hemodynamically stable patient without signs of life-threatening methylxanthine toxicity such as ventricular dysrhythmias or seizures, therapy with MDAC may be sufficient. If the serum theophylline or caffeine concentration does not decline after the administration of AC or if the patient's clinical status deteriorates, hemodialysis is indicated.

Treatment of Acute-on-Chronic Methylxanthine Toxicity

Patients chronically receiving theophylline or caffeine who acutely overdose should be initially managed in the same manner as patients with acute overdose, although action concentrations for dialysis are the same for chronic toxicity. Total body stores of the methylxanthines are higher in patients who are chronically exposed, and the threshold for toxicity may be reached at lower serum concentrations.

SUMMARY

- Caffeine is the most widely used methylxanthine, and as a result of novel products such as energy drinks and caffeinated alcoholic beverages, there are increasing numbers of poisoning from these products.
- Methylxanthine toxicity results from both the use of medicinals and therapeutics as well as foods and beverages.
- There are significant differences in the clinical presentation and management of patients with acute and chronic methylxanthine poisoning. Supportive care and treatment of GI, cardiovascular, CNS, metabolic, and musculoskeletal effects are the mainstay of therapy. The unique properties of methylxanthines necessitate specific therapies for the GI, cardiovascular, and CNS toxicities of methylxanthines.
- Methods of enhanced elimination, particularly extracorporeal elimination by charcoal hemoperfusion, hemodialysis, or combined charcoal hemoperfusion and hemodialysis in series, as well as gut dialysis with MDAC, are effective treatments for patients with methylxanthine toxicity.
- Selective β_2 -adrenergic agonists are widely used for the treatment of bronchospasm. Selective β_2 -adrenergic agonist toxicity typically results from excessive therapeutic use of these agents, but illicit use of clenbuterol or the admixture of clenbuterol with drugs of abuse has increased.

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F. ANESTHETICS AND RELATED MEDICATIONS

67 LOCAL ANESTHETICS

David R. Schwartz and Brian Kaufman

HISTORY AND EPIDEMIOLOGY

Local anesthetics are xenobiotics that block excitation of and transmission along a nerve axon in a predictable and reversible manner. The anesthesia produced is selective to the chosen body part in contrast to the nonselective effects of a general anesthetic. Local anesthetics do not require the circulation as an intermediate carrier, and they usually are not transported to distant organs. Therefore, the actions of local anesthetics are largely confined to the structures with which they come into direct contact. Local anesthetics may provide analgesia in various parts of the body by topical application, injection in the vicinity of peripheral nerve endings and major nerve trunks, or via instillation within the epidural or subarachnoid spaces. The various local anesthetics differ with regard to their potency, duration of action, and degree of effects on sensory and motor fibers. Toxicity may be local or systemic. With systemic toxicity, the central nervous system (CNS) and cardiovascular systems typically are affected.

Until the 1880s, the only xenobiotics available for pain relief were centrally acting depressants such as alcohol and opioids, which blunted the perception of pain rather than attacking the root cause. The coca shrub (*Erythroxylon coca*) was brought back to Europe from Peru by Karl Von Scherzer, an Austrian explorer, in the mid-1800s. Some of the coca leaves were analyzed by the chemist Albert Niemann, who in 1860 successfully extracted and named the active principle, the alkaloid cocaine ([Chap. 78](#)). Sigmund Freud studied the use of cocaine to cure morphine addiction. Koller at the Ophthalmological Clinic at the University of Vienna dissolved coca powder in distilled water; instilled the solution in the conjunctival sacs of a frog, a rabbit, a dog, and himself; and noted that their corneas as well as his own could be touched without evidence of a reflex blink. In 1884, Koller performed an operation for glaucoma with only topical cocaine anesthesia; the news spread rapidly, leading to diversification of use.⁴³

Although the clinical benefits of cocaine anesthesia were significant, so were its toxic and addictive potential. At least 13 deaths were reported in the first 7 years after the introduction of cocaine in Europe, and within 10 years after the introduction of cocaine as a regional anesthetic, reviews of “cocaine poisoning” appeared in the literature.^{70,90} The toxicity of cocaine, coupled with the tremendous advantages it provided for surgery, led to a search for less toxic substitutes.

After the elucidation of the chemical structure of cocaine (the benzoic acid methyl ester of the alkaloid ecgonine) in 1895, other amino esters were examined. Synthetic compounds with local anesthetic activity were introduced, but they were highly toxic or irritating or had an impractically brief clinical effect. In 1904, Einhorn synthesized procaine, but its short duration of action limited its clinical utility. Research turned to focus on synthesis of xenobiotics with more prolonged durations of action.

The potent, long-acting local anesthetics dibucaine and tetracaine were synthesized in 1925 and 1928, respectively, and were introduced into clinical practice shortly thereafter. However, these anesthetics were not safe for regional anesthetic techniques because of potential systemic toxicity secondary to the combination of high potency, delayed metabolism, and the larger volumes of drug required for regional anesthesia compared with local anesthesia. On the other hand, these drugs were very useful for spinal anesthesia, which required much smaller volumes.

Lofgren synthesized lidocaine from a series of aniline derivatives in 1943. This amino amide combined high tissue penetrance and a moderate duration of action with acceptably low systemic toxicity. Additionally, the metabolites of lidocaine did not include para-aminobenzoic acid (PABA), which causes allergic reactions to all amino ester anesthetics. Subsequent to the release of lidocaine in 1944, several other amino amide compounds were introduced into clinical practice. These included mepivacaine in 1956, prilocaine in 1959, bupivacaine in 1963, etidocaine in 1971, and ropivacaine in 1996.

Considering how frequently local anesthetics are administered, both within and outside health care facilities, clinically significant toxic reactions are relatively uncommon, and most are iatrogenic. In reports of fatalities resulting from toxic exposures reported to US poison centers, local anesthetics are rarely implicated, representing less than 0.5% of cases ([Chap. 136](#)). Most poisonings result from inadvertent injection of a therapeutic dose into a blood vessel, repeated use of a therapeutic dose, or unintentional administration of a toxic dose. The amide local anesthetics have largely replaced the esters in clinical use because of their increased stability and relative absence of hypersensitivity reactions (see Pharmacology below). Poisoning from topical benzocaine is relatively common because of the large number of nonprescription products available for treatment of teething and hemorrhoids. In addition, there is widespread use of

benzocaine, mostly as a spray, for topical mucosal anesthesia before intubation, upper endoscopy, and transesophageal echocardiography. With nonprescription use, toxic effects after exposure are typically mild, and death rarely occurs. Toxicity usually occurs as a therapeutic misadventure, but child abuse or neglect should be considered if the patient is younger than 2 years, and suicide should be considered in older children and adults.

Benzocaine spray may be the most important cause of severe acquired methemoglobinemia in the hospital setting³ (Chap. 127). Between November 1997 and March 2002, the US Food and Drug Administration (FDA) received 198 reported adverse events secondary to benzocaine products. A total of 132 cases (66.7%) involved definite or probable methemoglobinemia; most were serious adverse events, and two deaths occurred.⁷⁹ In these cases, a single spray of unspecified duration of 20% benzocaine was the dose most commonly reported. Because of the difficulty in limiting the dose to the manufacturer's recommendation given the current formulations available, these authors recommend a metered dosing preparation and prominent package warnings.

PHARMACOLOGY

Local anesthetics fall into one of two chemically distinct groups: amino esters and amino amides (Fig. 67–1). The basic structure of all local anesthetics consists of three major components: a lipophilic, aromatic ring connected by an ester or amide linkage to a short alkyl, intermediate chain that is bound to a hydrophilic tertiary (or less commonly, secondary) amine. The amine is a base (proton acceptor) that is partially charged at physiologic pH.

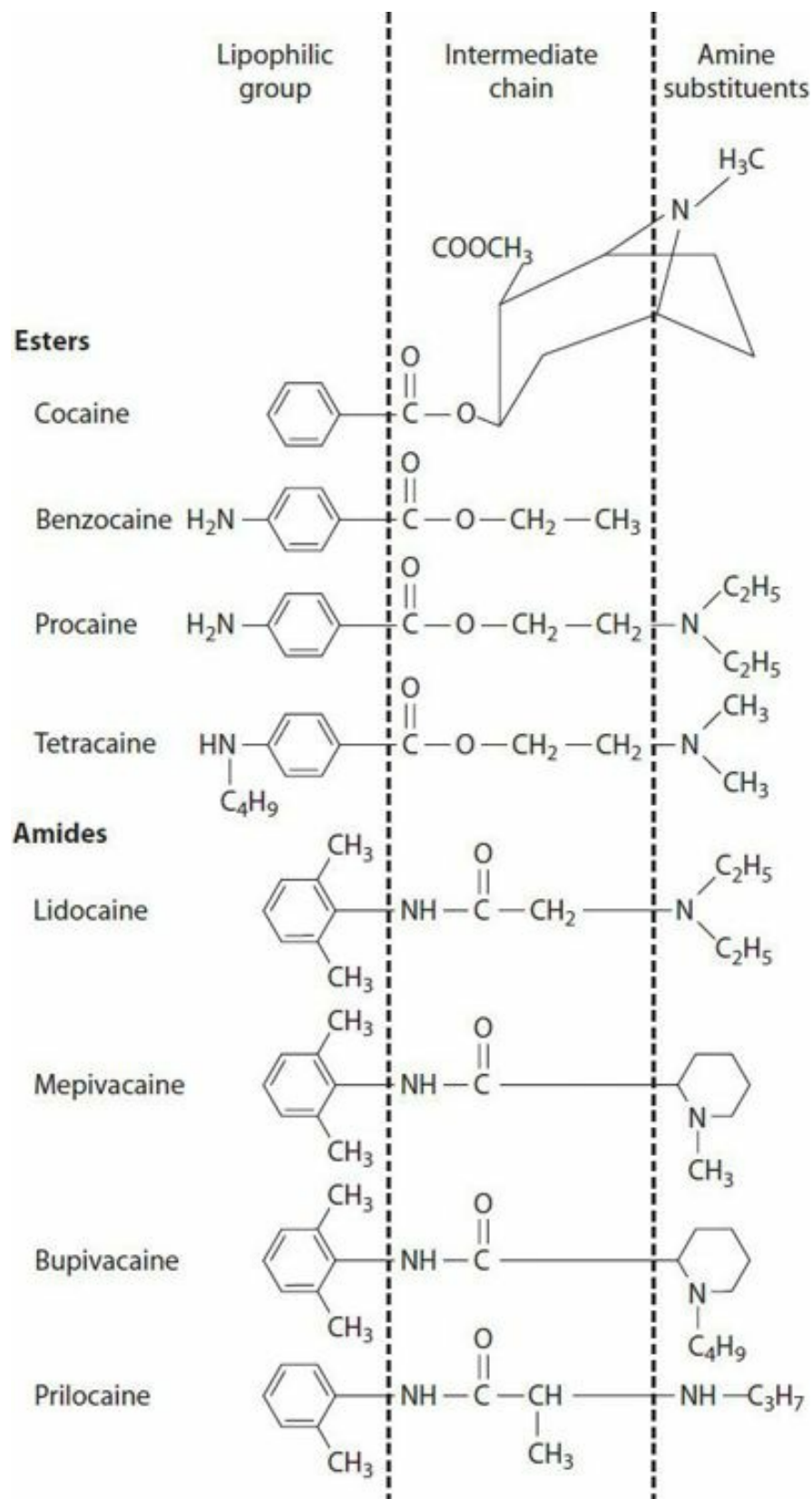


FIGURE 67-1. Representative local anesthetics.

All local anesthetics function by reversibly binding to specific receptor proteins within the membrane bound sodium channels of conducting tissues. These receptors can be reached only via the cytoplasmic (intracellular) side of the cell membrane. Blockade of ion conductance through the sodium channel eventually leads to failure to initiate and propagate action potentials (Fig. 67-2). The analgesic effect results from inhibiting axonal transmission of the nerve impulse in small-diameter myelinated and unmyelinated nerve fibers carrying pain and temperature sensation. Conduction block of these fibers occurs at lower concentrations than in the larger fibers responsible for touch, motor function, and proprioception.²³ This likely occurs in myelinated nerves because smaller fibers have closer spacing of the nodes of Ranvier. Given that a fixed number of nodes must be blocked for conduction failure to occur, the shorter critical length of nerve is reached sooner by the locally placed anesthetic in small fibers.³⁷ For unmyelinated fibers, the smaller diameter limits the distance that such fibers can passively propagate the electrical impulse. In addition, differential nerve block may relate to voltage and time dependence of the affinity of local anesthetics to the sodium channels.

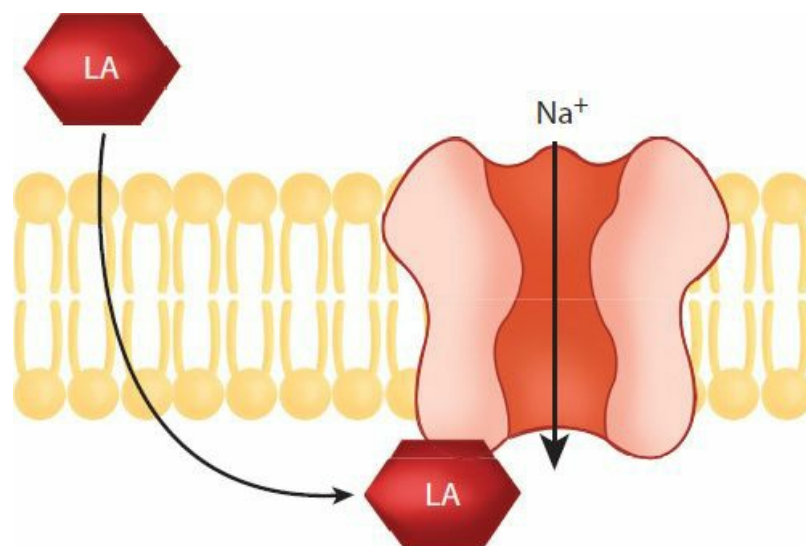


FIGURE 67–2. The multi-unit sodium channel is embedded in the nerve cell membrane. Local anesthetics (LA) enter the nerve cell at the exposed membranes of the nodes of Ranvier and bind to the cytoplasmic side of the sodium channel (also located at the node of Ranvier) and alter sodium conductance.

The sodium channel may exist in three states ([Chap. 24](#)). At resting membrane potential or in the hyperpolarized membrane, the channel is closed to sodium conductance. With an appropriate activating stimulus, the channel opens, allowing rapid sodium influx and membrane depolarization. Milliseconds later, the channel is inactivated, terminating the fast sodium current. Blockade is much stronger for channels that are activated (open) or inactivated than for channels that are resting. Pain fibers have a higher firing rate and longer action potential (ie, more time with the sodium channel open or inactivated) than other fiber types and therefore are more susceptible to local anesthetic action.⁵¹

These effects also occur in conductive tissues in the heart and brain that rely on sodium current. Although sodium channel blockade initially was believed to be the sole cause of systemic toxicity, mechanisms are more complex, especially in the heart, and may occur at systemic concentrations lower than previously thought.⁷² Local anesthetics may interact with other cellular systems at clinically relevant concentrations. For example, lidocaine inhibited muscarinic signaling in *Xenopus* oocytes at less than 50% of the concentration required for sodium channel blockade.⁵⁰ Growing evidence indicates that local anesthetics can directly affect many other organ systems and functions such as the coagulation, immune, and respiratory systems, all at concentrations much lower than those required to achieve sodium channel blockade.^{17,49,50} Study of these less well-described effects may help elucidate both therapeutic and toxic phenomena that are incompletely explained.

The primary determinant of the onset of action of a local anesthetic is its pK_a , which affects the lipophilicity of a drug ([Table 67–1](#)). All the local anesthetics are weak bases, with a pK_a between 7.8 and 9.3. At physiologic pH (7.4), xenobiotics with a lower pK_a have more uncharged molecules that are free to cross the nerve cell membrane, producing a faster onset of action than xenobiotics with a higher pK_a . The onset of action also is influenced by the total dose of local anesthetic administered, which affects the concentration responsible for diffusion.

TABLE 67–1. Pharmacologic Properties of Local Anesthetics^{48,100}

	pK_a	Protein Binding (%)	Log D^a	Relative Potency	Duration of Action	Approximate Maximum Allowable Subcutaneous Dose (mg/kg)
Esters						
Chloroprocaine	9.3	Unknown	1.17	Intermediate	Short	10
Cocaine	8.7	92	1.14	Low	Medium	3
Procaine	9.1	5	0.72	Low	Short	10
Tetracaine	8.4	76	2.23	High	Long	3
Amides						
Bupivacaine	8.1	95	2.45	High	Long	2
Etidocaine	7.9	95	3.16 ^b	High	Long	4
Lidocaine	7.8	70	2.36	Low	Medium	4.5
Mepivacaine	7.9	75	0.93	Intermediate	Medium	4.5
Prilocaine	8.0	40	0.75	Intermediate	Medium	8
Ropivacaine	8.2	95	1.92	Intermediate	Long	2–3

^aLog D is the octanol/water partition coefficient at a pH of 7. ^bLog D for etidocaine is at a pH of 7.4.

Local anesthetic potency is highly correlated with the lipid solubility of the xenobiotic. Therefore, the aromatic side of the anesthetic is the primary determinant of potency. The hydrophilic amine is important in occupying the sodium channel, which involves an ionic interaction with the charged form of the tertiary amine. The length of the intermediate chain is another determinant of local anesthetic activity, with three to seven carbon equivalents providing maximal activity.²³ Shorter or longer intermediate chain lengths are associated with rapid loss of local anesthetic action, suggesting that a critical length of physical separation of the aromatic group from the tertiary amine is required for sodium channel blockade to occur.

The degree of protein binding influences the duration of action of a local anesthetic. Anesthetics with greater protein binding remain associated with the neural membrane for a longer time interval and therefore have longer durations of action.²³ When high serum concentrations are achieved, a higher degree of protein binding increases the risk for cardiac toxicity.

PHARMACOKINETICS

A distinction must be made between local disposition (distribution and elimination) and systemic disposition of the anesthetic. Local distribution is influenced by several factors, including spread of local anesthetic by bulk flow, diffusion, transport via adjacent blood vessels, and binding to proximate tissues. Local elimination occurs through systemic absorption, transfer into the general circulation, and local hydrolysis of amino ester anesthetics. Systemic absorption decreases the amount of local anesthetic that is available for anesthetic effect, thereby limiting the duration of the block. Systemic absorption depends on the avidity of binding of local anesthetics to tissues near the site of injection and on local perfusion. Both these factors vary with the site of injection. In general, areas with greater blood flow will have more rapid and complete systemic uptake of local anesthetic, for example, intravenous (IV) > tracheal > intercostal > paracervical > epidural > brachial plexus > sciatic > subcutaneous.

Because of their lipophilicity, local anesthetics readily cross cell membranes, the blood–brain barrier, and the placenta. After being absorbed, systemic tissue distribution is highly dependent on tissue perfusion. After local anesthetics enter into the venous circulation, they pass through the lungs, where significant uptake may occur, thereby lowering peak arterial concentrations. Thus, the lungs may serve as a buffer against systemic toxicity,⁶³ but the capacity of the lungs to accumulate drug is saturable. Part of the reason why most local anesthetic–induced seizures result from unintentional intravascular bolus injection rather than absorptive uptake is that lung uptake of these drugs exceeds 90%. The very high peak venous concentrations produced by rapid injection usually are necessary to produce toxic arterial concentrations.

All local anesthetics, except cocaine, cause peripheral vasodilation by direct relaxation of vascular smooth muscle. Vasodilation enhances vascular absorption of the local anesthetic. Addition of epinephrine (5 µg/mL or 1:200,000) to the local anesthetic solution decreases the rate of vascular absorption, thereby improving the depth and prolonging the duration of local action. Local anesthetic mixed with epinephrine also decreases bleeding into the surgical field and serves as a marker for inadvertent intravascular injection (by producing tachycardia) when a test dose of the mixture is injected through a needle or catheter.⁷⁶

Significant drawbacks to epinephrine use include uncomfortable side effects such as palpitations and tremors, local tissue ischemia, and life-threatening systemic adverse reactions in susceptible patients (eg, myocardial ischemia and

hypertensive crises). Inadvertent intravascular injection of local anesthetics mixed with epinephrine can be fatal, although generally the epinephrine in these mixtures is very dilute.⁶⁷

The two classes of local anesthetics undergo metabolism by different routes (Chap. 78). The amino esters are rapidly metabolized by plasma cholinesterase to the major metabolite, PABA. The amino amides are metabolized more slowly in the liver to a variety of metabolites that do not include PABA.²² Patients with enzymatic mutations, low or absent concentrations of plasma cholinesterase or pseudocholinesterase are at increased risk for systemic toxicity from ester local anesthetics. Factors that decrease hepatic blood flow or impair hepatic function increase the risk for toxic reactions to the amino amides and make management of serious reactions more difficult. The patient's age, as it relates to liver enzyme activity and plasma protein binding, influences the rate of metabolism of local anesthetics. Whereas lidocaine's terminal half-life after IV administration averaged 80 minutes in volunteers ages 22 to 26 years, the half-life was 138 minutes in those ages 61 to 71 years⁸⁴ (Chap. 64). Newborns with immature hepatic enzyme systems have prolonged elimination of amino amides, which is associated with seizures when high continuous infusion rates are used.^{1,73} Lidocaine elimination is reduced by congestive heart failure or coadministration of xenobiotics that reduce hepatic blood flow, thus explaining the increased risk of toxicity with cimetidine and propranolol.⁹⁶ Propranolol and cimetidine also potentially decrease lidocaine clearance by inhibiting hepatic CYP450 enzymes.

Local anesthetics are often mixed to take advantage of desirable pharmacokinetics. Ideally, rapid-acting, relatively short-duration local anesthetics such as chloroprocaine or lidocaine can be combined with the longer latency, long-acting tetracaine or bupivacaine. In practice, the advantages of the mixtures are small, and toxicities are additive.⁵ Administration of one local anesthetic increases the free plasma fraction of another by displacement from protein-binding sites.⁵⁴

Local anesthetics usually cannot penetrate intact skin in sufficient quantities to produce reliable anesthesia.¹¹ Efficient skin penetration requires the combination of a high water content and a high concentration of the water-insoluble base form of the local anesthetic. This combination of properties is achieved by mixing lidocaine and prilocaine in their base forms in a 1:1 ratio (eutectic mixture of local anesthetics {EMLA}).¹⁵ Application for at least 45 minutes is required to achieve adequate dermal analgesia. Local anesthetic uptake continues for several hours during application. A liposomal formulation of 4% lidocaine (ELA-Max) facilitates skin absorption. It is as effective as EMLA for topical anesthesia.³² In addition, a 4% tetracaine gel preparation is used in children for topical skin anesthesia with an onset of action and efficacy at least as good as EMLA and without any systemic side effects.

CLINICAL MANIFESTATIONS OF TOXICITY

Although the most common adverse reactions to local anesthetics are vasovagal events associated with injection,¹¹³ the following sections focus on their local and systemic toxicity.

Toxic Reactions

Regional Side Effects and Tissue Toxicity. At a sufficient concentration, all local anesthetics are directly cytotoxic to nerve cells. However, in clinically relevant doses, they rarely produce localized nerve damage.^{58,83} Significant direct neurotoxicity may result from intrathecal injection or infusion of local anesthetics for spinal anesthesia. In this setting, lidocaine has an increased risk for both persistent lumbosacral neuropathy and a syndrome of painful but self-limited postanesthesia buttock and leg pain or dysesthesia referred to as transient neurologic symptoms.⁵³ Nerve damage often is attributed to use of excessively concentrated solutions or inappropriate formulations. Several reports of cauda equina syndrome are associated with use of hyperbaric 5% lidocaine solutions for spinal anesthesia. Hyperbaric solutions are denser than cerebrospinal fluid. This neurotoxicity appears to be a phenomenon that occurs when the anesthetic is injected through narrow-bore needles or through continuous spinal catheters. This process may result in very high local concentrations of the anesthetic that might pool around the sacral roots because of inadequate mixing.⁹⁷ The mechanism of this neurotoxicity is unknown but is believed to be independent of sodium channel blockade.⁵³ Because an equally effective block can be achieved with injection of larger volumes of lower concentration, 5% lidocaine should be avoided and bupivacaine used instead. There is a significant (up to 10-fold) increase in the development of new neurologic dysfunction after receiving a neuraxial block in patients with preexisting peripheral neuropathy a fact emphasizing informed consent.⁴⁶

Similar severe neurotoxic reactions occur after massive subarachnoid injection of chloroprocaine during attempted epidural anesthesia.⁹⁴ The neurotoxicity initially appeared to be associated with use of the antioxidant sodium bisulfite and the low pH of the commercial solution rather than use of the anesthetic itself.¹¹⁵ Although chloroprocaine has been reformulated without bisulfite, new animal data suggest that it is the anesthetic itself that may be responsible for the neurotoxicity.¹¹¹ Skeletal muscle changes are observed after intramuscular injection of local anesthetics, especially the more potent, longer acting xenobiotics. The effect is reversible, and muscle regeneration is complete within 2 weeks after injection of local anesthetics.⁸

Although rare, transient or prolonged postoperative neuropathy after peripheral nerve or plexus block is well recognized. Likely mechanisms include direct injury of the nerve related to intraneuronal injection and local anesthetic neurotoxicity. The frequency of peripheral neuropathies reported after peripheral nerve blockade varies from 0% to more than 5%.¹² The use of ultrasound guidance to direct needle position may reduce this complication because of direct visualization of the peripheral nerve, avoiding traumatic injury and allowing for injection of less local anesthetic to produce adequate nerve block. Comparative studies have shown conflicting results and were likely underpowered. Recently, analysis of 12,868 ultrasound-guided nerve blocks for peripheral regional anesthesia found that the incidences of postoperative neurologic symptoms lasting longer than 5 days and 6 months were 0.18% and 0.008%, respectively.¹⁰⁵ Visualization of the target site via ultrasound guidance may well be shown to also decrease local anesthetic systemic toxicity by averting inadvertent intravascular injection.

Systemic Side Effects and Toxicity

Allergic Reactions. Allergic reactions to local anesthetics are extremely rare. Fewer than 1% of all adverse drug reactions caused by local anesthetics are immunoglobulin (Ig) E mediated.⁴⁰ In one study designed to determine the prevalence of true local anesthetic allergy in patients referred to an allergy clinic for suspected hypersensitivity, skin prick and intradermal testing results were negative for all 236 subjects tested.⁹ As noted, the amino esters are responsible for the majority of true allergic reactions. When hydrolyzed, the amino ester local anesthetics produce PABA, a known allergen (Chap. 55). Cross-sensitivity to other amino ester anesthetics is common. Some multidose commercial preparations of amino amides may contain the preservative methylparabens (Chap. 55), which is chemically related to PABA and is the most likely cause of the much rarer allergic reactions attributed to amino amides. Preservative-free amino amides, including lidocaine, can be used safely in patients who have reactions to drug preparations containing methylparabens unless the patient is specifically sensitive to lidocaine. Again, if the patient with a history of allergic reaction to a particular drug requires a local anesthetic, a paraben preservative-free drug from the opposite class can be chosen because there is no cross-reactivity between the amides and esters.

Methemoglobinemia. Methemoglobinemia is a frequent adverse effect of topical and oropharyngeal benzocaine and is occasionally reported with lidocaine, tetracaine, or prilocaine use. The diagnosis can be established by direct measurement of methemoglobin with a cooximeter. Most reports of methemoglobinemia associated with local anesthetics are the result of an excessive dose or a break in the normal mucosal barrier for topical anesthetics (Chap. 127).

Benzocaine is metabolized to aniline and then further metabolized to phenylhydroxylamine and nitrobenzene, which are both potent oxidizing agents (Chap. 127). Although reports describe methemoglobinemia resulting from standard doses of benzocaine topical oropharyngeal spray given for laryngoscopy or gastrointestinal upper endoscopy,^{30,79} affected patients commonly have abnormal mucosal integrity as occurs with thrush or mucositis. Prilocaine is an amino ester local anesthetic primarily used in obstetric anesthesia because of its rapid onset of action and low systemic toxicity in both the mother and fetus. Use of large doses of prilocaine may lead to the development of methemoglobinemia.^{48,65} Prilocaine is an aniline derivative that, when metabolized in the liver, produces ortho-toluidine, another oxidizing agent.⁴⁸ A direct relationship exists between the amount of epidural prilocaine administered and the incidence of methemoglobinemia. A dose greater than approximately 8 mg/kg is generally necessary to produce symptoms, which may not become apparent until several hours after epidural administration of the drug. EMLA cream, often used in the outpatient setting for minor dermal procedures, may result in significant methemoglobinemia, which has been reported in children and rarely in adults.⁴² Standard doses of EMLA cream used for circumcision in term neonates are associated with minimal production of methemoglobin, but risks may be increased in neonates with metabolic disorders.¹⁰⁹ When clinically indicated, affected patients with symptomatic methemoglobinemia should be treated with IV methylene blue (Chap. 127 and Antidotes in Depth: A42).

Systemic Toxicity. Systemic toxicity for all local anesthetics correlates with serum concentrations. Factors that determine the concentration include: dose; rate of administration; site of injection (absorption occurs more rapidly and completely from vascular areas, such with neck blocks and intercostal blocks); the presence or absence of a vasoconstrictor; and the degree of tissue-protein binding, fat solubility, and pK_a of the local anesthetic.⁷⁸ The brain and heart are the primary target organs for systemic toxicity because of their rich perfusion, moderate tissue-blood partition coefficients, lack of diffusion limitations, and presence of cells that rely on voltage-gated sodium channels to produce an action potential.

Recommendations for maximal local anesthetic doses designed to minimize the risk for systemic toxic reactions are published.¹⁰⁷ These maximal recommended doses aim to prevent infiltration of excessive drug. However, because most episodes of systemic toxicity from local anesthetics, with the exception of methemoglobinemia from topical drug, occur secondary to unintentional intravascular injection rather than from overdosage, limiting the maximal dose will not prevent most toxic systemic reactions.¹⁰²

Toxicity is also related to the metabolism for a given local anesthetic. The rapidity of elimination from the plasma influences the total dose delivered to the CNS or heart. The amino esters are rapidly hydrolyzed in the plasma and

eliminated, explaining their relatively low potential for systemic toxicity. The amino amides have a much greater potential for producing systemic toxicity because termination of the therapeutic effect of these drugs is achieved through redistribution and slower metabolic inactivation.³⁶ Another factor that creates difficulty in specifying the minimal toxic plasma concentration of lidocaine results from the fact that its N-dealkylated metabolites are pharmacologically active. Although these factors make it difficult to establish safe doses of local anesthetics, Table 67–2 summarizes the estimates of minimal toxic IV doses of various local anesthetics.

TABLE 67–2. Toxic Intravenous (IV) Doses of Local Anesthetics

<i>Local Anesthetic</i>	<i>Minimum IV Toxic Dose of Local Anesthetic in Humans (mg/kg)</i>
Procaine	19.2
Chlorprocaine	22.8
Tetracaine	2.5
Lidocaine	6.4
Mepivacaine	9.8
Bupivacaine	1.6
Etidocaine	3.4

Central Nervous System Toxicity. Systemic toxicity in humans usually presents with CNS abnormalities. IV infusion studies in volunteers demonstrate an inverse relationship between anesthetic potency and dose required to induce signs of CNS toxicity.¹⁰⁴ A similar relationship exists between the convulsive concentration and the relative anesthetic potency. In humans, seizures are reported at serum concentrations of approximately 2 to 4 $\mu\text{g/mL}$ for bupivacaine and etidocaine. Concentrations in excess of 10 $\mu\text{g/mL}$ are usually required for production of seizures when less potent drugs such as lidocaine are administered. Despite the strong relationship between local anesthetic potency and CNS toxicity, several other factors influence the CNS effects, including the rate of injection, drug interactions, and acid–base status.²⁵

The rapidity with which a particular serum concentration is achieved influences the toxicity of the anesthetic. Volunteers could tolerate an average dose of 236 mg of etidocaine and a serum concentration of 3 $\mu\text{g/mL}$ before onset of CNS symptoms when the anesthetic was infused at a rate of 10 mg/min. However, when the infusion rate was increased to 20 mg/min, the same individuals could tolerate only an average of 161 mg of the drug, which produced a serum concentration of approximately 2 $\mu\text{g/mL}$.¹⁰³

Centrally acting local anesthetics can modify the clinical presentation of a systemic toxic reaction. In general, CNS-depressant drugs minimize the signs and symptoms of CNS excitation and increase the threshold for local anesthetic–induced seizures. Flumazenil increases the sensitivity of the CNS to the amino amide anesthetics.¹⁴

Both metabolic and respiratory acidoses increase local anesthetic–induced CNS toxicity. Acidemia decreases plasma protein binding, increasing the amount of free drug available for CNS diffusion despite promoting the charged form of the amine group. The convulsive threshold of various local anesthetics is inversely related to arterial PCO_2 .^{27,33,34} Hypercarbia may lower the seizure threshold by several mechanisms: (1) increased cerebral blood flow, which increases drug delivery to the CNS; (2) increased conversion of the drug base to the active cation in the presence of decreased intracellular pH; and (3) decreased plasma protein binding, which increases the amount of free drug available for diffusion into the brain.^{16,27,33,34}

A gradually increasing serum lidocaine concentration usually produces a stereotypical pattern of symptoms and signs (Fig. 67–3). In an awake patient, the initial effects include tinnitus, lightheadedness, circumoral numbness, disorientation, confusion, auditory and visual disturbances, and lethargy. Subjective side effects occur at serum concentrations between 3 and 6 $\mu\text{g/mL}$. Significant psychological effects of local anesthetics are also reported. Near-death experiences and delusions of actual death are described as specific symptoms of local anesthetic toxicity.⁶⁸ Thus, the appearance of psychological symptoms during administration of local anesthetics should not be disregarded as unrelated nervous reactions or effects of sedatives given as premedication but rather as a possible early sign of CNS toxicity.

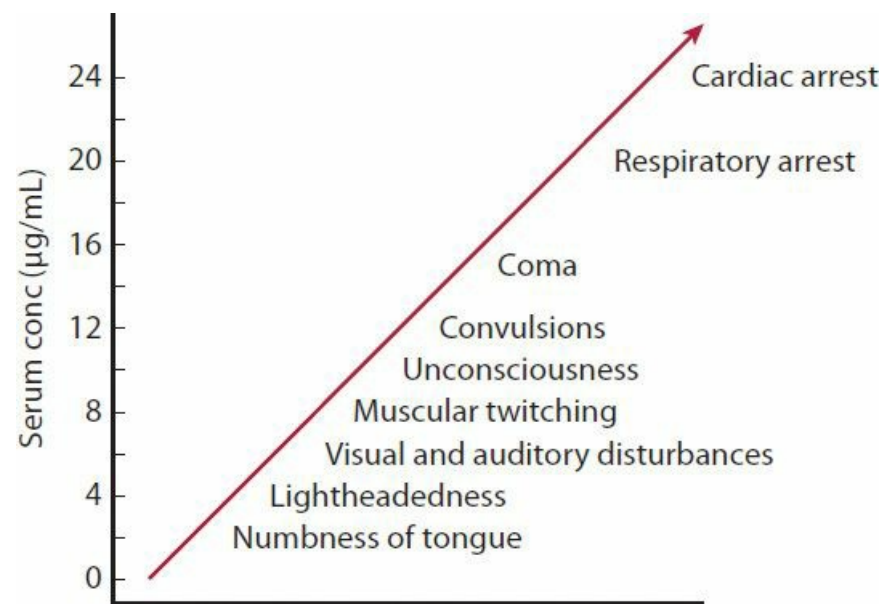


FIGURE 67–3. Relationship of signs and symptoms of toxicity to serum lidocaine concentrations.

Clinical signs, usually excitatory, then develop, and include shivering, tremors, and ultimately generalized tonic–clonic seizures. Objective CNS toxicity usually is evident at lidocaine concentrations between 5 and 9 µg/mL. Seizures may occur at concentrations above 10 µg/mL, with higher concentrations producing coma, apnea, and cardiovascular collapse. The excitatory phase has a wide range of intensity and duration, depending on the chemical properties of the local anesthetic. With the highly lipophilic, highly protein-bound drugs, the excitement phase is brief and mild. Toxicity from a large IV bolus of bupivacaine may present without any CNS excitement, with bradycardia, cyanosis, and coma as the first signs.⁹⁹ Rapid intravascular injection of lidocaine may produce a brief excitatory phase followed by generalized CNS depression with respiratory arrest. Seizures may follow even a small dose injected into the vertebral or carotid artery (as may occur during stellate ganglion block).⁵⁷ A relative overdose produces a slower onset of effects (usually within 5–15 minutes of drug injection), with irritability progressing to seizures.

The mechanism of the initial CNS excitation involves a selective block of cerebral cortical inhibitory pathways in the amygdala.^{110,114} The resulting increase in unopposed excitatory activity leads to seizures. As the concentration increases further, both inhibitory and excitatory neurons are blocked, and generalized CNS depression ensues.

Treatment of Local Anesthetic Central Nervous System Toxicity

At the first sign of possible CNS toxicity, administration of the drug must be discontinued. One hundred percent oxygen should be supplied immediately, and ventilation should be supported if necessary. Patients with minor symptoms usually do not require treatment, provided adequate respiratory and cardiovascular functions are maintained. The patient must be followed closely so that progression to more severe effects can be detected.

Although most seizures caused by local anesthetics are self-limited, they should be treated quickly because the hypoxia and acidemia produced by prolonged seizures may increase both CNS and cardiovascular toxicity.^{80,82} Intubation is not mandatory, and the decision to intubate must be individualized. Maintaining adequate ventilation is of proven value, but modest hyperventilation, in theory, might decrease CNS toxicity. By decreasing CNS extraction of drug, lowering extracellular potassium, and hyperpolarizing the neuronal cell membrane, normalizing (lowering) PCO₂ may decrease the affinity or accelerate separation of the local anesthetic from the sodium channel. Ultra-short-acting barbiturates and benzodiazepines have been used for treatment of local anesthetic–induced seizures, but either of these medication groups can also exacerbate circulatory and respiratory depression.^{25,75} Propofol 1 mg/kg IV was as effective as thiopental 2 mg/kg IV in stopping bupivacaine induced seizures in rats and has been used successfully in a patient with uncontrolled muscle twitching secondary to local anesthetic toxicity.^{10,44} However, propofol may cause significant bradydysrhythmias and even asystole, especially when used with other xenobiotics that cause bradycardia. Whether propofol interacts with local anesthetics to enhance their bradydysrhythmic effects is not known, and it is not possible to generally recommend propofol over benzodiazepines for treatment of local anesthetic CNS toxicity. Neuromuscular blockers are proposed as adjunctive treatment for local anesthetic induced seizures. They block muscular activity, decreasing oxygen demand and lactic acid production. However, neuromuscular blockers should never be used to treat seizures per se because they have no anticonvulsant effect and can make clinical diagnosis of ongoing seizures problematic by abolishing muscle contractions. To avoid this potentially lethal complication, chemical paralysis should be used only to facilitate endotracheal intubation if needed, unless continuous electroencephalography is also used. If used, short-acting neuromuscular blockers are desirable, facilitating subsequent repeated neurologic assessments. Succinylcholine may not be ideal because of its significant side effects, including hyperkalemia and dysrhythmias. The use of nondepolarizing neuromuscular blockers with less potential

for cardiac side effects, such as rocuronium, should be considered (Chap. 69).

When severe systemic toxicity occurs, the cardiovascular system must be monitored closely because cardiovascular depression may go unnoticed while seizures are being treated. Because local anesthetic–induced myocardial depression may occur even with preserved blood pressure, it is important to be aware of early signs of cardiac toxicity, including electrocardiographic (ECG) changes.

If toxicity results from ingestion of liquid medications, as most are, activated charcoal is generally indicated, but benefits are unproven. If the patient presents immediately after ingestion, gastric lavage with a nasogastric tube may be considered. Induction of emesis is contraindicated even after oral administration because of the risk of seizures and aspiration. Contaminated mucous membranes should be washed off. Hemodialysis is not of proven utility and may be impractical, as is hemoperfusion.

Cardiovascular Toxicity. Cardiovascular side effects are the most feared manifestations of local anesthetic toxicity. Shock and cardiovascular collapse may be related to effects on vascular tone, inotropy, and dysrhythmias related to indirect CNS and direct cardiac and vascular effects of the local anesthetic. Animal studies and clinical observations clearly demonstrate that for most local anesthetics, CNS toxicity develops at significantly lower serum concentrations (exception: bupivacaine) than those needed to produce cardiac toxicity, that is, they have a high cardiovascular:CNS toxicity ratio.^{57,81,82,99} When cardiac toxicity occurs, management may be exceedingly difficult. Some of the discrepancy between the incidence of CNS and cardiac toxicity may result from a detection bias. Not only can the treating physicians fail to recognize cardiac effects because of preoccupation with CNS manifestations of toxicity, but early cardiac toxicity may be quite subtle. An experimental study attempting to identify early warning signs of bupivacaine-induced cardiac toxicity in pigs evaluated bupivacaine-induced changes in cardiac output, heart rate, blood pressure, and ECG.⁸⁸ A 40% reduction in cardiac output was not associated with significant change in heart rate or blood pressure, the latter secondary to a direct vasoconstrictive effect of bupivacaine at the concentrations produced.¹⁸

Changes in systemic vascular tone induced by local anesthetics may be mediated by direct effect on vascular smooth muscle or indirectly via effects on spinal cord sympathetic outflow. Predictably, sympathetic blockade after spinal anesthesia or epidural anesthesia above the T5 dermatome results in peripheral venodilation and arterial dilation. Shock may result when high doses of anesthetic are used in hypovolemic patients. Local anesthetics have a biphasic effect on peripheral vascular smooth muscle. Whereas lower doses produce direct vasoconstriction, higher doses are associated with severe cardiovascular toxicity and cause vasodilation, contributing to cardiovascular collapse.

All local anesthetics directly produce a dose dependent decrease in cardiac contractility, with the effects roughly proportional to their peripheral anesthetic effect. Although the classic anesthetic action of sodium channel blockade in heart muscle accounts in large part for the negative inotropy by affecting excitation–contraction coupling, it does not explain the entire difference in myocardial depression produced by different anesthetics.²⁸ Poorly understood effects on calcium handling or effects of the intracellular drug directly on contractile proteins or mitochondrial function may be operable.²⁸

Blockade of the fast sodium channels of cardiac myocytes decreases maximum upstroke velocity (V_{\max}) of the action potential (Chaps. 16 and 17 and Fig. 64–1). This effect slows impulse conduction in the sinoatrial and atrioventricular (AV) nodes, the His-Purkinje system, and atrial and ventricular muscle.²¹ These changes are reflected on ECG by increases in PR interval and QRS duration. At progressively higher anesthetic concentrations, hypotension, sinus arrest with junctional rhythm, and eventually cardiac arrest occur.⁴ Asystole has been described in patients who received unintentional IV bolus injections of 800 to 1000 mg of lidocaine.^{4,35} Cardiovascular toxicity of local anesthetics usually occurs after a sudden increase in serum concentration, as in unintentional intravascular injection. Cardiovascular toxicity is rare in other circumstances because high serum concentrations are necessary to produce this effect and because CNS toxicity precedes cardiovascular events, providing a warning. Cardiac toxicity usually is not observed with lidocaine use in humans until the serum lidocaine concentration greatly exceeds 10 $\mu\text{g/mL}$ unless the patient is also receiving xenobiotics that depress sinus and AV nodal conduction such as calcium channel blockers, β -adrenergic antagonists, or cardioactive steroids.

Bupivacaine is significantly more cardiotoxic than most other local anesthetics commonly used. Inadvertent intravascular injection produces near simultaneous signs of CNS and cardiovascular toxicity.

Animal studies have compared the dose or serum concentrations of local anesthetics required to produce irreversible circulatory collapse with those necessary to produce seizures.^{26,81,82} This cardiovascular collapse:CNS toxicity (CC:CNS) ratio for lidocaine is approximately 7; therefore, CNS toxicity should become evident well before potentially cardiotoxic concentrations are reached. In contrast, the CC:CNS ratio for bupivacaine is 3:7. Bupivacaine produces myocardial depression out of proportion to its anesthetic potency and, more important, may cause refractory ventricular dysrhythmias.¹⁰¹ Enhanced cardiovascular toxicity may relate to enhanced CNS effects at cardiovascular centers,¹¹² direct effects on myocyte metabolism, and important differences related to sodium channel blockade. Although lidocaine and bupivacaine both block sodium channels in the open or inactivated states, lidocaine quickly dissociates from the channel at diastolic potentials, allowing rapid recovery from block during diastole (fast on–fast off). Therefore, sodium channel blockade with lidocaine is much more pronounced at rapid heart rates (accounting for the antidysrhythmic effects for ventricular tachycardia).⁶⁷ On the other hand, at high concentrations, bupivacaine rapidly binds to and slowly dissociates

from sodium channels (fast on–slow off), with significant block accumulating at all physiologic heart rates.²¹ Accordingly, at heart rates of 60 to 150 beats/min, approximately 70 times more lidocaine is needed than bupivacaine to produce an equal effect on V_{\max} of the action potential. Enhanced conduction block in Purkinje fibers and ventricular muscle cells sets up a reentrant circuit responsible for the ventricular tachydysrhythmias induced by bupivacaine.⁷⁴

Bupivacaine, a potent and long-acting amide anesthetic, not only has the highest potential for cardiovascular toxicity, but these effects are quite refractory to conventional therapy. Bupivacaine has an asymmetrically substituted carbon, and the kinetics of sodium channel binding are stereospecific.⁶⁰ The S (levo)-enantiomer levobupivacaine is significantly less cardiotoxic than the R (dextro)-enantiomer despite having similar anesthetic properties.^{6,72} Consequently, bupivacaine, the racemic mixture of both enantiomers, is more cardiotoxic than levobupivacaine, which contains only the levo-enantiomer.⁴¹ The stereospecific effect on sodium channels seems to differ between the heart and the peripheral nerves because the local anesthetic potency of levobupivacaine is the same as, or perhaps even greater than, that of bupivacaine.^{31,85} Ropivacaine is a pure enantiomer and is less cardiotoxic than bupivacaine, but it is also slightly less potent as an anesthetic.^{91,92}

Effects other than sodium channel blockade may contribute to cardiotoxicity. Lipophilic local anesthetics such as bupivacaine may directly impair mitochondrial energy transduction via two mechanisms: (1) uncoupling of oxygen consumption and adenosine triphosphate (ATP) synthesis and (2) inhibition of complex I in the respiratory chain.¹⁰¹ This effect is related to the lipophilic properties of the drug rather than to stereospecific effects on ion channels. Lidocaine has no effect on mitochondrial respiration, and ropivacaine has less effect than bupivacaine.¹²¹ There is no difference between the two bupivacaine enantiomers. These effects occur with higher concentrations of the local anesthetic, as occur after unintentional intravascular injection.

Low dose bupivacaine-induced cardiotoxic effects are described in humans under certain circumstances and at concentrations that are not associated with seizure activity in pigs.^{55,120} Severe cardiac toxicity is described after injection of a small subcutaneous dose of bupivacaine in a patient with secondary carnitine deficiency.¹²⁰ Myocytes are highly dependent on oxidation of free fatty acids for energy. Interference with this mechanism via bupivacaine-induced inhibition of carnitine-acylcarnitine translocase has been proposed to contribute to the cardiotoxicity of lipophilic local anesthetics¹²⁰ (Chap. 48, Fig. 48–2, and Antidotes in Depth: A20). Bupivacaine may produce dysrhythmias by blocking GABAergic neurons that tonically inhibit the autonomic nervous system.⁴⁵ In addition to its other effects on the heart, bupivacaine may induce a marked decrease in cardiac contractility by altering Ca^{2+} release from sarcoplasmic reticulum.⁶⁶

In a large series of patients receiving bupivacaine, systemic toxicity occurred in only 15 of 11,080 nerve blocks.⁷⁷ Of these patients, 80% convulsed; the other 20% had milder symptoms. A series of cases was described in which bupivacaine use, particularly at 0.75% concentration, was associated with severe cardiovascular depression, ventricular dysrhythmias, and even death. Pregnant women were disproportionately affected. Some of these patients required prolonged resuscitation, and restoration of adequate spontaneous circulation proved exceedingly difficult.⁹⁵ In 1983, 49 incidents of cardiac arrest or ventricular tachycardia that occurred over a 10-year period were presented to the US FDA Anesthetic and Life Support Advisory Committee. Among these cases, 0.75% bupivacaine was used in 27 obstetric patients with 10 deaths, and 0.5% bupivacaine was used in 8 obstetric patients with 6 deaths. Among the 14 nonobstetric patients, 5 died. The overall mortality rate was 21 of 49 (43%). Partly as a result of these reports, in 1984, the FDA withdrew approval of bupivacaine 0.75% for use as obstetric anesthesia.⁹⁵

Acid–base and electrolyte status influence the cardiac toxicity of a given drug because all depressant properties are potentiated by acidosis, hypoxia, or hypercarbia.¹³ Table 67–3 outlines the spectrum of acute local anesthetic reactions.

TABLE 67–3. Types of Local Anesthetic Reactions

<i>Cause</i>	<i>Major Clinical Features</i>
Local anesthetic toxicity (intravascular injection)	Immediate seizure or dysrhythmias
Reaction to catecholamine	Tachycardia, hypertension, headache
Vasovagal reaction	Bradycardia, rapid onset and recovery, hypotension, pallor
Allergic reaction	Anaphylaxis
High spinal or epidural block	Bradycardia, hypotension, respiratory distress, respiratory arrest

LABORATORY STUDIES

In cases of possible local anesthetic toxicity, an ECG should be obtained to detect dysrhythmias and conduction disturbances. Serum electrolytes, blood urea nitrogen, creatinine, and a blood gas analysis should be obtained to help assess the cause of cardiac dysrhythmias. Cooximetry should be obtained in patients in whom methemoglobinemia is suspected clinically. Rapid, sensitive assays are available for measuring concentrations of lidocaine and its monoethylglycylxylidide (MEGX) metabolite. When properly interpreted, the results of these assays may be used to prevent lidocaine toxicity and to identify lidocaine toxicity in the nontherapeutic setting. Assays for determining serum concentrations of other local anesthetics are not routinely available. Treatment should never be delayed while waiting for results of xenobiotic concentration determinations.

TREATMENT

Treatment of Local Anesthetic Cardiac Toxicity

Treatment of cardiovascular complications of local anesthetics is complicated by the complex effects of local anesthetics on the heart. Initial therapy should focus on correcting the physiologic derangements that may potentiate the cardiac toxicity of local anesthetics, including hypoxemia, acidemia, and hyperkalemia.^{13,98} Prompt support of ventilation and circulation limits hypoxia and acidemia. Early recognition of potential cardiac toxicity is critical to achieving a good outcome because patients with cardiac toxicity that goes unrecognized for any interval are more difficult to resuscitate.⁷ If a potentially massive intravascular local anesthetic injection is suspected, maximizing oxygenation of the patient before cardiovascular collapse occurs is critical.

Intravenous Fat Emulsion

While investigating the relationship between lipid metabolism and bupivacaine toxicity (described earlier), a rat study of bupivacaine induced asystolic arrest showed that pretreatment with IV fat emulsion (IFE) increased the dose of bupivacaine by 50% that was necessary to induce toxicity.¹²² In addition, a dose of bupivacaine that was uniformly fatal in control rats resulted in universal survival in animals that also received fat emulsion.¹²² Subsequent studies of local anesthetic toxicity have demonstrated accelerated return of cardiac function after IFE both in intact animals and in isolated hearts.^{117,118}

In clinical reports, epinephrine has limited efficacy in the treatment of cardiac arrest that results from bupivacaine toxicity. This could possibly be secondary to inhibition of intracellular cyclic adenosine monophosphate production by bupivacaine. The efficacy of IFE was demonstrated when compared with epinephrine for resuscitation of bupivacaine induced cardiovascular collapse in a rodent model.¹¹⁹

An infusion of a 20% IFE was successfully used to resuscitate a patient from a prolonged cardiac arrest caused by bupivacaine toxicity. The patient rapidly stabilized with IFE after failing to improve with 20 minutes of advanced cardiopulmonary resuscitation (CPR).¹⁰⁰ Subsequently, several case reports have been published describing successful use of IFE (in various formulations) to treat patients in cardiac arrest after regional anesthesia with various local anesthetics including bupivacaine, ropivacaine, and levobupivacaine.^{52,62,116} Although the majority of reports and potential mechanisms of action (see later discussion) suggest that IFE would be most useful in the treatment of systemic effects of lipid-soluble local anesthetics, a recent case report documents reversal of severe neurotoxicity related to lidocaine, which is far less lipophilic.⁵⁹ However, when lipid solubility is expressed as the octanol/water partition coefficient at physiologic pH (Log D), it becomes clear that lidocaine toxicity should be amenable to treatment with IFE (Table 67–1).

The mechanism by which IFE reverses local anesthetic toxicity is uncertain. One of the hypotheses is that the exogenous fat emulsion provides a competing source for binding of lipid-soluble local anesthetics, a circulating lipid sink. This view is supported by a study that demonstrated decreased cardiac bupivacaine concentrations after IFE.¹¹⁸ Another possibility is that the fat emulsion load might overwhelm the inhibition of the carnitine acylcarnitine translocase by mass action, increasing mitochondrial free fatty acids, thereby increasing myocardial energy production, making the heart more likely to respond to resuscitation. In isolated guinea pig heart preparations exposed to high concentrations of bupivacaine and ropivacaine for 10 minutes, cardiomyocyte mitochondria had reduced oxygen consumption and concentration dependent morphologic swelling.⁴⁷ Because the brain does not use lipid for energy production and IFE can reverse local anesthetic CNS toxicity, nonmetabolic processes are clearly involved.⁸⁹ For example, IFE has positive inotropic effects in isolated heart preparations and reversed bupivacaine-induced cardiac depression at lipid concentrations less than those needed to reduce aqueous bupivacaine concentration.¹⁰⁶

Increasing clinical data suggest that an IV bolus of fat emulsion may be lifesaving in patients with refractory cardiovascular collapse secondary to local anesthetic overdose. Twenty-two peer-reviewed case reports from 2006 to 2011 describe the effective use of IFE in local anesthetic systemic toxicity.⁸⁹ Thirteen of the cases involve bupivacaine. Although optimal dosing is uncertain,¹¹⁰ based on accumulating experience, the use of IFE for local anesthetic systemic toxicity has been endorsed by multiple organizations, including the American Society of Regional Anesthesia and Pain

Medicine (ASRA) and the American College of Medical Toxicology. The most recent and detailed guidelines by the ASRA⁸⁶ suggest dosing for a patient in cardiac arrest is 1.5 mL/kg bolus of 20% IFE over one minute while continuing chest compressions followed by continuous infusion of 0.25 mL/kg/min. For persistent cardiovascular collapse, the bolus may be repeated once or twice, and the infusion rate should be doubled. If there is evidence of recovery, the infusion should be continued for at least 10 minutes after stability. IFE should be given after signs of local anesthetic toxicity become manifest¹²³ (Antidotes in Depth: A20).

In addition to lipid therapy, standard advanced cardiac life support (ACLS) protocols should be followed when dealing with most local anesthetic cardiac toxicity. Hypotension in sinus rhythm results from both peripheral vasodilation and myocardial depression and should be treated with α - and β -adrenergic agonists. Atropine supplemented with electrical pacing should be used to treat bradycardia. The effectiveness of epinephrine in reversing local anesthetic-induced cardiac depression is variable in animal models, and the ASRA guidelines recommend using only small doses (eg, $<1 \mu\text{g/kg}$) for hypotension in this setting. The dysrhythmic effects of epinephrine are of particular concern. Amrinone (currently inamrinone), a phosphodiesterase III inhibitor, was evaluated for treatment of bupivacaine-induced cardiac toxicity.^{39,61} Anesthetized pigs with cardiovascular collapse induced by bupivacaine infusion survived when they were treated with amrinone; all the control animals died of irreversible cardiac arrest.⁶¹ An IV phosphodiesterase III inhibitor, milrinone is the most available and would be a good choice for reversing bupivacaine-induced cardiac depression.¹⁰⁴ An infusion of 0.375 to 0.75 $\mu\text{g/kg/min}$ (without a loading dose), with adjustments for renal insufficiency, should be considered.

Bupivacaine-induced dysrhythmias often are refractory to cardioversion, defibrillation, and pharmacologic treatment. Lidocaine, phenytoin, magnesium, bretylium, amiodarone, calcium channel blockers, and combined therapy with clonidine and dobutamine have all been used in animal models with variable results.^{29,69,71} Therapy for bupivacaine toxicity should be directed toward dissociating bupivacaine from the myocardial sodium channel, thereby reversing the drug's effects on cardiac conduction. Lidocaine competes with bupivacaine for cardiac sodium channels and at high doses may displace it. Anecdotal reports suggest that lidocaine has occasionally helped in this application.²⁴ However, concern persists about additive CNS effects when lidocaine is used to treat bupivacaine cardiac toxicity, and the guidelines suggest avoidance of calcium channel blockers, β -adrenergic antagonists, and local anesthetics.

With toxicity from the longer acting, highly lipid-soluble, protein-bound amide local anesthetics (bupivacaine and etidocaine), if the patient does not respond promptly to therapy, CPR can be expected to be difficult and prolonged (1–2 hours) before depression of the cardiac conduction system spontaneously reverses as a result of redistribution and metabolism of the drugs.^{2,93} Vital organ perfusion is seriously compromised during CPR despite optimal chest compression. The significance of this problem increases with the duration of resuscitation; therefore, rapid initiation of cardiopulmonary bypass should be considered if practical. Its use has resulted in a successful outcome in some cases of lidocaine and bupivacaine overdose.^{38,64} Cardiopulmonary bypass provides circulatory support that is far superior to that provided by closed-chest cardiac massage. The improved perfusion prevents tissue hypoxia and the development of metabolic acidosis, which in turn decreases the binding of local anesthetics to myocardial sodium channel receptors. Hepatic blood flow is better maintained, enhancing local anesthetic metabolism, and increased myocardial blood flow helps redistribute local anesthetics out of the myocardium.⁶⁴

Cardiac pacing was used successfully for treatment of cardiac arrest after unintentional administration of a 2 g bolus of lidocaine into a cardiopulmonary bypass circuit as the patient was being removed from bypass.⁸⁷ Pharmacologic therapy was unsuccessful, and resumption of bypass was necessary. Forty-five minutes after the injection, AV pacing restored perfusion and permitted discontinuation of bypass.

Use of sodium bicarbonate early in resuscitation to prevent acidemia mediated potentiation of cardiac toxicity may have been beneficial in some cases,²⁴ but paradoxical effects on intracellular pH during CPR argue against its use in the absence of strong experimental or clinical data. In another canine model, an infusion of 2 mL/kg 50% dextrose plus 1 unit/kg insulin was superior to saline or dextrose alone in reversing bupivacaine-induced cardiac depression²⁰ (Antidotes in Depth: A17). Effects on potassium current, calcium handling, and myocardial energy utilization (by providing an alternative energy substrate) all may have contributed to the salutatory effects of the insulin infusion.

Prevention of Systemic Toxicity of Local Anesthetics

Despite the development of new, relatively less toxic amide local anesthetics such as levobupivacaine and ropivacaine, severe CNS and cardiovascular effects remain a risk. Several cases of ropivacaine induced cardiac arrest are reported.^{19,52,56} In these cases, patients with both asystolic arrest and ventricular fibrillation associated arrest were successfully resuscitated. Nonetheless, it is clear that prevention is more prudent and effective than treatment of toxicity. The keys to prevention are to use the lowest possible anesthetic concentration and volume consistent with effective anesthesia and to avoid a significant intravascular injection. The latter is accomplished by ensuring extravascular placement demonstrated repetitively by ultrasonographic guidance and by careful, slow aspiration of a needle or catheter before injection; injection of a small test dose of anesthetic mixed with epinephrine to assess a cardiovascular response if injection is intravascular; and use of slow, fractional dosing of large-volume injections with vigilance for early signs of

CNS and cardiac toxicity.

SUMMARY

- Local anesthetics are frequently used xenobiotics that provide surgical analgesia and acute and chronic pain relief.
- The analgesic effect of local anesthetics is primarily caused by inhibition of neural conductance secondary to sodium channel blockade.
- Systemic toxicity, which primarily affects the heart and brain, is also largely related to sodium channel blockade.
- Severe systemic toxicity usually occurs secondary to inadvertent intravascular injection.
- If cardiovascular collapse and cardiac arrest occur, especially in the setting of bupivacaine toxicity, resuscitation may be difficult and prolonged. A novel therapy, IFE, has been shown to reverse, by uncertain mechanisms, local anesthetic toxicity.
- Cardiopulmonary bypass may be useful because it provides cardiovascular support, limits exacerbating factors such as tissue hypoxia and acidemia, and improves hepatic blood flow, thereby increasing local anesthetic metabolism.

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A20 ANTIDOTES IN DEPTH

Intravenous Fat Emulsion

Theodore C. Bania

INTRODUCTION

The use of intravenous fat emulsion (IFE) as an antidote is most extensively studied for the treatment of local anesthetic systemic toxicity. However, new applications that are being investigated and reported include the treatment of overdose from lipophilic xenobiotics such as calcium channel blockers, cyclic antidepressants, and β -adrenergic antagonists, among others.

HISTORY

IFE has been used as a source of parenteral nutrition for over 40 years and is also used as a diluent for intravenous drug delivery of highly lipophilic xenobiotics such as amphotericin and propofol. Recently, liposomal suspensions containing local anesthetics such as bupivacaine have been formulated that slowly release xenobiotics to increase the duration of anesthetic effect.

Although rare, bupivacaine toxicity is usually refractory to standard cardiac resuscitative measures ([Chap. 67](#)). In the setting of cardiovascular collapse, fatalities are frequent. Previously, cardiopulmonary bypass was the only effective treatment for these patients, as most cases were unresponsive to less invasive therapy. IFE was first evaluated in several animal models and was successful for the treatment of bupivacaine toxicity. Because of the success in animal models and the ineffectiveness of other therapies, IFE was attempted in humans and multiple case reports document apparent benefit. Subsequently, IFE was recommended by several anesthesia specialty societies for the treatment of local anesthetic toxicity. The initial proposed mechanism of action of IFE is the binding of local anesthetic in the serum lipid phase and decreasing the amount of xenobiotic at the site of toxicity. Subsequently, IFE was evaluated in several animal models of toxicity from lipid soluble xenobiotics. Based on these studies, IFE was used in several case reports of poisoning.

PHARMACOLOGY

Chemistry/Preparation

IFE is composed of two types of lipids: triglycerides and phospholipids. Triglycerides are hydrophobic molecules that are formed when three fatty acids are linked to one glycerol. The fatty acid chain lengths vary, producing different triglycerides. The primary triglycerides in IFE are linoleic, linolenic, oleic, palmitic, and stearic acids; their concentrations vary slightly in the different commercially available fat emulsions. These long-chain triglycerides (12 or more carbons) are extracted from safflower oil and/or soybean oil, depending on the brand of the emulsion.⁷⁹ Newer fat emulsions contain long-chain triglycerides in addition to medium-chain triglycerides (6–12 carbons) derived from coconut, olive, and fish oils, but they are currently not available in the United States.^{54,84}

Phospholipids contain two fatty acids bound to glycerol and a phosphoric acid moiety that is located at the third hydroxyl group ([Fig. A20–1](#)). Phospholipids are amphipathic; that is, the nonpolar fatty acids are hydrophobic while the polar phosphate head is hydrophilic. This imparts important pharmacological properties to this carrier molecule, allowing it to solubilize nonpolar xenobiotics in aqueous serum. IFE phospholipids are extracted from egg yolks.

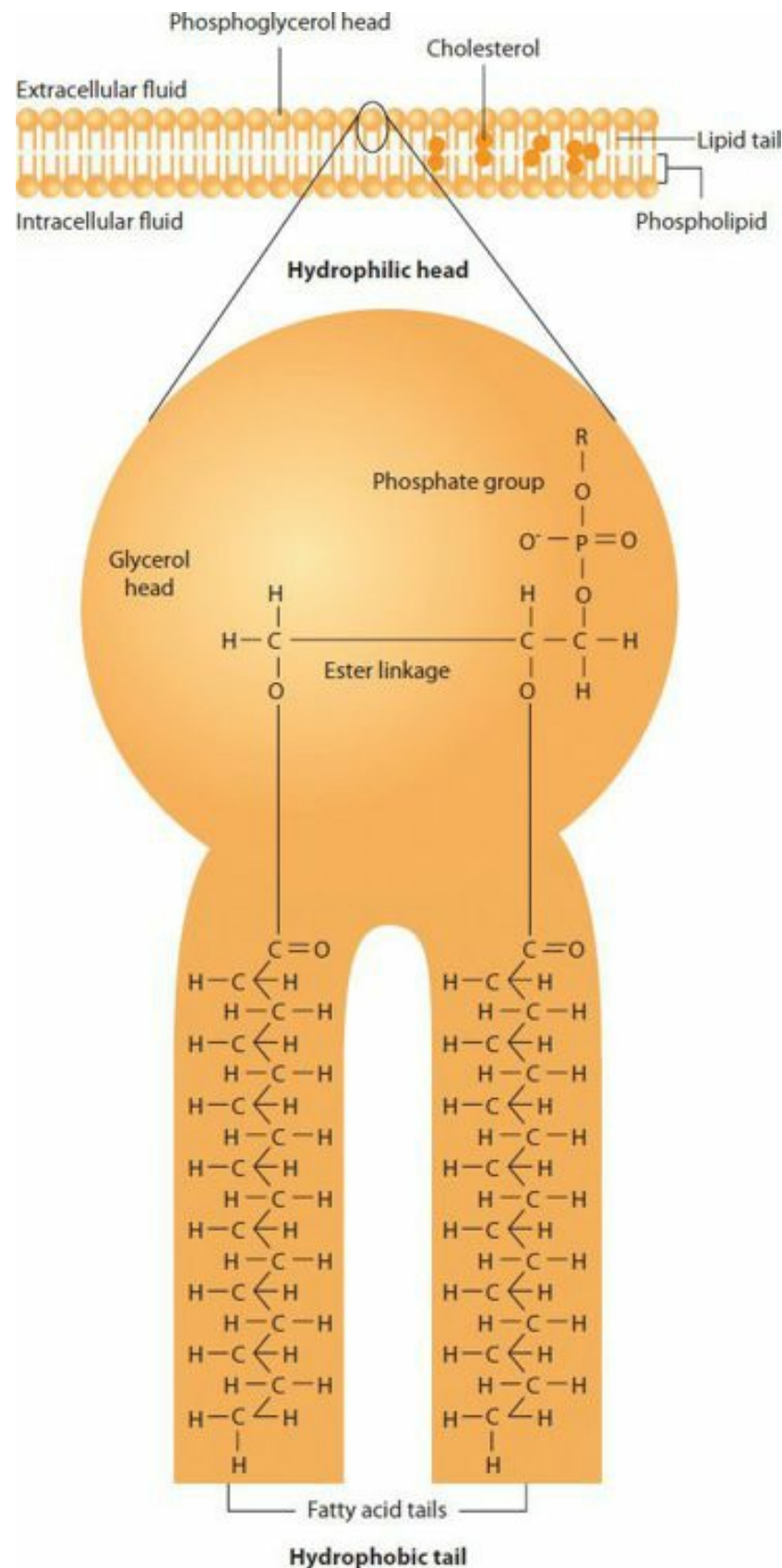


FIGURE A20–1. Biologic membranes are comprised of phospholipids that have a hydrophilic phosphoglycerol “head” and hydrophobic fatty acid “tails.”

The lipids in IFE are dispersed in the serum by forming an emulsion of small lipid droplets. To create the emulsion droplets, the phospholipids form a layer around a triglyceride core. The hydrophobic fatty acid component of the phospholipid molecule is directed toward the triglycerides while the hydrophilic glycerol component is directed outward away from the triglyceride core. The presence of small amounts of glycerol, which is hydrophilic, allows the lipid droplets to be suspended as an emulsion in water and serum.

IFE is a white, milky liquid. It is sterile and nonpyrogenic with a pH of about 8 (range, 6–9). IFEs are isoosmotic solutions (260–310 mOsm/L) and can be delivered through a peripheral or central vein.⁷⁹

IFE has different globule sizes depending on their uses.¹⁵ Microemulsions containing droplet sizes less than 0.1 µm are used for drug delivery. Mini-emulsions containing droplet sizes greater than 0.1 µm but less than 1.0 µm are used for parenteral nutrition. Droplet sizes in commercially available nutritional IFEs range from 0.4 to 0.5 µm. Phospholipid

emulsifying xenobiotics such as egg phosphatide are added and prevent droplet coalescence. After intravenous administration, IFEs are found in the serum as lipid droplets that resemble chylomicrons and turn the serum turbid or milky. Macroemulsions containing droplet sizes greater than 1.0 μm are used for chemoembolization. These macroemulsions contain chemotherapeutics that are delivered intraarterially directly into the tumor blood supply. The lipid droplets occlude the artery and slowly release the chemotherapeutic.

Related Lipid Formulations

Most case reports documenting successful treatment of local anesthetic toxicity with lipids have utilized Intralipid or standard long-chain triglyceride mixtures. IFE containing mixtures of long-chain and medium-chain triglycerides such as Medialipid (Braun, Germany) and Liposyn III (Hospira Inc., Lake Forest, IL) have been successfully used in clinical cases of poisoning, suggesting that all currently available parenteral lipid products will be effective.^{30,87} IFE containing medium-chain triglycerides are not routinely available in the United States.

Lipid emulsions containing both long-chain and medium-chain triglyceride mixtures may be more effective at partitioning xenobiotics. In human serum, a mixture of long-chain and medium-chain triglycerides increased the extraction of bupivacaine, ropivacaine, and mepivacaine compared to long-chain triglyceride mixtures.⁶⁷ However, in a rodent model of bupivacaine toxicity, long-chain and medium-chain mixtures were equally effective in reversing bupivacaine toxicity, but the long-chain mixture resulted in fewer recurrences of asystole after resuscitation and lower myocardial bupivacaine concentrations.⁴⁴

Mechanism of Action

The mechanisms of action of IFE in toxicology are not clearly understood. The three proposed mechanisms of action of IFE are modulation of intracellular metabolism, a lipid sink or sponge mechanism, and activation of ion channels.

Modulation of Intracellular Metabolism. In experimental models of poisoning from xenobiotics that alter intracellular energy metabolism, toxicity was successfully treated with IFE, suggesting that repairing or circumventing this dysfunction may be involved. Bupivacaine blocks carnitine-dependent mitochondrial lipid transport and inhibits adenosine triphosphatase (ATPase) synthetase in the electron transport chain.^{13,94} Verapamil inhibits intracellular processing of fatty acids,^{37,38} but it also inhibits insulin release and produces insulin resistance.³⁸ The cyclic antidepressant amitriptyline depresses human myocardial contraction independent of an effect on conduction³⁰ and inhibits medium- and short-chain fatty acid metabolism.⁸⁷ Propranolol changes intracellular energy from primarily fatty acid to carbohydrate-dependent metabolism.⁴⁹

Theoretically, adding excess fatty acids may overcome blocked or inhibited enzymes by mass action, providing energy to an energy “starved” heart, reversing toxicity. Some support for this mechanism comes from the IFE effect in reversing myocardial depression resulting from myocardial ischemia.⁸⁰ In a canine model employing 10 minutes of regional myocardial ischemia, treatment with IFE following ischemia resulted in improved systolic wall thickening. In the same canine model, pretreatment with oxfenicine, which blocks carnitine palmitoyltransferase-1, blocked the beneficial effect of IFE.³⁸ This finding suggests that the effects of IFE on myocardial contraction following ischemia are mediated by mitochondrial metabolism.

Unfortunately, there is limited experimental evidence to support a modulation of intracellular energy metabolism as the mechanism of action of the IFE. Some evidence comes from studies in bupivacaine toxicity. In an isolated rat heart model of bupivacaine-induced cardiotoxicity, doses of IFE in the perfusate that were too low to significantly decrease bupivacaine concentrations reversed bupivacaine-induced cardiac dysfunction.⁷⁶ Similarly, in an in vivo model of bupivacaine-induced toxicity when rodents were pretreated with a single dose of a fatty-acid oxidation inhibitor (CVT-4325), IFE was unable to rescue these rodents, implying that IFE works by providing energy in the form of free fatty acids.⁵⁹ Although these results imply that IFE works by a mechanism other than binding bupivacaine and suggest a metabolic effect, other studies support the theory that IFE works by a nonmetabolic mechanism. In one study, verapamil toxicity was induced when rodents were pretreated with the fatty acid oxidation inhibitor oxfenicine or control solution. Both groups were then resuscitated with IFE.³ There were no significant differences in survival time and mean arterial pressure between the oxfenicine-treated and control groups. Analogous to some models of bupivacaine toxicity, this study implies that in verapamil toxicity, IFE works by a mechanism other than mitochondrial energy supply.

Lipid Sink or Sponge Mechanism. In the lipid sink or sponge mechanism, IFE “soaks up” lipid-soluble xenobiotic and removes it from the site of toxicity. In a variation of this mechanism, IFE may pull the xenobiotic out of the aqueous plasma, which bathes the tissue, and into a nonaqueous part of the plasma that is not in contact with the site of toxicity. IFE may also alter the distribution of lipid-soluble xenobiotics and redistribute them away from the site of toxicity into an area with high lipid content (ie, create a “lipid conduit”). Some experimental support comes from studies of bupivacaine toxicity. In an isolated heart model, hearts perfused with bupivacaine until asystole were then treated with control or IFE. The IFE-treated hearts had a faster recovery from asystole, a lower concentration of bupivacaine in the tissue, and a higher concentrations

of bupivacaine in the venous effluent.⁹⁵ Stronger evidence for the lipid sink/sponge mechanism is seen in the effect of lipid emulsion on the pharmacokinetics and tissue distribution of bupivacaine in rats. Lipid emulsion decreased the distribution of bupivacaine into tissue, resulting in decreased concentrations in the brain and myocardium.⁷¹ Similarly, in a pharmacokinetic study of clomipramine toxicity, following IFE infusion, concentrations of clomipramine increased and volume of distribution decreased, in addition to an increase in blood pressure.²⁸ In a pharmacokinetic study of amiodarone toxicity, IFE pretreatment resulted in higher concentrations of amiodarone and higher blood pressures compared to pretreatment with saline.⁵⁸ In a well-perfused swine model, IFE decreased amitriptyline concentrations in the brain by 25% and decreased the heart-to-plasma ratio.³⁰ In a successful resuscitation from bupropion overdose, bupropion concentrations increased dramatically after IFE administration.⁸¹ Concentrations also increased following successful treatment of verapamil.¹⁹ These findings in experimental models and case reports can be explained by the lipid sink/sponge model, where IFE pulls a xenobiotic away from the site of toxicity, although the increased concentrations could be explained by an increased perfusion of tissues and release of the drug.

Additional indirect evidence supports the lipid sink/sponge and a nonmetabolic mechanism. While the myocardium can utilize fatty acids for metabolism, the central nervous system (CNS) does not use fatty acids to a substantial degree, implying that the reversal in sedation results from xenobiotic removal from the CNS as opposed to an altered metabolism. This reversal of CNS effects was demonstrated in two animal models of thiopental sedation,^{10,66} whereas in another animal model of thiopental anesthesia, IFE increased the CNS effects. These findings may support the lipid sink/sponge mechanism, as in this model it was proposed that the IFE kept serum thiopental concentration high, permitting additional thiopental diffusion into the CNS.³⁶ Reversal of CNS effects is also described in several clinical cases where the neurologic effects of bupivacaine were reversed with IFE,⁴⁸ and arousal was reported in olanzapine toxicity.⁵⁶ Additionally, a nonmetabolic effect of IFE in reversing toxicity is described in an in vitro model of methemoglobin formation. IFE added to whole blood blocked methemoglobin formation subsequent to exposure to the lipid-soluble glycerol trinitrate in a dose-dependent manner. IFE did not block methemoglobin production from non-lipid-soluble compounds such as 2-amino-5-hydroxytoluene or sodium nitrite, which supports a nonmetabolic effect of IFE and implies reversal of effect is related to lipid solubility.⁶⁹

The degree of lipid solubility of a xenobiotic can be measured using the partition coefficients log P or log D. Both measure the xenobiotic partition between a lipophilic organic phase (usually octanol) and a polar aqueous phase (usually water) and are the logarithm of the ratio of concentration of the xenobiotic between the two phases. Log P measures the partition of the nonionized form of the xenobiotic between the two phases, while log D measures the partition of both the un-ionized and the ionized form of the xenobiotic and varies based on pH. Log D can be reported across a range of pH values, and the log D at pH of 7 is considered an evaluation of lipid solubility in normal plasma. When determining if a xenobiotic is lipid soluble, the log P is most commonly reported. The log D at pH of 7 may represent a more accurate estimation of lipid solubility in a normal physiologic state, while the log D at a lower pH might more accurately represent lipid solubility during xenobiotic toxicity with hemodynamic compromise. Variations in lipid solubility may be clinically important and may alter the amount of xenobiotic partitioning into the serum lipid. In an in vitro model, the distribution of bupivacaine and ropivacaine in fat emulsion decreased at lower pH.⁵¹

Activation of Ion Channels. The mechanism of action of IFE may be the activation of, both Ca^{2+} and Na^{+} channels. Linolenic acid and stearic acid decreased bupivacaine-induced Na^{+} blockade in a human cardiac Na^{+} channel model.⁵⁵ Fatty acids directly activate myocardial Ca^{2+} channels and induce a dose-dependent increase in the Ca^{2+} current. Oleic, linoleic, and linolenic acids act directly on the Ca^{2+} channel to increase Ca^{2+} current.³²

Mechanism of Action: Conclusion. Despite the lack of definitive studies on mechanisms of action, the lipid sink/sponge model is the most likely, since beneficial effects from IFE are most frequently noted for lipid-soluble xenobiotics independent of their mechanisms of toxicity. Multiple consequential mechanisms of action may exist, and depending on the xenobiotic, the mechanism(s) of action may vary and be multifactorial.

Pharmacokinetics

Lipid droplets that are less than 1 μm are primarily removed from circulation as they pass through the capillaries of adipose and hepatic tissue. The capillary endothelium in these tissues contains lipoprotein lipase, which hydrolyzes triglycerides, releasing fatty acids and glycerol that then diffuses into the cells. Fatty acids enter the cardiac myocyte either by passive diffusion or protein-mediated transport.⁷⁵

The half-life of IFE is 30 to 60 minutes and can vary substantially depending on the patient's clinical status, IFE dose, and droplet size.¹⁷ More than 2.5 g of lipid/kg/d (12.5 mL/kg of 20% IFE or 875 mL in a 70 kg person) overwhelms lipoprotein lipase activity, resulting in decreased clearance. Larger droplet sizes have slower clearances and are removed by reticuloendothelial phagocytosis. These larger droplets are more likely to induce an inflammatory response, obstruct the microvasculature, and produce capillary fat emboli.

Pharmacodynamics

Once inside the cells, fatty acids are used as energy or resynthesized into triglycerides and stored. For use as energy, triglycerides are transported into the mitochondria by carnitine palmitoyltransferase, where they undergo β oxidation sequentially releasing acetylcoenzyme A (acetyl-CoA) as the fatty acid chain is reduced in length. These acetyl-CoA molecules enter the Krebs cycle, where they ultimately generate adenosine triphosphate (ATP) (Figs. 13–3 and 13–8). Although glucose, lactate, and fatty acid metabolism may ultimately lead to the production of acetyl-CoA, fatty acid metabolism produces the largest amount of energy. For example, one mole of glucose produces 38 ATP, while one mole of stearic acid produces 146 ATPs⁹⁷; the metabolism of longer fatty acid chains may produce more ATP.

ROLE IN LOCAL ANESTHETIC TOXICITY

IFE was first studied as an antidote to bupivacaine toxicity. In a rodent model, pretreatment with IFE (10%–30%) followed by a continuous infusion of bupivacaine (10 mg/kg/min) increased the dose of bupivacaine needed to induce asystole.⁹⁶ In the second part of this study, bupivacaine was infused into rodents until the development of cardiac arrest. Rodents were resuscitated with IFE (30% IFE, 7.5 mL/kg bolus, then 3 mL/kg/min for 2 minutes) or an equivalent volume of saline. Animals were more successfully resuscitated with IFE from larger doses of bupivacaine than when treated with saline. The LD₅₀ for saline resuscitation was 12.5 mg/kg, which increased to 18.5 mg/kg with IFE resuscitation. In a larger animal model, canines were administered bupivacaine until cardiac arrest and then resuscitated with IFE (20% IFE, 4 mL/kg bolus, then 0.5 mL/kg/min for 10 minutes) or saline. IFE resulted in a dramatic survival benefit—all animals survived following IFE versus none in the control arm.⁸⁹ In rodent models, IFE was superior to epinephrine, vasopressin, and the combination in bupivacaine toxicity.^{14,93} These findings were not reproduced in several swine models in which epinephrine was superior to IFE and epinephrine alone or epinephrine plus IFE was superior to vasopressin alone or vasopressin plus IFE in bupivacaine toxicity.³² IFE was not effective in reversing local anesthetic toxicity and had minimal effect on bupivacaine and mepivacaine distribution.⁷¹ It is worth noting, however, that pH was not recorded in this study and the lipid solubility of bupivacaine is lower as pH decreases. This may explain the inability of IFE to change the distribution of the local anesthetics. Additionally, the swine model may not be appropriate to evaluate lipid resuscitation therapy. Swine develop complement activation-related pseudoallergy (CARPA), an acute hypersensitivity reaction to liposomes. CARPA is characterized by mottling, hypoxia, and cardiovascular instability, which might compromise IFE resuscitation. This may explain the incongruous effect of IFE in these swine models and hypotension when IFE is administered in some swine models.^{30,90}

Based on the experimental evidence in bupivacaine toxicity, IFE was successfully used in several reported human cases of cardiovascular collapse from local anesthetic overdose. The first human case occurred following the inadvertent intravenous administration of bupivacaine and mepivacaine during an interscalene block.⁶³ The patient developed cardiac arrest and was treated with cardiopulmonary resuscitation (CPR) and advanced cardiac life support (ACLS) for 20 minutes, but only had return of spontaneous circulation following administration of the first dose of IFE (100 mL of 20% IFE followed by 0.5 mL/kg/min for 2 hours). The second successfully treated case occurred when a patient developed asystole after inadvertent intravenous administration of ropivacaine during an axillary plexus block.⁴⁵ The patient received CPR and ACLS and had return of spontaneous circulation 10 minutes after IFE administration (100 mL of 20% or 2 mL/kg followed by an infusion at 10 mL/min for an additional dose of 100 mL). A comparable example was a 60 year-old man with diabetes, coronary artery disease, and end-stage kidney failure who became unresponsive and developed ventricular fibrillation and torsade de pointes after administration of mepivacaine and bupivacaine for a supraclavicular brachial plexus block. He received CPR and ACLS for 10 minutes and then was treated with IFE (250 mL of 20% over 30 minutes). His pulse and blood pressure returned 11 minutes later.⁸⁶

In addition to its use during resuscitation, IFE has been used to treat milder symptoms of local anesthetic toxicity such as CNS symptoms and dysrhythmias without loss of pulse. A patient developed agitation, dizziness, unresponsiveness, and atrial premature contractions and bigeminy after administration of mepivacaine and prilocaine for a brachial plexus block. IFE treatment alone (1 mL/kg of 20%, repeated at 3 minutes for a total of 100 mL, followed by a continuous infusion of 0.25 mL/kg/minutes or 14 mL/min) rapidly resolved his dysrhythmia and restored consciousness.⁴⁷ A 75 year-old woman developed a seizure, wide complex dysrhythmia, and hypotension following levobupivacaine administration for a lumbar plexus block. She was treated with propofol, metaraminol, and IFE (20%, 100 mL over 5 minutes). During IFE infusion, the QRS narrowed and blood pressure and electrocardiogram normalized within 10 minutes.²⁰ A 13 year-old patient developed ventricular tachycardia at 150 beats/min after receiving lidocaine with epinephrine and ropivacaine for a lumbar plexus block. Treatment with IFE alone (150 mL or 3 mL/kg of 20% IFE over 3 minutes) restored a normal QRS complex within 2 minutes. Subsequent reviews of published human case reports document 19 case reports using IFE for resuscitation for local anesthetic toxicity, and the majority report improvement.^{11,35,62,64,85}

ROLE IN NON-LOCAL ANESTHETIC TOXICITY

IFE was first studied as an antidote to bupivacaine toxicity and then evaluated for calcium channel blocker, cyclic antidepressant, β -adrenergic antagonist, organic phosphorus compounds, amiodarone, cocaine, and thiopental toxicity. In a controlled rodent study, a continuous infusion of verapamil followed by treatment with 12.4 mL/kg bolus of 20% IFE resulted in an increase in heart rate and survival compared with control.⁷⁸ In a larger animal model of verapamil toxicity in which animals also received calcium and atropine, 7 mL/kg of 20% IFE over 30 minutes resulted in improved blood pressure and survival.⁴

In an experimental model of clomipramine toxicity,²⁸ rabbits were given clomipramine until mean arterial pressure decreased to 50% of baseline. They were then treated with sodium bicarbonate (3 mL/kg of 8.4%), IFE (12 mL/kg of 20%), or sodium chloride (12 mL/kg of 0.9%). IFE resulted in an increase in mean arterial pressure greater than sodium chloride and sodium bicarbonate. In a second part of this study, clomipramine was administered until cardiovascular collapse, which was followed by resuscitation with sodium bicarbonate (2 mL/kg of 8.4%) or IFE (8 mL/kg of 20%) delivered over 2 minutes. With four animals in each study arm, IFE markedly improved survival compared to sodium bicarbonate (100% versus 0%).

In a rodent model using a constant infusion of propranolol, IFE decreased QRS prolongation, but the study was underpowered to detect an effect on heart rate or survival.¹¹ In another rodent and rabbit model of propranolol toxicity, IFE resulted in an increase in blood pressure.⁶ In contrast, in a metoprolol model, IFE was not effective in reversing hypotension and bradycardia, which was attributed to the lower lipid solubility of metoprolol compared to propranolol.⁷

In an oral organic phosphorus compound toxicity model, IFE administered 20 minutes after parathion exposure prolonged the time to apnea compared to saline and administering IFE 5 minutes after exposure.¹⁶

In a rodent model of thiopental anesthesia, IFE administered postanesthesia resulted in an increase in respiratory rate compared to saline.⁶⁶ Similarly, in a model of thiopental anesthesia, pretreatment with IFE decreased anesthesia time as measured by a return in righting reflex in rodents.¹⁰ However, in one animal model of thiopental anesthesia, IFE increased the CNS effects.³⁶

In a rodent model of cocaine toxicity, IFE was administered as pretreatment for cocaine toxicity. Pretreatment with IFE blunted the hypotensive effect of cocaine and increased survival.⁸

Based on the experimental evidence, IFE use was expanded to non-local anesthetic toxicity. IFE was successfully used to resuscitate a 17-year-old patient with prolonged cardiovascular collapse after bupropion and lamotrigine overdose. In this case, the patient had experienced seizures and underwent ACLS and CPR for 70 minutes, with return of spontaneous circulation after IFE administration (a bolus of 100 mL of 20%).⁷²

In the largest case series to date of IFE in non-local anesthetic toxicity, using the Toxicology Investigators' Consortium (ToxIC) database, investigators report nine cases with drug-induced cardiovascular collapse treated with IFE in addition to standard resuscitative measures. Five of the nine patients treated with IFE survived, although several adverse effects were probably or possible as a result of the IFE such as acute respiratory distress syndrome (ARDS), acute kidney injury, and deep vein thrombosis.²¹ Subsequent reviews and published human case reports document more than 55 case reports of IFE for resuscitation in non-local anesthetic toxicity. Improvement is reported for amlodipine, diltiazem, verapamil, atenolol, nebivolol, propranolol, carvedilol, flecainide, haloperidol, amitriptyline, dosulepin, doxepin, imipramine, quetiapine, venlafaxine, carbamazepine, lamotrigine, phenobarbital, diphenhydramine, bupropion, hydroxychloroquine, cocaine, and bromadiolone.^{12,12,64,85} Despite these successful reports, data are limited by reporting biases, therapeutic effects resulting from additional coadministered therapies, and coingestant xenobiotic toxicity. Current case report data only suggest a possible benefit of IFE tricyclic antidepressant bupropion, lipophilic β -adrenergic antagonist, and calcium channel blocker toxicity.¹²

ADVERSE EFFECTS AND SAFETY ISSUES

The adverse effects attributed to IFE administration are infrequent and limited primarily to pulmonary toxicity and pancreatitis.^{12,91} The doses and short durations of administration used in most patients result in full recovery without any significant adverse effects.^{12,35,64,85} Based on case reports, a dose of 1.5 mL/kg bolus of 20% IFE followed by 0.25 mL/kg/min or 15 mL/kg/h to infuse for 30 to 60 minutes appears to be safe in xenobiotic-induced cardiac arrest and severe toxicity.

Because of the limited number of case reports, toxicity from IFE remains a concern. Pulmonary toxicity is reported when IFE is used as a source of parenteral nutrition. In patients with ARDS, 500 mL of 20% IFE administered over 8 hours resulted in increased pulmonary artery pressures, pulmonary shunting, pulmonary vascular resistance, and decreased partial pressures of oxygen in the alveoli/fraction of inspired oxygen (P_{AO_2}/FIO_2).⁸³ Similar results were found in patients with ARDS administered 500 mL of 10% IFE over 4 hours, resulting in an increase in pulmonary shunting and a decrease in the

fraction of PAO_2/FIO_2 .³⁴ The pulmonary effect of IFE in ARDS may be related to infusion rate. In patients with ARDS, 500 mL of 20% IFE infused over 5 hours resulted in an increase in pulmonary pressures, while a slower infusion over 10 hours left pulmonary pressures unchanged.⁵⁰ There are conflicting results of the effects of IFE in patients without ARDS. In septic and nonseptic patients without ARDS, 500 mL of 20% IFE administered over 10 hours resulted in an increase in pulmonary artery pressures and pulmonary shunting.⁸² In patients with chronic obstructive pulmonary disease and pneumonia, 500 mL of 10% IFE administered over 4 hours had no pulmonary effects, and in a group of healthy postoperative patients this dose actually decreased pulmonary shunting and increased PAO_2/FIO_2 ratio.³⁴

In these studies, when pulmonary effects occurred, they were mild and resolved after the IFE infusion was stopped or within 3 to 4 hours. Larger doses may result in clinically significant toxicity and more prolonged effects. However, studies using fat emulsions with medium-chain triglycerides have shown less pulmonary toxicity.^{18,73}

IFE may cause pulmonary toxicity by at least two mechanisms. IFE may occlude the pulmonary vasculature with microfat emboli. Macrophages containing lipid droplets can be demonstrated in the bronchioalveolar lavage fluid of ARDS patients treated with IFE.⁴² Experimental evidence also suggests that a substantial amount of the high concentrations of linoleic acid in IFE is converted to arachidonic acid and then into vasoactive prostaglandins. Indomethacin, an inhibitor of prostaglandin synthesis, prevented any pulmonary vascular effect caused by IFE in a sheep model.⁵³

Adverse effects resulting from IFE use in resuscitation from xenobiotic toxicity are uncommon. Investigators using the ToxIC database report that three of the five patients successfully resuscitated with IFE developed ARDS that was probably attributed to IFE.³⁵ It is difficult to attribute the etiology solely to IFE as these patients were predisposed to ARDS due to xenobiotic toxicity, hypotension, and potential aspiration.

Elevated triglycerides and pancreatitis is reported when IFE is used for parenteral nutrition. The precise mechanism of IFE-induced pancreatitis is unknown but may be the result of the large concentration of triglycerides forming large lipid droplets that obstruct the small vessels of the pancreas, leading to ischemia. Lipase then degrades the triglycerides, releasing cytotoxic free fatty acids.

Hyperamylasemia and pancreatitis were reported in two cases of IFE use in treatment of xenobiotic toxicity. Following successful resuscitation with IFE from bupivacaine-induced cardiac arrest, an elevated amylase concentration without associated elevated lipase or associated symptoms was reported.⁸¹ Elevated lipase concentrations were reported after administering IFE to a 13 year-old girl who developed delayed seizures and cardiac arrest following an amitriptyline ingestion. Lipase concentrations peaked at 1849 U/L 5 days after IFE and was associated with elevated triglycerides and abdominal pain.⁴²

Large doses and/or rapid infusions of IFE have the potential to induce a fat overload syndrome. Fat overload syndrome is characterized by hyperlipemia, fever, fat infiltration, hepatomegaly, jaundice, splenomegaly, anemia, leukopenia, thrombocytopenia, coagulation disturbances, seizures, and coma. Multiple end-organ dysfunction is attributed to inadequate clearance of lipids and sludging in the lungs, brain, kidney, retina, and liver.^{15,17,25,31,39,42,68,70,77} Because of the rapid redistribution of most local anesthetics, prolonged IFE infusion should not be required ([Chap. 67](#)). However, many other lipid-soluble xenobiotics have a long duration of toxicity, and prolonged and repeated IFE infusions may be recommended, predisposing to fat overload syndrome.

Particularly when administered early in the clinical course of an overdose, IFE has the potential to increase gastrointestinal absorption or facilitate distribution of lipid-soluble xenobiotics, resulting in increased toxicity. Although this currently remains a theoretical concern, some animal models suggest certain xenobiotics could partition into IFE and contribute to additional toxicity. In an orogastric model of amitriptyline overdose, IFE increased amitriptyline concentrations and resultant toxicity.⁶¹ In a model of thiopental anesthesia, IFE increased sedation, possibly by increasing concentrations of thiopental in the serum, permitting extended time for distribution into the CNS.³⁶ IFE also has the potential to interact with other essential antidotes. If an antidote is lipid soluble, it may be incorporated by the IFE and result in decreased effectiveness. Both thiopental and lidocaine are highly lipid soluble, and IFE may decrease their effectiveness. In a rodent model, pretreatment with IFE delayed the peak effect and prolonged the duration of effect of epinephrine on mean arterial pressure.⁹ Clinical data are absent. IFE has been used with several medications during resuscitation from bupivacaine toxicity, including epinephrine, atropine, amiodarone, vasopressin, sodium bicarbonate, magnesium sulfate, calcium chloride, naloxone, and metaraminol.^{12,36,64,85}

The addition of IFE to high-dose insulin-euglycemia (HIE) was evaluated in a model of severe verapamil toxicity, and there was no improvement in hemodynamics, metabolic parameters, or survival.⁵ Therefore, while other resuscitative xenobiotics should be used as indicated, there is no evidence yet to support or refute the simultaneous use of IFE and HIE therapy.

Hyperlipidemia after using IFE may interfere with laboratory studies and make them uninterpretable.⁴² This interference may last for several hours and may depend on the type of laboratory system used. IFE may alter analytical test results and result in erroneous measurement, no significant effect, or the inability to perform a laboratory test. In vitro testing of IFE demonstrated that colorimetric methods were more prone to the effects of IFE than potentiometric methods. In the setting of

IFE, glucose measurement by colorimetric method did not accurately report hypoglycemia. For example, a glucose concentration of 2.7 mmol/L (48.6 mg/dL) may be falsely reported as 12.4 mmol/L (223.2 mg/dL). Centrifugation at 140,000 g for 10 minutes minimized most interference. Troponin-I, sodium, potassium, chloride, calcium, bicarbonate, or urea assays had the least interference. Albumin and magnesium assays demonstrated significant interference. Amylase, lipase, phosphate, creatinine, total protein, alanine aminotransferase, creatine kinase, and bilirubin became unmeasurable.²² The effect of IFE on toxicology testing is unknown. Ideally, analytic testing should be performed prior to the IFE administration.

Based on a risk benefit analysis, relative contraindication to IFE is egg or soybean allergy, disorders of fat metabolism, and liver disease. Consideration should also be made in patients with myocardial ischemia and infarction. In animal models, IFE increased dysrhythmias and impaired cardiac pump performance when administered during ischemia^{40,74} but was of benefit when administered after the resolution of ischemia. In an ischemic myocardial cell, fatty acid metabolism is thought to result in lipid peroxidation and free radical production, which increases dysrhythmias and impairs myocardial performance.⁷¹

Pregnancy and Lactation

IFE is a pregnancy category C pharmaceutical. It is not known whether IFE can cause fetal harm when administered to gravid patients. Potentially, large doses can result in elevated triglyceride concentrations, and lipid globules may potentially occlude placental vasculature. Risk of potential toxicity should be weighed against potential benefit to the pregnant woman and fetus. There is no reported risk of IFE on the nursing infant.

DOSING AND ADMINISTRATION

Although the optimal dosing regimen for human poisonings remains undefined, several animal models of high-dose IFE have been performed. In both rodent and canine models of verapamil toxicity, 12.4 and 7 mL/kg boluses of 20% IFE were given,^{5,78} and in a rabbit model of clomipramine, 12 mL/kg of 20% IFE was used.⁷⁹ These animal models used large doses of xenobiotic and were designed to produce a rapid onset of toxicity; it is difficult to extrapolate to typical human cases. In a rodent model, the LD₅₀ of IFE is 67 mL/kg, which is much higher than the current recommended clinical doses.

Additionally, only microscopic abnormalities were observed in the lung and liver at doses of 60 and 80 mL/kg, which improved over 24 hours. Higher doses of IFE also are more effective than lower doses. In a model of verapamil toxicity, higher doses up to a maximum of 18.6 mL/kg of 20% IFE were more effective in improving blood pressure, acidemia, and survival than lower doses. Higher doses improved hemodynamic parameters transiently, but may have also resulted in overall decreased survival times.⁶⁰

The dose of IFE administered depends on the implicated xenobiotic and the patient's clinical condition. Dosing is best defined for local anesthetic toxicity, specifically bupivacaine, with generalization of this dosing regimen to poisoning by other local anesthetics and other xenobiotics. The American Society of Regional Anesthesia and Pain Management, the Association of Anesthetists of Great Britain and Ireland, and the American Heart Association^{23,57} have similar guidelines and recommendation on the use of IFE in local anesthetic toxicity. Lipid treatment is recommended for clinically severe cardiovascular toxicity or rapid progression of toxicity.

The recommended dose of 20% IFE is 1.5 mL/kg bolus followed by 0.25 mL/kg/min or 15 mL/kg/h to run for 30 to 60 minutes.^{23,57} The bolus may be repeated several times for persistent dysrhythmias, and the infusion rate can be increased if blood pressure decreases. For local anesthetic poisoning, earlier recommendations limited use of IFE only to situations following the failure of standard resuscitative measures. As a result of the experimental evidence and many successful case reports, some authors recommend adding IFE at the first signs of local anesthetic toxicity or, in the setting of cardiovascular collapse, to use IFE concomitantly with CPR and ACLS and to avoid high doses of epinephrine.⁹² We recommend that rapid progression of local anesthetic toxicity affecting the CNS (agitation, confusion, seizures) or cardiovascular system (hypertension, tachycardia, ventricular dysrhythmias, hypotension, conduction blocks) should be treated with IFE. In the setting of cardiovascular collapse, IFE can be used with CPR and standard ACLS. IFE should be stored for easy and rapid access in operating rooms or in areas where local anesthetics are frequently used.⁶⁵ Generalization of this practice to other xenobiotics is not currently studied or recommended.

Experimental evidence indicates that IFE may be potentially beneficial in verapamil,^{4,60,79} clomipramine,^{28,29} propranolol,^{6,26} amiodarone,¹⁷ and cocaine⁸ toxicity, and this may be extrapolated to other lipid-soluble calcium channel blockers, cyclic antidepressants, or lipophilic β -adrenergic antagonists. These xenobiotics will usually demonstrate continued absorption, long duration of toxicity, severe hypotension, and either dysrhythmias or bradycardia over several hours or days. The precise indications and dose of IFE for these situations has not been studied, and it is not known if boluses or infusion are more effective. The reasonable safe total dose is also unknown but would depend upon the degree of toxicity and response to previous doses of IFE. Based on the current data available from animal models and clinical case reports, the American College of Medical Toxicology published interim guidance on the use of IFE in lipophilic xenobiotic

toxicity.¹ Published guidance states that IFE is a reasonable consideration in serious hemodynamic, or other, instability from a xenobiotic with a high degree of lipid solubility, even if the patient is not in cardiac arrest. However, IFE can be considered for patients with hemodynamic instability refractory to standard resuscitation measures. No standards for use were set, and the dosing recommended was similar to the dose recommended for local anesthetic toxicity. We recommend that IFE be used in the setting of severe toxicity (prolonged cardiovascular instability such as hypotension, severe bradycardia or dysrhythmias or seizures) resulting from a lipid soluble xenobiotic despite maximal treatment with standard resuscitation measures. When used, we recommend a bolus dose of 1.5 mL/kg of 20% IFE, which should be followed by an infusion for 30 to 60 minutes of 0.25 mL/kg/min or 15 mL/kg/h. Repeat boluses of IFE can be administered for persistent severe symptoms.

Propofol is formulated as a 10% lipid emulsion, but it is not recommended for use in lipid rescue because of the adverse effect of the propofol from the dose needed to achieve lipid rescue.⁸⁸ A 1.5 mL/kg bolus of 20% IFE equates to 3 mL/kg of the 10% lipid emulsion in the propofol solution. A normal dose of propofol (1%) for general anesthesia is 2.5 mg/kg or 0.25 mL/kg.⁶⁸ If propofol is used as a lipid rescue agent, it would deliver a bolus of 12 times the recommended dose of propofol. This would exacerbate any drug-induced hypotension and bradycardia.

FORMULATION AND ACQUISITION

IFE is available in 5%, 10%, 20%, and 30% solutions. The 20% solution is recommended and used most often. The 30% solution is a pharmacy bulk admixture and is used to prepare dilute concentrations. The 30% solution should be diluted before administration and has not been used clinically for xenobiotic toxicity.

There are some current shortages reported for IFE. There are no recommended alternative agents, but if available, dose adjustment can be made to the lower and higher concentrations, and medium chain preparations can be used as a substitute.

SUMMARY

- IFE is recommended for the treatment of local anesthetic systemic toxicity, particularly in the case of rapidly progressive toxicity or cardiac arrest.
- In local anesthetic systemic toxicity, IFE can be used with standard resuscitation medications and should be stored where local anesthetics are administered.
- IFE use for other xenobiotics is unclear at this time, although animal data and some human case reports support its use for several lipid-soluble xenobiotics such as verapamil, clomipramine, and some lipophilic β -adrenergic antagonists.
- IFE use for other xenobiotics should be considered when severe toxicity resulting from a lipid-soluble xenobiotic persists despite maximal treatment with standard resuscitation measures.
- For both local anesthetic and non-local anesthetic toxicity, a bolus dose of 1.5 mL/kg of 20% IFE should be followed by an infusion for 30 to 60 minutes of 0.25 mL/kg/min or 15 mL/kg/h. Repeat boluses of IFE can be administered for persistent severe signs and symptoms.

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68 INHALATIONAL ANESTHETICS

Brian Kaufman

HISTORY AND EPIDEMIOLOGY

The earliest description of the use of an inhalational anesthetic was made by Paracelsus, a Swiss physician and alchemist who prepared a mixture of diethyl ether, alcohol, and water called sweet oil of vitriol. He described the administration of this preparation to hens that fell into what appeared to be a deep sleep from which they recovered unharmed. In 1735, Wilhelm Froben gave this substance its modern name of “ether.” Ether was used topically, particularly via the intranasal route, as a treatment of headache, nervous diseases, and fits.

Modern anesthetic practice often is stated to have begun in 1846 at the Massachusetts General Hospital, when the dentist William Morton gave the first public demonstration of the ability of inhaled ether vapor to alleviate the pain of surgery. Oliver Wendell Holmes chose the Greek-related noun anesthesia (without feeling) to characterize the process.

Observations on circulatory and respiratory physiology eventually led to an understanding of the effects of inhalation gases and vapors. In the last decade of the 18th century, centers for the pneumatic treatment of disease were established in Birmingham and Bristol, England. Experiments with ether that was inhaled via a funnel and with nitrous oxide were conducted at these institutions. After Humphry Davy described his own pleasurable and exhilarating experience when he inhaled the “laughing” gas, many of his colleagues and friends inhaled nitrous oxide to experience its inebriating effects. Davy also described how inhalation of nitrous oxide relieved headache and the pain of an erupting molar tooth. Although Davy recognized the analgesic properties of nitrous oxide and its possible application for surgery, he failed to pursue the idea.

The public soon took up the use of nitrous oxide in the form of nitrous oxide frolics. Audience members at itinerant medicine shows volunteered to experience the exhilarating effects of nitrous oxide inhalation. At one such show in 1844 in Hartford, Connecticut, a man under the influence of nitrous oxide injured his leg but felt no pain. Dr. Horace Wells, a dentist in the audience that day, inhaled nitrous oxide the following day and had his partner painlessly remove a troublesome tooth. A subsequent public demonstration of the use of nitrous oxide for dental extraction was partly unsuccessful, leaving his colleagues doubtful regarding its efficacy and safety and thereby impeding its general acceptance as a surgical anesthetic.

In Great Britain in 1847, James Simpson, an obstetrician, first used ether to relieve the pain of labor. He subsequently adopted chloroform for this purpose because of its more pleasant odor and more rapid induction and emergence. The clergy and other physicians opposed the concept of relieving pain during childbirth, but the method ultimately was accepted after Queen Victoria gave birth to Prince Leopold with chloroform given by John Snow.

Over the next century, several volatile anesthetics were introduced, including ethyl chloride in 1848, divinyl ether in 1933, trichloroethylene in 1934, and ethyl vinyl ether in 1947. All had significant safety problems associated with their use, including combustibility and direct organ toxicity.

Advances in fluorine chemistry led to the cost-effective incorporation of fluorine into molecules used in the development of modern anesthetics. Fluroxene was the first of the new fluorinated anesthetics to be widely used clinically. However, this anesthetic was flammable and hepatotoxic. It was largely replaced by the nonflammable halothane, which was synthesized in 1951 and introduced into clinical practice in 1956. Methoxyflurane was evaluated in humans in 1960 but is no longer used because of nephrotoxicity ([Chap. 19](#)) and hepatotoxicity. Other halogenated hydrocarbons with improved clinical properties have been introduced, including enflurane, isoflurane, desflurane, and sevoflurane ([Fig. 68–1](#)). The inert gas xenon may be a useful anesthetic and is both cardio- and neuroprotective in experimental studies.⁴³ The clinical use of xenon is limited both by its cost and difficulty to manufacture. Although xenon is environmentally friendly compared with presently used anesthetic gases, its toxicity is relatively unknown but is believed to be minimal.

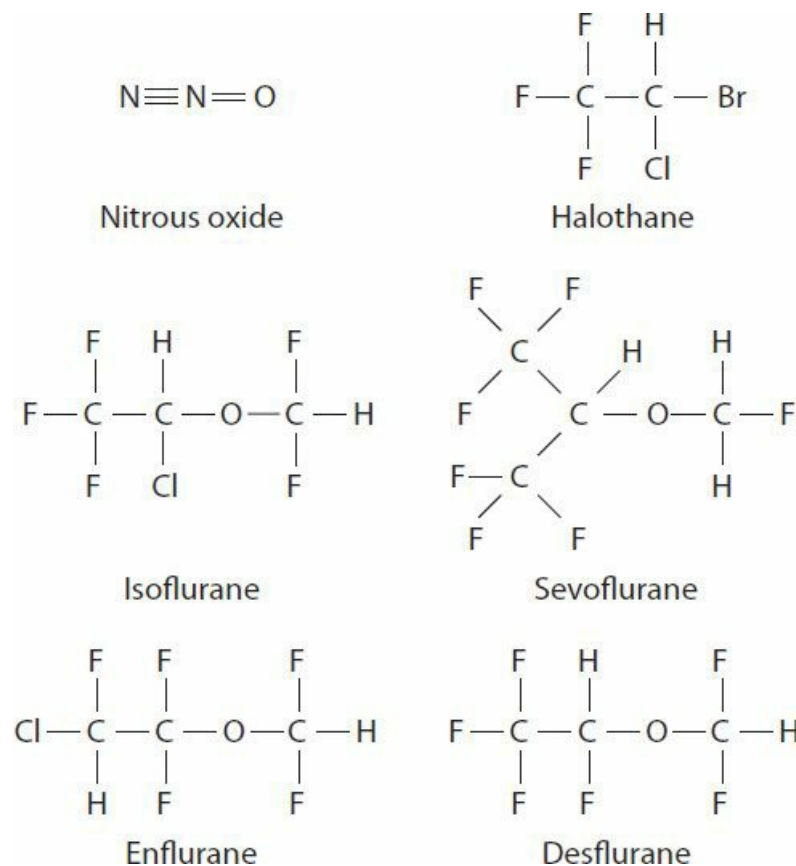


FIGURE 68–1. The inhalational anesthetics.

PHARMACOLOGY

Inhalational anesthetics remain the most popular anesthetics used for maintenance of anesthesia primarily because they are easily and safely administered by modern anesthesia machines and are rapidly titratable to effect. Inhalational anesthetics used in current clinical practice include nitrous oxide, halothane, isoflurane, sevoflurane, and desflurane.

Because a wide range of chemically distinct xenobiotics can produce anesthesia, a unique receptor for the inhaled anesthetics is improbable. More likely, the volatile anesthetics cause general anesthesia by modulating synaptic function from within cell membranes. Anesthetics interact with many proteins. The most likely, but not yet proven, targets for the inhalational anesthetics are the ion channels that control ion flow across the cytoplasmic membrane.¹¹ An in-depth discussion is beyond the scope of this chapter, but several concepts are important to consider. First, more than 20 different ion channels have been identified, each controlling various anion and cation flows. The results of these ion channel effects include release of inhibitory neurotransmitters and inhibition of excitatory neurotransmitters. In fact, each anesthetic type has variable actions. The receptor for γ -aminobutyric acid type A (GABA_A) is the best studied and plays an important role because GABA_A is an inhibitory neurotransmitter. The interaction of all of these receptor effects produces the condition we refer to as general anesthesia. Many of the adverse effects of the inhalational anesthetics result directly from ion channel effects in nonneural tissue, primarily cardiac cell membranes.

Reversible changes in neurologic function cause loss of perception and reaction to pain, unawareness of immediate events, and loss of memory of those events. The common pharmacologic mechanisms for general anesthesia include the physical–chemical behavior of volatile hydrocarbons within the hydrophobic regions of biologic membrane lipids and proteins.

The potency of the various inhaled anesthetics correlates with their physicochemical properties. The dominant theories of the molecular mechanisms by which volatile anesthetics affect membrane function are based on the lipid solubility of the xenobiotics and experimental demonstration of pressure reversal of anesthesia. Anesthetic potency correlates directly with the relative lipid solubility of each xenobiotic, suggesting that the primary molecular actions of anesthetics occur in the lipid portion of cell membranes. This mechanism is known as the Meyer-Overton lipid solubility theory. Potential membrane regions for anesthetic action include the hydrophobic areas of proteins and protein–lipid interface regions, as well as the phospholipid matrix. High pressures (100–200 atm) can reverse the anesthetic effects of several xenobiotics, suggesting that anesthesia results from increasing membrane volume at normal atmospheric pressure, an effect known as the volume expansion theory.

PHARMACOKINETICS

Because the inhaled anesthetics enter the body through the lungs, the factors that influence their absorption by blood and distribution to other tissues, particularly the brain, include the solubility of the xenobiotic in blood, blood flow through the lungs, blood flow distribution to the various organs, solubility of the anesthetic in tissue, and the mass of the tissue. The goal of inhalation anesthesia is to develop and maintain a satisfactory partial pressure of anesthetic in the brain, the primary site of action.

The pharmacokinetics of anesthetics can be linked to their pharmacodynamics by considering anesthetic potency. The linkage exists because anesthesia strives to achieve and maintain a desired alveolar concentration. For the inhaled anesthetics, potency is commonly designated by the minimum alveolar concentration (MAC) of the anesthetic. MAC is the alveolar concentration at 1 atm that prevents movement in 50% of subjects in response to a painful stimulus. MAC is used when comparing the effects of equipotent doses of anesthetics on various organ functions.

NITROUS OXIDE

Nitrous oxide (N_2O) is the most commonly used inhalational anesthetic in the world, but its safety is debated.²⁷ In 2008, the toxicity of nitrous oxide was exhaustively reviewed both from its chemical perspective and its clinical activity, and the authors concluded that a ban on its use is not required.⁴⁴ Its advantages include a mild odor, absence of airway irritation, rapid induction and emergence, potent analgesia, and minimal respiratory and circulatory effects. When administered in a modern operating room (OR) using current standards of monitoring to prevent unintentional hypoxia, nitrous oxide is a remarkably safe xenobiotic. Unfortunately, nitrous oxide also has a potential for abuse, particularly among hospital and dental personnel.²⁶ Death and permanent brain injury are reported but do not generally result from direct toxic effects; instead, they are secondary to hypoxia as a result of simple asphyxiation¹⁵ (Chap. 124).

Nitrous oxide is also used as a food additive to generate foam, a property exploited to produce whipped cream. Sold in supermarkets as “bulbs,” death has occurred secondary to asphyxiation, when a homemade mouthpiece “whippets” failed to separate from the user after unconsciousness occurred during use.⁴²

Death also has occurred when patients received commercially prepared nitrous oxide from tanks contaminated with impurities such as nitric oxide or nitrogen dioxide. Pulmonary toxicity resulting from similar contaminants has been reported after illicit preparation of nitrous oxide from the combustion of ammonium nitrate fertilizer.³³

Injury may result from the physical properties of this anesthetic. Nitrous oxide is 35 times more soluble in blood than is nitrogen. When nitrous oxide is inhaled, any compliant air-containing space, such as the bowel, increases in size; noncompliant spaces, such as the eustachian tubes, exhibit an increase in pressure. These effects occur because nitrous oxide diffuses along the concentration gradient from the blood into a closed space much more rapidly than nitrogen can be transferred in the opposite direction. Clinical consequences include rapid progression of a pneumothorax to a tension pneumothorax, tympanic membrane rupture with hearing loss, bowel distension, and tracheal or laryngeal trauma caused by increased endotracheal cuff pressure resulting from replacement of air by a larger volume of nitrous oxide. Nitrous oxide may be particularly dangerous in patients who have suffered air emboli, and its use should be immediately discontinued upon recognition of these events. When intracranial or neuraxial air is injected during placement of an epidural catheter, it also can theoretically expand upon subsequent exposure to nitrous oxide.

Hematologic Effects

Bone marrow suppression was first recognized as a complication of long-term nitrous oxide exposure in the 1950s, when the gas was used to sedate intubated patients who had severe tetanus.²⁵ Leukopenia with hypoplastic bone marrow and megaloblastic erythropoiesis typically developed 3 to 5 days after initial exposure and was followed by thrombocytopenia. Recovery usually occurred within 4 days after the anesthetic was discontinued. Healthy patients undergoing routine surgical procedures demonstrate mild megaloblastic bone marrow changes within 12 hours of exposure to 50% nitrous oxide and marked changes within 24 hours.⁴⁰ Critically ill patients may be more sensitive to the effects of nitrous oxide on the bone marrow, with megaloblastic changes described after only one hour of exposure, but changes are unlikely in individuals with less than 6 hours of exposure in the absence of preexistent folate or cobalamin deficiencies.³

The hematologic effects of exposure to nitrous oxide strongly resemble the biochemical characteristics of pernicious anemia.^{2,38,39} Vitamin B_{12} , or cyanocobalamin, is a bound coenzyme of cytoplasmic methionine synthase. The cobalt moiety in the enzyme functions as a methyl carrier in its transfer from 5-methyltetrahydrofolate to homocysteine to form methionine (Fig. 68–2). Nitrous oxide oxidizes the cobalt ion, converting vitamin B_{12} from the active monovalent form (Co^+) to the inactive divalent form (Co^{2+}), which irreversibly inhibits methionine synthase.³⁸ The metabolic consequences of this inhibition are significant because methionine and tetrahydrofolate are required for both DNA synthesis and myelin production. This interference is responsible for the development of bone marrow depression and polyneuropathy resembling the characteristic findings that occur in pernicious anemia.³⁹

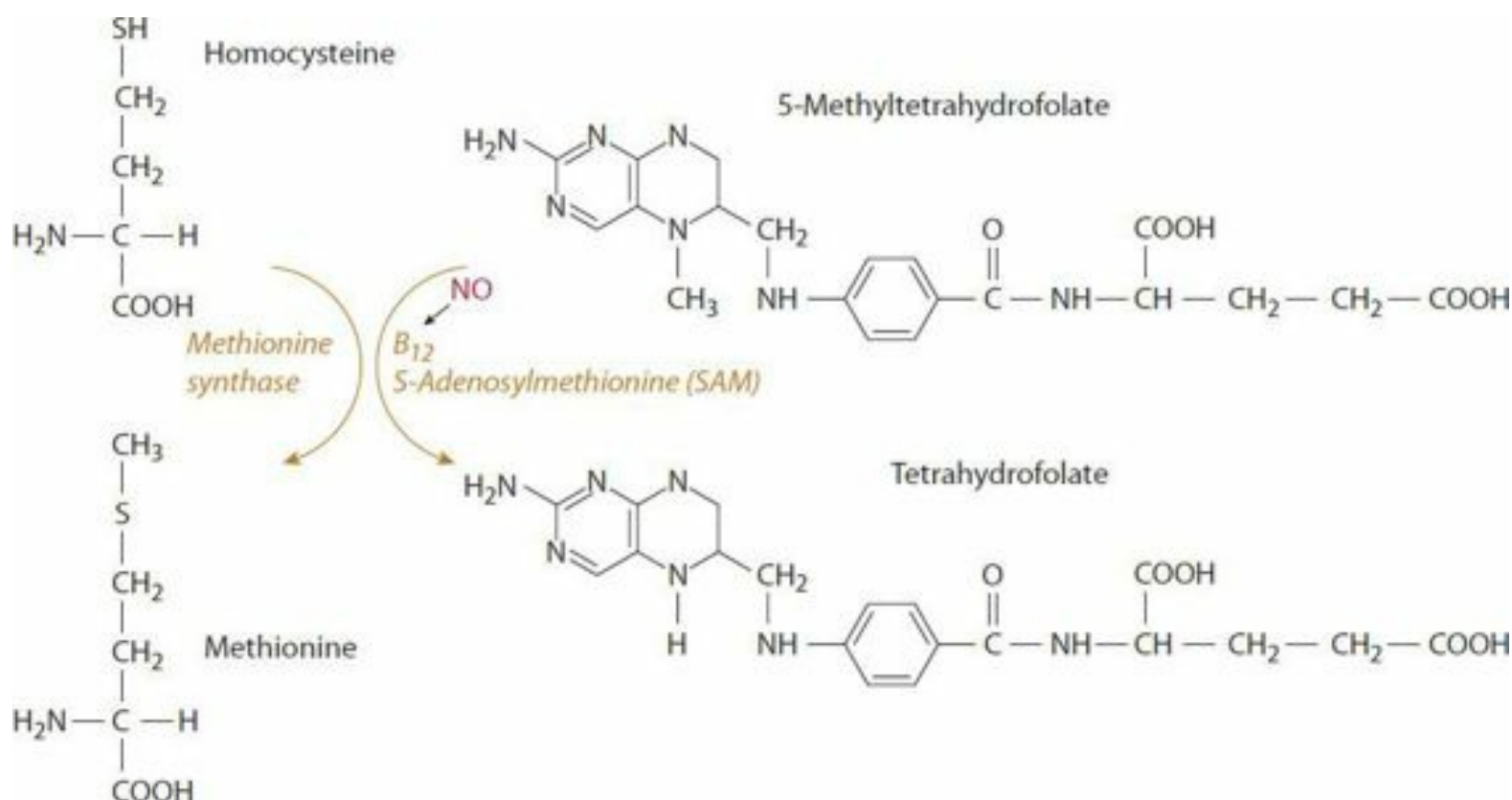


FIGURE 68–2. Hematologic effects of exposure to nitrous oxide (NO) resemble those characteristic of pernicious anemia and are related to oxidation and inactivation of vitamin B₁₂. The irreversible blockade of methionine synthase impairs DNA synthesis and myelin production.

Neurologic Effects

Disabling polyneuropathy in health care workers who habitually abused nitrous oxide was first described in 1978.²⁶ This neurologic disorder improved slowly when the patients abstained from further nitrous oxide abuse. This neuropathy is clinically indistinguishable from subacute combined degeneration of the spinal cord associated with pernicious anemia.⁴⁵ The syndrome of nitrous oxide neuropathy is characterized by sensorimotor polyneuropathy, often combined with signs of posterior and lateral spinal cord involvement. Signs and symptoms include numbness and paresthesias in the extremities, weakness, and truncal ataxia. Neurologic changes usually develop only after several months of frequent exposure to nitrous oxide, although neurologic manifestations may develop within days of use in patients with subclinical cyanocobalamin deficiency. Those at risk include individuals who chronically abuse the gas and those who are occupationally exposed for prolonged periods to environments contaminated with high concentrations of nitrous oxide.⁵ Animal studies demonstrate that methionine synthase is inactivated by exposure to greater than 1000 parts per million (ppm) of nitrous oxide. This scenario is highly unlikely in modern ORs, where inhalational anesthetics are scavenged, but it may occur in poorly ventilated dental offices. This problem probably is markedly underdiagnosed because the neurologic changes that occur in mild cases mimic other more common neurologic conditions.⁹

Immunologic Effects

Recently, concern has been raised regarding detrimental effects of nitrous oxide on immune function. Nitrous oxide is associated with varied effects on immune function with evidence of decreased proliferation of human peripheral blood mononuclear cells and decreased neutrophil chemotaxis. A large multicenter controlled trial (ENIGMA) evaluated 2050 patients undergoing major surgery, comparing a group receiving 80% oxygen/20% nitrogen with those receiving 70% nitrous oxide/30% oxygen.³⁵ On subgroup analysis, the group receiving nitrous oxide demonstrated significant increases in the incidence of wound infection, pneumonia, and atelectasis. Because the differences may be related to beneficial effects of high inspired oxygen concentrations rather than detrimental effects of nitrous oxide, follow-up studies (ENIGMA II) are being done to address these methodologic concerns.³⁶

Cardiovascular Effects

The use of nitrous oxide is associated with an increased risk of cardiovascular complications in the perioperative period. Serum homocysteine concentrations increase for days after operative exposure to nitrous oxide.³⁴ This occurs because conversion of homocysteine to methionine is methionine synthase dependent. Increased homocysteine concentrations are an independent risk factor for cardiac morbidity. In the ENIGMA trial, patients anesthetized with nitrous oxide had

significantly greater incidence of electrocardiographic abnormalities and cardiac enzyme elevations.³⁶ There was also a trend to a higher incidence of confirmed myocardial infarction in the nitrous oxide group as well as an increased long-term risk of myocardial infarction.²⁷

Treatment

General. Removal of the acutely affected person from the toxic environment should be the initial intervention. Individuals who have developed toxicity from occupational exposure or abuse of the gas should be educated about the relationship between their activities and their clinical findings.

Specific. Vitamin B₁₂ may help patients with a vitamin B₁₂ deficiency who develop megaloblastic anemia and neurologic dysfunction after brief exposure to nitrous oxide, but it is not beneficial in patients who have toxicity resulting from more chronic exposure. The reason for the ineffectiveness of vitamin B₁₂ in this situation is uncertain.

The bone marrow abnormalities associated with nitrous oxide toxicity may be reversed by administration of a single 30 mg intravenous (IV) dose of folinic acid (Antidotes in Depth: A10). Methionine has also been successfully used when vitamin B₁₂ treatment alone has failed to improve neurologic symptoms.⁴⁷

HALOGENATED HYDROCARBONS

The inhaled anesthetics were initially considered biochemically inert. Toxicity after administration was poorly explained, although it is now clear that the metabolites of the inhalational anesthetics are responsible for acute and chronic toxicities, which are predictable and dose related.

Halothane Hepatitis

Two distinct types of hepatotoxicity are associated with halothane use. The first is a mild dysfunction that develops in approximately 20% of exposed patients. Patients often are asymptomatic but exhibit modestly elevated serum aminotransferase concentrations within a few days of anesthetic exposure. Recovery is complete.²² In contrast, a life-threatening hepatitis occurs in approximately 1 in 10,000 exposed patients and produces fatal massive hepatic necrosis in 1 in 35,000 patients.⁴⁸ Because the histologic findings of massive hepatocellular necrosis are indistinguishable from many of the causes of viral hepatitis,⁵² differentiating halothane hepatitis from other causes of hepatitis in the postoperative period is difficult without definitive serologic studies. Jaundice, which is common after anesthesia and surgery, usually results from factors such as preexisting liver disease, blood transfusion, sepsis, or other causes of hepatitis. Thus, halothane hepatitis is a diagnosis of exclusion or inclusion based on the chemical history.

Several studies report an association between multiple exposures to halothane and subsequent development of hepatitis.^{37,51,56} In one study, 95% of cases of halothane hepatitis occurred after repeat exposures, 55% of which involved reexposure within 4 weeks.⁵⁶ Under these circumstances, hepatic dysfunction usually is more severe, and the latency before clinical presentation usually is shorter than when the syndrome develops after initial exposure to halothane.⁵¹

Obesity is a risk factor commonly implicated in halothane hepatotoxicity.^{1,53} Increased fat stores may act as a “reservoir” for halothane, with slow and prolonged release into the circulation and subsequent increase in production of potentially hepatotoxic metabolites.

Most cases of halothane hepatitis occur in middle-aged patients, with women having twice the risk.²² Genetic factors may play a role in some patients, as indicated by a report of this syndrome in three pairs of related Mexican women.²¹

Mechanism of Toxicity. Halothane is the most extensively metabolized inhalational anesthetic. Approximately 20% of the absorbed anesthetic undergoes oxidative metabolism, principally by CYP2E1 in the liver, to trifluoroacetic acid. Reduction to trifluorochloroethane and difluorochloroethylene is a minor route of halothane metabolism that requires the absence of oxygen and the presence of an electron donor (Fig. 68–3). These volatile metabolites are free radicals, which may directly produce acute hepatic toxicity by irreversibly binding to and destroying hepatocellular structures. Alternatively, by acting as haptens, they may trigger an immune-mediated hypersensitivity response.^{41,54} The high percentage of patients with halothane hepatitis who had recent reexposure is most consistent with the latter mechanism in which the first exposure primes the development of antibodies to a haptenized protein.²²

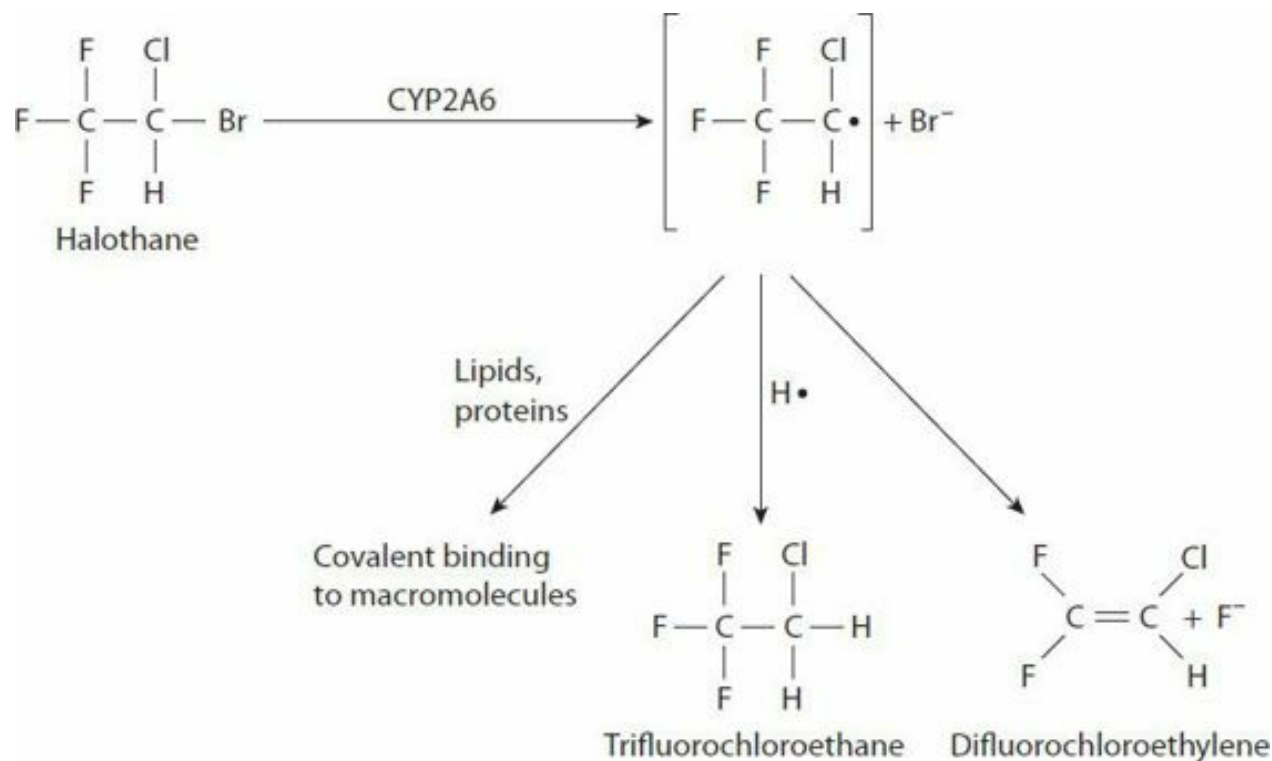


FIGURE 68–3. Reductive metabolism of halothane results in the formation of a reactive metabolite that may directly bind macromolecules and create neoantigens or undergo further metabolism to trifluorochloroethane and difluorochloroethylene. CYP = cytochrome P450.

The use of halothane for inhalational anesthesia has markedly decreased in North America with the widespread availability of newer, safer halogenated anesthetics. Halothane is still widely used in some countries because it is inexpensive and provides a smooth induction of anesthesia.

Isoflurane and desflurane are pungent gases that can be airway irritants. Isoflurane, desflurane, and sevoflurane all appear to have low hepatotoxic potential. An immune form of hepatitis has been reported with all anesthetics except sevoflurane. Cross-sensitivity may exist, such that prior exposure to one anesthetic triggers hepatotoxicity upon subsequent exposure to a different anesthetic.

Nephrotoxicity

The kidneys are the only other organ at risk for toxicity from modern inhalational anesthetics. Methoxyflurane is an anesthetic that was introduced in 1962. By 1966, it was linked to the development of vasopressin-resistant polyuric renal insufficiency (nephrogenic diabetes insipidus) in 16 of 94 patients receiving prolonged methoxyflurane anesthesia for abdominal surgery¹³ (Chap. 19). Polyuria was associated with a negative fluid balance, elevations of serum sodium and urea nitrogen concentrations, osmolality, and a fixed urinary osmolality approximating that of serum. Kidney abnormalities lasted from 10 to 20 days in most patients but persisted for more than one year in three patients. Subsequent studies demonstrated that kidney toxicity was caused by inorganic fluoride (F^-) released during biotransformation of methoxyflurane.⁵⁰ The risk of toxicity was highly correlated with both the total dose of methoxyflurane (concentration times duration) and the peak serum F^- concentration.¹² The nephrotoxic serum F^- concentration is 50 to 60 $\mu\text{mol/L}$.¹² The factors that enhance biotransformation such as obesity and enzyme induction also increase the risk of toxicity. Although the precise mechanism by which fluoride produces its toxic effect on the kidneys is not clear, one hypothesis is that fluoride inhibits adenylate cyclase, thereby interfering with the normal action of antidiuretic hormone on the distal convoluted tubules.

Although methoxyflurane is no longer used, lessons learned regarding its toxicity are applied when evaluating the nephrotoxic potential of other fluorinated anesthetics. Of the currently used anesthetics (halothane, isoflurane, desflurane, sevoflurane), only sevoflurane undergoes biotransformation by defluorination.

Approximately 5% of sevoflurane is metabolized. This process occasionally results in sufficient serum F^- concentrations to produce transient decreases in urine-concentrating ability.²⁴ However, clinically evident renal impairment almost never occurs with use of sevoflurane.¹⁸ In volunteer studies, exposure to sevoflurane that resulted in high serum fluoride concentrations did not result in any urine-concentrating defects. In patients with chronic kidney disease (CKD), the risk of postoperative kidney dysfunction is believed to be worse with exposure to inhalational anesthetics. However, studies demonstrate that deterioration of kidney function does not occur after exposure to desflurane and isoflurane,³¹ possibly because intrarenal fluoride concentrations are more important than serum fluoride concentrations in the development of nephrotoxicity.

Sevoflurane reacts with the alkali within carbon dioxide absorbers to produce several degradation products, including a vinyl ether called compound A ($\text{CF}_2\text{C}(\text{CF}_3)\text{OCH}_2\text{F}$). Compound A causes renal tubular necrosis in rats, especially at the corticomedullary junction.^{23,55} The extent of nephrotoxicity is determined by both the concentration of compound A and the duration of exposure. Compound A is also conjugated, and its breakdown products are nephrotoxic.

Technical Issues. Extensive clinical experience with several million patients who were exposed to sevoflurane and 4000 closely studied volunteers failed to demonstrate nephrotoxicity.³¹ Higher concentrations of compound A are generated during low-flow anesthesia, use of high concentrations of sevoflurane, and increased temperature conditions. A high fresh-gas flow rate dilutes the concentration of compound A. Concern that higher compound A concentrations are generated when a low fresh-gas flow rate (eg, <2 L/min) is used in a closed circuit led to the current sevoflurane package labeling, which warns against fresh-gas flow rates below 2 L/min in a circle absorber system.³⁰

Some controversy exists regarding the safety of low-flow sevoflurane anesthesia. Although there have been no clinical reports of sevoflurane-induced nephrotoxicity as measured by changes in blood urea nitrogen (BUN), serum creatinine, or creatinine clearance, clinical data demonstrate transient nephrotoxicity when more subtle measurements of glomerular and tubular function are used.^{16,18,20} For example, when young, healthy patients without underlying kidney disease were anesthetized with low-flow sevoflurane for a mean of 6.7 hours, transient but statistically significant increases in urinary glucose and protein excretion were documented without any changes in BUN, creatinine, or creatinine clearance.²⁰ The clinical significance of such transient abnormalities in kidney function is uncertain. Regardless, it seems prudent to avoid the practice of low-flow sevoflurane in patients with CKD until clinical data document safety. Newer carbon dioxide absorbents that are free of strong alkali are now available to decrease generation of compound A.

INHALATIONAL ANESTHETIC-RELATED CARBON MONOXIDE POISONING

Pharmacology

Desflurane and isoflurane contain a difluoromethoxy moiety that can be degraded to carbon monoxide (CO). This process occasionally results in patient exposure to toxic CO concentrations. CO production resulting from intraoperative desflurane degradation has been reported with carboxyhemoglobin levels as high as 36%.⁷ Although there was no evidence of patient harm in this case, morbidity or mortality could occur at this level in patients with concurrent disease ([Chap. 125](#)). The true incidence of CO exposure during clinical anesthesia is unknown. Routine detection of intraoperative CO exposure is now possible using multiwavelength pulse cooximeters, but these more expensive devices are not yet widely used, and conventional pulse oximeters that are routinely used in ORs cannot detect CO.⁸

Carbon monoxide production is inversely proportional to the water content of CO_2 absorbents. Soda lime (a granular mixture of calcium, sodium, and potassium hydroxide) is the most frequently used CO_2 absorbent. It is sold wet (13%–15% water by weight), but may dry with high gas-inflow rates. Higher concentrations of CO are most apt to be present during the first case after a weekend because of drying of CO_2 absorbent from a continuous inflow of dry oxygen over the weekend if the anesthesia machine has not been used.¹⁷

Other factors influence the concentration of CO that may result from anesthetic degradation, including temperature (higher temperature increases CO formation), type of absorbent, choice of anesthetic, and concentration of anesthetic. Strong alkalis, such as potassium and sodium hydroxide, initiate the reaction that forms CO.

Mass spectrometry (available in some ORs) cannot directly detect CO because its molecular weight is equivalent to that of nitrogen, a gas usually present in much greater amounts. In addition, detection of CO by fragmentation products is not possible by mass spectrometry because CO_2 is present in greater amounts and has similar fragmentation products.

Unfortunately, the diagnosis of CO poisoning during anesthesia is difficult because the main clinical features of toxicity are masked by anesthesia, and no routinely available means can identify CO within the breathing circuit or detect when the CO_2 absorbent has been desiccated. Delayed neurologic sequelae from intraoperative CO poisoning are likely missed on the anesthesiologist's postoperative patient evaluation.⁵⁸

The product labels of desflurane and isoflurane have been altered to include a precaution that the CO_2 absorbent should be replaced when a practitioner suspects the absorbent is desiccated. However, the problem associated with this warning is the lack of a reliable method for determining when the absorbent is fully or partially desiccated.

If an anesthetic machine is found with the fresh-gas flow on at the beginning of the day, a reasonable practice is to replace the absorbent. Newer CO_2 absorbents that are less likely to degrade anesthetics are now available. These newer absorbents have decreased amounts of strong bases.

LONG-TERM USE OF HALOGENATED ANESTHETICS IN INTENSIVE CARE UNITS

Halogenated anesthetics have been used since the 1990s in intensive care units (ICUs) for long-term sedation of patients receiving mechanical ventilation since the 1990s and more recently as part of the treatment for patients with refractory status epilepticus. Use has been limited by concerns regarding atmospheric pollution and high costs (because of a lack of rebreathing systems in the ICU). The development of anesthetic-conserving devices for use with ICU ventilators has addressed these issues. Potential advantages include more rapid wakeup and shorter times to extubation with minimal risk of toxicity.³²

Clinical studies report the use of isoflurane and sevoflurane for ICU sedation. In one study, 19 patients were mechanically ventilated for more than 24 hours in the ICU with sevoflurane used for sedation.³² Toxic effects of sevoflurane were not found even though serum fluoride concentrations often exceeded 50 μmol (the concentration suggested to be the nephrotoxic threshold).¹²

Isoflurane is being used as a first-choice for long-term sedation during mechanical ventilation in some ICUs. Experimental models demonstrate that isoflurane is potentially neurotoxic, primarily through induction of neuronal apoptosis. In rats, isoflurane substantially decreases local glucose utilization in various brain regions, including the thalamus.

Reversible psychomotor dysfunction was reported in 3.6% of 335 patients who received isoflurane for more than 12 hours as a primary sedative during mechanical ventilation in a general ICU.⁴ Psychomotor dysfunction occurred in 42% of patients age 4 years or younger but in only 1.3% of patients older than 4 years. The psychomotor dysfunction only occurred in patients who received the isoflurane for greater than 24 hours.

Isoflurane is an alternate treatment for patients with refractory status epilepticus. Reversible magnetic resonance imaging (MRI) abnormalities developed in two patients who received inhaled isoflurane for a prolonged time (35 and 85 days).¹⁹ Serial MRIs demonstrated the development of hyperintense T2 signals involving the medulla, cerebellar cortex, deep cerebellar nuclei, thalamus, and hypothalamus bilaterally. These abnormalities improved after discontinuation of the isoflurane.

CHRONIC EXPOSURE TO WASTE ANESTHETIC GASES

Waste anesthetic gases are defined as inhalation gases and vapors that are released into work areas associated with or adjacent to the administration of a gas or volatile liquid for anesthetic purposes. Because anesthesia machines are not airtight and consist of hundreds of parts, it is inevitable that clinical personnel will be exposed to waste anesthetic gases. Exposure to waste anesthetic gas produces short- and long-term effects. Common short-term effects are lethargy and fatigue in staff members who are exposed to significant quantities of waste anesthetic gas. Chronic long-term effects correlate with the concentration of gas and duration of exposure. Animal studies demonstrate that exposure to high concentrations of nitrous oxide and halogenated xenobiotics can cause cellular, mutagenic, carcinogenic, and teratogenic effects.

The US government has been involved with the regulation and management of waste anesthetic gas since 1970. The OR environment in this country is highly regulated and monitored, but exposure limits vary in other countries and can exceed the concentrations permitted in the United States. Even in a modern working environment with low-leakage anesthesia machines, scavenging systems, and high room ventilation exchange rates, exposure to inhalational anesthetics could not be kept below acceptable threshold concentrations in all cases. However, a cause-and-effect relationship between human exposure to waste anesthetic gases and poor reproductive outcomes could not be identified in an analysis requested by the American Society of Anesthesiologists.¹⁰

Dentists and dental assistants are often exposed to greater concentrations of waste anesthetic gases than are individuals working in well-vented ORs. An epidemiologic survey compared 15,000 dentists who used nitrous oxide in their practices to 15,000 dentists who did not.⁹ A 1.2- to 1.8-fold increase in hepatic, kidney, and neurologic disease was found in the dentists and their chair-side assistants who were chronically exposed to trace concentrations of nitrous oxide. For those with heavy office use of nitrous oxide, a fourfold increase in the incidence of neurologic complaints compared with the nonexposed group was observed. Female dental assistants who were exposed to nitrous oxide had a two- to threefold increase in spontaneous abortion rates, reduced fertility, and a higher rate of congenital abnormalities in their offspring.⁹

ABUSE OF HALOGENATED VOLATILE ANESTHETICS

Fatal or life-threatening complications occur when halogenated inhalational anesthetics are used for nonanesthetic purposes such as suicide attempts, mood elevation, and topical treatment of herpes simplex labialis. When ingested, halothane usually produces gastroenteritis with vomiting followed by depressed levels of consciousness, hypotension, shallow breathing, bradycardia with extrasystoles, and acute respiratory distress syndrome (ARDS). Coma usually resolves within

72 hours.^{14,57} The diagnosis should be suspected when these features occur in a patient with the sweet or fruity odor of halothane on the breath. Supportive care, including endotracheal intubation and nasogastric lavage, should be provided. Full recovery can occur without permanent organ injury.

Intravenous injections of halothane may occur as a suicide attempt or unintentionally during anesthesia induction. A young patient who was found unconscious and hypotensive with ARDS after self-administered IV injection of halothane was not successfully resuscitated.⁶ A 16 year-old girl received an unintentional IV injection of 2.5 mL of halothane during anesthesia induction.⁴⁹ She became unconscious and apneic within 30 seconds but began to awaken within 2 to 3 minutes. Four hours later, she developed ARDS but subsequently made a full recovery.

Transient coma and apnea probably are secondary to a halothane bolus reaching the brain on its first pass through the bloodstream. Redistribution then occurs, explaining the rapid awakening. The ARDS that develops after injection of halothane may result from a direct toxic effect of high concentrations of this hydrocarbon on the pulmonary vascular bed. After injection, the anesthetic likely travels as a bolus during the first passage through the pulmonary circulation because of its poor solubility in blood.

Hospital personnel are involved in most reported cases of halothane abuse by inhalation.⁴⁶ Inhalation of halothane produces a pleasurable sensation similar to that described with glue sniffing ([Chap. 84](#)). Death may result from upper airway obstruction after loss of consciousness or from dysrhythmias. Death occurred in a student nurse anesthetist suggested to have applied a full 250 mL bottle of enflurane over 3 hours to “cold sores” on her lower lip.²⁸

SUMMARY

- Inhalational anesthetics remain a popular choice for maintenance of anesthesia because of their safety and titratability.
- Toxicity is uncommon and can result from a variety of mechanisms.
- Health care practitioners who use these anesthetics should be knowledgeable about their pharmacology and potential toxicity.

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69 NEUROMUSCULAR BLOCKERS

Kenneth M. Sutin

HISTORY AND EPIDEMIOLOGY

Curare is the generic term for the resinous arrowhead poisons used to paralyze hunted animals.¹⁰⁴ The curare alkaloids are derived from the bark of the Strychnos vine, and the most potent alkaloids, the toxiferines, are derived from Strychnos toxifera. Fortunately for the hunters who used curare, ingestion of their prey did not cause paralysis. Sir Walter Raleigh discovered the use of curare in Guyana in 1595, and he was the first person to bring curare to Europe. Curare played a pivotal role in the discovery of the mechanism of neuromuscular transmission. In 1844, Claude Bernard placed a small piece of dry curare under the skin of a live frog and observed that the frog became limp and died.⁷ He performed an immediate autopsy and discovered that the heart was beating. Because direct muscle stimulation produced contraction but nerve stimulation did not, Bernard concluded that curare paralyzed the motor nerves. He later observed, however, that bathing the isolated nerve did not affect neuromuscular transmission, leading him to conclude: “Curare must act on the terminal plates of motor nerves.”¹⁵ Curare was also used by Nobel Laureate physiologists Charles Sherrington, John Eccles, and Bernard Katz to further elucidate neuromuscular physiology. Its first clinical use was described in 1878 when Hunter used curare to treat patients with tetanus and seizures.¹⁰⁴ In 1932, Raynard West used curare to reduce the muscular rigidity of hemiplegia.¹⁰⁴ The use of curare (d-tubocurarine) in anesthesia spanned almost 60 years until it was replaced by superior agents that caused less histamine release and hypotension.

More recent nonmedical uses of succinylcholine have been less benign.² The anesthesiologist Dr. Carl Coppolino was accused of murdering his wife in 1965 by succinylcholine injection.⁷⁰ In 1983, shortly after Dr. Michael Swango began his internship at Ohio State University Hospital, patients began dying inexplicably, and he was relieved of his duties.⁹⁷ After multiple residencies and jobs over 14 years, extending as far as Mnene Hospital in Zimbabwe, the prosecution secured Swango’s guilty plea for the murder of three victims. The toxicologic analysis of the remains of the 7 year-old victim revealed succinylcholine in the liver and gallbladder and its metabolite succinylmonocholine in multiple organs, which assisted in the Swango conviction.

With the advent of new modalities of drug delivery, toxicologists must be attuned to possible malicious intent. Emergency personnel responding to a 911 call observed the widow removing an insulin pump reservoir from her dead husband’s body with the stated intent to donate the costly equipment.⁴ A natural cause of death was presumed, yet surprisingly, forensic analysis revealed etomidate and laudanosine (a metabolite of atracurium) in the victim’s liver.

Understanding the pharmacokinetics of the depolarizing and nondepolarizing neuromuscular blockers (NMBs) improves care in the emergency department, intensive care unit (ICU), and operating room. Understanding and early recognition of the complications of each NMB limit associated morbidity and mortality.

MECHANISM OF NEUROMUSCULAR TRANSMISSION AND BLOCK

The purpose of an NMB is to selectively and reversibly inhibit transmission at the skeletal neuromuscular junction (NMJ). All NMBs possess at least one positively charged quaternary ammonium moiety that binds to the postsynaptic nicotinic acetylcholine (nACh) receptor at the NMJ, inhibiting its normal activation by acetylcholine (ACh). The nACh receptor is a ligand-gated ion channel that consists of four different protein subunits in a pentameric structure surrounding a central channel. The nACh receptor found in human skeletal muscle is present in two primary forms: a mature type found at the NMJ ($\alpha\beta\epsilon\delta$) or as a fetal (immature) type found on muscle at extrajunctional regions of the muscle fiber ($\alpha\alpha\beta\gamma\delta$). Before discussing the mechanism of neuromuscular block, it is first helpful to understand normal neuromuscular transmission and excitation–contraction coupling (Fig. 69–1).

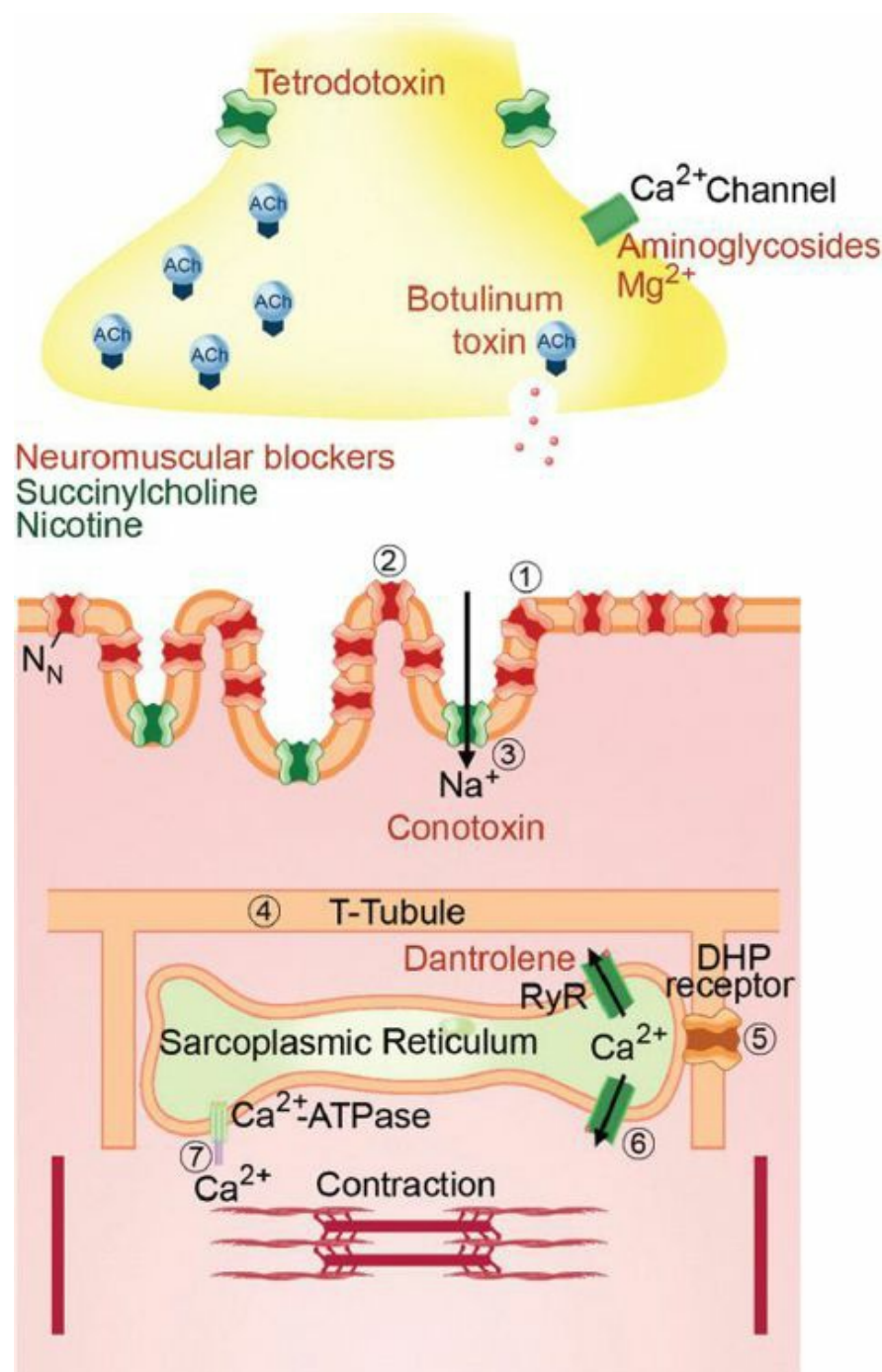


FIGURE 69–1. Excitation–contraction coupling in skeletal muscle. At the neuromuscular junction, acetylcholine (●) released from the presynaptic nerve terminal crosses the 50-nm synaptic cleft to reach the nicotinic acetylcholine (nACh) receptor (■). When agonist simultaneously occupies both receptor sites, this ion channel opens, becoming nonselectively permeable to monovalent cations, resulting in an influx of Na^{+} and an efflux of K^{+} . This produces local membrane depolarization (end plate potential), which, in turn, opens voltage-activated Na^{+} channels (■). A depolarization of sufficient amplitude generates a propagated muscle action potential (MAP), which is conducted along the muscle membrane and down the transverse (T) tubules. In the T tubule, the MAP triggers a voltage-activated calcium channel, the dihydropyridine receptor (DHP) (■), which then activates the skeletal muscle ryanodine receptor (RyR) channel (■). To allow the fastest activation of mammalian skeletal muscle, calcium diffusion is not necessary for activation of RYR-1; instead, there is a direct electrical (protein) linkage between the dihydropyridine receptor and the ryanodine receptor.²⁹ Active ATPase driven calcium reuptake terminates muscle contraction. Many factors influence the activity of the RYR-1 channel, including Ca^{2+} , Mg^{2+} , and anesthetic drugs such as inhalational anesthetics that accelerate Ca^{2+} release in persons susceptible to malignant hyperthermia. Antagonists such as conotoxin are red and agonists such as nicotine are green.

Therapeutic and toxicologic skeletal muscle paralysis may occur by several mechanisms. For example, tetrodotoxin blocks voltage-sensitive sodium channels, preventing action potential conduction in the motor neuron. On the other hand, botulinum toxin blocks ACh release from the presynaptic neuron by inhibiting the binding of ACh-containing vesicles to the neuronal membrane in the region of the synaptic cleft. Modulation of postsynaptic ACh receptor activity at the NMJ may produce paralysis by one of two mechanisms: depolarizing (phase I block) and nondepolarizing (phase II block). Succinylcholine is the only depolarizing neuromuscular blocker (DNMB) in current clinical use. Nicotine at high doses may also cause a depolarizing block. All other drugs discussed are nondepolarizing neuromuscular blockers (NDNMBs).

The process of depolarizing neuromuscular blockade requires several steps. First, two molecules of succinylcholine must bind to each α site of the nACh receptor. This action causes a prolonged open state of the nACh receptor ion channel. The initial depolarization generates a muscle action potential and usually causes brief contractions (fasciculations). In contrast to ACh, succinylcholine is not hydrolyzed efficiently by junctional (true) acetylcholinesterase (AChE); thus, the effect of succinylcholine lasts much longer than ACh. Persistence of succinylcholine at the ACh receptor causes a sustained local muscle endplate depolarization that, in turn, causes the voltage-gated sodium channel in the perijunctional region to remain in a prolonged inactive state, inducing a desensitization block. The muscle is temporarily refractory to presynaptic release of ACh (phase I block).

The NDNMBs cause skeletal muscle paralysis by competitively inhibiting the effects of ACh and thus preventing muscle depolarization. One molecule of an NDNMB bound to a single nACh receptor (also on the α site) is sufficient to competitively inhibit normal channel activation. Because the NDNMBs do not block voltage-gated sodium channels on the skeletal muscle membrane, direct electrical stimulation with a current sufficient to cause membrane depolarization will still elicit a muscular contraction. The NDNMBs are classified by duration of action as ultrashort, short, intermediate, and long. They are also classified by chemical structure as either a synthetic benzylisoquinolinium or an aminosteroid (Table 69–1).

TABLE 69–1. Pharmacology of Selected Neuromuscular Blockers

Generic Name	Class	Duration	Initial Dose (mg/kg) ^{a,b}	Onset (minutes) ^c	Clinical Duration (minutes) ^d
Succinylcholine	Depolarizer	Ultrashort	0.6–1	1–1.5	3–7
Atracurium	Nondepolarizer,	Intermediate	0.4	2–4	20–40
Cisatracurium	benzylisoquinolinium	Intermediate	0.1	2–4	20–40
Pancuronium	Nondepolarizer,	Long	0.1	3–6	60–90
Rocuronium	aminosteroid	Intermediate	0.6	1.5–3	30–40
Vecuronium		Intermediate	0.1	2–4	20–40
	Renal Excretion (%) ^e	Biliary Excretion (%) ^f	Metabolite	Histamine Release	Effect on Heart Rate
Succinylcholine	<10	Minimal	Succinic acid	Minimal	Bradycardia (rare)
Atracurium	5–10	Minimal	Laudanosine	Minimal	No
Cisatracurium	10–20	Minimal	Laudanosine	No	No
Pancuronium	40–60	10–20	3-Desacetyl-pancuronium ^g	No	Tachycardia
Rocuronium	10–20	50–70	No	No	Tachycardia at high dose
Vecuronium	15–25	40–70	3-Desacetyl-vecuronium ^h	No	No

^aCisatracurium is labeled as milligram of base per milliliter. Other drugs are labeled and packaged as milligram of salt per milliliter. ^bTypical initial dose is approximately $2 \times ED_{95}$ (mg/kg). ^cOnset is time from bolus to 100% block. ^dClinical duration is time from drug injection until 25% recovery of single twitch height. ^ePercent renal excretion in the first 24 hours of unchanged drug; if high, associated with prolongation of clinical effect. ^fPercent biliary excretion in first 24 hours of unchanged drug; if high, associated with prolongation of clinical effect. ^gActive metabolite.

Data from Donati F: Neuromuscular blocking drugs for the new millennium: current practice, future trends—comparative pharmacology of neuromuscular blocking drugs. *Anesth Analg*. 2000;90(suppl):S2–S6; McManus MC: Neuromuscular blockers in surgery and intensive care, part 1. *Am J Health Syst Pharm*. 2001;58:2287–2299; and Murray MJ, Cowen J, DeBlock H, et al: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med*. 2002;30:142–156.

NDNMBs also block nACh receptors on the prejunctional nerve terminal and inhibit ACh-stimulated ACh production and release⁸⁸ by blocking local autoregulation of available ACh. This effect reduces the available pool of ACh and augments the extent of neuromuscular block.⁹

PHARMACOKINETICS

The NMBs are highly water soluble and relatively insoluble in lipids. Thus, they are rapidly distributed in the extracellular space and very slowly permeate lipid membranes such as the gut, placenta, and the normal blood–brain barrier. For this reason, they are devoid of central nervous system (CNS) effects. Because these drugs distribute in the extracellular space, their dosage is based on ideal body mass. In obese patients, estimation of drug requirement according to total body mass results in the administration of an excessive dose.

The speed of onset of an NMB is inversely related to its molar potency (ie, ED_{95} expressed as moles NMB drug per kilogram body weight).^{52,53} Stated differently, the greater the affinity of the NDNMB for the ACh receptor, the fewer molecules per kilogram of tissue are required to produce a given degree of ACh receptor occupancy. Atracurium is the only

drug that does not follow this generalization because it is a mixture of 10 isomers, each having a different receptor affinity (cisatracurium consists of only one isomer).

In general, small, fast-contracting muscles such as the extraocular muscles are more susceptible to neuromuscular block than are larger, slower muscles such as the diaphragm. This is the so-called respiratory sparing effect. After an intravenous (IV) bolus of an NDNMB, paralysis of the diaphragm is coincident with paralysis of laryngeal muscles because high tissue perfusion results in rapid drug distribution and diffusion into the NMJ of all tissues.²¹ However, recovery from an NMB is fastest for the diaphragm and intercostal muscles; intermediate for the large muscles of the trunk and extremities; and slowest for the adductor pollicis, larynx, pharynx, and extraocular muscles.²¹

COMPLICATIONS OF NEUROMUSCULAR BLOCKERS

Complications associated with the use of NMBs include (a) problems associated with the care of a paralyzed patient (eg, undetected hypoventilation resulting from ventilator or airway problems, impaired ability to monitor neurologic function, unintentional patient awareness, peripheral nerve injury, deep vein thrombosis, and skin breakdown); (b) immediate side effects; and (c) effects occurring after prolonged drug exposure.^{77,78}

Consciousness

Even though NMB drugs do not affect consciousness, misconceptions about these drugs persist.⁶⁷ The pupillary light reflex, an important indicator of midbrain function, is preserved in healthy subjects who receive NDNMBs³⁸ because pupillary function is mediated by muscarinic cholinergic receptors, for which the NMBs have no affinity.

Histamine Release

Muscle relaxants may elicit dose- and injection rate-related nonimmunologic (non-IgE-mediated) histamine release from tissue mast cells by an uncertain mechanism (Table 69–1). The drugs most commonly associated with histamine release are atracurium and succinylcholine.⁷³

Anaphylaxis

Perioperatively, anaphylactic reactions are rare, with an incidence of 1:3500 to 1:20,000, and up to 60% are related to NMBs.⁷³ Rocuronium is responsible for 43% and succinylcholine for 23% of all NMB-associated anaphylaxis. In up to half of these patients, there is no prior exposure to an NMB, and cross-sensitization by another allergen is the likely explanation.⁶⁰ Pancuronium is the drug that is least associated with serious allergic reactions.¹⁰³

Control of Respiration

At subparalyzing doses, NDNMBs blunt the hypoxic ventilatory response (HVR) but not the ventilatory response to hypercapnia.^{26,27} HVR returns to normal when chemical paralysis is completely reversed. Hypoventilation resulting from blunting of the HVR, especially when combined with the residual effects of other drugs used during anesthesia (eg, opioids or inhalational anesthetics), may cause delayed respiratory failure (eg, after general anesthesia).

Autonomic Side Effects

Nicotinic ACh receptors found in autonomic ganglia, similar to those at the NMJ, are pentamers composed of α and β subunits. In general, they are less susceptible to block by NMBs.⁶⁸ There is one notable exception. At the same dose that produces neuromuscular block, tubocurarine also blocks nACh receptors at the parasympathetic ganglia, causing tachycardia, and at the sympathetic ganglia, blunting the sympathetic response.⁹² In combination with tubocurarine-related histamine release, the sympathetic block may cause significant hypotension, especially in patients with heart failure or hypovolemia.⁹ This is an important reason why tubocurarine is no longer available in the United States.

The muscarinic receptors (M_1 – M_5) are members of the seven-transmembrane G-protein–coupled receptor family. As such, they are structurally unique and mostly unaffected by NMBs. At clinical doses, pancuronium elicits dose- and injection rate–related increases in heart rate, blood pressure, cardiac output, and sympathetic tone.^{22,93,98} This is attributed to a selective block of parasympathetic transmission at the cardiac muscarinic receptors (atropinelike effect),⁹³ block of presynaptic (feedback) muscarinic receptors at sympathetic nerve terminals, and perhaps an indirect norepinephrine-releasing effect at postganglionic fibers.²²

Dysrhythmias, including bradycardia, junctional rhythms, ventricular dysrhythmias, and cardiac arrest, occur rarely after use of succinylcholine. Dysrhythmias most likely result from stimulation of the cardiac muscarinic receptors and can be prevented by pretreatment with 15 to 20 μ g/kg IV of atropine. Bradycardia is uncommon, but it may be especially severe

in children during anesthetic induction when large or repeated doses of succinylcholine are given.

Interactions of Neuromuscular Blockers with Other Xenobiotics and Pathologic Conditions

NMBs have significant interactions with many xenobiotics and coexisting medical conditions. These interactions may affect the neuromuscular system at any level, from the CNS to the muscle itself^{84,102} (Table 69–2). In most neuromuscular diseases, such as muscular dystrophy, Guillain-Barré syndrome, myasthenia gravis, and postpolio syndrome, the sensitivity to NDNMB is increased, so a small dose of NMB produces a profound degree of block.^{1,11,40} However, persons with myasthenia gravis typically demonstrate resistance to the effects of succinylcholine.^{1,11} In individuals with myopathy in whom the specific cause is not yet known, it is prudent to avoid succinylcholine because of the possible sensitivity to malignant hyperthermia (MH), hyperkalemia, or rhabdomyolysis; in place of succinylcholine, a short-acting NDNMB can be used (to lessen the chance of prolonged weakness).

TABLE 69–2. Effect of Prior Administration of Xenobiotics on Subsequent Response to Succinylcholine or Nondepolarizing Neuromuscular Blockers

<i>Antibiotic</i>	<i>Response to Succinylcholine</i>	<i>Response to Nondepolarizer</i>	<i>Comments</i>
Aminoglycosides (eg, amikacin, gentamicin)	Potentiates	Potentiates	Dose-related decrease in presynaptic ACh release. May decrease postjunctional response to ACh. Partially reversible with calcium administration. Effect of neostigmine unpredictable.
Anticholinesterase, peripheral acting: neostigmine, edrophonium	Prolongs succinylcholine (except edrophonium)	No effect	Neostigmine, pyridostigmine, and physostigmine inhibit plasma AChE and prolong succinylcholine block. Edrophonium does not inhibit plasma cholinesterase.
Anticholinesterase, centrally acting: donepezil	Potentiates		Inhibits AChE (junctional >> plasma); long half-life (70 hours).
β -Adrenergic antagonist: propranolol	Potentiates in cats, effects in humans uncertain	Potentiates	When given alone, may unmask myasthenic syndrome. Blocks ACh binding at postsynaptic membrane. Reversal of block with neostigmine may cause severe bradycardia.
β -Adrenergic antagonist: esmolol	Mild prolongation	Slows onset of rocuronium	Competes for PChE.
Botulinum toxin	?	Early potentiation, delayed resistance	Acutely, subclinical systemic denervation leads to hypersensitivity.
Calcium channel blockers	Potentiates	Potentiates	Causes calcium channel block pre- and postjunctionally. Verapamil has local cholinesterase inhibitor effect on nerve. May inhibit block reversal by cholinesterase inhibitor.
Carbamazepine	?	Inhibits, shortened duration	Chronic therapy causes resistance to NDNM, except for atracurium.
Cardioactive steroids	More prone to cardiac dysrhythmias	Pancuronium increases catecholamines and may cause dysrhythmias	
Dantrolene	?	Potentiates	Blocks excitation-contraction coupling by blocking ryanodine receptor channel in sarcoplasmic reticulum of skeletal muscle.
Furosemide <10 μ g/kg 1–4 mg/kg	Potentiates/inhibits	Potentiates/inhibits	Biphasic dose response in cats: protein kinase inhibition at low doses and phosphodiesterase inhibition at high doses. Diuretic-related hypokalemia potentiates pancuronium in cats.
Glucocorticoids	?	Inhibits	Chronic steroid use induces resistance to pancuronium and decrease plasma cholinesterase activity by 50%. Steroids \pm NDNM associated with myopathies.
Inhalational anesthetics: isoflurane	Potentiates	Potentiates	Decrease CNS activity and potentiates NMB in anesthetic doses: dependent fashion (postsynaptic and muscle effects). Halothane causes less muscle relaxation than isoflurane.
Lidocaine	Potentiates	Low-dose potentiates block. High-dose inhibits nerve terminals and blocks ACh binding site at postsynaptic membrane.	The fast Na^+ channel blockers decrease action potential propagation, ACh release, postsynaptic membrane sensitivity, and muscle excitability. Weak inhibitor of PChE.
Lithium carbonate	Prolongs onset and duration	Prolongs effect of pancuronium	Inhibits synthesis and release of ACh. Lithium alone may cause myasthenic reaction.
Magnesium	Potentiates; may block fasciculations	Potentiates; may also prolong block	Decreases prejunctional ACh release, postjunctional membrane sensitivity, and muscle excitability.
NDNM: pancuronium, vecuronium, rocuronium	"Precurarization" with NDNM shortens the onset and decreases side effects of succinylcholine. Pancuronium increases block duration.	Chronic NDNM induces resistance to their effect. Mixing different NDNMs may cause greater than additive effects, especially combining pancuronium with tubocurarine or metocurine.	Prior NDNM inhibits plasma AChE and prolongs mivacurium and succinylcholine block. Rank order: pancuronium > vecuronium > atracurium. Heterozygote for atypical PChE may develop phase II block when given succinylcholine and pancuronium.
Organic phosphorus compounds	Potentiates	?	Irreversible PChE inhibitor. May totally block enzyme activity.
Phenelzine (MAOI)	Prolongs	?	Decreases PChE activity.
Phenytoin	?	Resistant, shortened duration	Acutely, potentiates NDNM paralysis. With chronic use (except for atracurium), phenytoin induces resistance to NDNM and increases drug metabolism. This increases the initial dose and decreases the repeat dosing interval.
Polypeptide antibiotics: polymyxin	Potentiates	Potentiates	May cause severe weakness. May induce postsynaptic neuromuscular block. Neostigmine increases block.

Succinylcholine	Small initial dose of succinylcholine may be used to limit muscular fasciculations.	Pancuronium and vecuronium slightly prolonged by prior succinylcholine	
Theophylline		Inhibits	Pancuronium and theophylline may increase cardiac dysrhythmias.
Cyclic antidepressants (CA)			Pancuronium and CA may cause cardiac dysrhythmias due to sympathetic effects.

ACh = acetylcholine; AChE = acetylcholinesterase; CA = cyclic antidepressant; MAOI = monoamine oxidase inhibitor; NDNMB = nondepolarizing neuromuscular blocker; NMB = neuromuscular blocker; NMJ = neuromuscular junction. Data from Crowe S, Collins L: Succinethonium and donepezil: a cause of prolonged paralysis. *Anesthesiology*. 2003;98:574–575; Raciuno F, Grandi L, Saliven P, et al: Sensitivity to vecuronium after botulinum toxin administration. *J Neurosurg Anesthesiol*. 1997;9:140–153; Fleming NW, Macres S, Antognini JF, Vengco J: Neuromuscular blocking action of succinethonium after antagonism of vecuronium by edrophonium, pyridostigmine or neostigmine. *Br J Anaesth*. 1996;77:492–495; Kaeser HE: Drug-induced myasthenic syndromes. *Acta Neurol Scand Suppl*. 1984;100:39–47; Kato M, Hashimoto Y, Horinouchi T, et al: Inhibition of human plasma cholinesterase and erythrocyte acetylcholinesterase by nondepolarizing neuromuscular blocking agents. *J Anesth*. 2000;14:30–34; Ostergaard O, Engback J, Viby-Mogensen J: Adverse reactions and interactions of the neuromuscular blocking drugs. *Med Toxicol Adverse Drug Exp*. 1989; 4:351–368; and Viby-Mogensen J: Interaction of other drugs with muscle relaxants. In: Katz RL, ed. *Muscle Relaxants: Basic and Clinical Aspects*. New York: Grune & Stratton; 1985:233–256.

Many pathologic conditions potentiate the duration or intensity of NDNMBs, such as respiratory acidosis, hypokalemia, hypocalcemia, hypermagnesemia, hypophosphatemia, hypothermia, shock, and liver or kidney failure.⁸⁷ Alternatively, sepsis and inflammatory conditions are associated with mild resistance to the effects of NDNMBs.⁷⁹

SUCCINYLCHOLINE

Pharmacology

Succinylcholine is a bis-quaternary ammonium ion composed of two molecules of ACh joined end to end at the acetate groups.²⁴ After a conventional IV induction dose (1 mg/kg), typical serum concentrations are approximately 62 µg/mL.⁸¹

Succinylcholine is hydrolyzed primarily by plasma cholinesterase (PChE, also known as pseudocholinesterase or butyrylcholinesterase; BChE, EC 3.1.1.8) and to a slight extent by alkaline hydrolysis. Hydrolysis is a two-step reaction; first succinylmonocholine and choline are formed, and then succinic acid and choline are formed (the latter two are normal products of intermediary metabolism). The first reaction is approximately six times faster than the second reaction. Less than 3% of the administered dose is excreted unchanged in the urine.³⁶ After an IV bolus, the plasma succinylcholine concentration increases abruptly, and there is a rapid onset of NMJ block. Later, the plasma succinylcholine concentration undergoes a rapid decline as a result of drug redistribution to extravascular tissues and hydrolysis in plasma. Finally, succinylcholine leaves the NMJ to reenter the plasma as a result of reversal of the concentration gradient.^{35,48}

Succinylcholine 1 mg/kg IV usually increases cerebral blood flow, cortical electrical activity, intracranial pressure,⁵⁴ and intraocular pressure, especially in lightly anesthetized patients. These effects, when they occur, are usually modest and of no clinical significance.

Toxicology

The important adverse drug reactions associated with succinylcholine include anaphylaxis, prolonged drug effect, hyperkalemia, acute rhabdomyolysis in patients with muscular dystrophy, MH in susceptible patients, muscle spasms or trismus in patients with myotonia congenita, and cardiac dysrhythmias.

Prolonged Effect

The effects of succinylcholine may last for several hours if metabolism is slowed because of decreased PChE concentration, abnormal PChE activity (genetic variant or drug inhibition), or a phase II block.¹⁷ Acquired PChE deficiency may be caused by hepatic disease, malnutrition, plasmapheresis, or pregnancy.¹⁷ Inactivation of PChE may be caused by fluoride poisoning, organic phosphorus compounds, and carbamates. However, even with only 20% to 30% of normal PChE activity, the clinical duration of succinylcholine is less than doubled.³¹

Many genetic variants of PChE are known. The most common atypical PChE (atypical type, homozygous; incidence 1:3000) can be assayed by its resistance to inhibition by the local anesthetic dibucaine.⁸⁵ A history of uneventful exposure to succinylcholine excludes the possibility of atypical PChE except in the case of hepatic transplantation. Dibucaine inhibits the ability of normal PChE to hydrolyze benzoylcholine by more than 70% (ie, dibucaine number >70), heterozygous atypical PChE by 40% to 60%, and homozygous atypical PChE by 30% or less. Fresh-frozen plasma or PChE concentrates may be infused to hasten recovery in the case of a genetic enzyme defect or an acquired PChE deficiency. However, to avoid the risks of transfusion, it is best to simply keep the patient sedated, intubated, and ventilated until the drug is metabolized. In this setting, spontaneous reversal usually occurs within 3 to 4 hours, although in rare cases, full recovery requires up to 12 hours.¹⁷ When the duration of succinylcholine is very prolonged, blood samples should be

drawn for measurement of PChE concentration and activity.

Prolonged nondepolarizing block may occur when unusually large IV doses of succinylcholine (3–5 mg/kg) are given over minutes.⁶² This is called phase II block, and it can be partially reversed by neostigmine.

Hyperkalemia

Succinylcholine 1 mg/kg IV typically causes serum K^+ concentration to increase within minutes by approximately 0.5 mEq/L both in normal individuals and in persons with kidney failure. The acute hyperkalemic response to succinylcholine is greatly exaggerated with coexisting myopathy or proliferation of extrajunctional muscle ACh receptors. However, the mortality is highest (approaching 30%) when rhabdomyolysis is present.³⁹ Severe, precipitous, potentially life-threatening hyperkalemia also occurs after succinylcholine administration in several conditions associated with proliferation of ACh receptors. These conditions include denervation (head or spinal cord injury, stroke, neuropathy, prolonged use of NDNMBs), muscle pathology (direct trauma, crush or compartment syndrome, muscular dystrophy), critical illness (hemorrhagic shock, neuropathy, myopathy, prolonged immobility), thermal burn or cold injury, and sepsis lasting several days (eg, intraabdominal infections). After a neurologic injury, susceptibility to hyperkalemia begins within 4 to 7 days and may persist indefinitely. In patients who have been in the ICU for more than one week, a prudent course is to avoid succinylcholine altogether because of the risk of hyperkalemic cardiac arrest, which is associated with a mortality rate of at least 19%.^{6,8,39} Severe hyperkalemia is modified, but not prevented, by a dose of an NDNMB sufficient to prevent succinylcholine-induced muscle fasciculations.

Severe or even fatal hyperkalemia is reported in a few patients who received succinylcholine immediately after exsanguinating hemorrhage or massive trauma. The mechanism for this condition differs from that after neurologic injury because of inadequate time for proliferation of extrajunctional ACh receptors. Succinic acid, a tricarboxylic acid cycle intermediate (which is also a metabolite of succinylcholine), facilitates activation of voltage-gated sodium channels in a dose-dependent fashion, increasing skeletal muscle excitability.⁴¹ In hemorrhagic shock, accumulation of succinic acid as a result of cell breakdown and anaerobic metabolism possibly augments the potassium-releasing effect of succinylcholine.

Rhabdomyolysis

Severe hyperkalemia rarely occurs in the absence of a clinical history that readily discloses an obvious risk factor, with one important exception. Acute or delayed onset of rhabdomyolysis, hyperkalemia, ventricular dysrhythmias, cardiac arrest, and death are reported in apparently healthy children who subsequently were found to have an undiagnosed myopathy.⁵⁸ Since March 1995, a black box warning on the package insert has stated that succinylcholine should be avoided in elective surgery in children, particularly in children younger than 8 years of age, because of the small risk of a previously undiagnosed skeletal myopathy, especially Duchenne muscular dystrophy. Sudden cardiac arrest occurring immediately after succinylcholine administration should always be assumed to be caused by hyperkalemia. If fever, muscle rigidity, hyperlactatemia, or metabolic and respiratory acidosis also is present, the presumptive diagnosis of MH should prompt immediate therapy with dantrolene.

Malignant Hyperthermia

MH is a syndrome characterized by extreme skeletal muscle hypermetabolism. It is most often initiated after exposure to an anesthetic that triggers a cycle of abnormal calcium release from the skeletal muscle sarcoplasmic reticulum, and it can have a variable presentation.⁹⁰ Although MH is strongly associated with certain myopathies, especially King-Denborough syndrome, central core disease, and multiminicore disease, the disorder is also associated with certain enzyme deficiencies (McArdle disease, carnitine palmitoyltransferase type II, and myoadenylate deaminase deficiency), myopathies (eg, Duchenne muscular dystrophy, hyperCKemia), and some myotonias. MH typically affects individuals who are otherwise healthy and most have had prior uneventful anesthesia.⁵⁶ It is inherited as an autosomal dominant trait with variable penetrance.⁶⁹ Triggering xenobiotics that can precipitate an attack of MH include succinylcholine and volatile inhalational anesthetics (the prototypical xenobiotic is halothane). In individuals who are considered MH susceptible (MHS), xenobiotics that can be administered safely include NDNMBs, nitrous oxide, propofol, ketamine, etomidate, benzodiazepines, barbiturates, opioids, and local anesthetics.

In human MH, there is a causal association with several unique defects involving a skeletal muscle receptor/regulatory protein, especially defects involving the calcium-activated calcium release channel found in skeletal muscle: the type 1 ryanodine receptor (or RYR-1, chromosome 19q13.1). Mutations of the RYR-1 receptor are detected in 50% to 70% of patients with MH, and more than 200 different mutations are described^{10,44} (Fig. 69–1). The structurally distinct type 2 ryanodine receptor (RYR-2) is the primary type expressed in cardiac muscle, and this could explain why the myocardium is relatively spared in the early phase of MH (with the exception of an acute hyperdynamic response).⁸⁹ Of practical importance, the existence of multiple mutations across multiple alleles means that genetic testing is not likely to prove useful in detecting all MHS individuals or in excluding the risk of MH.

Although the prevalence of a genetic disorder associated with MH is one in 3000 to one in 8500, the observed incidence of fulminant MH in patients exposed to general anesthesia when triggering anesthetic agents are used is one in 62,000 to one in 84,000.^{83,90} Each year in the United States, there are an estimated 700 cases of MH.⁵⁵ In the MHS population, after exposure to anesthesia with known triggers, clinical manifestations develop less than half the time. For this reason, a previous uneventful anesthetic exposure does not preclude development of MH on a subsequent exposure.³ In the operating room, MH most often presents abruptly soon after initial exposure to a triggering anesthetic, but the onset of MH may be delayed several hours during the anesthesia,⁷⁶ or it may occur as long as 12 hours after surgery. In addition, recrudescence of MH can occur within 24 to 36 hours after an initial episode in up to 25% of patients.

The immediate systemic manifestations of MH result from extreme skeletal muscle hypermetabolism. The uncontrolled release of calcium from the terminal cisternae of the sarcoplasmic reticulum causes skeletal muscle contraction. Although generalized muscular rigidity is a specific sign of MH, it is only observed in 40%; masseter spasm is a sensitive finding observed in 27% of MH patients.⁵⁶ Futile calcium cycling by sarcoplasmic Ca^{2+} -ATPase rapidly depletes intracellular ATP and leads to anaerobic metabolism. Clinically, MH presents as skeletal muscle hypermetabolism with an increase in cardiac output and sinus tachycardia. Increased CO_2 production causes hypercapnia. Increased O_2 consumption can cause mixed venous O_2 desaturation (below the normal value of 75%), arterial hypoxemia, anaerobic metabolism, metabolic acidosis, and elevation of lactate concentration, cyanosis, and skin mottling. Excess heat production leads to a rapid increase in core temperature with hyperthermia.⁴² Other clinical findings include tachycardia, cardiac dysrhythmias, hyperkalemia, rhabdomyolysis, and disseminated intravascular coagulopathy.

The earliest signs of MH include an early and rapid increase in CO_2 production, causing an increase in arterial, venous, and end-tidal CO_2 . This is followed by or associated with tachycardia, tachypnea, hypertension or labile blood pressure, and skeletal and jaw muscle rigidity. Despite the name of the syndrome, hyperthermia is not a universal finding in MH, and moreover, it may be a late sign.¹⁰¹ Acute potassium release from skeletal muscle cells may produce life-threatening hyperkalemia. Subsequent rhabdomyolysis may exacerbate the elevation of potassium by causing acute kidney injury. In late-stage MH, cardiac decompensation results from hyperkalemia, heart failure, vascular collapse, or myocardial ischemia (especially with coexisting coronary artery disease). A standardized MH clinical grading scale based on patient history, clinical observations, and laboratory studies is commonly used to rank the qualitative likelihood (ranging from “almost never” to “almost certain”) that an adverse event represents a true episode of MH.⁵⁷ Points are assigned based on the clinical likelihood that observations are inappropriate for a given patient (eg, respiratory acidosis occurring abruptly despite sustained mechanical ventilation).

The differential diagnosis of MH includes antipsychotic malignant syndrome, propofol infusion syndrome, serotonin syndrome, thyroid storm, pheochromocytoma, baclofen withdrawal, malignant syndrome during withdrawal of dopaminergic drugs to treat Parkinson disease, tetanus, meningitis, poisoning by salicylates, amphetamines, cocaine, or antimuscarinics, unintentional intraoperative hyperthermia, heat stroke, and transfusion reactions. Of note, early septic shock is also associated with hypermetabolism, increased cardiac output, and fever, however, in contrast to MH, early septic shock is associated with an elevated mixed venous O_2 saturation (typically >75%).

Rarely, MH is triggered by severe exercise in a hot climate, IV potassium (which depolarizes the muscle membrane), antipsychotics, or infection.^{20,47} There is increased awareness of a possible link between MH and exertional heat illness or exertional rhabdomyolysis (ER; eg, a patient with ER who at a later time developed MH).^{12,13} Most patients with heat-related illness do not have MH, even if, on occasion, some patients have demonstrated a favorable response to dantrolene. Furthermore, a presumptive diagnosis of heat related illness does not necessarily exclude the diagnosis of MH and one must maintain clinical suspicion for possible MH, especially since environmental factors can be a sole precipitating factor in the absence of anesthetics.⁴⁴

One theory of the pathogenesis of MH suggests that MH-triggering xenobiotics interact with an abnormal RYR-1 channel, causing it to stay in a prolonged open state and leading to rapid efflux of calcium from the skeletal muscle sarcoplasmic reticulum into the myoplasm. Succinylcholine prolongs muscle depolarization, leading to elevated myoplasmic calcium concentration. This action initiates accelerated calcium-activated calcium release from the myoplasmic reticulum.³⁹ However, not all cases of MH can be explained by an RYR-1 mutation.³² For example, MH is also associated with defects in the CACNA1S protein that encodes a subunit of the skeletal muscle L-type calcium channel (known as the dihydropyridine receptor) and possibly with certain disorders of sodium channels (observed in the myotonic disorders).^{32,75}

The antidote for MH is dantrolene, and the key aspects of MH therapy are rapid initial diagnosis, discontinuation of triggering anesthetics, and immediate therapy with dantrolene (within minutes). By partially blocking calcium release from skeletal muscle sarcoplasmic reticulum, dantrolene rapidly reverses the signs and symptoms of hypermetabolism (Antidotes in Depth: A21). The precise mechanism of dantrolene activity is not known, but it modulates several calcium pathways.⁴⁴ Before the introduction of dantrolene, the mortality rate of MH was 64%.⁵⁵ When patients with an acute phase MH are treated immediately with dantrolene, removal of triggering agents, and supportive measures (volume resuscitation, active

cooling, control of hyperkalemia), the mortality rate is less than 5%.⁵⁵ Factors associated with an increase in mortality are a muscular body habitus, development of disseminated intravascular coagulation, and a longer duration of anesthesia before the peak in end-tidal carbon dioxide.⁵⁵ Even if administration is delayed for hours or days, dantrolene may still improve survival after an acute phase of MH. Patients with significant dysrhythmias can be treated with standard antidysrhythmics; however, calcium channel blockers must not be given with dantrolene because they may precipitate hyperkalemia and severe hypotension⁹¹ (Table 69–3).

Notes:

- Each vial of dantrolene contains 20 mg of dantrolene and 3 g of mannitol. Each vial should be reconstituted with at least 60 mL of sterile, preservative-free water. Dissolution of the lyophilized dantrolene in water is slow and requires thorough mixing.
- The guideline above may not apply to every patient and of necessity must be altered according to specific patient needs.
- Sudden unexpected cardiac arrest in children: Children younger than about 10 years of age who experience sudden cardiac arrest after succinylcholine administration in the absence of hypoxemia and anesthetic overdose should be treated for acute hyperkalemia first. In this situation, calcium chloride should be administered along with means to reduce serum potassium. They should be presumed to have subclinical muscular dystrophy, and a pediatric neurologist should be consulted.

CBC = complete blood count; ICU = intensive care unit; IV = intravenous.

TABLE 69–3. Suggested Therapy for Malignant Hyperthermia (MH)

Acute Phase Treatment of MH

1. Call for help. Immediately summon experienced help when MH is suspected.
2. Discontinue triggers volatile inhalational anesthetics and succinylcholine.
3. Hyperventilate with 100% O₂ with flow ≥ 10 L/min and monitor end-tidal CO₂.
4. Halt procedure as soon as possible, and continue sedation and analgesia with nontriggering agents (eg, opioids and benzodiazepines).
5. Administer dantrolene sodium, initial IV bolus of 2–3 mg/kg followed by additional boluses (every 15 minutes), until signs of MH are controlled (tachycardia, rigidity, increased end-tidal CO₂, hyperthermia). Typically, a total dose of 10 mg/kg IV controls symptoms, but occasionally 30 mg/kg may be required.
6. Monitor core temperature closely (tympanic membrane, nasopharynx, esophagus, rectal, or pulmonary artery) and actively cool the patient with core temperature $>39^{\circ}\text{C}$, (immersion in ice-water slurry, peritoneal or gastric lavage can also be useful, surface cool and/or surface cooling).
7. Hyperkalemia is common and should be treated aggressively with hyperventilation, IV calcium gluconate or chloride, sodium bicarbonate, IV dextrose, and insulin. Hypokalemia should be treated with caution because of the potential for rhabdomyolysis induced hyperkalemia.
8. Sodium bicarbonate. Consider 1–2 mEq/kg if blood gas values not yet obtained, or if clinically indicated.
9. Monitor continuously: electrocardiogram, pulse oximetry, end-tidal CO₂, core temperature, central venous pressure, urine output; and serially measure: arterial and mixed venous blood gases, metabolic profile (especially potassium), calcium, CBC, coagulation indices, and creatine kinase.
10. Dysrhythmias usually respond to dantrolene and correction of acidosis and hyperkalemia. If dysrhythmias persist or are life threatening, standard antidysrhythmics may be used including amiodarone, magnesium, and procainamide
 - Calcium channel blockers (verapamil or diltiazem) are not to be used to treat dysrhythmias because they may cause hyperkalemia and cardiac arrest.
11. Ensure adequate urine output by hydration and/or administration of mannitol or furosemide. Insert a urinary bladder catheter and consider central venous or pulmonary artery catheterization.
- 12 For emergency consultation, refer to the Malignant Hyperthermia Association of the United States (MHAUS) at <http://www.mhaus.org/>. Call the MH Emergency Hotline:
 - Inside United States or Canada, call 800-MH-HYPER (800-644-9737)
 - Outside the United States and Canada, call 001 315-464-7079

Postacute Phase Treatment of MH

1. Observe the patient in an ICU setting for at least 24 hours because recrudescence of MH occurs in 25% of cases, particularly after a fulminant case resistant to treatment. Observe for pulmonary edema, renal failure, and compartment syndrome.
2. Administer dantrolene 1 mg/kg IV q4.6h or 0.25 mg/kg/h by infusion for at least 24 hours after the episode.

3. Serially monitor arterial blood gases, metabolic profile, CBC, creatine kinase, calcium, phosphorus, coagulation indices, urine and serum myoglobin, and core body temperature until they return to normal values.
4. Counsel the patient and family regarding MH and further precautions.
 - For nonemergency patient referrals, contact MHAUS at 800-644-9737, 1 North Main Street, PO Box 1069, Sherburne, NY 13460.
 - Report patients who have had an acute MH episode to the North American MH Registry of MHAUS at 888-274-7899.
 - Alert family members to the possible dangers of MH and anesthesia.
5. Recommend an MH medical ID tag or bracelet for the patient, which should be worn at all times.

Notes:

- Each vial of dantrolene contains 20 mg of dantrolene and 3 g of mannitol. Each vial should be reconstituted with at least 60 mL of sterile, preservative-free water. Dissolution of the lyophilized dantrolene in water is slow and requires thorough mixing.
- The guideline above may not apply to every patient and of necessity must be altered according to specific patient needs.
- Sudden unexpected cardiac arrest in children: Children younger than about 10 years of age who experience sudden cardiac arrest after succinylcholine administration in the absence of hypoxemia and anesthetic overdose should be treated for acute hyperkalemia first. In this situation, calcium chloride should be administered along with means to reduce serum potassium. They should be presumed to have subclinical muscular dystrophy, and a pediatric neurologist should be consulted.

CBC = complete blood count; ICU = intensive care unit; IV = intravenous.

Persons who have experienced a possible episode of MH or have a positive family history should be referred to the Malignant Hyperthermia Registry and may be considered for muscle biopsy and muscle testing. The fresh tissue specimen is placed in a tissue bath perfused with Krebs solution, and halothane or caffeine is added. According to the North America Malignant Hyperthermia Group, an MH-susceptible individual is one who demonstrates a positive muscle contraction in response to either halothane or caffeine.

Muscle Spasms

Masseter muscle rigidity (MMR) was observed in 0.3% to 1.0% of children when general anesthesia was induced with succinylcholine and halothane (a technique now obsolete), and, at present, it is much less frequently encountered. MMR is clinically significant because it may complicate airway management and herald the onset of MH.⁸²

When administered to persons genetically predisposed to myotonia, succinylcholine may precipitate tonic muscular contractions, ranging from trismus (which may prevent orotracheal intubation) to severe generalized myoclonus and chest wall rigidity²⁸ (which may prevent ventilation). Because the myotonic contractions are independent of neural activity, they cannot be aborted by an NDNMB. Usually the contractions are self-limited, but occasionally they can be life-threatening if an airway cannot be established and hypoxemia ensues.

NONDEPOLARIZING NEUROMUSCULAR BLOCKERS

Pharmacology

Table 69–1 summarizes the pharmacology and toxicity of the NDNMBs.^{46,71,72,78} Whereas atracurium is composed of 10 different isomers, each having its unique pharmacokinetic and pharmacodynamic profile, cisatracurium contains only the 1R-cis and 1'R-cis isomers. Both atracurium and cisatracurium exhibit organ-independent elimination and are rapidly metabolized by spontaneous (nonenzymatic) temperature- and pH-dependent Hoffmann degradation and, to a lesser extent, by ester hydrolysis. The latter is catalyzed by nonspecific plasma esterases distinct from the PChE that hydrolyzes succinylcholine. In addition, significant drug metabolism or elimination occurs in the liver and kidney.³⁰

Toxicology

The most important toxic effects of the NDNMBs are accumulation of laudanosine and persistent weakness. In general, limiting the drug dose and monitoring the drug effect with a portable nerve stimulator reduce the incidence of prolonged weakness.

Laudanosine. Metabolism of atracurium and cisatracurium generates laudanosine, which crosses the blood–brain and placental barriers and may cause neuroexcitation but lacks any neuromuscular blocking activity.²⁵ Metabolism of each atracurium molecule generates one molecule of laudanosine.⁸⁰ Cisatracurium is an improvement over atracurium because it produces one-third as much laudanosine (and is three times more potent).^{34,51}

In the CNS, laudanosine has an inhibitory effect at the γ -aminobutyric acid, nACh, and opioid receptors. At high serum

concentrations in experimental animals, laudanosine causes dose-related neuroexcitation, myoclonic activity (>14 µg/mL), and generalized seizures^{14,34} (>17 µg/mL). In humans, the toxic serum laudanosine concentration is unknown, and seizures directly attributable to atracurium have not been observed even after prolonged infusion in the ICU.^{34,105} In ICU patients who received a 72-hour infusion of atracurium (1 mg/kg/h), the highest serum laudanosine concentrations (10–20 µg/mL) were observed in patients with an impaired glomerular filtration rate.⁶³ Laudanosine is excreted primarily in the bile, and its elimination is prolonged in patients with liver disease, biliary obstruction, and kidney disease.⁸⁶

Persistent Weakness Associated with Nondepolarizing Neuromuscular Blockers

Short-term blockade with a NDNMB usually resolves promptly upon discontinuation. When an NDNMB is administered for more than 48 hours, there is a risk that weakness will persist longer than anticipated based on the kinetics of drug elimination. In addition, critical illness is associated with dysfunction of the peripheral nerve, NMJ, and muscle (Table 69–4). For instance, in the ICU, persistent weakness is observed in 68% to 100% of patients with sepsis or multiple organ failure^{19,33,100} and in 20% to 30% of patients who receive NDNMB for only 48 to 72 hours.⁶⁵ Persistent weakness is multifactorial and associated with illness severity, sepsis, acute respiratory distress syndrome, multiorgan failure, hyperglycemia, NDNMBs; systemic corticosteroids, muscle injury, thermal injury, and electrolyte, endocrine, and nutritional disorders.^{18,23,43,64} Many xenobiotics given to patients in the ICU can cause weakness by themselves or potentiate the effects of NDNMBs.^{45,84} Progressive weakness and acute respiratory failure have even been described after discharge from the ICU and may be life threatening if not immediately recognized.⁵⁹ Patients who develop persistent weakness have a 2.5 to 3.5 fold increase in ICU mortality⁶⁵ and ICU stay.

TABLE 69–4. Acute Neuromuscular Pathology Associated with Critical Illness or Nondepolarizing Neuromuscular Blockers				
	Critical Illness Polyneuropathy	Residual Neuromuscular Block	Disease (Cachectic) Myopathy	Critical Illness Myopathy
Sensory	Moderate to severe, distal > proximal	Normal	Normal	Normal
Motor	Symmetric weakness, lower > upper extremity, proximal > distal or diffuse, respiratory failure	Diffuse symmetric weakness, respiratory failure	Diffuse weakness, proximal > distal	Symmetric weakness, proximal > distal or diffuse, respiratory failure
Creatine phosphokinase	Normal	Normal	Normal	Elevated in ≤50%
Electrodiagnostic studies (EMG, NCV)	Axonal degeneration of motor > sensory, reduced sensory and motor compound action potentials, normal NCV	Fatigue at NMJ assessed by fade on repetitive nerve stimulation	Normal EMG and NCV	Myopathic changes, muscle membrane inexcitability, normal NCV
Muscle biopsy	Denervation atrophy	Normal	Atrophy of type 2 fibers, no myosin loss, no necrosis	Atrophy of type 2 (fast-twitch) fibers, myosin loss, mild myonecrosis, no inflammatory infiltration

EMG = electromyography; NCV = nerve conduction velocity; NMJ = neuromuscular junction.
Data from Bolton CF: Critical illness polyneuropathy and myopathy. *Crit Care Med*. 2001;29:2388–2390; Lacomis D: Critical illness myopathy. *Curr Rheumatol Rep*. 2002;4:408–408; Lacomis D, Campellone IV: Critical illness neuromyopathies. *Adv Neurol*. 2002;88:325–335; and Leijten FSS, de Weerd AWF: Critical illness polyneuropathy: a review the literature, definition and pathophysiology. *Clin Neurol Neurosurg*. 1994;96:10–19.

REVERSAL OF NEUROMUSCULAR BLOCKADE

Pharmacology

Termination of NMB effect initially results from drug redistribution and later from drug elimination, metabolism, or chemical antagonism. Pharmacologic antagonism of a partial NDNMB is achieved by giving a reversal agent that inhibits junctional AChE and increases ACh at the NMJ. This increase in ACh can overcome the competitive inhibition caused by a residual NDNMB. The commonly used anti-ChEs are polar molecules that possess a quaternary ammonium (Table 69–5). Neostigmine and pyridostigmine are hydrolyzed by ChE and form short-lived carbamyl complexes (half-life, 15–20 minutes) with the esteratic site of the enzyme.⁵ In contrast, edrophonium is not hydrolyzed by ChE; rather, it forms an electrostatic interaction and a hydrogen bond with the cationic site of ChE that is both competitive and reversible. Neostigmine and pyridostigmine, but not edrophonium, inhibit PChE and thus prolong the effects of xenobiotics metabolized by this enzyme, such as succinylcholine.³¹

TABLE 69–5. Pharmacology of Intravenous Neuromuscular Blockade Reversal Drugs and Coadministered Antimuscarinics

<i>Anticholinesterases</i>			
	<i>Neostigmine</i>	<i>Pyridostigmine</i>	<i>Edrophonium</i>
Initial dose (mg/kg)	0.04–0.08	0.2–0.4	0.5–1.0
Onset (minute)	7–11	10–16	1–2
Duration (minute)	60–120	60–120	60–120
Recommended antimuscarinic	Glycopyrrolate	Glycopyrrolate	Atropine
<i>Antimuscarinics</i>			
	<i>Glycopyrrolate</i>	<i>Atropine</i>	
Structure	Quaternary ammonium	Tertiary amine	
Initial dose (mg/kg)	0.01–0.02	0.02–0.03	
Onset (minute)	2–3	1	
Duration (minute)	30–60	30–60	
Elimination	Renal	Renal	
Crosses blood-brain barrier	No	Yes	

TOXICOLOGY OF REVERSAL AGENTS

The most common and troublesome clinical side effect of ChE inhibition is bradycardia, which usually is prevented by coadministration of an antimuscarinic.¹⁶ Bradydysrhythmias may be severe and lead to nodal or idioventricular rhythm, complete heart block, or even asystole.⁶⁶ These side effects occur more frequently in patients with preexisting bradycardia and those receiving chronic β -adrenergic antagonist therapy. They are not necessarily prevented by prior administration of atropine.⁹⁶ Other problems that may result from excess ChE inhibition are hypersalivation, lacrimation, bronchospasm, increased bronchial secretions, abdominal cramping from intestinal hyperperistalsis, cell division, and increased bladder tone. After general anesthesia, use of anti-ChE reversal agents may increase the incidence of nausea, vomiting, and abdominal cramps.⁵⁰ Because atropine crosses the blood–brain barrier, it may produce central anticholinergic syndrome.

DIAGNOSTIC TESTING

Quantitative methods for analysis of blood and tissue NDNMB and metabolite concentrations using high-performance liquid chromatography and mass spectrometry are described.^{49,94}

Succinylcholine and succinylmonocholine can be assayed by gas chromatography and mass spectrometry in blood, urine, or the site of intramuscular injection.^{81,95} Less than 3% of administered succinylcholine and 10% of its metabolite succinylmonocholine are excreted in the urine. However, both the parent drug and the metabolite undergo spontaneous hydrolysis, especially in alkaline conditions.⁹⁹ Historically, detection of succinylcholine has proven difficult because of its rapid hydrolysis. However, techniques for detecting this parent compound in tissues even after embalming are described.³⁷ Because succinic acid is also a product of normal intermediary metabolism, assay of this metabolite is not useful for positive identification of prior succinylcholine exposure.⁷⁴ Surprisingly, the presence of succinylmonocholine in forensic samples also cannot prove prior exposure to succinylcholine. Succinylmonocholine in concentrations of 0.01 to 0.20 $\mu\text{g/g}$ has been detected in tissues of six autopsy cases with no history of succinylcholine exposure.⁶¹

SUMMARY

- Succinylcholine is the only DNMB in current clinical use. Its immediate adverse effects include dose- and rate-related histamine release and modulation of autonomic tone.
- Acute and potentially fatal hyperkalemia may occur after succinylcholine administration, particularly in patients with certain myopathies (eg, Duchenne muscular dystrophy).

- In MH, acute onset of severe hypermetabolism, causing acidosis, rhabdomyolysis, hyperkalemia, and death occurs if treatment with dantrolene and aggressive cooling is not rapidly administered.
- The most important complications associated with use of NDNMBs are undetected hypoventilation and prolonged drug effect. NDNMBs have clinically important interactions with many xenobiotics and coexisting medical conditions.
- In most neuromuscular diseases, sensitivity to NDNMBs is increased. In renal failure, active metabolites of pancuronium and vecuronium may accumulate and cause prolonged block.

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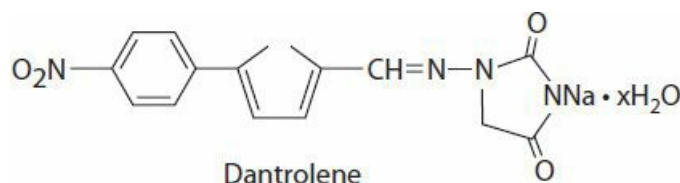
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A21 ANTIDOTES IN DEPTH

Dantrolene Sodium

Kenneth M. Sutin



INTRODUCTION

Dantrolene produces relaxation of skeletal muscle without causing complete paralysis, and it is the only xenobiotic proven to be effective for both treatment and prophylaxis of malignant hyperthermia (MH).⁸ MH should be considered when hyperthermia is associated with severe hypermetabolism, increased CO₂ production, metabolic acidosis with elevated lactate, hyperkalemia, and rhabdomyolysis, especially when the course is fulminating and refractory to supportive therapy.

HISTORY

Dantrolene was first synthesized in 1967.²⁹ Four years later, the xenobiotic was first used clinically in oral form to treat skeletal muscular spasticity caused by neurologic disorders.⁶ The ability of intravenous (IV) dantrolene to rapidly reverse MH (muscle rigor, acidosis, and temperature rise) was first reported in swine in 1975¹¹ and in humans in 1982.¹⁶ The delay from dantrolene discovery to clinical use was in part due to the difficulty encountered in formulating a parenteral (water-soluble) solution of the lipid-soluble drug.

PHARMACOLOGY

Although dantrolene is a hydantoin derivative that is structurally similar to local anesthetics and anticonvulsants, it possesses none of their properties.^{17,33} The drug is highly lipophilic and relatively insoluble in water. It exhibits variable absorption by the small intestine. Oral bioavailability is up to 70%, and peak blood concentrations are achieved 3 to 6 hours after ingestion.¹⁷ Dantrolene is reversibly bound to plasma proteins, especially albumin.

Quantitative analysis of dantrolene and its metabolites has been performed using reverse phase, high-performance liquid chromatography.¹ After a 2.4 mg/kg IV dose, the mean serum dantrolene concentration is 4.2 µg/mL.⁸ This concentration produced a 75% reduction in twitch contraction of skeletal muscle.⁸ The therapeutic serum concentration in humans is estimated at 2.8 to 4.2 µg/mL.⁸

Pharmacokinetics are well described by a two-compartment model with an initial volume of distribution of 3.24 L and a secondary compartment volume of 22.4 L.²³ Most of the drug is eliminated by the liver; dantrolene is metabolized by 5-hydroxylation of the hydantoin ring or by reduction of the nitro group to an amine.³³ Up to 20% of administered dantrolene is excreted in the urine as the 5-hydroxydantrolene metabolite, which is half as potent as the parent drug.³³ In adults, the elimination half-life is 6 to 9 hours for dantrolene and 15.5 hours for the 5-hydroxydantrolene metabolite.³³ In one study of children aged 2 to 7 years, the dantrolene elimination half-life was 10 hours and that for 5-hydroxydantrolene was 9 hours.¹⁸

At therapeutic concentrations, dantrolene inhibits binding of [³H]ryanodine to the ryanodine receptor type 1 (RYR-1) on the sarcoplasmic reticulum membrane of skeletal muscle,²² causing a dose-dependent inhibition of both the steady state and peak concentrations of calcium release.³⁰ This reduces the free myoplasmic calcium, thereby directly inhibiting excitation-contraction coupling.¹⁹ Dantrolene causes skeletal muscle weakness but not complete paralysis, and this plateau effect may

be related to its low water solubility. This plateau effect (achieved at a serum concentration of 4.2 µg/mL) produces a 75% reduction of skeletal muscle twitch contraction and a 42% reduction in hand grip strength.⁸ Dantrolene does not change the electrical properties or excitation of nerve, excitation–contraction coupling at the neuromuscular junction, or skeletal muscle, and it does not alter sarcoplasmic calcium reuptake. Because dantrolene does not bind to the cardiac ryanodine receptor (RYR-2), it has minimal cardiac effects^{10,32,35} and no effect on smooth muscle.

ROLE IN MALIGNANT HYPERTHERMIA AND OTHER HYPERTHERMIAS

Dantrolene is indicated for treatment of skeletal muscle hypermetabolism characteristic of MH and, following an acute episode of MH, to prevent recrudescence. Long-term oral dantrolene therapy is used rarely to treat chronic spasticity.¹⁵ Historically, dantrolene was used prophylactically in MH-susceptible individuals; however, current practice is simply to avoid exposure to MH-triggering xenobiotics during anesthesia in potentially susceptible patients (Table 30–1). Dantrolene should be considered for patients with severe hypermetabolism when the diagnosis of MH cannot be excluded with certainty, especially when there is coexisting respiratory and metabolic acidosis, coagulopathy, hyperthermia, and rhabdomyolysis.⁷ In typical fulminant MH, the diagnosis is not subtle, and the course of treatment is obvious once the diagnosis is considered. This is not true when the clinical presentation is atypical. Atypical clinical presentations of MH in the presence or absence of triggering anesthetics are reported, especially in MH-susceptible individuals.

Dantrolene has been used to treat acute hyperthermia other than that caused by MH, including neuroleptic malignant syndrome,²⁴ heat stroke,² serotonin toxicity,¹² monoamine oxidase inhibitor overdose,¹³ methylenedioxymethamphetamine (“ecstasy”) overdose,^{20,26} intrathecal baclofen withdrawal,¹⁴ and thyroid storm.⁵ Given the lack of evidence-based support, dantrolene therapy is not recommended for indications other than MH. However, because (a) the differential diagnosis of a hyperthermic syndrome does not necessarily exclude (and often includes) MH, (b) the definitive diagnosis of a hyperthermic syndrome may be subtle or delayed, and (c) MH may occur simultaneously with another hyperthermic syndrome,²¹ consideration should be given to dantrolene therapy when MH cannot be specifically excluded; its use may be lifesaving. It bears emphasis that dantrolene given for hyperthermia is not a substitute for aggressive cooling.

ADVERSE EFFECTS AND SAFETY ISSUES

The alkaline pH of the reconstituted dantrolene causes venous irritation (pain) and thrombophlebitis with an incidence of 9%.³ Unintended extravasation can cause tissue necrosis, highlighting that dantrolene should only be given through a central vein or a large peripheral vein. There is no evidence to suggest allergic cross-reactivity with dantrolene in patients with prior phenytoin allergy.

When given to healthy persons or for MH prophylaxis or treatment, dantrolene causes skeletal muscle weakness (but not paralysis) in 15% to 22% of cases, as well as diaphragm weakness (dyspnea).^{3,34} In healthy volunteers, dantrolene 2.5 mg/kg does not reduce respiratory rate, vital capacity, or peak expiratory flow rate.⁸ However, in patients with diminished respiratory reserve (eg, end-stage pulmonary disease, preexisting neuromuscular disease), dantrolene may precipitate respiratory failure.^{3,17} Dantrolene may cause gastrointestinal upset, nausea, and vomiting. Other reported side effects include dizziness, somnolence, disorientation, ptosis, blurred vision, and difficulty swallowing.^{3,8,34} Uncommonly, compartment syndrome is observed and, even though likely secondary to MH or trauma, may be associated with dantrolene administration.³

Dantrolene and verapamil should not be used in combination because of the risk of hyperkalemia and hypotension; however, the mechanistic details of this drug interaction remain unclear.^{17,25,27} IV calcium salts are safe to administer with dantrolene if needed, such as for the treatment of cardiac dysrhythmias or hyperkalemia (during an episode of MH).

When dantrolene is given orally for more than 2 months to treat skeletal muscle spasticity, there is a 1.8% risk of dose- and duration-related chronic hepatitis, including elevated aminotransferase concentrations, hyperbilirubinemia, or jaundice³¹ that may not be fully reversible after dantrolene is discontinued.⁴

PREGNANCY AND LACTATION

Dosing during pregnancy is based on total body weight. Dantrolene crosses the placenta and is excreted in breast milk. When the maternal blood concentration achieved 0.99 µg/mL, the neonatal cord blood and serum concentration was 0.68 and 0.72 µg/mL, respectively.²⁸ The neonatal drug elimination half-life is about 20 hours.²⁸ Peak concentrations of dantrolene in breast milk 36 hours after maternal dantrolene 2.5 mg/kg given intravenously were 1.2 µg/mL, and the elimination half-life was 9 hours from breast milk.⁹ At the concentrations achieved in serum or breast milk, there are no reports of significant adverse effects on the neonate; however, it is suggested the breast feeding resume 48 hours after the last dose of dantrolene.⁹

DOSING AND ADMINISTRATION

The initial dose of dantrolene for treatment of acute MH is an IV bolus of 2 to 3 mg/kg in the adult and pediatric population.¹⁸ For a typical adult, 10 bottles of dantrolene are simultaneously reconstituted for the initial dose. Also, initial dosing probably should be determined by total body weight given that dantrolene is lipophilic; however, its pharmacokinetics in obesity are not determined.⁸ Redosing of 2 to 3 mg/kg IV is repeated every 15 minutes until the signs of hypermetabolism are reversed or until a total dose of approximately 10 mg/kg has been administered. Occasionally, however, doses in excess of 10 mg/kg have been required. The key point is that the total dose of dantrolene is determined by titration to a metabolic end point—resolution of skeletal muscle hypermetabolism. When an effective dose of dantrolene is given, signs of muscle hypermetabolism start to normalize usually within 30 minutes.¹⁶

Following successful termination of the acute episode of hypermetabolism, it is recommended that dantrolene therapy be continued 1 mg/kg IV every 6 hours for at least 24 hours to prevent recrudescence. Alternatively, a maintenance infusion can be started 5 hours after the initial dose (ID) according to the formula:

$$\text{Maintenance Infusion: (mg/kg/24 hours)} = \text{ID} \times 1.096$$

For example, if the ID of dantrolene is 5 mg/kg, it is continued as an infusion 5.48 mg/kg/24 h.²³

FORMULATION

Dantrolene is supplied as a sterile lyophilized powder in a 70 mL vial that contains 20 mg dantrolene sodium, 3 g mannitol (to maintain tonicity), and sodium hydroxide (to maintain a pH of 9.5 after reconstitution in 60 mL of sterile water). The dantrolene powder must be reconstituted in preservative-free sterile water for injection (and not 0.9% sodium chloride or dextrose-containing solutions) as this hastens dissolution and prevents precipitation. Prewarming the water to a maximum of 102°F (39°C) may decrease the time to dissolve the powder; this can be accomplished by storing sterile water in a warmed cabinet. There is, however, no evidence that prewarming improves clinical outcome, and the current formulation of Dantrium reconstitutes in about 20 seconds. After addition of 60 mL sterile water to each vial, the dantrolene bottles are shaken until the solution becomes clear (indicating the powder is fully dissolved). The final solution is isotonic and has pH of approximately 9.5. The extreme alkalinity of the reconstituted solution can corrode glass and thus must not be transferred into a glass bottle.

SUMMARY

- Dantrolene is the only specific antidote to treat malignant hyperthermia. The initial dose of dantrolene for treatment of acute MH is an IV bolus of 2 to 3 mg/kg in the adult and pediatric population, which is repeated every 15 minutes until clinical signs of hypermetabolism are corrected.
- The therapeutic serum concentration in humans is estimated at 2.8 to 4.2 µg/mL. Most of the drug is eliminated by the liver; it is metabolized by 5-hydroxylation of the hydantoin ring or by reduction of the nitro group to an active metabolite.
- Dantrolene is relatively lipophilic and crosses the placenta and is excreted in breast milk.
- MH Hotline: 800-644-9737.

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G. PSYCHOTROPICS

CASE STUDY 5

History A 54 year-old man presented to the emergency department (ED) complaining that he was weak and dizzy and felt as if he was about to pass out. His past medical history was significant for opioid dependence. He recently saw an alternative medical provider and was given a natural remedy to help him detoxify. Prior to therapy, he was on daily methadone, but transitioned to hydrocodone in preparation for treatment. He was treated by his provider approximately 3 to 4 hours before presentation and sent to the ED because he was unwell. He denied nausea, vomiting, diarrhea, lacrimation, or other symptoms consistent with opioid withdrawal. In triage, his pulse was 35 beats/min, so the patient was rushed to the critical care area.

Immediate Assessment and Management On arrival to the critical care area he was awake but complaining of weakness. Vital signs were: blood pressure, 128/62 mm Hg; pulse, 35 beats/min, respiratory rate, 14 breaths/min; temperature, 98.4°F (36.9°C); oxygen saturation, 98% on room air; and glucose, 110 mg/dL. A general physical examination was unremarkable and specifically noted the absence of mydriasis, piloerection, rhinorrhea, or lacrimation. An electrocardiogram (ECG) was obtained (Fig. CS5–1), which was notable for sinus bradycardia with a QT interval of approximately 600 msec and an abnormally shaped T wave. Blood was sent for a complete blood count and electrolytes. The patient was attached to continuous cardiac monitoring.

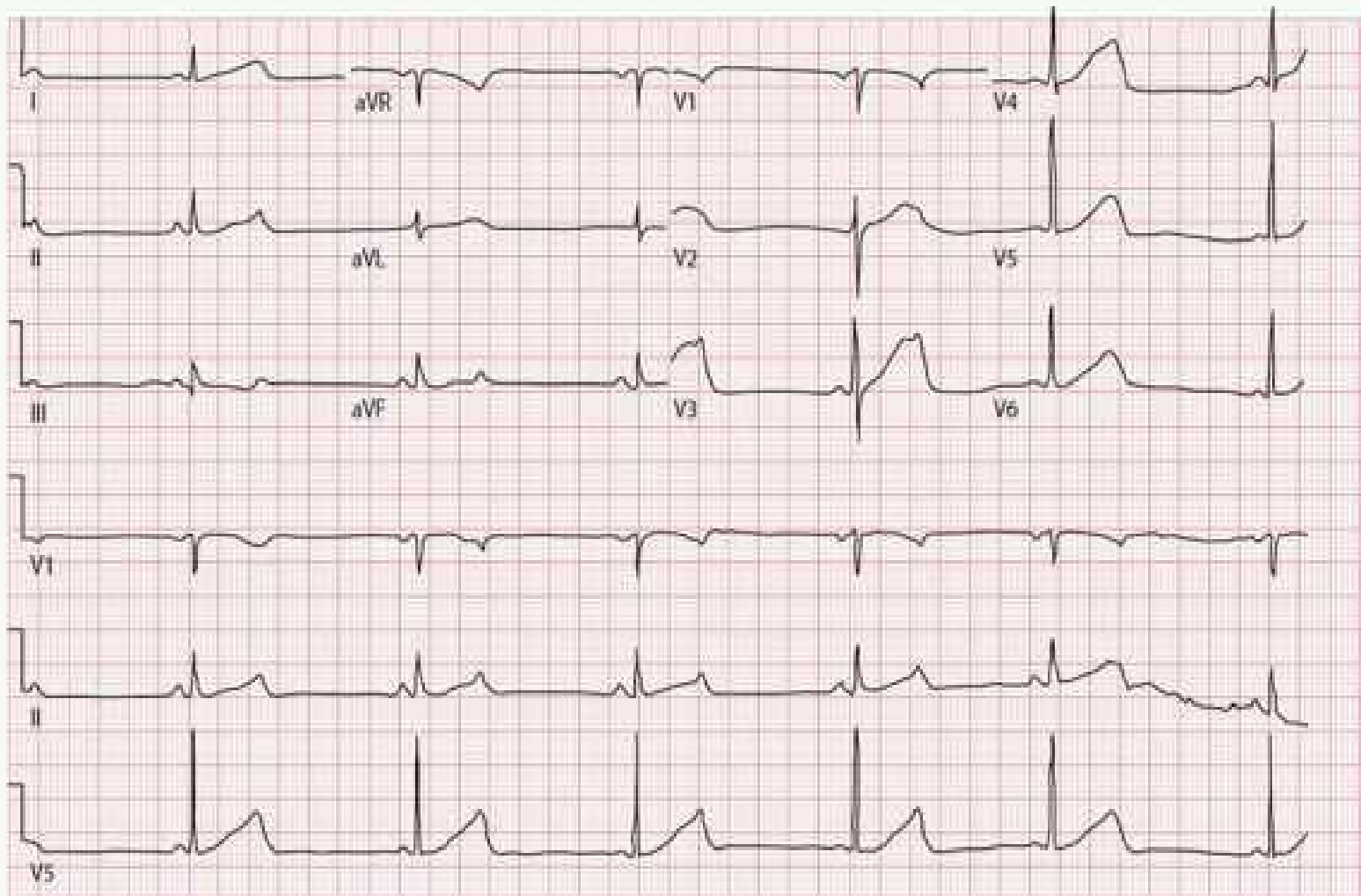


FIGURE CS5–1. Initial electrocardiograph demonstrating sinus bradycardia at a heart rate of 35 beats/min with a normal axis, normal PR interval of 120 msec, a normal QRS duration of 80 msec, and prolonged QT interval at nearly 600 msec with an abnormal T-wave morphology.

Suddenly, the patient lost consciousness and became pulseless. A rhythm strip captured the event (Fig. CS5–2), which was determined to be torsade de pointes (TdP) (Chap. 16). The event was self-limited but recurred, at which time he was given 2 g of magnesium sulfate intravenously followed by a continuous magnesium infusion at 1 g/h. His cardiac rhythm returned to sinus, and he was moved to the cardiac intensive care unit (CCU) where a temporary transvenous pacemaker was inserted.



FIGURE CS5–2. Electrocardiograph associated with loss of consciousness demonstrating the transition from bradycardia to ventricular ectopy followed by a run of torsade de pointes.

What Is the Differential Diagnosis? In addition to congenital and acquired intrinsic cardiac conditions and electrolyte abnormalities ([Chap. 19](#)), numerous xenobiotics from diverse chemical classes are associated with QT interval prolongation and the risk of TdP. These xenobiotics, which typically share an ability to block myocardial potassium channels ([Chap. 16](#)), can be found throughout this text. Common classes of xenobiotics in which some members are associated with QT interval prolongation and some specific examples are listed in [Table CS5–1](#). Readers are referred to www.crediblemeds.com, a comprehensive Web site that stratifies pharmaceuticals by risk. It is noteworthy that many nonpharmaceutical xenobiotics also are listed in the table and text.

TABLE CS5–1. Xenobiotics Classes Associated with QT Interval Prolongation and Torsade de Pointes

Class/Chapter	Specific Examples
β-Adrenergic antagonists	Sotalol
Antibiotics	Macrolides and fluoroquinolones
Anticonvulsants	Carbamazepine
Antidysrhythmics	(Class IA, IC, and III antidysrhythmics)
Antimalarials	Chloroquine, mefloquine, halofantrine
Antipsychotics	Phenothiazines, citalopram
Caustics	Hydrofluoric acid
Cyclic antidepressants	Most
Drugs of abuse	Cocaine
Herbals	Ibogaine
Metals	Arsenic, barium, cesium
Opioids	Methadone
Pesticides	Organic phosphorus compounds

What Rapid Clinical and Laboratory Analyses Can Help Determine the Etiology and Guide Therapy for This Patient’s Presentation? Because the differential diagnosis is so extensive, broad laboratory testing is not advocated to determine the etiology in patients with unclear causes for QT interval prolongation. Instead, efforts should be directed at thorough history taking, as the cause may become evident. Patients should have routine electrolytes measured, because hypokalemia, hypocalcemia, and hypomagnesemia can all either be the primary cause of QT interval prolongation or be contributory when another etiology exists. Since these electrolyte abnormalities can be rapidly corrected in most circumstances, they represent easy and important interventions. When acute overdose is suspected, gastrointestinal decontamination can help limit drug absorption or enhance elimination ([Chap. 8](#)).

Further Diagnosis and Treatment Laboratory evaluation demonstrated normal concentrations of magnesium and calcium, but hypokalemia (2.5 mEq/L) was identified. The patient stated that he had received ibogaine therapy to treat his opioid dependence, and ibogaine is associated with both bradycardia and QT interval prolongation ([Chap. 45](#)). While in the CCU, he had several episodes of ventricular ectopy but no recurrent TdP. His hypokalemia was corrected with supplemental potassium, and an echocardiogram showed no signs of structural heart disease. Several days later he was discharged with a normal heart rate and mild QT interval prolongation (470 msec).

70 ANTIPSYCHOTICS

David Juurlink

HISTORY AND EPIDEMIOLOGY

The development of antipsychotic drugs changed the practice of psychiatry. Prior to the introduction of chlorpromazine in 1950, patients with schizophrenia were treated with nonspecific sedatives such as barbiturates and chloral hydrate. Highly agitated patients were housed in large mental institutions and often placed in physical restraints, and thousands underwent surgical disruption of the connections between the frontal cortices and other areas of the brain (leucotomy). By 1955, approximately 500,000 patients with psychotic disorders were hospitalized in the United States. The advent of antipsychotics in the 1950s revolutionized the care of these patients. These drugs, originally termed major tranquilizers and subsequently neuroleptics, dramatically reduced the characteristic hallucinations, delusions, thought disorders, and paranoia—the “positive” symptoms of schizophrenia.

Shortly after the introduction of these drugs, it became apparent that they caused significant toxicity following overdose, a common occurrence in patients with mental illness. Moreover, they were also associated with a host of adverse effects, principally involving the endocrine and nervous systems. The latter includes the extrapyramidal syndromes (EPS), a constellation of disorders that are relatively common, sometimes irreversible and occasionally life threatening.

The search for new drugs led to the development of multiple antipsychotics of several chemical classes. These drugs exhibited varying potencies and markedly different adverse effect profiles. The novel antipsychotic clozapine was first synthesized in 1959, but it did not enter widespread clinical use until the early 1970s. Clozapine was unusual because it conferred a relatively low risk of EPS, but also because it was often effective in patients who had not responded well to other xenobiotics. Moreover, unlike the other available xenobiotics, it often improved the “negative” symptoms of schizophrenia such as avolition, alogia, and social withdrawal—symptoms that, while often less outwardly apparent than the positive symptoms, result in significant disability. Reports of life-threatening agranulocytosis led to the withdrawal of clozapine from the market in 1974, although it was reintroduced in 1990.^{9,49} However, the unique therapeutic and pharmacologic properties of clozapine led to its characterization as an atypical antipsychotic, the forerunner and prototype of many other second-generation antipsychotics that have now largely supplanted the earlier xenobiotics.

Most antipsychotic toxicity occurs by one of two mechanisms. Following overdose, antipsychotic toxicity is dose dependent and reflects an extension of the effects of the drug on neurotransmitter systems and other biologic processes. The features of antipsychotic drug overdose are therefore generally predictable based upon an understanding of the pharmacology of the drug. Unpredictable (idiosyncratic) adverse reactions also occur in the context of routine therapeutic use. These toxicities result from individual susceptibility, are sometimes pharmacogenetic in nature, and are less reliably correlated with the dose. In both types of toxicity, the severity of illness can range from minor to life threatening, depending on a number of other factors, including concomitant drug exposures, comorbidity, and access to medical care.

The true incidence of antipsychotic overdose and adverse reactions is not known with certainty. Some patients may not seek medical attention, whereas others may be misdiagnosed. Even among those who seek medical attention and are correctly diagnosed, notification of poison centers or other adverse event reporting systems is discretionary and incomplete (Chap. 136). With these limitations in mind, a few observations can be made.

In 2011, poison control centers in the United States were contacted about more than 3.6 million potential toxic exposures.¹⁶ Antipsychotic exposures are reported together with sedative-hypnotics, but these collectively represented 168,416 exposures (6.13% of all exposures). The vast majority of poison center calls involving antipsychotics pertain to intentional overdoses in patients 20 years or older, most of whom have a good outcome. However, antipsychotics were associated with more fatalities than any other group ($n = 401$ deaths), and most exposures involved atypical antipsychotics. Importantly, poison center data underestimate the annual incidence of poisoning and mortality associated with antipsychotics and likely identify only a small minority of adverse drug reactions involving these drugs.

Although all antipsychotics can exhibit significant toxicity in overdose, a substantial body of clinical experience and some observational data suggest that the low potency, first-generation antipsychotics such as thioridazine, chlorpromazine, and mesoridazine are associated with greater toxicity than other antipsychotics.^{17,19} Inferences regarding the relative toxicity of the antipsychotics derived from administrative data should be extrapolated to individual patients with caution,^{17,40} but at least one well done retrospective cohort study supports the notion that thioridazine is associated with

greater cardiovascular toxicity than other antipsychotics.¹⁹

PHARMACOLOGY

Classification

Antipsychotics can be classified in several ways, according to their chemical structure, their receptor binding profiles, or as “typical” or “atypical” antipsychotics. [Table 70–1](#) outlines the taxonomy of some of the more commonly used antipsychotics. Classification by chemical structure was most useful prior to the 1970s, when phenothiazines and butyrophenones constituted most of the antipsychotics in clinical use. Currently, the number of different compounds and their structural heterogeneity renders this scheme of little utility to clinicians. It is worth noting, however, that the phenothiazine antipsychotics bear a high degree of structural similarity to the tricyclic antidepressants (TCAs) ([Fig. 70–1](#)) and share many of their manifestations in overdose. The phenothiazines can be further classified according to the nature of the substituent on the nitrogen atom at position 10 of the center ring as either aliphatic, piperazine, or piperidine compounds.

TABLE 70–1. Classification of Commonly Used Antipsychotics

Classification	Compound	Usual Daily Adult Dose (mg)	Volume of Distribution (L/kg)	Half-Life (Range, hours)	Protein Binding (%)	Active Metabolite	Lipophilicity (LogD)
Typical Antipsychotics							
Butyrophenones	Droperidol	1.25–30	2–3	2–10	85–90	N	2.85
	Haloperidol	1–20	18–30	14–41	90	Y	2.80
Diphenylbutylpiperidines	Pimozide	1–20	11–62	28–214	99	Y	3.74
Phenothiazines							
Aliphatic	Chlorpromazine	100–800	10–35	18–30	98	Y	3.01
	Methotrimeprazine	2–50	23–42	17–78	NR	Y	6.5
	Promazine	50–1000	30–40	8–12	98	N	—
	Promethazine	25–150	9–25	9–16	93	Y	2.73
Piperazine	Fluphenazine	0.5–20	220	13–58 ^a	99	NR	4.29
	Perphenazine	8–64	10–35	8–12	>90	NR	3.94
	Prochlorperazine	10–150	13–32	17–27	>90	NR	3.69
	Trifluoperazine	4–50	NR	7–18	>90	Y	4.04
Piperidine	Mesoridazine	100–400	3–6	2–9	98	Y	1.45
	Thioridazine	200–800	18	26–36	96	Y	3.60
	Pipotiazine	25–250 (monthly IM depot)	7.5	3–11	NR	N	–1.81
Thioxanthenes	Chlorprothixene	30–300	11–23	8–12	NR	NR	—
	Flupenthixol	3–6	7–8	7–36	NR	NR	—
	Thiothixene	5–30	NR	12–36	>90	NR	2.96
	Zuclopenthixol	20–100	10	20	NR	NR	–2.18
Atypical Antipsychotics							
Benzamides	Amisulpride	50–1200	5.8	12	16	N	–1.42
	Raclopride	3–6	1.5	12–24	NR	N	1.19
	Remoxipride	150–600	0.7	3–7	80	Y	2.1
	Sulpiride	200–1200	0.6–2.7	4–11	14–40	N	0.6
Benzepines							
Dibenzodiazepine	Clozapine	50–900	15–30	6–17	95	Y	3.40
Dibenzosazepine	Loxapine ^b	20–250	NR	2–8	90–99	Y	2.91
Thienobenzodiazepine	Olanzapine	5–20	10–20	21–54	93	N	3.20
Dibenzothiazepine	Quetiapine	150–750	10	3–9	83	N	1.82
Indoles							
Benzisoxazole	Risperidone	2–16	0.7–2.1	3–20	90	Y	1.88
	Paliperidone	1–12 mg (IM 25–150 monthly)	7	23	74	N	0.60
Imidazolidinone	Sertindole	12–24	20–40	24–200	99	Y	—
Benzothiazide	Ziprasidone	40–160	2	4–10	99	N	2.75
Quinolones	Aripiprazole	10–30	5	47–68	99	Y	5.55

^aThe atypical profile of loxapine is lost at doses >50 mg/d, it is sometimes therefore categorized as a typical antipsychotic. ^bFor hydrochloride salt, mesoridazine and decanoate have onsets of 3 to 4 days and 5 to 12 days, respectively.

NR = not reported.

Data from References 10, 12, 14, 37, 54, and 60.

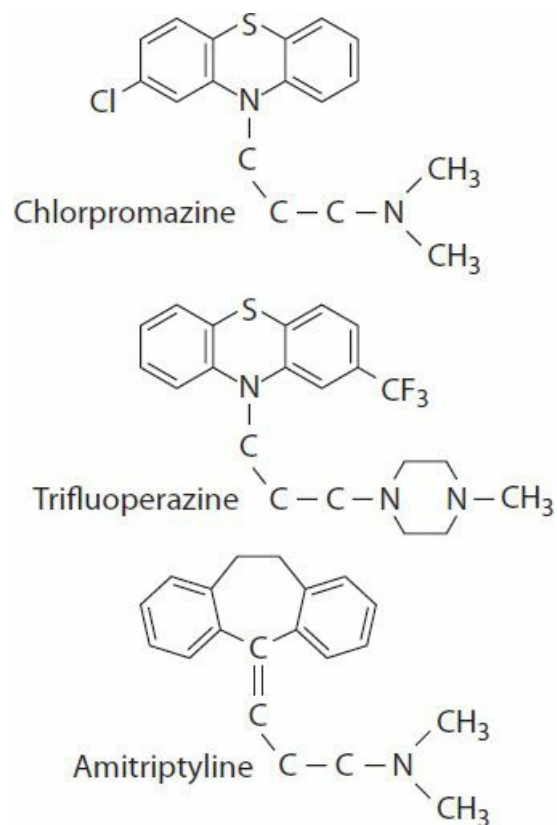


FIGURE 70–1. Structural similarity between phenothiazines and cyclic antidepressants.

Of greater clinical utility is the classification of antipsychotics according to their binding affinities for various receptors ([Table 70–2](#)). However, by far the most widely used classification system categorizes antipsychotics as either typical or atypical. Typical (also called traditional, conventional or, increasingly, first-generation) antipsychotics dominated the first 40 years of antipsychotic therapy. They were subcategorized according to their affinity for the D₂ receptor as either low potency (exemplified by thioridazine and chlorpromazine) or high potency (exemplified by haloperidol). They ameliorated the positive symptoms of schizophrenia, such as hallucinations, delusions, paranoia, and disorganization of thought, but were of little benefit for the sometimes disabling negative symptoms including avolition, alogia, flattening of affect, and social withdrawal. Moreover, they were associated with acute, subacute, and long-term motor disturbances collectively referred to as EPS.

TABLE 70–2. Toxic Manifestations of Selected Antipsychotics

	<i>α</i> ₁ -Adrenergic Antagonism	Muscarinic Antagonism	Fast Sodium Channel (<i>I</i> _{Na}) Blockade	Delayed Rectifier (<i>I</i> _K) Current Blockade
Clinical effect	Hypotension	Central and peripheral anticholinergic effects	QRS widening; rightward T40msec; myocardial depression	QT interval prolongation; torsade de pointes
Typical Antipsychotics				
Chlorpromazine	+++	++	++	++
Fluphenazine	-	-	+	+
Haloperidol	-	-	+	++
Loxapine	+++	++	++	+
Mesoridazine	+++	+++	+++	++
Perphenazine	+	-	+	++
Pimozide	+	-	+	++
Thioridazine	+++	+++	+++	+++
Trifluoperazine	+	-	+	++
Atypical Antipsychotics				
Aripiprazole	++	-	-	-
Clozapine	+++	+++	-	+
Olanzapine	++	+++	-	-
Quetiapine	+++	+++	+	- to +
Remoxipride	-	-	-	-
Risperidone	++	-	-	-
Sertindole	+	-	-	++
Ziprasidone	++	-	-	+++

Data from References 18, 21, 45, 96, and 98.

The concept of antipsychotic atypicality has evolved over time with the introduction of new compounds^{94,113} and connotes different properties to pharmacologists and clinicians. From a clinical perspective, atypical antipsychotics (sometimes termed second-generation antipsychotics) treat both the positive and negative symptoms of schizophrenia, are less likely than traditional drugs to produce EPS at clinically effective doses, and cause little or no elevation of the serum prolactin concentration.⁵⁷ From a pharmacologic perspective, most atypical antipsychotics also inhibit the action of serotonin at the 5-HT_{2A} receptor. More than a dozen atypical antipsychotics are now in clinical use or under development. Despite their considerably higher cost, these drugs have largely supplanted traditional antipsychotics because of their effectiveness in treating the negative symptoms of schizophrenia and their somewhat more favorable adverse effect profile, in addition to the perception that they cause fewer long-term adverse effects than conventional antipsychotics—a belief that may result, in part, from the use of higher doses of older drugs in studies comparing the tolerability of typical and atypical antipsychotics.⁴⁸ Considerable controversy exists regarding the superiority of these drugs over those of the first-generation antipsychotics, and it is worth noting that the use of the newer antipsychotics for other indications is extremely common, including their use as adjunctive treatment for major depression, eating disorders, attention-deficit hyperactivity disorder, insomnia, posttraumatic stress disorder, personality disorders, and Tourette syndrome.⁶⁸ However, the most extensive off-label use of these drugs is for the management of agitation associated with cognitive impairment in the elderly.

Mechanisms of Antipsychotic Action

Of the many contemporary theories of schizophrenia, the most enduring has been the dopamine hypothesis.¹⁰⁷ First advanced in 1967 and supported by in vivo data,¹ this theory holds that the “positive symptoms” of schizophrenia (hallucinations, delusions, paranoia, and disorganization of thought) result from excessive dopaminergic signaling in the mesolimbic and mesocortical pathways.⁷³ This hypothesis was borne in part from the observation that hallucinations and delusions could be produced in otherwise normal individuals by drugs that increase dopaminergic transmission, such as cocaine and amphetamine, and that these effects could be blunted by dopamine antagonists.

There are at least five subtypes of dopamine receptors (D₁ through D₅), but schizophrenia principally involves excess signaling at the D₂ subtype,¹⁰⁷ and antagonism of D₂ neurotransmission is the sine qua non of antipsychotic activity. Antipsychotics have different potencies at this receptor, reflected by the dissociation constant (K_d), which in turn reflects release of the drug from the D₂ receptor. For example, the receptor releases clozapine and quetiapine more rapidly than it

does any other drugs.^{105,107}

Dopamine receptors are present in many other areas of the central nervous system (CNS), including the nigrostriatal pathway (substantia nigra, caudate, and putamen, which collectively govern the coordination of movement), tuberoinfundibular pathway, hypothalamus and pituitary, and area postrema of the brainstem, which contains the chemoreceptor trigger zone (CTZ). Antipsychotic-related blockade of D₂ neurotransmission in these areas is associated with many of the beneficial and adverse effects of these drugs. For example, D₂ antagonism in the CTZ alleviates nausea and vomiting, whereas blockade of hypothalamic D₂ receptors increases pituitary prolactin release, resulting in gynecomastia and galactorrhea. Blockade of nigrostriatal D₂ receptors underlies many of the movement disorders associated with antipsychotic therapy.^{119,132}

Antipsychotics interfere with signaling at other receptors to varying degrees, including muscarinic receptors, H₁ histamine receptors, and α -adrenergic receptors. The extent to which these receptors are blocked at therapeutic doses can be used to predict the adverse effect profile of each antipsychotic.²¹ For example, drugs that antagonize muscarinic receptors at clinically effective doses (most notably the aliphatic and piperidine phenothiazines as well as clozapine, loxapine, olanzapine, and quetiapine) often produce anticholinergic adverse effects during routine use and can produce pronounced anticholinergic manifestations following overdose (Table 70–2). Similarly, blockade of peripheral α_1 -adrenergic receptors by the aliphatic and piperidine phenothiazines, clozapine, risperidone, and others renders them more likely to cause postural hypotension during therapy and clinically important hypotension following overdose. In contrast, haloperidol overdose is not characterized by marked antimuscarinic effects or hypotension.

Several antipsychotics also block voltage-gated fast sodium channels (I_{Na}). Although this effect is of little consequence during therapy, in the setting of overdose this can slow cardiac conduction (phase 0 depolarization) and impair myocardial contractility. This effect, most notable with the phenothiazines, is both rate- and voltage-dependent, and is therefore more pronounced at faster heart rates and less negative transmembrane potentials.¹⁸ Blockade of the delayed rectifier potassium current (I_{Kr}) can produce prolongation of the QT interval, creating a substrate for development of torsade de pointes.⁷⁸ QT interval prolongation is sometimes evident during maintenance therapy, particularly in patients with previously unrecognized repolarization abnormalities or additional risk factors for QT prolongation. This effect may partially explain the dose-dependent increase in risk of sudden cardiac death among patients treated with typical and atypical antipsychotics.^{92,93}

Several antipsychotics exhibit a relatively high degree of antagonism at the 5-HT_{2A} receptor, which conveys two important therapeutic properties: (1) greater effectiveness for the treatment of the negative symptoms of schizophrenia and (2) a significantly lower incidence of extrapyramidal side effects. Others antipsychotics are distinguished by unique effects at different receptors. For example, loxapine and clozapine inhibit the presynaptic reuptake of catecholamines and antagonize γ -aminobutyric acid (GABA)_A receptors,¹¹² which may explain the apparent increase in seizure activity with these antipsychotics.⁸⁹ A more detailed description of the pharmacology of the most commonly used second-generation antipsychotics is warranted in light of their increasing role in therapy.

Clozapine, a dibenzodiazepine compound, binds to dopamine receptors (D₁–D₅) and serotonin receptors (5-HT_{1A/1C}, 5-HT_{2A/2C}, 5-HT₃, and 5-HT₆) with moderate to high affinity.^{9,90,98} It also antagonizes α_1 -adrenergic, α_2 -adrenergic, and H₁ histamine receptors. It has the highest binding affinity of any atypical antipsychotic at M₁ muscarinic receptors.⁹⁷ Despite this feature, clozapine paradoxically activates the M₄ subtype of the muscarinic receptor and frequently produces sialorrhea during therapy.⁹⁶

Olanzapine, a thienobenzodiazepine, binds avidly to serotonin (5-HT_{2A/2C}, 5-HT₃, and 5-HT₆) and dopamine receptors (D₁, D₂, and D₄), although its potency at D₂ receptors is lower than that of most traditional antipsychotics.^{60,98} It is an exceptionally potent H₁ antagonist, binding more avidly than pyrilamine, which is a widely used antihistamine. It is also has a high affinity for M₁ receptors and is a relatively weak α_1 antagonist.

Risperidone, a benisoxazole derivative, has high affinity for several receptors, including serotonin receptors (5-HT_{2A/2C}), D₂ dopamine receptors, and α_1 and H₁ receptors.^{60,96,98} It has no appreciable activity at M₁ receptors. Its primary metabolite (9-hydroxyrisperidone) is nearly equipotent as the parent compound at D₂ and 5-HT_{2A} receptors.⁶⁰ Available orally and as a long-acting parenteral preparation, paliperidone is the major active metabolite of risperidone and exhibits a similar receptor-binding profile.

Quetiapine, a dibenzothiazepine, is a weak antagonist at D₂, M₁, and 5-HT_{1A} receptors, but it is a potent antagonist of α_1 -adrenergic and H₁ receptors.⁶⁰ Of its 11 metabolites, at least 2 are pharmacologically active, but they circulate at low concentrations and likely contribute little to its clinical effect. A considerable proportion of fatalities involving antipsychotic drugs reported to North American Poison Control Centers involve quetiapine, usually in combination with other drugs.¹⁶

Ziprasidone, a benzothiazole derivative, is an antagonist at dopaminergic D₂ and several serotonin (5-HT_{2A/2C}, 5-HT_{1D}, and 5-HT₇) receptors, but it also displays agonist activity at 5-HT_{1A} receptors.^{60,61,98} Its α₁-antagonist activity is particularly strong, with a binding affinity approximately one tenth that of prazosin. In addition, it is a strong inhibitor of the delayed rectifier channel (I_{Kr}) and can significantly prolong repolarization.^{61,70}

Aripiprazole, a quinolinone derivative, is a novel compound that binds avidly to dopamine D₂ and D₃ receptors and serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2B} receptors.^{77,98} Some evidence suggests that its efficacy in the treatment of schizophrenia and its lower propensity for EPS may relate to partial agonist activity at dopamine D₂ receptors.⁷⁶ Aripiprazole acts as a partial agonist at serotonin 5-HT_{1A} receptors but is an antagonist at serotonin 5-HT_{2A} receptors. Its principal active metabolite, dehydroaripiprazole, has affinity for dopamine D₂ receptors and thus has pharmacologic activity similar to that of the parent compound.⁷⁷

Like aripiprazole, bifeprunox is a partial agonist at D₂ and 5-HT_{1A} receptors. It has been characterized as a third-generation antipsychotic and has no appreciable affinity for serotonin 5-HT_{2A} and 5-HT_{2C} histaminergic or muscarinic receptors.^{28,80,106}

Amisulpride is a substituted benzamide derivative that preferentially blocks dopamine receptors in limbic rather than striatal structures. At low doses, it blocks presynaptic D₂ and D₃ receptors, thereby accentuating dopamine release, while at high doses it blocks postsynaptic D₂ and D₃ receptors. It has relatively low affinity for serotonergic, histaminergic, adrenergic, and cholinergic receptors.

Sertindole is a second-generation antipsychotic drug that was recently reintroduced into the market after being voluntarily withdrawn in 1998 over concerns about its effects on the QT interval. It binds to striatal D₂ receptors, although less avidly than olanzapine, and also exhibits antagonism at 5-HT_{2A} and α₁-adrenergic receptors.^{59,86,111} It is estimated that 3.1% to 7.8% of patients receiving sertindole develop QT intervals greater than 500 milliseconds.¹³⁰

PHARMACOKINETICS AND TOXICOKINETICS

With a few exceptions, the antipsychotics have similar pharmacokinetic characteristics regardless of their chemical classification. Most are lipophilic, have a large volume of distribution, and are generally well absorbed, although anticholinergic effects may delay absorption of some antipsychotics. Serum concentrations generally peak within 2 to 3 hours after a therapeutic dose, but this can be prolonged following overdose.

Most antipsychotics are substrates for the various isozymes of the hepatic cytochrome P450 (CYP) enzyme system. For example, haloperidol, perphenazine, thioridazine, sertindole, and risperidone are extensively metabolized by the CYP2D6 system, which is functionally absent in approximately 7% of white patients and overexpressed in 1% to 25% of patients, depending on ethnicity.⁵³ These polymorphisms appear to influence the tolerability and efficacy of treatment with these antipsychotics during therapeutic use^{15,29,30,56,124} but are unlikely to significantly alter the severity of acute antipsychotic overdose.

Drugs that inhibit CYP2D6 (such as paroxetine, fluoxetine, and bupropion) can increase the concentrations of these antipsychotics and increase the risk of adverse effects. In contrast, metabolism of clozapine is primarily mediated by CYP1A2, and increased clozapine concentrations can result following exposure to CYP1A2 inhibitors such as fluvoxamine, macrolide and fluoroquinolone antibiotics, as well as after smoking cessation, because smoking induces CYP1A2.³⁵ The kidney plays a relatively small role in the elimination of antipsychotics, and dose adjustment is generally not necessary for patients with kidney disease.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Table 70–3 lists the adverse effects of antipsychotics. Some of these effects develop primarily following overdose, but others can occur during the course of therapeutic use.

TABLE 70–3. Adverse Effects of Antipsychotics

Cardiovascular	Tachycardia
Clinical	Hypotension (orthostatic or resting)
Electrocardiographic	Myocardial depression
	QRS complex widening
	Right deviation of terminal 40 msec of QRS axis
	QT interval prolongation
	Torsade de pointes
	Nonspecific repolarization changes
Central nervous system	Somnolence, coma
	Respiratory depression, loss of airway reflexes
	Hyperthermia
	Seizures
	Extrapyramidal syndromes
	Central anticholinergic syndrome
Dermatologic	Impaired sweat production
	Cutaneous vasodilation
Endocrine	Amenorrhea, oligomenorrhea, or metrorrhagia
	Breast tenderness and galactorrhea
Gastrointestinal	Impaired peristalsis
	Dry mouth
Genitourinary	Urinary retention
	Ejaculatory dysfunction
	Priapism
Ophthalmic	Mydriasis or miosis; visual blurring

Adverse Effects During Therapeutic Use

The Extrapyramidal Syndromes. The EPS (Table 70–4) are a heterogeneous group of disorders that share the common feature of abnormal muscular activity. Among the typical antipsychotics, the incidence of EPS appears to be highest with the more potent antipsychotics such as haloperidol and flupentixol, and lower with less potent antipsychotics such as chlorpromazine and thioridazine. Atypical antipsychotics are associated with an even lower incidence of EPS. Although the physiologic mechanisms for this observation are not fully understood, several hypotheses have been put forth. In addition to the aforementioned antagonism of 5-HT_{2A} receptors, some atypical antipsychotics dissociate more rapidly from the D₂ receptor and incite a lower degree of nigrostriatal dopaminergic hypersensitivity during chronic use.^{57,58,71} However, it is important to note that EPS can occur during treatment with any antipsychotic drug, regardless of typicality or potency.

TABLE 70–4. The Extrapyramidal Syndromes

<i>Disorder</i>	<i>Time of Maximal Risk</i>	<i>Features</i>	<i>Postulated Mechanism</i>	<i>Possible Treatments</i>
Acute dystonia	Hours to a few days	Sustained, involuntary muscle contraction, torticollis, including blepharospasm, oculogyric crisis	Imbalance of dopaminergic/cholinergic transmission	Anticholinergics, benzodiazepines
Akathisia	Hours to days	Restlessness and unease, inability to sit still	Mesocortical D ₂ antagonism	Dose reduction, trial of alternate drug, propranolol, benzodiazepines, anticholinergics
Parkinsonism	Weeks	Bradykinesia, rigidity, shuffling gait, masklike facies, resting tremor	Postsynaptic striatal D ₂ antagonism	Dose reduction, anticholinergics, dopamine agonists
Neuroleptic malignant syndrome	2–10 days	Many (Table 70–5): altered mental status, motor symptoms, hyperthermia, autonomic instability, catatonia, mutism	D ₂ antagonism in striatum, hypothalamus, and mesocortex	Cooling, benzodiazepines, supportive care, consider dantrolene, bromocriptine, amantadine, or other direct-acting dopamine agonists
Tardive dyskinesia	3 months to years	Late onset involuntary choreiform movements, buccolinguo-masticatory movements	Excess dopaminergic activity	Recognize early and stop offending antipsychotic; addition of another antipsychotic; cholinergics

Data from References 88 and 119.

Acute dystonia. Acute dystonia is a movement disorder characterized by sustained involuntary muscle contractions, often involving the muscles of the head and neck, including the extraocular muscles and the tongue, but occasionally involving the extremities. These contractions are sometimes referred to as limited reactions, reflecting their transient nature rather than their severity. All the currently available antipsychotics are associated with the development of acute dystonic reactions.¹¹⁹ Spasmodic torticollis, facial grimacing, protrusion of the tongue, and oculogyric crisis are among the more common manifestations. Laryngeal dystonia is a rare but potentially life-threatening variant that is easily misdiagnosed because it can present with throat pain, dyspnea, stridor, and dysphonia rather than the more characteristic features of dystonia.³⁸

Acute dystonia typically develops within a few hours of starting of treatment but may be delayed for up to a few days. Left untreated, dystonia resolves slowly over several days once the offending antipsychotic is withdrawn. Risk factors for acute dystonia include male gender, young age (children are particularly susceptible), a previous episode of acute dystonia, and recent cocaine use.^{120,132} Although the reaction may appear dramatic and sometimes is mistaken for seizure activity, it is rarely life threatening. Of note, drugs other than antipsychotics can sometimes cause acute dystonia, particularly metoclopramide, antidepressants, some antimalarials, histamine H₂-receptor antagonists, anticonvulsants, and cocaine.¹²⁰

Treatment of acute dystonia. Acute dystonia is generally more distressing than serious, but rare cases compromise respiration, necessitating supplemental oxygen and, occasionally, assisted ventilation.^{38,120} The response to parenteral anticholinergics often is rapid and dramatic, and every effort should be made to administer benztropine as the first-line agent (2 mg intravenously {IV} or intramuscularly {IM} in adults, or 0.05 mg/kg in children). Often, diphenhydramine is more readily available and can be used instead (50 mg IV or IM in adults, or 1 mg/kg in children). Parenteral benzodiazepines such as lorazepam (0.05–0.10 mg/kg IV or IM) or diazepam (0.1 mg/kg IV) should be considered if patients do not respond to anticholinergics, but they may also be effective as initial therapy. It is important to recognize that because the elimination half-life of most anticholinergics is shorter than that of most antipsychotics, dystonia can recur, and administering additional doses of an anticholinergic may be necessary over the next 48 to 72 hours.²⁷ Patients in whom acute dystonia jeopardizes respiration should be observed for at least 12 to 24 hours after initial resolution.

Akathisia. Akathisia (from the Greek phrase “not to sit”) is characterized by a feeling of inner restlessness, anxiety, or sense of unease, often in conjunction with the objective finding of an inability to sit still. Patients with akathisia frequently appear uncomfortable or fidgety. They may rock back and forth while standing, or may repeatedly cross and uncross their legs while seated. Akathisia can be difficult to diagnose and is easily misinterpreted as a manifestation of the underlying psychiatric disorder rather than an adverse effect of therapy.

Akathisia is common and may be an important determinant of adherence to therapy. Like acute dystonia, akathisia tends to occur relatively early in the course of treatment and coincides with peak antipsychotic concentrations in serum.¹³² The incidence appears highest with typical, high-potency antipsychotics and lowest with atypical antipsychotics. Although most cases develop within days to weeks after initiation of treatment or an increase in dose, a delayed-onset (tardive) variant is also recognized.

The pathophysiology of akathisia is incompletely understood but appears to involve antagonism of postsynaptic D₂

receptors in the mesocortical pathways.^{71,119} Interestingly, a similar phenomenon is described in patients following the initiation of treatment with antidepressants, particularly the selective serotonin reuptake inhibitors (Chap. 75).^{8,67}

Treatment of akathisia. Akathisia can be difficult to treat. A reduction in the antipsychotic dose is sometimes helpful, as is substitution of another (generally atypical) antipsychotic. Treatment with lipophilic β -adrenergic antagonists such as propranolol may reduce the symptoms of akathisia, but little evidence supports their use.^{65,88} Benzodiazepines produce short-term relief, and anticholinergics such as benztropine or procyclidine may reduce manifestations of akathisia, but they are more likely to be effective for akathisia induced by antipsychotics with little or no intrinsic anticholinergic activity.^{20,66}

Parkinsonism. Antipsychotics can produce a parkinsonian syndrome characterized by rigidity, akinesia or bradykinesia, and postural instability. It is similar to the idiopathic Parkinson disease, although the classic “pill-rolling” tremor is often less pronounced.⁸⁸ The syndrome typically develops during the first few months of therapy, particularly with high-potency antipsychotics. It is more common among older women, and in some patients it may represent iatrogenic unmasking of latent Parkinson disease. Parkinsonism is thought to result from antagonism of postsynaptic D_2 receptors in the striatum.¹¹⁹

Treatment of drug-induced parkinsonism. The risk of drug-induced parkinsonism can be minimized by using the lowest effective dose of antipsychotic. The addition of an anticholinergic often attenuates symptoms, at the expense of additional side effects. This strategy often is effective in younger patients, although the routine use of prophylactic anticholinergics is not recommended. Addition of a dopamine agonist such as amantadine is sometimes used, particularly in older patients who may be less tolerant of anticholinergics, but this may aggravate the underlying psychiatric disturbance.⁶⁹

Tardive dyskinesias. The term tardive dyskinesia was coined in 1952 to describe the delayed onset of persistent orobuccal masticatory movements occurring in three women after several months of antipsychotic therapy.¹¹⁹ The adjective tardive, meaning delayed, was used to distinguish these movement disorders from the Parkinsonian movements described above. The incidence of tardive dyskinesia in younger patients is approximately 3% to 5% per year but rises considerably with age. A prospective study of older patients treated with high potency typical antipsychotics identified a 60% cumulative incidence of tardive dyskinesia after 3 years of treatment.⁵³ Potential risk factors for tardive dyskinesia include alcohol use, affective disorder, prior electroconvulsive therapy, diabetes mellitus, and various genetic factors.¹¹⁹

Several distinct tardive syndromes are recognized, including the classic orobuccal lingual masticatory stereotypy, chorea, dystonia, myoclonus, blepharospasm, and tics. It is generally accepted that the atypical antipsychotics are associated with a lower incidence of tardive dyskinesia and other drug-related movement disorders. However, whether this is true of all atypical antipsychotics is unclear. Among the atypical antipsychotics, clozapine is associated with the lowest incidence of tardive dyskinesia and risperidone with the highest incidence (when higher doses are used), but the reasons for this observation are uncertain.^{115,116,119}

Treatment of tardive dyskinesia. Tardive dyskinesia is highly resistant to the usual pharmacologic treatments for movement disorders. Anticholinergics do not alleviate tardive dyskinesia and indeed may worsen it. Calcium channel blockers, β -adrenergic antagonists, benzodiazepines, and vitamin E have all been used with limited success.³⁶ Clozapine appears to suppress tardive dyskinesia temporarily. Although discontinuation of the causative antipsychotic may not produce total relief of symptoms, when possible, the antipsychotic should be discontinued as soon as signs or symptoms begin.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS) is a potentially life-threatening drug-induced emergency. First described in 1960 in patients treated with haloperidol, this syndrome has been associated with virtually every antipsychotic.³² The reported incidence of NMS ranges from 0.2% to 1.4% of patients receiving antipsychotics,^{2,23,114} but less severe episodes may go undiagnosed or unreported. As a result, much of what is known about the epidemiology and treatment of NMS is speculative and based upon case reports and case series.

The pathophysiology of NMS is incompletely understood but appears to involve abrupt reductions in central dopaminergic neurotransmission in the striatum and hypothalamus, altering the core temperature setpoint,⁴³ and leading to impaired thermoregulation and other manifestations of autonomic dysfunction. Blockade of striatal D_2 receptors contributes to muscle rigidity and tremor.^{13,25,121} In some cases, a direct effect on skeletal muscle may play a role in the pathogenesis of hyperthermia.⁴³ Altered mental status is multifactorial and may reflect hypothalamic and spinal dopamine receptor antagonism, a genetic predisposition, or the direct effects of hyperthermia and other drugs.⁴⁴ Serotonin also appears to play a role in the pathogenesis of NMS, because antipsychotics that antagonize 5-HT_{2A} receptors seem to be associated with a lower incidence of NMS.⁴

Although NMS most often occurs during treatment with a D_2 receptor antagonist, withdrawal of dopamine agonists can produce an indistinguishable syndrome. The latter typically occurs in patients with long-standing Parkinson disease who abruptly change or discontinue treatment with dopamine agonists such as levodopa/carbidopa, amantadine, or bromocriptine.¹³ The resulting disorder is sometimes referred to as the parkinsonian-hyperpyrexia syndrome, and mortality rates of up to 4% are reported.⁷⁹ Hospitalization for aspiration pneumonia, a common occurrence in older patients with Parkinson disease, is a particularly high-risk setting for this complication, and is particularly dangerous because the

cardinal manifestations of NMS are easily misattributed to the combined effects of pneumonia and the underlying movement disorder.

The vast majority of NMS cases occur in the context of therapeutic use of antipsychotics rather than following overdose. Postulated risk factors for the development of NMS include young age, male gender, extracellular fluid volume contraction, use of high-potency antipsychotics, depot preparations, cotreatment with lithium, multiple drugs in combination, and rapid dose escalation.^{2,24,63,81} One large observational study⁸¹ suggests that treatment with high-potency first-generation antipsychotics is associated with a more than 20-fold increase in the risk of NMS, although this may partly reflect heightened suspicion of the disorder in patients receiving those antipsychotics. The mortality rate of NMS associated with first-generation antipsychotics is estimated at approximately 16%, whereas the rate associated with second-generation antipsychotics is estimated at 3%.¹¹⁸

The manifestations of NMS include the tetrad of altered mental status, muscular rigidity (classically described as “lead pipe”), hyperthermia, and autonomic dysfunction. These symptoms can appear in any sequence, although a review of 340 NMS cases found that mental status changes and rigidity usually preceded the development of hyperthermia and autonomic instability.¹²² Occasionally, rigidity is not present when creatine kinase concentrations are elevated but emerges thereafter.⁸² Signs typically evolve over a period of several days, with the majority occurring within 2 weeks of initiation. However, it is important to recognize that NMS can occur even after prolonged use of an antipsychotic, particularly following a dose increase, the addition of another agent, or the development of intercurrent illness. It is also worth noting that the clinical course of NMS can fluctuate rapidly, sometimes waxing and waning dramatically over a few hours.

There is no universally accepted set of criteria for the diagnosis of NMS, and more than a dozen sets of criteria have been proposed.^{3,23,34,63} The operating characteristics of these criteria have not been formally evaluated, in part because of the absence of a gold standard. An international group has published the results of a Delphi consensus panel regarding the diagnosis of NMS.⁴² While these too have not yet been validated, the criteria and their relative importance are shown in Table 70–5.

TABLE 70–5. Suggested Diagnostic Criteria for the Neuroleptic Malignant Syndrome⁴³

<i>Criterion</i>	<i>Priority Score^a</i>
Exposure to a dopamine antagonist or withdrawal of a dopamine agonist in previous 72 hours	20
Hyperthermia (>100.4°F [38.0°C]) on at least two occasions, measured orally	18
Rigidity	17
Mental status alteration (reduced or fluctuating level of consciousness)	13
Creatine kinase elevation (at least four times the upper limit of normal)	10
Sympathetic nervous system lability, defined as at least two of: Blood pressure elevation (SBP or DBP ≥ 25% above baseline) Blood pressure fluctuation (≥ 20% DBP change or ≥ 25% SBP change in 24 hours) Diaphoresis Urinary incontinence	10
Hypermetabolic state (defined as heart rate increase ≥25% above baseline and respiratory rate increase ≥50% above baseline)	5
Negative workup for other toxic, metabolic, infectious, or neurologic causes	7

^aPriority scores sum to 100 and represent the perceived importance of eight criteria (distilled using a Delphi process from 64 distinct diagnostic features) relative to others. For example, a characteristic drug exposure history (20 points) is deemed approximately two times as important as creatine kinase elevation (10 points) and four times as important as the presence of a hypermetabolic state (5 points). Scores are not meant to be added, and no threshold is defined.

DBP = diastolic blood pressure; SBP = systolic blood pressure.

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It may be difficult to distinguish NMS from other toxin-induced hyperthermia syndromes, such as the anticholinergic (antimuscarinic) syndrome ([Chap. 49](#)) and serotonin toxicity ([Chap. 75](#)), all of which share the common features of elevated temperature, altered mental status, and neuromuscular abnormalities. The most important differentiating feature is the medication history, with dopamine antagonists, antimuscarinics, and direct or indirect serotonin agonists (often in combination) as the most likely causal agents, respectively. The time course of the illness may also help differentiate among the disorders. Serotonin toxicity and the antimuscarinic syndrome tend to develop rapidly after exposure to causative substances, while NMS typically develops more gradually, often waxing and waning over several days or more. Occasionally, clinicians must attempt to differentiate NMS from these disorders in the absence of a reliable medication history. The physical examination can be of some utility in this regard.⁸⁷ While NMS is classically characterized by rigidity, the presence of ocular or generalized clonus is more suggestive of serotonin toxicity, particularly when accompanied by shivering and hyperreflexia, features that are not typical of NMS. Because skeletal muscle contraction is effected by nicotinic rather than muscarinic transmission, patients with antimuscarinic syndrome have few muscular abnormalities. However, such patients can sometimes be resistant to physical restraint, giving the appearance of increased muscle tone.

Treatment of neuroleptic malignant syndrome: General measures. Treatment recommendations are largely based on general physiologic principles, case reports, and case series. Therapy should be individualized according to the severity and duration of illness and the modifying influences of comorbidity.^{13,95,123} The provision of good supportive care is the cornerstone for treatment of NMS. It is essential to recognize the condition as an emergency and to withdraw the offending antipsychotic immediately. When NMS ensues after abrupt discontinuation of a dopamine agonist such as levodopa, the drug should be reinstituted promptly. Most patients with NMS should be admitted to an intensive care unit. Supplemental oxygen should be administered, and assisted ventilation may be necessary in cases of respiratory failure, which can result from central hypoventilation, loss of protective airway reflexes, or rigidity of the chest wall muscles.

The hyperthermia associated with NMS is multifactorial in origin and, when present, warrants aggressive treatment. Submersion in an ice-water bath is rapidly effective, although this may be impractical in some settings ([Chap. 30](#)). Other strategies include the use of active cooling blankets, the placement of ice packs in the groin and axillae, or evaporative cooling, which can be accomplished by removing the patient's clothing and exposing the patient to cooled water or towels immersed in ice water, while maintaining constant air circulation with the use of fans.¹²⁷

Hypotension should be treated initially with generous volumes of isotonic crystalloid, followed by vasopressors if necessary. Alkalinization of the urine with sodium bicarbonate may reduce the incidence of myoglobinuric acute kidney injury (AKI) in patients with high creatine kinase concentrations, but maintenance of intravascular volume and adequate renal perfusion are of far greater importance. Tachycardia does not require specific treatment, but bradycardia may necessitate the use of transcutaneous or transvenous electrical pacing. Venous thromboembolism is a major cause of morbidity and mortality in patients with NMS, and prophylactic doses of low-molecular-weight heparin should be considered in patients who likely will be immobilized for more than 12 to 24 hours.

Treatment of neuroleptic malignant syndrome: Pharmacologic measures. Benzodiazepines are the most widely used pharmacologic adjuncts for treatment of NMS and are considered first-line therapy. Dantrolene and bromocriptine are not well studied, and their incremental benefit over good supportive care is debated.^{95,100} However, these drugs are associated with relatively little toxicity, and their use is therefore easily justified, particularly in patients with moderate or severe NMS.

Benzodiazepines are frequently used in the management of NMS because of their rapid onset of action, which is particularly important when patients are agitated or restless. They attenuate the sympathetic hyperactivity that characterizes NMS by facilitating GABA-mediated chloride transport and producing neuronal hyperpolarization, in a fashion analogous to their beneficial effects in cocaine toxicity.⁴⁴ The primary disadvantage of benzodiazepines is that they may cloud the assessment of mental status.

Dantrolene reduces skeletal muscle activity by inhibiting ryanodine receptor calcium release channels, interfering with calcium release from the sarcoplasmic reticulum. In theory, this process should reduce body temperature and total oxygen consumption. It also should lessen the risk of myoglobinuric AKI. Dantrolene has been suggested to be particularly useful when muscular rigidity is a prominent feature of NMS.¹³ It can be given by mouth (50–100 mg/d) or by IV infusion (2–3 mg/kg/d, or up to 10 mg/kg/d in severe cases), although the latter requires laborious reconstitution. A review of 271 published cases of NMS that included information regarding drug treatment found that combination therapy including dantrolene was associated with a prolonged clinical recovery, but also that dantrolene monotherapy was associated with higher mortality than other treatment modalities including supportive care.⁹⁵ The authors concluded that dantrolene was not an evidence-based therapy. However, it is also a relatively nontoxic drug that remains a reasonable therapeutic option in patients with NMS, particularly those with prominent and refractory rigidity.

Bromocriptine is a centrally acting dopamine agonist that is given orally or by nasogastric tube at doses of 2.5 to 10 mg, 3 to 4 times daily. The rationale for its use rests in the belief that reversal of antipsychotic-related striatal D₂ antagonism will ameliorate the manifestations of NMS. Other dopamine agonists anecdotally associated with success include

ropinirole, levodopa,^{84,110} and amantadine.^{41,52,114} When these drugs are used, they should be tapered slowly after the patient improves to minimize the likelihood of recrudescence NMS. In severe cases, dantrolene and a dopamine agonist can be used in combination. Of note, dopaminergic agents may be associated with exacerbation of underlying psychiatric illness.

Electroconvulsive therapy. Electroconvulsive therapy (ECT) has been reported to dramatically improve the manifestations of NMS, presumably by enhancing central dopaminergic transmission. In one report, five patients received an average of 10 ECT treatments, and resolution generally occurred after the third or fourth session.⁸³ Whether this result represents a true effect of ECT or simply the natural course of NMS with good supportive care alone is not clear. As with drug therapies for NMS, the efficacy of ECT remains unclear and its indications speculative, but its use seems reasonable in patients with severe, persistent, or treatment-resistant NMS and for those with residual catatonia or psychosis following resolution of other manifestations.^{13,84}

Adverse Effects on Other Organ Systems. Sedation, dry mouth, and urinary retention occur commonly with antipsychotics, particularly during the initial period of therapy. These symptoms occur most commonly with drugs having potent antihistaminic and antimuscarinic activity. All antipsychotics can lower the seizure threshold, but seizures are uncommon during therapeutic use. Because hypothalamic dopamine inhibits pituitary prolactin release, hyperprolactinemia and galactorrhea can occur. All antipsychotics are associated with metabolic derangements, including weight gain, dyslipidemia, and steatohepatitis. The metabolic syndrome appears most commonly in association with clozapine, olanzapine, and chlorpromazine.³¹ Rare but dramatic instances of glucose intolerance, including fatal cases of diabetic ketoacidosis, are also described.^{6,47,91,117} The mechanism of this is incompletely understood, but it is not adequately explained by the weight gain associated with antipsychotic therapy, because glucose disturbances often develop shortly after therapy is instituted. Other idiosyncratic reactions reported with use of antipsychotics include photosensitivity, skin pigmentation, and cholestatic hepatitis (particularly with the phenothiazines), myocarditis, and agranulocytosis, which occurs with many antipsychotic drugs, most notably clozapine (in up to 2% of patients).⁷⁵ Most of these conditions result from an immunologically based hypersensitivity reaction and develop during the first month of therapy. Finally, an increasing number of reports associate antipsychotics with venous thromboembolism.^{46,55} This may partially explain the high incidence of thromboembolic disease found in patients with NMS (see above).

Acute Overdose

Antipsychotic overdose can produce a spectrum of toxic manifestations affecting multiple organ systems, but most serious toxicity involves the CNS and cardiovascular systems. Some of these manifestations are present to a minor degree during therapeutic use, although they tend to be most pronounced during the early period of therapy and dissipate with continued use.

Impaired consciousness is a common and dose-dependent feature of antipsychotic overdose, ranging from somnolence to coma. It may be associated with impaired airway reflexes, but significant respiratory depression is uncommon. Many antipsychotics, including several of the atypical drugs, are potent muscarinic antagonists and can produce anticholinergic features in overdose.^{11,21,26} Peripheral manifestations include tachycardia, decreased production of sweat and saliva, flushed skin, urinary retention, diminished bowel sounds and mydriasis, although miosis also occurs. These findings may be present in isolation or coexist with central manifestations, including agitation, delirium, psychosis, hallucinations, and coma, some of which may be mistakenly attributed to the underlying psychiatric illness.

Mild elevations in body temperature are common and reflect impaired heat dissipation as a result of impaired sweating, and increased heat production in agitated patients. Hyperthermia should always prompt a search for other features of NMS. Tachycardia is a common finding in patients with antipsychotic overdose and reflects reduced vagal tone and, when present, a compensatory response to hypotension. Bradycardia is distinctly uncommon, and while it may be a preterminal finding, its presence should prompt a search for alternate causes including an ingestion of negative chronotropic drugs such as β -adrenergic antagonists, calcium channel blockers, cardiac glycosides, and opioids. Hypotension is a common feature of antipsychotic overdose and is generally due to peripheral α_1 -adrenergic blockade and decreased myocardial contractility.

The electrocardiographic (ECG) manifestations of antipsychotic overdose exhibit similarities to those of cyclic antidepressant toxicity (Chaps. 16 and 71) and include widening of the QRS complex and a rightward deflection of the terminal 40 msec of the QRS complex, typically manifesting as a tall, broad terminal component of the QRS complex in lead aVR. These changes reflect blockade of the inward sodium current (I_{Na}). Prolongation of the QT interval results from blockade of the delayed rectifier potassium current (I_{Kr}), creating a substrate for development of torsade de pointes.⁷⁸ This situation is sometimes evident during maintenance therapy and may underlie the apparent increase in sudden cardiac death among users of antipsychotics.^{92,93} A published meta-analysis of the operating characteristics of the ECG in patients with cyclic antidepressant toxicity found the ECG was a relatively poor predictor of seizures, dysrhythmia, and death.⁷ However, the ECG is a dynamic instrument, particularly in the initial hours following overdose, and few studies have

evaluated longitudinal changes in the ECG.⁶⁴

DIAGNOSTIC TESTS

The diagnosis of antipsychotic poisoning is supported by the clinical history, the physical examination, and a limited number of adjunctive tests. Both the clinical and ECG findings are nonspecific and can occur following overdose of several different drug classes, including CAs, skeletal muscle relaxants, carbamazepine, and first-generation antihistamines such as diphenhydramine. Moreover, the absence of typical ECG changes does not exclude a significant antipsychotic ingestion, particularly in the initial phase of an overdose, and at least one additional ECG should be performed in the subsequent 2 to 3 hours.

Abdominal radiography may reveal radioopacities in the gastrointestinal tract, as some solid dosage forms of phenothiazines are radiopaque. However, these tests are neither sensitive nor specific, and they are not routinely recommended.

Serum concentrations of antipsychotics are not widely available, do not correlate well with clinical signs and symptoms, and do not help guide therapy. Comprehensive urine drug screens using high-performance liquid chromatography, gas chromatography–mass spectrometry, or tandem mass spectrometry may indicate the presence of antipsychotics, but these tests are available at only a few hospitals and in most instances provide only a qualitative result. Blood and urine immunoassays for CAs may yield a false-positive result in the presence of phenothiazines.^{5,99}

MANAGEMENT

The care of a patient with an antipsychotic overdose should proceed with the recognition that other drugs, particularly other psychotropics, may have been coingested and can confound both the clinical presentation and management. Regularly encountered coingestants include other psychotropic drugs such as antidepressants, sedative-hypnotics, anticholinergics, valproic acid, and lithium, as well as ethanol and nonprescription analgesics such as acetaminophen and aspirin.

Supportive care is the cornerstone of treatment for patients with antipsychotic overdose. Supplemental oxygen should be administered if hypoxia is present. Patients with altered mental status should receive thiamine and naloxone, along with parenteral dextrose if hypoglycemia present. Intubation and ventilation are rarely required for patients with single drug ingestions but may be necessary for patients with very large overdoses of antipsychotics or ingestion of other CNS depressants. All symptomatic patients should undergo continuous cardiac monitoring. In addition, an ECG should be recorded upon presentation and reliable venous access obtained. Asymptomatic patients with a normal ECG obtained 6 hours after overdose are at exceedingly low risk of complications and no longer require cardiac monitoring. Symptomatic patients and those with an abnormal ECG should have continuous monitoring for a minimum of 24 hours.

Gastrointestinal Decontamination

Gastrointestinal decontamination with activated charcoal (1 g/kg by mouth or nasogastric tube) should be considered for patients who present within a few hours of a large or multidrug overdose. Although this intervention is time sensitive, many antipsychotics exhibit significant antimuscarinic activity and slow gastric emptying, thereby increasing the likelihood that activated charcoal will be beneficial. Although it is unknown whether activated charcoal improves clinically important outcomes, a Bayesian analysis of pharmacokinetic data from a series of quetiapine overdoses concluded that activated charcoal use led to a 35% reduction in the fraction of quetiapine absorbed.⁵⁰ Orogastric lavage and whole-bowel irrigation likely will not improve clinical outcomes and should not be routinely employed in the management of antipsychotic overdose.

Treatment of Cardiovascular Complications

Vital signs should be monitored closely. Hypotension may result from peripheral α -adrenergic blockade and is most likely to occur with older, low potency antipsychotics such as thioridazine.⁷⁶ The hypotension should be treated initially with appropriate titration of 0.9% sodium chloride solution (30–40 mL/kg). If vasopressors are required, direct-acting agonists such as norepinephrine or phenylephrine are preferred over dopamine, which is an indirect agonist and likely will be ineffective. Vasopressin or its analogs may also be used, although direct-acting vasopressors should be used with great caution in patients who have coingested a negative inotropic drug such as a β -adrenergic antagonist or calcium channel blocker. Continuous blood pressure monitoring may be warranted in such cases.

Progressive widening of the QRS complex is uncommon and reflects sodium channel blockade and slowing of phase 0 depolarization in the His-Purkinje system. This may be associated with reduced cardiac output and malignant ventricular dysrhythmias. Much of what is known about the treatment of sodium channel blocker toxicity derives from the cyclic antidepressant literature. Treatment recommendations are extended to sodium-channel-blocking antipsychotic drugs by analogy. Sodium bicarbonate (1–2 mEq/kg) is the first-line therapy for ventricular dysrhythmias and should be considered

for patients with dysrhythmias or QRS widening >0.12 msec. The rationale for this strategy is based upon the treatment of cyclic antidepressant overdose (Antidotes in Depth: A5). At least two mechanisms underlie the beneficial effects of sodium bicarbonate. First, the degree of sodium channel blockade is partially overcome by an increase in extracellular sodium. Indeed, hypertonic saline alone may be beneficial. Second, the binding of these drugs to the sodium channel is pH dependent, with less extensive binding at higher pH.

Repeated boluses of bicarbonate can be given to achieve a target blood pH of 7.5, although many toxicologists recommend continuous infusions.¹⁰⁹ If the patient is intubated, hyperventilation also can be used but is not comparably efficacious. If significant conduction abnormalities or ventricular dysrhythmias persist despite the use of sodium bicarbonate, lidocaine (1–2 mg/kg followed by continuous infusion) is a reasonable second-line antidysrhythmic. Although lidocaine is also a sodium channel antagonist, it exhibits rapid on/off sodium channel binding with preferential binding in the inactivated state and may lessen the cardiotoxicity associated with antipsychotic drug overdose.¹⁰⁸ Class IA antidysrhythmics (procainamide, disopyramide, and quinidine), class IC antidysrhythmics (propafenone, encainide, and flecainide), and class III antidysrhythmics (amiodarone, sotalol and bretylium) can aggravate cardiotoxicity and should not be used. When administering sodium bicarbonate to patients with antipsychotic overdose, caution must be taken to avoid hypokalemia, as many of these antipsychotics block cardiac potassium channels thereby prolonging the QT interval. Hypokalemia can exacerbate this blockade, potentially leading to torsade de pointes, particularly in overdoses involving amisulpride or ziprasidone.

Sinus tachycardia related to anticholinergic activity should not be treated unless it is associated with active ischemia, which, although uncommon, may complicate antipsychotic overdose in patients with existing coronary disease. Should symptomatic sinus tachycardia occur, a short-acting β -adrenergic antagonist such as esmolol may be preferable. Prolongation of the QT interval requires no specific treatment other than monitoring and correction of potential contributing causes such as hypokalemia and hypomagnesemia. Torsade de pointes should be treated with cardioversion followed by IV magnesium sulfate, taking care to prevent hypotension, which is dose- and rate-dependent. Overdrive pacing with isoproterenol or transcutaneous or transvenous pacing should be considered if the patient does not respond to magnesium sulfate, although in theory this therapy may worsen the rate-dependent sodium channel blockade.

Many antipsychotics, including olanzapine, quetiapine, and sertindole, exhibit a high degree of lipophilicity in addition to significant cardiovascular toxicity. Recently, considerable enthusiasm has emerged for the use of high-dose intravenous fat emulsion therapy for patients with significant overdoses of drugs displaying these characteristics. The rationale for this therapy rests, in part, in the concept that highly lipophilic drugs will selectively partition into the exogenous fat, thereby minimizing toxicity at the biophase. This treatment has been extensively studied in animal models of bupivacaine toxicity,^{33,125,126} but published experience with antipsychotics is limited to a handful of case reports.^{39,72,133} Dosing for fat “rescue” is not well established, but a popular protocol involves 20% lipid emulsion given as a bolus (1.5 mL/kg) followed by an infusion of 0.25 mL/kg/min for 30 to 60 minutes, with adjustment of therapy according to the individual response (Antidotes in Depth: A20). Extracorporeal circulatory support has been associated with survival in severe quetiapine overdose and may be an option in selected centers.⁶²

Treatment of Seizures

Seizures associated with antipsychotic overdose are generally short lived and often require no pharmacologic treatment. Multiple or refractory seizures should prompt a search for other causes, including hypoglycemia and ingestion of other proconvulsant medications. When treatment is necessary, benzodiazepines such as lorazepam or diazepam generally suffice, although phenobarbital may be necessary. Although phenytoin is part of the standard algorithm for status epilepticus, it is of limited effectiveness for xenobiotic-induced seizures; barbiturates such as phenobarbital or thiopental are preferred. Refractory seizures should respond to propofol infusion or general anesthesia. Seizures complicated by hyperthermia are considerably more ominous and warrant aggressive lowering of body temperature with aggressive rapid cooling measures. Finally, seizures can abruptly lower serum pH and may abruptly increase the cardiotoxicity of these drugs by enhancing binding to the sodium channel; therefore, an ECG should be obtained following resolution of seizure activity.

Treatment of the Central Antimuscarinic Syndrome

Many of the older and newer-generation antipsychotics have pronounced anticholinergic properties. Case reports and observational studies suggest that the cholinesterase inhibitor physostigmine (Antidotes in Depth: A9) can safely and effectively ameliorate the agitated delirium associated with the central anticholinergic syndrome by indirectly increasing synaptic acetylcholine concentrations.^{25,102–104} Doses of 1 to 2 mg are usual, administered cautiously after ensuring QRS widening is not present. Although benzodiazepines will control agitation, they will further impair alertness, obfuscating the assessment of mental status and increasing the risk of complications.²²

Physostigmine has been used successfully in patients with antipsychotic overdose,^{22,101,104,128,129} but it should be used with caution. It should not be used in patients with dysrhythmias, any degree of heart block, or widening of the QRS

complex. If physostigmine is used, it should be given in 0.5 mg increments slowly every 3 to 5 minutes, with close observation of the patient. If bradycardia, bronchospasm, or bronchorrhea develops, these can be treated with glycopyrrolate 0.2 to 0.4 mg IV. Atropine is often more widely available and could be used, but it crosses the blood–brain barrier and may aggravate any associated delirium. The effects of physostigmine are transient, typically ranging in duration from 30 to 90 minutes, and additional doses are often necessary. Of note, physostigmine does not prevent other complications of antipsychotic overdose, particularly those involving the cardiovascular system.

Other commonly used cholinesterase inhibitors, such as edrophonium, neostigmine, or pyridostigmine, should not be used to treat anticholinergic delirium because they do not cross the blood–brain barrier. Case reports involving other anticholinergics suggest that cholinesterase inhibitors used for treatment of dementia (eg, tacrine, donepezil, and galantamine) may be alternatives to physostigmine for patients able to take medications orally.^{51,74,85}

Enhanced Elimination

No pharmacologic rationale supports the use of multiple-dose activated charcoal or manipulation of urinary pH to increase the clearance of antipsychotics. One volunteer study found that urinary acidification may increase remoxipride elimination,¹³¹ but this practice is impractical and possibly dangerous. Because most antipsychotics exhibit large volumes of distribution and extensive protein binding (Table 70–1), extracorporeal removal is unwarranted and should be considered only if the patient has coingested other xenobiotics amenable to extracorporeal removal.

SUMMARY

- Over the past decade, atypical antipsychotics have supplanted traditional antipsychotic drugs, which were associated with greater toxicity in overdose and a higher incidence of extrapyramidal symptoms. Consequently, atypical antipsychotics are now implicated in the majority of overdoses.
- With all antipsychotics, significant toxicity can occur either during the course of therapy or following overdose.
- Of the various toxicities that arise during therapeutic use, NMS is the most dangerous. It may be difficult to recognize, but should be considered in any unwell patient treated with antipsychotics, particularly in the 2 weeks following a change in therapy or in a patient with severe intercurrent illness.
- The principal manifestations of antipsychotic overdose involve the CNS and cardiovascular system. Depressed mental status, hypotension, and anticholinergic signs are nonspecific features that support the diagnosis of antipsychotic overdose, particularly in conjunction with typical ECG findings of sodium channel blockade and QT interval prolongation. Most fatalities following antipsychotic overdose occur in cases involving coingestion of other CNS depressants or cardiotoxic medications.
- Supportive care is the mainstay of therapy for patients with antipsychotic overdose, although selective use of nonspecific antidotes, such as activated charcoal, sodium bicarbonate, or physostigmine may improve outcomes in selected patients. Particularly severe or refractory cardiovascular toxicity may warrant a trial of lidocaine or intravenous lipid emulsion, although these interventions are not well studied in this setting.

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71 CYCLIC ANTIDEPRESSANTS

Erica L. Liebelt

HISTORY AND EPIDEMIOLOGY

The term cyclic antidepressant (CA) refers to a group of pharmacologically related xenobiotics used for treatment of depression, neuralgic pain, migraines, enuresis, and attention deficit hyperactivity disorder. Most CAs have at least three rings in their chemical structure. They include the traditional tricyclic antidepressants (TCAs) imipramine, desipramine, amitriptyline, nortriptyline, doxepin, trimipramine, protriptyline, and clomipramine, as well as other cyclic compounds such as maprotiline and amoxapine.

Imipramine was the first TCA used for treatment of depression in the late 1950s. However, the synthesis of iminodibenzyl, the “tricyclic” core of imipramine, and the description of its chemical characteristics date back to 1889. Structurally related to the phenothiazines, imipramine was originally developed as a hypnotic for agitated or psychotic patients and was serendipitously found to alleviate depression. From the 1960s until the late 1980s, the TCAs were the major pharmacologic treatment for depression in the United States. However, by the early 1960s, cardiovascular and central nervous system (CNS) toxicities were recognized as major complications of TCA overdoses. The newer CAs developed in the 1980s and 1990s were designed to decrease some of the adverse effects of older TCAs, improve the therapeutic index, and reduce the incidence of serious toxicity. Other CAs include the tetracyclic drug maprotiline and the dibenzoxapine drug amoxapine.

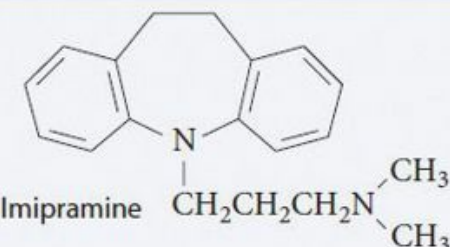
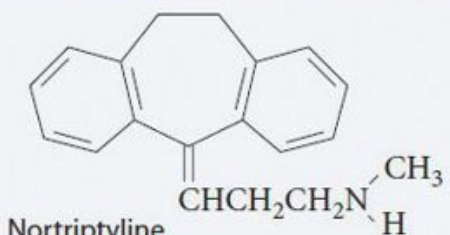
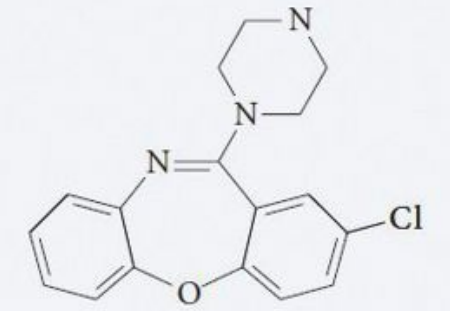
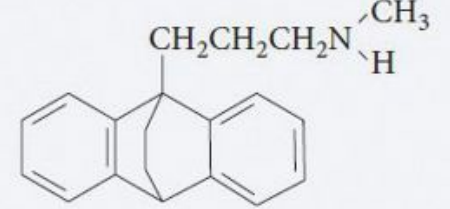
The epidemiology of CA poisoning has evolved significantly in the past 30 years, resulting in great part from the introduction of the selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants for the treatment of depression. Although the use of CAs for depression has decreased over the past 20 years, other medical indications, including chronic pain, obsessive-compulsive disorder, and, particularly in children, enuresis and attention deficit hyperactivity disorder have emerged, resulting in their continued use. The antidepressants are a leading cause of drug-related self-poisonings in the developed world, primarily because of their ready availability to people with depression or chronic pain who by virtue of their diseases are at high risk for overdose. However, despite the increase in SSRI use and overdose, patients with TCA overdoses continue to have higher rates of hospitalization and fatality than do those with SSRI overdose.

Children younger than 6 years have consistently accounted for approximately 12% to 13% of all CA exposures reported to poison centers during each of the last 15 years ([Chap. 136](#)). Despite the emergence of the SSRIs in the early 1990s, TCAs are still frequently prescribed by pediatric office based practices for many of the conditions noted above. Following the October 2004 US Food and Drug Administration Black Box Warning about the increased risk of suicidal behavior associated with antidepressant use, several reports have described significant declines in antidepressant dispensing in children compared to historical trends.²⁵ Nevertheless, CA poisoning likely will continue to be among the most lethal unintentional drug ingestions in younger children because only one or two adult-strength pills can produce serious clinical effects in young children.

PHARMACOLOGY

In general, the TCAs can be classified into tertiary and secondary amines based on the presence of a methyl group on the propylamine side chain ([Table 71–1](#)). The tertiary amines amitriptyline and imipramine are metabolized to the secondary amines nortriptyline and desipramine, respectively, which themselves are marketed as antidepressants. In therapeutic doses, the CAs produce similar pharmacologic effects on the autonomic system, CNS, and cardiovascular system. However, they can be distinguished from each other by their relative potencies.¹¹²

TABLE 71–1. Cyclic Antidepressants—Classification by Chemical Structure

Tertiary Amines	
Amitriptyline Clomipramine Doxepin Imipramine Trimipramine	 Imipramine
Secondary Amines	
Desipramine Nortriptyline Protriptyline	 Nortriptyline
Amoxapine	
Maprotiline	

At therapeutic doses, CAs inhibit presynaptic reuptake of norepinephrine and/or serotonin, thus functionally increasing the amount of these neurotransmitters at CNS receptors. The tertiary amines, especially clomipramine, are more potent inhibitors of serotonin reuptake, whereas the secondary amines are more potent inhibitors of norepinephrine reuptake. Although these pharmacologic actions formed the basis of the monoamine hypothesis of depression in the 1960s, antidepressant actions of these drugs appear to be much more complex.

Extensive research has led to the “receptor sensitivity hypothesis of antidepressant drug action,” which postulates that following chronic CA administration, alterations in the sensitivity of various receptors are responsible for antidepressant effects. Chronic TCA administration alters the number and/or function of central β -adrenergic and serotonin receptors. In addition, TCAs modulate glucocorticoid receptor gene expression and cause alterations at the genomic level of other receptors.⁸ All of these actions likely play a role in the antidepressant effects of TCAs.

Additional pharmacologic mechanisms of CAs are responsible for their side effects with therapeutic dosing and clinical effects following overdose. All of the CAs are competitive antagonists of the muscarinic acetylcholine receptors, although they have different affinities. The CAs also antagonize peripheral α_1 -adrenergic receptors. The most prominent effects of CA overdose result from binding to the cardiac sodium channels, which is also described as a membrane-stabilizing effect (Fig. 71–1) (Chap. 16). The tricyclic antidepressants are potent inhibitors of both peripheral and central postsynaptic histamine receptors. Finally, animal research demonstrates that the CAs interfere with chloride conductance by binding to the picrotoxin site on the γ -aminobutyric acid (GABA)–chloride complex.¹⁰²

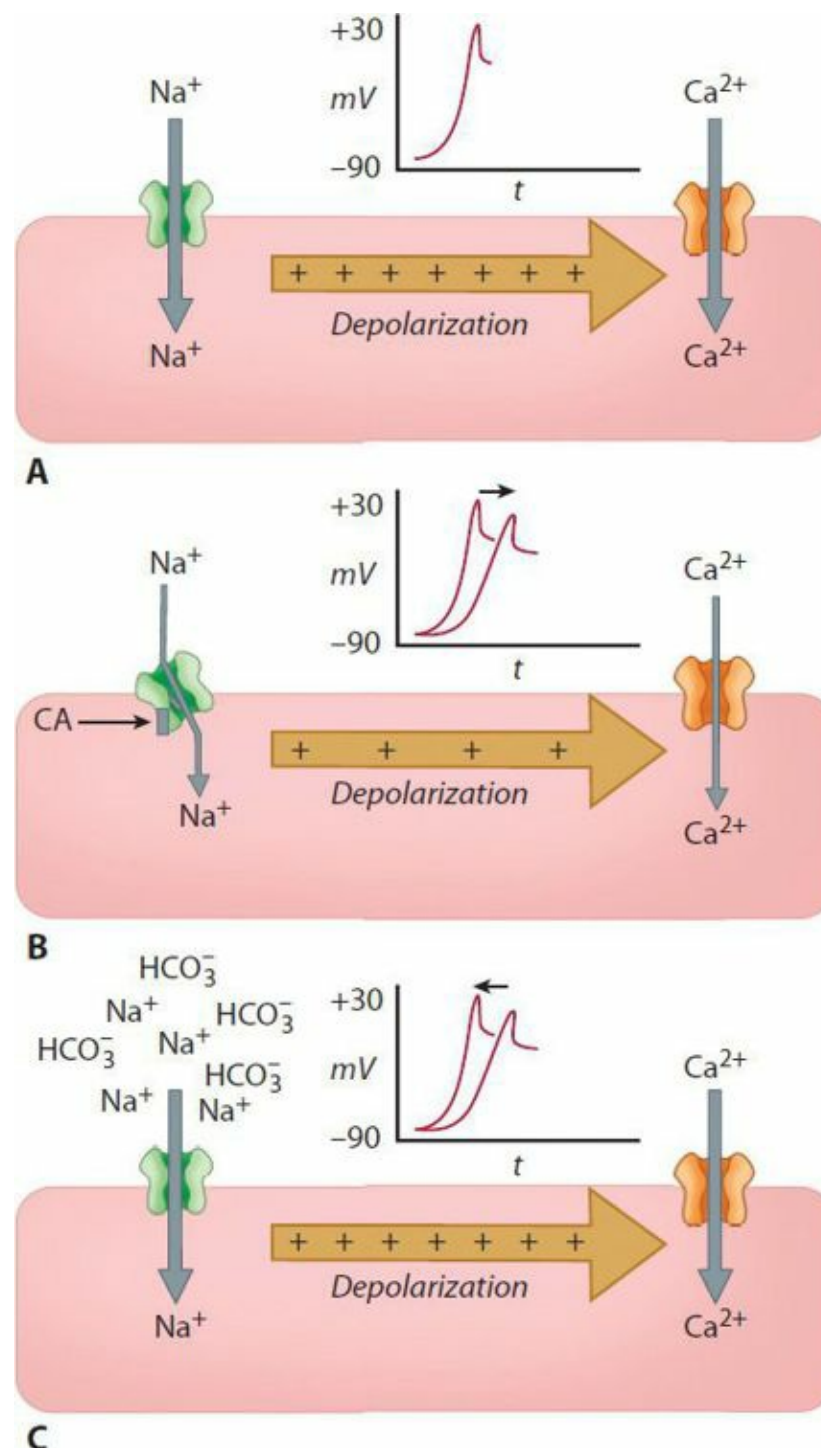


FIGURE 71-1. Effects of cyclic antidepressants (CAs) on the fast sodium channel. (A) Sodium depolarizes the cell, which both propagates conduction; allowing complete cardiac depolarization; and opens voltage-dependent Ca²⁺ channels, producing contraction. (B) CAs and other sodium channel blockers alter the conformation of the sodium channel, slowing the rate of rise of the action potential, which produces both negative dromotropic and inotropic effects. (C) Raising the Na⁺ gradient across the affected sodium channel speeds the rate of rise of the action potential, counteracting the drug-induced effects. Raising the pH removes the CA from the binding site on the Na⁺ channel. See Fig. 71-3 for the effects noted on the electrocardiograph.

Amoxapine is a dibenzoxapine CA derived from the active antipsychotic loxapine. Although it has a three-ringed structure, this drug has little similarity to the other tricyclics. It is a potent norepinephrine reuptake inhibitor, has no effect on serotonin reuptake, and blocks dopamine receptors. Maprotiline is a tetracyclic antidepressant that predominantly blocks norepinephrine reuptake. Both of these CAs have a slightly different toxic profile than the traditional TCAs.^{55,56,112}

PHARMACOKINETICS AND TOXICOKINETICS

The CAs are rapidly and almost completely absorbed from the gastrointestinal (GI) tract, with peak concentrations 2 to 8 hours after administration of a therapeutic dose. They are weak bases (high pK_a). In overdose, the decreased GI motility caused by anticholinergic effects and ionization in gastric acid delay CA absorption. Because of extensive first-pass metabolism by the liver, the oral bioavailability of CAs is low and variable, although metabolism may become saturated in

overdose, increasing bioavailability.

The CAs are highly lipophilic and possess large and variable volumes of distribution (15–40 L/kg). They are rapidly distributed to the heart, brain, liver, and kidney, where the tissue to plasma ratio generally exceeds 10:1. The octanol/water partition coefficient (Log P) is an often cited measure of lipid-solubility with the Log D representing Log P at physiological pH—a more representative measure. The latter pharmacologic property becomes important when evaluating the potential effectiveness of lipid emulsion therapy for CA toxicity. Some examples of Log D values for CAs are amitriptyline, 3.96; nortriptyline, 2.86; imipramine, 2.06; desipramine, 1.05; and doxepin, 2.93.

Less than 2% of the ingested dose is present in blood several hours after overdose, and serum CA concentrations decline biexponentially. The CAs are extensively bound to α_1 -acid glycoprotein (AAG) in the plasma, although differential binding among the specific CAs is observed.² Changes in AAG concentration or pH can alter binding and the percentage of free or unbound drug.^{87,95} Specifically, a low blood pH (which often occurs in a severely poisoned patient) may increase the amount of free drug, making it more available to exert its effects. This property serves as one basis for alkalization therapy (see below).

The CAs undergo demethylation, aromatic hydroxylation, and glucuronide conjugation of the hydroxy metabolites. The tertiary amines imipramine and amitriptyline are demethylated to desipramine and nortriptyline, respectively. The hydroxy metabolites of both tertiary and secondary amines are pharmacologically active and may contribute to toxicity. The glucuronide metabolites are inactive.

Genetically based differences in the activity of the CYP2D6 enzymes, which are responsible for hydroxylation of imipramine and desipramine, account for wide interindividual variability in metabolism and steady-state serum concentrations.¹⁹ “Poor metabolizers” may recover more slowly from an overdose or demonstrate toxicity with therapeutic dosing.¹⁰⁶ The metabolism of CAs also may be influenced by concomitant ingestion of ethanol and other medications that induce or inhibit the CYP2D6 isoenzyme (Chap. 13, Appendix). Patient variables such as age and ethnicity also affect CA metabolism.

Elimination half-lives for therapeutic doses of CAs vary from 7 to 58 hours (54–92 hours for protriptyline), with even longer half-lives in the elderly. The half-lives may also be prolonged following overdose as a result of saturable metabolism. A small fraction (15%–30%) of CA elimination occurs through biliary and gastric secretion. The metabolites are then reabsorbed in the systemic circulation, resulting in enterohepatic and enterogastric recirculation and reducing their fecal excretion. Finally, less than 5% of CAs are excreted unchanged by the kidney.

PATHOPHYSIOLOGY

The CAs slow the recovery from inactivation of the fast sodium channel, slowing phase 0 depolarization of the action potential in the distal His-Purkinje system and the ventricular myocardium (Fig. 71–1 and Fig. 22–2; Chap. 16). Impaired depolarization within the ventricular conduction system slows the propagation of ventricular depolarization, which manifests as prolongation of the QRS interval on the electrocardiogram (ECG) (Fig. 71–1). The right bundle branch has a relatively longer refractory period, and it is affected disproportionately by xenobiotics that slow intraventricular conduction. This slowing of depolarization results in a rightward shift of the terminal 40 millisecond (T40-msec) of the QRS axis and the right bundle branch block pattern that is noted on the ECG of patients who are exposed to, or overdose with, a CA.¹¹⁴

Because CAs are weakly basic, they are increasingly ionized as the ambient pH falls, and less ionized as the pH rises. Changing the ambient pH therefore likely alters their binding to the sodium channel. That is, since it is probable that 90% of the binding of CA to the sodium channel occurs in the ionized state, alkalinizing the blood facilitates the movement of the CA away from the hydrophilic sodium channel and into the lipid membrane.

Sinus tachycardia is due to the antimuscarinic, vasodilatory (reflex tachycardia), and sympathomimetic effects of the CAs. Wide-complex tachycardia most commonly represents aberrantly conducted sinus tachycardia rather than ventricular tachycardia. However, by prolonging anterograde conduction, nonuniform ventricular conduction may result, leading to reentrant ventricular dysrhythmias.

Electrophysiologic studies in a canine model demonstrate that QRS prolongation is rate dependent, a characteristic effect of the class I antidysrhythmics (Chap. 64). In these studies, when the heart rate could not accelerate because of a crushed sinus node, the dogs never developed QRS prolongation. Furthermore, pharmacologic induction of bradycardia prevents or narrows wide-complex tachycardia by allowing time for recovery of the sodium channel from inactivation.^{4,94} However, since bradycardia adversely affects cardiac output, induction of bradycardia is not recommended.

A Brugada ECG pattern, specifically type 1 or “coved” pattern, is rarely associated with CA overdose. The Brugada syndrome originates from a structural change in the myocardial sodium channel that results in functional sodium channel alterations similar to those caused by the CAs.^{11,77} It is possible that this small cohort of patients may have had subclinical Brugada syndrome that was uncovered by the CA (Chap. 16).

QT interval prolongation can occur in the setting of both therapeutic use and overdose of CAs. This apparent

prolongation of repolarization results primarily from slowed depolarization (ie, QRS prolongation) rather than altered repolarization.⁹⁰ Although QT prolongation predisposes to the development of torsade de pointes, this dysrhythmia is uncommon in patients with CA poisoning due to the prominent tachycardia.

Hypotension is caused by direct myocardial depression secondary to altered sodium channel function, which disrupts the subsequent excitation-contraction coupling of myocytes and impairs cardiac contractility. Peripheral vasodilation from α -adrenergic blockade by CAs also contributes prominently to postural hypotension. In addition, downregulation of adrenergic receptors may cause a blunted physiologic response to catecholamines.⁷⁶

Agitation, delirium, and depressed sensorium are primarily caused by the central anticholinergic and antihistaminic effects. Hemodynamic effects are likely to contribute in only the most severely poisoned patients. Details regarding the exact mechanism of CA-induced seizures remain elusive. CA-induced seizures may result from a combination of an increased concentration of monoamines (particularly norepinephrine), muscarinic antagonism, neuronal sodium channel alteration, and GABA inhibition.⁷⁸

Acute respiratory distress syndrome (ARDS) may occur in the setting of CA overdose. In one study, amitriptyline exposure caused dose-related vasoconstriction and bronchoconstriction in isolated rat lungs.¹⁰⁵ Many substances implicated in ARDS, such as platelet-activating factor and protein kinase activation, were important in mediating amitriptyline-induced impairment of lung function in this experimental model. Another animal model demonstrated that acute amitriptyline poisoning causes dose-dependent rises in pulmonary artery pressure, pulmonary edema, and sustained vasoconstriction that could be attenuated by either calcium channel inhibition or a nitric oxide donor.⁶⁶

CLINICAL MANIFESTATIONS

The toxic profile is qualitatively the same for all of the first-generation TCAs but is slightly different for some of the other CAs.¹¹² The progression of clinical toxicity is unpredictable and may be rapid. Patients commonly present to the emergency department (ED) with minimal apparent clinical abnormalities, only to develop life-threatening cardiovascular and CNS toxicity within hours.

The CAs have a low therapeutic index, meaning that a small increase in serum concentration over the therapeutic range may result in toxicity. Acute ingestion of 10 to 20 mg/kg of most CAs causes significant cardiovascular and CNS manifestations (therapeutic dose, 2–4 mg/kg/d). Thus, in adults, ingestions of more than 1 g of a CA is usually associated with life-threatening effects. As few as two 50 mg imipramine tablets may cause significant toxicity in a 10 kg toddler (ie, 10 mg/kg). In a series of children with unintentional TCA exposure, all patients with reported ingestions of more than 5 mg/kg manifested clinical toxicity.⁷²

Acute Toxicity

Most of the reported toxicity from CAs derives from patients with acute ingestions, especially in patients who are chronically taking the medication. Clinical manifestations of these two cohorts do not appear to be different, and most studies do not distinguish between them.

Acute Cardiovascular Toxicity. Cardiovascular toxicity is primarily responsible for the morbidity and mortality attributed to CAs. Refractory hypotension due to myocardial depression probably is the most common cause of death from CA overdose.^{20,104} Hypoxia, acidosis, volume depletion, seizures, or concomitant ingestion of other cardiodepressant or vasodilating drugs can exacerbate hypotension.

The most common dysrhythmia observed following CA overdose is sinus tachycardia (rate, 120–160 beats/min in an adult), and this finding is present in most patients with clinically significant TCA poisoning. The ECG typically demonstrates intraventricular conduction delay that manifests as a rightward shift of the T40-msec QRS axis and a prolongation of the QRS complex duration. These findings can be used to identify and risk stratify, respectively, patients with CA poisoning (see Diagnostic Testing). PR, QRS, and QT interval prolongation can occur in the setting of both therapeutic and toxic amounts of TCAs.⁶⁸

Wide-complex tachycardia is the characteristic potentially life-threatening dysrhythmia observed in patients with severe toxicity (**Fig. 71–2A–C**). Ventricular tachycardia may be difficult to distinguish from aberrantly conducted sinus tachycardia which occurs more commonly. In the former cases, the preceding P wave may not be apparent because of prolonged atrioventricular conduction, widened QRS interval, or both. Ventricular tachycardia occurs most often in patients with prolonged QRS complex duration and/or hypotension.^{63,108} Hypoxia, acidosis, hyperthermia, seizures, and β -adrenergic agonists may also predispose to ventricular tachycardia.^{63,108} Fatal dysrhythmias are rare, as ventricular tachycardia and fibrillation occur in only approximately 4% of all cases.^{41,85} Both the Brugada type I ECG pattern and torsade de pointes are uncommon with acute TCA overdose.

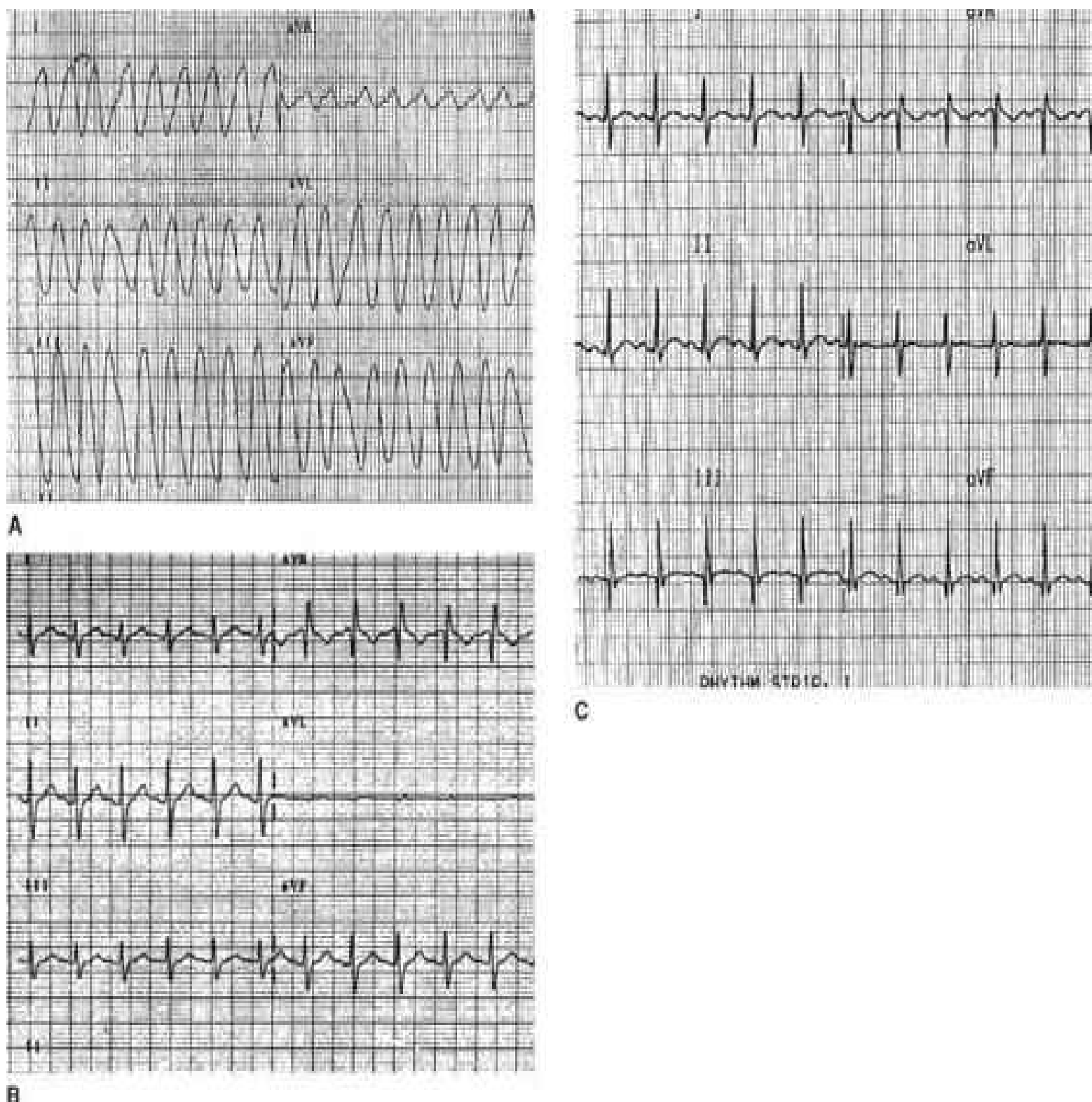


FIGURE 71-2. (A) Electrocardiograph (ECG) shows a wide-complex tachycardia with a variable QRS duration (minimum, 220 msec). (B) ECG 30 minutes after presentation following sodium bicarbonate shows narrowing of the QRS interval to a duration of 140 msec and an amplitude of RaV_R of 6.0 mm. (C) ECG 9 hours after presentation shows further narrowing of the QRS interval to 80 msec and decrease in the amplitude of RaV_R to 4.5 mm. (Reproduced with permission from Liebelt EL: Targeted management strategies for cardiovascular toxicity from tricyclic antidepressant overdose: the pivotal role for alkalization and sodium loading. *Pediatr Emerg Care*. 1998;14:293–298.)

Acute Central Nervous System Toxicity. Altered mental status and seizures are the primary manifestations of CNS toxicity. Delirium, agitation, and/or psychotic behavior with hallucinations may be present and most likely result from antagonism of muscarinic and histaminergic receptors. These alterations in consciousness usually are followed by lethargy, which is followed by rapid progression to coma. The duration of coma is variable and does not necessarily correlate or occur concomitantly with ECG abnormalities.⁵⁶

Seizures usually are generalized and brief, most often occurring within 1 to 2 hours of ingestion.²⁸ The incidence of seizures is similar to ventricular tachycardia and occurs in an estimated 4% of patients presenting with overdose and 13% of fatal cases.¹¹⁵ Status epilepticus is uncommon. Abrupt deterioration in hemodynamic status, namely hypotension and ventricular dysrhythmias, may develop during or within minutes after a seizure.^{28,63,108} This rapid cardiovascular

deterioration likely results from seizure-induced acidosis that exacerbates cardiovascular toxicity. The risk of seizures with CA overdoses may be increased in patients undergoing long-term therapy or who have other risk factors such as history of seizures, head trauma, or concomitant drug withdrawal.¹⁰⁰ Myoclonus and extrapyramidal symptoms may also occur in CA-poisoned patients.

Cessation of CAs may produce a drug discontinuation syndrome in some patients, which is typified by GI and somatic distress, sleep disturbances, movement disorders, and mania.³⁷

Other Clinical Effects. Anticholinergic effects can occur early or late in the course of CA toxicity. Pupils may be dilated and poorly reactive to light. Other anticholinergic effects include dry mouth, dry flushed skin, urinary retention, and ileus. Although prominent, these findings are typically clinically inconsequential.

Reported pulmonary complications include ARDS, aspiration pneumonitis, and multisystem organ failure. ARDS may be the result of aspiration, hypotension, pulmonary infection, and excessive fluid administration, along with the primary toxic effects of CAs.^{96,97} Bowel ischemia, pseudoobstruction, and pancreatitis are reported in patients with CA overdose.⁷⁴

Death directly caused by CA toxicity usually occurs in the first several hours after presentation and is secondary to refractory hypotension in patients who reach health care facilities. Late deaths (>1–2 days after presentation) usually are secondary to other factors such as aspiration pneumonitis, adult respiratory distress syndrome from refractory hypotension, and/or infection.²¹

Chronic Toxicity

Chronic CA toxicity usually manifests as exaggerated side effects, such as sedation and sinus tachycardia, or is identified by supratherapeutic drug concentrations in the blood in the absence of an acute overdose.³⁹ Unlike chronic theophylline and aspirin poisoning, chronic CA toxicity does not appear to cause life-threatening toxicity.

A sparse literature describes the clinical course of this cohort. However, a recent case report described chronic amitriptyline overdose in a child (15 mg/kg a day for a month), which resulted in status epilepticus and significant cardiac conduction abnormalities but normal neurological outcome.²⁶ Genetic analysis of this patient's CYP450 system showed two copies of wild-type alleles for the genes responsible for CYP2D6 activity; thus, concluding the patient was not a "rapid metabolizer." Several possible protective mechanisms are presented and further illustrate the complexity of this drug, its metabolism, and toxicity. These include a unique pharmacogenomics profile that yields an abnormal receptor profile or metabolic pathway (eg, polymorphism in the gene for myocardial fast sodium channels), another medication causing a beneficial drug-drug interaction, a cardioprotective role for caffeine if the patient's intake was high causing adenosine receptor antagonism and the protective effect from other drugs the patient was taking—guanfacine and clonidine—adrenergic medications that may have offered some protective effect from the α -adrenergic blockade caused by amitriptyline.

Several reports describe sudden death in children taking therapeutic doses of CAs.^{88,89,107} QT prolongation with resultant torsade de pointes, advanced atrioventricular conduction delays, blood pressure fluctuations, and ventricular tachycardia are postulated mechanisms, although whether any of these effects contributed to the deaths is unknown. Prospective studies using 12-lead ECG, 24-hour ECG recording, and Doppler echocardiography in children receiving therapeutic doses of CAs have failed to find any significant cardiac abnormalities when compared to children not taking CAs.^{14,31} However, authors recommend that CAs not be initiated or continued in any child with a resting QT interval greater than 450 msec or with bundle branch block.³⁴ This is an ongoing area of research as it becomes problematic in making decisions about pharmacotherapy interventions.

Unique Toxicity from “Atypical” Cyclic Antidepressants

Although the incidence of serious cardiovascular toxicity is lower in patients with amoxapine overdoses, the incidence of seizures is significantly greater than with the traditional CAs.^{56,65} Moreover, seizures may be more frequent, or status epilepticus may develop.⁷⁷ Similarly, the incidences of seizures, cardiac dysrhythmias, and duration of coma are greater with maprotiline toxicity compared to the CAs.⁵⁵

DIAGNOSTIC TESTING

Diagnostic testing for patients with CA poisoning primarily relies on indirect bedside tests (ECG) and other qualitative laboratory analyses. Quantification of CA concentration provides little help in the acute management of patients with CA overdose but provides adjunctive information to support the diagnosis.

Electrocardiography

The ECG can provide important diagnostic information and may predict clinical toxicity after a CA overdose. CA toxicity

results in distinctive and diagnostic ECG changes that may allow early diagnosis and targeted therapy when the clinical history and physical examination are unreliable.

A T40-msec axis between 120° and 270° is associated with CA toxicity and was a sensitive indicator of drug presence in one study.^{22,79,114} A terminal QRS vector between 130° and 270° discriminated between 11 patients with positive toxicology screens for CAs and 14 patients with negative toxicology screens.⁷⁹ With further analyses, this report concluded that the positive and negative predictive values of this ECG parameter for CA ingestions were 66% and 100%, respectively, in a population of 299 general overdose patients. A retrospective study reported that a CA-poisoned patient was 8.6 times more likely to have a T40-msec axis greater than 120° than was a non-CA-poisoned patient.¹¹⁴ This parameter was a more sensitive indicator of CA-induced altered mental status but not necessarily of seizure or dysrhythmia. However, the T40-msec axis is not easily measured in the absence of specialized computer-assisted analysis, which limits its practical utility. An abnormal terminal rightward axis can be estimated by observing a negative deflection (terminal S wave) in leads I and aV_L and a positive deflection (terminal R wave) in lead aV_R (Fig. 71-3).

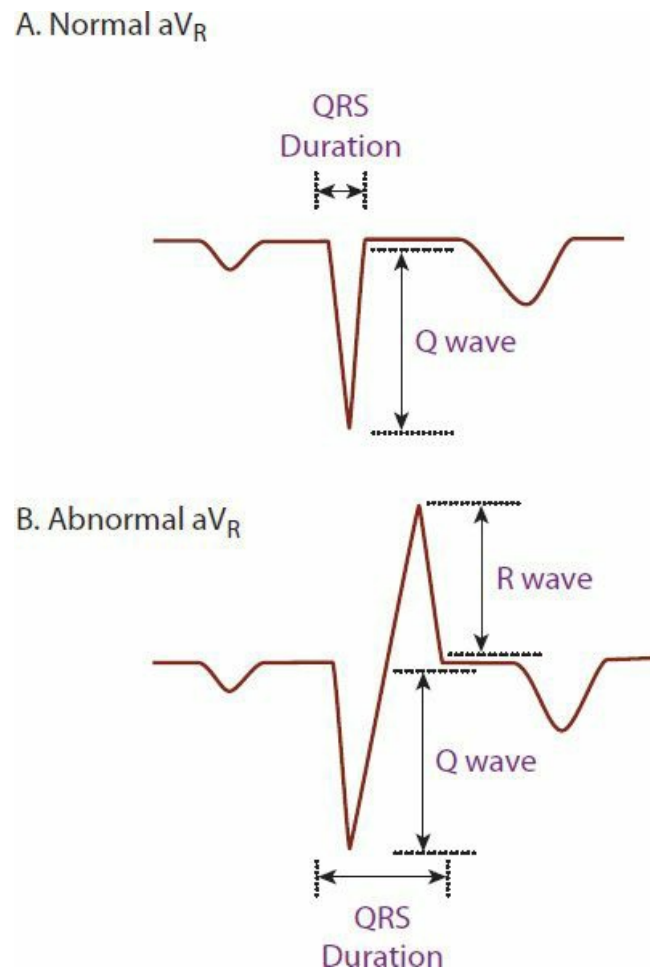


FIGURE 71-3. (A) Normal QRS complex in lead aV_R . (B) Abnormal QRS complex in a patient with cyclic antidepressant (CA) poisoning. The R wave in lead aV_R is measured as the maximal height in millimeters of the terminal upward deflection in the QRS complex. In this example, the QRS complex duration is prolonged, indicating significant CA poisoning.

The maximal limb lead QRS complex duration is an easily measured ECG parameter that is a sensitive indicator of toxicity. One investigation reported that 33% of patients with a limb lead QRS interval greater than or equal to 100 msec developed seizures and 14% developed ventricular dysrhythmias.¹⁷ No seizures or dysrhythmias occurred in those patients whose QRS interval remained less than 100 msec. There was a 50% incidence of ventricular dysrhythmias among patients with a QRS duration greater than or equal to 160 msec. No ventricular dysrhythmias occurred in patients with a QRS duration less than 160 msec. Subsequent studies confirmed that a QRS duration greater than 100 msec is associated with an increased incidence of serious toxicity, including coma, need for intubation, hypotension, seizures, and dysrhythmias, making this ECG parameter a useful indicator of toxicity.^{22,61}

Evaluation of lead aV_R on a routine ECG may also predict toxicity (Figs. 71-2 and 71-3). When prospectively studied, 79 patients with acute CA overdoses demonstrated that the amplitude of the terminal R wave and R/S wave ratio in lead aV_R (R_{aV_R} , R/S_{aV_R}) were significantly greater in patients who developed seizures and ventricular dysrhythmias.⁶¹ The sensitivity of $R_{aV_R} = 3$ mm and $R/S_{aV_R} = 0.7$ in predicting seizures and dysrhythmias was comparable to the sensitivity of QRS = 100 msec.

The type 1 Brugada pattern is similar to a right bundle branch block (rSR'), with downsloping ST elevations ("coved") in the right precordial leads (V1–V3).^{11,77} This pattern is neither highly sensitive nor specific for CA toxicity, and it is reported in patients with cocaine and phenothiazine toxicity as well as those on class IA antidysrhythmic therapy. In one series of more than 400 patients with CA overdose, a significant increase in adverse outcomes (ie, seizures, widened QRS interval, and hypotension) was identified in those patients with a Brugada ECG pattern compared to those who did not have the pattern.¹¹ However, there were no deaths or dysrhythmias in the nine patients with this pattern.

Serial ECGs should be obtained because the ECG changes can be dynamic. ECG parameters should always be interpreted in conjunction with the clinical presentation, history, and course during the first several hours to assist in decision making regarding interventions and disposition.⁶²

Laboratory Tests

Determination of serum CA concentrations has limited utility in the immediate evaluation and management of patients with acute overdoses. In one study, serum drug concentrations failed to accurately predict the development of seizures or ventricular dysrhythmias.¹⁷ The pharmacologic properties of CAs—namely, large volumes of distributions, prolonged absorption phase, long distribution half-lives, pH-dependent protein binding, and the wide interpatient variability of terminal elimination half-lives—explain the limited value of serum concentrations in this situation. Any concentration above the therapeutic range (50–300 ng/mL, including active metabolites) may be associated with adverse effects, and is an indication to decrease or discontinue the medication.

Although CA concentrations greater than 1000 ng/mL usually are associated with significant clinical toxicity such as coma, seizures, and dysrhythmias, life-threatening toxicity may be observed in patients with serum concentrations less than 1000 ng/mL.^{17,57} Serious toxicity at lower concentrations probably results from a number of factors, including the timing of the specimen in relation to the ingestion and the limitations of measuring the concentration in blood and not the affected tissue. Quantitative concentrations usually cannot be readily obtained in most hospital laboratories. However, qualitative screens for CAs using an enzyme-multiplied immunoassay test are available at many hospitals. Unfortunately, false-positive results can occur with many drugs such as carbamazepine, cyclobenzaprine, thioridazine, diphenhydramine, quetiapine, and cyproheptadine (Chap. 6). Thus, the presence of a CA on a qualitative assay should not be relied upon to confirm the diagnosis of CA poisoning in the absence of corroborating historical or clinical evidence.

Quantitative concentrations may be helpful in determining the cause of death in suspected overdose patients. CA concentrations reported in lethal overdoses typically range from 1100–21,800 ng/mL. CA concentrations may increase more than fivefold because of postmortem redistribution (Chap. 34).⁵ Measurement of liver CA concentration or the parent-to-metabolite drug ratio may be useful in the postmortem setting.

MANAGEMENT

Any person with a suspected or known ingestion of a CA requires immediate evaluation and treatment (Table 71–2). The patient should be attached to a cardiac monitor, and intravenous access should be secured. Early intubation is advised for patients with CNS depression and/or hemodynamic instability because of the potential for rapid clinical deterioration. A 12-lead ECG should be obtained for all patients. Laboratory tests, including concentrations of glucose and electrolytes, should be performed for all patients with altered mental status, as well as blood gas analysis to both assess the degree of acidemia and guide alkalinization therapy. Aggressive interventions for maintenance of blood pressure and peripheral perfusion must be performed early to avoid irreversible damage. Both children and adults receiving cardiopulmonary resuscitation have recovered successfully despite periods of asystole exceeding 90 minutes.^{24,27,79,101} The options for GI decontamination discussed in the following section should then be considered.

TABLE 71–2. Treatment of Cyclic Antidepressant (CA) Toxicity

<i>Toxic Effect</i>	<i>Treatment</i>
Sinus rhythm with a QRS >100 msec	Sodium bicarbonate: 1–2 mEq/kg IV boluses at 3 to 5 minute intervals to reverse the abnormality or to a target serum pH ≤ 7.55 Controlled ventilation (if clinically indicated for hypoventilation)
Wide-complex tachycardia/ventricular tachycardia	Sodium bicarbonate: 1–2 mEq/kg IV boluses to reverse the dysrhythmias or to a target serum pH ≤ 7.55 Correct hypoxia, acidemia, hypotension Consider lidocaine: 1 mg/kg slow IV bolus, followed by infusion of 20–50 $\mu\text{g/kg/min}$ Consider hypertonic saline (3% sodium chloride) Consider magnesium sulfate 25–50 mg/kg (maximum 2 g) IV over 2 min Consider IV fat emulsion therapy 1.5 mL/kg bolus of 20%, repeated every 5 minutes until cardiovascular stability is restored; may consider infusion of 0.25 mL/kg per minute for 30 to 60 minutes with a maximum dose of 12 mL/kg
Torsade de pointes	Magnesium sulfate Overdrive pacing (caution due to rate dependence of CA)
Hypotension	0.9% sodium chloride boluses (up to 30 mL/kg) Correct hypoxia, acidemia Sodium bicarbonate: 1–2 mEq/kg IV boluses to a target serum pH of ≤ 7.55 Norepinephrine in standard titrated doses Consider IV fat emulsion therapy 1.5 mL/kg bolus of 20%, repeated every 5 minutes until cardiovascular stability is restored; may consider infusion of 0.25 mL/kg per minute for 30–60 minutes with a maximum dose of 12 mL/kg
Seizures	Benzodiazepines Secure airway with intubation if necessary Correct hypoxia, acidemia Barbiturates Continuous infusion of midazolam or propofol if barbiturates fail Consider neuromuscular paralysis/general anesthesia with EEG monitoring if all other measures fail
Refractory poisoning	Consider intravenous fat emulsion in moribund patients Consider extracorporeal mechanical circulation (extracorporeal membrane oxygenation, cardiopulmonary bypass), no evidence to support hemodialysis or hemoperfusion

Gastrointestinal Decontamination

Induction of emesis is contraindicated, given the potential for precipitous neurologic and hemodynamic deterioration. Because of the potential lethality of large quantities of CAs, orogastric lavage should be considered in the symptomatic patient with an overdose. Although the benefits of orogastric lavage for CA toxicity are not substantiated by controlled trials, the potential benefits of removing significant quantities of a highly toxic drug must be weighed against the risks of the procedure ([Chap. 8](#)).¹⁸ Because the anticholinergic actions of some CAs may decrease spontaneous gastric emptying, attempts at orogastric lavage up to 12 hours after ingestion may yield unabsorbed drug. Because of the potential for rapid

deterioration of mental status and seizures, orogastric lavage should be performed only after endotracheal intubation has ensured airway protection. Orogastric lavage in young children with unintentional ingestions of CAs may be associated with more risk and impracticalities, such as the inadequate hole size of pediatric tubes, and less benefit given the amount of drug usually ingested. Activated charcoal should be administered in nearly all cases. Irrespective of age, an additional dose of activated charcoal several hours later is reasonable in a seriously poisoned patient in whom unabsorbed drug may still be present in the GI tract or in the case of desorption of CAs from activated charcoal. It is important to monitor for the development of an ileus to prevent abdominal complications from additional doses of activated charcoal.⁷⁴

Wide-Complex Dysrhythmias, Conduction Delays, and Hypotension

The mainstay therapy for treating wide-complex dysrhythmias and for reversing conduction delays and hypotension is the combination of serum alkalinization and sodium loading. Increasing the extracellular concentration of sodium, or sodium loading, may overwhelm the effective blockade of sodium channels, presumably through gradient effects (Fig. 71-1). Controlled in vitro and in vivo studies in various animal models demonstrate that hypertonic sodium bicarbonate effectively reduces QRS complex prolongation, increases blood pressure, and reverses or suppresses ventricular dysrhythmias caused by CAs.^{82,92-94} These studies showed a clear benefit of hypertonic sodium bicarbonate when compared to hyperventilation, hypertonic sodium chloride, or nonsodium buffer solutions. A systematic review of all animal and human studies published before 2001 revealed that alkalinization therapy was the most beneficial therapy for consequential dysrhythmias and shock¹⁶ (Antidotes in Depth: A5).

The optimal dosing and mode of administration of hypertonic sodium bicarbonate and the indications for initiating and terminating this treatment are unsupported by controlled clinical studies. Instead, the information is extrapolated from animal studies, clinical experience, and an understanding of the pathophysiologic mechanisms of CA toxicity. A bolus, or rapid infusion over several minutes, of hypertonic sodium bicarbonate (1–2 mEq/kg) should be administered initially.^{70,98} Additional boluses every 3 to 5 minutes can be administered until the QRS interval narrows and the hypotension improves (Fig. 71-2). Blood pH should be carefully monitored after several bicarbonate boluses, aiming for a target pH of no greater than 7.50 or 7.55. Because CAs may redistribute from the tissues into the blood over several hours, it may be reasonable to begin a continuous sodium bicarbonate infusion to maintain the pH in this range. Differences in outcomes between repetitive boluses versus bicarbonate infusions are not well studied. Although diluting sodium bicarbonate in 5% dextrose in water and infusing it slowly renders it less able to increase the sodium gradient across the cell, the beneficial effects of pH elevation still warrant its use once the patient is stabilized. No evidence supports prophylactic alkalinization in the absence of cardiovascular toxicity (eg, QRS < 100 msec). In addition, alkalization would inevitably cause a decrease in potassium, which may cause QT prolongation and potentially contribute to other dysrhythmias. Hypertonic sodium chloride (3% NaCl) reverses cardiotoxicity in several animal studies,^{47,71,82} and numerous reports and extensive clinical experience support its efficacy in humans.^{16,48,49,73} However, the dose of hypertonic saline for CA poisoning has never been evaluated in humans for safety or efficacy, and the dose suggested by animal studies (up to 15 mEq/kg) exceeds the amount that most clinicians would consider safe (1–2 mEq/kg). Hypertonic sodium chloride is associated with a hyperchloremic metabolic acidosis, an undesired effect that highlights one benefit of hypertonic sodium bicarbonate. However, hypertonic saline could be considered in situations in which alkalinization with sodium bicarbonate is not possible.

Hyperventilation of an intubated patient is a more rapid and easily titratable method of serum alkalinization but is not as effective as sodium bicarbonate in reversing cardiotoxicity.^{51,70} Simultaneous hyperventilation and sodium bicarbonate administration may result in profound alkalemia and should be performed only with extreme caution and careful monitoring of pH. Hyperventilation without bicarbonate administration may be indicated in patients with ARDS or congestive heart failure in whom administration of large quantities of sodium is contraindicated.

Alkalinization and sodium loading with hypertonic sodium bicarbonate and or hypertonic saline along with controlled ventilation (if clinically indicated) should be administered to all CA overdose patients presenting with major cardiovascular toxicity and altered mental status. Indications include conduction delays (QRS > 100 msec) and hypotension. It is imperative to initiate treatment until CA toxicity can be excluded because of the risk of rapid and precipitous deterioration. Although commonly assumed, it is unclear whether the failure of the QRS complex to narrow with sodium bicarbonate treatment excludes CA toxicity.

It is unclear whether alkalinization and sodium loading is effective for reversing the Brugada pattern. The sparse available literature is equivocal.^{12,77} It would seem prudent to administer sodium bicarbonate in the presence of a presumed CA-induced Brugada pattern, especially with concomitant signs of other CA toxicity.

Alkalinization may be continued for at least 12 to 24 hours after the ECG has normalized because of the redistribution of the drug from the tissue. However, the time observed for resolution or normalization of conduction abnormalities is extremely variable, ranging from several hours to several days, despite continuous bicarbonate infusion.⁶² We recommend stopping alkalinization when the patient's mental status improves and there is improvement, but not necessarily normalization, of abnormal ECG findings.

Antidysrhythmic Therapy

Lidocaine is the antidysrhythmic most commonly advocated for treatment of CA-induced dysrhythmias, although no controlled human studies demonstrate its efficacy.⁸⁶ Because lidocaine has sodium channel blocking properties, some investigators argue against its use in CA poisoning.¹ These theoretical concerns are not well supported in the literature, and the class IB antidysrhythmic channel binding kinetics may prove favorable. Although limited data also suggest that the IB antidysrhythmic phenytoin prevents or reverses conduction abnormalities,^{43,69} these data were poorly controlled for other confounding factors, such as blood pH and sodium bicarbonate administration; they had very small numbers; and, in some, the cardiotoxicity was not severe. Since phenytoin exacerbates ventricular dysrhythmias in animals²¹ and fails to protect against seizures,¹⁰ its use is no longer recommended.

The use of class IA (quinidine, procainamide, disopyramide, and moricizine) and class IC (flecainide, propafenone) antidysrhythmics is absolutely contraindicated because they have similar pharmacologic actions to CAs and thus may worsen the sodium channel inhibition and exacerbate cardiotoxicity. Class III antidysrhythmics (amiodarone, bretylium, and sotalol) prolong the QT interval and, although unstudied, may be contraindicated as well (Chap. 64).

Because magnesium sulfate has antidysrhythmic properties, it may be beneficial in the treatment of ventricular dysrhythmias. Animal studies of the effects of magnesium on CA-induced dysrhythmias yield conflicting results.^{52,53} However, successful use of magnesium sulfate in the treatment of refractory ventricular fibrillation after TCA overdose is reported.^{24,27,54,91} A case control study suggested that magnesium sulfate and sodium bicarbonate resulted in lower fatality incidence and shorter intensive care unit stay compared to sodium bicarbonate alone.²⁹ When dysrhythmias fail to reverse after alkalization, sodium loading, and a trial of lidocaine, or magnesium sulfate may be warranted.

Slowing the heart rate in the presence of CAs may allow more time during diastole for CA unbinding from sodium channels and result in an improvement in ventricular conduction.^{3,92} This may abolish the reentry mechanism for dysrhythmias and was one rationale for the past use of physostigmine and propranolol. Thus, decreasing the sinus rate may itself be effective in abolishing ventricular dysrhythmias by eliminating rate-dependent conduction slowing. Propranolol terminated ventricular tachycardia in an animal model but also caused significant hypotension and death.⁹⁴ In one case series, patients developed severe hypotension or had a cardiac arrest shortly after receiving a β -adrenergic antagonist.³⁶ Other animal studies suggest that preventing or abolishing tachycardia by sinus node destruction, or by using bradycardic agents that impede sinus node automaticity without affecting myocardial repolarization or contractility, may successfully prevent CA-induced ventricular dysrhythmias.^{3,4} The combined negative inotropic effects of β -adrenergic antagonists and CAs, along with the significant cardiac and CNS effects reported with physostigmine use, do not support their routine use in the management of CA-induced tachydysrhythmias.

Hypotension

Standard initial treatment for hypotension should include volume expansion with isotonic saline or sodium bicarbonate. Hypotension unresponsive to these therapeutic interventions necessitates the use of inotropic or vasopressor support and possibly extracorporeal cardiovascular support.

No controlled human trials are available to guide the use of vasopressor therapy. The pharmacologic properties of CAs complicate the choice of a specific agent. Specifically, CA blockade of neurotransmitter reuptake theoretically could result in depletion of intracellular catecholamines. This could blunt the effect of dopamine, which is dependent on the release of endogenous norepinephrine for its inotropic activity. This suggests that a direct-acting vasopressor such as norepinephrine is more efficacious than an indirect-acting catecholamine such as dopamine.

In fact, limited clinical data suggest that norepinephrine is more efficacious than dopamine.¹⁰⁹ In a retrospective study of 26 adult hypotensive patients receiving nonstandardized therapy, response rates to norepinephrine (5–53 $\mu\text{g}/\text{min}$) were significantly better than response rates to dopamine (5–10 $\mu\text{g}/\text{kg}/\text{min}$).¹¹⁰ Patients who did not respond to dopamine at vasopressor doses (10–50 $\mu\text{g}/\text{kg}/\text{min}$) responded to norepinephrine (5–74 $\mu\text{g}/\text{min}$). Animal data comparing various treatments are conflicting, and their direct applicability to clinical human poisoning is limited.^{32,111} Both norepinephrine and epinephrine increased the survival rate in CA-poisoned rats. In addition, epinephrine was superior to norepinephrine when used both with and without sodium bicarbonate, and the most effective treatment regimen in this study was epinephrine plus sodium bicarbonate; neither precipitated dysrhythmias. The authors propose that epinephrine is more efficacious because it augments myocardial perfusion more than norepinephrine and improves the recovery of CA sodium channel blockade by hyperpolarization of the membrane potential through its stimulation of increased potassium intracellular transport.

Based on the available data, pharmacologic effects, theoretical concerns, and experience, norepinephrine (0.1–0.2 $\mu\text{g}/\text{kg}/\text{min}$) is recommended for hypotension that is unresponsive to volume expansion and hypertonic sodium bicarbonate therapy. Central venous pressure and or pulmonary artery catheterization may be necessary to guide the choice of additional vasopressor or inotropic agents, especially in the presence of other cardiodepressant drugs.

If these measures fail to correct hypotension, extracorporeal life support measures should be considered.

Extracorporeal membrane oxygenation, extracorporeal circulation, and cardiopulmonary bypass are successful adjuncts for refractory hypotension and life support when maximum therapeutic interventions fail.^{42,101,113} These modalities can provide critical perfusion to the heart and brain and maintain metabolic function while giving the body time to metabolize and eliminate the CA by maintaining hepatorenal blood flow.

Emerging Therapies

Vasopressin is increasingly being used in the setting of vasodilatory shock with successful increases in arterial blood pressure based on its vasoconstrictive actions from several mechanisms. Its successful use for intractable hypotension due to CA toxicity, unresponsive to α -receptor agonists and pH manipulation, has been described and warrants further investigation.⁹

Intravenous fat emulsion is reported to be effective in reversing cardiovascular toxicity due to several lipophilic drugs including amitriptyline and clomipramine. Its utilization and effectiveness appears logical given their pharmacological properties—Log D and Log P—octanol/water partition coefficient discussed previously.

Several controlled animal studies have demonstrated improved survival in clomipramine-induced cardiovascular collapse when intravenous lipid emulsion is given either as pretreatment or resuscitation in comparison with saline controls and sodium bicarbonate infusion.⁴⁴ Other animal studies failed to demonstrate any benefit.^{7,64} Specifically, one failed to demonstrate a statistically significant benefit in amitriptyline-poisoned rats pretreated with intravenous fat emulsion.⁷ Case series and case reports demonstrate clinical improvement when lipids have been administered for cardiovascular collapse or instability refractory to other therapies.^{38,44,50,58,99} The dosing and timing of administration are variable as well as other concomitant therapies, making it difficult to reach any definitive conclusions regarding its effectiveness. In addition, significant adverse reactions and complications have been noted including ARDS and pancreatitis. More data is emerging allowing more evidence-based criteria for its use and dosing. Certainly for patients with refractory hypotension and or ventricular dysrhythmias, fat emulsion therapy should be strongly considered, given the high mortality rate with these medications (Antidotes in Depth: A20).

Central Nervous System Toxicity

Seizures caused by CAs usually are brief and may stop before treatment can be initiated. Recurrent seizures, prolonged seizures (>2 minutes), and status epilepticus require prompt treatment to prevent worsening acidosis, hypoxia, and development of hyperthermia and rhabdomyolysis. Benzodiazepines are effective as first-line therapy for seizures. If this therapy fails, barbiturates or propofol should be administered. Propofol controlled refractory seizures resulting from amoxapine toxicity.⁷⁵ Failure to respond to barbiturates or propofol should lead to consideration of neuromuscular paralysis and general anesthesia with continuous electroencephalographic monitoring. Phenytoin is not recommended for seizures because data not only demonstrate a failure to terminate seizures but also suggest enhanced cardiovascular toxicity.^{9,21}

Use of flumazenil in a patient with known or suspected CA ingestion is contraindicated. Several case reports of patients with CA overdoses describe seizures following administration of flumazenil⁵⁹ (Antidotes in Depth: A27). Physostigmine was used in the past to reverse the acute CNS toxicity of CAs (Antidotes in Depth: A9). However, physostigmine is not recommended because it may increase the risk of cardiac toxicity, cause bradycardia and asystole, and precipitate seizures in acutely CA-poisoned patients.⁸⁴

Enhanced Elimination

No specific treatment modalities have demonstrated clinical significant efficacy in enhancing the elimination of CAs. Some investigators propose multiple doses of activated charcoal to enhance CA elimination because of their small enterohepatic and enterogastric circulation.⁶⁷ Human volunteer studies and case series of patients with CA overdoses suggest that the half-life of CAs may be decreased by multiple-dose activated charcoal (MDAC).¹⁰⁷ Activated charcoal reduced the apparent half-life of amitriptyline to 4 to 40 hours in overdose patients, compared to previously published values of 30 to more than 60 hours.¹⁰⁷ Changes in the severity or duration of clinical toxicity, however, were not reported. Other investigators showed that in human volunteers MDAC reduced the half-life of therapeutic doses of amitriptyline approximately 20% compared with no activated charcoal administration. However, the methodologic flaws and equivocal findings of these studies and the lack of any positive outcome data for this intervention from additional studies do not provide evidence supporting its use in this setting.^{23,40} Pharmacokinetic properties of CAs (large volumes of distribution, high plasma protein binding) weighed against the small increases in clearance and the potential complications of MDAC, such as impaction, intestinal infarction, and perforation, do not warrant its routine use.^{23,74} One additional dose of activated charcoal may be given to decrease GI absorption in patients with evidence of significant CNS and cardiovascular toxicity if bowel sounds are present.

Measures to enhance urinary CA excretion have a minimal effect on total clearance. Urinary alkalization does not

enhance, and may reduce, urinary clearance due to passive reabsorption of the unionized CA from an alkaline urine. Hemodialysis is ineffective in enhancing the elimination of CAs because of their large volumes of distribution, high lipid solubility, and extensive protein binding.⁴⁵ Hemoperfusion overcomes some of the limitations of hemodialysis but may not be effective because of the large volumes of distributions of CAs. Although several uncontrolled case reports and a case series described improvement in cardiotoxicity during hemoperfusion, this finding may be coincidental.^{13,24,35}

Hospital Admission Criteria

All patients who present with known or suspected CA ingestion should undergo continuous cardiac monitoring and serial ECG for a minimum of 6 hours. Recommendations in the older literature for 48 to 72 hours of intensive care unit monitoring even for patients with minor CA ingestions stem from isolated case reports of late-onset dysrhythmias, CNS effects, and sudden deaths.⁸³ However, review of these cases shows inadequate GI decontamination, inadequate therapeutic interventions, and significant ongoing complications of overdose. Several retrospective studies demonstrate that late, unexpected complications in CA overdoses such as seizures, dysrhythmias, and death did not occur in patients who had few or no major signs of toxicity at presentation or a normal level of consciousness and a normal ECG for 24 hours.^{20,27,30,85} A disposition algorithm has been proposed based on clinical signs and symptoms.^{6,108} If the patient is asymptomatic at presentation, undergoes GI decontamination, has normal ECGs, or has sinus tachycardia (with normal QRS complexes) that resolves, and the patient remains asymptomatic in the health care facility for a minimum of 6 hours without any treatment interventions, the patient may be medically cleared for psychiatric evaluation (if appropriate) or discharged home as appropriate.

A prospective study of 67 patients used the Antidepressant Overdose Risk Assessment (ADORA) criteria to identify patients who were at high risk for developing serious toxicity and proposed criteria for hospitalization.³³ In this study, the presence of QRS interval greater than 100 msec, cardiac dysrhythmias, altered mental status, seizures, respiratory depression, or hypotension on presentation to the ED (or within 6 hours of ingestion, if the time was known) was 100% sensitive in identifying patients with significant toxicity and subsequent complications. Criteria specific for intensive care unit admission (other than patients requiring ventilatory and or blood pressure support), versus an inpatient bed with continuous cardiac monitoring, are less clear and probably are institution dependent.¹⁰³

The disposition of patients with persistent isolated sinus tachycardia, prolonged QT interval with no concomitant altered mental status, or blood pressure changes, is not clearly defined. Previous studies demonstrate that these two parameters alone are not predictive of subsequent clinical toxicity or complications.^{33,34} In addition, the sinus tachycardia may persist for up to one week following ingestion. However, a study of isolated CA overdose patients reported that a heart rate greater than 120 beats/min and QT interval greater than 480 msec were associated with an increased likelihood of major toxicity.²² These patients are candidates for observation units with continuous ECG monitoring and serial ECGs for 24 hours.

Inpatient Cardiac Monitoring

The duration of cardiac monitoring in any patient initially exhibiting signs of major clinical toxicity depends on many factors. Certainly the duration of CA cardiotoxicity and neurotoxicity may be prolonged, and using normalization of ECG abnormalities as an end point for therapy and discharge is problematic. Some studies document the variable resolution and normalization of QRS prolongation and T40-msec axis rotation.^{81,97} Based on the available literature, it is reasonable to recommend that after the mental status and blood pressure normalize, and the ECG improves, patients who exhibited significant poisoning should be monitored for another 24 hours off of all of therapy, including alkalization, antidysrhythmics, and inotropics/vasopressors.

SUMMARY

- CA poisoning continues to be a cause of serious morbidity and mortality worldwide.
- The distinctive characteristics of these drugs can cause significant CNS and cardiovascular toxicity, the latter being responsible for mortality as a result of overdose of these drugs. Cardiovascular toxicity ranges from mild conduction abnormalities and sinus tachycardia to wide-complex tachycardia, hypotension, and asystole. CNS toxicity includes delirium, lethargy, seizures, and coma.
- The ECG is a simple, readily available diagnostic test that can predict the development of significant toxicity, particularly seizures and/or dysrhythmias.
- Management strategies are based primarily on the pathophysiology of these drugs, namely, sodium channel blockade in the myocardium. Alkalization and sodium loading with hypertonic sodium bicarbonate is the principal therapy for cardiovascular toxicity.
- Guidelines for observing or admitting patients to the hospital may be based on initial clinical presentation or

development of clinical effects and ECG changes.

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72 LITHIUM

Howard A. Geller

Lithium	
MW	= 6.94 Da
Lithium concentration (serum):	
Therapeutic concentration for bipolar depression	= 0.6–1.2 mEq/L (mmol/L)

HISTORY AND EPIDEMIOLOGY

The Swedish chemistry student Arfwedson discovered lithium in 1817.^{8,131} Lithium derives its name from the Greek word for stone, lithos, from which it was first isolated. The therapeutic use of lithium has a long history beginning in the mid 19th century, when lithium salts were used to treat individuals with gout and were noted to improve symptoms of mania and depression.¹¹⁶ The soft drink 7-Up was originally formulated with lithium as its “active ingredient.”⁸ During the 1930s and 1940s, lithium was used as a salt substitute (“Westsal”) for patients with congestive heart failure but was discontinued after several cases of acute lithium poisoning were described.⁸⁷ The beneficial effects of lithium on bipolar disorder were “rediscovered” by Cade in 1949, when he noticed the calming effect of lithium carbonate on guinea pigs.⁵² The same year, however, the US Food and Drug Administration (FDA) banned the use of lithium in response to reported poisonings.¹³⁹ The FDA lifted the ban in 1970 and approved the use of lithium for the treatment of mania.

Currently, lithium is the most efficient long-term therapy for treatment and prevention of bipolar affective disorders,^{51,81} with a demonstrated antisuicidal effect and an ability to improve the manic and depressive symptoms of the illness, as well as to augment the therapeutic efficacy of other therapies that have failed to achieve symptom remission.^{16,45,53,78,81,108,111,131} Investigations on the use of lithium for compulsive gambling have also demonstrated beneficial results,⁹³ and it is under investigation for use in neurodegenerative disorders such as Alzheimer disease, stroke, amyotrophic lateral sclerosis, Huntington disease, multiple sclerosis, and traumatic brain injury.^{23,47,142,199} In most industrialized nations, approximately one in 1000 persons is prescribed one or more of the various lithium formulations.^{84,121,122}

PHARMACOLOGY

Lithium, the simplest xenobiotic in the modern pharmacopoeia, has a complex mechanism of action that has not been completely elucidated even after more than 50 years of clinical use. Psychotropics modifying monoamine neurotransmission form the basis of modern psychopharmacology. The current paradigm of neuropsychiatric therapeutics implies that because xenobiotics that affect the neurotransmission of dopamine are most efficacious, this receptor-drug exemplar defines the disease. Multiple lines of investigation have shown that beyond simple monoamine balance, the interaction between multiple signaling cascades, neurotrophic and neuroprotective systems is not only involved in the pathogenesis of mood disorders, but also the cellular and molecular means of the action of lithium.¹⁵⁵ Additionally, the understanding that a particular receptor only undergoes a single agonist-receptor activation has been replaced by the growing comprehension that agonist binding causes activation of multiple pathways of downstream signaling, with a myriad of results.²⁵ Lithium illustrates this new paradigm through its multiple direct and indirect effects.

Clinically, the therapeutic effects of lithium and similar mood-stabilizing pharmaceuticals become evident only after chronic administration, so their mechanism of action is unlikely solely the result of acute biochemical interactions. One of the central processes involved in the therapeutic effects of lithium, and potentially the pathogenesis of mood disorders, is its interaction with the β form of glycogen synthase kinase 3 (GSK-3). GSK-3 β is a serine/threonine kinase originally described with the regulation of glycogen synthesis in response to insulin.²⁵ Subsequently it has been shown to influence multiple systems, including gene transcription, neuronal function and neurogenesis, synaptic plasticity, and the circadian cycle, as well as cellular structure, apoptosis, and cell death. In fact, GSK-3 β phosphorylates more than 100 substrates, with a suggestion of many more.¹⁰¹ Each of these systems are implicated in the pathophysiology of mood disorders.^{25,155}

Postmortem tissue from the ventral prefrontal cortex of patients with major depressive disorder showed elevated GSK-3 β activity as well as decreased activity in the GSK-3 β modifying enzyme, Akt (also known as protein kinase B).^{102,103} GSK-3 β is inadequately inhibited in association with mood disorders and is inhibited in humans treated with lithium.¹⁰¹ Overactivity of this enzyme is associated with neuronal degeneration and sensitivity to apoptotic stimulation. Dysregulation of GSK-3 β is implicated in tumor growth and the neurofibrillary tangles of Alzheimer disease.^{56,191} It also is a key regulator of neuronal cell fate, with a proapoptotic effect in many settings.^{5,22,24,26,101,118,131,161} It is involved in regulating the activity of β -catenin, Jun, and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), transcription factors important in embryonic patterning, cell proliferation, neuronal modeling and plasticity, neuronal signal transduction, memory consolidation, and cytoskeletal remodeling. Its other targets include transcription factors such as c-Jun, nuclear factor activated T-cells, proteins bound to microtubules (Tau, microtubule-associated protein 1B, kinesin light chain), cell cycle mediators (cyclin D), and metabolic regulators (glycogen synthase, pyruvate dehydrogenase).^{153,155} Hypoxia contributes to increased GSK-3 β activity, which may be counteracted or inhibited with mood-stabilizing drugs. Vascular depression, or depression after stroke, is an organic model of major depression.^{94,133} The finding that this depressive state responds similarly to intervention with mood stabilizers lends further support to the GSK-3 β hypothesis.^{70,79,90,150,190}

Many older generation antipsychotics are now known to affect GSK-3 β signaling in mice.¹¹⁹ GSK-3 β activity is regulated not only by first- and second-generation antipsychotics but also through 5-HT neurotransmission and activation of 5-HT_{2A} receptors as well as through monoamine-affecting antidepressants which modify these neurotransmitters.^{22–28,117} Atypical antipsychotics and antagonists of D₂ dopamine receptors, as well as 5-HT_{2A} serotonin receptors, may exert some of their utility through inhibition of GSK-3 β activity.^{22,25}

The link between neuropsychiatric illness and these centrally placed mediators of signaling comes from exploration of dopamine neurotransmission (Fig. 72–1). Scaffolding proteins, the β -arrestins, are traditionally associated with the termination of G protein–coupled receptor (GPCR) signaling and desensitization. After a receptor is stimulated, GPCRs are phosphorylated, leading to the β -arrestin recruitment that uncouples the receptor from the G protein and leads to GPCR internalization. β -Arrestins also act as scaffolds for the formation of a protein complex that allows for GPCRs to signal independently from G proteins.^{22,24,26,71} Dopaminergic neurotransmission through GPCRs is mediated through a complex that involves Akt, β -arrestin 2 (β Arr2), and protein phosphatase 2A (PP2A). Akt is a serine/threonine kinase that is additionally regulated through phosphatidylinositol-mediated signaling.²⁵ Akt activity results from an equilibrium between phosphorylation (activation) and dephosphorylation (inactivation).²⁷ Regulation of GSK-3 β activity is achieved through phosphorylation of its N-terminal serine residue, leading to inhibition.¹¹⁸ The Akt- β Arr2-PP2A complex, when activated, dephosphorylates (deactivates) Akt, which leads to the activation of GSK-3 β through loss of inhibition (loss of phosphorylation).^{25,27,70}

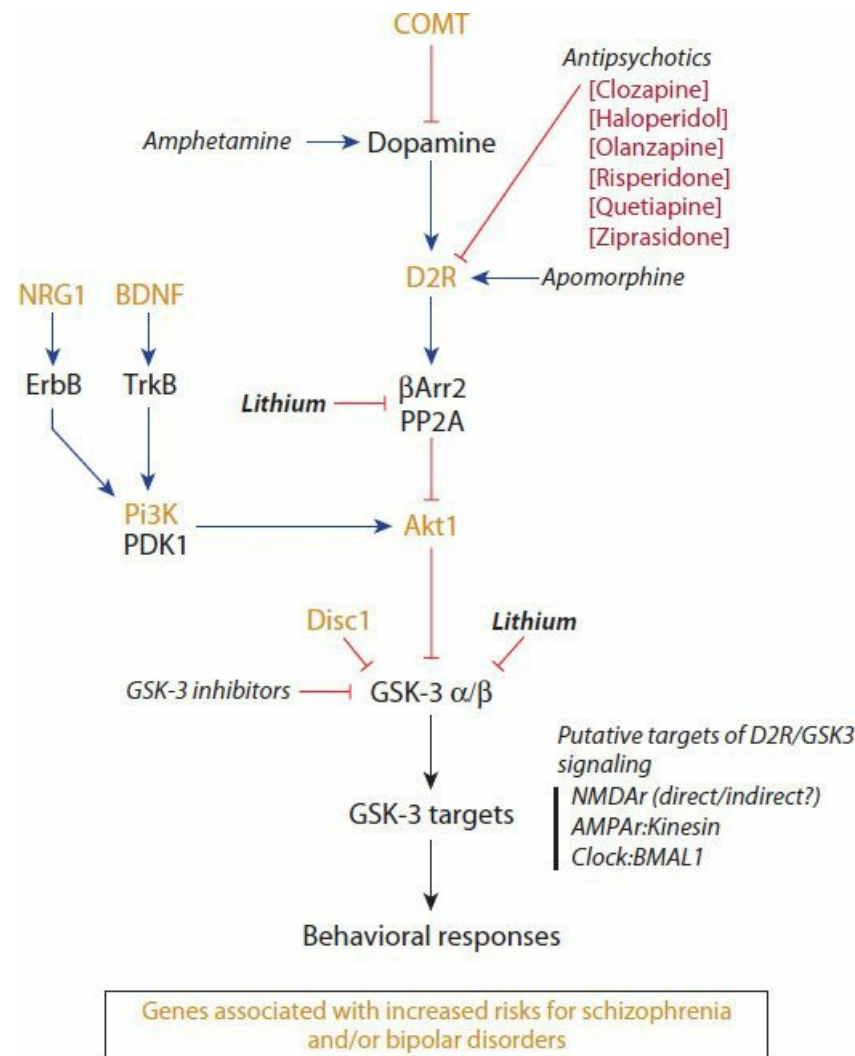


FIGURE 72–1. Regulation of Akt/GSK-3 signaling by psychoactive drugs and related network of gene products associated with mental disorders. Proteins labeled in orange are the product of genes associated with an increased risk of developing schizophrenia and/or bipolar disorders. Blue arrows indicate activation, and the red T-arrows indicate inhibition. Black arrows indicate actions that can either activate or inhibit the function of specific substrates. Behavioral changes in dopaminergic responses have been reported in Akt1 and β -arrestin 2 knock out mice and in GSK-3 β -HET mice. Akt = GSK-3 β modifying enzyme; COMT = catechol-O-methyltransferase; D2R = D₂ dopamine receptor; Disc1 = Disrupted-in-Schizophrenia 1; GSK-3 = glycogen synthase kinase 3; NRG1 = neuregulin 1; PDK1 = phosphatidylinositol-dependent kinase 1; Pi3K = phosphatidylinositol 3-kinase. (Adapted with permission from Beaulieu JM, Gainetdinov RR: The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev.* 2011;63:182–217.)

Lithium is a direct inhibitor of GSK-3 β that can also inhibit its activity indirectly through a mechanism involving Akt activation.^{26,27,48,101} Lithium activates Akt by disrupting assembly of the Akt- β Arr2-PP2A complex through displacement of the magnesium cofactor required for assembly.^{25–27} Through disruption of this complex, which normally promotes Akt inactivation, lithium promotes Akt activation, leading to increased phosphorylation (inactivation) of GSK-3 β . This is demonstrated in β -arrestin knockout mice, which, unable to create this complex, are resistant to the behavioral effects of lithium.^{25,27,70,101}

Identification of the Akt- β Arr2-PP2A signaling complex as a target of lithium lends credence to the use of lithium as an adjunct to enhance the action of atypical antipsychotics and antidepressants in poorly responsive subjects by acting through Akt-GSK-3 β signaling.^{25,27,101}

Inhibition of GSK-3 β by lithium is thought to be neuroprotective by modifying the downstream targets and effectors of GSK-3 β activity.^{5,23,27,70,91,110,150,162} Lithium is implicated in the neuroprotective modulation of the bcl-2 gene, which is known for its role in preventing apoptosis and in downregulation of the proapoptotic protein p53. Lithium increases bcl-2 concentrations in cultured nervous tissue of both rats and humans.^{49,129} Additional support comes from patients undergoing long-term therapy with either lithium or valproic acid (VPA) who show prefrontal cortex volumes significantly greater than in patients not treated with either agent, suggesting a protective effect in humans.^{47,162} Further evidence points toward a neuroprotective and neurotrophic effect of lithium with evidence to support benefit in such diverse neurodegenerative conditions as Parkinson disease (in a mice model of Parkinson disease using N-methyl-4-pheynyl-1,2,3,6-tetrahydropyridine {MPTP}),¹⁹⁸ Huntington disease,¹⁶⁸ amyotrophic lateral sclerosis (ALS),⁶⁸ stroke and multiple sclerosis,^{23,47} traumatic brain injury,¹⁹⁹ and Alzheimer disease.^{5,19,22,25,42,131,136}

It would be naïve to assume that lithium has a single mechanism of action, and it is plausible that other mechanisms, such as the inhibition of inositol monophosphatases, also contribute to its pleiotropic effects on behavior. Compelling evidence has bridged a link between the current molecular targets and downstream regulators of the effects of lithium with the classic proposed mechanism of action, the inositol-depletion hypothesis.

Among the first proposed mechanisms of action of lithium was the inositol-depletion hypothesis.⁹⁰ Inositol is a six-carbon sugar that forms the backbone of a number of cellular signaling mechanisms. Lithium treatment results in a decreased myo-inositol (the most biologically active stereoisomer of inositol) concentration in the cerebral cortex.^{34,90,131} Abnormalities in regional brain myo-inositol concentrations are thought to occur in bipolar patients. This theory is partially supported by experimental magnetic resonance spectroscopy data.^{173,197} Myo-inositol is phosphorylated to form phosphatidyl inositol (PIP), which is further phosphorylated and combined with diacylglycerol (DAG) to form phosphatidyl 4,5-bisphosphate (PIP₂). Upon stimulation of a cell, G protein-coupled receptors activate phospholipase C (PLC), which hydrolyzes PIP₂ to release the secondary messengers DAG and inositol 1,4,5-trisphosphate (IP₃).^{34,92} Each of these secondary messengers in turn initiates a cascade of events, including activation of protein kinase C, which is important for calcium homeostasis and neurotransmitter release,^{131,173} as well as independent mobilization and regulation of intracellular calcium.^{149,162,173} Many extracellular signals, including some serotonin receptor subtypes, neurotrophin signaling pathways, receptor tyrosine kinase pathways, and G protein-mediated signaling, activate PLC to exert their actions.^{80,154,155}

Serial dephosphorylation of IP₃ leads to regeneration of myo-inositol and recycling of the inositol pool. Two enzymes involved in this pathway are inhibited by lithium. The first enzyme, inositol 1,4-bisphosphate 1-phosphatase (IPPase), dephosphorylates the bisphosphate to inositol monophosphate (IMP). The second enzyme, inositol 1-monophosphatase (IMPase), dephosphorylates IMP to myo-inositol⁴ (Fig. 72–2).

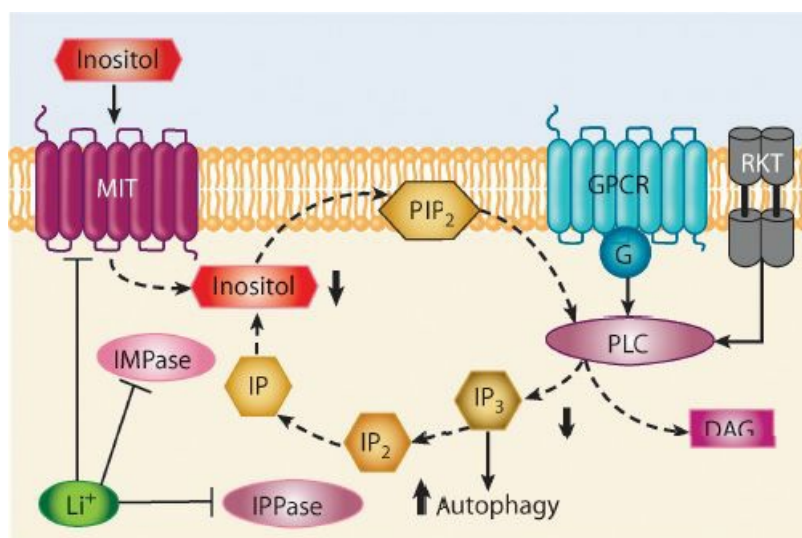


FIGURE 72–2. The actions of lithium on inositol depletion and autophagy induction. Extracellular signal binding to its cell surface receptor, either G protein-coupled receptor (GPCR) or RTK, activates phospholipase C (PLC), which hydrolyzes the phospholipid phosphatidyl bisphosphate (PIP₂) to yield second messengers inositol triphosphate (IP₃) and diacylglycerol (DAG). IP₃ is recycled by enzymes inositol bisphosphate phosphatase (IPPase) and inositol monophosphatase (IMPase) and converted to inositol (mainly myo-inositol), which is required for PIP₂ resynthesis. Lithium decreases intracellular inositol levels by directly inhibiting IPPase, IMPase, and myo-inositol transporter (MIT) that uptakes extracellular inositol. Decreased intracellular inositol levels are expected to subsequently reduce PIP₂ and prevent the formation of IP₃ and DAG, thus blocking transmembrane signaling and triggering the induction of autophagy. Lines with solid arrows represent stimulatory connections; lines with flattened ends represent inhibitory connections. Dashed lines represent pathways with reduced activity as a result of lithium treatment. IP = inositol monophosphate; IP₂ = inositol bisphosphate. (Adapted with permission from Chiu CT, Chuang DM: Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders. *Pharmacol Ther.* 2010;128:281–304.)

The inhibition of IMPase is interesting and important. Lithium inhibits IMPase by “uncompetitively” binding to the enzyme-substrate complex and preventing the release of phosphate. It performs this function by displacing a magnesium ion from the active site after hydrolysis. This is the same mechanism by which lithium directly inhibits GSK-3β.⁴⁸ Uncompetitive refers to the inhibitor binding to the enzyme-substrate complex; the higher the concentration of the substrate, the more the enzyme is inhibited.^{70,86,127} Uncompetitive inhibitors only bind to the enzyme-substrate complex, inhibiting the reaction at that point. Uncompetitive inhibitor kinetics are related proportionally to the concentration of the enzyme–

substrate complex and cannot be overcome by increasing the concentration of the substrate, unlike a competitive inhibitor.¹⁵⁰ This supports a theory about the pathophysiology of bipolar disorder involving an excess of myoinositol and is one reason why the mood-stabilizing effects of lithium are thought to occur only in bipolar patients.⁹⁰ The nature of the action of lithium serves as a regulator to preferentially block pathologic signaling caused by excessive myoinositol while leaving the normal signaling intact. As described, IMPase is an important step in the cellular recycling of the inositol pool and is inhibited by lithium.

Myoinositol is also generated de novo from glucose-6-phosphate by inositol synthase, which forms IMP. The inhibition of IMPase by lithium subsequently leads to myoinositol depletion by preventing the conversion of the newly synthesized IMP to myoinositol. Interestingly, VPA also inhibits inositol synthase, illustrating a potential mechanism for the synergy of these complementary mood stabilizers.^{60,115} A third mechanism of intracellular diminution of inositol by lithium (as well as VPA and carbamazepine) is the effect of lithium on reducing activity and transcription of the sodium myoinositol transporter, preventing the uptake of exogenous myoinositol by the cell. This mechanism of inhibition may be overcome by increased extracellular concentration of myoinositol.⁹⁰

The result of these effects is depletion of the inositol pool available to the cell, causing a series of events at different points in the signal transduction cascade that leads to differential gene transcription and expression. This sequence ultimately is responsible for some of the observed clinical effects of lithium on the central nervous system (CNS).¹⁷⁰ Experimental data using dextroamphetamine as a model for clinical mania demonstrate increased regional inositol signaling in the human brain that is attenuated by pretreatment with lithium, lending support to the hypothesis.³¹

The inositol depletion hypothesis, while an original attempt to explain in molecular terms the therapeutic effects of lithium, does not fully elucidate nor replicate the clinical disease or response to therapy. In vivo studies with more drastic inositol depletion than that which occurs from lithium therapy fail to replicate predicted behavioral patterns. Studies in knockout mice lacking various isoforms of inositol monophosphatase fail to replicate the antidepressant or antimanic effects of lithium. The model remains an attractive one, and the flaws may represent species variation with validity more in humans with bipolar disorder than the mouse model illustrates.^{23,131,169} However, there may be a synergy with other proposed mechanisms of lithium's effect. Using a yeast model, it was shown that GSK-3 β is required for de novo inositol synthesis, and that loss of GSK-3 β activity leads to inositol depletion. This finding links the two targets of not only lithium, but other mood stabilizing pharmaceuticals.¹²

In summary, although the precise mechanism of action is unknown, some common features of investigation have emerged. The potential targets, widely found and disparate in function, all seem to be inhibited by lithium in an uncompetitive fashion, most commonly through displacement of a divalent cation, usually Mg²⁺. The systems affected by this inhibition vary widely. Downstream targets seem to modulate secondary cell messengers and intracellular signal transduction, transcription factors and gene expression, and neuronal plasticity and cellular differentiation. Further study is needed to elucidate the complex interaction of these pathways with the action of lithium to form an integrated hypothesis.

PHARMACOKINETICS AND TOXICOKINETICS

The volume of distribution of lithium is between 0.6 and 0.9 L/kg. It has no discernible protein binding and distributes freely in total body water, with the exception of the cerebrospinal fluid (CSF), from which it is actively extruded.^{62,81,163} The extrusion is believed to occur through an active transport process involving sodium/lithium exchange at the arachnoid processes.⁵⁹ The immediate-release preparations of lithium are rapidly absorbed from the gastrointestinal (GI) tract. Peak serum concentrations are achieved within 1 to 2 hours. Sustained-release products demonstrate variable absorption, with a delay to peak of 4 to 5 hours.^{81,182} In overdose, a longer delay to reach peak concentrations or multiple peaks may occur.^{58,812} Chronic therapy prolongs the elimination of lithium, as does advancing age.⁸¹ Although lithium is rapidly absorbed, tissue distribution is a complex phenomenon, with a significant delay in reaching a steady state. Lithium exhibits preferential uptake into the kidney, thyroid, bone, and other organs and tissues such as the liver and muscle. Lithium distribution into the brain can take up to 24 hours to reach equilibrium. Lithium is concentrated in red blood cells (RBCs) by both passive diffusion and active transport. The RBC concentration may correlate closely with the brain concentration, although this does not appear to be clinically useful.⁴³ The pharmacokinetic profile of lithium is described as an open, two-compartment model.^{62,81}

Each 300 mg lithium carbonate tablet contains 8.12 mEq of lithium.⁸¹ Ingestion of a single 300 mg tablet is expected to acutely increase the serum lithium concentration by approximately 0.1 to 0.3 mEq/L (assuming a volume of distribution of approximately 0.6–0.9 L/kg and a patient weight of 50–100 kg).

Lithium undergoes no metabolic transformation and is eliminated almost entirely (95%) by the kidneys, with a small amount eliminated in the feces.⁶² Lithium is also found in sweat, saliva, and breast milk.^{57,185} In an adult with normal kidney function, lithium clearance varies from 10 to 40 mL/min.^{81,181} At steady-state equilibrium, total body clearance equals renal clearance.

Lithium is handled by the kidneys much in the same way as sodium. Lithium is freely filtered, and more than 80% is reabsorbed by the proximal tubule. Evidence also indicates a small amount of reabsorption by the loop of Henle and distal tubule.^{36,69,112,181} Lithium excretion is therefore dependent on factors that affect the glomerular filtration rate (GFR) or decrease sodium concentration. Any condition that makes the kidney sodium avid such as volume depletion or salt restriction increases lithium reabsorption in the proximal tubule.^{82,181} Thus, risk factors for development of lithium toxicity include advanced age with its decrease in GFR; use of thiazide diuretics, nonsteroidal antiinflammatory drugs (NSAIDs), or angiotensin-converting enzyme (ACE) inhibitors; decreased sodium intake; and low-output heart failure.^{101,113}

The therapeutic index of lithium is narrow. The generally accepted steady-state therapeutic range of serum lithium concentrations is 0.6 to 1.0 mmol/L, although much disagreement exists about whether this serum concentration truly reflects therapeutic efficacy.^{81,121} Both in therapeutic and overdose situations, clinical signs and symptoms seem to be a more valuable indicator of brain lithium concentrations.^{17,140}

CLINICAL MANIFESTATIONS

Similar to other xenobiotics having prolonged redistributive phases and tissue burdens, lithium exposure can be divided into three main categories of toxicity: acute, acute-on-chronic, and chronic. In acute lithium toxicity, the patient has no body burden of lithium present at the time of ingestion. The toxicity that develops depends on the rates of absorption, distribution, and elimination. In chronic toxicity, the patient has a stable body burden of lithium as serum concentration is maintained in the therapeutic range, and then some factor disturbs this balance, either by enhancing absorption, or more commonly, decreasing elimination. For chronic users of lithium, small perturbations in the equilibrium between intake and elimination may lead to toxicity. In acute-on-chronic toxicity, the patient ingests an increased amount of lithium (intentionally or unintentionally) in the setting of a stable body burden. With tissue saturation, any additional lithium leads to signs and symptoms of toxicity.

Acute Toxicity

Acute ingestions of lithium-containing preparations produce clinical findings similar to that of ingestions of other metal salts, with predominant early GI symptoms. Nausea, vomiting, and diarrhea are prevalent. Significant volume losses may result from these symptoms. Patients may complain of lightheadedness and dizziness, and they may be orthostatic. Neurologic manifestations are a late finding in acute toxicity as the lithium redistributes slowly into the CNS.

Chronic Toxicity

Lithium is primarily a neurotoxin. The earliest case reports of lithium toxicity described predominantly neurologic symptoms.^{175,187} Most importantly, neurotoxicity does not correlate with serum concentrations. The initial clinical condition of the patient and the duration of exposure to an elevated concentration seem to be more closely predictive of outcome than the initial serum lithium concentration.^{3,9,88,167}

The tremor of lithium is likely one of the most commonly encountered drug-induced tremors in clinical practice, with approximately 27% of patients developing it.¹⁴¹ The tremor can diminish over time but may increase with toxicity. Other findings of chronic toxicity include fasciculations, hyperreflexia, choreoathetoid movements, clonus, dysarthria, nystagmus, and ataxia.¹⁸² Mental status is often altered and may progress from confusion to stupor, coma, and seizures.^{121,134} Electroencephalographic changes are most frequently reported as “slowing.”¹⁷¹ The progression of these symptoms follows no order, and any patient undergoing chronic therapy may have one or any combination of these features.

The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is a descriptive syndrome of the irreversible neurologic and neuropsychiatric sequelae of lithium toxicity.^{3,97,151} SILENT is defined as neurologic dysfunction that is caused by lithium in the absence of prior neurologic illness and persists for at least 2 months after cessation of the drug. Case reports support these findings and this definition. However, as is true in most case reports, confounders make wide applicability of the findings difficult. Because of the polypharmacy prevalent in psychiatry, long-term neurologic sequelae attributed to lithium are frequently described in patients using lithium in combination with other xenobiotics, such as haloperidol, chlorpromazine, carbamazepine, phenytoin, aspirin, VPA, amitriptyline, β -adrenergic antagonists, calcium channel blockers, ACE inhibitors, diuretics, and NSAIDs.^{3,65,89,128,138} However, there exist reports of patients using lithium without coingestants and no comorbid illness who sustained lasting dysfunction as a result of lithium toxicity.^{9,105,145,167} Cerebellar findings seem to predominate in patients with SILENT.^{1–3,130,151} One of the predictors of persistent neurologic dysfunction may be the concomitant finding of hyperpyrexia, an ominous finding in patients with lithium toxicity.^{83,130} The mechanism of the persistent dysfunction is unclear, but demyelination and cellular loss are proposed.^{3,130,165}

Acute-on-Chronic Toxicity

Patients undergoing chronic therapy who acutely ingest an additional amount of lithium (either intentionally or unintentionally) are at risk for signs and symptoms of both acute and chronic toxicity. These patients may display prominent GI and neurologic symptoms and may be difficult to diagnose and manage. Serum lithium concentrations in cases of acute or chronic toxicity may be difficult to interpret, and therapy should be guided by the clinical status of the patient.

Other Systemic Manifestations of Chronic Lithium Therapy

The most common adverse effect of chronic lithium therapy is nephrogenic diabetes insipidus which can develop within weeks of the initiation of therapy and affects up to 40% of patients (Chap. 19).^{85,144}

Lithium inhibits the transport of sodium through the amiloride-sensitive epithelial Na⁺ channel (ENaC), which is also the main route of entry for lithium. Lithium has a twofold higher affinity than sodium for entry through this channel, without a corresponding means of extrusion and thus becomes concentrated intracellularly.^{106,181,182}

Lithium is believed to inhibit magnesium-dependent G proteins that activate vasopressin-sensitive adenylate cyclase, leading to decreased generation of cAMP in the cell membranes of distal tubular cells.^{35,50,180,186}

Decreased cAMP leads to reduced expression and translocation of the vasopressin-regulated water channel aquaporin-2 (AQP2), making the distal tubules resistant to the action of vasopressin, and thus unable to make a concentrated urine.^{6,35,120,188} Additionally, there is potential mechanistic overlap with GSK-3 β . GSK-3 β exhibits tonic inhibition of cyclooxygenase-2 (COX-2). With GSK-3 β inhibition by lithium, this inhibition is removed and increased COX-2 activity leads to increased prostaglandin expression in the renal medulla. Increased prostaglandin expression is important in nephrogenic diabetes insipidus through regulation of glomerular blood flow,^{156,157} as well as increasing the degradation of AQP2, further decreasing the ability to form a concentrated urine.^{106,107,156,157}

Chronic lithium therapy is also associated with chronic tubulointerstitial nephropathy, as manifested by the development of renal insufficiency with little or no proteinuria and biopsy findings of tubular cysts. This association was demonstrated in a biopsy-based study of 24 chronically treated patients, although the overall prevalence of this condition is low.⁸⁵

Lithium is associated with a number of endocrine disorders. The most prevalent endocrine manifestation of chronic lithium therapy is hypothyroidism.³⁹ The etiology is multifactorial. Lithium is selectively concentrated in the thyroid gland and competes for iodide transport, synthesis of triiodothyronine (T₃), responsiveness of the gland to thyroid-stimulating hormone (TSH), release of T₃ and tetraiodothyronine (T₄), and peripheral conversion of T₄ to T₃.^{39,73} Additionally, lithium decreases responsiveness of peripheral tissues to T₃ and increases antithyroglobulin antibodies if already present, it does not induce development de novo (Fig. 56–1).^{13,110,143} Although hypothyroidism is most common, hyperthyroidism and frank thyrotoxicosis are also reported.^{33,41,110} However, hyperthyroidism, by altering proximal tubule function, leads to decreased lithium excretion.²⁰ Thus, hyperthyroidism may lead to chronic lithium toxicity through impaired elimination, and the elevated lithium concentrations may mask the manifestations of hyperthyroidism.^{18,143}

The combination of hyperparathyroidism and hypercalcemia is frequently reported with chronic lithium therapy, most commonly in older women. The mechanism is thought to be modification of calcium feedback on parathyroid hormone release through alteration of a calcium-sensing receptor that prevents suppression of parathyroid hormone release in response to elevated calcium,¹⁵⁹ although stimulation of parathyroid hormone release, parathyroid gland hyperplasia, and adenomas are alternative suggested mechanisms.^{11,114,132,178}

Lithium is associated with a number of electrocardiographic (ECG) abnormalities, although the evidence for significant toxicity is lacking. Most reports are uncontrolled case reports without corroborating experimental data or biologic plausibility. The most commonly reported manifestation has been T-wave flattening or inversion, primarily in the precordial leads,¹⁴⁷ although prolongation of the QT interval is also noted.^{109,184,192} One study associated elevated serum lithium concentrations with QT prolongation above 440 msec, although the number of patients studied was small.⁹⁶ Associations have been made between lithium and sinoatrial dysfunction, with resultant bradycardia.^{10,77,146,172,179} However, many of these cases had either electrolyte disturbances or multiple other cardioactive xenobiotics involved that would be more likely causative.^{44,172,179,189} Numerous case reports have linked lithium with an ECG pattern that is consistent with a myocardial infarction, without evidence of biochemical markers of injury.^{104,152} Lithium blocks cardiac sodium channels in a transfected Chinese hamster ovary cell. This is the putative link between lithium therapy and the unmasking of a Brugada pattern as well as cardiomyopathy.^{7,46,55,193,196} For the most part, lithium has few consequential effects on cardiac function, even in overdose, and malignant dysrhythmias or significant dysfunction is very uncommon.

Developmentally, in utero exposure to lithium increases the incidence of congenital heart defects, specifically Ebstein anomaly.^{57,150,195} Additionally, many effects similar to those that occur in patients undergoing chronic therapy are found in infants exposed in utero, including thyroid disease and neurotoxicity.⁷⁵

Lithium causes a leukocytosis and an increase in neutrophils. It has been proposed as an adjunct to chemotherapy-

induced neutropenia, other marrow suppressive therapies, and acquired immunodeficiency syndrome (AIDS).⁵⁴ Although lithium increases the total neutrophil count, no improved clinical outcomes are documented, and its use has been superseded by recombinant colony-stimulating factors.^{66,150,160}

DIAGNOSTIC TESTING

Because of the prevalence of lithium use, therapeutic drug monitoring is readily available in most settings, and concentrations should be readily obtainable.¹⁹⁴ A lithium concentration should be requested upon patient presentation and serial measurements requested or considered in most instances, especially after ingestion of sustained-release preparations. Emphasis should be placed on the lithium concentration as a marker of exposure and response to therapy but not necessarily as a determinant of toxicity or treatment. The history, clinical signs, and symptoms rather than the absolute lithium concentration should guide therapy. The sample must be sent in an appropriate lithium-free tube, because use of lithiated-heparin tubes may lead to clinically false-positive results.¹¹³ Serum electrolyte concentrations and kidney function should be monitored because kidney function is important in determining the need for more aggressive therapy, including enhanced elimination techniques such as hemodialysis. If the patient is hypernatremic, nephrogenic diabetes insipidus should be suspected, and determinations of serum and urine osmolality and electrolytes help confirm the diagnosis ([Chap. 19](#)). If thyroid disease is suspected, thyroid function tests should be obtained. If a deliberate ingestion has occurred, a serum acetaminophen concentration should be obtained. An ECG is also indicated. The complete blood count may indicate a leukocytosis, as a stress response or due to the hematologic effects of lithium.

MANAGEMENT

The initial management and stabilization should begin with assessment and, if necessary, support of airway, breathing, and circulation. Lithium rarely, if ever, affects the patient's airway or breathing, although coingestants may. Emesis, which occurs with significant frequency after acute exposure, may lead to aspiration and respiratory compromise. After the patient is stable, the characteristics of the exposure should be determined while the physical examination and laboratory assessment commence. The formulation and nature of the product should be ascertained and most importantly, identified as immediate-release or sustained-release. Also, whether or not lithium is part of the patient's medication regimen may help determine whether the ingestion is acute, acute-on-chronic, or chronic.

Gastrointestinal Decontamination

For patients who present after an acute overdose or an acute-on-chronic overdose, a risk benefit analysis of GI decontamination must be undertaken. Two factors should be considered. With an acute overdose and predominance of early GI symptoms, including emesis, self-decontamination may already have started. Second, immediate-release preparations are often rapidly absorbed and may not lend themselves to GI evacuation.

Few GI decontamination options are available. Lithium is a monovalent cation that does not bind readily to activated charcoal.¹²³ Because of the danger of a depressed level of consciousness, potential loss of protective airway reflexes, and generally prominent emesis, no beneficial effect from activated charcoal is expected unless indicated for treatment of a potential coingestant. Induced emesis is no longer recommended. Orogastric lavage has essentially no role in the acute management of a patient with a lithium overdose unless indicated for a coingestant. Whereas immediate-release preparations of lithium are rapidly absorbed and typically produce emesis, sustained-release formulations of lithium (ie, controlled-release tablets) compounded in a slowly dissolving film-coated formulation often make the tablet too large to fit through even the largest lavage tube.

Sodium polystyrene sulfonate (SPS) is a cationic exchange resin often used for the treatment of severe hyperkalemia. It binds potassium in exchange for sodium, allowing elimination of excess potassium in the feces. Because of the similarity between potassium and lithium, use of SPS has been proposed for decontamination of patients being treated for lithium toxicity. A number of models have examined the effectiveness of this technique.¹²³⁻¹²⁵ Use of SPS has many theoretical benefits, including demonstrated effectiveness of lithium binding compared with activated charcoal and the ability of orally administered SPS to reduce serum concentrations of intravenously administered lithium in mice.¹²³ Unfortunately, the finding that doses used to increase lithium elimination also lead to significant hypokalemia in human subjects limits the application of this technique.¹⁶⁴ In a murine model, potassium supplementation with SPS was found to mitigate this process but only at the expense of elevating lithium concentrations.¹²⁵ Two reports in the literature demonstrate increased lithium elimination with SPS, one in a healthy volunteer and another in a patient with an acute overdose. However, the serum potassium concentration was not reported in either case.⁷⁴ In a retrospective cohort review of 12 chronically poisoned patients, it was suggested that SPS reduced the elimination half-life of lithium by 50%. However, many of the patients had altered kidney function that was corrected at the same time as the intervention (which was not standardized), and no clinical outcomes were reported.⁷⁶ At present, use of SPS in the management of the lithium-poisoned patient cannot be routinely

recommended, until further clinical trials can be performed.

Whole-bowel irrigation (WBI) is the only GI decontamination that has some demonstrated efficacy in eliminating lithium from volunteer human subjects. In one of the few clinical trials of WBI, the serum lithium concentrations of 10 normal volunteers who had ingested sustained-release lithium carbonate were plotted against time over a 72-hour period. In the second phase of the trial, when the volunteers received 2 L/h of polyethylene glycol solution one hour after the ingestion, there was a significant reduction (67%) in the serum concentration, even as early as one hour after the therapeutic intervention.¹⁷⁴ WBI is recommended for patients manifesting significant toxicity (ie, neurologic dysfunction) and who have ingested sustained-release preparations and have no contraindications (eg, protected airway, no obstruction or ileus) (Antidotes in Depth: A2).

Fluid and Electrolytes

The critical initial management of the lithium-poisoned patient should focus on restoration of intravascular volume, both in acute poisonings with GI losses and in chronic poisonings with toxic effects that are often the result of disturbances of kidney function and lithium elimination. Many patients with lithium toxicity have volume-responsive decreases in kidney function,¹⁵⁸ which can be managed by infusion of 0.9% sodium chloride solution at 1.5 to 2 times the maintenance rate. This therapy increases renal perfusion, increases the GFR, and lithium elimination. Urine output must be closely monitored and any electrolyte abnormalities corrected. Caution must be used in patients with prerenal acute kidney injury (AKI), chronic kidney disease (CKD), and congestive heart failure. Monitoring for the development of hypernatremia in patients suspected of having nephrogenic diabetes insipidus is critical.^{120,181,182}

Lithium-induced nephrogenic diabetes insipidus may be reversed by discontinuation of the drug and repletion of electrolytes and water. However, nonreversible effects are reported.^{106,181} Clinical application of amiloride to mitigate lithium-induced polyuria is described, although the potential for volume contraction and stimulation of lithium reabsorption limits recommendation of this drug as a routine adjunct to acute care.^{30,64,106,158}

Any attempt to enhance elimination of lithium by forced diuresis using loop diuretics (furosemide), osmotic agents (mannitol), carbonic anhydrase inhibitors (acetazolamide), or phosphodiesterase inhibitors (aminophylline) should be avoided. An initial small increase in elimination may be achieved, but typically salt and water depletion subsequently develop followed by increased lithium retention. Sodium bicarbonate for urinary alkalization should also be avoided because it does not significantly increase elimination over volume expansion with sodium chloride and may lead to hypokalemia, alkalemia, and fluid overload.

Extracorporeal Drug Removal

Debate surrounds the efficacy and practicality of using enhanced elimination techniques in cases of lithium poisoning. Lithium does have pharmacokinetic properties that make it amenable to extracorporeal removal,^{21,63,95,100,112} and with these characteristics, it would seem to be an ideal candidate for hemodialysis. In fact, hemodialysis is often recommended for treatment of acute, acute-on-chronic, and chronic lithium toxicity.^{14,63,98,148,182,199} However, some characteristics of lithium make extracorporeal elimination difficult. Lithium is predominantly localized intracellularly and diffuses slowly across cell membranes.⁶³ When traditional intermittent hemodialysis is used for chronic exposures, clearance of the blood compartment is often followed by a rebound phenomenon of redistribution from tissue stores, leading to recurrent increased serum concentrations. The clinical significance of this rebound is uncertain, but without additional elimination this can redistribute back into target tissues.³⁸ There have only been three cases reported of clinical deterioration after rebound from an extracorporeal elimination method, likely as a result of failed decontamination in an extended release ingestion.^{37,40,71} An additional complicating factor is that the brain, the “target organ” of toxicity, is not amenable to a rapid artificial elimination process. Attempts have been made to correlate the serum concentration with the lithium concentration in the CSF and brain. But in the few studies where CSF concentrations were obtained, although serum and CSF lithium concentrations seemed to correlate, brain concentrations and toxicity did not.^{92,99} Magnetic resonance spectroscopy studies of bipolar patients with steady-state lithium concentrations demonstrated a significant variability between brain and serum concentrations, especially within the therapeutic range.⁶⁷ In addition, because of the toxicokinetic profile of lithium, serum concentrations do not correlate well with toxicity.^{81,99,182}

Some consensus is emerging regarding when to perform an extracorporeal elimination technique (extracorporeal treatment {ECTR}). The Extracorporeal Treatments in Poisoning Workgroup (ExTRIP) has performed an extensive analysis of the data available regarding lithium. Their most recent consensus provides the following analysis: “ECTR should be performed in severe Li poisoning,” graded (1, D). The “1” indicates that more than 85% of their members strongly recommend, and the D that there is a very low level of evidence (no observational studies or randomized controlled trials).⁶¹ Hemodialysis or an alternative extracorporeal technique is clearly indicated for three groups of patients. The first group consists of patients who are manifesting severe signs and symptoms of neurotoxicity, such as alterations in mental status or seizures. The second group consists of patients who have AKI or CKD and show signs or

symptoms of lithium toxicity. Such patients are unable to eliminate their lithium burden on their own and should undergo hemodialysis. The third group consists of patients who show little or no sign of toxicity but who cannot tolerate sodium repletion therapy; these patients who should be considered for early hemodialysis include those with congestive heart failure or such “redistributive diseases” as liver failure, pancreatitis, or sepsis.

For a patient who belongs to this last group, the next step is to determine the probability that the patient will develop toxicity if elimination is not enhanced. The criteria for hemodialysis originated from a case series of 23 patients and a review of 100 other patients published in 1978, which was before the introduction of sustained-release products.⁸⁸ These recommendations have never been prospectively evaluated (or subsequently reevaluated).^{15,63,72} The ExTRIP group proposes the consensus recommendations based on the classification of the overdose and categories based on serum concentrations⁶¹ (Table 72–1).

TABLE 72–1. Consensus Recommendations for Hemodialysis

<i>Characterization</i>	<i>Reasonable</i>	<i>Suggested</i>	<i>Recommended</i>
Acute with normal GFR	>2.5 mEq/L	>4.0 mEq/L	>6.0 mEq/L
Chronic with normal GFR	>2.5 mEq/L	>3.5 mEq/L	>5.0 mEq/L
Acute or chronic with kidney disease (GFR <60 mL/min)	>2.0 mEq/L	>2.5 mEq/L	>3.0 mEq/L

GFR = glomerular filtration rate.

Interestingly, the above serum concentrations and recommendations are irrespective of symptomatology. Additional consensus recommends ECTR for acute neurologic dysfunction such as confusion, decreased level of consciousness, and seizures. It is also suggested to use ECTR for hyperthermia. Whether hemodialysis diminishes or enhances the risk of permanent neurologic sequelae is a subject of debate.^{176,177} Although no controlled studies have analyzed this important management question, the preponderance of evidence suggests a reduced risk.^{3,9,15,63,95,99,137,148,151,166,182}

Continuous venovenous hemodialysis and continuous venovenous hemodiafiltration are two continuous renal replacement therapies (CRRTs) commonly used in the treatment of patients with AKI or volume overload and for elimination of xenobiotics.^{14,29,183} Both techniques are effective in patients who are hemodynamically unstable because blood flow through the filter is pump driven and is not dependent on the arterial blood pressure.^{72,135} Other continuous techniques that use patient blood pressure as the basis of flow through the system also may have application here.¹⁸³ Traditional intermittent hemodialysis (IHD) offers clearance rates that vary between 50 and 170 mL/min with blood flows of 250 mL/min or more.^{63,126,148,183} Although CRRT techniques offer lower clearance per hour than does IHD, their overall daily clearances are similar.⁶³ With continued improvements in techniques, use of high volumes, and high dialysate flow rates, clearances are improving, approaching more than half the clearance per hour achieved by IHD in some studies.⁷³² One case of a rebound concentration was reported in a patient treated with continuous arteriovenous hemodiafiltration,³² and one case with use of combined renal replacement therapies, including venovenous techniques, showed no rebound.¹⁴ Unfortunately, CRRT requires prolonged anticoagulation with its inherent risks. Nevertheless, these techniques may be beneficial in patients who are hemodynamically unstable, or they may be used in series with traditional dialysis in other patients to prevent redistribution of lithium and rebound of serum concentrations (Chap. 10).

After an initial run of an ECTR such as IHD, repeat intermittent IHD should be continued until serum lithium concentrations are consistently below 1.0 mEq/L.

Peritoneal dialysis (PD) offers no increased efficacy of clearance of lithium over the natural clearance of normal kidneys.^{15,63} Although recommended in the past, given its lack of efficacy coupled with its infrequent use and potential for serious complications such as bowel perforation, PD has no role in the management of lithium-poisoned patients.

SUMMARY

- Lithium is a simple ion with extensive current usage and extremely varied and complex clinical and pathophysiologic effects.
- It is available in multiple formulations, both immediate release and sustained release, and has an essential role in clinical psychiatry.
- Because of the complexity of the pharmacokinetic profile of lithium, toxicity may develop in a wide range of conditions and may be precipitated by both intentional overdose and therapeutic misadventure.
- The care of lithium-poisoned patients should be predicated on rapid clinical evaluation of the condition of the patient

coupled with identification of the type of poisoning

- Management includes the use of volume resuscitation and WBI and hemodialysis or other extracorporeal techniques, when indicated, to prevent or treat severe neurologic morbidity and to prevent mortality.

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73 MONOAMINE OXIDASE INHIBITORS

Alex F. Manini

HISTORY AND EPIDEMIOLOGY

Monoamine oxidase inhibitors (MAOIs) have a unique history, pharmacology, and toxic syndromes associated with their use. This drug class has fallen in and out of favor with scientists and clinicians over the last several decades. While toxicity from MAOI ingestion is becoming less common due to more limited clinical usage of the traditional nonselective MAOIs, an understanding of MAOI toxicity is fundamental to any clinician who takes care of patients with acute poisoning.

Monoamine oxidase (MAO) was discovered in 1928 and named by Zeller when the enzyme was recognized to be capable of metabolizing primary, secondary, and tertiary amines such as tyramine and norepinephrine.¹³¹ Subsequently, the “monoamine hypothesis” postulated depression as a monoamine deficiency state and MAOIs targeted monoamine metabolism for therapeutic benefit. In the early 1950s, iproniazid, a drug previously used to treat tuberculosis, was found to produce favorable behavioral adverse events. By the mid 1950s, it was demonstrated that iproniazid inhibited MAO, and it then became the first antidepressant used clinically.⁴⁶

In the late 1960s, two MAO isoforms were identified each with substrate and inhibitor specificity. This determination led to the development of selective MAOIs in attempts to minimize the many food and drug interactions that occur with the traditional nonselective MAOIs. Nonselective MAOIs proved to be potent and efficient antidepressants and became first-line therapy for depression. In the 1970s, alternative therapies for depression, such as tricyclic antidepressants, were developed and achieved clinical success without as many food interactions.

Intentional MAOI overdose is relatively uncommon and accounts for a dwindling number of annual exposures reported to the American Association of Poison Control Centers. From 2000 to 2010 there was a decreasing trend in the number of exposures with only 228 exposures reported in 2010,¹⁶ representing less than 1% of all antidepressant exposures. Of the reported exposures in 2010, there were only five cases of “major toxic effect” (defined as life-threatening signs or symptoms) and no deaths were reported. Over the past two decades, annual reported MAOI exposures have decreased 34% since 1985 (Chap. 136). Global MAOI exposure rates declined in proportion with the United States, with the possible exception of exposures to moclobemide, a drug not approved by the US Food and Drug Administration (FDA).³³

PHARMACOLOGY

Chemistry

Monoamines, also known as biogenic amines, include the neurotransmitters norepinephrine, dopamine, and serotonin, which share the presence of a single amine group and the ability to be metabolized by MAO. Monoamine oxidase is a flavin-containing enzyme present on the outer mitochondrial membrane of central nervous system (CNS) neurons, hepatocytes, and platelets. In a two-step reaction, MAO catalyzes the oxidative deamination of its various substrates. The reaction liberates H_2O_2 , a reactive oxygen species. Deamination by MAO is one of two major routes of elimination of monoamines, the other being extracellular degradation by catechol-O-methyltransferase (COMT). Serotonin, which is not metabolized by COMT, is the exception to this rule.

Monoamine Neurotransmitter Stores

Monoamine neurotransmitter synthesis, vesicle transport, vesicle storage, uptake, and degradation are described in detail in Chap. 14. In the neuron, MAO functions as a “safety valve” to metabolize and inactivate any excess monoamine neurotransmitter molecules. Once monoamines reenter the cytoplasm from the synaptic cleft, they can either reenter vesicles for further storage and release, or can be rapidly enzymatically degraded by MAO.

MAO Isoforms

There are two MAO isoforms, each with their own substrate and inhibitor specificity (Table 73–1). MAO-A preferentially metabolizes norepinephrine and serotonin, and MAO-B preferentially metabolizes benzylamine in vitro. Both isoforms metabolize tyramine and dopamine with comparable efficiency, but they are localized to differing anatomic regions, with

MAO-A concentrated in the intestine and liver, whereas MAO-B is concentrated in the basal ganglia of the brain.²²

TABLE 73–1. Monoamine Oxidase (MAO) Isoforms: Substrate Affinities and Localization

	<i>MAO Isoforms</i>	
	<i>MAO-A</i>	<i>MAO-B</i>
Substrate affinity		
Dopamine	Moderate	Moderate
Epinephrine	Moderate	Moderate
Norepinephrine	High	Low
Serotonin	High	Low
Tyramine	Moderate	Moderate
Localization		
Brain	Low	High
Intestine	Moderate	Low
Liver	Moderate	Moderate
Placenta	High	Absent
Platelets	Absent	High

Mechanism of Action

MAOIs are transported into the neuron by the Na⁺-dependent membrane norepinephrine-reuptake transporter.⁷³ Inhibition of MAO prevents presynaptic degradation of monoamines, thus increasing the concentration of monoamine neurotransmitters available for synaptic storage and subsequent release (Fig. 73–1). Inhibition of MAO also results in indirect release of norepinephrine into the synapse, via displacement from presynaptic vesicles in a manner similar to amphetamines.¹¹⁶

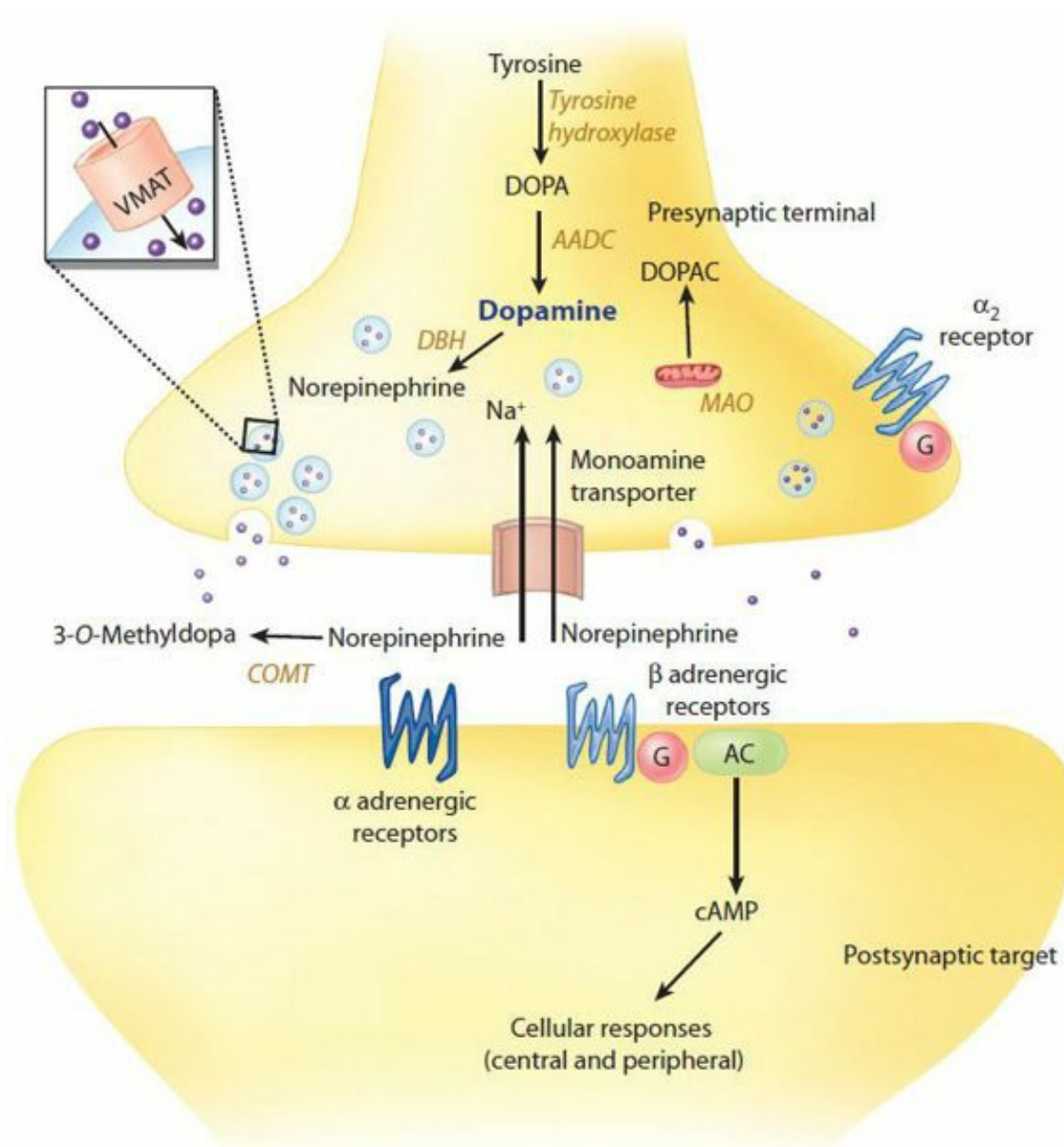


FIGURE 73–1. Sympathetic nerve terminal. Dopamine is synthesized in the sympathetic nerve cell and transported into vesicles where it is converted to norepinephrine (NE) and stored in vesicles (●). An action potential causes the vesicles to migrate to and fuse with the presynaptic membrane. NE diffuses across the synaptic cleft and binds with and activates postsynaptic α and β -adrenergic receptors. Neuronal NE reuptake occurs via the monoamine transporter. NE is transported back into vesicles by the vesicular monoamine transporter (VMAT; inset) or metabolized to 3,4 dihydroxyphenyl acetic acid (DOPAC) by mitochondrial monoamine oxidase (MAO). NE that diffuses away from the synaptic cleft is inactivated by catechol-O-methyl transferase (COMT). AADC = aromatic L-amino acid decarboxylase; DBH = dopamine beta-hydroxylase; NET = NE transporter.

Elevated synaptic concentrations of serotonin are most closely correlated with the antidepressant therapeutic effects of MAOIs. The enzymatic inhibition produced by MAOIs precedes the clinical effects by as long as 2 weeks. This finding, which is similar to other antidepressants, may relate to the relatively slow downregulation of postsynaptic CNS serotonin receptors.⁹⁴

MAOIs impair norepinephrine synthesis due to dopamine- β -hydroxylase inhibition. Impaired norepinephrine synthesis leads to eventual depletion of norepinephrine stores. Additionally, indirect dopamine agonism occurs via elevated synaptic concentrations of dopamine. Dopamine agonism results in β -adrenergic stimulation, peripheral vasodilation, and direct α -adrenergic stimulation at high doses.

The hydrazide MAOIs (eg, phenelzine, isocarboxazid) are thought to be cleaved to liberate pharmacologically active products (eg, hydrazides), which are cleared by acetylation in the liver.

First-Generation MAOIs: Nonselective and Irreversible

Monoamine oxidase inhibitors are a chemically heterogeneous group of xenobiotics (Fig. 73–2). First-generation MAOIs

(ie, irreversible and nonselective) in clinical use include the reactive hydrazide derivatives (phenelzine, isocarboxazid) and an amphetamine derivative (tranylcypromine).⁴⁵ First-generation MAOIs bind covalently to MAO and irreversibly inhibit the function of the enzyme. Thus, patients taking these MAOIs are depleted of the enzyme until new MAO is synthesized, a process that typically takes up to 3 weeks. Patients taking first-generation MAOIs remain at risk for food and xenobiotic interactions during much of this period. Because nonselective MAOIs inhibit both isoforms of MAO (ie, MAO-A and MAO-B), inhibition of intestinal and hepatic degradation of biogenic amines occurs. As a result, patients who receive these xenobiotics must be placed on a restrictive diet to prevent adverse events resulting from the absorption of undigested tyramine from the gut.

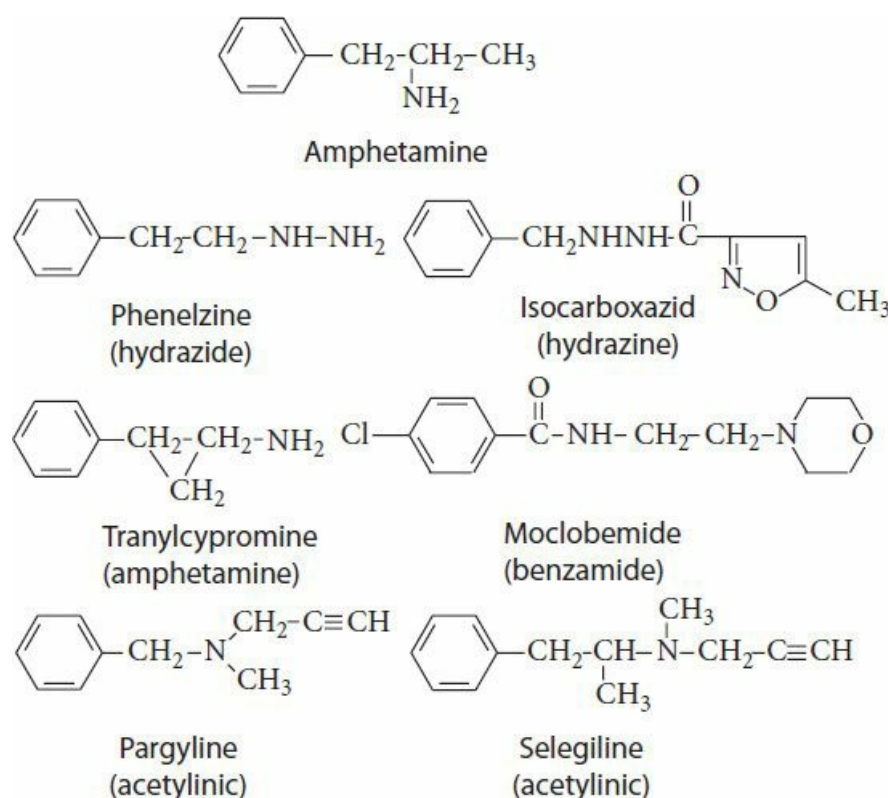


FIGURE 73–2. Structural similarities between amphetamine and the MAOIs. The words in parentheses are the chemical classes of the monoamine oxidase inhibitor (MAOI).

Phenelzine, isocarboxazid, and tranylcypromine are currently FDA approved for treatment of refractory depression.^{58,77} Pargyline, previously approved for use as an antihypertensive due to decreased peripheral vascular resistance, is no longer routinely used.¹²⁶ Phentermine is a nonselective MAOI, which is prescribed for the short term treatment of obesity.¹²²

Other enzyme systems inhibited by first-generation MAOIs include amine oxidases such as diamine oxidase and semicarbazide-sensitive oxidases, arylamine N-acetyltransferase (by tranylcypromine), ceruloplasmin, alcohol dehydrogenase (by tranylcypromine), dopa decarboxylase, L-glutamic acid decarboxylase, γ -aminobutyric acid (GABA) decarboxylase and GABA transaminase (by hydrazide MAOIs), alanine aminotransferase (by phenelzine), and other pyridoxine (B_6)-containing enzyme systems.⁴⁹ The clinical implications of inhibiting these diverse enzyme systems, other than alcohol dehydrogenase and cytochrome P450,¹⁰³ are poorly understood.

Second-Generation MAOIs: Selective and Irreversible

Selective MAOIs preferentially inhibit one of the two MAO isoforms, although isoform selectivity is lost as the dose is increased.

MAO-A Inhibitors. Clorgyline is an MAO-A inhibitor structurally related to pargyline. Once thought to be useful for treatment of depression, it has not found widespread use in psychiatry due to disappointing results from clinical trials. However, clorgyline is now being investigated in congestive heart failure and may see a future role in the treatment for those patients.

MAO-B Inhibitors. Selegiline is a selective MAO-B inhibitor that is FDA approved for the treatment of Parkinson disease,⁵⁸ although it does exhibit weak MAO-A inhibition at therapeutic doses.⁶⁸ Selegiline transdermal system is FDA approved for treatment of major depressive disorder in adults as an alternative to the traditional oral delivery system.^{6,58,98} Rasagiline is another MAO-B selective MAOI that is FDA approved to treat Parkinson disease.¹⁹

Third-Generation MAOIs: Selective and Reversible

Reversible inhibitors of monoamine oxidase-A (RIMAs) are a class of drugs that selectively and reversibly inhibit MAO-A.⁵⁸ These xenobiotics were developed in an effort to compensate for the limitations of first- and second-generation MAOIs (see Clinical Manifestations). RIMAs can be displaced by tyramine from the active site of the enzyme MAO-B, thereby enabling peripheral metabolism of the amine. Because tyramine is not present in high concentrations in the brain, MAO-A continues to be inhibited and the antidepressant effects are achieved.⁵⁸ Moclobemide is the most widely studied RIMA and is approved as an antidepressant in Europe and other parts of the world.³³ However, due to lack of financial incentives to gain approval, the drug is not currently available in the United States. Brofaromine and toloxatone are other RIMAs that were recently introduced but are less well studied.

Naturally Occurring MAOIs

The extract of the plant St. John wort (*Hypericum perforatum*) is licensed in Germany for use as an antidepressant. Although the major constituents, hypericin or hyperforin have weak MAOI activity, it is uncertain whether this activity is responsible for its antidepressant effect. However, MAOI activity explains sporadic reports of hypertensive crises, cardiovascular collapse during anesthesia, and serotonin toxicity associated with use of this herbal product.^{52,85}

Ayahuasca, a hallucinogenic beverage used by South American natives, is an ethnobotanical mixture of dimethyltryptamine and harmala alkaloids that circumvents gastrointestinal (GI) MAO. Dimethyltryptamine, which is a potent visual hallucinogen, is derived from several local plant species,²⁶ but is not orally bioavailable because of its first-pass metabolism by MAO.⁷⁴ When *Banisteriopsis caapi*, a plant containing the MAO-inhibiting harmala alkaloids, is mixed with dimethyltryptamine-containing plants, the bioavailability of this hallucinogenic amine is improved.^{74,75}

MAO-B activity in tobacco plants has prompted studies to find a link between the lower platelet MAO-B activity of smokers and their lower rate of Parkinson disease.¹⁸ This finding has led to interest in studying other MAO-B inhibitors for potential applications as neuroprotective xenobiotics.¹³⁰

Miscellaneous and Experimental MAOIs

Other xenobiotics with nonselective MAO inhibitory properties are used for purposes unrelated to MAO inhibition. Furazolidone is an antimicrobial used to treat protozoan-related diarrhea and bacterial enteritis. Procarbazine is a hydrazide derivative indicated as a chemotherapeutic for Hodgkin lymphoma and some brain tumors. Linezolid is an antibiotic that produces weak, nonselective MAO inhibition.^{29,112,120} Azure B, a metabolite of methylene blue, is a high-potency reversible inhibitor of monoamine oxidase.⁸⁶

Research is active for novel MAO combination xenobiotics that target multiple mechanistic approaches for the treatment of dementia and parkinsonism.²⁷ Ladostigil combines the cholinergic effects of a carbamate with the aminergic effects of MAO-B inhibition.¹⁰⁴ M30 is an actively researched xenobiotic that combines iron chelation and radical scavenger effects with irreversible, nonselective MAO inhibition.³⁵ Neither xenobiotic has been approved by the FDA.

PHARMACOKINETICS AND TOXICOKINETICS

Monoamine oxidase inhibitors are absorbed readily when given by mouth, and peak plasma concentrations are reached within 2 to 3 hours. Like other antidepressants, these xenobiotics are lipophilic and readily cross the blood-brain barrier. MAOIs are hepatically metabolized by both oxidation (various CYP450 isoenzymes, including CYP2D6 and CYP2C19) and acetylation (N-acetyltransferase), to metabolites that are excreted in the urine.⁸

Like the original MAOI, iproniazid, phenelzine and isocarboxazid are metabolized to hydrazides. The rate of metabolism of the hydrazide MAOIs is dependent on the N-acetyltransferase phenotype (ie, “acetylator status”) of the patient (ie, fast or slow). About one-half of the US population, but as low as 10% of Native Americans, have a recessive single gene trait that effects the N-acetyltransferase enzyme in the liver and contributes to exaggerated clinical effects despite standard therapeutic dosing or even mild overdose.

The clinical effects of MAOI inhibition occur rapidly and are usually maximal within a few days. First-generation (ie, irreversible) MAOIs have durations of effect that far surpass their pharmacologic half-lives, and recovery from their effects requires the synthesis of new enzyme over a period of up to 3 weeks (the “washout period” is a misnomer as the effective period is dependent on enzyme regeneration).¹¹⁷ Thus, when switching from one serotonergic (ie, MAOI, SSRI, cyclic antidepressant) to another, a sufficient time period of 2 to 3 weeks must be allowed to prevent an adverse drug interaction. Due to the long half-life of fluoxetine and its active metabolite, norfluoxetine, a time period of 5 weeks is recommended when switching from fluoxetine to an MAOI.

PATHOPHYSIOLOGY

As discussed above (see Mechanism of Action), MAOIs contribute to adrenergic stimulation via release of norepinephrine from sympathetic nerve terminals.⁶⁴ This phenomenon may lead to hyperadrenergic crises particularly in the presence of foods or xenobiotics that serve as substrates for, or enhancers of, monoamine formation, such as tyramine.⁶³ In addition, norepinephrine release combined with MAO inhibition may result in so-called “autopotential,” or synergistic sympathomimetic effects. Autopotential may be responsible for paradoxical or hypertensive reactions sometimes observed following therapeutic doses of MAOIs.^{5,23}

Hydrazide MAOIs (eg, phenelzine) inactivate pyridoxal 5' phosphate, the cofactor necessary for neuronal decarboxylation of glutamic acid to the inhibitory neurotransmitter GABA. In addition, hydrazides may complex with pyridoxine, the precursor of pyridoxal 5' phosphate, thus enhancing its urinary elimination and further inhibiting the formation of neuronal GABA.⁸⁴ Decreased availability of neuronal GABA leads to CNS excitation following overdose of hydrazide MAOIs (Chaps. 58 and 120).⁶¹

Impaired GABA_A activity may contribute to symptoms of CNS excitation such as seizures, which occur in MAOI overdose. In animal models, isocarboxazid and tranylcypromine directly inhibit GABA-mediated Cl⁻ influx at GABA_A receptors.¹¹³ The exact binding site of MAOIs on the GABA_A receptor complex is unknown. GABA effects appear to be most localized in the caudate-putamen and nucleus accumbens areas in one animal model.⁸⁴ Elevated neuronal glutamate concentrations due to MAOI effects may also synergistically enhance CNS excitation.¹⁰⁶

CLINICAL USES

Many authors recommend the prescription of nonselective MAOIs only for resistant or atypical depression with prominent neurovegetative symptoms.³⁰ However, selective and reversible MAOIs are the subject of renewed clinical applicability and basic science research interest. MAO-B selective xenobiotics, such as selegiline, are widely used for the treatment of Parkinson disease. Reversible inhibitors of MAO, such as moclobemide, are used in Europe for depression, phobias, anxiety, and other select indications.¹²⁹ Current applicability of a new generation of experimental MAOIs is being investigated as neuroprotective xenobiotics for a variety of neurodegenerative diseases.¹³⁰

HYPERADRENERGIC CRISIS

Hyperadrenergic crises may occur in patients with MAO-A inhibition when tyramine-containing foods such as aged cheeses and fermented drinks are eaten (Table 73–2).¹³⁰ Tyramine is an indirect-acting sympathomimetic amine with an amphetaminelike mechanism of action.¹³² The MAO-A present in the intestinal wall and liver extensively metabolizes dietary amines preventing them from entering the circulation, but in the presence of irreversible MAO-A inhibition this protective mechanism is lost, allowing tyramine and other dietary monoamines to enter the circulation.¹² This enzymatic failure results in an amphetaminelike induction of norepinephrine from peripheral adrenergic neurons and provocation of hyperadrenergic crisis. A meal that contains 6 to 8 mg of tyramine per serving can potentially precipitate this reaction, and ingestion of a total of 25 to 50 mg can produce a severe and possibly life-threatening reaction.^{28,118,124} A recent European study of biogenic amines contained in retail meat products (eg, sausage, cold cuts) found that such products contained up to 50 mg/kg tyramine which would pose a high risk for individuals receiving first-generation MAOI therapy.⁸² Additionally, despite compliance with diet, chronically elevated cytoplasmic and synaptic concentrations of norepinephrine due to therapeutic MAOI administration can lead to adrenergic crises in some patients. Dietary restrictions and recommendations for patients prescribed first-generation MAOIs are summarized in Table 73–2.^{28,118,124} As detailed above, a time period of 3 weeks is sufficient to allow a normal diet to be resumed.¹¹⁹

TABLE 73–2. Dietary Restrictions for Patients Taking MAOIs

<i>Low Tyramine Content</i> (0–4 mg/serving)	<i>Moderate Tyramine Content</i> (4–8 mg/serving)	<i>High Tyramine Content</i> (> 8 mg/serving)
Chocolate	Avocado/guacamole	Aged, mature cheeses
Cottage cheese, cream cheese, yogurt, sour cream	Banana peels or stewed whole bananas	Broad beans or fava beans
Distilled alcohol	Meat extracts	Fermented sausage
Nonoverripe fruit	Overripe fruit/figs	Liver
Soy sauce	Pasteurized light and pale beers	Red wines, selected beers
		Smoked, pickled, aged, putrefying meats or fish, caviar
		Yeast and meat extracts

Recommendation: Foods with *high* tyramine content should be avoided, those with *moderate* content should be consumed in restricted moderation, and those with *low* content may be cautiously consumed.

The clinical syndrome of tyramine-related hyperadrenergic crisis is characterized by hypertension, headache, flushing, diaphoresis, mydriasis, neuromuscular excitation, and potential cardiac dysrhythmias.¹²¹ This reaction is subjectively reported in up to 10% of patients taking MAOIs chronically,⁹² and can occur up to 3 weeks following discontinuation of the drug.¹²⁷ Monoamine oxidase inhibitors specific for the MAO-B isoform are less likely to predispose to food or drug interactions by maintaining significant hepatic MAO-A activity; however, isoform specificity is lost as dose is increased.

SEROTONIN TOXICITY

Any xenobiotic with serotonin-potentiating activity can interact with the MAOIs to produce serotonin toxicity. Combinations of xenobiotics commonly implicated in this reaction are involved with serotonin synthesis (eg, L-tryptophan), release (eg, amphetamines), agonism (eg, triptans metabolized by MAO), neuromodulation (eg, lithium), or reuptake inhibition (eg, selective serotonin reuptake inhibitors, meperidine, dextromethorphan). Animal studies have demonstrated that both meperidine¹⁰⁸ and dextromethorphan¹⁰⁹ administration can lead to fatal serotonin toxicity. Serotonin toxicity most commonly occurs in patients receiving combination therapy with two or more serotonergic agents; however, it may rarely occur with just one serotonergic agent.⁸³

Clinically, serotonin toxicity runs a spectrum of severity,¹³ and is described in detail in [Chap. 75](#). Minor findings can include akathisia, myoclonus, hyperreflexia, diaphoresis, penile erection, shivering, hyperactive bowel sounds, and tremor. Tremor and hyperreflexia are typically greater in the lower extremities. Shivering is classically described as similar to “wet dog shakes,”⁴³ and can occur at a range of body temperatures.⁸⁰ Severe signs and symptoms can include life-threatening autonomic instability, muscular rigidity, and hyperthermia.

Several diagnostic schemes for serotonin toxicity exist.^{13,24,47,93,114} However, the key diagnostic criterion is exposure to a serotonergic. Because no diagnostic test is yet available, the diagnosis of serotonin toxicity must be established on clinical grounds. The onset of clinical symptoms may occur within minutes after a change in medication or self-poisoning.⁶⁹ Most patients with serotonin toxicity develop symptoms within 6 hours. Key clinical features of MAOI-induced serotonin toxicity are summarized in [Table 73–3](#).

TABLE 73–3. Comparison of Clinical Manifestations Due to MAOI Toxicity

<i>Clinical Category</i>	<i>Hyperadrenergic Crisis</i>	<i>Serotonin Toxicity</i>	<i>MAOI Overdose</i>
Onset	Minutes to hours	Minutes to hours	≤ 24 hours
Duration	Hours	Hours	Days
Temperature	Normal	Elevated	Elevated
Neurologic	Headache, hemorrhagic stroke Neuromuscular excitation	Akathisia, hyperreflexia, shivering, tremor, seizures, autonomic instability, coma Myoclonus, "wet dog shakes," muscular rigidity	Neuropsychiatric effects, neuromuscular effects, headache, seizures Myoclonus, muscular rigidity
Cardiovascular	Hypertension, dysrhythmias, myocardial injury	Hypertension, hypotension, tachycardia, palpitations, dysrhythmias	Hypertension (early), hypotension (late), tachycardia, palpitations, dysrhythmias, myocardial injury
Gastrointestinal	Nausea	Hyperactive bowel sounds	Nausea, vomiting, diarrhea
Dermatologic	Flushing, diaphoresis	Diaphoresis	Flushing, piloerection, diaphoresis
Ophthalmologic	Mydriasis	Mydriasis	Mydriasis, ocular clonus

MAOI = monoamine oxidase inhibitor.

OVERDOSE

Monoamine oxidase inhibitor overdose may result in severe and life-threatening clinical manifestations, especially if the MAOI is a first-generation drug such as phenelzine. Classically, the clinical course involves a biphasic response characterized by initial CNS excitation and peripheral sympathetic stimulation that terminates in coma and cardiovascular collapse.⁶⁶ This biphasic model is hypothesized to result from an initial adrenergic crisis followed by inhibition of norepinephrine release,¹³² and is supported by animal studies.^{37,41} Additionally, depletion of norepinephrine stores may be partially or fully responsible for late hypotension observed in MAOI overdose. Toxic dose-response relationships in man are unclear, but overdose of 5 mg/kg of a first-generation MAOI is potentially life threatening.^{11,66} Clinical manifestations of MAOI overdose are summarized in [Table 73–3](#).

Patients with MAOI overdose are initially asymptomatic for several hours. Delays in clinical toxicity are well described.^{70,72,96} Unstudied hypotheses that might explain this phenomenon include all of the following: initial reversible binding to MAO, cumulative effects, time-dependent alterations to MAO substrate stores, individual acetylator status, and hydrolysis of the hydrazide MAOIs. While clinical toxicity should generally be apparent within the first several hours (initially with neuromuscular and sympathetic effects),⁶⁶ maximal toxicity may be delayed up to 24 hours after overdose.^{66,72,96}

Neurologic effects can be considered neuropsychiatric, neuromuscular, mental status alteration, seizures, and chronic effects. Neuropsychiatric effects include agitation, akathisia, and hallucinations. Neuromuscular effects include flailing and tremor of the extremities, nystagmus, opsoclonus, fasciculation, myoclonus, hypertonia, hyperreflexia, muscular irritability, and muscular rigidity, the latter of which may lead to secondary effects such as hyperthermia and rhabdomyolysis. Effects on mental status alteration include a variable spectrum from confusion to coma, the latter of which is a typically end-stage finding. Seizures may be either partial or generalized, and decorticate or decerebrate rigidity may alternate with periods of flaccid paralysis.

Severe hyperthermia (> 106°F) due to MAOI toxicity may have a multifactorial etiology and is an ominous sign.¹⁰⁷ Temperature dysregulation may be due to adrenergic crisis, muscular hypertonia, or CNS effects. Secondary effects from severe hyperthermia include disseminated intravascular coagulation and metabolic acidosis.⁷²

Cardiovascular effects follow the previously described initial hyperadrenergic crisis followed by cardiovascular collapse. Thus, initially, hypertension, tachycardia, palpitations, and tachydysrhythmias are to be expected.⁵⁵ In severe poisoning, late toxicity can include development of hypotension, reflex tachycardia or bradycardia, bradydysrhythmias, and sudden death.^{70,97} Alterations in myocardial supply/demand dynamics may lead to myocardial injury with elevations of serum cardiac biomarkers (eg, troponin I). Myonecrosis⁸⁸ and myocarditis¹²⁵ are also attributed to MAOI overdose.

Abnormalities on electrocardiography (ECG) may include ischemic changes on ECG (contiguous lead findings of T-wave inversion or ST-segment depression/elevation). Peaked T waves, in the presence⁶⁶ or absence⁹¹ of hyperkalemia, are also noted. Myocardial manifestations associated with catastrophic CNS processes (eg, intracranial hemorrhage) can also lead to T-wave inversions.

In addition to the effects mentioned above and listed in [Table 73–3](#), reported complications of MAOI overdose include acute kidney failure,^{66,70,88,97} fetal demise,⁹⁷ and hemolysis.^{66,72}

Selegiline Overdose

Selegiline is metabolized to L-methamphetamine, which may result in hypertension and tachycardia, even at therapeutic doses.^{1,7,101} Postmarketing surveillance safety data on the selegiline transdermal system demonstrated that only 13 (< 1%) out of 1516 patients studied reported a hypertensive event, none of which were objectively confirmed.⁸¹ Selegiline overdose produces hallucinations and convulsions and is associated with elevated urinary concentrations of L-methamphetamine and L-amphetamine.^{32,57}

Moclobemide Overdose

Moclobemide overdose typically produces mild to moderate CNS depression (drowsiness, disorientation), GI effects (nausea), and cardiovascular effects (tachycardia and mild hypertension).^{33,76} Serotonin toxicity due to the ingestion of moclobemide, alone⁵⁰ and in combination with other serotonergics^{78,87,123,128} is well described. In massive overdose, fatalities attributed solely to the toxic effects of moclobemide are reported.^{17,34,40}

OTHER ADVERSE DRUG REACTIONS

Clinically significant drug interactions with MAOIs can be due to serotonergic effects (see Serotonin Toxicity) and alterations to drug metabolism. Chronic use of phenelzine is also associated with an isoniazidlike peripheral neuropathy,⁴² possibly explained by pyridoxine deficiency.¹¹⁵ Administration of opioids with serotonergic properties (eg, meperidine, dextromethorphan) is absolutely contraindicated due to risk of precipitating the serotonin toxicity.^{13,39,100,108,109} Adverse drug reactions with other coadministered drugs that are metabolized by cytochrome P450 may be problematic, as first-generation MAOIs have an extensive inhibitory effect on CYP2C9, CYP2C19, and CYP2D6.^{8,103} Thus, barbiturates (eg, phenobarbital) and benzodiazepines (eg, diazepam, lorazepam) that are metabolized by hepatic cytochrome P450 may produce prolonged sedation and respiratory depression. [Table 73–4](#) summarizes analgesic safety in combination with MAOI drugs.³⁹

TABLE 73–4. Analgesic Safety When Combined with MAOIs

<i>Analgesic Class</i>	<i>Safe</i>	<i>Monitor Closely and Consider Alternative</i>	<i>Avoid Combination (Contraindicated)</i>
Nonprescription	Acetaminophen Aspirin Nonsteroidal antiinflammatory drugs		Dextromethorphan
Opioids	Buprenorphine Codeine Morphine Oxycodone	Propoxyphene	Meperidine Pentazocine
Nonopioids	Inhalational anesthetics Nitroglycerin	Barbiturates ^a Benzodiazepines ^a	Tramadol
Local anesthetics	Lidocaine		Cocaine

^aDrugs metabolized by hepatic cytochrome P450 may produce prolonged sedation and respiratory depression when combined with MAOIs. MAOI = monoamine oxidase inhibitor.

WITHDRAWAL REACTIONS

Monoamine oxidase inhibitor withdrawal may be severe, beginning 24 to 72 hours after discontinuation. Classically, MAOI withdrawal symptoms are the worst following discontinuation of high therapeutic doses of tranylcypromine and isocarboxazid.⁹ Symptoms range from nausea, vomiting, and malaise, to CNS symptoms such as agitation, psychosis, and convulsions. Treatment is generally supportive and typically involves a benzodiazepine such as diazepam and restarting the medication if clinically indicated.

DIAGNOSTIC TESTING

The clinical utility of therapeutic drug monitoring in the routine use of MAOIs is limited. Evaluation of MAO activity is not routinely available, requires a fresh specimen (preferably jejunal biopsy),⁶⁵ and is therefore not recommended. Experimental evidence suggests that inhibition of human platelet MAO-B activity by at least 85% may be associated with a favorable clinical antidepressant response to phenelzine.^{31,36}

Evaluation of MAOI toxicity remains a clinical diagnosis. Serum concentrations of MAOIs that correlate meaningfully with clinical effects are not well established. In addition, serum concentrations of any antidepressant, in general, can be misleading when obtained postmortem for forensic purposes.^{90,99} Hyperglycemia and leukocytosis may be present. Elevations in serum lactate concentrations and metabolic acidosis may be present from seizures, muscular hypertonia, or hyperthermia.

Measurement of blood and urinary concentrations of MAO substrates may provide indirect evidence of MAOI effects. MAOIs may cause increase serum serotonin, increase or decrease serum norepinephrine, increase urinary epinephrine and norepinephrine, and decrease urinary serotonin metabolites. Due to the indirect nature of this testing and the fact that its interpretation is fraught with confounding factors (eg, if the patient is receiving vasopressors), the routine measurement of serum and urinary MAO substrates is not recommended in the assessment of MAOI toxicity. Of note, patients taking selegiline¹⁰⁵ and tranylcypromine¹³³ may test positive for amphetamines on drug screens due to their metabolites.

MANAGEMENT

Out of Hospital

Decisions regarding referral to the emergency department (ED) must take into account factors such as patient age, intent of exposure, symptoms, as well as timing of exposure. All patients with MAOI exposures who display suicidal intent should be referred to an ED for evaluation. Children with exposure to even one adult formulation MAOI tablet or selegiline patch should be referred to the ED due to the potential for late-onset significant toxicity.³ Patients who exhibit more than mild headache or minimal diaphoresis following an acute MAOI ingestion should be referred to an ED. Observation at home is warranted in patients who are asymptomatic and more than 24 hours have elapsed since the time of ingestion. Due to

paucity of data at this time, patients with selegiline patch ingestion should be referred to the ED for observation, even if suicidal intent is absent.

Prehospital

Induction of emesis is not recommended.³ Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of MAOI if no contraindications are present.² Transportation to the hospital should not be delayed in order to administer activated charcoal. Use of intravenous benzodiazepines for seizures and external cooling measures for severe hyperthermia ($> 106^{\circ}\text{F}$ [$> 41.1^{\circ}\text{C}$])¹⁰⁷ should be performed in consultation or authorization with medical direction from emergency medical services, by a written treatment protocol or policy, or with direct medical oversight.

Initial Approach in the Emergency Department

As with any serious ingestion, initial stabilization must include rapid assessment of the airway, breathing, and circulation as well as establishment of intravenous access, supplemental oxygen, and cardiac monitoring. Evidence of hyperthermia or hemodynamic instability following MAOI ingestion may be a manifestation of significant toxicity. Intravenous volume repletion should begin while gastrointestinal decontamination is considered. In any patient with altered mental status who will likely deteriorate progressively, early orotracheal intubation may facilitate safe gastric decontamination measures. Subsequent management should focus on stabilization of hyperthermia, seizures, and muscular rigidity.

Gastrointestinal Decontamination

Patients who overdose with MAOIs are more likely to benefit from gastrointestinal decontamination than most other overdose patients because of their high potential for morbidity and mortality.^{59,89} Orogastic lavage with a large bore orogastric tube (36–40 French) should be considered if a life-threatening ingestion is suspected to have occurred within several hours prior to presentation.^{39,59,89} Single-dose activated charcoal should be orally administered for ingestions presenting within several hours, unless contraindications are present. Whole bowel irrigation with oral polyethylene glycol electrolyte solution likely has limited utility unless there are coingestions with other sustained-release preparation medications. The lack of early clinical findings of poisoning should not dissuade the use of gastrointestinal decontamination given the potential for delayed clinical deterioration.

Cooling Measures

Severe hyperthermia must be treated with aggressive cooling. Use of ice baths (first choice for life-threatening hyperthermia),¹¹⁰ cold water, and fans are the mainstay of treatment (Chap. 30). There is no available evidence to support use of invasive cooling devices (ie, catheter based) or noninvasive devices such as cooling blankets. Indications for ice bath immersion to treat MAOI toxicity include rectal temperature greater than 106°F (41.1°C),¹⁰⁷ rigidity, and altered mental status. Benzodiazepines help control muscular rigidity, seizures, and agitation that may contribute to amelioration of hyperthermia and tachycardia. Patients with refractory hyperthermia despite the above measures may require neuromuscular blockade, using nondepolarizing paralytics, in conjunction with tracheal intubation and ventilation. The depolarizing paralytic succinylcholine should be avoided in severe MAOI toxicity due to the risk of precipitating lethal dysrhythmia due to hyperkalemia in the setting of rhabdomyolysis. Neuromuscular blockade eliminates hyperthermia that results from muscular rigidity, and can be employed if first-line treatments are unsuccessful. Antipyretics such as acetaminophen are unlikely to be efficacious because the hyperthermia is not due to alterations in the hypothalamic temperature set point.¹⁰⁷

Blood Pressure Control

Because there is characteristic fluctuation in vital signs associated with MAOI overdose, hemodynamic monitoring should be instituted even for patients who initially are stable. When supporting the patient's blood pressure, preference should be given to titratable drugs with a rapid onset and termination of action because of the potential for rapid hemodynamic changes. Use of β -adrenergic antagonists is contraindicated for control of hypertension in MAOI-related toxicity because the action of monoamines (eg, norepinephrine) at the neuronal synapse in the autonomic nervous system could result in refractory hypertension due to unopposed α -adrenergic agonism.⁹⁵

Patients who are normotensive at baseline and who experience MAOI-related severe hypertension can be treated with a short-acting α -adrenergic antagonist such as phentolamine (intravenous 2–5 mg) for effective control.¹² Other therapies such as nitroprusside and nitroglycerin may be preferred because they allow for titratable blood pressure control.²¹ Tyramine-related hypertensive crises can successfully be controlled with the dihydropyridine calcium channel blockers such as nifedipine and possibly the oral α -adrenergic antagonists such as terazosin but should be used with caution.^{20,48} Particular caution must be exercised in patients with baseline hypertension because overly aggressive blood pressure lowering may reduce cerebral perfusion pressure sufficiently to cause cerebral ischemia.

Patients who are hypotensive may require aggressive support with intravenous fluid resuscitation and vasopressors. Direct-acting sympathetic agents (eg, epinephrine, norepinephrine) can be used safely in patients taking MAOIs.¹⁴ Rather than causing release of a stored pool of norepinephrine, these xenobiotics bind directly with postsynaptic α - and β -adrenergic receptors.

Dopamine is contraindicated in hypotensive patients who have overdosed on MAOIs for several reasons. The indirect action of dopamine administration may produce a synergistic effect with MAOI, resulting in excessive adrenergic activity and exaggerated rises in blood pressure. In addition, most of the α -adrenoceptor mediated vasoconstriction of dopamine is secondary to norepinephrine release; in the presence of MAOIs, norepinephrine synthesis may be impaired from concomitant dopamine- β -hydroxylase inhibition, and dopamine may not reliably raise blood pressure if cytoplasmic and vesicular neuronal stores have been depleted. Finally, in the presence of impaired norepinephrine release or α -adrenergic blockade by any cause, unopposed dopamine-induced vasodilation from action on peripheral dopamine and β adrenoceptors may paradoxically lower blood pressure further.

Dysrhythmias

Due to the unique pharmacologic and toxicokinetic considerations of MAOI toxicity, adherence to advance cardiac life support protocols may not provide optimal results.⁴ In any stable patient, removal of the offending xenobiotic as well as correction of hypoxia, hypokalemia, and hypomagnesemia, if present, is a rational initial step.

Patients with immediately life-threatening dysrhythmias require rapid cardioversion. In the presence of the nonperfusing dysrhythmias such as ventricular fibrillation, pulseless ventricular tachycardia, and torsade de pointes unsynchronized electrical defibrillation is the treatment of choice.

Stable patients with ventricular tachycardia may benefit from a trial of antidysrhythmic drugs such as amiodarone or lidocaine. High-quality studies evaluating the use of these xenobiotics in the setting of MAOI overdose are not available.

Hemodynamically significant supraventricular tachycardia from MAOI toxicity should be corrected to prevent myocardial ischemia or infarction, ventricular dysrhythmia, and high-output heart failure. Benzodiazepines are safe and effective to treat sinus tachycardia, as long as respiratory status remains monitored. Adenosine and synchronized cardioversion are unlikely to be useful in the setting of ongoing presence of the MAOI, but may be considered in rare cases that are unresponsive to benzodiazepines. In patients with borderline hypotension, nondihydropyridine calcium-channel antagonists such as diltiazem and verapamil are relatively contraindicated because they may further lower blood pressure.

Hemodynamically significant bradycardia from MAOI toxicity may be refractory to standard advance cardiac life support protocols. An initial approach with intravenous fluid and atropine is a rational first-line therapy to temporize the patient with bradycardia and hypotension. Epinephrine and isoproterenol may also be administered while a pacemaker (transcutaneous or transvenous) is considered.

Management of CNS Manifestations

In acute altered mental status, hypoglycemia should be rapidly excluded.^{15,102} Mild to moderate CNS excitation may be treated with small incremental doses of parenteral diazepam. Seizures should be treated with benzodiazepines such as lorazepam in standard incremental doses. Empiric administration of pyridoxine (vitamin B₆), intravenously at 70 mg/kg, up to 5 g in adults should be considered in patients with status epilepticus, particularly following massive ingestions of hydrazide-derived MAOIs such as phenelzine which may deplete endogenous pyridoxine stores (Antidotes in Depth: A14).¹¹⁵ Theoretically, phenytoin is not likely to be useful for treatment of MAOI-induced seizures because there is no distinct seizure focus, but rather generalized neuronal dysfunction in the presence of MAOI (and metabolites) in the CNS.

Cyproheptadine

Cyproheptadine is a nonselective serotonin antagonist that is recommended as third-line therapy (after benzodiazepine administration and cooling measures) for MAOI-induced serotonin toxicity.¹³ Cyproheptadine prevents lethality in animal models of serotonin toxicity⁷⁹ and reportedly is beneficial in humans although its efficacy has not been rigorously established.^{38,44} It should be strongly considered when the diagnosis of serotonin toxicity is likely, especially if incomplete response has been achieved with aggressive cooling and benzodiazepine therapy.⁶² In addition, its use to treat neuromuscular rigidity and hyperthermia associated with MAOI overdose has been reported.^{10,25}

The recommended initial dose in adults is 12 mg orally, to be followed by 2 mg every 2 hours while symptoms continue.¹³ A dose of 12 to 32 mg will bind 85% to 95% of serotonin receptors.⁵⁴ The dose of cyproheptadine used to treat the serotonin toxicity may cause sedation, but this effect is a goal of therapy and should not deter clinicians from using the drug. Relative contraindications to its use include acute asthma exacerbation, GI obstruction, and age less than 2 years (due to lack of safety information for this age group).

Dantrolene

Use of dantrolene in patients with serotonin toxicity is not recommended (Antidotes in Depth: A21). Case reports citing its utility with off-label usage probably involved misdiagnosis.^{13,53} Malignant hyperthermia, for which dantrolene is actually indicated, is a disease that is completely unrelated to serotonin toxicity. In animal models of serotonin toxicity, dantrolene administration has no effect on survival.^{51,79} In addition, dantrolene has been implicated in the fatality of one case of serotonin toxicity.⁵⁶

Extracorporeal Elimination

The utility of extracorporeal measures, such as hemodialysis, to treat MAOI toxicity remains to be demonstrated. The ability to dialyze a xenobiotic depends largely on its protein binding the volume of distribution. Unfortunately, data regarding protein binding and volumes of distribution of the first-generation MAOI drugs such as isocarboxazid are not well characterized. Use of peritoneal dialysis⁶⁷ and hemodialysis⁷¹ to treat MAOI overdose has been reported in the literature. However, time to resolution of symptoms for all cases did not differ (~ 24 hours) from those in which hemodialysis was not employed. Therefore, extracorporeal elimination is not recommended in the management of MAOI overdose unless other indications are present such as severe acidemia or life-threatening hyperkalemia, or the need to eliminate dialyzable toxic coingestions.

Disposition

Recommendations for the ideal time frame for observation of patients with suspected MAOI overdose are limited by a paucity of relevant studies in the clinical toxicology literature. Patients with presumed MAOI (selective or nonselective) overdose should be observed with telemetry monitoring, preferably in an intensive care unit, for at least 24 hours regardless of the initial clinical findings. This recommendation takes into account the potential for delayed-onset of clinical toxicity as well as the potential for severe morbidity and mortality.^{70,72,96} However, patients with MAOI–food or MAOI–xenobiotic interactions may not require hospital admission if the interaction is mild, resolution of symptoms is complete, and the patient has been observed for 4 to 8 hours.

SUMMARY

- Toxicity from MAOI exposures is becoming less common due to more limited clinical usage of the traditional nonselective MAOIs; however, clinical and research use of selective MAOIs and RIMAs is increasing.
- Inhibition of MAO has effects on myriad neuronal neurotransmitters, which are responsible for the majority of the therapeutic and toxic effects of MAOIs.
- The clinical effects of MAOI overdose may be life threatening and should be managed aggressively.
- Aside from overdose, other consequential manifestations of MAOI toxicity may include hyperadrenergic crisis and the serotonin toxicity.

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74 SEDATIVE-HYPNOTICS

David C. Lee

HISTORY AND EPIDEMIOLOGY

Sedative-hypnotics are xenobiotics that limit excitability (sedation) and or induce drowsiness and sleep (hypnosis). Anxiolytics (formerly known as minor tranquilizers) are medications prescribed for their sedative-hypnotic properties. Mythology of ancient cultures is replete with stories of xenobiotics that cause sleep or unconsciousness ([Chap. 1](#)). Sedative-hypnotics overdoses were described in the medical literature soon after the commercial introduction of bromide preparations in 1853. Other commercial xenobiotics that subsequently were developed include chloral hydrate, paraldehyde, sulfonyle, and urethane.

The barbiturates were introduced in 1903 and quickly supplanted the older xenobiotics. Barbiturates dominated the sedative-hypnotic market for the first half of the twentieth century. Due to their narrow therapeutic index and substantial potential for abuse, they quickly became a major health problem. By the 1950s, barbiturates were frequently implicated in overdoses and were responsible for the majority of drug-related suicides. As fatalities from barbiturates increased, attention shifted toward preventing their abuse and finding less toxic alternatives.²³ The “safer” drugs of that era included methypylon, glutethimide, ethchlorvynol, bromides, and methaqualone. Unfortunately, many of these sedative hypnotics also had significant adverse drug reactions. After the introduction of benzodiazepines in the early 1960s, barbiturates and the other alternatives were quickly replaced as commonly used sedatives in the United States.

Intentional and unintentional overdoses with sedative-hypnotics occur frequently. According to the American Association of Poison Control Centers, sedative-hypnotics is consistently one of the top five classes of xenobiotics associated with overdose fatalities ([Chap. 136](#)). With the ubiquitous worldwide use of sedative-hypnotics, they may be associated with a substantially higher number of overdoses and deaths than are officially reported.

Chlordiazepoxide, the first commercially available benzodiazepine, was initially marketed in 1960. Since then, more than 50 benzodiazepines have been marketed, and more are being developed. Compared with barbiturate overdoses, overdoses of benzodiazepines alone account for relatively few deaths.^{37,48,59} Most deaths associated with benzodiazepines result from mixed overdoses with other respiratory depressants.^{48,134}

Benzodiazepines remain the most popular prescribed anxiolytics. However, newer hypnotic pharmaceuticals zolpidem, zaleplon, zopiclone, and eszopiclone have replaced benzodiazepines as the most commonly prescribed pharmaceutical sleep aids. Melatonin and ramelteon are emerging as popular sleep aids whose effects are mediated through melatonin receptor subtypes MT₁ and MT₂ specifically.^{134,140,160} Dexmedetomidine, a central α_2 -adrenergic agonist, is now increasingly used in the hospital setting for short-term sedation.^{30,37,40,121,129,139,160,170,173,176,177,210}

This chapter focuses primarily on pharmaceuticals prescribed for their sedative-hypnotic effects, many of which interact with the γ -aminobutyric acid-A (GABA_A) receptor ([Table 74–1](#)). Specific sedative-hypnotics such as ethanol and γ -hydroxybutyric acid are discussed in more depth in their respective chapters ([Chaps. 80 and 83](#)).

TABLE 74–1. Pharmacology of Sedative-Hypnotics

	Equipotent Dosing Oral Dose (mg) ^a	<i>t</i> _{1/2} (minutes)	Protein Binding (%)	Vd (L/kg)	Active Metabolite Important
Benzodiazepines					
<i>Full agonist activity at the benzodiazepine site</i>					
Alprazolam (Xanax)	1.0	10–14	80	0.8	No
Chlordiazepoxide (Librium)	50	5–15	96	0.3	Yes
Clozapate (Transene)	15	97	0.9	Yes	
Clonazepam (Klonopin)	0.5	18–50	85.4	Unclear	Yes
Diazepam (Valium)	10	20–70	98.7	1.1	Yes
Estazolam (ProSom)	2.0	8–31	93	0.5	No
Flunitrazepam ^b (Rohypnol)	1.0	16–35	80	1.0–1.4	Yes
Flurazepam (Dalmane)	30	2.3	97.2	3.4	Yes
Lorazepam (Ativan)	2.0	9–19	90	1–1.3	None
Midazolam (Versed)	—	3–8	95	0.8–2	Yes
Oxazepam (Serax)	30	5–15	Unclear	Unclear	No
Temazepam (Restoril)	30	10–16	97	0.75–1.37	No
Triazolam (Halcion)	0.25	1.5–5.5	90	0.7–1.5	Yes
<i>Nonbenzodiazepines active mainly at the type I benzodiazepine site</i>					
Eszopiclone (Lunesta)	7	6	55	1.3	No
Zaleplon (Sonata)	20	1.0	92	0.54	No
Zolpidem (Ambien)	20	1.7	92	0.5	No
Barbiturates					
Amobarbital (Amytal)	—	8–42	Unclear	Unclear	Unclear
Aprobarbital ^b (Alurate)	—	14–34	Unclear	Unclear	Unclear
Butobarbital (Butisol)	—	34–42	Unclear	Unclear	Unclear
Barbital ^b	—	6–12	25	Unclear	Unclear
Mephobarbital (Mebaral)	—	5–6	40–60	Unclear	Yes
Methohexital (Brevital)	—	3–6	73	2.2	Unclear
Pentobarbital (Nembutal)	100	15–48	45–70	0.5–1.0	Unclear
Phenobarbital (Luminal)	30	80–120	50	0.5–0.6	No
Primidone (Mysoline)	—	3.3–22.4	19	Unclear	Yes
Secobarbital (Seconal)	—	15–40	52–57	Unclear	Unclear
Thiopental (Pentothal)	—	6–46	72–86	1.4–6.7	Unclear
Other					
Chloral hydrate (Aquachloral)	NA	4.0–9.5	35–40	0.6–1.6	Yes
Dexmedetomidine (Precedex)	NA	2	94	1.5	No
Ethchlorvynol ^b (Placidyl)	NA	10–25	30–40	4	Unclear
Etomidate (Amidate)	NA	2.9–5.3	98	2.5–4.5	Unclear
Glutethimide ^b (Doriden)	NA	5–22	47–59	2.7	Unclear
Meprobamate ^b (Miltown)	NA	6–17	20	0.75	Unclear
Methaqualone ^b (Quaalude)	NA	19	80–90	5.8–6.0	Yes
Methypyrton ^b (Nodular)	NA	3–6	60	0.97	Unclear
Paraldehyde ^b (Paral)	NA	7	Unclear	0.9	Unclear
Propofol (Diprivan)	NA	4–23	98	2–10	No
Ramelteon (Rozerem)	NA	1–2.6	82	High	Yes

^aThese data are approximations of equipotent doses of sedatives affecting the benzodiazepine receptor and several barbiturates. All the full agonist benzodiazepines have similar anxiolytic, anxiolytic, sedative, and hypnotic effects. These effects are a reflection of dose and serum concentration. There can be significant variation of these effects according to age and sex. ^bNot presently available in the United States.

NA = not applicable; Vd = volume of distribution.

PHARMACODYNAMICS/TOXICODYNAMICS

All sedative-hypnotics induce central nervous system (CNS) depression. Most clinically effective sedative-hypnotics produce their physiologic effects by enhancing the function of GABA-mediated chloride channels via agonism at the GABA_A receptor. These receptors are the primary mediators of inhibitory neurotransmission in the brain (Chap. 14). The GABA_A receptor is a pentameric structure composed of varying polypeptide subunits associated with a chloride channel on the postsynaptic membrane. These subunits are classified into families (eg, α , β , γ). Variations in the five subunits of the GABA receptor confer the potency of its sedative, anxiolytic, hypnotic, amnestic, and muscle relaxing properties. The most common GABA_A receptor in the brain is composed of $\alpha_1\beta_2\gamma_2$ subunits. Almost all sedative-hypnotics bind to GABA_A receptors containing the α_1 subunit. One exception may be etomidate, which produces sedation at the β_2 unit and anesthesia at the β_3 subunit.^{32,99,114,131,189} Benzodiazepines will be effective only at GABA_A receptors with the γ_2 subunit. Even within classes of sedative-hypnotics, there will be varying affinities for differing subunits of the GABA receptor.^{42,99}

Many sedative-hypnotics also act at receptors other than the GABA_A receptor. Trichloroethanol and propofol, also inhibit glutamate-mediated N-methyl-D-aspartate (NMDA) receptors, thereby inhibiting excitatory neurotransmission.^{34,124,146} Certain benzodiazepines may inhibit adenosine metabolism and reuptake, thereby potentiating both A₁-adenosine (negative dromotropy) and A₂-adenosine (coronary vasodilation) receptor-mediated effects.^{110,157} Benzodiazepines can also interact with serotonergic pathways. For example, diazepam modulates morphine analgesia via interactions with serotonin receptors. In addition, the anxiolytic effects of clonazepam can be partially explained by upregulation of serotonergic receptors, specifically 5-HT₁ and 5-HT₂.^{9,111,199} Newer sleep aids, such as melatonin and ramelteon, do not appear to act at the GABA_A receptor. Instead, they are agonists at melatonin receptor subtypes MT₁ and MT₂ in the suprachiasmatic nucleus of the brain.^{15,140,160,168,175} Dexmedetomidine, a central α_2 -adrenergic agonist similar to clonidine, induces a state of “cooperative sedation.”¹⁷⁰

PHARMACOKINETICS/TOXICOKINETICS

Most sedative-hypnotics are rapidly absorbed via the gastrointestinal (GI) tract, with the rate-limiting step consisting of dissolution and dispersion of the xenobiotic. Barbiturates and benzodiazepines are primarily absorbed in the small intestine. Clinical effects are determined by their relative ability to penetrate the blood–brain barrier. Xenobiotics that are highly lipophilic penetrate most rapidly. The ultrashort-acting barbiturates are clinically active in the most vascular parts of the brain (gray matter first), with sleep occurring within 30 seconds of administration. Table 74–1 lists individual sedative-hypnotics and some of their pharmacokinetic properties.

After initial distribution, many of the sedative-hypnotics undergo a redistribution phase as they are dispersed to other body tissues, specifically fat. Xenobiotics that are redistributed, such as the lipophilic (ultrashort-acting) barbiturates and some of the benzodiazepines (diazepam, midazolam), may have a brief clinical effect as the early peak concentrations in the brain rapidly decline.

Many of the sedative-hypnotics are metabolized to pharmacologically active intermediates. This is particularly true for chloral hydrate and some of the benzodiazepines. Benzodiazepines can be demethylated, hydroxylated, or conjugated with glucuronide in the liver. Glucuronidation results in the production of inactive metabolites. Certain benzodiazepines, such as diazepam, are demethylated which produces active intermediates with a more prolonged half-life than the parent compound. Because of the individual pharmacokinetics of sedative-hypnotics and the production of active metabolites, there is often little correlation between the duration of effect and biologic half-lives.

Most sedative-hypnotics, such as the highly lipid-soluble barbiturates and the benzodiazepines, are highly protein bound. These drugs are poorly filtered by the kidneys. Elimination occurs principally by hepatic metabolism. Chloral hydrate and meprobamate are notable exceptions. Xenobiotics with a low log D (octanol-to-water partition coefficient), such as meprobamate and the longer-acting barbiturates, are poorly protein bound and more subject to renal excretion. Phenobarbital is a classic example of a drug whose elimination can be enhanced through urinary alkalization. Most other sedative-hypnotics are not amenable to urinary pH manipulation.

Overdoses of combinations of sedative-hypnotics enhance toxicity through synergistic effects. For example, both barbiturates and benzodiazepines act on the GABA_A receptor, but barbiturates prolong the opening of the chloride ionophore, whereas benzodiazepines increase the frequency of ionophore opening.¹⁶² Various sedative-hypnotics may increase the affinity of another xenobiotic at its respective binding site. For example, pentobarbital increases the affinity of γ -hydroxybutyric acid (GHB) for its non-GABA binding site.¹⁶⁴ Propofol potentiates the effect of pentobarbital on chloride influx at the GABA_A receptor.¹³³ Propofol also increases the affinity and decreases the rate of dissociation of benzodiazepines from their site on the GABA_A receptor.^{21,181} These actions increase the clinical effect of each xenobiotic and may lead to deeper central nervous system (CNS) and respiratory depression.

Another mechanism of synergistic toxicity occurs via alteration of metabolism. The combination of ethanol and chloral hydrate, historically known as a “Mickey Finn,” has additive CNS depressant effects. Chloral hydrate competes for alcohol and aldehyde dehydrogenases, thereby prolonging the half-life of ethanol. The metabolism of ethanol generates the reduced form of nicotinamide adenine dinucleotide, which is a cofactor for the metabolism of chloral hydrate to trichloroethanol, an active metabolite. Finally, ethanol inhibits the conjugation of trichloroethanol, which, in turn, inhibits the oxidation of ethanol (Fig. 74–1).^{1,17,19,56,87,101,125,142,153,154,161,200} The end result of these synergistic pharmacokinetic interactions is enhanced CNS depression.

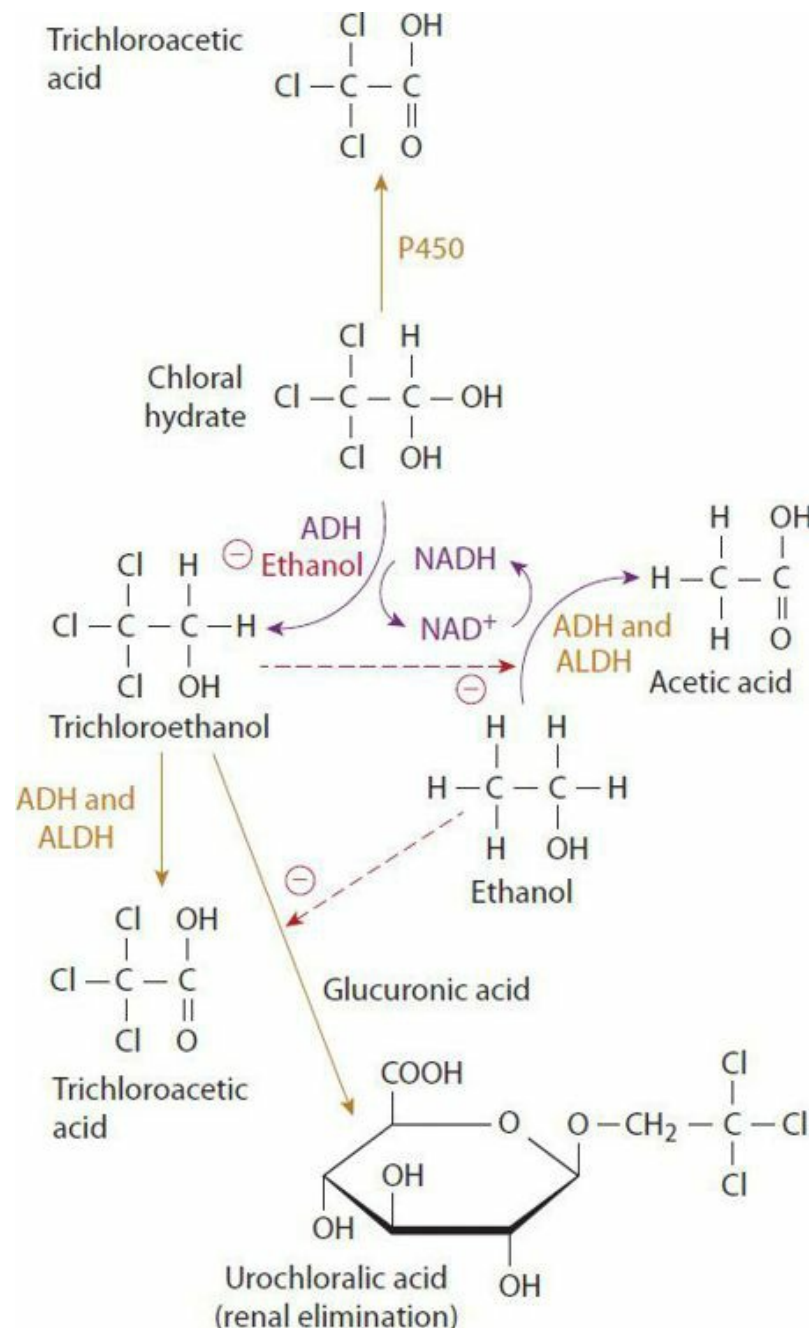


FIGURE 74–1. Metabolism of chloral hydrate and ethanol, demonstrating the interactions between chloral hydrate and ethanol metabolism. Note the inhibitory effects (dotted lines) of ethanol on trichloroethanol metabolism and the converse.

Multiple drug–drug interactions can occur that may prolong the half-life of many sedative-hypnotics and significantly increase their potency or duration of action. The half-life of midazolam, which undergoes hepatic metabolism via cytochrome CYP3A4, can change dramatically in the presence of certain drugs that compete for its metabolism, or that induce or inhibit CYP3A4.^{118,184} For example, the half-life of midazolam rises 400-fold when coadministered with itraconazole.^{8,163} Various receptor and metabolic enzyme alterations resulting in upregulation or downregulation may occur in the setting of acute or chronic exposure to certain sedative-hypnotics.

TOLERANCE/WITHDRAWAL

Ingestions of relatively large doses of sedative-hypnotics may not have predictable effects in patients who chronically use them. This is due to tolerance, defined as the progressive diminution of effect of a particular drug with repeated

administrations that results in a need for greater doses to achieve the same effect. Tolerance occurs when adaptive neural and receptor changes (plasticity) occur after repeated exposures. These changes include a decrease in the number of receptors (downregulation), reduction of firing of receptors (receptor desensitization), structural changes in receptors (receptor shift), or reduction of coupling of sedative-hypnotics and their respective GABA_A related receptor site (Chap. 15). Tolerance can also be secondary to pharmacokinetic factors, such as enhanced elimination after repetitive doses. However, in most cases, tolerance to sedative-hypnotics is caused by pharmacodynamic changes such as receptor downregulation.¹⁶³

Cross-tolerance readily exists among the sedative-hypnotics. For example, chronic use of benzodiazepines not only decreases the activity of the benzodiazepine site on the GABA receptor but also decreases the binding affinity of the barbiturate sites.^{4,69} Many sedative-hypnotics are also associated with drug dependence after chronic exposure. Some of these, classically the barbiturates, benzodiazepines, and ethanol, are associated with life-threatening withdrawal syndromes.

CLINICAL MANIFESTATIONS

Patients with sedative-hypnotic overdoses may exhibit slurred speech, ataxia, and incoordination. Larger doses result in stupor or coma. In most instances, respiratory depression parallels CNS depression. However, not all sedative-hypnotics cause significant hypoventilation. Oral overdoses of benzodiazepines alone may lead to sedation and hypnosis, but rarely life-threatening hypoventilation. Typically, the patient may appear comatose but have relatively normal vital signs. In contrast, large intravenous doses of benzodiazepines may lead to potentially life-threatening respiratory depression. Single overdoses of zolpidem and its congeners do not typically cause life-threatening respiratory depression in adults.^{22,52,60,195}

Although the physical examination is rarely specific for a particular sedative-hypnotic, it can sometimes offer clues of exposure based on certain physical and clinical findings (Table 74–2). Hypothermia is described with most of the sedative-hypnotics but may be more pronounced with barbiturates.^{71,142} Barbiturates may cause fixed drug eruptions that often are bullous and appear over pressure-point areas. Although classically referred to as “barbiturate blisters,” this phenomenon is not specific to barbiturates as other CNS depressants including carbon monoxide, methadone, imipramine, glutethimide, and benzodiazepines can all cause bullous eruptions over pressure points. Methaqualone can cause muscular rigidity and clonus.^{2,20,26,70,143} Glutethimide can result in anticholinergic signs and symptoms.^{3,10,28} Chloral hydrate use may result in vomiting, gastritis, and cardiac dysrhythmias.^{17,19,24,56,76,87,88,116,179,188,200,212} Meprobamate overdoses may present with significant hypotension due to myocardial depression.^{27,38,67,73,81,155,216}

TABLE 74–2. Clinical Findings of Sedative-Hypnotic Overdose

<i>Clinical Signs</i>	<i>Sedative-Hypnotics</i>
Hypothermia	Barbiturates, bromides, ethchlorvynol
Unique odors	Chloral hydrate (<i>pear</i>), ethchlorvynol (<i>new vinyl shower curtain</i>)
Cardiotoxicity	
Myocardial depression	Meprobamate
Dysrhythmias	Chloral hydrate
Muscular twitching	γ-hydroxybutyric acid, methaqualone, propofol, etomidate
Acneiform rash	Bromides
Fluctuating coma	Glutethimide, meprobamate
Gastrointestinal hemorrhage	Chloral hydrate, methaqualone
Discolored urine	Propofol (green/pink)
Anticholinergic	Glutethimide

Large or prolonged intravenous doses of sedative-hypnotics may also be associated with toxicities due to their diluents. Propylene glycol is a classic example of a diluent that may accumulate with prolonged infusions of certain medications such as lorazepam. Rapid infusions of propylene glycol may induce hypotension. Accumulated amounts of propylene glycol may lead to metabolic acidosis and a hyperosmolar state with elevated serum lactate

concentrations.^{7,123,132,152,183,185,204,207,213} In one study, two-thirds of critical care patients given high doses of lorazepam (0.16 mg/kg/h) for more than 48 hours had significant accumulations of propylene glycol as manifested by hyperosmolality and an anion gap metabolic acidosis⁷ (Chap. 55).

DIAGNOSTIC TESTING

When overdose is a primary concern in the undifferentiated comatose patient without a clear history, laboratory testing may be useful to exclude metabolic abnormalities. This may include electrolytes, liver enzymes, thyroid function tests, blood urea nitrogen, creatinine, glucose, venous or arterial blood gas analysis, and cerebrospinal fluid analysis. With any suspected intentional overdose, a serum acetaminophen concentration should be obtained. Diagnostic imaging studies, such as computed tomography scans of the head, may be warranted on a case by case basis.

Routine laboratory screening for “drugs of abuse” generally is not helpful in the management of undifferentiated comatose adult patients. However, screening may be useful for epidemiologic purposes in a particular community. These tests vary in type, sensitivity, and specificity. Furthermore, many sedative-hypnotics are not included on standard screening tests for drugs of abuse. For example, a typical benzodiazepine urine screen identifies metabolites of 1,4-benzodiazepines, such as oxazepam or desmethyldiazepam. Many benzodiazepines that are metabolized to alternative compounds remain undetected and thus may exhibit a false-negative result on the benzodiazepine-screening assay. Benzodiazepines that are 7-amino analogs, such as clonazepam and flunitrazepam, may not be detected because they do not have a metabolite with a 1,4-benzodiazepine structure. Alprazolam and triazolam are not detected because they undergo minimal metabolism.⁴⁵

Specific concentrations of xenobiotics such as ethanol or phenobarbital may be helpful to confirm or disprove exposure. However, specific concentrations of most other sedative-hypnotics are not routinely performed in hospital laboratories. Abdominal radiographs may detect chloral hydrate in the gastrointestinal tract because of its potential radiopacity (Chap. 5). Although immediate identification of a particular sedative-hypnotic may be helpful in predicting the length of toxicity, it rarely affects the acute management of the patient. One exception is phenobarbital, for which urinary alkalization and multiple-dose activated charcoal (MDAC) may enhance elimination.^{50,92,128,141}

MANAGEMENT

Death secondary to sedative-hypnotic overdose usually results from cardiorespiratory collapse. Careful attention should focus on monitoring and maintaining adequate airway, oxygenation, and hemodynamic support. Supplemental oxygen, respiratory support, and prevention of aspiration are the cornerstones of treatment. Hemodynamic instability should be treated initially with volume expansion. With proper supportive care and adequate airway and or respiratory support as needed, patients with sedative-hypnotic overdoses should eventually recover. Patients with meprobamate and chloral hydrate overdoses may present with both respiratory depression and cardiac toxicity. Meprobamate toxicity may be associated with myocardial depression and significant hypotension, often resistant to standard intravenous fluid resuscitation.²⁷ The cardiotoxic effects of chloral hydrate include lethal ventricular dysrhythmias, resulting from its active halogenated metabolite trichloroethanol. In the setting of cardiac dysrhythmias from chloral hydrate, judicious use of β -adrenergic antagonists is recommended.^{17,19,200,212}

The use of gastrointestinal decontamination should be decided on a case by case basis. The benefits of activated charcoal (AC) must be balanced with the risks of its aspiration and subsequent potential for pulmonary toxicity. The use of AC should be determined judiciously based on the current mental status of the patient, the potential for further deterioration, the xenobiotic(s) ingested, and the expected clinical course. Phenobarbital overdose is one particular scenario in which MDAC may be considered. MDAC increases phenobarbital elimination by 50% to 80%.^{11,12,16} However, in the only controlled study in intubated, phenobarbital-poisoned patients who were randomized to single-dose activated charcoal versus MDAC, no statistical difference was demonstrated in outcome measures (time to extubation and length of hospitalization).¹²⁷ AC may have potential benefits in certain situations after ensuring adequate airway protection (Antidotes in Depth: A1).

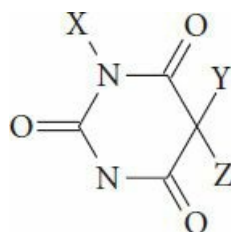
Although the efficacy of delayed orogastric lavage is controversial, orogastric lavage may be considered in overdoses with xenobiotics that slow GI motility or that are known to develop concretions, specifically phenobarbital and meprobamate.^{27,75,150} Orogastric lavage in the setting of oral benzodiazepine overdoses alone is not recommended, as the benefits of lavage are minimal compared to the significant risks of aspiration (Chap. 8). No antidote counteracts all sedative-hypnotic overdoses. Flumazenil, a competitive benzodiazepine antagonist, rapidly reverses the sedative effects of benzodiazepines as well as zolpidem and its congeners.^{90,148,166,198,202,209} However, flumazenil can precipitate life-threatening benzodiazepine withdrawal in benzodiazepine-dependent patients. Flumazenil use is also associated with seizures, especially in patients who have overdosed on tricyclic antidepressants^{72,109,166,167,194,209} (Antidotes in Depth: A22).

Because the lethality of sedative-hypnotics is associated with their ability to cause respiratory depression,

asymptomatic patients can be downgraded to a lower level of care after a period of observation with no signs of respiratory depression. Patients with symptomatic overdoses of long-acting sedative hypnotics, such as meprobamate and clonazepam, or drugs that can have significant enterohepatic circulation, such as glutethimide, may require 24 hours of observation in the intensive care unit ([Chap. 11](#)). Patients with mixed overdoses of various sedative-hypnotics and CNS depressants also warrant closer observation for respiratory depression due to synergistic respiratory depressant effects.

SPECIFIC SEDATIVE-HYPNOTICS

Barbiturates



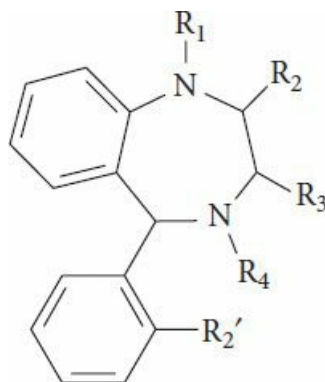
Barbital became the first commercially available barbiturate in 1903. Although many other barbiturates were subsequently developed, their popularity has greatly waned since the introduction of benzodiazepines. Barbiturates are derivatives of barbituric acid (2,4,6-trioxo-hexa-hydropyrimidine), which itself has no CNS depressant properties. The addition of various side chains influences the pharmacologic properties. Barbiturates with long side chains tend to have increased lipophilicity, potency, and slower rates of elimination. However, the observed clinical effects also depend on absorption, redistribution, and the presence of active metabolites. For this reason, the duration of action of barbiturates (like those of benzodiazepines) may not correlate well with their biologic half-lives.

Oral barbiturates are preferentially absorbed in the small intestine and are eliminated by both hepatic and renal mechanisms. Longer-acting barbiturates tend to be more lipid soluble, more protein bound, have a higher pK_a , and are metabolized almost completely by the liver. Renal excretion of unchanged drug is significant for phenobarbital, a long-acting barbiturate with a relatively low pK_a (7.24). Alkalinizing the urine with sodium bicarbonate to a urinary pH of 7.5 to 8.0 can increase the amount of phenobarbital excreted by 5- to 10-fold. This procedure is not effective for the short-acting barbiturates because they have higher pK_a values, are more protein bound, and are primarily metabolized by the liver with very little unchanged drug excreted by the kidneys (*Antidotes in Depth: A5* and [Chap. 10](#)). Although several authors have questioned the clinical benefit of urinary alkalinization,¹⁴¹ this practice is still recommended to enhance renal elimination of phenobarbital.

Barbiturates (especially the shorter-acting barbiturates) can accelerate their own hepatic metabolism by cytochrome P450 enzyme autoinduction. Phenobarbital is a nonselective inducer of hepatic cytochromes, the greatest effects being on CYP2B1, CYP2B2, and CYP2B10, although CYP3A4 is also affected.^{82,117,145,159,182} Not surprisingly, a variety of interactions are reported following the use of barbiturates. Clinically significant interactions as a result of enzyme induction lead to increased metabolism of β -adrenergic antagonists, corticosteroids, doxycycline, estrogens, phenothiazines, quinidine, theophylline, and many other xenobiotics.

Similar to other sedative-hypnotics, patients with significant barbiturate overdoses present with CNS and respiratory depression. Hypothermia and cutaneous bullous lesions are often present. These two signs are also described for other patients with sedative-hypnotic overdoses, but they may be more pronounced with barbiturates.^{14,44} Early deaths caused by barbiturate ingestions result from respiratory arrest and cardiovascular collapse. Delayed deaths result from acute kidney failure, pneumonia, acute respiratory distress syndrome, cerebral edema, and multiorgan system failure as a result of prolonged cardiorespiratory depression.^{3,58}

Benzodiazepines



The commercial use of benzodiazepines began with the introduction of chlordiazepoxide for anxiety in 1961 and diazepam for seizures in 1963. Benzodiazepines are used principally as sedatives and anxiolytics. Clonazepam is the only benzodiazepine approved for use as a chronic anticonvulsant. Benzodiazepines may rarely cause paradoxical psychological effects, including nightmares, delirium, psychosis, and transient global amnesia.^{84,103,106,203,206,215} The incidence and intensity of CNS adverse events increases with age.¹⁰²

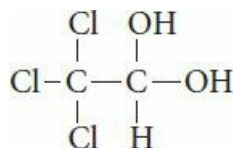
Similar to barbiturates, variations of the benzodiazepine side chains influence potency, duration of action, metabolites, and rate of elimination. Most benzodiazepines are highly protein bound and lipophilic. They passively diffuse into the CNS, their main site of action. Because of their lipophilicity, benzodiazepines are extensively metabolized via oxidation and conjugation in the liver prior to their renal elimination.

Benzodiazepines bind nonselectively to “central” benzodiazepine sites located throughout the brain. These sites contain the GABA_A α and γ subunits.^{42,193} The binding of the benzodiazepine to its particular site changes the GABA receptor to “lock” into a position that promotes GABA binding to the GABA receptor. Benzodiazepines that are active at the α_1 subunit are hypothesized to affect anxiety, sleep, and amnesia, whereas those that are active in the α_2 and α_3 subunits tend to have greater anxiolytic properties. “Peripheral” benzodiazepine sites are found throughout the body, with the greatest concentrations in steroid-producing cells in the adrenal gland, anterior pituitary gland, and reproductive organs. These sites are not affiliated with the GABA receptor (Antidotes in Depth: A23).

One unique property of the benzodiazepines is their relative safety even after substantial ingestion, which probably results from their GABA receptor properties.^{42,119} Unlike many other sedative-hypnotics, benzodiazepines do not open GABA channels independently at high concentrations. Benzodiazepines are not known to cause any specific systemic injury, and their long-term use is not associated with specific organ toxicity. Deaths resulting from isolated benzodiazepine ingestions alone are extremely rare. Most often deaths are secondary to a combination of alcohol or other sedative-hypnotics.^{156,203,206} Supportive care is the mainstay of treatment.

Tolerance to the sedative effects of benzodiazepines occurs more rapidly than does tolerance to the antianxiety effects.^{93,137} Abrupt discontinuation following long-term use of benzodiazepines may precipitate benzodiazepine withdrawal. This is characterized by autonomic instability, changes in perception, paresthesias, headaches, tremors, and seizures. Withdrawal from benzodiazepines is common, manifested by almost one-third of long-term users.⁸⁴ Alprazolam and lorazepam are associated with more severe withdrawal syndromes compared with chlordiazepoxide and diazepam.^{84,85} This is likely due to the fact that both chlordiazepoxide and diazepam have active metabolites. Withdrawal may also occur when a chronic user of a particular benzodiazepine is switched to another benzodiazepine with different receptor activity.⁹⁶

Chloral Hydrate



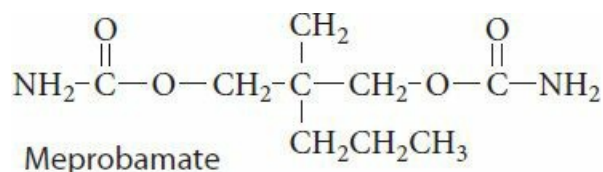
First introduced in 1832, chloral hydrate belongs to one of the oldest classes of pharmaceutical hypnotics, the chloral derivatives. Although still used sporadically in children, its use has substantially decreased.^{1,95,125} Chloral hydrate is well absorbed but is irritating to the GI tract. It has a wide tissue distribution, rapid onset of action, and rapid hepatic metabolism by alcohol and aldehyde dehydrogenases. Trichloroethanol is a lipid soluble, active metabolite that is responsible for the hypnotic effects of chloral hydrate. It has a serum half-life of 4 to 12 hours and is metabolized to inactive trichloroacetic acid by alcohol dehydrogenases. It is also conjugated with glucuronide and excreted by the kidney as urochloralic acid. Less than 10% of trichloroethanol is excreted unchanged.

Metabolic rates in children vary widely because of variable development and function of hepatic enzymes, in particular glucuronidation.^{18,101} The elimination half-life of chloral hydrate and trichloroethanol is markedly increased in children

younger than 2 years. This may be especially of concern in neonates and in infants exposed to repetitive doses.

Acute chloral hydrate poisoning is unique compared with that of other sedative-hypnotics. Cardiac dysrhythmias are believed to be the major cause of death.⁵⁷ Chloral hydrate and its metabolites reduce myocardial contractility, shorten the refractory period, and increase myocardial sensitivity to catecholamines. Persistent cardiac dysrhythmias (ventricular fibrillation, ventricular tachycardia, torsade de pointes) are common terminal events.¹⁰⁰ Standard antidysrhythmics often are ineffective, and β -adrenergic antagonists are considered the treatment of choice.^{17,19,24,94,179,200,212} In addition to cardiotoxicity, chloral hydrate toxicity may cause vomiting, hemorrhagic gastritis, and rarely gastric and intestinal necrosis, leading to perforation and esophagitis with stricture formation.^{88,188} Chloral hydrate is radiopaque and may be detected on radiographs; however, a negative radiograph should not be used to exclude chloral hydrate ingestion. Few hospital-based laboratories have the ability to rapidly detect chloral hydrate or its metabolites.

Meprobamate/Carisoprodol



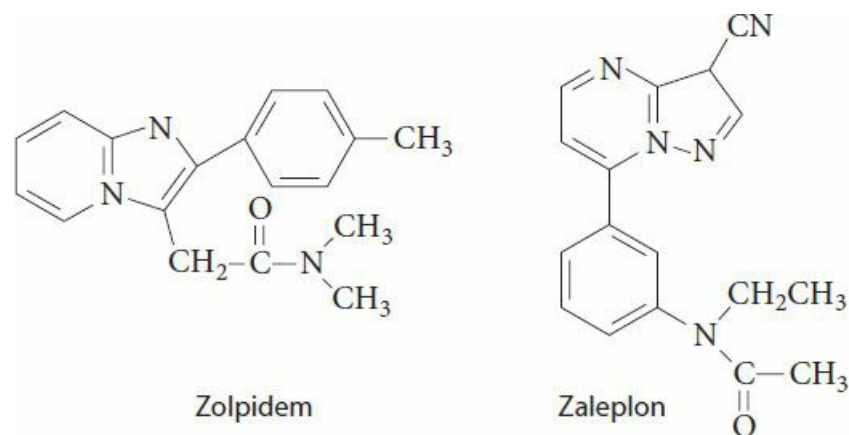
Meprobamate was introduced in 1950 and was used for its muscle-relaxant and anxiolytic characteristics. Carisoprodol, which was introduced in 1955, is metabolized to meprobamate. Both drugs have pharmacologic effects on the GABA_A receptor similar to those of the barbiturates. Like barbiturates, meprobamate can directly open the GABA-mediated chloride channel and may inhibit NMDA receptor currents.¹³⁵ Both are rapidly absorbed from the GI tract. Meprobamate is metabolized in the liver to inactive hydroxyl and glucuronide metabolites that are excreted almost exclusively by the kidney. Of all the nonbarbiturate tranquilizers, meprobamate is most likely to produce euphoria.^{73,74} Unlike most sedative-hypnotics, meprobamate causes profound hypotension from direct myocardial depression.²⁷ Adherent masses or bezoars of pills have been discovered in the stomach at autopsy after large meprobamate ingestions.¹⁵⁰ Orogastric lavage with a large-bore tube and MDAC may be indicated for patients with significant meprobamate ingestion. However, the potential benefits of orogastric lavage must be weighed against the risks of aspiration. Whole-bowel irrigation may be helpful if multiple pills or small concretions are suspected. Patients can experience recurrent toxic manifestations as a result of concretion formation with delayed drug release and absorption. Careful monitoring of the clinical course is essential even after the patient shows initial improvement because recurrent and cyclical CNS depression can occur.¹⁵⁰

Bromides

Bromides were used in the past as “nerve tonics,” headache remedies, and anticonvulsants. Although medicinal bromides have largely disappeared from the US pharmaceutical market, bromide toxicity still occurs through the availability of bromide salts of common drugs, such as dextromethorphan.¹¹² Poisoning also may occur in immigrants and travelers from other countries where bromides are still therapeutically used.⁴⁹ An epidemic of more than 400 cases of mass bromide poisoning occurred in the Cacuo municipality of Luanda Province, Angola, in 2007. According to a World Health Organization report, the etiology of the bromide exposure in these cases was believed to be table salt contaminated with sodium bromide. Although the majority of persons affected were children, no actual deaths were attributed to bromide poisoning in this epidemic.²⁰¹

Bromides tend to have long half-lives, and toxicity typically occurs overtime as concentrations accumulate in tissue. Bromide and chloride ions have a similar distribution pattern in the extracellular fluid. It is postulated that because the bromide ion moves across membranes slightly more rapidly than the chloride ion, it is more quickly reabsorbed in the tubules from the glomerular filtrate than the chloride ion. Although osmolar equilibrium persists, CNS function is progressively impaired by a poorly understood mechanism, with resulting inappropriateness of behavior, headache, apathy, irritability, confusion, muscle weakness, anorexia, weight loss, thickened speech, psychotic behavior, tremulousness, ataxia, and, eventually, coma. Delusions and hallucinations can occur. Bromide can lead to hypertension, increased intracranial pressure, and papilledema.^{6,25,49,68,174,180,214} Chronic use of bromides also produces dermatologic changes called bromoderma, with the hallmark characteristic of a facial acneiform rash.^{64,180} Toxicity with bromides during pregnancy may lead to accumulation of bromide in the fetus.¹²⁶ A spurious laboratory result of hyperchloremia with decreased anion gap may result from the interference of bromide with the chloride assay on older analyzers²⁰⁸ (Chap. 19). Thus, an isolated elevated serum chloride concentration with neurologic symptoms should raise suspicion of possible bromide poisoning.

Zolpidem/Zaleplon/Zopiclone/Eszopiclone

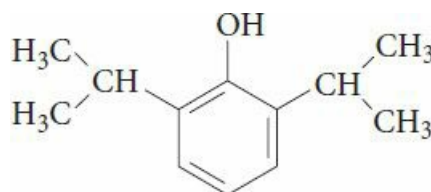


These oral xenobiotics have supplanted benzodiazepines as the most commonly prescribed sleep aid medications.⁴⁶ Although they are structurally unrelated to the benzodiazepines, they bind preferentially to the benzodiazepine site subtype in the brain that contains the GABA_A α_1 subunit.⁴² They have a lower affinity for benzodiazepine sites that contain the other α isoforms, therefore they have potent hypnotic effects with less potential for dependence and anticonvulsant properties.⁶³ Each of these xenobiotics has a relatively short half-life (≤ 6 hours), with zaleplon exhibiting the shortest half-life (1 hour). Unlike benzodiazepines that prolong the first two stages of sleep and shorten stages 3 and 4 of rapid eye movement sleep, zolpidem and its congeners all decrease sleep latency with little effect on sleep architecture. Because of their receptor selectivity, they appear to have minimal effect at other sites on the GABA_A receptor that mediate anxiolytic, anticonvulsant, or muscle-relaxant effects.^{86,190}

They are hepatically metabolized by various CYP450 enzymes. Zolpidem is mainly metabolized by CYP3A4. Zaleplon is primarily metabolized by aldehyde oxidase, but CYP3A4 is also involved in parent compound oxidation. Zopiclone is primarily metabolized by CYP3A4 and CYP2C8, whereas eszopiclone is metabolized mainly by CYP3A4 and CYP2E1. Various pharmacokinetic interactions with inhibitors or inducers of CYP450 enzymes and these medications are reported.⁶²

In isolated overdoses, drowsiness and CNS depression are common. However, prolonged coma with respiratory depression is exceptionally rare. Isolated overdoses usually manifest with depressed level of consciousness without respiratory depression. For example, even at 40 times the therapeutic dose of zolpidem, no biologic or electrocardiographic abnormalities were reported.⁵² Zopiclone overdoses are rarely associated with methemoglobinemia.⁵¹ Tolerance to zolpidem and its congeners occurs, and as expected, withdrawal follows abrupt discontinuation of chronic use. The withdrawal syndrome is typically mild.^{61,197} Flumazenil may reverse the hypnotic or cognitive effects of these xenobiotics (Antidotes in Depth: A22).^{90,209} Due to increasing prevalence of these xenobiotics, they have been associated with increasing hospitalizations especially when ingested with other sedative hypnotics.²¹⁸ Deaths have resulted when zolpidem was taken in large amounts with other CNS depressants.⁵²

Propofol



Propofol is a rapidly acting intravenous sedative-hypnotic that is both a postsynaptic GABA_A agonist and induces presynaptic release of GABA.^{115,181} Propofol is also an antagonist at NMDA receptors.^{80,165,217} In addition, propofol interacts with dopamine, promotes nigral dopamine release possibly via GABA_B receptors,^{120,151} and has partial agonist properties at dopamine (D₂) receptors.¹⁴⁹ Propofol is used for procedural sedation and either induction or maintenance of general anesthesia. It is highly lipid soluble, so it crosses the blood-brain barrier rapidly. The onset of anesthesia usually occurs in less than one minute. The duration of action after short-term dosing is usually less than 8 minutes due to its rapid redistribution from the CNS.

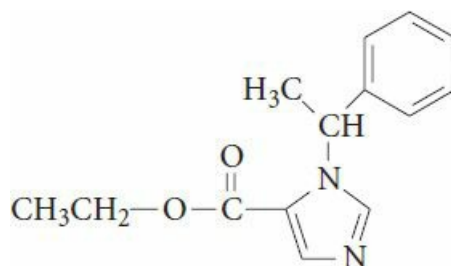
Propofol use is associated with various adverse events. Acutely, propofol causes dose-related respiratory depression. Propofol may decrease systemic arterial pressure and cause myocardial depression. Although short-term use of propofol does not typically cause dysrhythmias or myocardial ischemia, atropine-sensitive bradycardias are noted, specifically

sinus bradycardia and Mobitz type 1 atrioventricular block.^{178,196,211} Short-term use of propofol in the perioperative setting is associated with a myoclonic syndrome manifesting as opisthotonus, myoclonus, and sometimes myoclonic seizurelike activity.^{104,113}

Prolonged propofol infusions, typically more than 48 hours at rates of 4 to 5 mg/kg/h or greater, are associated with a life-threatening propofol-infusion syndrome involving metabolic acidosis, cardiac dysrhythmias, and skeletal muscle injury.^{77,78} The clinical signs of propofol infusion syndrome often begin with the development of a new right bundle branch block and ST segment convex elevations in the electrocardiogram precordial leads.⁷⁷ Predisposing factors to the development include young age, severe brain injury (especially in the setting of trauma), respiratory compromise, concurrent exogenous administration of catecholamines or glucocorticoids, inadequate carbohydrate intake, and undiagnosed mitochondrial myopathy. Some authors propose a “priming” and “triggering” mechanism for propofol infusion syndrome with endogenous glucocorticoids, catecholamines, and possibly cytokines as “priming” agents, and exogenous catecholamines and glucocorticoids in the setting of high-dose propofol infusion as “triggering” stimuli.¹⁸⁶ Propofol is suggested to induce disruption of mitochondrial free fatty acid utilization and metabolism, causing a syndrome of energy imbalance and myonecrosis similar to mitochondrial myopathies.^{29,158,187} Case reports associate propofol with metabolic acidosis, elevated lactate concentration, and fatal myocardial failure in both children and young adults. However, this syndrome is also reported in older adults.¹²² Cases of metabolic acidosis may be associated with an inborn disorder of acylcarnitine metabolism.²⁰⁵ Prolonged propofol infusions may unmask previously undiagnosed myopathy that would cause them to be at increased risk for propofol infusion syndrome, especially in children. Despite the increasing number of reports of propofol infusion syndrome in the literature, a direct cause and effect relationship remains to be fully elucidated.

The unique nature of the carrier base of propofol, a milky soybean emulsion formulation, is associated with multiple adverse drug events. It is a fertile medium for many organisms, such as enterococcal, pseudomonal, staphylococcal, streptococcal, and candidal strains. In 1990, the US Centers for Disease Control and Prevention reported an outbreak of *Staphylococcus aureus* associated with contaminated propofol. This carrier base also impairs macrophage function,²⁹ causes hypertriglyceridemia^{41,83,91,158,187} and histamine-mediated anaphylactoid reactions,^{43,79,187} and impairs platelet and coagulation function.^{5,39}

Etomidate



Etomidate is an intravenous nonbarbiturate, hypnotic primarily used as an anesthesia induction agent. It is active at the GABA_A receptor, specifically the β_2 and β_3 subunits.^{32,114} Only the intravenous formulation is available in the United States. The onset of action is less than 1 minute and its duration of action is less than 5 minutes.

Etomidate is commercially available as a 2 mg/mL solution in a 35% propylene glycol solution. Propylene glycol toxicity from prolonged etomidate infusions is implicated in the development of hyperosmolar metabolic acidosis (Chap. 55).^{89,98,183,185} Etomidate has minimal effect on cardiac function, but rare cases of hypotension are reported.^{53-55,169} Etomidate has both proconvulsant and anticonvulsant properties.^{33,130} Involuntary muscle movements are common during induction and may be caused by etomidate interaction with glycine receptors at the spinal cord level.^{36,107,108}

Etomidate depresses adrenal production of cortisol and aldosterone; therefore, it is associated with adrenocortical suppression, usually after prolonged infusions.^{147,191,192} Etomidate has been associated with increased morbidity and mortality in critically ill and trauma patients.^{35,65} However, other authors question the clinical significance of adrenal suppression from etomidate administration and dispute its association with adverse outcomes.^{66,171,172} In the appropriate setting, etomidate does not appear to have any greater risk of significant adverse events compared with its counterparts.

Dexmedetomidine

Dexmedetomidine is a central α_2 -adrenergic agonist that decreases central presynaptic catecholamine release, primarily in the locus coeruleus. It has a terminal half-life of 1.8 hours and its volume of distribution is less than 1 L/kg. When dexmedetomidine is used to help wean patients from ventilators, sedation is achieved with less associated delirium as compared with other agents.^{121,170} It is also used for procedural sedation in certain settings such as interventional radiology

procedures and awake fiberoptic intubations. When compared with propofol, dexmedetomidine sedation may lessen opioid requirements in postoperative patients. Dexmedetomidine has been used as an adjunctive agent in benzodiazepine, opioid, or ethanol withdrawal.^{37,40,47,138,144,176,177}

Dexmedetomidine has minimal effect at the GABA_A receptor. Unlike other sedative-hypnotics, it is not associated with significant respiratory depression. Although mechanistically similar to clonidine, dexmedetomidine does not appear to cause as much respiratory depression as clonidine. Dexmedetomidine is said to induce a state of “cooperative sedation,” in which a patient is sedated but yet able to interact with health care providers. Dexmedetomidine may also have analgesic effects.³¹

Dexmedetomidine is currently only approved for use for less than 24 hours. Extensive safety trials have not yet explored its use beyond 24 hours. Unlike clonidine, rebound hypertension and tachycardia have not been described upon cessation. Because dexmedetomidine decreases central sympathetic outflow, its use should probably be avoided in patients whose clinical stability is dependent on high resting sympathetic tone. The most common adverse effects from its use are nausea, dry mouth, bradycardia, and varying effects on blood pressure (usually hypertension followed by hypotension). Slowing of the continuous infusion may help to prevent or lessen the hypotensive effects.³¹ In one case, a 60-fold overdose in a child was associated with hypoglycemia.¹³

Ramelteon and Melatonin

Ramelteon is a synthetic melatonin-analog that is FDA approved for the treatment of chronic insomnia. Ramelteon is thought to decrease both latency to sleep induction and length of persistent sleep.¹⁶⁰ Melatonin (N-acetyl-5-methoxytryptamine) and melatonin-containing products are sold as dietary supplements. Melatonin is naturally synthesized from tryptophan by the enzyme 5-hydroxyindole-O-methyltransferase, primarily within the pineal gland in humans. Melatonin and ramelteon both act as agonists at MT₁ and MT₂ receptors, which are G protein–coupled receptors mainly located in the suprachiasmatic nucleus of the brain.¹²⁷ Ramelteon is specific for MT₁ and MT₂ receptors, whereas melatonin is active at other melatonin receptors not likely involved in sleep. MT₁ receptors appear to be involved in sleep induction, whereas MT₂ receptors are involved in regulation of the circadian sleep-wake cycle in humans.¹⁶⁸

Ramelteon is administered as an oral medication that is rapidly absorbed but undergoes significant first-pass metabolism. Ramelteon is metabolized primarily by CYP1A2. The half-life of ramelteon with therapeutic use is roughly 1.5 hours.

Adverse effects of ramelteon are often mild and usually include dizziness, fatigue, and headache. The endocrine effects of long-term exposure to ramelteon seem to be limited to subclinical increases in serum prolactin concentration in women and do not appear to affect adrenal or thyroid function.¹³⁶ In addition, ramelteon has a low abuse potential and does not appear to be associated with a withdrawal syndrome or with rebound insomnia.^{60,97,105} As of yet, there are no reported cases of significant toxicity from ramelteon overdose.

SUMMARY

- Treatment is largely conservative with little need for GI decontamination.
- Sedative-hypnotics encompass a wide range of xenobiotics that predominantly interact with the GABA_A receptor but can also have varying mechanisms of action.
- Patients with sedative-hypnotic overdoses often present with the primary manifestation of CNS depression; however, death typically results from respiratory depression and subsequent cardiovascular collapse in the setting of concurrent coingestion of other CNS depressants.
- Careful monitoring, airway protection, and proper supportive care are the cornerstones of treatment. Specific antidotes such as flumazenil and treatments such as hemodialysis are rarely indicated.

Acknowledgment

Kathy Lynn Ferguson, DO, contributed to this chapter in previous editions.

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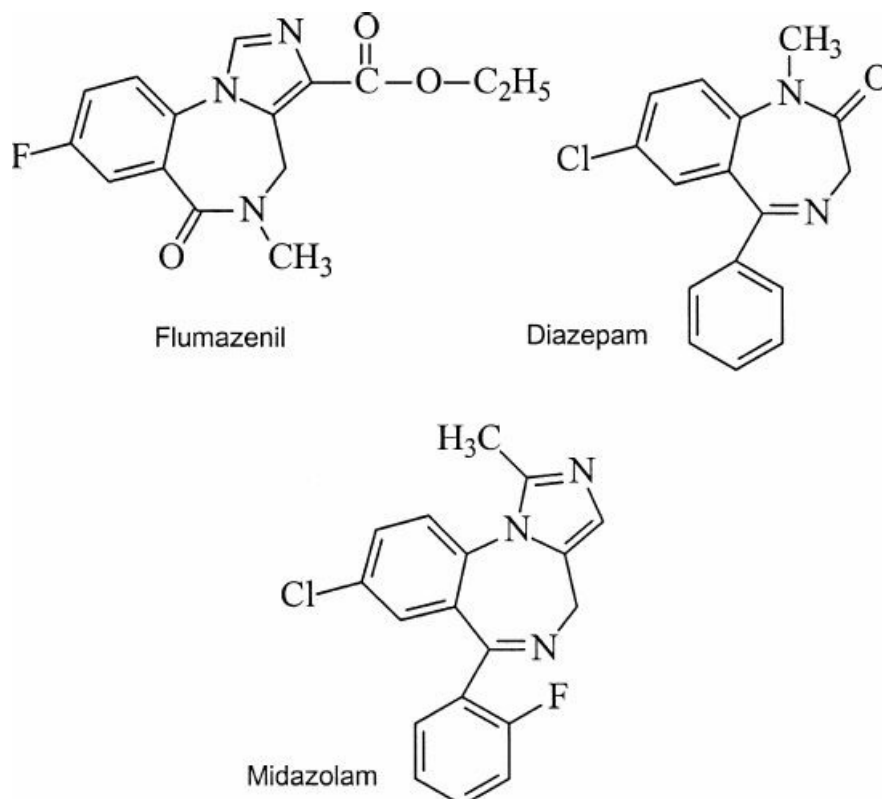
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A22 ANTIDOTES IN DEPTH

Flumazenil

Mary Ann Howland



INTRODUCTION

Flumazenil is a competitive benzodiazepine receptor antagonist. Its role in patients with an unknown overdose is limited because seizures and dysrhythmias may develop when the effects of a benzodiazepine are reversed if the patient has taken a mixed overdose. Flumazenil also has the potential to induce benzodiazepine withdrawal symptoms, including seizures in patients who are benzodiazepine dependent. Flumazenil does not reliably reverse the respiratory depression induced by intravenous (IV) benzodiazepines.²¹ Flumazenil is the ideal antidote for the relatively few patients who are both naïve to benzodiazepines and who overdose solely on a benzodiazepine as well as benzodiazepine-naïve patients whose benzodiazepine component must be reversed after procedural sedation. Because the duration of effect of flumazenil is shorter than that of most benzodiazepines, repeat doses may be necessary and vigilance is warranted. Flumazenil has no role in the management of ethanol intoxication. Flumazenil may be considered for patients with hepatic encephalopathy although further study is necessary before it can be recommended.⁴ Case reports raise the possibility of a role for flumazenil in patients with paradoxical reactions to therapeutic doses of benzodiazepines.⁷¹ Flumazenil was not effective in overdose of baclofen in which a benzodiazepine receptor is not involved.¹⁵ Flumazenil is effective for overdoses of zolpidem and zaleplon, nonbenzodiazepines that interact with β_1 receptors, a subclass of central benzodiazepine receptors.^{43,53,56}

HISTORY

The initial work of Haefely and Hunkeler⁶⁷ on chlordiazepoxide synthesis led to an attempt to develop benzodiazepine derivatives that would act as antagonists.³³ This endeavor was initially unsuccessful but led to the promising γ -aminobutyric acid (GABA) hypothesis as the benzodiazepine mechanism of action. In 1977 radioligand binding identified

specific high-affinity benzodiazepine binding sites. Other investigators simultaneously isolated a product produced by a *Streptomyces* species that had the basic 1,4-benzodiazepine structure. Synthetic derivatives of this molecule led to the creation of benzodiazepines with potent anxiolytic and anticonvulsant activity and diminished sedative and muscle-relaxing properties. Testing revealed these derivatives had high in vitro binding affinities, but lacked in vivo activity. An inability to enter the central nervous system (CNS) was considered an explanation for the discordance. During an experiment that attempted to demonstrate CNS penetration of these derivatives, diazepam given to incapacitate the animals had a surprisingly weak effect. This lack of potency led to the discovery of a benzodiazepine antagonist. Further modifications led to the synthesis of flumazenil (Ro 15-1788).^{20,57}

PHARMACOLOGY

Mechanism of Action

The benzodiazepine receptor modulates the effect of GABA on the GABA_A receptor by increasing the frequency of Cl⁻ channel opening, leading to hyperpolarization. Agonists such as diazepam stimulate the benzodiazepine receptor to produce anxiolytic, anticonvulsant, sedative-hypnotic, amnestic, and muscle relaxant effects. Flumazenil is a water-soluble benzodiazepine analog with a molecular weight of 303 Da. It is a competitive antagonist at the benzodiazepine receptor, with very weak agonist properties both in animal models and in humans.⁵² Inverse agonists bind the benzodiazepine receptor and result in the opposite effects of anxiety, agitation, and seizures. Antagonists, such as flumazenil, competitively occupy the benzodiazepine receptor without causing any functional change and without allowing an agonist or inverse agonist access to the receptor. The zero set point of intrinsic activity may be influenced by the activity of the GABA system or by chronic treatment with benzodiazepines.²⁴ Positron emission tomography investigations reveal that 1.5 mg of flumazenil leads to an initial receptor occupancy of 55%, whereas 15 mg causes almost total blockade of benzodiazepine receptor sites.⁶⁰

PHARMACOKINETICS AND PHARMACODYNAMICS

Table A22–1 summarizes the physicochemical and pharmacologic properties of flumazenil.^{21,37} Volunteer studies demonstrate that the ability of flumazenil to reverse the effects of sedating doses of IV benzodiazepines (eg, 30 mg diazepam, 3 mg lorazepam, 10 mg midazolam) is dose dependent and begins within minutes.¹⁸ Peak effects occur within 6 to 10 minutes.²¹ Most individuals achieve complete reversal of benzodiazepine effect with a total IV dose of 1 mg, titrated in 0.2 mg aliquots.^{5,14} A 3 mg IV dose produces similar effects that last approximately twice as long as the 1 mg dose.

TABLE A22–1. Physicochemical and Pharmacologic Properties of Flumazenil

pK _a	Weak base
LogD	1.15 (octanol/aqueous PO ₄ buffer)
Volume of distribution	1.06 L/kg
Distribution half-life (t _{1/2α})	≤5 minutes
Metabolism	Hepatic: three inactive metabolites High clearance
Elimination	First order
Protein binding	54%–64%
Elimination half-life (t _{1/2β})	53 minutes
Onset of action	1–2 minutes
Duration of action	Dependent on dose and elimination of benzodiazepine, time interval, dose of flumazenil, and hepatic function

ROLE IN CONSCIOUS SEDATION

A number of studies evaluated patients who received midazolam or diazepam (average doses of 10 and 30 mg,

respectively) as conscious sedation for endoscopy or cardioversion.^{6,13,14,17,39,40} When a benzodiazepine is given for conscious sedation during a procedure, flumazenil appears safe and effective for reversal of sedation and partial reversal of amnesia and cognitive impairment.²⁷ Most patients respond to total doses of 0.4 to 1 mg.²¹ Administering flumazenil slowly at a rate of 0.1 mg/min minimizes the disconcerting symptoms associated with rapid arousal, such as confusion, agitation, and emotional lability. Residual sedation becomes evident within 20 to 120 minutes, depending on the dose and pharmacokinetics of the specific agonist benzodiazepine and the dose of flumazenil.²⁷ For this reason, patients must be carefully monitored and subsequent doses of flumazenil titrated to clinical response. Because the amnestic effect of benzodiazepines and the cognitive and psychomotor effects are not fully reversed, posttreatment instructions should be reinforced in writing and given to a responsible caregiver accompanying the patient.^{18,27} Because of the risk of resedation, health care professionals infrequently elect to use flumazenil.

Two patients undergoing endoscopy who developed seizures following benzodiazepine reversal are reported.⁶⁴ One patient had a history of seizures, and the other had no obvious etiology. Both patients recovered uneventfully.

ROLE IN PARADOXICAL REACTIONS

Paradoxical reactions to benzodiazepines are unpredictable and documented in as many as 1% to 10% of adults and in 3.4% of children.^{30,48,49} Common features include worsening restlessness, agitation, disorientation, flailing, and dysphoria.^{26,28,54,71} The mechanism is unclear and has been attributed to a disinhibition reaction.²³ These reactions are reported to occur from several minutes to 210 minutes after initiation of sedation.^{28,71} Management strategies include administering higher doses of the benzodiazepines, adding other drugs such as opioids or droperidol, stopping the procedure, and using flumazenil.^{26,49,54,71} IV flumazenil was administered to six adults with paradoxical reactions to midazolam in 0.1 mg aliquots. Doses of 0.2 to 0.5 mg were effective in all the patients with a response occurring within 30 seconds.⁷¹ Attention to other causes of unexpected behavior such as hypoxia or hypoglycemia must be addressed and corrected.

ROLE IN THE OVERDOSE SETTING

Although the flumazenil package insert carries an indication for the management of benzodiazepine overdose, the role of flumazenil in the overdose setting is controversial.^{41,68} The first argument against flumazenil use is the rare morbidity and mortality associated with benzodiazepine use. An analysis of 702 patients who had taken benzodiazepines alone or in combination with ethanol or other drugs and were subsequently admitted to a medical intensive care unit over a 14-year period revealed a 0.7% fatality rate (five deaths) and 9.8% complication rate (69 patients).³⁶ In comparison, the fatality rate for patients with nonbenzodiazepine related overdoses was 1.6% (55 of 3430 patients). In the pure benzodiazepine group, two patients died and 18 (12.5%) of 144 patients had complications, mostly aspiration pneumonitis and decubitus ulcers. Proponents of flumazenil therapy suggest that some of the 29 diagnostic procedures used in the patients were unnecessary, and some of the complications could have been prevented by the use of flumazenil. Others suggest that many of the cases of aspiration pneumonitis occurred prior to hospital admission and that the patients also suffered from trauma and infectious diseases, making most diagnostic procedures necessary.

In an effort to develop indications for safe and effective use of flumazenil, overdosed comatose patients were retrospectively assigned to either a low-risk or non-low-risk group.³¹ Low-risk patients had CNS depression with normal vital signs, no other neurologic findings, no evidence of ingestion of a tricyclic antidepressant by history or electrocardiography, no seizure history, and absence of an available history of chronic benzodiazepine use. All other patients fell into the non-low-risk category. Of 35 consecutive comatose patients, 4 were assigned to the low-risk group. Flumazenil resulted in complete awakening in three patients and partial awakening in the fourth patient in the low-risk group, with no adverse events. In the non-low-risk group of 31 patients, flumazenil caused complete awakening in four patients and partial awakening in five patients. Seizures occurred in five patients, of whom only one had a history of seizures, five were long-term benzodiazepine users, four had abnormal vital signs prior to reversal, and three had evidence of hyperreflexia or myoclonus. Therefore, although flumazenil use probably was safe and effective in the low-risk group, few patients could be considered low risk. The risk of seizures appears substantial in non-low-risk patients.

The risks of flumazenil usually outweigh the benefits in patients with overdoses.⁶¹ When non-benzodiazepine-dependent patients ingest benzodiazepines alone in overdose, as rarely occurs in adults but might be expected in children, the risks associated with flumazenil are limited.^{41,73} Table A22–2 summarizes the indications for flumazenil use in the overdose setting.

TABLE A22–2. Indications for Flumazenil Use in the Overdose Setting

Pure benzodiazepine overdose in a nontolerant individual who has

- Central nervous system depression
- Normal vital signs, including SaO₂
- Normal electrocardiogram
- Otherwise normal neurologic examination

ROLE IN NONBENZODIAZEPINE TOXICITY

Hepatic Encephalopathy

Hepatic encephalopathy is considered a reversible metabolic encephalopathy characterized by a spectrum of CNS effects. Symptoms may progress from confusion and somnolence to coma. One current hypothesis implicates an increase in GABAergic tone in the development of encephalopathy.^{7,63}

Animal studies of hepatic encephalopathy secondary to galactosamine or thioacetamide (hepatotoxins) demonstrate an increase in GABA effect, which is antagonized by flumazenil, bicuculline (a GABA receptor antagonist), and isopropylbicyclophosphate chloride (a calcium channel blocker).⁷ Cerebrospinal fluid (CSF) from these animals contained a benzodiazepine receptor ligand with agonist activity. Rat studies involving hepatic encephalopathy resulting from acute liver ischemia showed only a slight response to flumazenil, but significant improvement after administration of a partial inverse agonist.^{12,69}

Human studies have detected benzodiazepine binding activity in the CSF (but not in serum) of patients with hepatic encephalopathy. One group identified four to 19 peaks representing benzodiazepine binding ligands from the frontal cortex of 11 patients who died of hepatic encephalopathy.¹⁰ Two of the peaks were further characterized as diazepam and N-desmethyldiazepam. Brain concentrations of these substances were 2 to 10 times higher than normal in six of the patients and were normal in five patients. Patients with idiopathic recurring stupor who have measurable “endozepines” (endogenous benzodiazepine ligands) in serum and CSF are reported.^{58,66}

Flumazenil improves the clinical and electrophysiologic responses of patients with hepatic encephalopathy and idiopathic recurring stupor.^{4,8,19,58,66} Some patients with encephalopathy have improved from stage IV to stage II encephalopathy following IV flumazenil. Maximal improvement after flumazenil lasts approximately 1 to 2 hours and gradually dissipates within 6 hours. The response rate in a meta-analysis averaged approximately 30%.²⁹ The proposed explanations for the unresponsiveness include cerebral edema, hypoxia, other systemic diseases or complications, and irreversible CNS damage.

Animal and human data convincingly support the concept that increased GABAergic tone is responsible for hepatic encephalopathy. Evidence for endogenous benzodiazepine ligands that enhance GABA action also are demonstrated but controversial.^{1,3} The source of these benzodiazepine receptor agonists is unclear, but diet and/or production by gut bacteria is postulated.⁷ Most authorities believe endogenous de novo synthesis is unlikely and propose prior benzodiazepine exposure and persistence of clinical effects as an explanation. Hyperammonemia, neurosteroids, and hemoglobin metabolites are also implicated in the pathophysiology of hepatic encephalopathy.^{3,11,59}

Flumazenil can lead to short term improvement of the clinical condition of a subgroup of patients with hepatic encephalopathy and may prove useful as an addition to conventional therapy.^{2,4,9} Existing guidelines recommend use be reserved for patients with acute hepatic encephalopathy and a history of benzodiazepine use.^{11,22} Additional research is necessary to prospectively identify responders, provide dosing considerations, and evaluate adverse events. There is no known survival benefit.

Ethanol Intoxication

Animal studies indicate that many of the actions of ethanol are mediated through GABA neurotransmission.⁶⁵ Acute ethanol administration appears to enhance GABA transmission and inhibit N-methyl-D-aspartate excitation. Chronic ethanol administration leads to downregulation of the GABA system. Ethanol enhances GABA_A induced chloride influx in a dose-dependent fashion without a direct effect on chloride. Flumazenil does not influence this action of GABA. Chronic ethanol use selectively increases the sensitivity to inverse benzodiazepine agonists, invoking a change in coupling or conformation of the receptor. These changes may explain the development of tolerance and the kindling and production of seizures that occur on ethanol withdrawal.

A randomized, double-blind, crossover study of eight male volunteers given IV ethanol to achieve a constant serum ethanol concentration of 160 mg/dL was conducted.¹⁶ Once stabilized, the volunteers were given either placebo or 5 mg flumazenil. Subjective and objective psychomotor tests were conducted, with no differences noted between volunteers

given flumazenil and volunteers given placebo. Thus the probability of ethanol reversal at the doses achieved appears unlikely.

Based on this information, flumazenil likely does not have a significant effect on ethanol intoxication, and low doses of flumazenil (< 1 mg) have no effect.^{44,47} The 5 mg doses reportedly produce favorable changes in sensorium, but these findings may be the result of confounding factors. Because we would not administer 5 mg flumazenil in the overdose setting to avoid the increased risk of adverse effects at this dose, flumazenil cannot be recommended for reversal of ethanol intoxication.

ADVERSE EFFECTS AND SAFETY ISSUES

Flumazenil has been studied in more than 3500 patients worldwide, including healthy volunteers and overdosed patients, or patients who had undergone conscious sedation. The safety of flumazenil in healthy volunteers is well established, with no discernible objective or subjective effects. However, seizures in benzodiazepine-dependent patients, dysrhythmias in patients who coingest a benzodiazepine and a prodysrhythmic xenobiotic, and resedation within 20 to 120 minutes in patients receiving benzodiazepines for conscious sedation are recognized adverse events associated with flumazenil administration.

The ability of flumazenil to precipitate acute benzodiazepine withdrawal seizures in a more controlled environment than the overdose setting was demonstrated by reversal of long-term benzodiazepine sedation in the intensive care unit. A study of 1700 patients revealed that 14 patients developed adverse drug reactions—probably one-half of these reactions were related to abrupt arousal.⁶ Two patients with a history of epilepsy developed tonic-clonic seizures, and one patient developed myoclonic seizures.⁶ Dose-dependent induction of withdrawal reactions is therefore suggested. Small total doses (< 1 mg) of titrated flumazenil may allow sufficient occupation of the benzodiazepine receptor sites by benzodiazepines to limit the occurrence of withdrawal seizures.

In a study of 12 patients receiving midazolam sedation for 4 ± 3 days, 0.5 mg flumazenil was administered as a rapid bolus. Serum norepinephrine and epinephrine concentrations rose within 10 minutes, returned to baseline within 30 minutes, and correlated with increased heart rate, blood pressure, and myocardial oxygen consumption.³⁸

Flumazenil causes a significant overshoot in cerebral blood flow and may cause a large increase in intracranial pressure in patients who receive midazolam for severe head injury.⁷⁵

Thirty published case studies involving 758 patients with drug overdoses were reviewed.²⁵ In total, 387 patients participated in double-blind study protocols and 371 patients in open-label studies.²⁵ Fifty percent of cases were of mixed overdoses. The doses of flumazenil ranged from 0.2 to 5 mg. Five cases of seizures were temporally related to flumazenil administration, all after large bolus doses. In three of the five patients, high concentrations of tricyclic antidepressants were present in the blood. The seizures resolved either without treatment or following administration of a small dose of a benzodiazepine. Dysrhythmias developed in two patients given small doses of flumazenil, both presumably associated with the presence of a tricyclic antidepressant. Of 497 patients enrolled in two clinical US studies sponsored by the manufacturer,²⁵ six patients developed seizures (five had coingested tricyclic antidepressants) and one patient who had taken a tricyclic antidepressant and carbamazepine had a junctional tachycardia, which normalized after several minutes. Thus, in reviewing 1255 patients, 11 patients had seizures and three developed dysrhythmias, for an incidence of approximately 0.9%. The consensus report was that (a) flumazenil is not a substitute for primary emergency care, (b) hypoxia and hypotension should be corrected before flumazenil is used, (c) when used, small titrated doses of flumazenil should be given, (d) flumazenil should not be used in patients with a history of seizures, evidence of seizures or jerking movements, or evidence of a tricyclic antidepressant overdose, and (e) flumazenil should not be used by inexperienced clinicians.

An analysis of all seizures associated with flumazenil gathered from previously published cases or reports to the manufacturer was published.⁶⁴ Forty-three patients had seizures and six patients died, but the author believed that none of the deaths were attributable to flumazenil.⁶⁴ Four patients developed status epilepticus; two were presumed to be caused by concomitant tricyclic antidepressant exposure, and the other two patients had received benzodiazepines to treat status epilepticus prior to flumazenil therapy. In six of 43 seizure episodes, the relationship to flumazenil use was believed to be inadequately defined. The remaining 37 patients were stratified into five categories. In category 1, seven patients were given flumazenil after they had received a benzodiazepine for treatment of a seizure disorder. Six of these seven patients received greater than 1 mg flumazenil. In category 2, 20 patients received flumazenil for reversal of a benzodiazepine in a mixed-drug overdose. Many of these patients had coingested tricyclic antidepressants. Thirteen of these patients received more than 1 mg flumazenil. Two of the patients in this group developed status epilepticus and died, possibly secondary to a severe tricyclic antidepressant overdose. Category 3 included five patients who received benzodiazepines for suppression of non-drug-induced seizures. Two of these five patients received more than 1 mg flumazenil. Category 4 included three patients with acute benzodiazepine overdoses in the presence of chronic benzodiazepine dependence. Category 5 included two patients who received a benzodiazepine for conscious sedation. Therefore, flumazenil use may place the patient at risk

for seizures by unmasking a toxic effect in mixed overdose, by removing the protective anticonvulsant effect in a patient with non-drug induced seizures, or by precipitating acute benzodiazepine withdrawal. Table A22–3 summarizes the contraindications and precautions to flumazenil use.

TABLE A22–3. Contraindications to Flumazenil Use	
History	Clinical
Seizure history or current treatment of seizures	Potential ECG evidence of cyclic antidepressant use: terminal rightward 40 ms axis, QRS or QT prolongation
Ingestion of a xenobiotic capable of provoking seizures or cardiac dysrhythmias	Hypoxia or hypoventilation*
Long-term use of benzodiazepines	Hypotension
	Head trauma

* = do not rely on flumazenil to reverse benzodiazepine induced respiratory depression.

Flumazenil has not consistently reversed benzodiazepine induced respiratory depression and is not suggested as the initial intervention should respiratory depression occur.^{21,46,50,62} It is likely that following oral overdose, benzodiazepine-induced respiratory insufficiency is related to smooth muscle relaxation resulting in a mechanical effect with an increase in upper airway resistance and obstructive apnea rather than a central effect.³² Although flumazenil might improve the clinical situation,^{32,55} other standard procedures such as airway repositioning, supplemental oxygen, bag-valve-mask ventilation, and endotracheal intubation, if indicated, should be used either prior to or during reversal.

PREGNANCY AND LACTATION

Flumazenil is US Food and Drug Administration (FDA) pregnancy category C. There are no adequate studies done in pregnant women.²¹ It is not known whether flumazenil is excreted in breast milk.²¹

DOSING AND ADMINISTRATION

Slow IV titration (0.1 mg/min), and waiting one minute between doses, to a total dose no higher than 1 mg seems most reasonable. Administration into a large freely running vein minimizes the potential for pain at the injection site. Resedation may occur at 20 to 120 minutes, and readministration of flumazenil may be necessary. Although not approved by the FDA, continuous IV infusion of flumazenil 0.1 to 1.0 mg/h in 0.9% sodium chloride solution or 5% dextrose in water has been used following the loading dose.^{43,72,74}

FORMULATION

Flumazenil is available by many manufacturers in a concentration of 0.1 mg/mL with parabens in 5 and 10 mL vials.

SUMMARY

- The risks of flumazenil appear to greatly outweigh the potential benefits of reversal when benzodiazepines are used chronically or acutely to treat a seizure disorder.
- Flumazenil is best avoided in the overdose setting when evidence indicates coingestion of a drug capable of causing seizures or dysrhythmias.
- Flumazenil should also not be used when involvement of a tricyclic antidepressant is strongly suggested based on history, clinical findings, or findings on electrocardiography (prolonged QRS complex).^{35,45,51,70}
- Any indication that theophylline, carbamazepine, chloral hydrate, chloroquine, and or chlorinated hydrocarbons was ingested is a contraindication to flumazenil use.⁷⁰
- In the event of flumazenil induced seizure, a therapeutic dose of a benzodiazepine such as diazepam or lorazepam should be effective; however, due to the competitive nature of flumazenil, higher doses will be necessary to reverse higher doses of flumazenil.

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75 SEROTONIN REUPTAKE INHIBITORS AND ATYPICAL ANTIDEPRESSANTS

Christine M. Stork

INTRODUCTION

In the United States, major depressive disorder is a leading cause of disability and affects 14.8 million American adults; it is also the largest cause of disability for adolescents and those 15 to 44 years of age.^{1,93} Although major depressive disorder can develop at any age, the median age at onset is 32 years and it is more prevalent in women.^{94,95} The exact etiology of depression and the mechanism by which increased serotonergic and norepinephrine neurotransmission modulates mood remains unclear. Antidepressants modulate the activity of serotonin and norepinephrine and dopamine to achieve their effect. The class of selective serotonin reuptake inhibitors (SSRIs) includes citalopram, escitalopram (active enantiomer of citalopram), fluoxetine, fluvoxamine, paroxetine, sertraline, and vilazodone (Fig 75–1). Atypical antidepressants extend the pharmacologic principles of SSRIs to achieve beneficial effects for patients with depression. The SSRIs and atypical antidepressants comprise the current standard for the treatment of depression.⁸⁰ SSRIs also are used to treat obsessive–compulsive disorders, panic disorders, alcoholism, obesity, and various nonpsychiatric disorders such as migraine headaches and chronic pain syndromes.^{11,125,131} They have excellent safety profiles when compared with monoamine oxidase inhibitors (MAOIs) and the cyclic antidepressants. Like many xenobiotics, the appropriateness of their use and the associated morbidity and mortality is questioned as the patient population has aged and the comorbidity profiles of those using the SSRIs have changed.

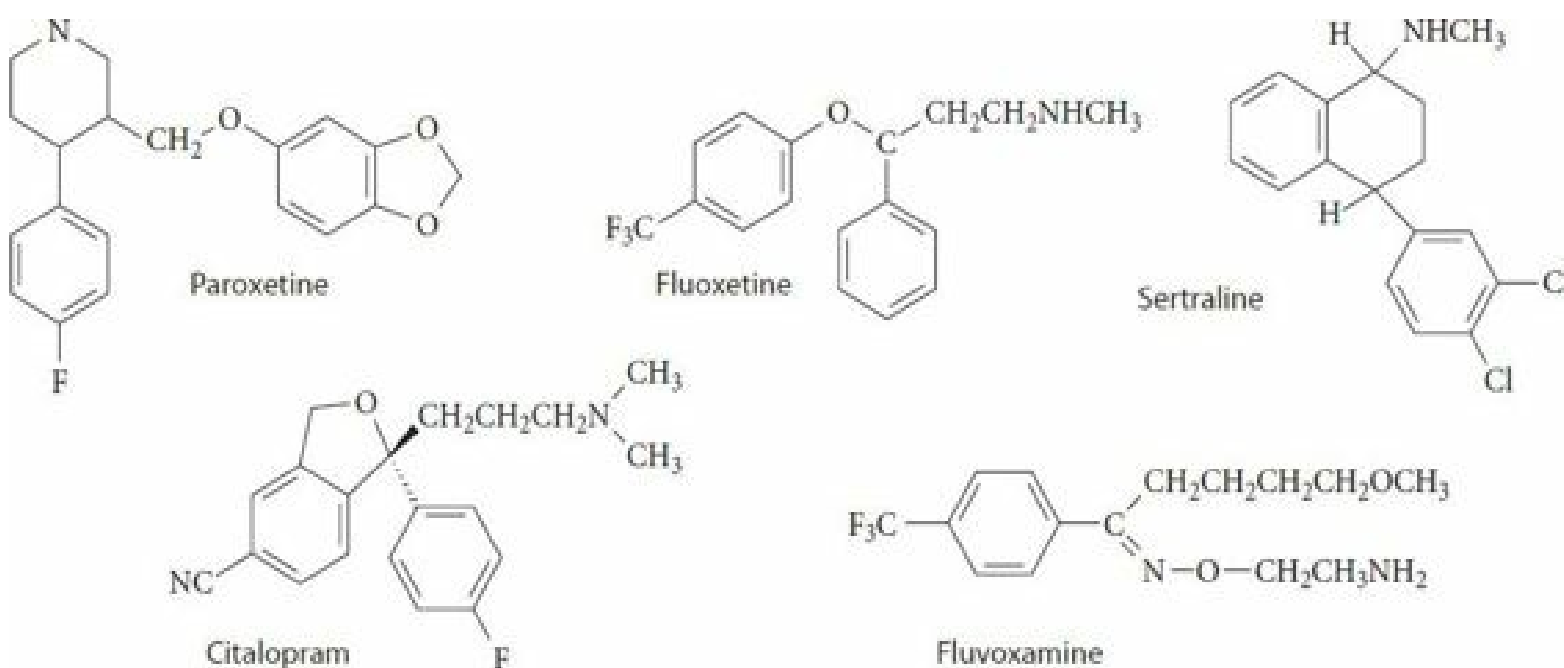


FIGURE 75–1. Structures of common selective serotonin reuptake inhibitors. Citalopram is shown as the S-enantiomer (escitalopram).

HISTORY AND EPIDEMIOLOGY

Serotonin (5-hydroxytryptamine) got its name after its initial discovery as a vasoconstrictor. Synonyms for 5-hydroxytryptamine include thrombotin, enteramin, substance DS, and 3-(β-aminoethyl)-5-hydroxyindole. SSRIs initially were marketed in the United States in the early 1980s and still are considered a first-line therapy for treatment of depressive disorders in the United States and Europe.⁶³ SSRIs are as effective as the cyclic antidepressants and MAOIs for the treatment of major depression and have fewer significant adverse events associated with their therapeutic use and are

less problematic in overdose (Chaps. 71 and 73). An increased risk of suicidal behavior is reported with the use of many antidepressants compared with herbals or counseling alone.¹⁰⁸ This is particularly true in children and adolescents, and may be related to delayed onset of therapeutic efficacy coupled with increased energy associated with the initiation of therapy.

PHARMACOLOGY

Table 75–1 lists the pharmacology, therapeutic doses, and metabolism of available SSRIs and atypical antidepressants. Modulation of serotonin and norepinephrine neurotransmission has a significant role in the treatment of depression.¹⁴⁶ There are seven widely known classes of serotonin receptors, with many exhibiting subtype classifications (Chap. 14). SSRIs selectively inhibit serotonin reuptake via the serotonin transporter due to the p-trifluoromethyl or p-fluoro substitution, present in many of these xenobiotics.¹⁸² Serotonin neurons are located almost exclusively in the median raphe nucleus of the brainstem, where they extend into and are in close proximity to norepinephrine neurons that are located primarily in the locus ceruleus (Fig. 75–2).¹⁰ The interplay between norepinephrine and serotonin likely explains the effectiveness of antidepressants that do not directly modulate serotonin neurotransmission.

TABLE 75–1. Drug Mechanism and Drug Information for Currently Available SSRIs and Atypical Antidepressants^a

Drug	Typical Daily Dose Range (mg)	<i>t</i> _{1/2} (hours)	Major Metabolic Enzyme	Major Active Metabolites	Major Active Metabolite <i>t</i> _{1/2}	Drug (s) or Metabolite (s) Inhibit CYP
SSRIs						
Citalopram (Celexa)	20–60	35–37	CYP19, 3A4, 2D6	Monodemethyl citalopram, didemethyl citalopram	59 hours	None/unknown
Escitalopram (Lexapro)	10–20	23–32	CYP19, 3A4, 2D6	S-(+)-Desmethylescitalopram	59 hours	None
Fluoxetine (Prozac) also sold as Sarafem	10–60	24–164	CYP2D6	Normofluoxetine	4–16 days	2D6 (d,l), CYP19 (d,l), 2D6 (d,l), 3A4 (m)
Fluvoxamine (Luvox)	100–300	15–29	1A2, 2D6	None	N/A	1A2, CYP19, 3A4
Paroxetine (Paxil)	10–50	23–44	2D6	None	N/A	2D6
Sertraline (Zoloft)	50–200	24	CYP19, 2D6, CYP19, 2D6, 3A4	Desmethysertraline	62–104 hours	CYP19 (d,l)
Venlafaxine (Effexor) also partial serotonin 5-HT _{2A} agonist	10–60	25	3A4, CYP19, 2D6	None	N/A	None/unknown
SSRI with α_1-adrenergic antagonism						
Trazodone (Desyrel)	50–600	5–9	2D6, 3A inhibition may increase concentration	Meta-chlorophenylpiperazine	?	None/unknown
SSRI with inhibition of reuptake of norepinephrine						
Desvenlafaxine (Provig)	50	11	CYP2D6, 2D6	None, unknown	N/A	None/unknown
Duloxetine (Cymbalta)	40–60	8–17	2D6, 1A2	None	N/A	2D6
Milnacipran (Savella)	25–200	8	Glucuronidation	None	N/A	None
Venlafaxine (Effexor)	75–225	3–4	2D6	O-desmethylenefluoxetine, depends on 3A4 and CYP19 for metabolism	10 hours	None/unknown
SSRI with α_1-adrenergic antagonism 5-HT_{2A}/5-HT_{2C} antagonist						
Mirtazapine (Remeron)	15–45	20–40	3A4	Desmethylnortazapine	Unknown	3A4 induction
Inhibition of reuptake of biogenic amines or dopamine						
Bupropion (Wellbutrin, Zyban)	150–450	9.6–20.9	2D6	Hydroxybupropion, erythrohydroxybupropion, thiohydroxybupropion	24–37 hours	None/unknown

^aThe *t*_{1/2} of all these compounds is large enough to consider.

SSRIs = selective serotonin reuptake inhibitors.

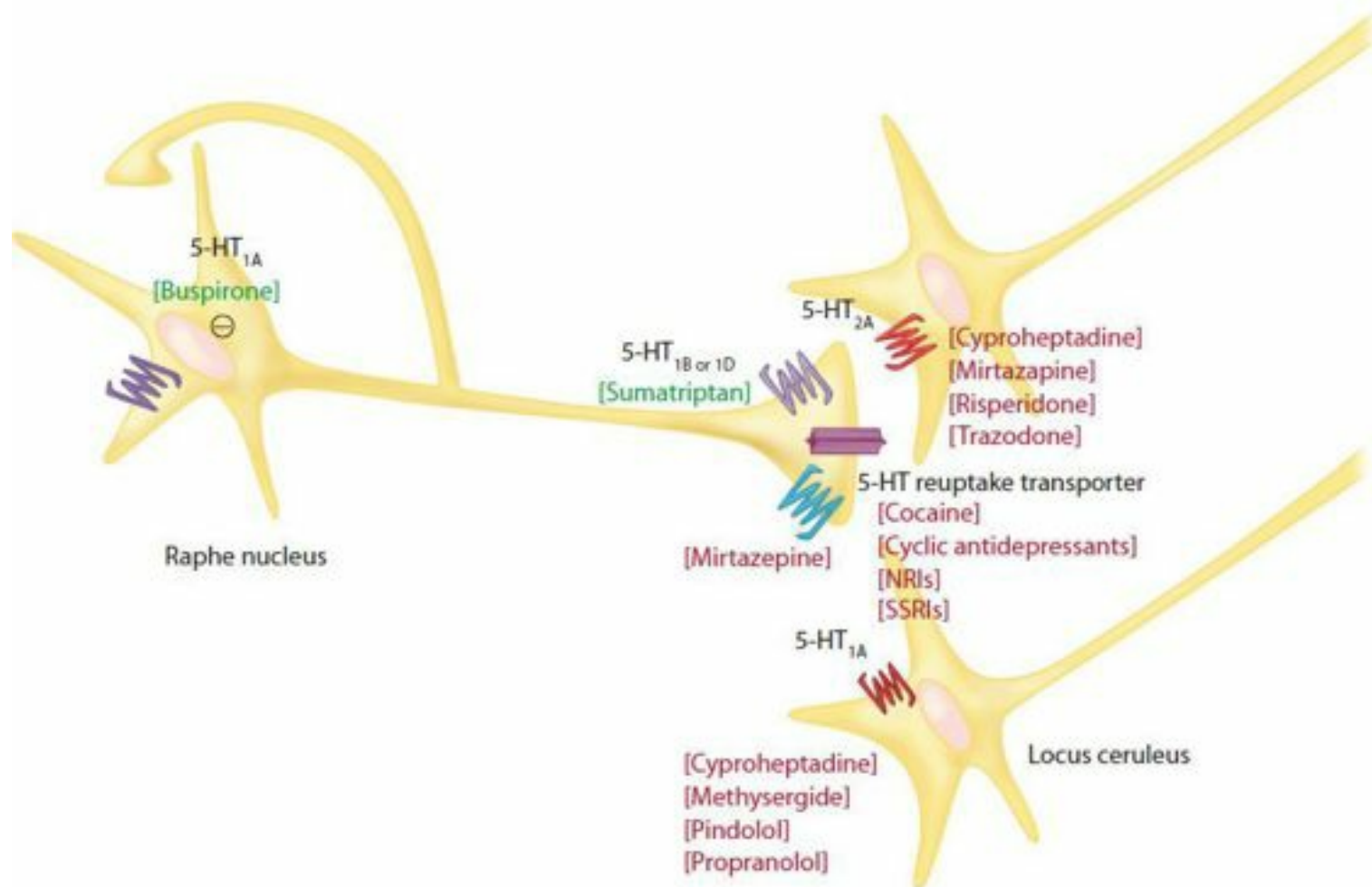


FIGURE 75–2. Neuroanatomy and effects of several common therapeutic drugs on serotonin neurotransmission in the brain. (Xenobiotics in green are agonists and those in red are antagonists.) NRIs = nonspecific reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

PHARMACOKINETICS AND TOXICOKINETICS

The SSRIs display diverse elimination patterns and have numerous active metabolites, which substantially increase both the duration of therapeutic effectiveness and the duration during which drug interactions and adverse drug effects can occur after the medication is discontinued (Table 75–1). Important pharmacokinetic and pharmacodynamic drug interactions are reported with therapeutic dosing (see Serotonin Toxicity). The SSRIs and their active metabolites are substrates for—and potent inhibitors of—CYP2D6 and other CYP isoenzymes.^{73,147} For example, fluoxetine, fluvoxamine, citalopram, venlafaxine, mirtazapine, paroxetine, and sertraline are substrates for CYP2D6, whereas paroxetine, norfluoxetine, and fluoxetine inhibit the same enzyme (Table 75–1). Alternatively, mirtazapine induces CYP3A4 enzymes, while trazodone and vilazodone metabolism may be decreased after this same enzyme is inhibited.^{160,163} The consequences of these interactions manifest when the metabolism of medications that rely on these enzymes for metabolic transformation is altered (Chap. 13). Genetic polymorphism typing holds promise in identifying patients at highest risk for both adverse drug events and antidepressant efficacy with therapeutic dosing.^{90,91}

PATHOPHYSIOLOGY

The causes of depression and mechanism by which antidepressants ameliorate depressive symptoms are not well understood. Some postulated causes of depression include decreased neuronal serotonin storage, decreased synaptic serotonin, increased serotonin receptor sensitivity, and serotonin over activity resulting in depressed dopamine neurotransmission.^{146,162,176,181} Others postulate that physiologic stress and associated atrophy of dendritic processes with a loss of neurons and glial elements occur.¹⁶ These changes were most pronounced in the prefrontal cortex and the hippocampus on autopsy of depressed patients. It is unclear how these changes occur, although it is likely that complex signaling pathways including disruptions in synaptic proteins and synaptic activity are contributory. In addition to the direct pharmacologic effect of increasing synaptic concentrations of serotonin, antidepressants increase neurogenesis in the prefrontal cortex and glia in oligodendrocytes and activate complementary factors such as brain derived neurotrophic factor and mitogen-activated protein kinase. The requirement for these endogenous mediators may explain previous research

finding no difference in the concentration of serotonin-binding sites or serotonin receptor activity between depressed patients who respond to SSRIs and those who do not respond.^{31,151} Although the causes of depression are diverse and not well understood, genetic polymorphisms of the serotonin transporter may also be involved with individual responses to SSRI therapy.¹⁴² Unlike cyclic antidepressants and other atypical antidepressants, SSRIs have little direct interaction with cholinergic receptors, γ -aminobutyric acid receptors, sodium channels, or adrenergic reuptake (Table 75–2).

TABLE 75–2. Receptor Activity of SSRIs and Related Antidepressants

Drug	Mechanism	Degree of Norepinephrine Reuptake Inhibition	Degree of Serotonin Reuptake Inhibition	Degree of Dopamine Reuptake Inhibition	Degree of Peripheral α -Adrenergic Agonism
SSRIs					
Citalopram (Celexa)	SSRI, antimuscarinic	0	++++	0	0
Escitalopram (Lexapro)	SSRI	0	++++	0	0
Fluoxetine (Prozac)	SSRI	0	++++	0	0
Fluvoxamine (Luvox)	SSRI	0	++++	0	0
Paroxetine (Paxil)	SSRI, antimuscarinic	+	++++	+	0
Sertraline (Zoloft)	SSRI	0	++++	+	+
Valazodone (Vibryd)	SSRI, 5-HT _{1A} agonist	0	++++	0	0
Other					
Bupropion (Wellbutrin, Zyban)	Inhibits reuptake of biogenic amines	++	+	+	+++
Duloxetine (Cymbalta)	SRI, norepinephrine reuptake inhibitor	++	++++	0	++
Desvenlafaxine (Pristiq)	SRI, norepinephrine reuptake inhibitor	++	++++	0	++
Milnacipran (Savella)	SRI, norepinephrine reuptake inhibitor	++	++++	0	0–+
Mirtazapine (Remeron)	α_2 -Adrenergic antagonism, 5-HT ₂ /5-HT ₁ antagonism	0	++++	0	+
Reboxetine (Edronax, Vestra)	Selective norepinephrine reuptake inhibitor	++++	0	0	++++
Trazodone (Desyrel)	SRI, α_1 -adrenergic antagonist	0	+	0	0–+
Venlafaxine (Effexor)	SRI, norepinephrine reuptake inhibitor	++	++++	0	++

+ = weak if any agonism; ++ = weak agonism; +++ = strong agonism; ++++ = very strong agonism; 0 = no effect.

SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

CLINICAL MANIFESTATIONS

Most effects that occur following overdose are direct extensions of the pharmacologic activity of SSRIs in therapeutic doses. Excess serotonergic stimulation is prominent and nonselective. Acute signs and symptoms include nausea, vomiting, dizziness, blurred vision, and, less commonly, central nervous system (CNS) depression and sinus tachycardia.^{26,28} Seizures and changes on electrocardiography (ECG), including prolongation of the QRS complex and QT interval duration, have been reported, but they rarely occur with most SSRIs, even after large overdoses (Table 75–3).^{88,143} Infrequently, SSRI overdose results in life-threatening effects. In two fatalities, the patient reportedly ingested 40 to 75 times the maximum daily dose of fluoxetine. Serum fluoxetine concentrations were 4500 and 6000 ng/mL, with the latter including a measured norfluoxetine concentration of 5000 ng/mL, which was more than 10 times higher than the therapeutic steady state serum.^{38,97}

TABLE 75–3. Predictive Analysis of the Relative Potential for Seizures and Abnormalities on Electrocardiography of SSRIs and Related Antidepressants

Drug	Seizures	QT Prolongation	QRS Prolongation
Classic SSRIs			
Citalopram (Celexa)	+++	+++	0—+
Escitalopram (Lexapro)	+++	+++	0—+
Fluoxetine (Prozac)	+	0	0—+
Fluvoxamine (Luvox)	+	0	0—+
Paroxetine (Paxil)	+	0	0—+
Sertraline (Zoloft)	+	0	0—+
Valazodone (Viibryd)	Unknown	Unknown	Unknown
Atypical Antidepressants			
Bupropion (Wellbutrin, Zyban)	++++	0—+	+
Desvenlafaxine (Pristiq)	+++	0—+	+++
Duloxetine (Cymbalta)	++++	Unknown	Unknown
Milnacipran (Savella)	Unknown	Unknown	Unknown
Mirtazapine (Remeron)	Unknown	Unknown	++
Reboxetine (Edronax, Vestra)	++++	Unknown	Unknown
Trazodone (Desyrel)	+	0	0
Venlafaxine (Effexor)	+++	0—+	+++

0 = does not cause; + = very rarely causes; ++ = rarely causes; +++ = causes; ++++ = very commonly causes.

SSRI = selective serotonin reuptake inhibitor.

Citalopram

Citalopram and its S(+) enantiomer escitalopram cause QT interval prolongation and seizures in a dose-related manner.¹⁷³ These effects are reported at doses as low as 400 mg for citalopram and 190 mg for escitalopram.^{35,185} In large case series, these effects typically occur after ingestions exceeding 600 mg citalopram or in patients with serum concentrations more than 40 times the expected therapeutic concentrations.^{74,138,139} In two of these series, seizures were an early finding, occurring within 2 hours, whereas the development of abnormalities on ECG were delayed for as long as 24 hours following ingestion.^{86,139} One case report, with concentrations at least 10 times the maximum therapeutic serum concentrations, documented prolongation of the QT interval and torsade de pointes occurring 32.5 hours after ingestion. Concentrations of citalopram and desmethylcitalopram were 477 mg/mL and 123.2 mg/mL, respectively.¹⁷¹

Although the mechanisms are unclear, experimental models suggest that the didesmethylcitalopram metabolite of citalopram prolongs the QT interval by blocking I_{Kr} , whereas high concentrations of both the parent drug and this metabolite result in seizures (Chaps. 16 and 64).^{25,32} The elimination half-life of the R-enantiomer of citalopram exceeds that of the S-enantiomer.¹⁷⁷ The implications of this difference on the formation and effects of racemic forms of didesmethylcitalopram are unclear.

Vilazodone

Vilazodone is a relatively new SSRI that is also a 5-HT_{1a} agonist. Although little data exist regarding vilazodone in overdose, the drug is expected to have similar effects to other SSRIs.²

MANAGEMENT

Treatment of patients with acute SSRI overdose is largely supportive. Dextrose and thiamine should always be considered for patients who present with altered mental status. Although cardiac manifestations after SSRI overdose are rare, a 12-lead ECG should be obtained to identify other cardiotoxic drugs, such as cyclic antidepressants, to which the patient may have access (Chaps. 16, 70, and 71). If overdose of citalopram or escitalopram is suspected, then 24 hours of cardiac monitoring is recommended to exclude the possibility of delayed QT interval prolongation and subsequent risk for ventricular dysrhythmias. After the patient is stabilized, oral activated charcoal (1 g/kg) may be useful to adsorb drug remaining in the gastrointestinal tract. In fact, lowering of blood concentrations and reduction in risk for QT interval prolongation is demonstrated when activated charcoal is given shortly after escitalopram and citalopram ingestion.^{58,59,174} Patients with small unintentional overdoses of SSRIs other than citalopram and escitalopram are not expected to develop

significant signs and symptoms of poisoning. Patients with well defined unintentional ingestions of up to 100 mg of citalopram and 50 mg of escitalopram can usually be managed safely at home with close observation.¹²⁷ Fatalities resulting from SSRIs are rare and most commonly occur after multiple drug ingestions and manifestations of drug interactions resulting from excess serotonergic effects (see Serotonin Toxicity).⁶⁸ Forensic analysis of individual cases of intentional ingestions suggests the minimum lethal concentrations of fluoxetine, paroxetine, and sertraline after isolated overdose are 0.63, 0.4, and 1.5 mg/L, respectively. Postmortem concentrations in case reports include a citalopram heart blood concentration of 3.35 mg/L, a whole blood concentration of 11.6 mg/L, and urine concentrations of 32.43 to 149.67 mg/L.^{84,114} When mono-N-desmethylcitalopram was measured, concentrations of 1.02 mg/L were found in the blood and 12.1 mg/L in the urine. An infant survived with citalopram plasma mono-N-desmethylcitalopram concentrations of 1.4 mg/L.¹¹⁷

ADVERSE EVENTS AFTER THERAPEUTIC DOSES

Adverse events commonly associated with therapeutic doses of SSRIs as well as with overdose include gastrointestinal symptoms such as anorexia, nausea, vomiting, diarrhea, sexual dysfunction—in both men and women—headache, insomnia, jitteriness, dizziness, and fatigue.¹⁸³ Less common adverse events include sedation, particularly following citalopram and paroxetine, which result from their weak anticholinergic activity, and anxiety following fluoxetine treatment.¹¹⁰ Serotonin activity inhibits platelet secretory response, platelet aggregation, and platelet plug formation.²¹ Although the effect increases in SSRIs with increased potency, clinical bleeding is rare, and significant only in patients concurrently on other antiplatelet medications, most notably aspirin.^{34,36} This effect may be of potential benefit in patients at risk for cardiovascular events.¹¹⁸ Other rarely reported adverse events include new-onset panic disorder, priapism, bradycardia, hepatotoxicity, and urinary incontinence.^{4,20,29,48,100,122,164} Movement disorders, most commonly akathisia, parkinsonism, myoclonus, and dystonia, also occur after SSRI use.^{7,154} These extrapyramidal adverse events may be related to the complex interplay between serotonergic and dopaminergic activity. Predisposing factors for the development of movement disorders include concomitant use of dopamine antagonists such as the antipsychotics.¹⁰⁴

The syndrome of inappropriate antidiuretic hormone (SIADH; Chap. 19) in which severe hyponatremia may occur rapidly is associated with SSRI use. In an animal model, the effect appears to be serotonin mediated, with increased concentrations of serum cortisol, adrenocorticotropin, and vasopressin reported.⁶¹ Rat studies demonstrated that stimulation of 5-HT_{1C} receptors increases antidiuretic hormone secretion.¹³⁷ However, human case control studies have not confirmed defects in osmoregulated release of vasopressin using water loading tests and measurement of vasopressin concentrations after 3 to 11 months of paroxetine use.¹¹⁶ A review of the literature identified women older than 70 years concomitantly receiving diuretic therapy and with low baseline serum sodium concentrations were at greatest risk for developing SIADH.^{22,98} Although reported to occur from 3 days to 4 months after initiation of therapy, a case-matched control study of 203 patients identified that SIADH occurs most frequently within the first 2 weeks of therapy.¹²¹ Hyponatremia may occur when switching from one SSRI to another.⁹ Efforts to predict risk through poor CYP2D6 genotype metabolizer status or high serum concentrations have not been successful.¹⁶⁷ Patients older than 50 years of age using SSRIs may be at increased risk for bone fracture presumably due to a serotonergic effect on osteoblasts and osteoclasts.¹⁴⁵ However, depression itself is also implicated in decreasing bone density in adults and children and the implications of these findings are unknown.¹⁷⁹

Serotonin Toxicity

The most common severe adverse event associated with SSRIs is the development of the serotonin toxicity. This is also referred to in life-threatening cases as serotonin syndrome and serotonin behavioral or hyperactivity syndrome. It was first described in patients treated with MAOIs who were given other xenobiotics that enhance serotonergic activity.^{37,72,130,161} However, ingestion of an MAOI is not required for serotonin toxicity to develop, and its occurrence is unpredictable (Table 75–4).

TABLE 75–4. Potential Causes of Serotonin Toxicity

Inhibitors of Serotonin Metabolism

Linezolid

Methylene blue

Monoamine oxidase inhibitors (nonselective)

Phenelzine, moclobemide, clorgyline, isocarboxazid

Harmine and harmaline from Ayahuasca preparations, psychoactive beverage used for religious purposes in the Amazon and Orinoco River basins³³

Blockers of Serotonin Reuptake

Bupropion¹²³

Clomipramine

Cocaine

Dextromethorphan¹⁵⁵

Fentanyl

Meperidine

Pentazocine

SSRIs

Citalopram

Fluoxetine

Fluvoxamine

Milnacipran

Paroxetine

Sertraline

Tramadol^{99, 135}

Trazodone

Venlafaxine

Serotonin Precursors or Agonists

L-tryptophan

Lysergic acid diethylamide (LSD)

Enhancers of Serotonin Release

Amphetamines, especially MDMA

Methylone

Buspirone

Butylone

Cocaine

Lithium

Mirtazapine

Pathophysiology. The pathophysiologic mechanism of serotonin toxicity is not completely understood but involves excessive selective stimulation of serotonin 5-HT_{2A} and perhaps 5-HT_{1A} receptors.²⁷ Animal models demonstrate that specific stimulation of 5-HT_{1A} receptors results in signs and symptoms of serotonin toxicity even when 5-HT_{2A} receptors were inactivated using a specific antagonist.⁴¹ However, a subsequent animal study and a human retrospective case series showed that the potency of 5-HT_{2A} antagonist therapy was directly related to resolution of the findings attributed to serotonin toxicity.⁶⁵ 5-HT_{1D} receptors are not implicated in cases of serotonin toxicity.

Serotonin toxicity occurs most frequently following use of combinations of serotonergic xenobiotics (Table 75–4), but may occur following high therapeutic dosing or overdoses of single serotonergic xenobiotics.^{40,77,92,133} Interactions resulting in serotonin toxicity can occur while switching serotonergic xenobiotics, particularly when an insufficient time lag occurs before initiating the alternative therapy.¹¹² Residual pharmacologic effects, receptor downregulation or upregulation, and the presence of active metabolites may be causative in these circumstances. For example, fluoxetine metabolism results in the active metabolite norfluoxetine, which has comparable pharmacologic effects and a half-life substantially longer than fluoxetine. The clearance of norfluoxetine takes approximately 2 weeks.

Although sporadic reports occur, selective MAO subtype B (MAO-B) inhibitor drug combinations and triptans (5-HT_{1B/1D} receptor agonists) are rarely reported to result in serotonin toxicity at therapeutic doses.^{53,56}

Manifestations. Signs of serotonin toxicity include altered mental status, agitation, tachycardia, myoclonus, hyperreflexia, diaphoresis, tremor, diarrhea, incoordination, muscle rigidity, and hyperthermia (Table 75–5). The clinical manifestations of serotonin toxicity are diverse, and minor manifestations are common after initiation of SSRI and atypical antidepressant therapy. In fact, a prospective study of depressed inpatients given clomipramine demonstrated that 16 of the 38 patients experienced manifestations consistent with the serotonin toxicity, with 14 having spontaneously resolution within one week without discontinuation of therapy.¹⁰⁷ Life-threatening effects invariably result from hyperthermia caused by excessive muscle activity that may be more prominent in the lower extremities. Sustained severe hyperthermia can lead to death through denaturation of essential protein and enzymatic function that ultimately results in elevated lactate and metabolic acidosis, rhabdomyolysis, renal and hepatic dysfunction, disseminated intravascular coagulation, or acute respiratory distress syndrome (Chap. 30).^{120,169}

TABLE 75–5. Diagnostic Criteria for Serotonin Toxicity

When a Serotonergic Xenobiotic Is Introduced

- Spontaneous clonus alone
- [Inducible or ocular clonus] with [agitation or diaphoresis]
- [Inducible or ocular clonus] with hypertonicity and fever (temperature > 100.4°F {38°C})
- Tremor with hyperreflexia

Adapted from Dunkley et al.⁵²

Diagnosis. Although fulminant life-threatening cases are easy to recognize, mild cases of serotonin toxicity are more difficult to distinguish from similar appearing disorders due to other causes. In an effort to determine diagnostic criteria, a study that included 38 cases of presumed serotonin toxicity suggested diagnostic criteria to include three of the following signs and symptoms—altered level of consciousness, agitation, myoclonus, hyperreflexia, diaphoresis, tremor, diarrhea, and incoordination—when other etiologies were excluded.¹⁶⁹ A modification, the Hunter Serotonin Toxicity Criteria, which included the variables myoclonus, agitation, diaphoresis, hyperreflexia, hypertonicity, and fever, was validated in 473 patients and found to correlate best with a clinical toxicologic diagnosis of serotonin toxicity (Table 75–5).⁵² Currently, no diagnostic test capable of determining whether a patient is experiencing serotonin toxicity is available. A single case report demonstrated increased urinary serotonin concentrations after serotonin toxicity.³⁹

Management. Treatment of patients with serotonin toxicity begins with supportive care and focuses on decreasing core body temperature and muscle activity. Because muscular rigidity is thought to be greatly responsible for hyperthermia and death, rapid external cooling in conjunction with aggressive use of sedative hypnotics such as benzodiazepines should limit complications and mortality (Chap. 30). In severe cases, neuromuscular blockade should be considered to achieve rapid muscle relaxation. The time course of the serotonin toxicity is variable and related to the time required to eliminate the offending xenobiotics. In most patients, the manifestations of serotonin toxicity resolve within 24 hours after the offending xenobiotic is removed. However, serotonin toxicity can be prolonged when it is caused by xenobiotics with long half-lives, protracted duration of effects, or active metabolites.

Animal models indicate that pretreatment with serotonin antagonists can prevent development of serotonin toxicity.^{64,83,165} Several case reports indicate the successful use of 4 mg oral cyproheptadine, an antihistamine with nonspecific serotonin antagonist effects at 5-HT_{1A} and 5-HT_{2A} receptors.^{72,105} Patients who typically responded had no hyperthermia and mild to moderate manifestations of serotonin toxicity. Evidence supports the use of cyproheptadine in this patient group. Current recommendation suggests doses of 8 to 16 mg orally repeated as needed. Further research is warranted to determine the success of higher doses given to gain sufficient 5-HT_{2A} antagonistic effects in more severely affected patients.⁶⁵ Other xenobiotics anecdotally reported to be successful for the treatment of symptoms caused by serotonin toxicity include methysergide, chlorpromazine, atypical antipsychotics, and propranolol.^{65,66,69,75,150} However, these therapies cannot be recommended at this time.

Differentiating Serotonin Toxicity from Neuroleptic Malignant Syndrome

Many features overlap between serotonin toxicity and the neuroleptic malignant syndrome (NMS; Chap. 70). Some authors call these “spectrum disorders” caused by drugs with antidopaminergic effects, proserotonergic effects, or both.¹⁶⁸ This position is supported by the finding that 5-HT_{2A} agonism results in an overall decrease in neuronal dopamine release. Some authors also report NMS after use of serotonin-enhancing xenobiotics. However, low concentrations of measured dopamine and normal concentrations of serotonin metabolites in NMS patients support the hypothesis of central dopaminergic hypoactivity in NMS.^{12,128} Although altered mental status, autonomic instability, and changes in neuromuscular tone that may result in hyperthermia are common to both disorders, many differences are apparent. It is now clear that the implicated xenobiotics, time course, pathophysiology, and manifestations are distinct (Table 75–6).⁶⁵ Signs and symptoms of serotonin toxicity develop within minutes to hours after exposure to the offending xenobiotics, whereas NMS typically develops days to weeks after daily exposure.⁷¹ In addition, after symptoms develop and offending xenobiotics are discontinued, NMS can last for as long as 2 weeks, whereas serotonin toxicity usually resolves quickly, and is directly correlated with the pharmacokinetic metabolic profile of the offending xenobiotic. A review of the literature indicates that patients presenting with serotonin toxicity are more likely to exhibit agitation, hyperactivity, clonus and myoclonus, ocular oscillations (opsoclonus), shivering, tremors, and lower limb hyperreflexia, whereas patients presenting with NMS were more likely to exhibit bradykinesia and lead pipe rigidity.⁶⁵

TABLE 75–6. Comparison of Neuroleptic Malignant Syndrome (NMS) and Serotonin Toxicity

	<i>NMS</i>	<i>Serotonin Toxicity</i>
Historical Diagnostic Clue		
Inciting drug pharmacology	Dopamine antagonist	Serotonin agonist
Time course of initiation of symptoms after exposure	Days to weeks	Hours
Duration of symptoms	Days to 2 weeks	Usually 24 hours
Symptoms		
Autonomic instability	+++	+++
Fever	+++	+++
Altered mental status (depressed/confusion)	+++	+++
Altered mental status (agitation/hyperactivity)	+++	+++
Lead pipe rigidity	+++	+
Tremor, hyperreflexia, myoclonus	+	+++
Shivering	–	+++
Bradykinesia	+++	–

– = not found; + = rare finding; +++ = common finding.

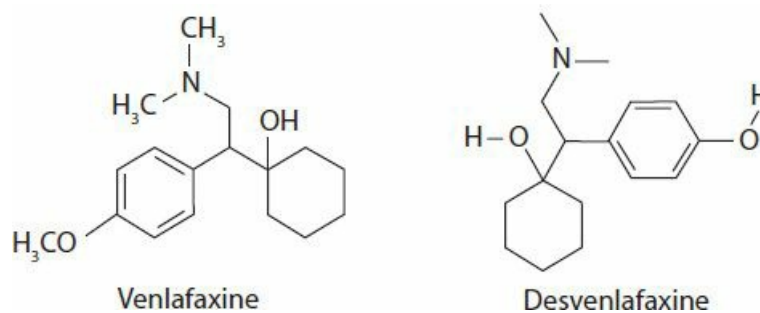
ATYPICAL ANTIDEPRESSANTS

Atypical antidepressants are defined as not belonging strictly to a set classification of antidepressants. They are not SSRIs, cyclic antidepressants, or MAOIs. Most are derivatives of SSRIs and have additional pharmacologic effects that were

selected in an attempt to decrease the undesirable side effects of traditional antidepressants.

Serotonin/Norepinephrine Reuptake Inhibitors

Venlafaxine.

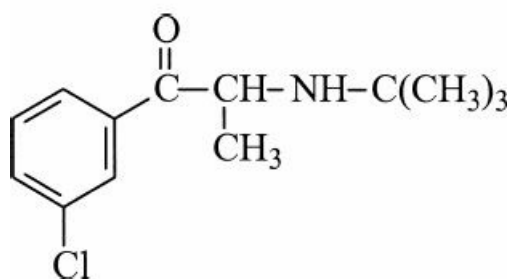


In addition to inhibiting serotonin reuptake, venlafaxine inhibits norepinephrine reuptake. Venlafaxine produces rapid downregulation of central β -adrenergic receptors, which may result in a faster onset of antidepressant effect.¹⁵⁶ Patients with acute venlafaxine overdose may present with nausea, vomiting, dizziness, tachycardia, CNS depression, hypotension, hypoglycemia, hyperthermia, hepatic toxicity, including zone 3 necrosis, rhabdomyolysis, and seizures^{57,134,158,180,186} (Chap. 23). Sodium and potassium channel blocking effects are rarely clinically apparent; however, QRS prolongation and QT prolongation may lead to ventricular tachycardia and result in death.^{17,24,149} One report indicated a positive incremental association of clinical toxicity with a maximum measured venlafaxine serum concentration of 25.8 $\mu\text{mol/L}$.¹¹⁹ Although no clinical data regarding efficacy are available, sodium bicarbonate may be helpful in attenuating the sodium channel blocking effects that leads to QRS prolongation (Antidotes in Depth: A5). In addition, gastrointestinal decontamination with activated charcoal with or without whole-bowel irrigation may decrease serum concentrations and decrease the incidence of seizures in select patients, particularly following the ingestion of extended-release formulations.^{102,103} Adverse events associated with chronic therapeutic doses of venlafaxine include alopecia, yawning, focal myositis facial flushing, and dose-related increases in blood pressure.^{46,49,54,87,136}

Desvenlafaxine, duloxetine, and milnacipran—similar drugs to venlafaxine—should be expected to have similar effects.^{51,101,109}

Other Atypical Antidepressants with Reuptake Inhibition as Part of Their Mechanism

Bupropion.



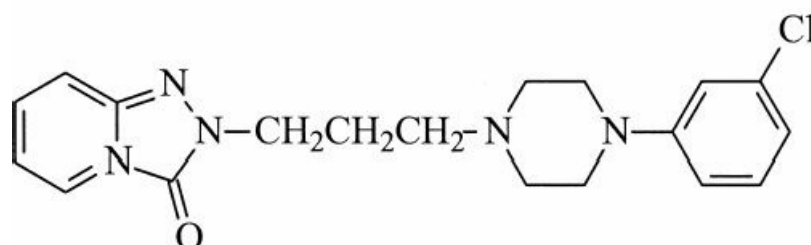
The use of bupropion, especially extended-release formulations, is common for the treatment of depression. Bupropion is also frequently used as in the treatment of smoking cessation therapy, attention deficit hyperactivity disorder, and, occasionally, in compulsive eating disorders.^{5,115} The pharmacologic mechanism of action of bupropion, a substituted cathinone (β -keto amphetamine) and its active metabolite, hydroxybupropion, include inhibition of the release and reuptake of dopamine and, to a lesser extent, serotonin and norepinephrine.⁸ Chronic doses above 450 to 500 mg/day place patients at risk for seizure.^{43,89} Frequent effects that occur following overdose include tachycardia, hypertension, gastrointestinal symptoms, and agitation.^{15,18} Large acute overdoses may result in seizures, QRS prolongation, or both.^{67,79,132,159} In some cases, effects were delayed for up to 10 hours, and seizures up to 24 hours, particularly following the ingestion of sustained-release preparations.^{78,159,166} Symptoms can continue for up to 48 hours.

Studies are conflicting as to whether seizures are caused by bupropion or its metabolite hydroxybupropion.^{60,140} Elevated bupropion and hydroxybupropion concentrations are documented after seizures. The exact mechanism for seizures caused by hydroxybupropion is unclear at this time.^{43,60,89,148} Treatment, when required for seizures, should be supportive

and includes judicious use of benzodiazepines. QRS prolongation is likely due to gap junction dysfunction and therefore may not be uniformly responsive to sodium bicarbonate (Antidotes in Depth: A5). Bupropion is a lipophilic drug with a logP of 3.47 and a logD at pH 7 of 3.08. These physiochemical characteristics and the ability of bupropion to effect myocardial conduction have led to the proposed use of intravenous fat emulsion after overdose. Intravenous fat emulsion therapy was used to successfully resuscitate a 17 year-old woman who ingested multiple drugs including bupropion even after sodium bicarbonate and advanced life support failed and should be considered in similar cases (Antidotes in Depth: A20).¹⁵⁹ Early after an overdose of sustained-release bupropion, activated charcoal should be considered, with use of multiple doses of activated charcoal or possibly whole-bowel irrigation after large, potentially life-threatening ingestions.

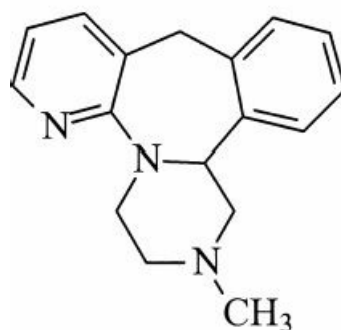
Other serious adverse events reported following chronic bupropion use include cholestatic and hepatocellular dysfunction and rhabdomyolysis, with isolated reports of chest pain, dystonia, trigeminal nerve dysfunction, mania, generalized erythrodermic psoriasis, erythema multiforme, dyskinesia, altered vestibular and sensory function, and serum sickness.^{6,39,42,45,50,70,96,111,172,184}

Trazodone.



Trazodone is an antagonist at 5-HT₂ receptors, a partial agonist at 5-HT₁, and a weak serotonin reuptake inhibitor. In addition, trazodone has peripheral α -adrenergic antagonist activity. CNS depression and orthostatic hypotension are the most common complications after acute overdose of trazodone.⁶² Trazodone is rarely reported to cause SIADH. This effect may be responsible for seizures, which rarely occur after acute overdose.^{13,175} Rarely, cardiac conduction delays are also reported following overdose.¹⁵⁷ Priapism, reported with trazodone, may occur occasionally after overdose.⁶² Management of hypotension includes supportive care and administration of fluids and vasopressors, if necessary.

Mirtazapine.



The mechanism of action of mirtazapine is unique. In addition to serotonin reuptake inhibition, mirtazapine increases neuronal norepinephrine and serotonin through α_2 -adrenergic antagonism.⁴⁴ Mirtazapine also blocks some subtypes of 5-HT receptors, including 5-HT₂ and 5-HT₃, which may have antidepressive effects.¹²⁹ The main effects that occur after acute mirtazapine overdoses include altered mental status, tachycardia, and hypothermia.^{113,178} Large overdoses may cause respiratory depression and prolongation of the QT interval.^{30,144} Rare adverse reactions associated with the therapeutic use of mirtazapine causing serotonin toxicity, hepatitis, hypertension, and reversible agranulocytosis is reported.^{3,81,85,126}

DRUG DISCONTINUATION SYNDROME

The term “drug discontinuation syndrome” is used to describe the physiologic manifestations that occur after abrupt antidepressant cessation. The choice of terminology between withdrawal syndromes and drug discontinuation syndromes is unclear, but they may relate to the manifestations occurring after therapeutic use versus misuse, that is, alcohol or heroin withdrawal and SSRI discontinuation syndrome. Drug discontinuation syndromes are commonly reported after abrupt discontinuation of conventional antidepressants, including cyclic antidepressants and MAOIs (Chaps. 71 and 73).¹⁰⁶ SSRIs cause a discontinuation syndrome that typically begins within 5 days after drug discontinuation and may last up to 3 weeks.⁷⁶ The most frequently reported symptoms include dizziness, lethargy, paresthesias, nausea, vivid dreams,

irritability, and depressed mood.¹⁵³ The risk factors associated with development of a discontinuation syndrome are not fully clarified; however, in a given individual, a genetic polymorphism of the 5-HT_{1A} receptor may play a role.¹²⁴ The syndrome is more common with SSRIs with shorter elimination half-lives (paroxetine > fluvoxamine > sertraline > fluoxetine). In addition, SSRIs with high-potency serotonin reuptake inhibition are more frequently implicated (paroxetine > sertraline > clomipramine > fluoxetine > venlafaxine > trazodone). Of the SSRIs, paroxetine most often results in a discontinuation syndrome, which is mild to moderate in 20% to 40% of patients receiving 20 mg daily.¹⁴ Several studies demonstrate that the vast majority of cases are attributed to paroxetine with an approximately 20% risk with sertraline, venlafaxine, and escitalopram and 10% risk with fluvoxamine.^{14,23} Fluoxetine discontinuation syndrome occurs less frequently, at only two cases per 1 million prescriptions.¹⁴¹ The long elimination half-life of fluoxetine and its active metabolite norfluoxetine probably decrease the incidence of discontinuation syndrome by providing a tapered effect following cessation.

Because of difficulty in distinguishing symptoms of discontinuation syndrome from underlying disease, many authors have proposed diagnostic criteria for the SSRI discontinuation syndrome.²³ All proposed criteria include discontinuation of the SSRI in concordance with CNS effects, gastrointestinal distress, or anxiety.¹⁷⁰ The prominent CNS findings include dizziness, ataxia, vertigo, sensory abnormalities, including electric shocklike sensations and paresthesia, and behavior abnormalities, including aggression and impulsivity.

The biochemical basis of the discontinuation syndrome appears to be similar to tryptophan depletion, which results in an acute decrease in synaptic serotonin.⁴⁷ In fact, abrupt discontinuation versus drug taper was a noted risk factor in paroxetine cases when compared with those who did not experience discontinuation symptoms.⁸² Although postulated, antimuscarinic withdrawal seems an unlikely cause because the antimuscarinic effects of desipramine failed to protect against paroxetine withdrawal in a human model.⁵⁵

Treatment of patients exhibiting the discontinuation syndrome should include supportive care and resumption of the discontinued drug or administration of another SSRI if the implicated drug is contraindicated.¹⁵² The drug then should be tapered at a rate that allows for improved patient tolerance. Many of the other antidepressants discussed in this chapter also result in discontinuation reactions. Symptoms appear similar to those reported following discontinuation of SSRIs and are treated in a similar manner.¹⁹

SUMMARY

- In acute overdose SSRIs or atypical antidepressants usually are not life threatening, although some produce seizures or cardiac toxicity. The management of these patients frequently is complicated because these patients likely have access to more life-threatening antidepressants such as tricyclic antidepressants and MAOIs.
- Monitoring for 24 hours is recommended for the delayed cardiotoxicity with citalopram or escitalopram as well as for delayed seizures following extended release bupropion ingestion.
- Drug interactions and adverse drug events are associated with serotonin reuptake inhibitors and may lead to acute life-threatening events, including serotonin toxicity.
- Serotonin toxicity can produce life-threatening hyperthermia and should be treated with aggressive cooling and sedation. Cyproheptadine may be useful in early cases, and neuromuscular blockade may be necessary in refractory cases.

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H. SUBSTANCES OF ABUSE

CASE STUDY 6

History Police were called to a public area where an adolescent man was shirtless and acting bizarrely. It was a hot summer day with a temperature of 92°F (33°C) and a dew point of 75°F (24°C). The man, who appeared confused, was pacing and gesturing as if he was hallucinating. When the police approached him, he began to run away, but after a struggle he was subdued. The paramedics were called because of his behavior. When they arrived, they found an agitated and confused young man whose arms and legs were restrained and in a full-body bag. He was diaphoretic with 6 to 7 mm pupils, and he was breathing rapidly and had a pulse of 180 beats/min. Because of the restraints, no other vital signs were obtained, and the patient was transported to the emergency department (ED).

Immediate Assessment and Management On arrival at the ED, a team of physicians, nurses, and hospital security personnel were able to remove the patient from the body bag, restrain him, and transfer him to a hospital stretcher. An arm was held in place, and an intravenous (IV) line was inserted. Blood was obtained for analysis, and midazolam (10 mg IV) was given. Within a few moments, the patient became more calm, and the following vital signs were obtained: blood pressure, 198/122 mm Hg; pulse, 188 beats/min; respiratory rate, 38 breaths/min; tympanic temperature, 104.6°F (40.3°C); oxygen saturation, 98% on room air; and glucose, 187 mg/dL. Physical examination revealed a diaphoretic young man who was mumbling incoherently and was hot to the touch. There were no signs of trauma, and his pupils were 7 mm and reactive to light. His chest was clear, and his heart was regular and tachycardic without extra sounds. His abdomen was soft and nontender with normal bowel sounds. Although a complete neurologic assessment was not performed, he was disoriented, distracted, and unable to follow commands. His pupils were reactive, and oculoccephalic reflexes were present. Muscle tone was increased symmetrically and reflexes were brisk, with three to four beats of clonus noted at both ankles. His toes were down-going.

What Is the Toxicological Differential Diagnosis? This patient presents with agitation, tachycardia, hypertension, hyperthermia, diaphoresis, mydriasis, and disorientation. While this presentation is fairly characteristic of a sympathomimetic toxic syndrome (Chaps. 3, 76, and 78) additional considerations must include alcohol and sedative-hypnotic withdrawal (Chaps. 15 and 81), hallucinogens (Chap. 82), and phencyclidine (Chap. 86). These and other etiologies for the hyperthermia are listed in Table CS6–1.

TABLE CS6–1. Xenobiotics and Interactions Associated with Life Threatening Hyperthermia

Alcohol withdrawal	Oxidative phosphorylation uncouplers
Anticholinergics (atropine, antihistamines)	(dinitrophenol, salicylates)
Malignant hyperthermia	Phencyclidine
Monoamine oxidase inhibitor overdose	Sedative-hypnotic withdrawal
Neuroleptic malignant syndrome	Serotonin toxicity
	Sympathomimetics (cocaine, amphetamines)

What Immediate Interventions Are Required? A rectal probe was inserted, and the patient's core temperature was noted to be 109.2°F (42.9°C). This single vital sign abnormality takes precedence over the others and requires emergent intervention regardless of the etiology. An additional 5 mg of IV midazolam was administered (Antidotes in Depth: A23) to further control the agitation, and the patient was placed in an ice-water bath (Chap. 30). While in the bath, another 5 mg of midazolam was needed to control his behavior. One liter of 0.9 sodium chloride was infused through the peripheral IV line, and a Foley catheter was inserted, which drained a scant amount of dark yellow urine.

Within 15 minutes, the patient's core temperature fell to 101.4°F (38.6°C); he was removed from the ice bath; dried; and placed on a clean, dry stretcher. At that time, the following vital signs were obtained: blood pressure, 148/94 mm Hg; pulse, 120 beats/min; respiratory rate, 24 breaths/min; core temperature, 99.2°F (37.3°C); oxygen saturation, 96% on room air; end-tidal carbon dioxide, 46 mm Hg.

What Rapid Clinical and Laboratory Analyses Can Help Exclude Life-Threatening Consequences of This Patient's Presentation? The consequences of hyperthermia include injury to many organ systems as outlined in Table CS6–2. An electrocardiogram (ECG) should be obtained, as it can rapidly detect critical myocardial injury and life-threatening electrolyte abnormalities. A rapid assessment of electrolytes, kidney and liver function, coagulation status, acid–base balance, creatine kinase, troponin, and a urinalysis are all indicated. Severe abnormalities should be addressed as detected. In this case, although the urine dipstick showed the large presence of blood, the urine was clear,

leading to a clinical suspicion of rhabdomyolysis. The patient was started on fluids at twice his maintenance requirement as well as a bicarbonate infusion (Antidotes in Depth: A5).

TABLE CS6–2. Major Organ System Complications of Hyperthermia

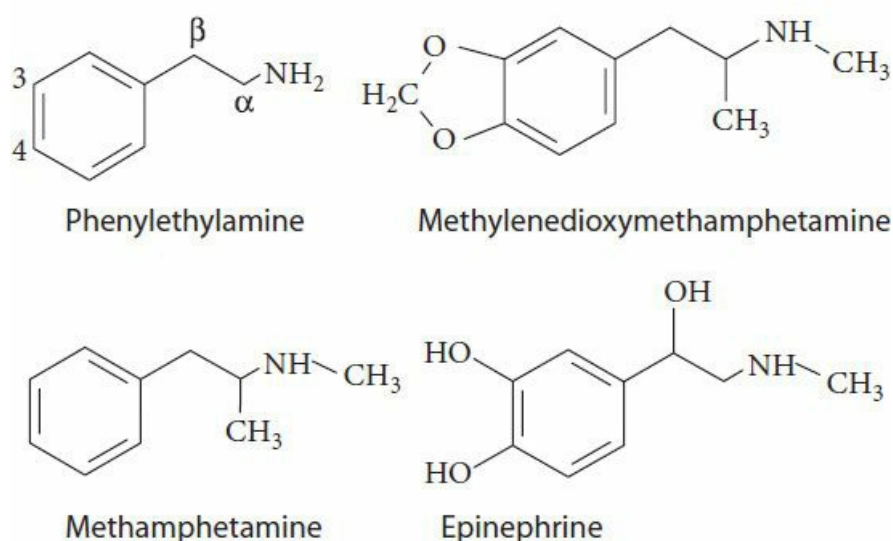
Organ System	Complication
Brain	Cerebral edema
Lungs	Acute respiratory distress syndrome
Heart	Myocardial stunning, Myocardial infarction
Gastrointestinal	Hepatic injury
Kidneys	Acute kidney injury
Hematological	Coagulopathy
Muscle	Rhabdomyolysis

Further Diagnosis and Treatment The patient remained calm and began to answer questions a few hours later. The ECG showed sinus tachycardia with normal intervals and no pattern of injury. However, the laboratory results were remarkable for a creatinine of 3.4 mg/dL, a bicarbonate of 12 mEq/L, an anion gap of 30 mEq/L, and a creatine kinase of greater than 100,000 IU/L. Although repeat electrolytes showed a rapid correction of the bicarbonate and anion gap, the creatinine continued to rise and the creatine kinase remained greater than 100,000 IU/L. A nephrology consult was obtained because of the potential need for hemodialysis, but the patient continued to have an adequate urine output and urine electrolytes demonstrated a retained ability to concentrate the urine.

The patient regained a normal mental status and related that the last thing he remembered was smoking crack cocaine. Over the course of a week, the creatine kinase fell, and the serum creatinine stabilized at 1.7 mg/dL. A referral was made to an outpatient detoxification center, and the patient was discharged.

76 AMPHETAMINES

David H. Jang



HISTORY AND EPIDEMIOLOGY

Amphetamine is the acronym for racemic β -phenylisopropylamine or α -methylphenylethylamine. Amphetamine is representative of a broader group of compounds with a shared structure known as phenylethylamines, which is a more precise term. Numerous substitutions are possible on the phenylethylamine structure, resulting in a variety of compounds, some with unique properties. For the purposes of this chapter, all phenylethylamines that are not actually amphetamine will be called amphetamines, and the name amphetamine specifically refers to β -phenylisopropylamine.

Amphetamine was first synthesized in 1887, but was essentially lost until the 1920s, when there were concerns about the supply of ephedrine for asthma therapy.⁷¹ The attempt to synthesize ephedrine led to the rediscovery of dextroamphetamine in the United States and methamphetamine (d-phenylisopropylmethylamine hydrochloride) in Japan.⁷¹ Amphetamine was first marketed by Smith, Kline, and French in 1932 as the nasal decongestant Benzedrine.¹⁵ Amphetamine tablets were later available in 1935 for the treatment of narcolepsy and were advocated as anorectants in 1938.⁷⁶

Both amphetamine and methamphetamine were supplied as stimulants for soldiers and prisoners of war in World War II. The stimulant and euphoric effects of amphetamine were recognized, with abuse reported as early as 1936.¹³⁷ As a result, Benzedrine inhalers were banned by the US Food and Drug Administration (FDA) in 1959. From 1950 to the 1970s, there were sporadic periods of widespread amphetamine use and abuse in the United States. In the 1960s, various amphetamines such as methylenedioxyamphetamine (MDA), para-methoxyamphetamine (PMA), and para-methoxymethamphetamine (PMMA) were popularized as hallucinogens.³⁴ The Controlled Substance Act of 1970 placed amphetamines in Schedule II to prevent the diversion of pharmaceutical amphetamines for nonmedicinal uses.⁵ Amphetamine abuse subsequently declined.⁹³

In the 1980s, use of methylenedioxy derivatives of amphetamine and methamphetamine surfaced and were able to circumvent existing regulations. The best known of these derivatives were 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyethamphetamine (MDEA).⁴⁶ Since the late 1980s, a dramatic resurgence of methamphetamine abuse has spread throughout much of the United States. A high purity preparation of methamphetamine hydrochloride was marketed in a large crystalline form termed “ice” by abusers.^{7,49} From 1991 to 1994, the number of methamphetamine-related deaths in the United States reported by medical examiners tripled from 151 to 433, with a disproportional distribution from the Los Angeles, San Diego, San Francisco, and Phoenix metropolitan areas. Methamphetamine use is particularly prevalent among men who have sex with men in New York City.⁷⁴ Because of the ease and low cost of methamphetamine synthesis and the local production, methamphetamine is the most common illicit drug produced by

clandestine laboratories in the United States.^{28,31} Since the mid-1990s, MDMA has become widely used by college students and teenagers in large gatherings, known as “rave” or “techno” parties in England, Australia, and the United States.^{135,136} Methcathinone (a khat-derived substance) use in the midwestern United States and 4-bromo-2,5-methoxyphenylethylamine (2CB) use in dance clubs were popular in the 1990s, but the use was not widespread.^{63,67,180} Recently, synthetic cathinones have resulted in serious toxicity and death³⁰; these drugs have been sold as “bath salts” or “legal highs” to circumvent existing laws. There are also older amphetamines such as PMA and PMMA that have made a resurgence, with recent reports of toxicity and deaths.

PHARMACOLOGY

The pharmacologic effects of amphetamines are complex, but their primary mechanism of action is the release of catecholamines, particularly dopamine, norepinephrine, and serotonin from the presynaptic terminals, leading to a hyperadrenergic state. Although there are conflicting mechanistic models of amphetamine induction of catecholamine release, these variable results may be directly correlated with the different concentrations of amphetamine used in experimental models. The mechanism of action of amphetamines are based on dopaminergic neurons; similar mechanisms occur with norepinephrine and serotonin. Two storage pools exist for dopamine in the presynaptic terminals: the vesicular pool and the cytoplasmic pool. The vesicular storage of dopamine and other biogenic amines is maintained by the acidic environment within the vesicles and the persistence of a stabilizing electrical gradient within the cytoplasm. This environment is maintained by an adenosine triphosphate (ATP)-dependent active proton transport system.^{117,147}

Amphetamines will enter the nerve cell either by passive diffusion or by exchange diffusion through a reuptake transporter that is partially dose dependent. At low concentrations, amphetamines release dopamine from the cytoplasmic pool by exchange diffusion at the dopamine reuptake transporter site in the membrane. At moderate concentrations, amphetamines diffuse through the presynaptic terminal membrane and interact with the neurotransmitter transporter on the vesicular membrane to cause exchange release of dopamine into the cytoplasm. Dopamine is subsequently released into the synapse by reverse transport at the dopamine reuptake site.^{147,161} At high concentrations, an additional mechanism is invoked as amphetamines diffuse through the cellular and vesicular membranes. Because amphetamine are bases, they alkalize the vesicles, permitting dopamine release from the vesicles and delivery into the synapse by reverse transport (Fig. 76–1).^{161,162} Amphetamines may also block the reuptake of catecholamines by competitive inhibition.^{72,177} However, the effects of this mechanism are considered minor. Amphetamines are structurally similar to amphetamine derived monoamine oxidase inhibitors such as tranylcypromine, so amphetamines are weak monoamine oxidase inhibitors, the clinical significance of which is unclear.¹³¹

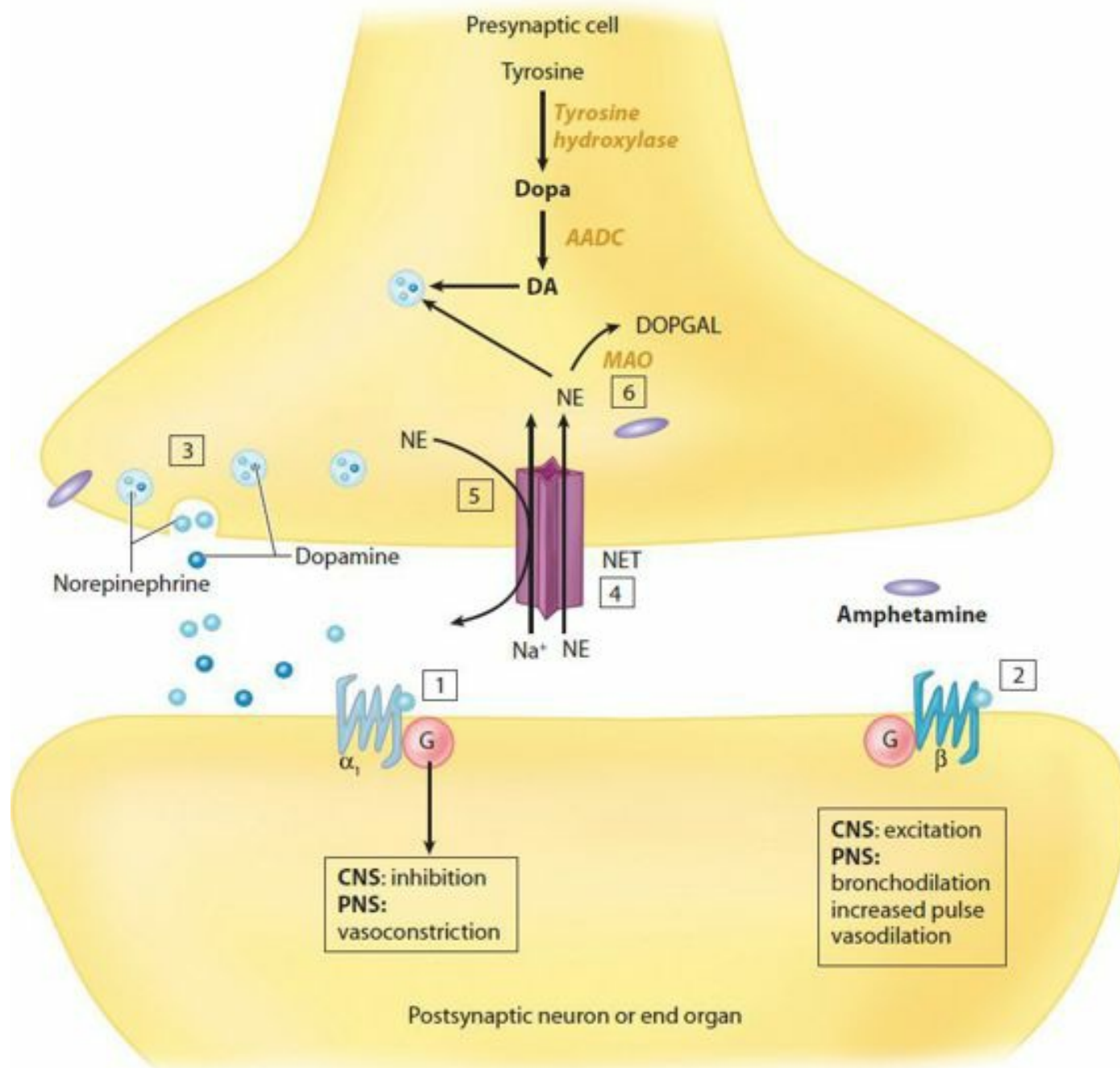

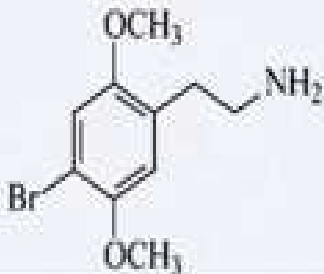
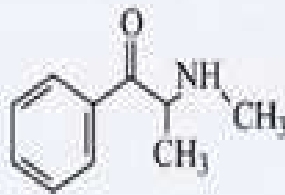
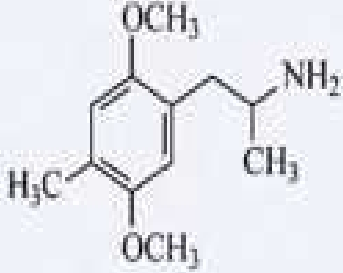
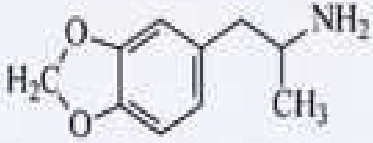



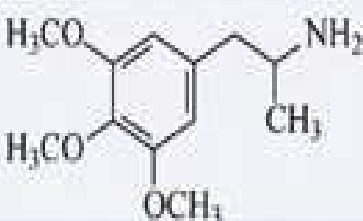


FIGURE 76–1. Noradrenergic nerve ending. The postsynaptic membrane may represent an end organ or another neuron in the CNS. The primary mechanism of action of amphetamines is the release of catecholamines, particularly dopamine and norepinephrine, from the presynaptic terminals. Two storage pools exist for dopamine in the presynaptic terminals: the vesicular pool and the cytoplasmic pool. The vesicular storage of dopamine and other biogenic amines is maintained by the acidic environment within the vesicles and the persistence of a stabilizing electrical gradient with respect to the cytoplasm. [1,2] Activating or antagonizing postsynaptic α - and β -adrenoceptors. [3] Amphetamines release dopamine from the cytoplasmic pool by exchange diffusion at the dopamine uptake transporter site in the membrane. [4] Amphetamines diffuse through the presynaptic terminal membrane and interact with the neurotransmitter transporter on the vesicular membrane to cause exchange release of dopamine into the cytoplasm. Dopamine is subsequently released into the synapse by reverse transport at the dopamine uptake site. [5] Amphetamine diffuses through the cellular and vesicular membranes, alkalinizing the vesicles, and permitting dopamine release from the vesicles and delivery into the synapse by reverse transport. [6] Inhibiting monoamine oxidase (MAO) to prevent NE degradation; or inhibiting COMT to prevent NE degradation. AADC = aromatic L-amino acid decarboxylase; β -hydroxylase = dopamine- β -hydroxylase; COMT = catechol-O-methyltransferase; CNS = central nervous system; DOPGAL = 3,4-dihydroxyphenylglycoaldehyde; G = G protein; NET = membrane NE uptake transporter; NME = normetanephrine; VMA2 = vesicle uptake transporter for NE; PNS = peripheral nervous system.

Binding selectivity to the neurotransmitter transporters largely determines the range of pharmacologic effects for the particular amphetamine. The affinity of MDMA for serotonin transporters is 10 times greater than that for dopamine and norepinephrine transporters; hence, it produces primarily serotonergic effects.⁶⁸ There are also other amphetamines that are predominantly serotonergic such as paramethoxyamphetamine and BromodragonFLY (Table 76–1).

TABLE 76–1. Examples of Amphetamines

<i>Xenobiotic</i>	<i>Clinical Manifestations</i>	<i>Structure</i>
4-Bromo-2,5-dimethoxyamphetamine (DOB)	Marked psychoactive effect, potency > mescaline Delayed onset of action, peak 3–4 hours Fantasy, mood altering for 10 hours, resolution 12–24 hours Agitation, sympathetic excess Sold as impregnated paper, like LSD	
4-Bromo-2,5-methoxyphenyl-ethylamine (2CB, MFT)	Relaxation Sensory distortion Agitation Hallucination Potency > mescaline	
Methcathinone (cat, Jeff, Khat, ephedrone)	Hallucinations Sympathetic excess	
4-Methyl-2,5-dimethoxyamphetamine (DOM/STP) (serenity, tranquility, peace)	Narrow therapeutic index Euphoria, perceptual distortion Hallucinations, sympathetic excess	
3,4-Methylenedioxyamphetamine (MDA, love drug)	Empathy, euphoria Agitation, delirium, hallucinations, death associated with sympathetic excess	
3,4-Methylenedioxyethamphetamine (MDEA, Eve)	Comparable to MDMA Sympathetic excess	
3,4-Methylenedioxymethamphetamine (MDMA, Adam, molly, ecstasy, XTC)	Psychotherapy "facilitator" Euphoria, empathy, nausea, anorexia, anxiety, insomnia Sympathetic excess	
para-Methoxyamphetamine (PMA)	Potent hallucinogen Sympathetic excess	
2,4,5-Trimethoxyamphetamine	Similar to mescaline	

The most identifiable effects of amphetamines are those caused by excessive catecholamine release and the resultant stimulation of many receptors that include α -adrenergic receptors, β -adrenergic receptors, dopamine, and serotonin. The majority of the serotonergic neurons in the central nervous system (CNS) are located in the raphe nuclei. Serotonin within the CNS regulate a wide variety of functions, including, but not limited to, mood, memory, temperature regulation, sleep, and pain.⁷¹ Serotonin is primarily responsible for the hallucinogenic and illusionic properties of amphetamines. Serotonin is also involved with the release of antidiuretic hormone, which may lead to hyponatremia, particularly with amphetamines with potent serotonergic effects such as MDMA.⁷⁵ Serotonin is also concerned with regulating fluid secretion and peristalsis. In addition, serotonin is involved in the regulation of many vascular beds, although the role of amphetamines in the regulation of the peripheral effects of serotonin is not clear.

Norepinephrine is another important neurotransmitter involved with amphetamines. Norepinephrine is found in the CNS and is also released from the postganglionic sympathetic fibers. The main noradrenergic nucleus in the CNS is the locus ceruleus. The release of excessive norepinephrine within the CNS from amphetamines results in decreased fatigue and increased attentiveness. Excessive norepinephrine in the peripheral nervous systems leads to many of the findings that occur with other sympathomimetic drugs such as cocaine. Norepinephrine will act on the adrenergic receptors (α and β), which mediate vasoconstriction and increased cardiac activity resulting in hypertension and tachycardia.

Dopamine also plays an important role in the setting of amphetamine use. The increase in CNS dopamine, particularly in the neostriatum, mediates stereotypical behavior and other locomotor activities.^{39,65,89,90} The activity of dopamine in the neostriatum appears to be linked to glutamate release and inhibition of γ -aminobutyric acid (GABA) ergic efferent neurons.^{65,90} Stimulation of the glutamatergic system contributes significantly to the stereotypical behavior, locomotor activity, and neurotoxicity of amphetamines.^{90,153,154} The effects of serotonin and dopamine on the mesolimbic system alter perception, cause psychotic behavior and anorexia.^{78,160}

Structure Modification

A phenylethylamine is any structure with an ethyl group backbone that has an aromatic group and a terminal amine. Specific substitutions made to the phenylethylamine backbone have led to the wide variety of novel drugs, described below. Substitutions at different positions of the phenylethylamine molecule alter the general pharmacology and clinical effects of amphetamines, as demonstrated by both animal and human observations. Large-group substitution at the α carbon reduces the stimulant and cardiovascular effects but retains the anorectic properties (such as phentermine). Substitution at the para position of the phenyl ring enhances the hallucinogenic or serotonergic effects of amphetamines (such as in para-chloroamphetamine and MDMA).⁴⁹ Although some of these generalizations enable an understanding of the effects of amphetamines, there are many exceptions, and such generalizations may not apply when large doses of a particular molecule are ingested. In terms of the spectrum of activities, methamphetamine results in the most potent cardiovascular effects, and 2,5-dimethoxy-4-bromoamphetamine (DOB) results in the most consequential hallucinogenic and serotonergic effects.¹⁰⁵ Table 76–2 further describes the pharmacology of specific substitutions.

TABLE 76–2. Specific Substitutions

<i>Substitution</i>	<i>Pharmacological Effect</i>
α -Carbon	Indirect acting Resists oxidation by monoamine oxidase
β -Carbon	Decreases central nervous system penetration Hydroxyl ($-\text{OH}$): necessary for adrenergic activity
Amino group	No substitution: α -adrenergic > β -adrenergic effects Larger group: β -adrenergic > α -adrenergic effects t-butyl group: β_2 -adrenergic selective Methyl ($-\text{CH}_3$) group: maximum α - and β -adrenergic effects
3-, 4- of aromatic ring	Hydroxylation at 3- and 4-: increased α - and β -adrenergic effects Absence of hydroxylation (at one or both positions) prevents degradation by catechol-O-methyltransferase
Halogenation	Increases neurotoxic properties of amphetamines by selective action on the serotonin system Enhances potency

Other certain substitutions are worth noting, such as the addition of an extra methyl group to the terminal amine in amphetamine to produce methamphetamine that greatly increases CNS activity. This extra methyl group also makes methamphetamine more lipid soluble, allowing faster penetration across the blood–brain barrier and more resistance to degradation by monoamine oxidase. In addition, amphetamines with this methyl group also possess strong stimulant, cardiovascular, and anorectic properties.¹⁰⁵ Addition of a methoxy group to either the 2 or 5 position of the aromatic ring on the amphetamine or methamphetamine compound increases serotonergic activity. Another important substitution to the phenylethylamine backbone is the addition of a halogen group (such as iodine or bromide), which increases the potency of the compound and leads to it being considered more neurotoxic when compared to nonhalogenated compounds. This is thought to be due to significant serotonin depletion leading to irreversible neuron damage.

Because amphetamines directly interact with neurotransmitter transporters, minor modifications of the molecule may significantly alter its pharmacologic profile.⁸² The addition of an α -methyl group in amphetamines confers resistance to metabolism by monoamine oxidase. These characteristics permit better oral bioavailability and longer duration of effect. The α -methyl group in the amphetamine structure also introduces chirality to the molecule. Except for MDMA and several other amphetamines, the d-enantiomers are typically 4 to 10 times more potent than the l forms of amphetamine.

Chronic administration of certain amphetamines to animals alters dopamine and serotonin transporter functions, depletes dopamine and serotonin in the neuronal synapses, and produces irreversible destruction of those neurons.^{14,60,141,142,147,176} The etiology of neuronal toxicity may be related to the generation of oxygen free radicals, resulting in the generation of toxic dopamine and serotonin metabolites as well as neuronal destruction. Based on animal models, dose, frequency and duration of exposure, and ambient temperature. Intact dopamine or serotonin transporters are necessary to produce neurologic injury. Xenobiotics that inhibit transporter function may prevent neurologic injuries in animals.⁶⁸ Significant differences are also noted across species; mice are typically resistant to MDMA-induced neurologic injury. Although not as well studied as MDMA, studies of former methamphetamine users demonstrated impaired memory and psychomotor functions, as well as corresponding dopamine transporter dysfunction and abnormal glucose metabolism on positron emission tomography scans. However, it is still not clear as to the difference in species susceptibility to neurologic injuries, the duration of effects in primates and humans, and functional consequences of neurotoxicity in humans. The potential for permanent neurologic effects associated with chronic amphetamine use in humans requires further study.

PHARMACOKINETICS AND TOXICOKINETICS

Absorption

Amphetamines can be administered intravenously, orally, intranasally, and by inhalational route, with good absorption. All amphetamines are rapidly absorbed, with bioavailability that ranges between 60% and 90% depending on the route of administration. Peak serum concentrations are achieved in approximately 3 to 6 hours postadministration.

Distribution

Following absorption, amphetamines are distributed to most compartments of the body. Most amphetamines are also relatively lipophilic and readily cross the blood–brain barrier. Amphetamines have large volumes of distribution, varying from 3 to 5 L/kg for amphetamine, 3 to 4 L/kg for methamphetamine and phentermine, and to 11 to 33 L/kg for methylphenidate. Some amphetamines such as pemoline have a small volume of distribution (0.2–0.6 L/kg).

Metabolism

Amphetamines are eliminated via multiple pathways, including diverse routes of hepatic transformations, and by renal elimination. For MDMA and its analogs, N-dealkylation, hydroxylation, and demethylation are the dominant hepatic pathways. Depending on the particular amphetamines, active metabolites of amphetamines and ephedrine derivatives may be formed. N-demethylation of methamphetamine and MDMA result in the formation of amphetamine and MDA, respectively.^{33,111} Dealkylation and demethylation are mainly performed by CYP1A2, CYP2D6, and CYP3A4, but they are also performed by flavin monooxygenase. Polymorphism of CYP2D6 in humans was recognized due to the diversity of rates of p-hydroxylation of amphetamines. Since its discovery, CYP2D6 polymorphism has been implicated in drug toxicity, substance use and abuse, and lack of drug efficacy in selected individuals.¹⁴⁸ Increased amphetamine toxicity is a potential concern in patients with decreased CYP2D6 activity. Although animals with CYP2D6 deficiency are more susceptible to MDMA toxicity, limited studies in humans do not demonstrate an association between mortality and CYP2D6 polymorphism.^{59,122} In general, because multiple enzymes and pathways (including renal) are involved in amphetamine metabolism, it is less likely that CYP2D6 polymorphism or drug interactions with CYP3A4 alone will significantly increase toxicity. However, it is unclear if toxicity is enhanced when multiple mechanisms for altering drug metabolism and kidney dysfunction are present simultaneously.

Elimination

Renal elimination of the parent compound is substantial for amphetamine (30%), methamphetamine (40%–50%), MDMA (65%), and phentermine (80%). Amphetamines are bases with a typical pK_a range of 9 to 10, and renal elimination varies depending on the urine pH, with elimination increasing as pH decreases. The half-life of amphetamines varies significantly: amphetamine, 8 to 30 hours; methamphetamine, 12 to 34 hours; MDMA, 5 to 10 hours; methylphenidate, 2.5 to 4 hours; and phentermine, 19 to 24 hours. Repetitive administration, which occurs typically during binge use, may lead to drug accumulation and prolongation of the apparent half-life and duration of effect.⁷⁷

CLINICAL MANIFESTATIONS

Acute Toxicity

Most of the complications associated with amphetamines are a result of an uncontrolled hyperadrenergic state similar to what occurs with other sympathomimetics such as cocaine, except the duration of effect may be longer (Table 76–3). Most patients with acute amphetamine toxicity manifest effects in the CNS and cardiovascular system. The majority of the specific effects are from excessive catecholamine release as opposed to direct effects from the amphetamines themselves. Refer to the section Individual Amphetamines for specific effects.

TABLE 76–3. Clinical Manifestations of Amphetamine Toxicity

Acute

Cardiovascular system

Aortic dissection

Dysrhythmias

Hypertension

Myocardial ischemia

Tachycardia

Vasospasm

Central nervous system

Agitation

Anorexia

Bruxism

Choreoathetoid movements

Euphoria

Headache

Hyperreflexia

Hyperthermia

Intracerebral hemorrhage

Paranoid psychosis

Seizures

Other sympathomimetic symptoms

Diaphoresis

Mydriasis

Nausea

Tachypnea

Tremor

Other organ system manifestations

Acute respiratory distress syndrome

Ischemic colitis

Muscle rigidity

Rhabdomyolysis

Laboratory abnormalities

Creatine phosphokinase elevated

Hyperglycemia

Hyponatremia

Leukocytosis

Liver enzymes elevated

Myoglobinuria

Chronic

Aortic and mitral regurgitation

Cardiomyopathy

Dopaminergic and serotonergic neuron damage

Pulmonary hypertension

Vasculitis

Central nervous system effects from acute amphetamine use include anxiety, agitation, hallucinations, mydriasis, diaphoresis, and hyperthermia.^{19,50,51,145} Psychosis appears to be a more prominent feature than following cocaine use.⁶⁵ Intracerebral hemorrhage and cerebral infarction are also reported with amphetamine use.^{53,86,113,129} Seizures may be the direct result of amphetamine use or may occur secondarily from hyponatremia as reported with MDMA and certain synthetic cathinones.¹⁸

Cardiovascular toxicity from acute amphetamine use involves hypertension, tachycardia, and dysrhythmias; this varies from premature ventricular complexes to ventricular tachycardia and ventricular fibrillation.⁸⁰ Other vascular complications reported with acute use include myocardial ischemia or infarction,^{115,169} aortic dissection,^{52,172} acute respiratory distress syndrome,^{165,171} obstetrical complications, fetal death,¹⁰⁴ and ischemic colitis.^{79,84} Other complications are metabolic acidosis, rhabdomyolysis,⁵⁴ acute kidney injury (acute tubular necrosis), and coagulopathy, often from uncontrolled agitation and hyperthermia^{43,73,167} (Fig. 5–29). Unless these systemic signs and symptoms are rapidly reversed, multiorgan failure and death may ensue.

Chronic Toxicity

Amphetamine users seeking intense “highs” may go on “speed runs” for days to weeks. Because of the development of tolerance, they use increasing amounts of amphetamine during these periods, usually without much nutritional sustenance or sleep, while attempting to achieve their desired euphoria.¹⁵¹ Acute psychosis resembling paranoid schizophrenia may occur during these binges and has contributed to both amphetamine-related suicides and homicides.⁵⁵ Return to a normal sensorium occurs within a few days after discontinuation of the drug. Once an amphetamine user experiences psychosis, it is likely to recur with subsequent use, even after prolonged abstinence, which may be related to a kindling phenomenon.¹¹⁴ Typically, after such binges, patients may sleep for prolonged periods of time, feel hungry and depressed when awake, and often have amphetamine cravings.^{95,99}

Compulsive repetitive behavior patterns from the use of amphetamines are reported in humans and animals. Individuals may constantly pick at their skin; grind their teeth (bruxism); or perform repetitive tasks, such as constantly cleaning the house or car. MDMA users often carry pacifiers to relieve bruxism. Choreoathetoid movements, although uncommon, are reported with acute and chronic amphetamine usage.^{94,106,110} The etiology of the choreoathetoid movements may be related to increased dopaminergic stimulation in the striatal area.

Necrotizing vasculitis is associated with amphetamine abuse. Angiography typically demonstrates beading and narrowing of the small- and medium-sized arteries (Fig. 5–29). Progressive necrotizing arteritis can involve multiple organ systems, including the brain, heart, gut, and kidney.^{17,35,98,110,164} Complications include cerebral infarction and hemorrhage, coronary artery disease, pancreatitis, and acute kidney injury. The etiology of the arteritis remains unclear. Although various contaminants associated with injection drug use are postulated as potential etiologies, in animal models oral and intravenous amphetamine administration is also associated with vasculitis, suggesting that this is a direct amphetamine effect. Cardiomyopathy is also reported with acute and chronic amphetamine abuse.^{157,178} Excessive catecholamine exposure may be responsible for their associated cardiomyopathies similar to patients with pheochromocytomas and chronic cocaine use.^{88,173} Other reported effects include valvular disease and pulmonary hypertension with certain amphetamines used as dieting agents such as fenfluramine, dexfenfluramine, and phentermine.^{146,163}

Finally, complications can result from intravenous drug use and from the associated contaminants. Contamination with microbials may lead to human immunodeficiency virus infection, hepatitis, and malaria. Bacterial and foreign body contamination may result in endocarditis, tetanus, wound botulism, osteomyelitis, and pulmonary and soft tissue abscesses.³⁴

DIAGNOSTIC TESTING

The choice and extent of diagnostic tests should be guided by the history and physical examination. In all patients with altered mental status, blood specimens should be sent for glucose, blood urea nitrogen, and electrolyte assays. An electrocardiogram should be obtained in all cases, and continuous cardiac monitoring should be initiated. A complete blood count, urinalysis, coagulation profile, creatine phosphokinase, chest radiograph, computed tomography scan of the head, and lumbar puncture may be necessary, depending on the clinical presentation.

Qualitative urine immunoassays are available for amphetamines, but several considerations limit their utility in the

management of acutely poisoned patients. While point of care urine tests are available, the turnaround time for many urine immunoassays is at least several hours so they rarely contribute to management in the acute setting. Another important limitation to consider is the rate of false-positive and false-negative results that are common with the amphetamine immunoassay. For example, many cold preparations contain pseudoephedrine, which is structurally similar and may cross-react with the immunoassay.^{36,41,57,132} Likewise, selegiline, a selective monoamine oxidase type B inhibitor used for the treatment of parkinsonism, is metabolized to amphetamine and methamphetamine. Other common drugs that produce false-positive outcomes include bupropion, trazodone, and amantadine.^{120,124} Even a true-positive result only means the patient has used certain amphetamines within the past several days and does not distinguish remote from acute use. False-negative results may occur with certain amphetamines such as MDMA and cathinones, which are not recognized on standard urinary drug testing.^{36,156} Although newer, rapid, serum qualitative drug screens are available, false-positive and false-negative results remain common and may be misleading and do not directly contribute to the acute management of patients. The gold standard for drug testing, gas chromatography–mass spectrometry analysis, can misidentify isomeric substances such as l-methamphetamine, which is present in nasal inhalers, with d-methamphetamine, if performed by inexperienced personnel.⁹⁶ In summary, the use of urine immunoassays should not guide clinical management of patients who present with suspected toxicity from amphetamines.

MANAGEMENT

The initial medical assessment of the agitated patient must include vital signs, a rapid glucose and a complete physical examination. Determination of core body temperature is essential to diagnose the presence and degree of hyperthermia, which is a frequent and rapidly fatal manifestation in patients with drug-induced delirium. Significant hyperthermia necessitates immediate interventions to achieve rapid cooling.^{16,23,62} Some patients require temporary physical restraint to gain pharmacologic control and prevent personal harm to themselves or others. Physical restraints should be discontinued as soon as possible; prolonged restraints may result in rhabdomyolysis and continued heat generation. Intravenous access should be obtained so that intravenous sedation can be initiated. In the event that intravenous access cannot be obtained, it is necessary to attempt to administer intramuscular benzodiazepines such as midazolam until definitive access is made.

The most appropriate choice of chemical sedation is a benzodiazepine because of the characteristic high therapeutic index, good anticonvulsant activity, and predictable pharmacokinetic properties. The benzodiazepines are effective not only for the treatment of delirium induced by acute overdose of cocaine, amphetamines, and other xenobiotics but also the delirium associated with ethanol and sedative-hypnotic withdrawal (Antidotes in Depth: A23).^{47,48,66,123} Sedation should be titrated rapidly until the patient is calm. In our clinical experience, cumulative benzodiazepine dosages required in the initial 30 minutes to achieve adequate sedation frequently exceed 100 mg of diazepam or its equivalent. Intravenous glucose (D₅₀W, 0.5–1 g/kg) and thiamine 100 mg should be given as indicated (Table 76–4).

TABLE 76–4. Management of Patients with Amphetamine Toxicity

Agitation

Benzodiazepines (usually adequate for the cardiovascular manifestations)

Diazepam 10 mg (or equivalent) intravenously, repeat rapidly until the patient is calm (cumulative dose may be as high as 100 mg of diazepam). An equivalent dose of intramuscular midazolam can be used if intravenous access is not available.

Seizures

Benzodiazepines

Barbiturates

Propofol for status epilepticus (typically will require endotracheal intubation)

Hyperthermia

External cooling

Control agitation rapidly

Gastric decontamination and elimination

Activated charcoal for recent ingestions

Hypertension

Control agitation first

α -Adrenergic antagonist (phentolamine)^a

Vasodilators (nitroprusside, nitroglycerin, or possibly nicardipine)

Delirium or hallucinations with abnormal vital signs

If agitated: benzodiazepines

^aAvoid β -adrenergic antagonists, especially with suspected cocaine toxicity.

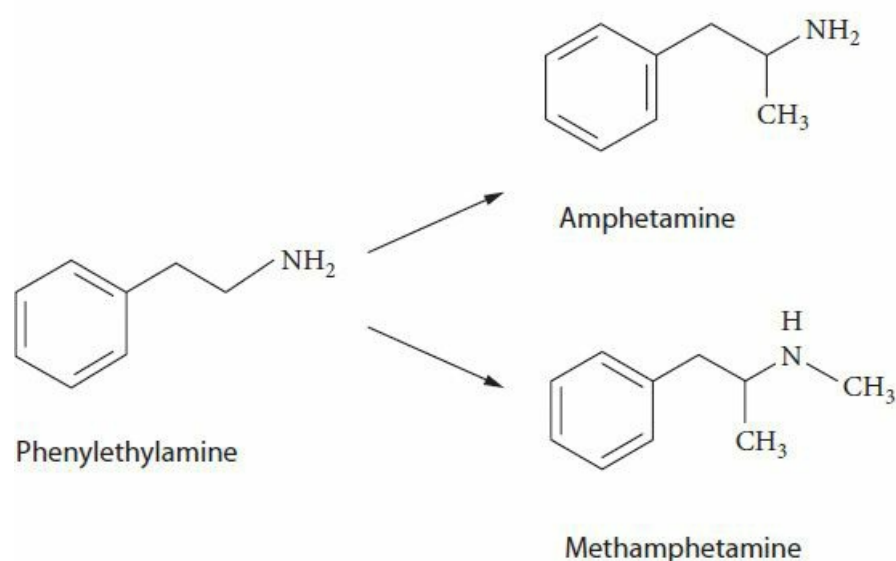
Antipsychotics, particularly potent dopamine antagonists such as haloperidol and droperidol, are frequently recommended by others for amphetamine-induced delirium. Antipsychotics may antagonize some of the effects of amphetamines via dopamine blockade, but they have not been shown to be as effective as benzodiazepines in experimental models.^{44,66,123} Additionally, antipsychotics may lower the seizure threshold, alter temperature regulation, cause acute dystonia, and precipitate cardiac dysrhythmias, and they do not interact with the benzodiazepine-GABA-chloride channel receptor complex. All of these effects may aggravate the clinical outcomes related to occult or concomitant cocaine toxicity and ethanol withdrawal.^{66,69,123} Based on these concerns, benzodiazepines should be utilized as first-line treatments in the management of acute toxicity from amphetamines.

Rhabdomyolysis from amphetamines usually results from psychomotor agitation and hyperthermia.¹⁴³ Sedation prevents further muscle contraction and heat production. External cooling should be instituted for hyperthermia. Adequate intravenous hydration and cardiovascular support should maintain urine output of at least 1 to 2 mL/kg/h. Although urinary acidification can significantly increase amphetamine elimination and decrease the half-lives of amphetamine and methamphetamine,^{11,12} pH manipulation does not decrease toxicity, and, in fact, it may increase the risk of acute kidney injury from rhabdomyolysis by precipitating ferrihemate in the renal tubules.⁴⁰ Patients with acute kidney injury, acidemia, and hyperkalemia may require urgent hemodialysis.

Amphetamine body packers, although uncommon, should be treated similarly to those who transport cocaine (Special Considerations: SC5). Any sympathomimetic symptom suggesting leakage of the packets requires surgical intervention.¹⁶⁸ Intravenous fluids, benzodiazepines, intubation, and external cooling may be necessary to stabilize these patients.

INDIVIDUAL AMPHETAMINES

Methamphetamine



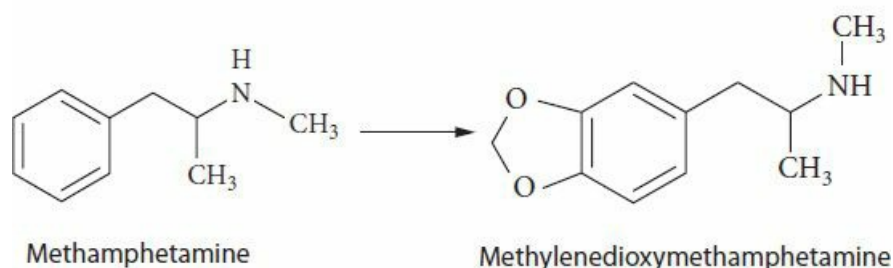
Methamphetamine is known by many names, including, but not limited to, “yaba,” “speed,” “go,” “crack,” “uppers,” and “dexies.” The terms “crystal,” “shard,” and “ice” refer to the crystalline form of methamphetamine. Methamphetamine was first synthesized from ephedrine in Japan in 1893, soon after the synthesis of amphetamine in 1887. Crystallized

methamphetamine was synthesized in 1919 through the reduction of ephedrine using red phosphorus. From the 1950s to the 1970s, there were multiple epidemics of methamphetamine abuse in the United States.⁶⁴ Methamphetamine is approved by the FDA for the short-term treatment of attention-deficit/hyperactivity disorder and obesity, and it is sold under the trade name Desoxyn as a Schedule II drug. It is also prescribed for off-label use for refractory depression and narcolepsy.

The production of methamphetamine is relatively simple, requiring minimal equipment and chemicals. There are many methods of methamphetamine production which initially utilize pseudoephedrine, ephedrine, or phenyl-2-propone (P2P). The primary ingredient of methamphetamine synthesis is ephedrine, which can be hydrogenated into methamphetamine. The ephedrine method, using pharmaceutical grade L-ephedrine, produces a product with few contaminants that is stereochemically pure.^{49,133} P2P, as an alternative ingredient, can be methylated into ephedrine and then transformed into methamphetamine.²² Because of the strict control of ephedrine and P2P, illicit chemists use phenylacetic acid to synthesize P2P.^{22,42} Lead acetate, which is used as a substrate for the reaction, has resulted in an epidemic of lead poisoning associated with methamphetamine abuse in Oregon.^{2,121} Mercury contamination was also documented, although clinical mercury toxicity has not been reported.²⁰ Methamphetamine laboratories use many xenobiotics, including phosphine gas, methylamine gas, chloroform, and hydrochloric acid^{3,81}; therefore, these laboratories pose a significant health risk to law enforcement officers and the general public, causing respiratory and ophthalmic irritation, headaches, and burns.^{28,155} Currently, the sale of other potential amphetamine synthetic ingredients, such as hydrochloric acid, hydrogen chloride gas, anhydrous ammonia, red phosphorus, and iodine, are also monitored and restricted in the United States.^{22,29}

Methamphetamine exists as a chiral molecule with two isomers that include levomethamphetamine and dextromethamphetamine. Although the levorotatory form is devoid of CNS stimulatory properties, it retains its vasoactive effects and is used in nonprescription nasal decongestant inhalers. In the racemic mixture, the dextrorotatory form is responsible for the entire stimulant effects observed with methamphetamines. Methamphetamine undergoes metabolism in the liver mainly to amphetamine and 4-hydroxymethamphetamine and has prolonged half-life of 19 to 34 hours, although the duration of its acute effects can be greater than 24 hours.⁴⁹

3,4-Methylenedioxymethamphetamine (MDMA)



3,4-Methylenedioxymethamphetamine, also known as MDMA, was first synthesized in 1912, and was rediscovered in 1965 by Shulgin. MDMA is known as “ecstasy,” “E,” “Adam,” “XTC,” “molly,” and “MDM,” and it is commonly abused by college students and teenagers.^{128,170,174} Other amphetamines that are similar to MDMA, include MDEA (“Eve”) and MDA (“love drug”), which have similar clinical effects, are also used or distributed as MDMA in areas of MDMA use. Amphetamines sold as MDMA include 2CB, 2,4-dimethoxy-4-(n)-propylthiophenylethylamine (2C-T7), and N-methyl-1-(3, 4-methylenedioxyphenyl)-2-butanamine (MBDB).^{27,63,92} The term “ecstasy” may be used for all these xenobiotics. Typically, MDMA is available in 50 to 200 mg colorful and branded tablets.

MDMA and similar analogs are so-called entactogens (meaning touching within), capable of producing euphoria, inner peace, and a desire to socialize.¹⁵² In addition, some psychologists used MDMA to enhance psychotherapy until the Controlled Substances Act of 1986 placed MDMA in Schedule I, thereby eliminating its medical use.¹¹⁹ People who use MDMA report that it enhances pleasure, heightens sexuality, and expands consciousness without the loss of control.⁷⁰ Negative effects reported with acute use included ataxia, restlessness, confusion, poor concentration, and impaired memory.¹⁵² MDMA has about one-tenth the CNS stimulant effect of amphetamine. Unlike amphetamine and methamphetamine, MDMA is a potent stimulus for the release of serotonin.^{24,45,72} The concentration of MDMA required to stimulate the release of serotonin is 10 times less than that required for the release of dopamine or norepinephrine. In animal models, the stereotypic and discriminatory effects of MDMA and its congeners can be distinguished from those of other amphetamines.²⁴

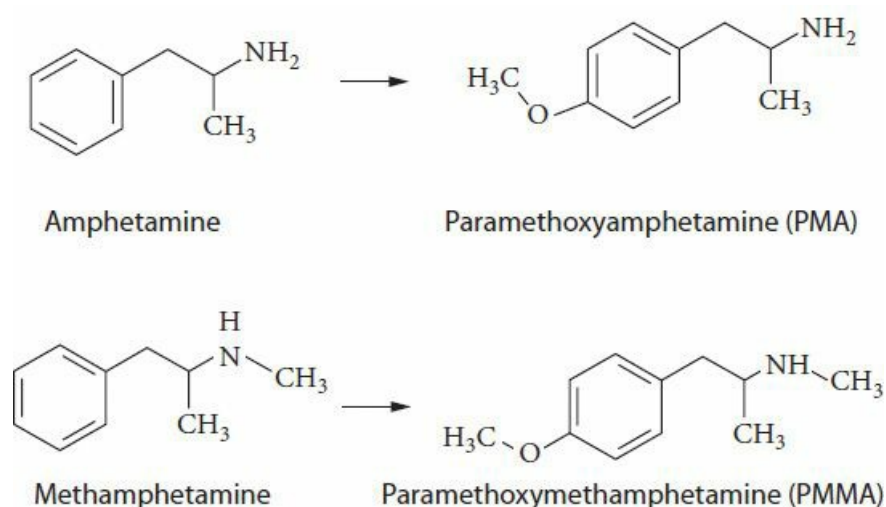
The sympathetic effects of MDMA are mild in low doses. However, when a large amount of MDMA is taken, the clinical presentation is similar to that of other amphetamines, and deaths can result from abuse.^{61,91,138} Those patients at greatest risk develop dysrhythmias, hyperthermia, rhabdomyolysis, and disseminated intravascular coagulation.¹³⁸ Significant hyponatremia is reported with MDMA use.^{1,21,75} MDMA and its metabolites increase the release of vasopressin

(antidiuretic hormone), and this may be related to the serotonergic effects.⁵⁶ Furthermore, substantial free water intake combined with sodium loss from physical exertion in dance clubs may exacerbate the development of hyponatremia.

Most recently, reports of poisoning from a form of MDMA known as Molly have emerged. Molly is initially thought to be a purified or crystallized form of MDMA that is typically taken orally. Molly use has increased due to what was perceived as a more rapid onset of symptoms and a subtler offset or “come down” period. Molly is also commonly viewed as a safer form of MDMA, since it is believed to contain no adulterants. The use of Molly is associated with adverse effects such as intracranial hemorrhage.⁸⁵ While Molly is often sold on the street as MDMA, Molly may not be pure MDMA but actually may contain 2C compounds, amphetamines that have two methoxy groups and a halogen such as iodine (2C-I) or bromide (2C-B). The compound 2C-I is known as “smiles.”

A major concern with MDMA use is its long-term effects on the brain. In numerous animal models, acute administration of MDMA leads to the decrease in serotonin reuptake transporter (SERT) function and number. Recovery of SERT function may take several weeks. Repetitive administration of MDMA ultimately results in permanent damage to serotonergic neurons, typically causing injury to the axons and the terminals while sparing the cell bodies.^{112,140,141} Some regeneration of synaptic terminals can occur even with neuronal damage, but functional recovery is incomplete. Intact SERT function is necessary for MDMA-induced neurotoxicity. Xenobiotics that inhibit the reuptake of serotonin prevent MDMA-induced neurotoxicity in animals. Animal data suggest that MDMA induces hydroxyl free-radical generation and decreases antioxidants in serotonergic neurons.¹⁴⁹ MDMA itself is not the ultimate neurotoxin, rather its metabolites 3-methyldopamine and N-methyl- α -methyldopamine appear to be responsible in animals.¹¹⁶ When antioxidants are depleted, neuronal damage may occur.

Paramethoxyamphetamine (PMA) and Paramethoxymethamphetamine (PMMA)-Monomethoxy Derivatives

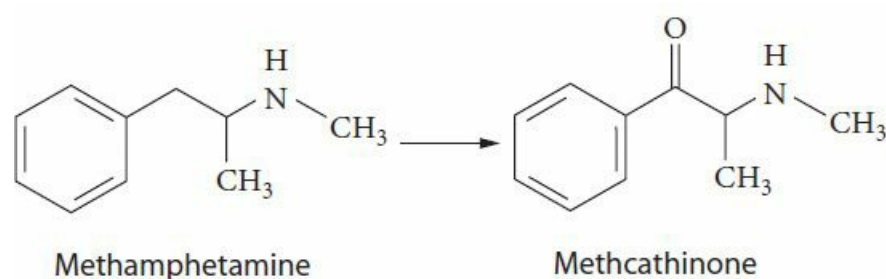


Para-methoxyamphetamine (PMA) is the 4-methoxylated analog of amphetamine, and para-methoxy-N-methylamphetamine (PMMA; methyl-MA) is the 4-methoxy analog of methamphetamine. PMA was first produced in 1973 and sold as a hallucinogen for a short period of time, and it reemerged in the 1990s. PMMA soon appeared after PMA, with multiple reports of death also emerging during that time.^{10,83,97,102} PMA and PMMA are commonly found as tablets or capsules sold as MDMA or “ecstasy.” While the effects of PMA and PMMA mimic some aspect of MDMA and methamphetamine, there are unique properties of PMA and PMMA, that make them considerably more lethal and earning the street name “death.” In recent years, there have been more than 100 fatalities and severe poisonings attributed to PMMA and PMA in the United States, Canada, and Europe.^{87,100,103,107,109}

Methoxy ring substitution of amphetamine or methamphetamine at the 3 or 4 positions (para substitution is the most common) yields PMA and PMMA derivatives that have significantly less sympathomimetic activity than amphetamine but very potent serotonergic activity.^{38,158} Both PMA and PMMA inhibit reuptake of serotonin and inhibit monoamine oxidase A found centrally and peripherally. The methoxy ring substitution is also responsible for poor penetration of the blood brain barrier.^{6,58}

PMA and PMMA poisoning lead to autonomic hyperactivity similar to what is observed in other amphetamines such as hypertension, tachycardia, and agitation. The use of PMA and PMMA results in a weak euphoric effect and delayed onset of CNS effects due to poor blood–brain barrier penetration. These properties will often lead users to repeatedly dose themselves that result in serious toxicity and are responsible for the seemingly high mortality rate.

Cathinones (Methcathinone, MDPV, and Mephedrone)—“Bath Salts”



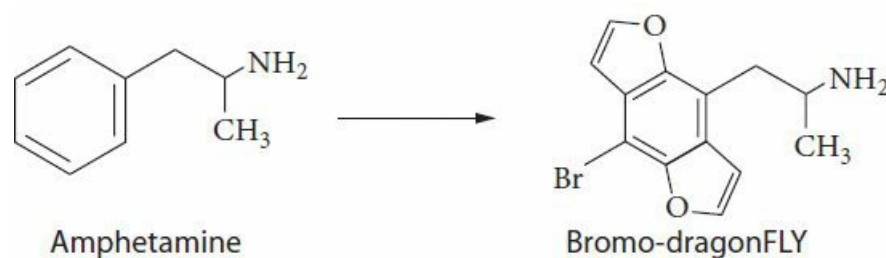
Cathinone ((S)-2-amino-1-phenyl-1-propanone) is a naturally occurring substance found in the leaves of the *Catha edulis* (khat) plant. Also known as guat and gat, the fresh leaves and stems are commonly used as a stimulant in Africa and certain Middle Eastern countries such as Yemen. While there are numerous other amphetamines in minute quantities, the primary active ingredient is cathinone. As the leaves age, cathinone is degraded to cathine, which has about one-tenth the stimulant effect of D-amphetamine. Imported fresh khat must be consumed within a week, before it loses much of its potency. The primary effects of khat are increased alertness, insomnia, euphoria, anxiety, and hyperactivity. Khat chewing is linked to cardiac and gastrointestinal disease.^{125,126}

The syntheses of cathinone derivatives were reported in the early 1920s, with the production of methcathinone in 1928 and mephedrone in 1929. Methcathinone, the methyl derivative of cathinone, was used in Russia as an antidepressant in the 1930s and 1940s. Also known as “Cat” and “Jeff,” cathinone has been used recreationally, most often in countries formerly part of the Soviet Union, but it also gained popularity in the United States, particularly in Michigan, in the 1990s. Synthetic cathinones have become popular drugs of abuse due to a combination of media attention and widespread Internet availability.^{134,150} Many other synthetic cathinones have been produced including methylone, mephedrone, butylone, methylenedioxypyrovalerone (MDPV), dimethylcathinone, ethcathinone, ethylone, 3- and 4-fluoromethcathinone, and MDPV.

The synthetic cathinones differ from other amphetamines because they contain a ketone at the β position. For this reason, they are often known as β -keto-amphetamines. The β -ketone group is responsible for increased polarity, which decreases penetration of the blood–brain barrier. They possess amphetaminelike properties and have sympathomimetic effects, although as a group, they are considered less potent. Some of the synthetic cathinones are reported to cause hyponatremia. Although the mechanism is not clear and may not be similar to MDMA,^{9,25,26,108,130} Reported complications include compartment syndrome, acute kidney injury, and sudden cardiac death.^{101,118,139,144,179} An irreversible Parkinson syndrome was also described in chronic users of intravenous methcathinone, particularly in Europe and Russia. The methcathinone was manufactured with the use of potassium permanganate to oxidize ephedrine or pseudoephedrine. In one case series, T1-weighted magnetic resonance imaging showed symmetric hyperintensity in the globus pallidus and in the substantia nigra and innominata in all active methcathinone users, suggestive of manganese poisoning, which was also confirmed with elevated whole blood concentrations.¹⁵⁹

Synthetic cathinones are often sold as “bath salts” or “plant food” and labeled as “not for human consumption” in an attempt to circumvent controlled substances legislation. The legal status differs among countries and changes over time. In the United States, the synthetic cathinones were initially unscheduled, but they are illegal for human consumption under the Federal Analogue Act of 1986. However, on September 7, 2011, the Drug Enforcement Administration used its emergency scheduling authority to enact temporary control, making possession or sale of methylenedioxypyrovalerone, methylone, and mephedrone illegal until recently, when permanent law has been enacted.

Bromo-dragonFLY



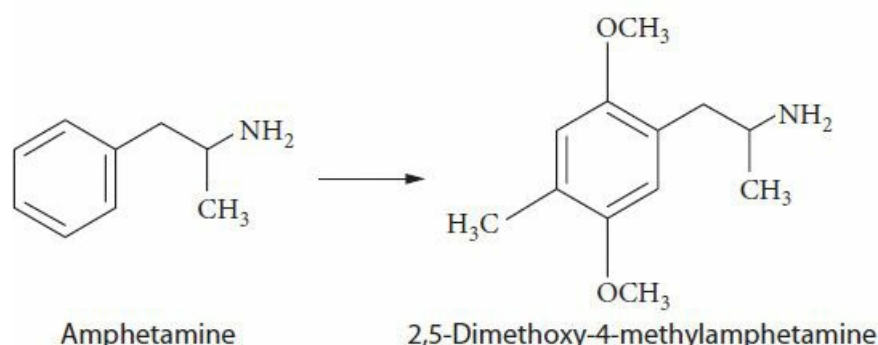
1-(8-Bromobenzo[1,2-b:4,5-b']difuran-4-yl)-2-aminopropane, also known as Bromo-dragonFLY (BDF), was first synthesized in 1998. BDF was named after its superficial structural resemblance to a dragonfly, similar to earlier and the less potent dihydrofuran series of compounds nicknamed FLY. BDF is a member of a new class of benzodifurans, which have been used as a potent research tools for investigation of the serotonin receptor family and for a time as potential antidepressants.

Structurally, BDF is closely related to other phenylethylamines such as DOB and 2C-B. BDF contains two furan rings on either side of the benzene ring, creating a fully aromatic tricyclic structure. There are a number of similar compounds to

BDF, differing by substitution of the bromide atom with other entities. BDF exists as R- and S-enantiomers, which are both biologically active. The R-enantiomer is considered more potent, with its potent hallucinogenic effect mediated through the 5-HT_{2A} serotonin receptor (also with affinity for the 5-HT_{2B} and 5-HT_{2C} serotonin receptors).¹²⁷

BDF is associated with deaths in Europe and the United States. Reports demonstrate delayed complications from severe peripheral vasoconstriction and limb ischemia that likely result from the potent serotonergic properties of BDF.^{4,37,166,175}

2,5-Dimethoxy-4-Methylamphetamine (DOM) and 2,5-Dimethoxy-4-Iodoamphetamine (DOI)



2,5-Dimethoxy-4-methylamphetamine (DOM), also known as STP, which stands for “Serenity, Tranquility, and Peace,” emerged in the 1960s as a hallucinogen. It was noted for its delayed onset of action and duration of effect that quickly led to its short-lived appearance. 2,5-Dimethoxy-4-iodoamphetamine (DOI) is another potent hallucinogen, previously sold as a substitute for lysergic acid diethylamide, or LSD.

Dimethoxy amphetamine derivatives are structurally characterized by methoxy ring substitution at the 2 and 5 positions on the aromatic ring, with varying additional substitution of hydrophobic moieties at the 4 position. DOM and DOI are both serotonin receptor agonists with selectivity at the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptor subtypes. Due to this selectivity, DOM and DOI are often used in scientific research involving study of the 5-HT₂ receptor subfamily. DOM exists as a chiral molecule, with the R-(-)-enantiomer considered the more potent.¹³

Potent hallucinogenic effects and dysphoria characterize the use of DOB and DOI, with minimal sympathomimetic effects. These symptoms can often be delayed with a prolonged duration of effect, sometimes refractory to the use of benzodiazepines. There is also report of reversible vasospasm with the use of these dimethoxy amphetamine derivatives.^{8,19}

SUMMARY

- Amphetamines, often created to evade designer drug laws, continue to increase dramatically throughout the United States.
- The extensive knowledge with regard to the modifications to the existing phenylethylamine backbone allows clinicians to predict the effects of the amphetamines. These effects are attributed to variable degrees of selectivity affecting dopamine, norepinephrine and serotonin.
- Many complications associated with amphetamines are similar to those of cocaine, such as agitation, hyperthermia, rhabdomyolysis, myocardial ischemia, and cerebral infarction.
- The management of acute amphetamine toxicity includes supportive care, with the judicious use of benzodiazepines and anticipation of complications of adrenergic toxicity such as hyperthermia and rhabdomyolysis.

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77 CANNABINOIDS

Jeff M. Lapoint

HISTORY AND EPIDEMIOLOGY

Cannabis has been used for more than 4000 years. The earliest documentation of the therapeutic use of marijuana is the fourth century B.C. in China.¹⁵⁶ Cannabis use spread from China to India to North Africa, reaching Europe around A.D. 500.¹²⁶ In colonial North America, cannabis was cultivated as a source of fiber. Like cocaine and morphine, cannabis was the focus of research efforts in the 19th century. Although the active chemical constituents of the former were isolated during this time, that of cannabis remained elusive.⁹¹ This is due to the fact that the active compounds of morphine and cocaine are both alkaloids and were possible to extract with the technological means of the time, whereas the methods to isolate the active terpenes in cannabis were not available to researchers until several decades later.

The first pure phytocannabinoid to be isolated was cannabinalol, in 1898. Synthesis of its structural isomers yielded the first synthetic cannabinoid years later— Δ^9 -tetrahydrocannabinol (THC). Cannabinalol was previously shown to lack psychoactive effects, but this new compound demonstrated similar effects to cannabis in a model of ataxia in dogs. Pure Δ^9 -THC was subsequently isolated from hashish extract in 1964, and the structure was elucidated in 1967.⁹²

Marijuana was used as an intoxicant from the 1850s until the 1930s when the US Federal Bureau of Narcotics began to portray marijuana as a powerful, addicting substance. Despite this, marijuana was listed in the US Pharmacopoeia from 1850–1942. In 1970, the Controlled Substances Act classified marijuana as a Schedule I drug.

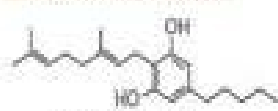
In all populations, cannabis use by males exceeds use by females. Currently, marijuana is the most commonly used illicit xenobiotic in the United States, yet it is legal in states such as Colorado and Washington. A study by the Substance Abuse and Mental Health Services Administration reported that in 2006 in the United States, 6.0% (14.8 million persons) 12 years of age or older used marijuana in the month prior to the survey; this prevalence is unchanged from previous years. The prevalence of past-month users aged 12 to 17 years was 6.7% (down from 8.2% in 2002). The number of first-time users was estimated to be 2.1 million, with 63.3% younger than 18 years of age.

Interest in synthetic cannabinoid receptor agonists (SCRAs) as potential therapeutics increased following the progress of the late 1960's, and several SCRAs similar in structure to THC were created. These semisynthetic compounds were based on the dibenzopyran ring structure of THC and had varying cannabinoid receptor binding affinity relative to THC. The search for a nonopioid analgesic sparked research and development efforts by pharmaceutical companies, most notably Pfizer, from the 1960s to 1980s.⁶³ Despite its efforts, no drugs came to market; new agents retained unwanted psychoactive side effects. During this period, extensive structure activity relationships for cannabinoids were developed.⁶²

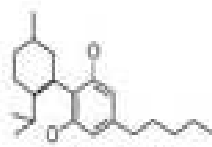
Subsequent synthetic compounds were developed as cannabinoid research tools and were important in the discovery of central and peripheral cannabinoid receptors (CB₁ and CB₂) in the 1980s.³² Many of these did not retain chemical similarity to THC but remained potent and efficacious agonists at CB₁ and CB₂.⁶² In the 1990s, the endogenous cannabinoids were discovered and have been since synthesized.⁸⁰ These free fatty acids are quickly hydrolyzed in vivo, a fact that previously limited potential for pharmaceutical development. More recently stable versions of endocannabinoids have been made (Fig. 77–1).

Cannabinoids

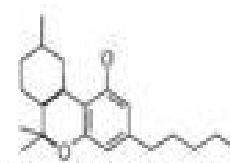
Phytocannabinoids



Cannabigerol

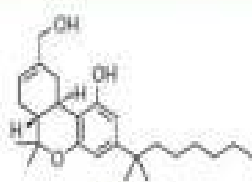


Cannabidiol

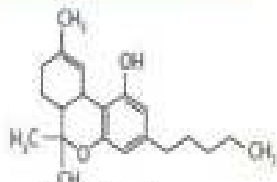


Tetrahydrocannabinol

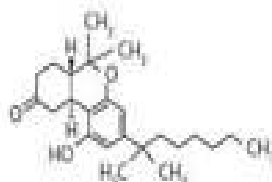
Classical synthetic cannabinoid receptor agonists



HU210

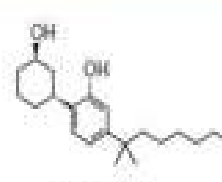


Dronabinol

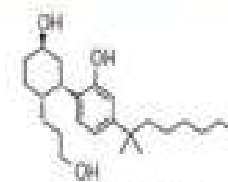


Nabilon

Nonclassical synthetic cannabinoid receptor agonists

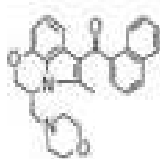


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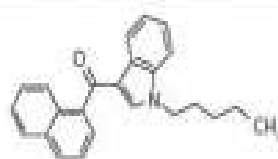


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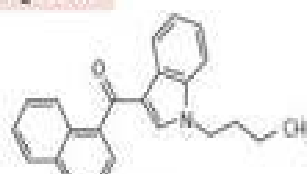
Aminoalkylindole synthetic cannabinoid receptor agonists



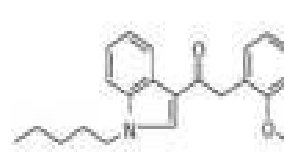
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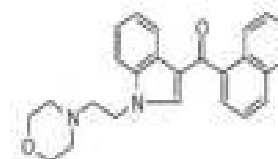
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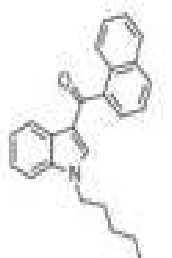
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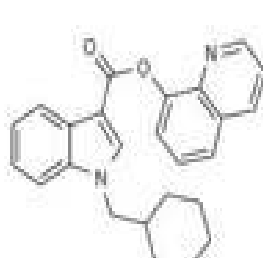
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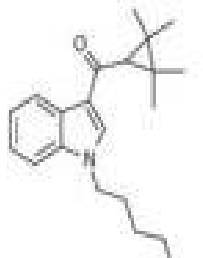
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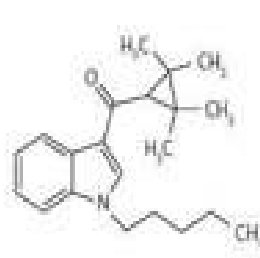
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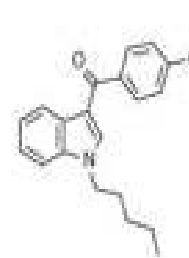
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XLR-11

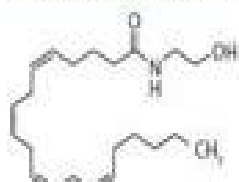


UR144



RCS-4

Endocannabinoids



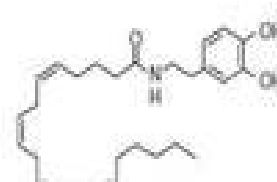
Anandamide



2-arachidonoylglycerol
(2AG)

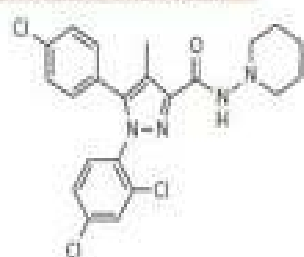


2-arachidonyl glyceryl
ether

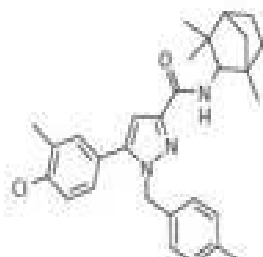


N-arachidonoyl dopamine

Cannabinoid antagonists

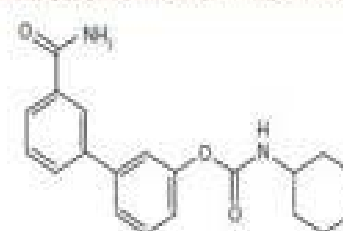


Rimonabant



SR 144,528

Fatty acid amide hydrolase inhibitor



URB 597

FIGURE 77-1. Cannabinoid structural classes.

In 2004, SCRA-laced herbal incense blends began to be available over the Internet and through smoke shops in

Western Europe.⁸⁴ Popular use and subsequent publicity increased resulting in several users presenting to emergency departments in Germany. As the result of efforts by the German government and THC Pharma, JWH-018 was isolated as the psychoactive ingredient present in these early incense blends. The discovery led to legislative action and subsequent ban of herbal incense—containing JWH-018 in Germany, but almost as soon as the ban took effect, incense manufacturers simply switched to a different SCRA—JWH-073. Since that time, many Western European countries have further legislated control of SCRA.

Incidence of exposure in the United States has been increasing over the past 3 years, and in November 2010, the Drug Enforcement Administration (DEA) began the process of declaring selected SCRA to be Schedule I substances on a temporary basis. As of March 2011, the DEA has listed several nonclassical cannabinoids as Schedule I, but as was the case in Germany, manufacturers have switched to other SCRA not yet scheduled and even marketed the products as such.

MEDICAL USES

Marijuana has been used medicinally for thousands of years to treat a seemingly endless array of conditions. However, modern medicine is burdened by an evidence-based system rather than the belief-based medicine of old. Therefore, potential medicinals must be proven through rigorous investigation to be not only safe but efficacious in the treatment of a targeted malady. While smoked marijuana and THC preparations have not proved overly dangerous in published studies, questionable efficacy has been demonstrated. Several issues must be considered when examining the body of evidence both for and against the medical use of cannabinoids. Marijuana is not the same entity as, nor is interchangeable with, Δ^9 -THC. While the latter may be the chief psychoactive constituent of marijuana, the multiple additional cannabinoids present in marijuana are biologically active and must be considered. Secondly, significant study design flaws limit the conclusions that can be drawn from existing studies. Finally, poor overall understanding of cannabinoid physiology may hamper future study design. Proposed uses for medical marijuana and the available evidence supporting that use are reviewed below.

Pain

Acute Pain. Studies examining the efficacy of THC in the setting of induced acute pain showed no improvement. These studies were limited by the lack of a positive control and examined only extremes of induced pain.²⁹ Smoked marijuana failed to attenuate thermal pain in volunteers, and an oral THC analog had no effect on postsurgical pain.⁶⁹

Chronic Pain. When used for the treatment of chronic and neuropathic pain, cannabinoids have had more favorable outcomes in published studies although design flaws severely limit the quality of evidence for medical use.¹⁰⁹ Initial trials of combined cannabinoid opioid therapy have been encouraging, and the principle may have mechanistic merit based on the knowledge that opioid and cannabinoid receptors can form heterodimers,¹²⁰ but lack of proper controls and the presence of confounders limit the accepted clinical applicability of cannabinoids as analgesics at this time.

Nausea and Vomiting

Trials of cannabinoids for treatment of chemotherapy-induced nausea and vomiting have repeatedly shown that serotonin antagonists such as ondansetron are superior compared to smoked marijuana or oral synthetic preparations.

Glaucoma

Trials investigating the efficacy of cannabinoids for the treatment of glaucoma have demonstrated their inferiority to longer acting traditional therapeutics, which have more significant effects on intraocular pressure and longer durations of effect.

Summary of Medical Use

In 2003, the Institute of Medicine undertook an extensive review of the evidence supporting the medical use of marijuana. It concluded that in some circumstances, cannabinoids show promise for use as therapeutics but the quality of current studies necessitated further research specifically for the treatment of chronic pain. In addition, smoked marijuana is a crude and unpredictable delivery mechanism, and safer, more precise methods of administration are needed.¹⁵² No data reviewed since that publication is sufficient to reverse that opinion.

Pharmaceutical cannabinoids are proposed for use in the management of many clinical conditions (Table 77–1) but have generally been approved only for the control of chemotherapy-related nausea and vomiting that are resistant to conventional antiemetics, for breakthrough postoperative nausea and vomiting, and for appetite stimulation in human immunodeficiency virus (HIV) patients with anorexia-cachexia syndrome.⁵⁵ The claims of benefit in the other medical conditions in Table 77–1 are not supported by evidence.^{6,154}

TABLE 77–1. Medical Conditions Proposed for Cannabinoid Use

Anorexia-cachexia syndrome secondary to HIV infection^a

Anxiety

Asthma

Depression

Epilepsy

Glaucoma

Head injury

Insomnia

Migraine headaches

Multiple sclerosis

Muscle spasticity and spasms

Nausea and vomiting (resistant)^a

Neurologic disorders

Pain

Parkinson disease

Tourette syndrome

^aUS Food and Drug Administration— approved use.

HIV = human immunodeficiency virus.

PHARMACOLOGY AND PATHOPHYSIOLOGY

The term “cannabinoid” refers to compounds that bind to and agonize the cannabinoid receptors regardless of whether they are derived from plants (phytocannabinoids), synthetic processes (synthetic cannabinoid receptor agonists), or endogenously existing neuromodulators (endocannabinoids). At one time the term may have been used to delineate a structural similarity to Δ^9 -THC, but this naming convention has largely been abandoned during the past 30 years of cannabinoid research as new compounds have been discovered and synthesized. The structural diversity of cannabinoid ligands and the absence of a true pharmacophore make nomenclature based purely on structure cumbersome and inconsistent. It is preferable then to use the term cannabinoid to denote receptor agonism and subclassify cannabinoids further based on origin and structure (Fig. 77–1).

Cannabis is a collective term referring to the bioactive substances from the Cannabis plant. The Cannabis genus (species sativa and indica) produces more than 60 chemicals (C21 group) called cannabinoids. In this chapter, the term “cannabis” encompasses all cannabis products. The major cannabinoids are cannabitol, cannabidiol (CBD), and tetrahydrocannabinol. The principal psychoactive cannabinoid is THC, or Δ^9 -tetrahydrocannabinol. Marijuana is the common name for a mixture of dried leaves and flowers of the C. sativa plant. Hashish and hashish oil are the pressed resin and the oil expressed from the pressed resin, respectively. The concentration of THC varies from 1% in low-grade marijuana up to 50% in hash oil. THC extracted from marijuana using butane (butane hash oil or BHO) can approach THC concentrations of 100%. Pure THC and a SCRA are available by prescription with the generic names of dronabinol and nabilone, respectively. Nabiximols is the generic name for an oral mucosal spray containing THC and cannabidiol, which is approved for medical use in Canada, the United Kingdom, and parts of Europe. Unregulated SCRA originally designed as research chemicals have emerged as designer drugs of abuse over the past 6 years.

Cannabinoid receptors are G protein linked neuromodulators that inhibit adenylate cyclase in a dose-dependent and stereospecific manner. While historically the cannabinoid receptor system is described as having a central CB₁ and a peripheral CB₂ receptor, recent evidence points to the central nervous system (CNS) presence of CB₂ receptors.¹³⁴ The two currently identified cannabinoid receptors are labeled CB₁ and CB₂ and are distinguished largely by their anatomic distribution and mechanisms of cellular messaging (Fig. 77–2).

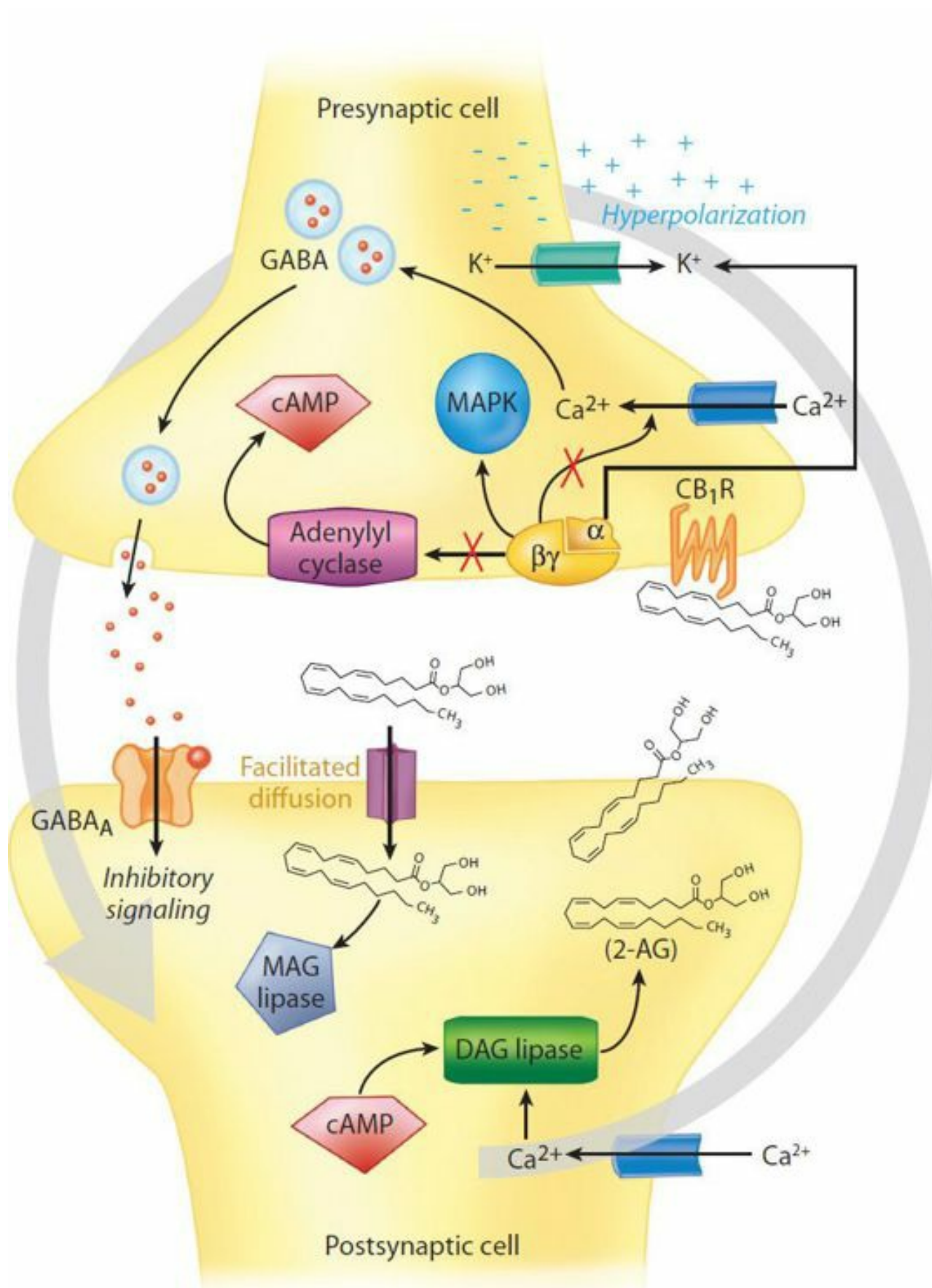


FIGURE 77–2. Endocannabinoids act as allosteric cellular messengers. In response to presynaptic γ -aminobutyric acid (GABA) release and postsynaptic binding resulting in increased cyclic AMP, endocannabinoids are synthesized on demand and bind to presynaptic cannabinoid receptors. Activation of these G protein receptors results in decreased presynaptic adenylyl cyclase, decreased cAMP, decreased calcium ion influx and increased potassium efflux. The net result is hyperpolarization of the presynaptic cell and decreased neurotransmitter release. After binding, endocannabinoids diffuse back to the post synaptic area where they undergo degradation by MAG lipase and fatty acid amide hydrolase. CB₁R = cannabinoid type 1 receptor; MPAK = mitogen-activated protein kinase; MAG lipase = monoacylglycerol lipase; DAG lipase = diacylglycerol lipase. (Adapted with permission from Seely KA, Prather PL, James LP, Moran JH: Marijuana-based drugs: innovative therapeutics or designer drugs of abuse? Mol Interv. 2011;11:36–51.)

CB₁ Receptors and the Psychogenic Effects of Cannabis

CB₁ receptors are the most numerous G protein coupled receptors in the mammalian brain accounting for the multiple and varied effects of Cannabis on behavior, learning, and mood as well as suggesting the enormous complexity of the endocannabinoid system.⁵⁴ The highest concentration of CB₁ receptors are located in areas of the brain associated with movement and higher functions of cognition and emotions. Relative lack of CB₁ receptors in the brainstem also explains lack of coma and respiratory depression seen with Cannabis use. CB₁ receptors are structurally comprised of seven transmembrane protein units coupled to pertussis-sensitive (decrease adenylate cyclase) G proteins. They exhibit genetic variation via splice variants and are found as heterodimers with a multitude of other receptor types.⁶³

CB₂ receptors have traditionally been thought of as existing in the periphery and mainly affecting immune response, although evidence now exists of their activity in the CNS. Isolated agonism of CB₂ receptors has been the target for novel pharmaceutical candidates as antiinflammatory agents with minimal success as psychoactive effects of CB₁ agonism were still evident.

Mechanism of Cellular Signaling

Cannabinoid receptors both in the CNS and in the periphery exist on the presynaptic terminus of various neurons. Depolarization in postsynaptic portion of the neuron and subsequent increase in intracellular Ca²⁺ leads to on-demand synthesis and release of endocannabinoids.¹⁰⁸ These free fatty acid-based messengers diffuse into the synapse and bind to the presynaptic cannabinoid receptor. Ligand binding causes conformational change in the G protein subunits and inhibition of adenylate cyclase, resulting in decreased intracellular cAMP concentrations, decreased activity of voltage-gated Ca²⁺ channels, and ultimately decreased neurotransmitter release (Fig. 77–2). Exogenous cannabinoids act in much the same way compared to endogenous compounds after receptor binding, except that binding affinity will vary among ligands and endogenous cannabinoids are rapidly metabolized by hydrolases.⁸⁰ Interestingly, some online chemical suppliers offer fatty acid amide hydrolase inhibitors for sale, along with various SCRAAs, perhaps providing a glimpse into future products more closely related to endocannabinoids coming to market.

Both receptors inhibit adenylate cyclase and stimulate K⁺ channel conductance.¹¹² CB₁ receptors are located either presynaptically or postsynaptically and their activation can inhibit or enhance the release of acetylcholine, L-glutamate, γ -aminobutyric acid, noradrenaline, dopamine, and 5-hydroxytryptamine.^{67,73,127}

The neuropharmacologic mechanisms by which cannabinoids produce their psychoactive effects have not been fully elucidated.^{56,67,112} Nevertheless, activity at the CB₁ receptors is believed to be responsible for the clinical effects of cannabinoids,^{12,37,67,140} including the regulation of cognition, memory, motor activities, nociception, and nausea and vomiting. Chronic administration of a cannabinoid agonist reduces CB₁ receptor density in several regions of the rat brain.¹³

PHARMACOKINETICS AND TOXICOKINETICS

Absorption

The pharmacokinetics of phytocannabinoids have been extensively reviewed.⁴⁷ The rate and completeness of absorption of cannabinoids depend on the route of administration and the type of cannabis product.

Inhalation of smoke containing THC results in the onset of psychoactive effects within minutes. From 10% to 35% of available THC is absorbed during smoking, and peak serum THC concentrations occur an average of 8 minutes (range, 3–10 minutes) after the onset of smoking marijuana. Peak serum concentrations depend on the dose. A marijuana cigarette containing 1.75% THC produces a peak serum THC concentration of approximately 85 ng/mL.⁵⁹

Ingestion of cannabis results in an unpredictable onset of psychoactive effects in 1 to 3 hours. Only 5% to 20% of available THC reaches the systemic circulation following ingestion. Peak serum THC concentrations usually occur 2 to 4 hours after ingestion, but delays up to 6 hours are described.⁸² Dronabinol has an oral bioavailability of approximately 10% with high interindividual variability.^{44,103} THC is detectable in serum 1.5 to 4.5 hours after ingestion of dronabinol; peak serum concentrations occur within 4 hours after ingestion.⁴³ Nabilone has an oral bioavailability estimated to be greater than 90% and reaches peak serum concentrations 2 hours after ingestion.¹²⁵ The therapeutic serum THC concentration for the treatment of nausea and vomiting is greater than 10 ng/mL.²²

Distribution

THC has a steady-state volume of distribution of approximately 2.5 to 3.5 L/kg.⁴⁷ Cannabinoids are lipid soluble and

accumulate in fatty tissue in a biphasic pattern. Initially, THC is distributed to highly vascularized tissues such as the liver, kidneys, heart, and muscle. Following smoking or intravenous administration, the distribution half-life is less than 10 minutes.⁶⁰ After the initial distribution phase, THC accumulates more slowly in less vascularized tissues and body fat. Repeated administration of Δ^8 -THC (an isomer of Δ^9 -THC) to rats over 2 weeks resulted in steadily increasing concentrations of Δ^8 -THC in body fat and liver but not in brain tissue. Once administration of Δ^8 -THC stopped, the cannabinoids were slowly released from fat stores as adipose tissue turned over.¹⁰⁷

THC crosses the placenta and enters the breast milk. Concentrations in fetal serum are 10% to 30% of maternal concentrations. Daily marijuana smoking by a nursing mother resulted in concentrations of THC in breast milk eightfold higher than concomitant maternal serum concentrations; THC metabolites do not accumulate in breast milk.¹¹⁴

Metabolism

THC is nearly completely metabolized by hepatic microsomal hydroxylation and oxidation (primarily CYP2C9 and CYP3A4).⁴⁷ The primary metabolite (11-hydroxy- Δ^9 -THC or 11-OH-THC) is active and is subsequently oxidized to the inactive 11-nor- Δ^9 -THC carboxylic acid metabolite (THC-COOH) and many other inactive metabolites.^{14,118}

The serum concentrations of THC and its metabolites change over time. Smoking a marijuana cigarette results in peak serum THC concentrations before finishing the cigarette. In six volunteers, peak serum THC concentrations occurred at 8 minutes (range, 6–10 minutes) after onset of smoking, peak 11-OH-THC at 13 minutes (range, 9–23 minutes), and peak THC-COOH at 120 minutes (range, 48–240 minutes) (Fig. 77–3).⁵⁹ Approximately 1 hour after beginning to smoke a marijuana cigarette, the THC to 11-OH-THC ratio is 3:1, and the THC to THC-COOH ratio is 1:2; at approximately 2 hours the ratios are 2.5:1 and 1:8, respectively; and at 3 hours the ratios are 2:1 and 1:16, respectively.⁵⁹ Ingestion of cannabis results in much more variable concentrations and time courses of THC and metabolites (Fig. 77–3). Nonetheless, at 2 to 3 hours postingestion, the ratios are similar to those after smoking: THC to 11-OH-THC is 2:1 and THC to THC-COOH ranges from 1:7 to 1:14.¹⁵⁰

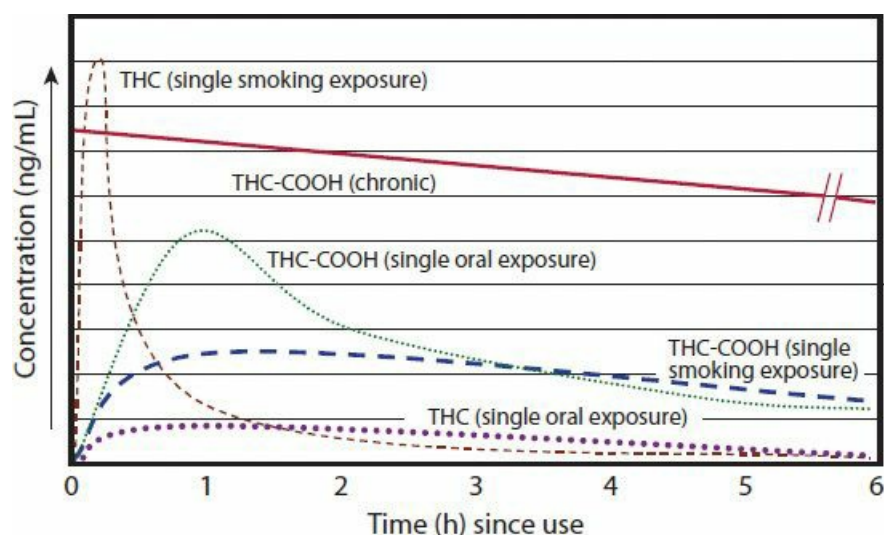


FIGURE 77–3. Estimated relative time course of THC and its major metabolite in the urine based on the route of exposure. THC = Δ^9 tetrahydrocannabinol; THC-COOH = Δ^9 THC carboxylic acid.

Of the many aminoalkylindole (AAI) SCRAAs isolated in “Spice” incense blends, human metabolic analyses have been published for JWH-018, JWH-073, and AM 2201.^{14,15} In contrast to THC, these cannabinoids are metabolized largely through hydroxylation and oxidation by CYP2C9 and CYP1A2 (with minor contributions of CYP2D6) to active metabolites that retain affinity for and in most are agonists at both CB₁ and CB₂ receptors.^{26,27} These metabolites undergo glucuronic acid conjugation in phase II metabolism.

Excretion

Reported elimination half-lives of THC and its major metabolites vary considerably. Following intravenous doses of THC, the mean elimination half-life ranges from 1.6 to 57 hours.⁴⁷ Elimination half-lives are expected to be similar following inhalation.^{47,59} The elimination half-life of 11-OH-THC is 12 to 36 hours, and the elimination half-life of THC-COOH ranges from 1 to 6 days.^{75,150}

THC and its metabolites are excreted in the urine and the feces. In the 72 hours following ingestion, approximately 15% of a THC dose is excreted in the urine and roughly 50% is excreted in the feces.^{1,20,153} Following intravenous

administration, approximately 15% of a THC dose is excreted in the urine and only 25% to 35% is excreted in the feces.¹⁵⁰ Inhalation is expected to produce results similar to intravenous administration.^{47,59} In 5 days, 80% to 90% of a THC dose is excreted from the body.^{51,64}

Cannabinoids were measured in the urine following smoking a marijuana cigarette containing 27 mg of THC (Fig. 77–3).⁸⁸ THC urine concentrations peaked at 2 hours (mean, 21.5 ng/mL; range, 3.2–53.3 ng/mL) after smoking and were undetectable (<1.5 ng/mL) in five of the eight subjects by 6 hours after smoking. Urine concentrations of 11-OH-THC peaked at 3 hours (77.3 ± 29.7 ng/mL). The primary urinary metabolite is the glucuronide conjugate of THC-COOH.¹⁵⁴ THC-COOH urine concentrations peak at 4 hours (179.4 ± 146.9 ng/mL),⁸⁹ and it has an average urinary excretion half-life of 2 to 3 days (range: 0.9–9.8 days).⁴⁷ Both 11-OH-THC and THC-COOH remained detectable in the urine of all eight subjects for the 8 hours of the study.⁸⁸

Following discontinuation of use, metabolites may be detected in the urine of chronic users for several weeks.^{36,70} Factors such as age, weight, and frequency of use only partially explained the long excretion period.³⁶

Primary urinary metabolites of nonclassical SCRA are summarized in Fig. 77–4.

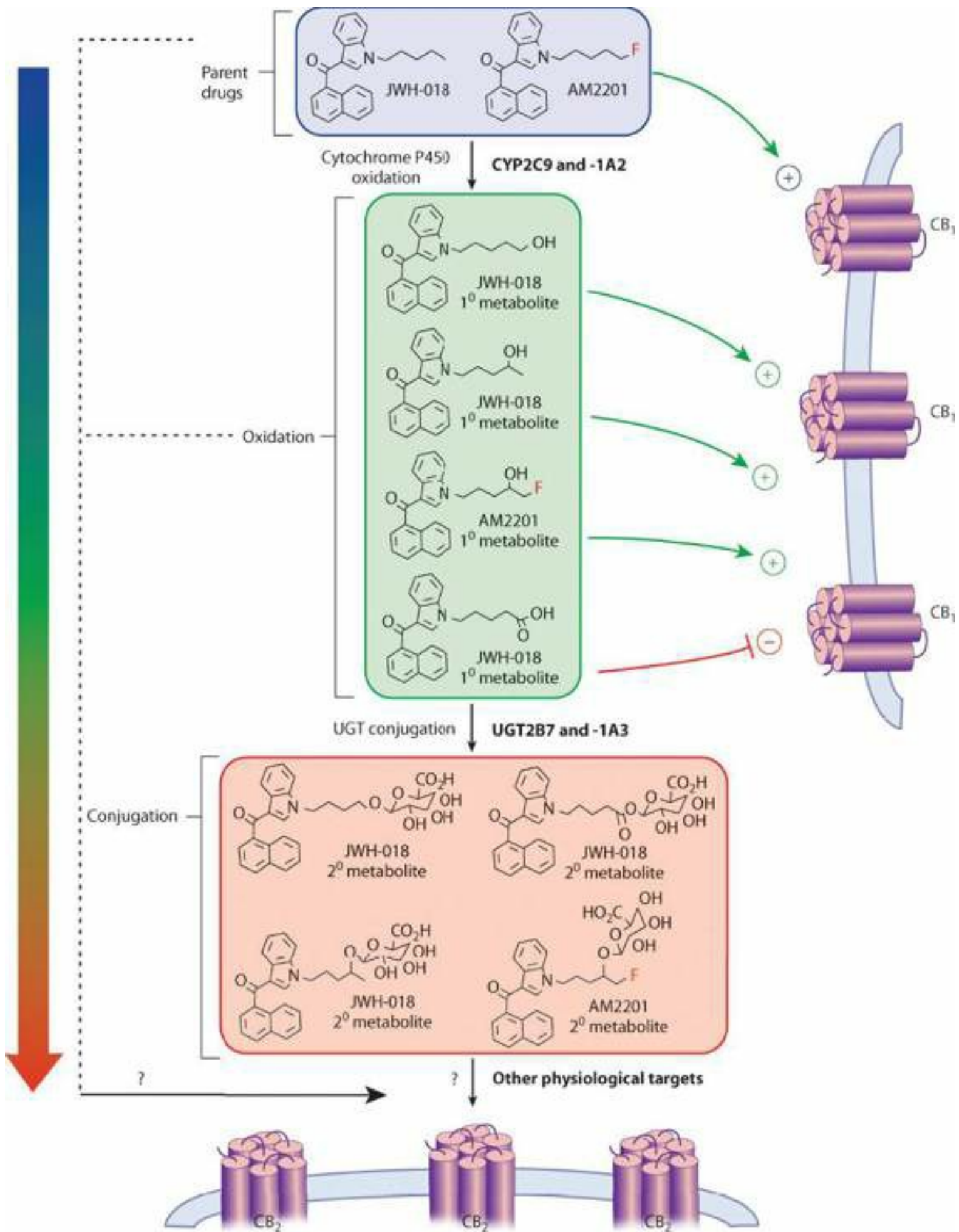


FIGURE 77-4. JWH-018 and AM2201 metabolism. Aminoalkylindole synthetic cannabinoid JWH-018 and its omega fluorinated analog AM2201 undergo oxidation by CYP2C9 and CYP1A9 to primary metabolites that retain affinity and ability to bind with cannabinoid receptors. One JWH-018 primary metabolite, acts as a antagonist at CB₁. Secondary metabolites are formed by conjugation. These metabolites may retain ability to bind to cannabinoid receptors but at this

time it is clear which do so and in what capacity (agonist, antagonist, or inverse agonist). (Adapted with permission from Chimalakonda KC, Seely KA, Bratton SM, et al.: Cytochrome P450-mediated oxidative metabolism of abused synthetic cannabinoids found in K2/Spice: identification of novel cannabinoid receptor ligands. *Drug Metab Dispos.* 2012;40:2174–2184.)

CLINICAL MANIFESTATIONS

The clinical effects of THC use, including time of onset and duration of effect, vary with the dose, the route of administration (ingestion is slower in onset than inhalation), the experience of the user, the vulnerability of the user to psychoactive effects, and the setting in which the drug is used. The concomitant use of CNS depressants such as ethanol, or stimulants such as cocaine, alters the psychological and physiologic effects of marijuana.

Psychological Effects

Use of marijuana produces variable psychological effects.³⁷ The variation, which occurs both between and within users, may be a result of drug tolerance, level or phase of clinical effects, strain of cannabis, physical and social settings, or user expectations or cognitive set. The most commonly self-reported effect is relaxation. Other commonly reported effects are perceptual alterations (heightened sensory awareness, slowing of time), a feeling of well-being (including giddiness or laughter), and increased appetite.⁴⁶

Physiologic Effects

Use of cannabis is associated with physiologic effects on cerebral blood flow, the heart, the lungs, and the eyes. In a controlled, double-blind positron emission tomography study,⁸⁹ intravenous THC increased cerebral blood flow, particularly in the frontal cortex, insula, cingulate gyrus, and subcortical regions. These increases in cerebral blood flow occurred 30 to 60 minutes after use and were still elevated at 120 minutes.⁹⁰ Similar blood flow changes result from smoking marijuana.¹¹¹

Common acute cardiovascular effects of cannabis use include increases in heart rate and decreases in vascular resistance.^{71,135} Cannabis produces dose-dependent increases in heart rate within 15 minutes of starting a marijuana cigarette (from a baseline mean of 66 beats/min to a mean of 89 beats/min) that reach a maximum (mean, 92 beats/min) 10 to 15 minutes after peak serum THC concentrations. These changes last for 2 to 3 hours.⁸ Increases in blood pressure may occur with cannabis use. In a study of six subjects, an increase in blood pressure from a baseline mean of 119/74 mm Hg to a mean of 129/81 mm Hg occurred but was not statistically significant.⁸ In a double-blind, controlled study of men being investigated for angina pectoris, smoking a marijuana cigarette resulted in statistically significant changes in blood pressure from a baseline mean of 123/79 mm Hg to a peak mean of 132/84 mm Hg.¹¹⁹ In contrast, repeated THC use resulted in significant slowing of heart rate (from a mean of 68 beats/min to a low of 62 beats/min) and lowering of blood pressure (from a mean of 116/62 mm Hg to a low of 108/53 mm Hg).¹⁰ Decreased vascular tone may cause postural hypotension accompanied by dizziness and syncope.

Inhalation or ingestion of THC produces a dose-related short-term decrease in airway resistance and an increase in airway conductance in both normal and asthmatic individuals.¹⁴² Smoking marijuana results in an immediate increase in airway conductance, which peaks at 15 minutes and lasts 60 minutes. Ingestion of cannabis produces a significant increase in airway conductance at 30 minutes, which peaks at 3 hours and lasts 4 to 6 hours.^{143,144,147} The mechanism for this effect is unclear.

The principal ocular effects of cannabis are conjunctival injection and decreased intraocular pressure. Cannabinoids, applied topically to a rabbit eye, resulted in hyperemia of the conjunctival blood vessels 2 hours after application.⁹⁶ Regardless of route of administration, cannabis causes a fall in intraocular pressure in 60% of users⁴⁵ by acting on CB₁ receptors in the ciliary body.¹¹⁷ The mean reduction in intraocular pressure is 25% and lasts 3 to 4 hours.

Physiological effects of novel SCRAAs have not been studied in any controlled settings.

ACUTE TOXICITY

In addition to the physiologic and psychological effects described above, acute toxicity may include decreases in coordination, muscle strength, and hand steadiness. Lethargy, sedation, postural hypotension, inability to concentrate, decreased psychomotor activity, slurred speech, and slow reaction time also may occur.^{106,153}

In young children, the acute ingestion of cannabis is potentially life threatening.⁸⁷ Ingestion of estimated amounts of 250 to 1000 mg of hashish resulted in obtundation in 30 to 75 minutes. Tachycardia (>150 beats/min) was found in one third of the children. Less commonly reported findings include apnea, cyanosis, bradycardia, hypotonia, and opisthotonus.

The acute toxicity profile of nonclassical SCRA stands in stark contrast to the relatively mild effects of smoked or ingested phytocannabinoid products and surprised both users and clinicians, who expected effects to be largely identical to marijuana and hashish. This is likely a result of AAI cannabinoids found in incense blends being more potent and efficacious at cannabinoid receptors as well as having active metabolites. Moreover, these products are unregulated, and the presence of additional contaminating xenobiotics, such as designer cathinones, methylxanthines, and long-acting β -adrenergic agonists such as clenbuterol must be considered.

Deciphering the recent case literature of SCRA toxicity is fraught with challenges as many of the published reports lack laboratory confirmation of exposure. In addition, cases involving spice blends carry the possibility that some adverse effects could result from the plant matter found with the SCRA. Finally, the concentration of SCRA varies by incense package, even of the same brand and lot, making dose estimation difficult if not impossible.

Agitation¹²⁹ and seizures are reported.^{81,128} In one report with laboratory confirmation, a patient experienced multiple seizures within 30 minutes after ingesting JWH-018 in powder form.⁸¹ The sample was confirmed as pure JWH-018, and it was later further analyzed, as was the patient's blood and urine, for the presence of cathinones or other xenobiotic contaminants, with none detected.

Psychosis (new onset, acute exacerbation of existing psychiatric disorders, and increased risk of psychosis relapse) and anxiety have resulted even after single doses.^{53,65,115}

Tachycardia was a common finding detailed in one series, and tachydysrhythmia requiring cardioversion has been described.⁸¹ Chest pain and increased troponin concentrations were observed in three patients who claimed to have smoked spice several days before presenting to hospital, but laboratory confirmation of SCRA exposure was not performed.⁹⁷

Diffuse pulmonary infiltrates and dyspnea requiring intubation and mechanical ventilation were reported in a habitual spice user. Laboratory confirmation revealed three parent SCRA (AM2201, JWH-122, and JWH-210).²

Accounts of acute kidney injury are described in a case series of 16 previously healthy patients. All patients reported smoking spice incense blends prior to presentation. The patients had flank pain, nausea, and vomiting with elevated serum creatinine concentrations. Laboratory confirmation was achieved in eight of the patients and a previously unreported SCRA was isolated (XLR-11). Several of the patients required hemodialysis, but all eventually recovered.¹⁰¹

ADVERSE REACTIONS

Acute Use

Cannabis users occasionally may experience distrust, dysphoria, fear, or panic reactions. Transient psychotic episodes are associated with cannabis use. Commonly reported adverse reactions at the prescribed dose of dronabinol or nabilone include postural hypotension, dizziness, sedation, xerostomia, abdominal discomfort, nausea, and vomiting. One case of acute pancreatitis (serum amylase concentration up to 3200 IU/mL) following a period of heavy cannabis use is reported, but the causal relationship is unclear.⁴⁴

Life-threatening ventricular tachycardia (200 beats/min) has been reported.¹²¹ In six individuals with acute cardiovascular deaths, postmortem whole-blood THC concentrations ranged from 2 to 22 ng/mL (mean, 7.2 ng/mL; median, 5 ng/mL).⁵ While the temporal association is clear, causality is less clear because three of the six people had significant preexisting cardiac pathology. The risk of myocardial infarction is increased five times over baseline in the 60 minutes after marijuana use but subsequently declines rapidly to baseline risk levels.⁹⁸ Atrial fibrillation with palpitations, nausea, and dizziness was temporally associated with smoking marijuana in four patients.^{38,79,138}

Chronic Use

Long-term use of cannabis is associated with a number of adverse effects.

Immune System. Cannabinoids affect host resistance to infection by modulating the secondary immune response (macrophages, T and B lymphocytes, acute phase and immune cytokines). However, an immune-mediated health risk from using cannabis has not been documented.⁷⁷

Respiratory System. Chronic use of marijuana is associated with clinical findings compatible with obstructive lung disease.¹⁴⁷ Smoking marijuana delivers more particulates to the lower respiratory tract than does smoking tobacco,¹⁵⁵ and marijuana smoke contains carcinogens similar to tobacco smoke. Case reports and a hospital-based case-control study suggest that cancers of the respiratory tract (mouth, larynx, sinuses, lung) are associated with daily or near daily smoking of marijuana, although exposure to tobacco smoke and ethanol may be confounding factors.^{21,142,145} A systematic review and a cohort study with 8 years of follow-up demonstrated no association between marijuana smoking and smoking-related cancers,^{49,93} and a population-based case-control study found that marijuana use was not associated with an increased risk of developing oral squamous cell carcinoma.¹²⁴

Cardiovascular System. Marijuana use may be a risk for individuals with coronary artery disease. An exploratory prospective study of self-reported marijuana use among patients admitted for myocardial infarction found that patients who used marijuana were at significantly increased risk for cardiovascular and noncardiovascular mortality compared with nonusers.^{98,103}

Reproductive System. Reduced fertility in chronic users is a result of oligospermia, abnormal menstruation, and decreased ovulation.¹⁷ Cannabis is a class C drug in pregnancy¹⁶ and affects birth weight and length but does not cause fetal malformations. Statistically significant reductions in birth weight (mean, 79 g less than nonusers) and length (mean, 0.5 cm shorter than nonusers) are reported in women who had urine assays positive for cannabis during pregnancy.¹⁵⁷ The results of three other studies are difficult to interpret because marijuana use in pregnancy was poorly documented.^{50,157} Epidemiologic studies based on self-reporting of cannabis use do not support an association between the use of cannabis during pregnancy and teratogenesis.^{78,85,157}

The effect of maternal use of cannabis during pregnancy on neurobehavioral development in the offspring has been studied. No detrimental effects are reported in children born to women who smoked marijuana daily (more than 21 cigarettes per week) in rural Jamaica.³⁴ Tremors and increased startle are reported in infants younger than 1 week of age whose mothers used cannabis during pregnancy.⁴⁰ These findings, which persisted beyond 3 days, were not associated with other signs of a withdrawal syndrome. There were no abnormalities in the children of parents who used greater than five cigarettes per week in Ottawa, Canada, at 12, 24, and 36 months of age, but lower scores in verbal and memory domains at 48 months of age are reported.^{39,41,51} The results of studies evaluating the effect of in utero exposure to cannabis on postnatal neurobehavioral development are equivocal because of methodologic concerns regarding exposure assessment and control of covariates,³¹ including the continued parental use of cannabis during the postnatal and early childhood periods. The role of second hand exposure to cannabis on postnatal and early childhood development of neurobehavioral problems has not been evaluated.

Endocrine System. In experimental animals, cannabis exposure is associated with suppression of gonadal steroids, growth hormone, prolactin, and thyroid hormone. In addition, cannabis alters the activity of the hypothalamic-pituitary-adrenal axis.¹⁷ In human studies, the results are inconsistent, long-term effects have not been convincingly demonstrated, and clinical consequences are undefined.¹⁷

Neurobehavioral Effects. There is a concern that chronic cannabis use results in deficits in cognition and learning that last well after cannabis use has stopped. Neuropsychological tests administered to 10 cannabis-dependent adolescents, eight adolescent noncannabis drug abusers, and nine nondrug users showed significant differences that persisted for the duration of the study (6 weeks of abstinence) between the cannabis group and the other groups in a visual retention test and a memory test.¹³² In a study of three experienced marijuana smokers, cannabis impaired arithmetic and recall tasks up to 24 hours after smoking.⁵² Adults who used cannabis more than seven times per week had impairments in math skills, verbal expression, and memory retrieval processes; people who used cannabis one to six times per week showed no impairments.¹¹ After 1 day of abstinence, 65 heavy marijuana users (median, use on 29 of past 30 days) showed greater impairment on neuropsychological tests of attention and executive functions than light marijuana users (median, use on 1 day of past 30 days).¹¹⁶ (The authors were uncertain whether this difference was caused by residual THC in the brain, a withdrawal effect from the drug, or a direct neurotoxic effect of cannabis.)

There is little evidence that adverse cognitive effects persist after stopping the use of cannabis⁶⁸ or that cannabis use causes psychosocial harm to the user.⁸⁶ The hypothesis that there is a causal association between cannabis use and psychosis has not been proven unequivocally.⁹ An “amotivational syndrome” is attributed to cannabis use. The syndrome is a poorly defined complex of characteristics such as apathy, underachievement, and lack of energy.^{25,131} The association of the syndrome with cannabis use is based primarily on anecdotal, uncontrolled observations.⁵⁶ Anthropologic field studies, evaluations of US college students, and controlled laboratory experiments have failed to identify a causal relationship between cannabis use and the amotivational syndrome.⁵⁶ A study evaluating the role of depression in the amotivational syndrome found significantly lower scores on “need for achievement” scales in heavy users (median, daily use for 6 years) with depressive symptoms compared with heavy users without depressive symptoms and light users (median, several times per month for 4.5 years) with or without depressive symptoms.¹⁰⁵ These data suggest that symptoms attributed to an amotivational syndrome are caused by depression, not cannabis. Another study found that behavior that could be interpreted as amotivation was inversely related to the perceived size of the reward.²⁵

Abuse, Dependence, and Withdrawal. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition, defines marijuana abuse as repeated instances of use under hazardous conditions; repeated, clinically meaningful impairment in social/occupational/educational functioning; or legal problems related to marijuana use. Marijuana dependence is defined as tolerance, compulsive use, impaired control, and continued use despite physical and psychological problems caused or exacerbated by use. The amount, frequency, and duration of cannabis use required to develop dependence are not well established.^{24,141} Much of the support for cannabis dependence is based on the existence of a withdrawal syndrome. In

animals repeatedly given cannabis, the administration of a CB₁ receptor antagonist produced signs of withdrawal.^{83,139} In humans, chronic users experience unpleasant effects when abstaining from cannabis.¹⁸ The time of onset of withdrawal symptoms is not well characterized.¹⁷ The most reliably reported effects are irritability, restlessness, and nervousness as well as appetite and sleep disturbances.¹³⁹ Other reported acute withdrawal manifestations include tremor, diaphoresis, fever, and nausea. These symptoms and signs are reversed by the oral administration of THC.^{9,48} The duration of withdrawal manifestations, without treatment, is not clearly established.^{19,139}

There is a single report of a withdrawal syndrome observed after heavy and prolonged nonclassical SCRA use.

Cannabinoid Hyperemesis Syndrome. Chronic, heavy marijuana use is associated with a clinical syndrome comprised of abdominal discomfort, nausea, and hyperemesis. Symptoms are often refractory to opioids and antiemetics.¹⁵¹ The hallmark of the syndrome is almost immediate relief of symptoms with bathing or showering in hot water, and a major diagnostic feature is compulsive bathing. The pathophysiology of this syndrome is unclear. However, relief with hot water may indicate dysfunction of pain perception, excess substance P release, and activation of TRPV1 (a G protein receptor that has been shown to interact with the endocannabinoid system and is the only known capsaicin receptor); these may play a role in elucidating the mechanism for this syndrome as well as providing new treatment modalities. Ultimately, successful treatment of the cannabinoid hyperemesis syndrome depends on cessation of marijuana use.^{3,23,33,42,136,137,151}

CANNABIS AND DRIVING

The perceptual alterations caused by cannabis suggest that its recent use should be associated with automobile crashes. However, neither experimental nor epidemiologic studies have provided definitive answers about the effects cannabis use has on driving ability. The published analytical studies of the relationship between cannabis and driving behavior and motor vehicle crashes have been reviewed.⁷ In experimental driving studies, cannabis impairs driving ability, but cannabis-using drivers recognize their impairment and compensate for it by driving at slower speeds and increasing following distance. However, the slower reaction time caused by cannabis results in impaired emergency response behavior.

The epidemiologic studies evaluating the association of cannabis use and traffic crashes provide no evidence that cannabis alone increases the risk of causing fatal crashes or serious injuries.^{7,110} A recent study comparing past driving records of subjects entering a drug treatment center with controls found that a self-reported history of cannabis use was associated with a statistically significant increase in adjusted relative risk for all crashes (relative risk, 1.49; 95% confidence interval, 1.17–1.89) and for “at fault” crashes (relative risk, 1.68; 95% confidence interval, 1.21–2.34).²⁸

DIAGNOSTIC TESTING

Cannabinoids can be detected in plasma or urine. Enzyme-multiplied immunoassay technique (EMIT) and radioimmunoassay (RIA) are routinely available; gas chromatography–mass spectrometry (GC-MS) is the most specific assay and is used as the reference method.

EMIT is a qualitative urine test that is often used for screening purposes. EMIT identifies the metabolites of THC. In these tests, the concentrations of all metabolites present are additive. For the EMIT II Cannabinoid 20 ng Assay, the cutoff concentration for distinguishing positive from negative samples is 20 ng/mL. A positive test means that the total concentration of all the metabolites present in the urine was at least 20 ng/mL. A positive urine test for cannabis only indicates the presence of cannabinoids, and it does not identify which metabolites are present or in what concentrations. Qualitative urine test results do not indicate or measure intoxication or degree of exposure. The National Institute on Drug Abuse guidelines for urine testing specify test cutoff concentrations of 50 ng/mL for screening and 15 ng/mL for confirmation.

Variables affecting the duration of detection of urinary metabolites include dose, duration of use, acute versus chronic use, route of exposure, and sensitivity of the method. In addition, factors affecting the quantitative values of urine THC and metabolites include urine volume, concentration, and pH. Using GC/MS, metabolites may be detected in the urine up to 7 days following a single marijuana cigarette.^{60,61}

The length of time between stopping cannabis use and a negative EMIT urine test (<20 ng/mL) depends on the extent of use. Release of THC from adipose tissue is important in drug testing because chronic users may release cannabinoids in quantities sufficient to result in positive urine tests for several weeks. In addition, vigorous exercise may stimulate the release of cannabinoids from fat depots. In light users being tested daily under observed abstinence, the mean time to the first negative urine test is 8.5 days (range, 3–18 days) and the mean time to the last positive urine is 18.2 days (range, 7–34 days).³⁶ In heavy users (mean, 9 years of using at least once a day) being tested under the same conditions, the mean time to the first negative urine test result (EMIT assay <20 ng/mL) was 19.1 days (range, 3–46 days) and the mean time to the last positive urine sample was 31.5 days (range, 4–77 days).³⁶

Standard laboratory analyses identify THC and its metabolites but cannot identify the source of the THC (eg, marijuana,

hashish, dronabinol). EMIT will not identify nabilone because it is not THC; however, nabilone can be specifically identified using high-performance liquid chromatography–tandem mass spectrometry.¹²²

Immunoassays may give false-negative and false-positive test results (Table 77–2). To help identify evidence tampering, negative urine immunoassays should be accompanied by examining the urine for clarity and measuring urinary specific gravity, pH, temperature, and creatinine.^{133,148}

TABLE 77–2. Xenobiotics or Conditions Reported to Produce Inaccurate Screening Test Results for Tetrahydrocannabinol

<i>False Negative^a</i>	<i>False Positive</i>
Bleach (NaOCl)	Dronabinol
Citric acid	Efavirenz
Detergent additives	Ethacrynic acid
Dettol	Hemp seed oil
Dilution	Nonsteroidal antiinflammatory drugs
Glutaraldehyde	Promethazine
Lemon juice	Riboflavin
Potassium nitrite (KNO ₂)	
Table salt (NaCl)	
Tetrahydrozoline	
Vinegar (acetic acid)	
Water	

^aXenobiotics producing false negative urine tests are usually added to a urine sample, not ingested.

EMIT will not detect nonclassical SCRA metabolites. Commercial urine immunoassays are available but generally need to be directed to a specific SCRA. High-performance liquid chromatography–tandem mass spectrometry or gas chromatography mass spectrometry are currently the mainstay of laboratory confirmation for SCRA, but their clinical utility is limited in all but retrospective instances. Further challenges are presented by the multitude of known nonclassical cannabinoids and doubly so by the rate new SCRA are introduced to the illegal high market.^{46,66,72,74,99,100,123,146,149}

PASSIVE INHALATION

Studies of passive exposure to marijuana smoke and the urinary excretion of cannabinoids have used enclosed spaces with nonsmokers present during and after active smoking.^{30,82,102,110,113} In an unventilated 6.9 × 8.2 × 7.9-foot room (12,225.8 L of air), five adult volunteers were exposed to the side stream smoke of 4 or 16 marijuana cigarettes (THC, 25 mg/cigarette) smoked simultaneously over one hour on each of six consecutive days.³¹ After being exposed to four marijuana cigarettes, four of the volunteers had at least one positive urine by EMIT assay (cutoff, 20 ng/mL) at some unspecified time during the six study days; exposure to 16 marijuana cigarettes resulted in positive EMIT assays only after the second day of exposure.

In a car (1650 L of air), three adult volunteers were exposed to the smoke from 12 marijuana cigarettes smoked by two people over 30 minutes.¹⁰² EMIT analyses of urine samples from one passive inhaler were positive at time 0 to 4 hours and on days 2 and 3; a second passive inhaler had one positive urine test at time 4 to 24 hours after exposure.

Three adult volunteers in a 10 × 10 × 8-foot unventilated room (21,600 L of air) were exposed to the side stream smoke of four marijuana cigarettes (THC, 27 mg/cigarette) smoked simultaneously over one hour.¹⁰⁴ The concentrations of cannabinoids in urine samples taken 20 to 24 hours after exposure were less than 6 ng/mL when analyzed using RIA methodology. Another study used an unventilated room (total volume of 27,950 L) containing three desks and a filing cabinet.⁸² Over 10 to 34 minutes, each of six volunteers smoked a marijuana cigarette (THC, 17.1 mg/cigarette) and left the room. Four nonsmoking adult males were in the study room for 3 hours from the start of smoking. The door was opened and closed 18 times during the study. The maximum urine cannabinoid concentration (measured by RIA) in the nonsmokers was 6.8 ng/mL at 6 hours after the start of smoking.

Another study used a closed 8 × 8 × 10-foot room (15,500 L of air) with each of four subjects smoking two marijuana cigarettes containing 2.5% THC on one occasion and 2.8% THC on a second occasion.¹¹³ On each occasion, two nonsmoking subjects were in the room for one hour from the onset of smoking. None of the nonsmokers' urine samples (0–24 hours) from either exposure period tested positive on an EMIT assay with a cutoff of 20 ng/mL. An identical experiment in a closed car (approximately 3500 L of air) resulted in one of 23 urine specimens testing positive at 6 hours.

Therefore, passive inhalation of marijuana smoke is unlikely to result in positive urine test results unless the exposure has been extreme.

SALIVA

Saliva samples may be used to establish the presence of cannabinoids and time of cannabis consumption. Cannabinoids (THC, THC-COOH, 11-OH-THC) in saliva may be from the smoke of the marijuana or hashish or from a preliminary metabolism in the mouth.¹³⁰ Saliva THC concentrations above 10 ng/mL are consistent with recent use and correlate with subjective intoxication and heart rate changes.⁹⁴

HAIR

Hair sample analysis is not useful in identifying THC or its metabolites. Only small quantities of non-nitrogen-containing substances, such as cannabinoids, are found in hair pigments.^{35,76,95}

SWEAT

The analysis of perspiration to test for cannabinoids is a recent development. Perspiration deposits drug metabolites on the skin, and these are renewed even after the skin is washed. Detection threshold is reported to be 10 ng/mL, but forensic confirmation by alternative means is required.⁷⁶

ESTIMATING TIME OF EXPOSURE

A measurable serum concentration of THC is consistent with recent exposure and toxicity, but there is poor correlation between serum THC concentrations and actual clinical effects.⁵⁷ The ratio of THC to THC-COOH has been used to estimate time of smoking marijuana. Similar concentrations of each indicate cannabis use within 20 to 40 minutes and imply intoxication. In naive users, a concentration of THC-COOH that is greater than THC indicates that use probably occurred more than 30 minutes ago. The high background concentrations of THC-COOH in habitual users make estimations of time of exposure unreliable in this population.

Serum concentrations of THC and THC-COOH were used in a logarithmic equation to predict the time since smoking a marijuana cigarette.⁸⁸ The ratio provided acceptable results up to 3 hours after smoking (predicted time of exposure averaged 27 minutes longer than actual exposure time), but more than 3 hours after smoking the predicted exposure time was overestimated by 3 hours. Mean overestimations of predicted exposure time of 2.5 to 4.2 hours for smoking and of 1.6 hours for ingestions are reported when serum samples are taken more than 4 hours after exposure.⁵⁹

Chronic use or oral administration of cannabis increases the concentration of 11-OH-THC relative to the concentrations of THC or THC-COOH. In these cases, estimating time of exposure based on relative concentrations is problematic.⁵⁸ In four subjects, ingestion of cannabis produced total serum metabolite concentrations less than 20 times the serum THC concentration for 3 hours after ingestion, suggesting that a ratio of this magnitude is consistent with recent oral consumption.⁸²

MANAGEMENT

Gastrointestinal decontamination is not recommended for patients who ingest cannabis products, nabilone, or dronabinol because clinical toxicity is rarely serious and responds to supportive care. In addition, a patient with a significantly altered mental status, such as somnolence, agitation, or anxiety, has risks associated with gastrointestinal decontamination that outweigh the potential benefits of the intervention.

Agitation, anxiety, or transient psychotic episodes should be treated with quiet reassurance and benzodiazepines (midazolam 1–2 mg intramuscularly or diazepam 5–10 mg intravenously) as needed.

The toxicity of SCRAAs should not be expected to mirror that of THC or prescription THC-based cannabinoids. Aggressive supportive care may be necessary.

Psychomotor agitation, anxiety, and convulsions should be treated with benzodiazepines as above. Laboratory evaluation should be initiated for signs of electrolyte disturbances and direct toxicity of the CNS, cardiovascular, renal, and musculoskeletal systems. Aggressive crystalloid fluid resuscitation should be given for rhabdomyolysis and acute kidney injury.

Antipsychotics should be avoided during any phase of undifferentiated agitated delirium. Should psychotic features persist into a subacute time frame after the resolution of sympathomimetic features, antipsychotic medications can be considered. Patients should be observed until asymptomatic.

If available, drug samples along with the patient's blood and urine, while not clinically useful, may aid in unknown designer SCRA identification and understanding of clinical effects.

There are no specific antidotes for cannabis or SCRA toxicity. Coingestants, such as cocaine, ethanol, designer amphetamines, methylxanthines, and long-acting β -adrenergic agonists should be identified and their effects anticipated and treated as indicated.

SUMMARY

- Phytocannabinoids have been used for centuries both as medicinal substances and as intoxicants.
- Despite the collective human history with cannabinoids, we are only now beginning to understand the endocannabinoid system and the consequences of alterations to that system.
- Medical use of THC and smoked marijuana have long existed, and while the safety profile of these xenobiotics are established, evidence of the efficacy of medical marijuana over the gamut of currently prescribed maladies is sparse. Still, the cannabinoid system provides an attractive target system for treatment of chronic pain and appetite modulation, but more rigorous and properly designed investigations are needed.
- The toxicity profile of traditional cannabinoids and designer SCRAAs used as drugs of abuse and research chemicals are as different as their chemical structures. Clinicians, users, and public health policy makers alike would do well to separate these groups of cannabinoids in both thought and practice.

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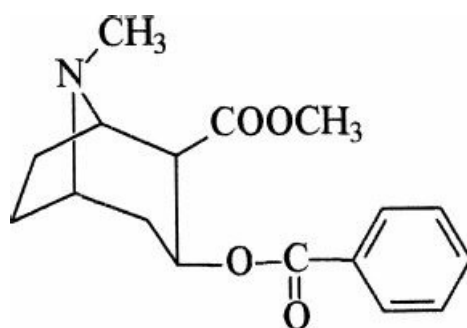
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78 COCAINE

Jane M. Prosser and Robert S. Hoffman



HISTORY AND EPIDEMIOLOGY

Cocaine is contained in the leaves of *Erythroxylum coca*, a shrub that grows abundantly in Colombia, Peru, Bolivia, the West Indies, and Indonesia. As early as the 6th century, the inhabitants of Peru chewed or sucked on the leaves for social and religious reasons. In the 1100s, the Incas used cocaine-filled saliva as local anesthesia for ritual trephinations of the skull.⁶⁸

In 1859, Albert Niemann isolated cocaine as the active ingredient of the plant. By 1879, Vassili von Anrep demonstrated that cocaine could numb the tongue.¹⁰⁸ However, Europeans knew little about cocaine until 1884, when the Austrian ophthalmologist Karl Koller introduced cocaine as an effective local anesthetic for eye surgery and Koller's colleague, Sigmund Freud, wrote extensively on the psychoactive properties of cocaine.⁵⁵ Following these revelations, Merck, Europe's main cocaine producer, increased production from less than 0.75 pounds in 1883 to more than 150,000 pounds in 1886.¹⁰⁴

Simultaneously, reports of complications from the therapeutic use of cocaine began to appear. In 1886, a 25 year-old man had a "pulseless" syncope after cocaine was applied to his eye to remove a foreign body.²¹¹ By 1887, more than 30 cases of severe toxicity were reported,¹⁸¹ and by 1895 at least eight fatalities resulting from a variety of doses and routes of administration were summarized in one article.⁵⁷ Recreational cocaine use was legal in the United States until the passage of the Harrison Narcotic Act of 1914, when cocaine was restricted to medical use. Not until 1982, however, was the first cocaine-associated myocardial infarction reported in the United States.²⁸

Currently, cocaine is an approved pharmaceutical. It is used primarily for topical anesthesia of cutaneous lacerations or during otolaryngology procedures as a vasoconstrictor and topical anesthetic. Although multiple factors have fostered a decline in the medicinal use of cocaine,^{18,63,130} the recreational use of cocaine remains a significant problem.

The United Nations office on Drugs and Crime estimates that there are 13 to 19 million cocaine users worldwide.³⁴ In the United States, it is estimated that there are 1.5 million cocaine users.⁴³

PHARMACOLOGY

The alkaloid form of cocaine, benzoylmethylecgonine, is a weak base that is relatively insoluble in water. It is extracted from the leaf by mechanical degradation in the presence of a hydrocarbon. The resulting product is converted into a hydrochloride salt to yield a white powder, cocaine hydrochloride, which is very water soluble. Cocaine hydrochloride can be insufflated, applied topically to mucous membranes, dissolved in water and injected, or ingested; however, it degrades rapidly when pyrolyzed. Smokable cocaine (crack) is formed by dissolving cocaine hydrochloride in water and adding a strong base. A hydrocarbon solvent is added, the cocaine base is extracted into the organic phase, and then evaporated. The term "free-base" refers to the use of cocaine base in solution.

Cocaine is rapidly absorbed following all routes of exposure; however, when applied to mucous membranes or ingested, its vasoconstrictive properties slow the rate of absorption and delay the peak effect. Bioavailability for smoking cocaine exceeds 90%, and is approximately 80% following nasal application.¹⁰⁰ Data for ingested cocaine and application

to other mucous membranes such as the urethra, vagina, or rectum are inadequately documented. Table 78–1 lists the typical onsets and durations of action for various routes of cocaine exposure.

TABLE 78–1. Pharmacology of Cocaine by Various Routes of Administration

Route of Exposure	Onset of Action (minutes)	Peak Action (minutes)	Duration of Action (minutes)	Relative Peak Concentrations (ng/mL)
Intravenous	<1	3–5	30–60	180 ± 56
Nasal insufflation	1–5	20–30	60–120	220 ± 39
Smoking	<1	3–5	30–60	203 ± 88
Gastrointestinal	30–60	60–90	Unknown	Unknown

Following absorption cocaine is approximately 90% bound to plasma proteins, primarily α_1 -acid glycoprotein.¹⁶⁴ Based on human volunteer studies with small doses of cocaine, the volume of distribution is reported to be about 2.7 L/kg,¹⁰⁰ but it is unclear if the volume of distribution changes with overdose.

The metabolism of cocaine is complex and dependent on both genetic and acquired factors. Three major pathways of cocaine metabolism are well described (Fig. 78–1). Cocaine undergoes N-demethylation in the liver to form norcocaine, a minor metabolite that rarely accounts for more than 5% of drug.^{96,205} However, norcocaine readily crosses the blood–brain barrier and produces clinical effects in animals that are quite similar to cocaine.^{13,103,192} Nearly half of a dose of cocaine is both nonenzymatically²⁰⁴ and enzymatically hydrolyzed⁴¹ to form benzoylecgonine (BE). When BE is injected into animals, some reports suggest that it is virtually inactive,^{105,200} while other studies demonstrate cerebral vasoconstriction³² and seizures.^{112,146} When either injected directly into the cerebral ventricles^{147,192} or applied to the surface of cerebral arteries,¹³³ BE is a potent vasoconstrictor. Although BE traverses the blood–brain barrier poorly,¹⁴⁸ the potential effects are of concern as some BE is probably formed from cocaine that has already entered the central nervous system (CNS). In vitro, BE has little or no effect on cardiac sodium or potassium channels.^{32,49} Finally, plasma cholinesterase (PChE) and other esterases metabolize cocaine to ecgonine methyl ester (EME). In normal individuals, between 32% and 49% of cocaine is metabolized to EME.^{4,96} Like BE, EME crosses the blood–brain barrier poorly.¹⁴⁷ Although many authors state that EME has little or no pharmacologic activity,^{146,147,189} diverse animal models demonstrate contradictory results, concluding that EME is a vasodilator,^{133,162,190} sedative, anticonvulsant,¹⁹² and protective metabolite against lethal doses of cocaine.⁸¹

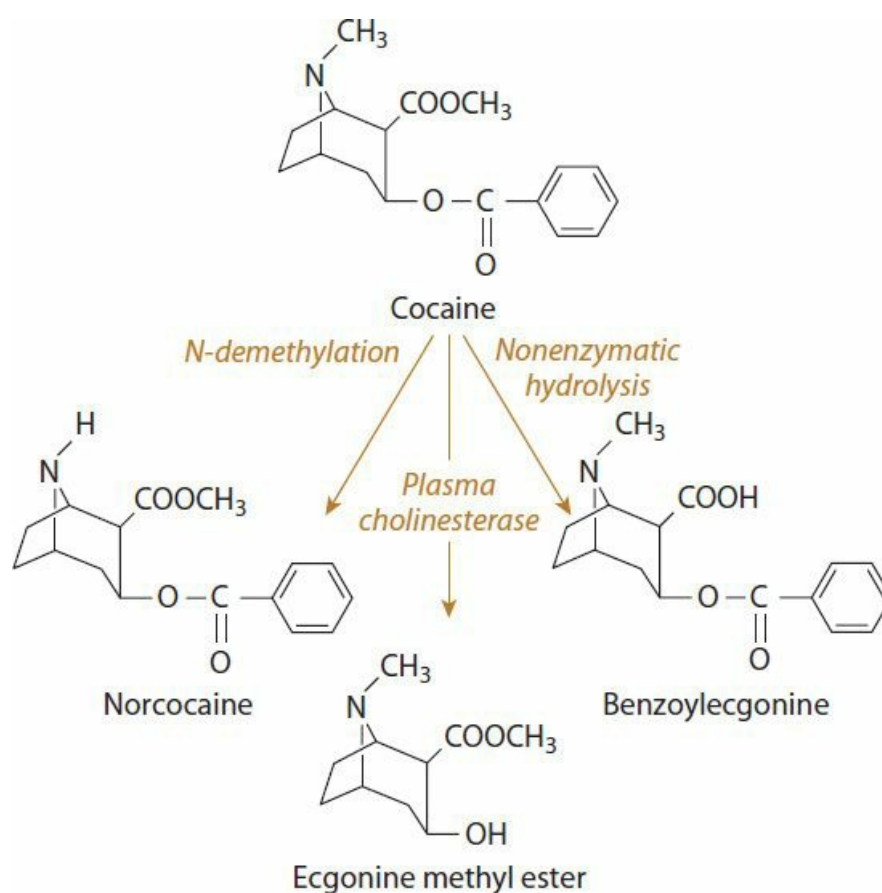


FIGURE 78–1. Metabolism of cocaine. The three principal metabolic pathways of cocaine are depicted.

The role of genetic or acquired alterations in PChE activity has been of interest for many years. Early in vitro studies showed that cocaine was poorly metabolized in serum from patients with succinylcholine sensitivity (low PChE activity). In subsequent studies and case series, patients with low PChE activity demonstrate increased sensitivity to cocaine,^{80,159} findings that are corroborated in multiple animal models.^{20,79,131}

Multiple other metabolites of cocaine are well characterized.³⁰ Several have clinical or diagnostic importance. In 1990, a unique metabolite was identified in patients who smoke cocaine, now known either as anhydroecgonine methyl ester (AEME) or methylecgonide.⁹⁸ The presence of this compound and its metabolite, ecgonidine, can be used to help determine the route of administration in cocaine users.¹⁸⁸ Additionally, AEME has demonstrable agonism at the muscarinic (M₂) receptors, which may have important clinical implications.²³⁰

Ethanol has a unique pharmacologic interaction with cocaine. A transesterification reaction between the two drugs produces benzoylethylecgonine, which is also called “ethyl cocaine” or “cocaethylene” (CE).¹³ In human volunteers given cocaine and ethanol, CE accounted for approximately 17% of the metabolites, producing a decrease in the amount of BE and an increase in the amount of EME formed.^{72,73} CE has a longer duration of action than cocaine and similar neurotoxic and cardiotoxic effects.

PATHOPHYSIOLOGY

Neurotransmitter Effects

Cocaine blocks the reuptake of biogenic amines. Specifically, these effects are described on serotonin and the catecholamines dopamine, norepinephrine, and epinephrine. Several animal investigations have elucidated the particular roles of each neurotransmitter. Mice lacking the dopamine transporter are relatively insensitive to the locomotor effects of cocaine.⁵⁹ Tachycardia emanates from adrenally derived epinephrine, whereas hypertension results from neuronally derived norepinephrine.^{209,210} Serotonin is an important modulator of dopamine and has a role in cocaine addiction, reward, and seizures.^{70,122,141}

Although much emphasis has been placed on the reuptake blockade of these biogenic amines, it is clear that this effect is insufficient to account for the clinical manifestations of cocaine toxicity. Other xenobiotics that block the reuptake of biogenic amines, such as cyclic antidepressants, produce quite distinct clinical manifestations²¹² (Chap. 71). Xenobiotics that block the effects of dopamine, epinephrine, and norepinephrine not only fail to protect against cocaine toxicity but actually exacerbate it.^{23,65,130,184} Although this may, in part, result from an unopposed α -adrenergic effect, hypertension and vasospasm fail to explain the increase in psychomotor agitation, seizures, and hyperthermia that result.^{23,65} These effects most likely result from an interaction between cocaine and excitatory amino acids. Cocaine increases excitatory amino acid concentrations in the brain,¹⁹⁹ and excitatory amino acid antagonists prevent both seizures and death in experimental animals.^{14,175} Finally, because experimental evidence in animals^{22,65,193} and clinical experience in humans demonstrate that sedation treats both the central effects of cocaine and the peripheral effects of biogenic amines, a newer model was proposed (Fig. 78–2). This model emphasizes the necessity of diffuse CNS excitation as a prerequisite for cocaine toxicity, explains experimental and clinical observations, and provides insight into the treatment of acute toxicity.

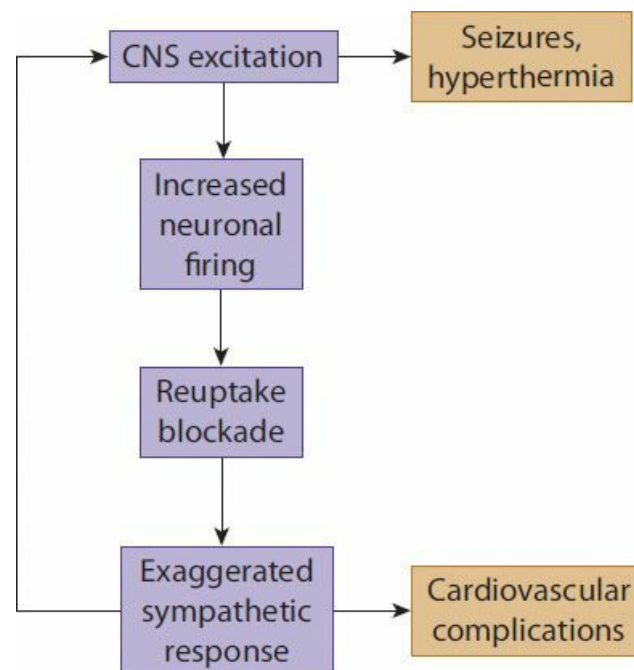


FIGURE 78–2. Cocaine induced central nervous system effects modulate peripheral events.

Cardiovascular Effects

Cocaine use is associated with myocardial ischemia and myocardial infarction (MI). The increased risk of MI results from several different mechanisms. Hypertension and tachycardia increase myocardial oxygen demand, induces vasospasm, accelerated atherogenesis, and hypercoagulability.

Vasospasm. Although increased myocardial oxygen demand may be sufficient to cause ischemia in some individuals, it is clear that cocaine also produces profound vasoconstriction. Evidence suggests that cocaine-induced vasoconstriction is mediated through both neuronal norepinephrine and BE.^{117,132} BE has a direct effect on vessels that appears to be calcium mediated.¹³² Additionally nicotine, which is simultaneously used by many substance users, has additive, if not synergistic, effects with cocaine.¹⁵²

Atherogenesis. Cocaine use accelerates atherosclerosis. Rabbits fed a normal diet supplemented with cholesterol do not develop atherosclerotic vascular disease. However, when that diet includes cocaine, rabbits develop classic atherosclerotic lesions.^{110,119,120} Experiments with human endothelial cells demonstrate that cocaine directly increases the permeability to lipids by altering tight junctions.¹¹¹ This probably promotes the formation of subendothelial atherosclerotic plaques.

Dysrhythmias. Like other local anesthetics (Chap. 67), cocaine blocks neuronal sodium channels, thereby preventing saltatory conduction. Because of homology between neuronal and cardiac sodium channels, cocaine also inhibits the rapid inward Na^+ current responsible for phase 0 depolarization of the cardiac action potential (Chaps. 16 and 71). Experimental evidence suggests that cocaine enters the sodium channel and binds on the inner membrane.^{35,109,169} Like many sodium channel blockers, binding is both pH and use dependent (ie, binding increases as pH falls or heart rate increases; Chap. 71).^{36,221} Furthermore, although norcocaine has a greater affinity for inactivated sodium channels, it has a much more rapid offset of action than cocaine.³⁵ Consequently, cocaine can be characterized as a Vaughan-Williams class 1C antidysrhythmic²²⁹ (Chap. 64). Cocaine-induced QRS prolongation is exacerbated by Vaughan-Williams class IA antidysrhythmics²²⁶ and ameliorated by hypertonic sodium bicarbonate, hypertonic sodium chloride, and lidocaine^{9,63,163}. Another effect of sodium channel blockade, the Brugada pattern, is also associated with cocaine use (Fig. 16–12).^{129,157}

In addition to its sodium channel-blocking properties, cocaine also blocks cardiac potassium channels (Chap. 16). This results in QT prolongation^{167,208,221} and may produce torsade de pointes.¹⁹¹ Cocaethylene also has dysrhythmogenic effects.¹⁵⁸ In vivo experiments demonstrated inhibition of the myocardial HERG potassium channels, which may explain this phenomenon.⁴⁹ In animal studies, CE is associated with increased incidence of dysrhythmias, prolonged myocardial depression, and increased lethality.^{105,225}

Hematologic Effects

Enhanced coagulation and impaired thrombolysis compound the effects of accelerated atherogenesis and vasospasm. Cocaine activates human platelets and causes α -granule release, resulting in platelet aggregation.^{75,116} Thus, even in the absence of endothelial injury, cocaine can initiate a thrombotic cascade while simultaneously enhancing the activity of plasminogen activator inhibitor type 1 (PAI-1), thereby impairing clot lysis.¹⁵¹

Pulmonary Effects

Bronchospasm. The association between cocaine use and asthma¹⁷⁸ was not recognized until smoked cocaine became prevalent.⁴⁷ Furthermore, experiments in human volunteers demonstrate that only smoked cocaine (not intravenous cocaine) produces bronchospasm.²⁰⁷ Although it is possible that bronchospasm results from direct administration of cocaine to the airways, inhaled contaminants of cocaine, or thermal insult, and the unique pyrolytic metabolite of cocaine that acts as a muscarinic agonist (AEME) produces bronchospasm in experimental animals.²⁵

CLINICAL MANIFESTATIONS

Many clinical manifestations of toxicity develop immediately following cocaine use. These are typically associated with the sympathetic overactivity, and their duration of effect is predictable based on the pharmacokinetics of cocaine use. Other manifestations, such as those associated with tissue ischemia, may present in a delayed fashion, with a clinical latency of hours to even days after last cocaine use. The reasons for this delay are not clear but may relate to the presence of an altered sensorium associated with acute cocaine use and its anesthetic effects (see Cessation of Use below).

Vital sign abnormalities that develop during cocaine toxicity are characteristic of the sympathomimetic toxic syndrome. Thus, varying degrees of hypertension, tachycardia, tachypnea, and hyperthermia occur. Although any of these vital sign abnormalities can be life threatening, experimental and clinical evidence suggests that hyperthermia is the most critical.^{23,65,138} Initially, with typically used doses, and at any time with a massive dose, apnea, hypotension, and bradycardia can result, all from direct suppression (anesthesia) of brainstem centers.^{117,130,144} These effects are fleeting and rarely noted when patients present to health care, as either the sympathetic overdrive rapidly ensues, or sudden death results. Additional sympathomimetic findings include mydriasis, diaphoresis, and neuropsychiatric manifestations.

Cocaine produces end-organ toxicity in virtually every organ system in the body. These events result from vasospasm, hemorrhage secondary to increased vascular shear force (dP/dT), or enhanced coagulation. Each organ system is discussed separately in the following sections.

Central Nervous System

Seizures, coma, headache, focal neurologic signs or symptoms, or behavioral abnormalities that persist longer than the predicted duration of effect of cocaine should alert the clinician to a potential catastrophic CNS event. Hemorrhage can occur at any anatomic site in the CNS. Subarachnoid, intraventricular, and intraparenchymal bleeding are all well described in association with cocaine use.^{2,39,125,136,171,194} Early discussions suggested an underlying predisposition due to the presence of arteriovenous malformations or congenital aneurysms,²²⁸ but subsequent larger studies failed to support this analysis, suggesting that effects can occur independently of preexisting disease.^{2,156,218} Ruptured intracerebral aneurysms in cocaine users are almost exclusively in the carotid artery circulation.^{2,156,218} Presumably, CNS bleeding is a manifestation of abnormal shear force. Spontaneous extraaxial bleeding is also associated with cocaine use.¹⁸³

Both vasospastic infarction and transient ischemic attack are reported in association with cocaine use.^{39,40,125} In one epidemiologic study, women younger than age 45 years who had strokes were seven times more likely to report cocaine use than controls.¹⁶⁸ Patients can present with any of the classic physical findings associated with thrombotic or embolic stroke. Vasospasm can injure the spinal cord, resulting in paralysis from an anterior spinal artery syndrome.^{39,150}

Seizures are commonly provoked by cocaine use.^{83,153} Cocaine use can serve as a trigger in patients with epilepsy, although an underlying focus is not necessary for seizures to occur.¹¹³

Headache is also well described in cocaine users. While the exact mechanism is unclear, hypertension or dysregulation of neurotransmitters may be contributory. In addition to typical tension headache, classic migraine and cluster headaches are also reported.^{166,185}

Eyes, Nose, and Throat

Sympathetic excess produces mydriasis through stimulation of the dilator fibers of the iris with characteristic retention of the ability to respond to light. Like other mydriatics, cocaine can produce acute narrow angle-closure glaucoma.⁷¹ Vasospasm of the retinal vessels causes both unilateral and bilateral loss of vision.^{82,127} Additionally, although cocaine produces excellent corneal anesthesia, it is highly toxic to the corneal epithelium. Following application of cocaine to the eye, the superficial corneal layer is shed, resulting in pain and decreased acuity.¹⁷² The loss of eyebrow and eyelash hair from thermal injury associated with smoking crack cocaine is called madarosis.²⁰⁶

Chronic intranasal insufflation of cocaine can produce perforation of the nasal septum. This finding most likely results from repeated ischemic injury with resultant cartilage loss. This ischemia is usually asymptomatic, and necrotic tissue is sloughed. At least one reported case of wound botulism (Chap. 41) has been associated with intranasal insufflation.

Presumably this resulted from accumulation of necrotic tissue in the nose, serving as a culture medium for *Clostridium botulinum*.¹¹⁵

Angioedema and oropharyngeal burns, located as far distally as the esophagus, are associated with smoking crack cocaine.^{21,26,107,145} These effects are most likely the result of inhalation or ingestion of superheated fumes and hot liquid (from the smoking apparatus) rather than direct toxicity from cocaine.

Pulmonary

Pneumothorax, pneumomediastinum, and pneumopericardium are reported following both smoked and intranasal cocaine use.^{134,173,187,212,215} These findings do not result directly from cocaine toxicity but rather are epiphenomena related to the mechanism of drug use. Following insufflation or inhalation, the user commonly performs a Valsalva maneuver in an attempt to retain the drug. Bearing down against a closed epiglottis increases intrathoracic pressure, and an alveolar bleb can rupture against the pleural, mediastinal, or pericardial surfaces.

Cocaine use exacerbates reversible airways disease, and it is common for patients to present with shortness of breath and wheezing.^{47,124,160,177} Like so many manifestations of cocaine toxicity, it is unclear whether this is a direct effect of cocaine or related to inhalation of some contaminant of the drug. However, as discussed above, the M₂ agonistic effects of the pyrolysis metabolite AEME might be contributory.

Crack lung is the term given to an acute pulmonary syndrome that occurs after inhalational use of crack cocaine. The syndrome is a poorly defined constellation of symptoms, including fever, hemoptysis, hypoxia, acute respiratory distress syndrome, and respiratory failure. It is associated with diffuse alveolar and interstitial infiltrates on chest radiography.¹⁷³ Histopathology shows diffuse alveolar damage and hemorrhage with inflammatory cell infiltration and hemosiderin-laden macrophages. Eosinophilia was noted in several cases.⁵³ The syndrome has been variously attributed to impurities mixed with the crack, carbonaceous material generated from pyrolysis, and direct cocaine toxicity.

Vasospasm and subsequent thrombosis of the pulmonary artery or its branches can produce pulmonary infarction.⁴² Patients present with shortness of breath and pleuritic chest pain characteristic of a pulmonary embolus. Clinical signs and symptoms of ventilation-perfusion (V/Q) mismatch ([Chap. 29](#)), as well as abnormalities on arterial blood gas analysis, are noted.

Cardiovascular

Chest pain or discomfort is a common emergency department complaint in cocaine users.¹⁷ Cocaine use is associated with cardiac ischemia and infarction in young people and may account for as much as 25% of myocardial infarctions in patients younger than 45 years of age.¹⁷⁰ Although myocardial infarction is of concern, only approximately 6% of patients with complaints referable to the heart will manifest biochemical evidence of myocardial injury.^{88,222} Many others will have an ischemic cardiac event, but for the remainder, the differential diagnosis is broad.¹¹⁸ Entities to consider include the pulmonary and esophageal etiologies described previously, referred abdominal symptoms (see [Abdominal](#)), chest wall injury,^{37,62,94,126,128} aortic dissection, coronary artery dissection,^{186,203} and dysrhythmias. No single sign or symptom or combination of signs and symptoms reliably identifies cardiovascular injury from among the discussed differential diagnosis.⁸⁸

Catecholamine-induced direct myocardial catecholamine toxicity contributes to both acute and chronic cardiac disease. Takotsubo cardiomyopathy is a reversible form of left ventricular apical ballooning associated with myocardial ischemia in the absence of atherosclerotic lesions. It is thought to result from catecholamine toxicity on the myocardium during high levels of stress and is also reported after cocaine use.⁵ Chronic cocaine use is associated with a dilated cardiomyopathy,^{76,118} the etiology of which is presumed to be the result of repeated subclinical ischemic events. Patients may present with signs and symptoms of congestive heart failure or pulmonary edema. The pathologic finding of contraction band necrosis also suggests that there may be some direct catecholamine toxicity as this finding only commonly occurs with cocaine and amphetamine use, pheochromocytoma, and in patients receiving high-dose vasopressors.^{51,219}

Abdominal

Abdominal pain, or other gastrointestinal complaints, suggests a broad differential diagnosis. Cocaine users have a disproportionate incidence of perforated ulcers.^{123,165,197} The etiology has not been elucidated but may be related to local ischemia of the gastrointestinal tract or increased acid production associated with sympathetic activity. Vasospasm produces ischemic colitis that can present with abdominal pain or bloody stools.^{128,155} More severe vasospasm, with or without thrombosis, can lead to intestinal infarction^{56,77,91,161} with attendant hypotension and metabolic acidosis. Signs and symptoms of bowel obstruction such as vomiting or distension might suggest body packing (gastrointestinal drug smuggling). Although less common, splenic¹⁵⁷ and renal infarctions^{44,149,182} may also occur. Spontaneous hemoperitoneum

is also reported, although occult trauma could not be definitively excluded.¹⁰

Animals frequently develop hepatotoxicity following cocaine administration. In human cocaine users, minor elevations of liver enzyme concentrations are common and rarely associated with symptoms.^{19,114} When more severe liver injury occurs, it is usually associated with multisystem organ dysfunction from hyperthermia or another type of hepatic injury.⁶ Isolated hepatic injury from cocaine is distinctly uncommon and may result from differences in metabolic pathways, as animals are known to make a hepatotoxic metabolite of cocaine that has not been described in humans.²¹⁷

Musculoskeletal

Rhabdomyolysis is common in all conditions that produce an agitated delirium and or hyperthermia; cocaine is no exception.^{31,93,179} Unlike most other toxicologic disorders, however, psychomotor agitation is not a prerequisite for cocaine-associated rhabdomyolysis.²³¹ Muscle injury may result from vasospasm or direct muscle toxicity; however, the mechanism remains unclear. Patients with cocaine toxicity present with a spectrum of illness that ranges from asymptomatic enzyme and electrolyte abnormalities characteristic of rhabdomyolysis, to localized or diffuse muscle pain, to frank compartment syndrome and acute kidney injury.⁴⁵

Limb ischemia associated with cocaine use is reported.⁶⁶ Vasospasm, accelerated atherogenesis, and increased thrombogenesis (see Pathophysiology) place users at increased risk.

Traumatic injury is also fairly common in the setting of cocaine use.¹⁴⁰ Clinicians should be aware of the possibilities of occult fractures or other injuries that may be masked by the anesthetic properties of cocaine or the patient's altered level of consciousness.^{130,139}

Neuropsychiatric

The neuropsychiatric effects of cocaine are most likely dose dependent. Low-dose administration produces alertness, exhilaration, hypersexual behavior, and other "desired" effects. These effects rarely bring users to health care facilities. As the cocaine dose increases, agitation, aggressive behavior, confusion, disorientation, and hallucinations can develop.

Other possible manifestations include a variety of movement disorders that most likely result from depletion or dysregulation of dopamine. Patients may develop acute dystonias^{22,50,216} or choreoathetoid movements that have been referred to as "crack-dancing."^{38,67}

Obstetrical

The majority of obstetrical findings associated with cocaine use involve developmental problems in the fetus and neonate and are probably a result of a combination of chronic vascular insufficiency from cocaine-induced spasm of the uterine artery or distal vessels and other risk factors, such as poor maternal nutrition, cigarette smoking, and a lack of prenatal care (Chap. 31). These events are extensively reviewed elsewhere.^{24,48,196} Acute cocaine use during pregnancy is associated with abruptio placentae, causing patients to present with abdominal pain and vaginal bleeding.^{1,52} The remaining maternal and fetal complications comprise every possible complication described in nonpregnant patients.

DIAGNOSTIC TESTING

Cocaine and benzoylecgonine, its principal metabolite, can be detected in blood, urine, saliva, hair, and meconium. Routine drug-of-abuse testing relies on urine testing using a variety of immunologic techniques (Chap. 6). Although cocaine is rapidly eliminated within just a few hours of use, BE is easily detected in the urine for 2 to 3 days following last use.⁴ When more sophisticated testing methodology is applied to chronic users, cocaine metabolites can be identified for several weeks following last use.²²⁴

Urine testing, even using rapid point-of-care assays, offers little to clinicians managing patients with presumed cocaine toxicity because it cannot distinguish recent from remote cocaine use. In addition, false-negative testing can result when there is a large quantity of urine in the bladder with very recent cocaine use or when the urine is intentionally diluted by increased fluid intake,²⁹ leading to a urine cocaine concentration below the cutoff value and interpretation of the test as negative. Under these circumstances, repeat testing is almost always positive. False-positive tests are extremely unlikely. However, external contamination is possible, particularly with hair testing.

While false-positive tests do occur, they are more common with hair testing than urine or blood because of the increased risk of external contamination.^{29,176} Because of the very low rate of false-positive results, confirmation of a positive urine is unnecessary for medical indications (Chap. 6).

The greatest benefit for cocaine testing is in cases of unintentional poisoning or suspected child abuse and neglect. Here confirmation of a clinical suspicion is essential to support a legal argument. In addition, there may be some usefulness for

urine testing of body packers, especially when the concealed xenobiotic is unknown.²¹⁴ While many body packers will have negative urine throughout their hospitalization, a positive urine test is suggestive of the concealed drug but obviously not confirmatory. More importantly, a conversion from a negative study on admission to a positive study not only confirms the substance ingested but also suggests packet leakage, which could be a harbinger of life-threatening toxicity (Special Considerations: SC5). Another indication for urine testing for cocaine occurs in young patients with chest pain syndromes where the history of drug use, specifically cocaine, is not forthcoming.⁸⁵ Routine diagnostic tests such as a bedside rapid reagent glucose, electrolytes, renal function tests, and markers of skeletal muscle and cardiac muscle injury are more likely to be useful than urine drug screening. An electrocardiogram (ECG) may show signs of ischemia or infarction, or dysrhythmias that require specific therapy. Unfortunately, in the setting of cocaine-associated chest pain, the ECG has neither the sensitivity nor the specificity necessary to permit exclusion or confirmation of cardiac injury.⁹⁰ Cardiac markers are therefore always required adjuncts when considering myocardial ischemia or infarction. Because cocaine use is associated with diffuse muscle injury, assays for troponin are preferred over myoglobin or myocardial band enzymes of creatine phosphokinase.⁸⁹ Additionally, computed tomography (CT) angiography of the coronary arteries has been reported to be a useful tool to exclude MI after cocaine use.²²⁰ This test exposes the patient to high levels of radiation, and relative risk versus benefit has not been studied. Chest radiography may be useful to exclude certain etiologies in patients with chest discomfort or to identify free air under the diaphragm when gastrointestinal perforation is suspected. Supplemental diagnostic studies, such as CT scans of the head, chest, or abdomen and functional cardiac imaging, should be guided by the clinical condition of the patient.^{33,46,69}

CESSATION OF USE

A cocaine withdrawal syndrome is not reported. Following binge use of cocaine, a “washed-out” syndrome occurs that is best described by dopamine depletion.^{202,213} Patients complain of anhedonia and lethargy, and they have trouble initiating and sustaining movement. However, they are arousable with minimal stimulation and usually remain cognitively intact.

Symptoms typically associated with cocaine toxicity can prevent in a delayed fashion after cessation of cocaine use. The reasons for this delay are multifactorial and not entirely apparent but may be related to prolonged elimination of metabolites such as CE; changes in receptor regulation¹⁵⁴; or affects on platelets, coagulation, and thrombolysis that incite a slow cascade leading to thrombosis.

MANAGEMENT

General Supportive Care

As in the case of all poisoned patients, the initial emphasis must be on stabilization and control of the patient’s airway, breathing, and circulation. If tracheal intubation is required, it is important to recognize that cocaine toxicity may be a relative contraindication to the use of succinylcholine.¹⁴² Specifically, in the setting of rhabdomyolysis, hyperkalemia may be exacerbated by succinylcholine administration, and life-threatening dysrhythmias may result (Chap. 69). Additionally, it is essential to recognize that PChE metabolizes both cocaine and succinylcholine.⁹⁹ Thus, their simultaneous use could either prolong cocaine toxicity or paralysis or both. Human data are insufficient to predict which interaction is more likely to occur. If hypotension is present, the initial approach should be infusion of intravenous 0.9% sodium chloride solution as many patients are volume depleted as a result of poor oral intake and excessive fluid losses from uncontrolled agitation, diaphoresis, and hyperthermia.

In the setting of cocaine toxicity it is important to recognize that both animal^{23,65} and human¹³⁸ experience suggests that elevated temperature represents the most critical vital sign abnormality. Determination of the core temperature is an essential element of the initial evaluation, even when patients are severely agitated. When hyperthermia is present, rapid cooling with ice water immersion preferably, or the combined use of mist and fanning, is required to achieve a rapid return to normal core body temperature (Chap. 30). Sedation or paralysis and intubation may be necessary to facilitate the rapid cooling process. Pharmacotherapy, including antipyretics, drugs that prevent shivering (chlorpromazine or meperidine), and dantrolene,⁵⁴ are not indicated as they are ineffective and have the potential for adverse drug interactions such as serotonin toxicity (meperidine) (Chap. 38) or seizures (chlorpromazine).

Sedation remains the mainstay of therapy in patients with cocaine-associated agitation. It is important to remember that cocaine use is associated with hypoglycemia due to catecholamine discharge.^{15,149} Clinical findings of hypoglycemia and increased catecholamines may be similar; consequently, a rapid bedside glucose should be obtained or hypertonic dextrose should be empirically administered if indicated, prior to or while simultaneously achieving sedation.

Both animal models^{23,65} and extensive clinical experience in humans support the central role of benzodiazepines. Antipsychotics have also been used in the treatment of acute cocaine intoxication. A meta-analysis evaluating benzodiazepines and antipsychotics in animal modes of cocaine toxicity found that both reduced mortality. However,

benzodiazepine treatment reduced mortality by 52% compared with only 29% for antipsychotics.⁷⁴ Although the choice among individual benzodiazepines is not well studied, an understanding of the pharmacology of these drugs allows for rational decision making. The goal is to use parenteral therapy with a drug that has a rapid onset and a rapid peak of action, making titration easy. Using this rationale, midazolam and diazepam are preferable to lorazepam, because significant delay to peak effect for lorazepam often results in oversedation when it is dosed rapidly or in prolonged agitation when the appropriate dosing interval is used. Drugs should be administered in initial doses that are consistent with routine practices and increased incrementally based on an appropriate understanding of their pharmacology. For example, if using diazepam, the starting dose might be 5–10 mg intravenously, which can be repeated every 3 to 5 minutes and increased if necessary. Large doses of benzodiazepines may be necessary (on the order of 1 mg/kg of diazepam). This may result from cocaine-induced alterations in benzodiazepine receptor function^{60,61,102} (Antidotes in Depth: A23).

On the rare occasion when benzodiazepines fail to achieve an adequate level of sedation, either a rapidly acting barbiturate or propofol should be administered. Controlled animal studies clearly show that the use of phenothiazines or butyrophenones is contraindicated.^{23,65,227} In animal models, these drugs enhance toxicity (seizures), lethality, or both. Additional concerns about these drugs include interference with heat dissipation, exacerbation of tachycardia, prolongation of the QT interval, induction of torsade de pointes, and precipitation of dystonic reactions.

Once sedation is accomplished, often no additional therapy is required. Specifically, hypertension and tachycardia usually respond to sedation and volume resuscitation. In the uncommon event that hypertension and or tachycardia persists, the use of a β -adrenergic antagonist or a mixed α - and β -adrenergic antagonists is contraindicated. Again, in both animal models and human reports, these drugs increase lethality and fail to treat the underlying central nervous system excitation.^{12,23,65,184,213} (See Specific Management below.) The resultant unopposed α -adrenergic effect may produce severe and life-threatening hypertension or vasospasm. A direct-acting vasodilator such as nitroglycerin, nicardipine, or an α -adrenergic antagonist (such as phentolamine) may be considered. Other nonspecific therapies for rhabdomyolysis such as intravenous fluid should also be considered.

Decontamination

The majority of patients who present to the hospital following cocaine use will not require gastrointestinal decontamination as the most popular methods of cocaine use are smoking and intravenous and intranasal administration. If the nares contain residual white powder presumed to be cocaine, gentle irrigation with 0.9% sodium chloride solution will help remove adherent material. Less commonly, patients may ingest cocaine unintentionally or in an attempt to conceal evidence during an arrest (body stuffing)^{78,101,135,201} or transport large quantities of drug across international borders (body packing).^{58,63} These patients may require intensive decontamination and possibly surgical removal²³² (Special Considerations: SC5).

Specific Management

End-organ manifestations of vasospasm that do not resolve with sedation, cooling, and volume resuscitation should be treated with vasodilators (such as phentolamine). When possible, direct delivery via intraarterial administration to the affected vascular bed is preferable. Because this approach is not always feasible, systemic therapy is typically indicated. Phentolamine can be dosed intravenously in increments of 1 to 2.5 mg and repeated as necessary until symptoms resolve or systemic hypotension develops.

Acute Coronary Syndrome. A significant amount of animal, in vitro, and in vivo human experimentation has been directed at defining the appropriate approach to a patient with presumed cardiac ischemia or infarction. In some instances, an approach that is similar to the treatment of coronary artery disease is indicated, although there are certain notable exceptions. An overall approach to care is available in the American Heart Association guidelines and a number of reviews.^{3,84,117,143}

High-flow oxygen therapy is clearly indicated as it may help overcome some of the supply–demand mismatch that occurs with coronary insufficiency. Aspirin is likely safe in patients with cocaine associated chest pain and is recommended for routine use.¹⁴³ In addition, administration of morphine is likely to be effective as it relieves cocaine-induced vasoconstriction.¹⁸¹ Morphine also offers the same theoretical benefits of preload reduction and reduction of catecholamine release in response to pain that is thought to be responsible for its usefulness in patients with coronary artery disease.

After these interventions, the treatment of patients with cocaine-associated chest pain begins to deviate from the standard accepted approach to patients with coronary artery disease. Nitroglycerin is clearly beneficial as it reduces cocaine-associated coronary constriction of both normal and diseased vessels and relieves chest pain and associated symptoms.⁸⁰ Interestingly, in several clinical trials of cocaine-associated chest pain, benzodiazepines are at least as effective or superior to nitroglycerin.^{8,92} Although the reasons for this are unclear, possible etiologies include blunting of central catecholamines or direct effects on cardiac benzodiazepine receptors. Either or both drugs can be used in standard dosing (Antidotes in Depth: A23).

Over the past decade, the benefits of β -adrenergic antagonism have been demonstrated in patients with CAD. In contrast, β -adrenergic antagonism increases lethality in cocaine-toxic animals^{23,65} and in humans, exacerbates cocaine-induced coronary vasoconstriction, and produces severe paradoxical hypertension.¹⁸⁴ Mixed alpha and beta adrenergic antagonists do not appear to offer any advantage in the treatment of patients with cocaine associated chest pain. For the treatment of coronary constriction, labetalol is no better than placebo.¹² This is likely due in part to the relative ratios receptor blockade. Intravenous labetalol has a relative $\beta:\alpha$ receptor blockage of 7:1.¹⁷⁴ Carvedilol has a ratio of 2.4:1.¹⁶

Thus, in the setting of cocaine use, β -adrenergic antagonism is absolutely contraindicated. The 2008 American Heart Association Guidelines for the treatment of cocaine-associated chest pain and MI state that use of β -adrenergic antagonists should be avoided in the acute setting.¹⁴³ If, after the measures mentioned previously have been initiated, hypertension or vasospasm is still present and treatment is indicated, phentolamine is preferred based on its demonstrable experimental and clinical results.^{87,117} If tachycardia does not respond to accepted therapies above, then diltiazem can be administered and titrated to effect.¹¹ Prior to the administration of any negative inotrope, it is essential to confirm that the tachycardia is not compensatory for a low cardiac output resulting from global myocardial dysfunction. Noninvasive methods of assessment of cardiac function have been used successfully in patients with cocaine-associated acute coronary syndromes.⁷

There are no data on the use of either unfractionated or low-molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, or clopidogrel. The recent American Heart Association guidelines recommend the administration of unfractionated heparin or low-molecular-weight heparin in patients with cocaine-associated MI.¹⁴³ The decision to use any of these medications should be based on a risk-to-benefit analysis. Consideration should be given to the possibility of underlying atherosclerotic heart disease. When acute thrombosis is likely, thrombolytic therapy should be considered. Mechanistically, cocaine inhibits endogenous thrombolysis through augmentation of the inhibitor of tissue plasminogen activator. Additionally, there is sufficient clinical evidence to support the safety of thrombolytic therapy in patients with cocaine-associated MI.^{80,86} Even though the number of patients treated with thrombolytic therapy is insufficient to demonstrate efficacy in terms of mortality, evidence of revascularization is encouraging. If available, cardiac catheterization with revascularization is preferable to thrombolysis.^{195,198} A high rate of stent thrombosis after MI is reported in cocaine users. Thrombolysis would not be expected to be useful in treating ischemia caused by vasospasm. Due to the high incidence of coexisting atherosclerotic disease and an increased hypercoagulable state in cocaine-associated MI, thrombolysis is an acceptable alternative when catheterization is unavailable. Standard contraindications such as persistent hypertension, aortic dissection, trauma, and altered mental status must be considered prior to thrombolysis.

Dysrhythmias. Most patients present with sinus tachycardia that resolves following sedation, cooling, rehydration, and time to metabolize the drug. Other stable dysrhythmias should be treated similarly and will often spontaneously revert because of the short duration of effect of cocaine. However, cocaine use is associated with atrial, supraventricular, and ventricular dysrhythmias, including torsade de pointes.^{97,118,191} Most notably, wide complex tachycardias result from sodium channel blockade.

When approaching patients with cocaine-associated dysrhythmias, there are several important points to consider. The first is that β -adrenergic antagonism is contraindicated. Furthermore, class 1A and 1C antidysrhythmics are also contraindicated because of their ability to exacerbate cocaine-induced sodium and potassium channel blockade.^{118,226} Additionally, although popular in many advanced cardiac life support dysrhythmia algorithms, the effects of amiodarone are largely unknown in the setting of cocaine toxicity. Because of the lack of data demonstrating a benefit for amiodarone, and because of concerns about its β -adrenergic antagonist effects, the use of this drug cannot be recommended. Finally, although adenosine and synchronized cardioversion may transiently help convert narrow complex tachycardias, if a substantial amount of cocaine is unmetabolized, the patient will likely revert back to the original dysrhythmia as these therapeutic interventions have short durations of effect. Thus for rapid atrial fibrillation and narrow complex reentrant tachycardias, a calcium channel blocker such as diltiazem is preferred. For wide-complex dysrhythmias, a trial of hypertonic sodium bicarbonate has demonstrable usefulness analogous to treating patients with cyclic antidepressant overdose (Antidotes in Depth: A5).^{106,116,163,181,221,226,239,246} When the use of hypertonic sodium bicarbonate fails to treat the dysrhythmia, lidocaine can be used. Although lidocaine blocks sodium channels, its fast-on, fast-off properties allow it to antagonize the effects of cocaine. The benefits and safety of lidocaine were demonstrated in multiple animal models^{64,69,75,81,226,246} and in humans with cocaine-associated MI.^{105,215}

Ischemic Stroke. The safety of thrombolysis in cocaine-associated ischemic stroke is uncertain. Cocaine use can increase the risk of both ischemic stroke and intracerebral hemorrhage. One study found no increase in intracerebral hemorrhage after administration of tissue plasminogen activator in patients who had recently used cocaine, although acute cocaine intoxication was not specifically investigated.¹³⁷

ADULTERANTS

Adulterants are present in illicit drugs for varied reasons, including impure manufacturing processes, increasing drug bulk,

and mimicking or enhancing effects. Historically, cocaine has included inert substances such as starches, sympathomimetic agents and other local anesthetics.²⁷

In 2003, a new adulterant, levamisole, was identified. Levamisole is an antihelminthic immunomodulator. It was withdrawn from the US market in 2000 primarily because of agranulocytosis. By 2009, the US Drug Enforcement Agency estimated that 69% of cocaine contained levamisole.¹²¹ Two primary categories of levamisole toxicity are identified. The first is hematologic effects, including neutropenia and agranulocytosis. The second is dermatologic effects, including vasculitis and purpura. Reexposure to cocaine with levamisole may cause recurrence of these symptoms. A multifocal inflammatory leukoencephalopathy is also reported after use of contaminated cocaine.

DISPOSITION

Patients who present to health care facilities with classic sympathomimetic signs and symptoms that resolve spontaneously in the absence of signs of end-organ damage can be safely discharged after short periods of observation. Once hyperthermia, rhabdomyolysis, or other signs of end-organ damage are evident, hospital admission is usually required. Patients who use cocaine are at increased risk for sudden death likely related in part to dysrhythmias and myocardial ischemia. In one series, patients with cardiac arrest after smoking crack cocaine were younger, more likely to survive, and less likely to have neurologic sequelae than case controls.⁹⁵

For patients with chest pain, a specific management algorithm has been derived based on substantial clinical experience. Those patients with clearly diagnostic or evolving ECGs suggestive of ischemia or infarction, positive cardiac biomarkers, dysrhythmias other than sinus tachycardia, congestive heart failure, or persistent pain require admission. Patients who become pain free and whose ECGs are stable are candidates for discharge if a single cardiac marker obtained at least 8 hours after the onset of chest pain is normal.²²³ The American Heart Association guidelines recommend 9 to 12 hours of observation for low- and intermediate-risk patients with cocaine-associated chest pain.¹⁴³

For all patients, it is essential to provide a referral for detoxification. Repeated cocaine use is the greatest risk factor for future cardiovascular complications.^{88,180,224} Additionally, cocaine use in patients treated for traumatic injury is a risk factor for subsequent death from unintentional injury.

SUMMARY

- A sympathomimetic toxidrome is the typical clinical presentation.
- Life-threatening hyperthermia may occur.
- Treatment of agitation should focus on rapid sedation with a benzodiazepine and cooling if indicated.
- Myocardial infarction and dysrhythmias occur via diverse mechanisms.
- Both ischemic and hemorrhagic stroke may occur.

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SC5 SPECIAL CONSIDERATIONS

Internal Concealment of Xenobiotics

Jane M. Prosser

Internal concealment of illicit xenobiotics is a significant concern for local and international police efforts as well as medical and public health practitioners. There are two distinct categories of concealment colloquially known as “body stuffers” and “body packers.” The term body stuffer refers to individuals who hide xenobiotics in a body cavity or ingest them in an attempt to hide evidence from law enforcement officers. The xenobiotics are ingested in an unplanned manner and are often poorly wrapped. The term body packer refers to individuals who conceal xenobiotics, typically in large quantities, in a premeditated fashion almost exclusively for the purposes of international smuggling.

BODY PACKERS

Internal concealment of xenobiotics for the purpose of smuggling was first reported in Canada in 1973. A 21 year-old man presented with a small bowel obstruction as a result of swallowing a condom filled with hashish. He had swallowed the condom in order to transport it into Canada after a trip to Lebanon.¹⁴ Internal xenobiotic smuggling has become a worldwide problem as increased surveillance at international borders has made conventional transportation of illegal xenobiotics more difficult. Improved detection of smugglers has increased the number of patients brought to the attention of health care providers. Pregnant women and children as young as 6 years of age have been used as body packers.^{3,6,9}

Airline and airport personnel are trained to identify people who may be xenobiotic couriers. Suspicious behavior includes not eating or drinking on the airplane, abnormal behavior while going through customs, and overt signs of xenobiotic toxicity.^{68,77}

Composition of Packages

Body packers typically swallow large numbers of well prepared packages, each filled with substantial amounts of xenobiotic. Packets may also be concealed by insertion into the vagina and rectum.^{15,82} The most frequently smuggled cargo is either heroin or cocaine, but other xenobiotics have been reported (Table SC5–1). Body packers often swallow 50 to 100 packages, and ingestion of as many as 500 has been reported.⁸³ Each package typically contains from 0.5 to 10 g of xenobiotic. Therefore, one person may carry as much as 1.5 kg of drug.⁷⁵ Lethal doses of cocaine and heroin are difficult to determine based in part on sparse data and on widely variable purity. For reference, death from cocaine toxicity is reported after ingestion of as little as 2 to 3 g.⁶³ As such, each packet should be considered to contain a potentially lethal dose.

TABLE SC5–1. Xenobiotics Associated with Internal Concealment	
Substances reported in body stuffer ingestion	
Cannabis ⁷⁶	
Cocaine hydrochloride ⁶⁴	
Crack cocaine ⁶⁴	
Heroin ⁴¹	
Methamphetamine ³²	
Prescription drugs ⁷⁶⁵	
Substances reported in body packer ingestion	
Cannabis ^a	
Cocaine powder and liquid ¹³	
Hashish ^b and hashish oil ⁵³	
Heroin ²⁴	
Methamphetamine ^a	

Methylenedioxymethamphetamine (ecstasy)^c

Oxycodone³

^aLow VHS, Dillon EK: Agony of the ecstasy: report of five cases of MDMA smuggling. *Australas Radiol.* 2005;49:400–403. ^bPamilo M, Suoranta H, Suramo I: Narcotic smuggling and radiography of the gastrointestinal tract. *Acta Radiol Diagn.* 1986;27:213–216. ^cTakekawa K, Ohmori T, Kido A, Oya ML: Methamphetamine body packer: acute poisoning death due to massive leaking of methamphetamine. *J Forensic Sci.* 2007;52:1219–1222.

A number of materials have been used for xenobiotic packaging. Some, like latex, are used as wrappers. Others such as carbon paper and aluminum foil are used to change the radiodensity and decrease the likelihood of detection with diagnostic and forensic imaging studies. Packages have been made using plastic bags, plastic wrap, condoms, finger cots, balloons, cellophane, wax, tape, rubber gloves, surgical ligatures, paraffin, and fiberglass.^{5,24,31,52,60}

Initial reports suggested a high rate of complications due to packaging failure.⁵² More recently, however, advances in the technology of packet construction have decreased rates of rupture.⁶⁰ A typical packet in current use is composed of a core of compacted xenobiotic covered by several layers of latex and encased in an outer wax coating.⁷⁷ Recently, the transport of xenobiotic in liquid form has been reported.

Important historical details include the number and contents of packets, the type of wrapping, time of ingestion, and any associated symptoms. Body packers, as well as those financing and receiving the packages, generally know exactly how many packets are being carried. However, the individual may be reluctant to give an accurate clinical history to the health care provider or legal authorities.

Bioavailability

The oral bioavailability of cocaine hydrochloride is approximately 30% to 40%, which is similar to intranasal administration.^{19,86} Rectal and vaginal bioavailability of cocaine hydrochloride and the oral, rectal, and vaginal bioavailability of crack cocaine have not been studied.

Oral exposure to heroin results in rapid first pass metabolism to morphine²⁶ and can be considered a morphine prodrug.^{19,38} The peak concentrations after 10 mg of oral heroin are similar to those expected from 10 mg of oral morphine.³ The rectal bioavailability of morphine has a 1:1 ratio with oral administration. Although heroin is rectally bioavailable,⁶⁷ one study examining the bioavailability after rectal suppository administration in two opioid dependent patients found it to be approximately 50% less than the oral bioavailability.²⁸

Clinical Manifestations

Body packers undergoing medical examination may be asymptomatic or may have clinical manifestations consistent with either xenobiotic toxicity or mechanical obstruction. Physical examination should be thorough, with a focus on findings related to these problems (**Chaps. 38 and 78**).

The packets may be too large to pass, and obstruction can occur at any point in the gastrointestinal tract. Individuals carrying packets containing opioids appear to be at higher risk of gastrointestinal obstruction, even with intact packets.²⁵ The reason for this is unclear, but may be related to microperforation of the package or contamination of the outside of the package during manufacture, resulting in opioid induced gastrointestinal stasis. Patients with a history of abdominal surgery may also be at increased risk of obstruction.^{12,36} Gastrointestinal perforation and peritonitis can result if the obstruction is untreated.¹² Dysphagia,⁷ esophageal perforation and mediastinitis,^{36,39} gastric ulcers,⁵⁶ gastric hemorrhage,^{16,36} esophageal obstruction,⁴⁴ hematochezia,⁷⁹ incarcerated hernias,⁷⁴ uterine ischemia,⁷ and septic shock²⁵ have resulted following packet rupture.

Laboratory Evaluation

Drug screening results may be difficult to interpret. Although generally, a positive result should raise concern for a ruptured packet, positive results may also be due to external contamination of the packet during preparation from a microperforation or from prior utilization. Thus, patients with packets that appear externally intact may have a positive urine drug screen.^{25,53} The rate of positive screens in asymptomatic patients may be as great as 52% to 72%.^{13,16} Screening typically correlates closely with the drug carried,²⁴ but it may be misleading as patients transporting any xenobiotic may ingest opioids for the purpose of slowing gastrointestinal transit time.⁵⁷ Additionally, patients may be carrying a combination of xenobiotics, known as “double breasting.”²⁵

A subsequent urine drug screen may be particularly useful in the setting of a patient with an initially negative screen. A screen that later becomes positive suggests a ruptured packet and is an indication for very close monitoring. This is of particular concern in the setting of a cocaine body packer when a change from a negative to a positive screen might indicate the potential for a precipitous decline.

Radiographic Evaluation

All suspected body packers should undergo radiographic evaluation. Plain abdominal radiographs have a sensitivity of 75% to 95%, but this varies based on the number of packets and their methodology of construction.^{5,52,81} Several authors suggest increased sensitivity with supine abdominal films.^{50,83} Packets can be visualized as multiple radiodense foreign bodies (**Figs. 5-8 A–C**). The “double condom sign” is a lucent ring surrounding the packet and results from air trapped in between layered wrappings.⁶¹ The “rosettelike” sign results from the air trapped in the knot when the condom or balloon is tied.⁷¹ Caution must be used when interpreting plain radiographic studies. In one series, 19% of patients had false-negative radiographs, with one patient subsequently passing 135 packets.⁵² False-positive results have also been reported due to constipation,⁴³ intraabdominal calcifications,⁷⁸ and bladder stones.⁸⁷ Contrast enhancement may increase the sensitivity of plain radiography.^{23,35,50}

Computed tomography (CT) scanning has a higher sensitivity than plain radiography,^{30,46} with sensitivities reported to range from 96% to 100%.^{1,22,88} Although likely to identify patients with multiple packets, a false-negative contrast CT scan following whole bowel irrigation was reported in a body packer who subsequently passed a single packet per rectum.²⁹ Retrospective review of the CT could not identify the packet. One study found a difference in Hounsfield units between packets containing cocaine (–219 HU) and heroin (–520 HU), suggesting that CT scanning can also potentially distinguish between package contents. However, other authors report a lack of utility of this measurement due to variation in drug formulation, compression, and packing materials⁸⁵.

Ultrasonography may be another useful screening tool to reduce radiation exposure, particularly for evaluation of women of childbearing age. However, its utility has only been evaluated in a few small case series.^{34,54} In one series of patients arrested on suspicion of body packing at an international airport, ultrasound examination correctly identified 40 of 42 body packers with positive plain radiographs. The two false-negative results occurred when packets were located low in the rectum.⁵⁴ More investigation is needed to determine the sensitivity and specificity of ultrasound for use in these patients.

Magnetic resonance imaging (MRI) is not likely to provide any additional information when evaluating the gastrointestinal tract. The utility of MRI may be limited for examining the bowel because of the presence of air and normal peristalsis.³³

Pregnant women may be targeted to become body packers due to hesitation from customs officials and health care providers to obtain radiographs. However, the average radiation dose of 100 millirads from an abdominal radiograph is much less than the threshold thought to induce fetal malformations. Consideration should also be given to the use of ultrasonography in this situation.⁹ In all patients, risk of exposure to radiation must be weighed against the risks of undiagnosed internal concealment of xenobiotics.

Management

Gastrointestinal decontamination is a vital element in the management of body packers. Initially, surgical intervention was thought to be necessary in all body packers secondary to perceived high rates of toxicity and death.^{21,73} The incidence of life-threatening complications has decreased due in part to both better packaging^{52,60} and to increased rates of detection of asymptomatic carriers. Currently, a more conservative nonsurgical approach is suggested for asymptomatic patients⁷⁷ and is supported by a several large series (**Fig. SC5–1**).^{4,5,13,52,68,81,83}

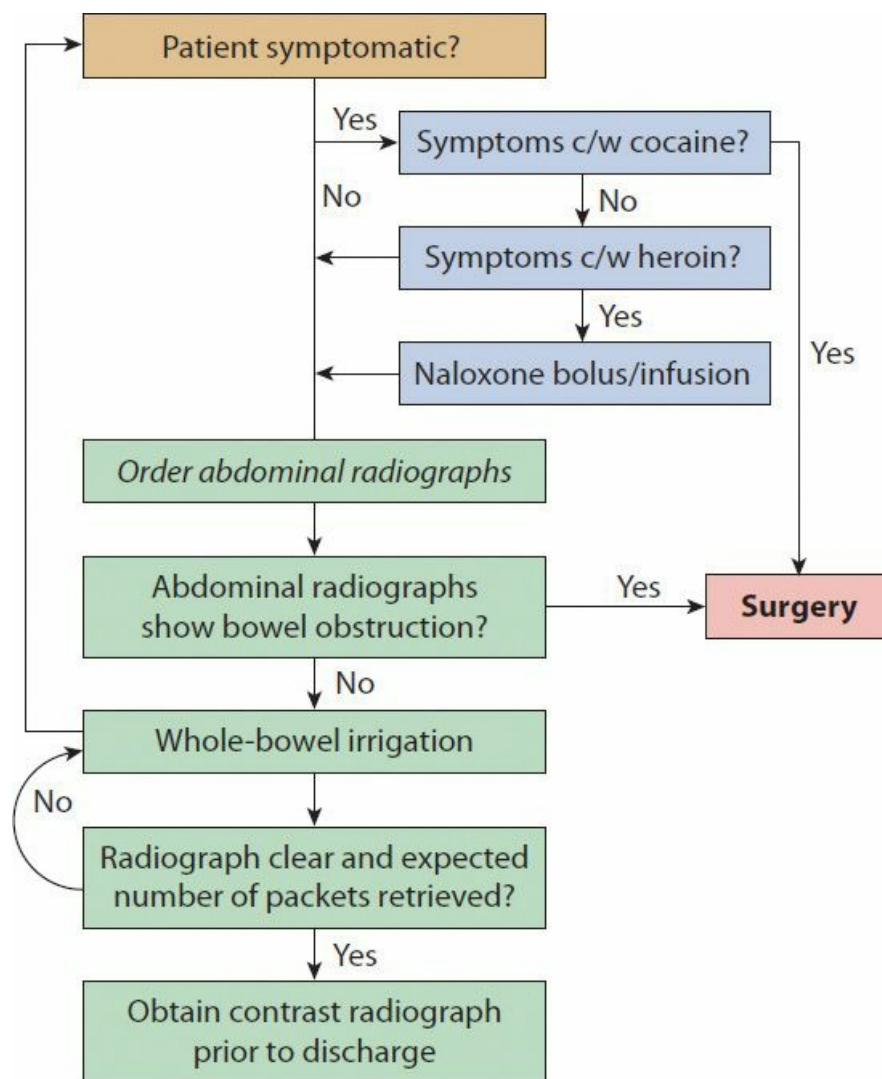


FIGURE SC5-1 Algorithm for managing cocaine or heroin body packers.

Treatment with activated charcoal (AC) is frequently suggested on the basis that cocaine and heroin are both well adsorbed to AC.⁴⁹ There are no data showing an actual benefit, and the large doses needed to adsorb the many grams of xenobiotic released during packet rupture may make AC impractical for use. Furthermore, AC may be detrimental if contamination of the peritoneal cavity occurs after gastrointestinal rupture or during surgery or if it obscures visualization should endoscopy become indicated. The risks and benefits must be weighed in each patient. AC is of questionable value in cocaine packers given the higher risk of the need for surgical intervention. Also, it is not likely to improve the outcome of symptomatic heroin body packers, as these patients can be successfully managed with opioid antagonists and mechanical ventilation. Therefore, the administration of AC is not likely to be of benefit.

The utility of whole bowel irrigation (WBI) to enhance elimination is generally accepted but has not been rigorously evaluated. There is a theoretical concern that polyethylene glycol could increase the water solubility of heroin should rupture occur,⁸¹ and that it may decrease the adsorption of cocaine to AC should AC be given.⁴⁹ Given the lack of in vitro data to support these risks,¹⁸ and its generally accepted benefit, WBI is recommended to decrease intestinal transit time (Antidotes in Depth: A2). Orogastric lavage is not indicated as packets are too large to fit through holes in the lavage tube.

Cathartics are sometimes recommended for gastrointestinal decontamination. Although oil-based cathartics were frequently used in the past,^{5,51} a non-oil-based medication such as magnesium citrate is preferred. Paraffin oil may actually dissolve some packet wrappers, potentially resulting in drug toxicity.⁸⁴ Safe use of pro-motility xenobiotics, such as metoclopramide and erythromycin, is also reported.⁸⁰ Enemas and manual disimpaction should be avoided or used with great caution, as packet rupture may occur.^{40,47}

Treatment of symptomatic patients depends on the nature of the xenobiotic ingested. Patients manifesting opioid toxicity should be treated with the opioid antagonist naloxone and mechanical ventilation if necessary. Opioid antagonists also improve gastrointestinal motility (Antidotes in Depth: A4). Surgical decontamination is generally not indicated for opioid poisoning, as optimal medical therapy should be adequate.

Rupture of a cocaine packet, however, is a life-threatening emergency that requires aggressive medical and surgical therapy (Chap. 78). Benzodiazepines or other sedatives such as propofol may be used as a temporizing measure, but surgical decontamination should be performed emergently in body packers with any sign of cocaine or amphetamine toxicity. Indications for surgery include, but are not limited to, hypertension, tachycardia, agitation or other alteration in

mental status, myocardial ischemia, bowel ischemia, seizures, respiratory distress, and the transition of a urine drug screen from negative to positive.

Surgical removal of the packets is the therapy of choice in the case of cocaine toxicity or mechanical obstruction, but it may not be definitive.^{31,59,70} In one series, 6 of 70 patients were found to have retained packets postoperatively.¹² Also, emergent surgical removal is associated with a high rate of postoperative infection and fascial dehiscence for reasons that are not well understood.^{11,12,70} Endoscopy^{66,69,81} and proctoscopy²⁷ have been used successfully for removal of packets in several cases. However, caution must be used as attempted endoscopic removal can cause packet rupture and resultant toxicity.⁷³

It is essential to ensure the passage of all packets prior to discharging a patient from medical care. Packets may remain even in patients with clear rectal effluent following WBI.³⁵ After negative plain radiographs are obtained, a confirmatory study should be done using contrast plain radiography or CT scan. However these modalities do not have 100% sensitivity and retained packets may be missed.²⁹ It is therefore recommended that patients be observed for twenty-four hours after the passage of three packet free stools⁵ and a negative confirmatory radiograph or CT scan (**Fig. SC5–1**). Complete gastrointestinal decontamination must be ensured before releasing the patient from close medical observation.

BODY STUFFERS

Body stuffers usually present to health care when they are taken into custody by law enforcement officers. Typically, the person has hastily ingested the xenobiotic or inserted it into the rectum or vagina to hide the evidence from the police. Since the person was not planning to conceal the xenobiotic, the xenobiotic may be unwrapped, as in the case of crack cocaine “rocks,”⁵⁵ or poorly wrapped in materials intended for distribution.

Pertinent historical information includes time of ingestion, xenobiotic, amount ingested, packaging, and symptoms consistent with xenobiotic ingestion. Unfortunately, an accurate history is often difficult to obtain. Patients who are recent arrestees may anticipate a secondary gain of delayed incarceration by reporting the ingestion of drugs; alternatively, the individuals may deny ingestion to avoid prosecution. Complicating the clinical picture is the possibility that law enforcement officers may assume internal concealment of illicit substances when they are unable to find a substance after the arrest.

Composition of Packages

Since xenobiotics are typically transported locally in plastic bags, condoms,⁷² balloons,⁸ glassine envelopes, aluminum foil,⁶⁵ or crack vials,³⁵ these are the most frequently reported wrappers. Reported amounts vary from one dose to up to 30 packages of unspecified dose.⁴¹ Cocaine, either in crack rocks or the hydrochloride salt form are most commonly ingested,⁶⁴ but other xenobiotics are also reported (**Table SC5–1**). Typically, the xenobiotics are ingested although other routes of exposure include the external auditory canal, rectum, and vagina.^{45,48,76}

The importance of obtaining a precise history related to packaging material is highlighted by an in vitro study examining the effects of packet construction, medium used for dissolution, and pH on release of cocaine from drug packets. Cocaine was released almost immediately from paper packaging and least readily from condoms. Cellophane packing led to intermediate serum concentrations compared to paper and condom wrapper. When packets were double or triple wrapped in cellophane, decreased concentrations were noted. All packets released more xenobiotic in an acidic medium.²

Clinical Manifestations

After oral ingestion of drug packets or crack rocks, toxicity is most frequently absent or mild.^{41,42} However, although most case series report low rates of complications, both significant toxicity and death occur.^{20,37,42,57} The time of onset of symptoms in body stuffers is typically within several hours.^{1,41,42} Following the ingestion of cocaine in crack vials, onset of symptoms may be delayed by 3 to 4 hours.³⁵

Most body stuffers reported in the literature had symptom onset, when present, within 6 hours after ingestion. Delayed symptoms after 6 hours can occur; however, in nearly all reported cases, these patients displayed symptoms at the time of medical contact. Two exceptions are noted in the literature. A 50 year-old woman reported ingesting xenobiotics at the time of incarceration. Seven hours later, a prison physician noted normal pulse and mental status, and she was placed in her cell to be observed by staff members every half hour. Prison staff documentation noted that she was “correct” and sat up 30 minutes before being found dead in the cell 11 hours after the time of ingestion. Postmortem examination revealed an open cocaine packet in the intestine.⁵⁸ A patient who placed methamphetamine in a plastic bag with a small hole in an attempt to create a sustained-release mechanism presented for care of abdominal pain 10 hours later. This patient remained without symptoms of methamphetamine intoxication until 42 hours after ingestion.³²

Laboratory Evaluation

Laboratory xenobiotic testing may be difficult to interpret in body stuffers, as these patients are often habitual substance users. Thus, a positive drug screen could be equally indicative of either prior use or current toxicity or both. Likewise, a negative result does not exclude recent ingestion or leaking packages. One study of 50 suspected body stuffers found that urine drug screening correctly classified the presence or absence of packets only 57% of the time.⁵¹ Several authors report toxicity or death occurring in the presence of a negative urine screen despite symptoms consistent with packet contents.^{25,32} One explanation is that patients may die of drug toxicity before substantial urinary excretion occurs.

Radiographic Evaluation

Although detection of stuffed xenobiotics may be possible by diagnostic imaging studies, the sensitivity is very poor.^{17,41,51} Plastic bags, crack vials, and staples (enclosing plastic bags) are rarely visualized.⁴¹ In one series of patients with crack vial ingestions, only 2 of 23 of abdominal radiographs were positive³⁵ in patients who subsequently passed vials. In two other series of cocaine body stuffers, all plain radiographs were negative.^{42,72} Several authors suggest that radiographic detection can be increased with oral contrast, although its utility has not been established.^{10,42} CT scanning may identify some packets missed on plain radiographs, but the sensitivity has not been investigated and missed packets have been reported with CT scanners as well.¹⁷ Therefore, CT scanning is not likely to be clinically useful in these patients.

Management

Body stuffers who exhibit xenobiotic toxicity should be managed according to standard principles for managing that xenobiotic or suspected xenobiotic ([Chaps. 38 and 78](#)).

Patients with gastrointestinal complaints should be evaluated for ileus or obstruction. Removal of packets has been performed by endoscopy,^{10,41,62} but is useful only for a small number of packets, as each package requires an additional passage of the endoscope. Endoscopy should be used with extreme caution as it may cause packet rupture with subsequent toxicity or aspiration of the packet with airway obstruction.⁷³ Bronchoscopic removal of pieces of a balloon wrapping in the airway was successful in one patient after attempted orogastric lavage led to balloon aspiration.⁸ Use of colonoscopy⁶⁸ is also reported but carries a risk of rupture similar to that associated with upper endoscopy. The need for surgical intervention has been reported in only one case. This patient presented with a complaint of epigastric pain 3 days after ingesting a large plastic bag filled with 15 to 20 smaller bags of cocaine. He showed no signs of cocaine toxicity but required surgical removal, as the bag was still retained in the stomach 4 days postingestion.¹⁷

Management of asymptomatic body stuffers has not been rigorously evaluated. Treatment with AC and WBI was often advocated for high-risk patients. Although these methods have not been proven to reduce morbidity or mortality, they offer theoretical benefits.^{35,41,42,72} AC may reduce the absorption of liberated xenobiotic as both heroin and cocaine are well adsorbed to AC. WBI may reduce intestinal transit time, leading to earlier passage of packets. However, it is unlikely to offer any clinical benefits, unless life-threatening amounts of xenobiotic (in packages) are ingested.

A therapeutic end point has not been established in part because packages are often not recovered from body stuffers. Review of more than 1000 published cases of body stuffers, involving a variety of packaging methods, reveals only a few cases in which onset of toxicity occurred more than 6 hours after ingestion (when the time of ingestion is reported) and was not present at the time of initial medical evaluation. There are several cases reported when onset of symptoms occurred between 8 and 10 hours postingestion of “crack rocks”; however, in all of these cases (except in the two cases noted above), symptoms were present at the time of initial health care contact.^{10,62}

Management strategies should consider the potential dose ingested, time since ingestion, and therapy administered. Because the vast majority of patients remain asymptomatic or develop symptoms shortly after medical contact, it is reasonable to observe asymptomatic patients given AC for 6 hours. Because rare patients may have more delayed presentations, patients who have ingested large, potentially lethal doses should be observed for longer periods of time in a closely monitored setting. Multiple stools devoid of packages or a lack of symptoms after 24 hours are reasonable end points for monitoring these patients.

LEGAL PRINCIPLES

Because clinical errors have the potential for life-threatening consequences, it is essential to evaluate patients within the context of their unique medical, social, ethical, and legal settings. It is important to remember there may be significant motivation to deny ingestion altogether or conceivably secondary gain from overreporting the dose in order to delay incarceration. Often, patients will refuse medical care either as an assertion of innocence or over concerns that evidence produced might be incriminatory.

In the United States, patients may refuse care if they are competent to do so. This includes body stuffers and body

packers who are under arrest. Patients with decisional capacity cannot be forced to take AC, WBI, any other form of therapy or diagnostic procedure. If in police custody, however, the individual may be kept in the hospital for an extended observation period. This strategy maintains the patient's medical autonomy as well as ensures clinical stability. If signs of life-threatening toxicity subsequently develop, the patient will most likely have lost decisional capacity, and therapy and management can proceed as medically necessary.

If a body packer who is not in legal custody presents for medical care, physicians may face an ethical dilemma. Calling the authorities is a violation of the patient's right to confidentiality. However, possession of large amounts of drugs may theoretically endanger the hospital staff as criminal elements expect drug delivery. Consultation with hospital legal counsel, risk management, and the ethics committee may be helpful in this situation ([Chap. 141](#)).

SUMMARY

- Patients with intestinal concealment of xenobiotic present a diagnostic and therapeutic challenge.
- History, laboratory, and radiologic studies must be interpreted with caution.
- Management strategies should focus on the xenobiotic ingested and be tailored to the needs of each individual patient.
- Gastrointestinal decontamination is the most important consideration in asymptomatic patients.
- A complex patient physician relationship is common and must be effectively transformed into a trusting relationship to ensure reliable and high quality care.

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A23 ANTIDOTES IN DEPTH

Benzodiazepines

Robert S. Hoffman, Lewis S. Nelson, and Mary Ann Howland

Benzodiazepines are used as first-line anticonvulsants for virtually all xenobiotic induced seizures; as sedatives of choice for most forms of xenobiotic induced agitation; as muscle relaxants for diverse disorders such as serotonin toxicity, neuroleptic malignant syndrome, and poisoning from strychnine or black widow spider envenomation; and as sedatives for withdrawal from ethanol, γ -hydroxybutyric acid, and other sedatives. Additional distinct indications for benzodiazepines can be found in overdose from chloroquine and possibly other quinine derived antimalarials, and in patients with cocaine associated myocardial ischemia and infarction. This Antidotes in Depth provides a summary of the clinical pharmacology of benzodiazepines in order to provide the reader with the background necessary to administer these drugs as safely and effectively as possible.

HISTORY

Most ancient texts make reference to the use of some plant or natural substance for sedation. By the mid to late 1800s, many of the natural sedatives were replaced by alcohol and chloral hydrate.¹⁷ The search for better sedatives with fewer side effects led to the development of barbiturates in the early 1900s followed by numerous others such as meprobamate, glutethimide, and ethchlorvynol (Chap. 74). Since the introduction of chlordiazepoxide in 1960,⁷⁷ benzodiazepines have gained acceptance as safe and effective drugs for a large variety of clinical indications. Over the intervening years, the number of benzodiazepines has increased, with each new drug demonstrating unique and complex pharmacology.

CHEMISTRY

All benzodiazepines share a common chemical structure, shown in Fig. A23–1. This structure links a benzene ring with a diazepine ring and gives rise to the name used to describe the drug class. The additional phenyl ring is present in all clinically important benzodiazepines and serves as a site of substitution that modulates certain pharmacologic characteristics. The pyrazolopyrimidines (zolpidem, zopiclone, and zaleplon) lack the typical benzodiazepine structure but have similar pharmacologic effects.²⁸ Since these pharmaceuticals are largely unstudied for the antidotal indications described above, they are not discussed in depth here. A discussion of the manifestations and treatment of overdose of benzodiazepines and similar xenobiotics can be found in Chap. 74.

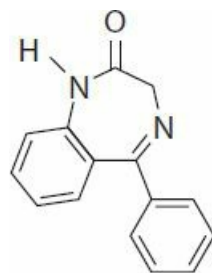


FIGURE A23–1. Generic structure of benzodiazepines.

γ -AMINOBUTYRIC ACID TYPE A RECEPTORS

Benzodiazepines target the γ -aminobutyric acid type A (GABA_A) receptor, which is a ligand-gated chloride channel, but have no appreciable binding to GABA_B. When GABA is present on its GABA_A receptor, benzodiazepines increase the frequency of channel opening, resulting in enhanced flow of negatively charged chloride ions into the cell with resultant hyperpolarization.⁸³ However, in the absence of GABA, benzodiazepines have no effect on chloride conductance. The

GABA_A receptor is assembled from five subunits that span the cell membrane in a circular fashion to create the chloride channel.⁵⁸ These subunits are coded as α , β , γ , δ , ϵ , θ , λ or ρ , and at least 19 isoforms of these subunits (such as α_{1-5}) are identified.¹³ If the isoforms of the known subunits could assemble randomly, several hundred thousand possible configurations of the GABA_A receptor would be possible.⁸⁵ However, it appears that a minimum of at least one α , one β , and either one γ or one δ subunit are required to form a functional chloride channel,⁸⁹ and as a result the actual number of configurations is limited. The most common configuration consists of one α , two β , and two γ isoforms.^{85,89}

BENZODIAZEPINE RECEPTORS

Rapidly evolving neuroscience has resulted in an exponential expansion in the understanding of benzodiazepine receptors. As a result multiple, potentially confusing nomenclatures have developed.

Central

The term “central benzodiazepine receptors” is used to refer to benzodiazepine binding sites on GABAergic neurons of the nervous system. Although benzodiazepine binding to the GABA_A receptor cannot occur unless at least one γ subunit is present,¹⁸ the actual site of benzodiazepine binding is located at the interface of an α and a γ subunit; most commonly an α_1 and a γ_2 subunit.^{13,85} Since most receptors only contain a single α subunit, only one benzodiazepine binding site usually exists on each GABA_A receptor. Anatomical variations in the α isoforms produce two common patterns of expression that account for some of the clinical variations between benzodiazepines and the pyrazolopyrimidines mentioned earlier. In older nomenclature, benzodiazepine type 1 (BZ₁) receptors were also called β_1 receptors. They have a predominance of the α_1 isoform, are located in the sensory and motor areas of the brain, and mediate sedative and hypnotic effects. Benzodiazepine type 2 (BZ₂) receptors were also called β_2 receptors. They have a predominance of the α_2 , α_3 , or α_5 isoforms, are located in the subcortical and limbic areas of the brain, and mediate anxiolytic and anticonvulsant effects.⁵⁷ Most typical benzodiazepines have substantial affinity for the α_1 , α_2 , α_3 , and α_5 isoforms, which explains their combined sedative-hypnotic, anxiolytic, and anticonvulsant effects. In contrast, the pyrazolopyrimidines (such as zolpidem) have high affinity for α_1 , intermediate affinity for α_2 and α_3 , and low affinity for α_5 isoforms, which explains their lack of anticonvulsant effect.^{28,59} The α_4 confers resistance to benzodiazepines. This older nomenclature (BZ and β receptors) is now simplified with GABA_A receptors classified as having high, low, or intermediate affinity benzodiazepine binding sites.⁷⁴

On the opposite side of the α isoform where the benzodiazepine receptor is located is an α - β interface. This interface holds the location of a binding site for neurosteroids (Fig. A23–2).³⁸ These neurosteroids are potent modulators of GABA_A receptor function and are important products of the tryptophan-rich sensory protein receptor (peripheral benzodiazepine receptor) stimulation (see below).

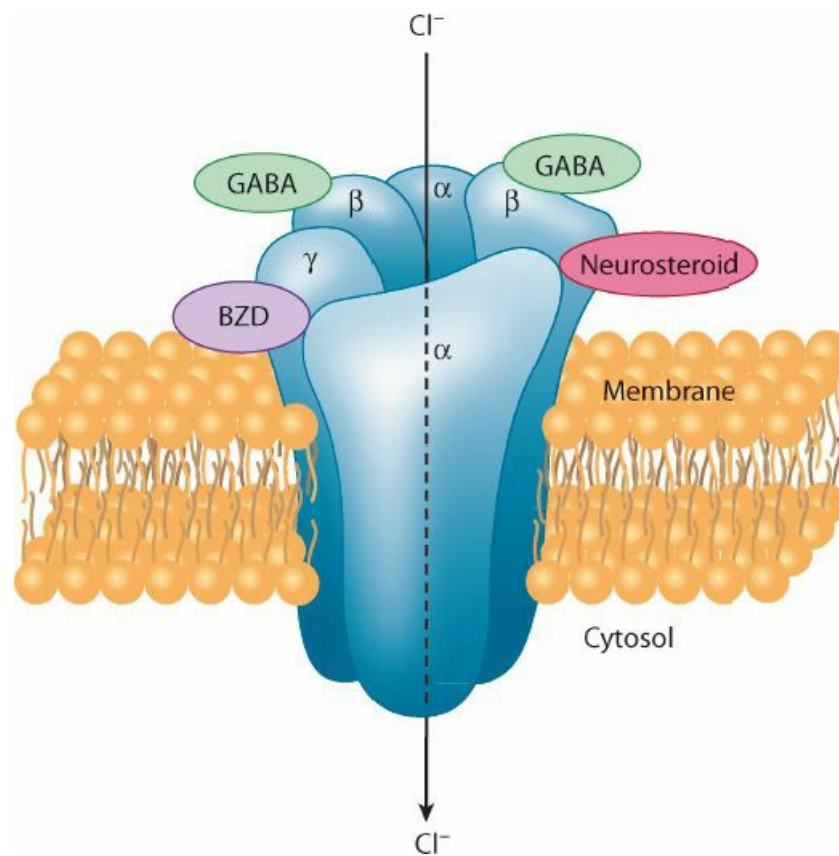


FIGURE A23–2. The γ -aminobutyric acid type A (GABA_A) chloride (Cl[−]) channel. The figure demonstrates a typical configuration of the GABA_A Cl[−] channel, which consists of two α , two β , and one γ isoforms. The benzodiazepine (BZD) receptor is located between an α and a γ subunit. Neurosteroid binding at the opposite side of the α isoform is a positive allosteric modulator.

Peripheral Tryptophan-Rich Sensory Protein

The term “peripheral benzodiazepine receptor” (PBR) was originally used in the 1970s to define any benzodiazepine binding sites outside of the nervous system.¹¹ Since these PBRs were subsequently identified in most tissues, including the central nervous system, the term is best applied to binding sites not located on GABAergic neurons. Other names for PBRs included BZ₃ or β_3 receptors to distinguish them from the “central receptors” described above.⁴⁷ However, numerous nonbenzodiazepines have high-affinity binding for these receptors, and their structure and function are so dissimilar from GABA_A-associated benzodiazepine binding sites that other names such as translocator protein (18 kDa), mitochondrial translocator protein (18 kDa), nuclear translocator protein (18 kDa), were appropriate.^{68,84,90} The most recent conventions have adopted the term tryptophan-rich sensory protein (TSPO) as this refers to its gene and denotes it as a tryptophan-rich sensory protein.²⁴ Although the term PBR remains attractive, for simplicity and consistency, the current term TSPO will be used in remainder of this discussion.

The TSPO participates in a heterotrimer structure that is composed of an isoquinoline binding protein, which is the actual receptor (TSPO); a voltage-dependent anion channel (VDAC); and an adenine nucleotide transporter (ANT).⁶⁸ Although the actual function of each subunit is not well appreciated, the minimal functional unit is the TSPO (18 kDa protein).⁴⁵ Sequencing of TSPOs demonstrates that they are highly conserved in nature, with DNA from bacteria and fungi having a nearly 50% homology of the isoquinoline binding domain with human DNA.^{24,27} Homology among mammals exceeds 75%.²⁷ These findings suggest that the PBRs perform a “housekeeping function,” that is, they are involved in a process or processes that are essential for life. In higher life forms, TSPOs can be found primarily in the brain, adrenal glands, heart, and kidney. The TSPO protein and the VDAC span the outer mitochondrial membrane, while the ANT bridges the outer and inner membranes (Fig. A23–3). TSPOs are implicated in cholesterol and protoporphyrin transport required for the synthesis of neurosteroids, heme, and bile salts; ischemia and reperfusion; regulation of calcium channels; mitochondrial respiration; apoptosis; microglial activation; and the immune response.^{27,68,84} More recently, TSPO ligands have been investigated as potential targets for a variety of disorders including anxiety, cancer, ischemia, and others.^{15,19,26,41,42,63,64,67,69,75,80,91} It is hypothesized that TSPO has two major roles: opening of the mitochondrial permeability transition pore (MPTP) leading to calcium influx and apoptosis,^{7,23,26,52} and, as noted above, in synthesis of neurosteroids that modulate GABA_A function.^{67,75}

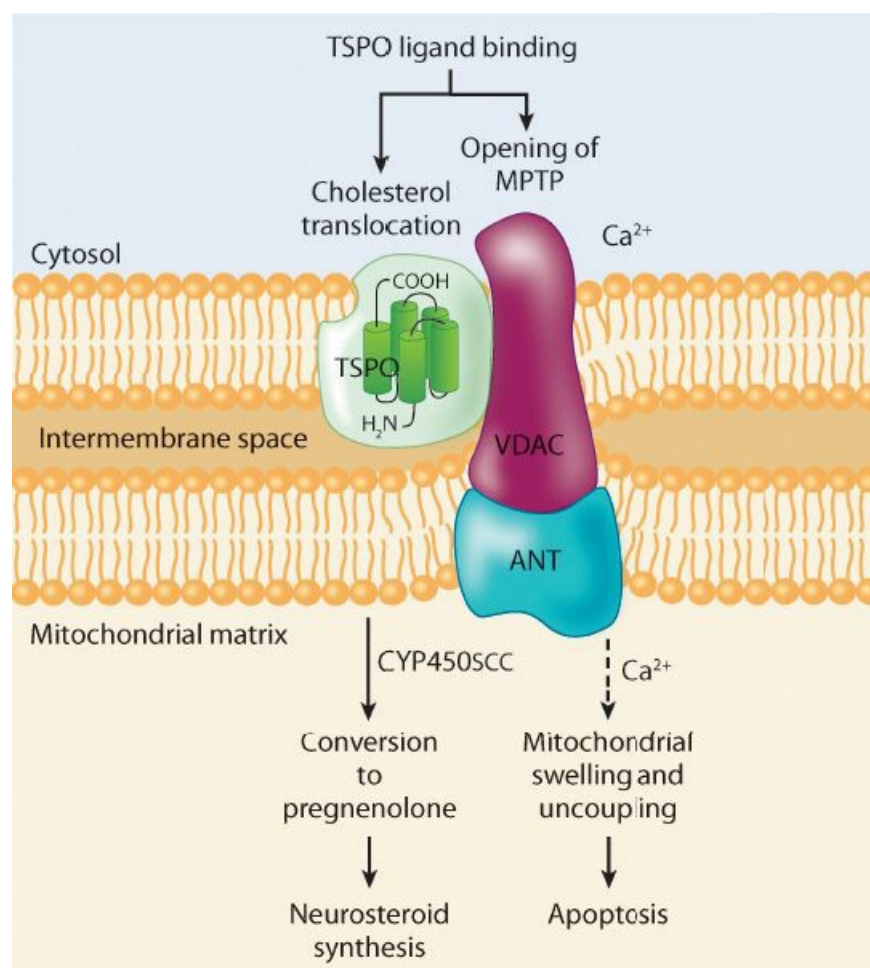


FIGURE A23–3. The “peripheral benzodiazepine receptor” has three main components: the tryptophan-rich sensory protein (TSPO; 18 kDa translocator protein), a voltage-dependent anion channel (VDAC), and an adenine nucleotide transporter (ANT), which are shown on the mitochondrial membrane. Stimulation of the TSPO can trigger influx of Ca²⁺ or cholesterol across the mitochondrial membrane. SCC = side chain cleavage; MPTP = mitochondrial permeability transition pore.

PHARMACOKINETICS AND PHARMACODYNAMICS

Benzodiazepines are usually administered to treat seizures, psychomotor agitation, or sedative-hypnotic withdrawal. Since these disorders often represent life-threatening emergencies, the initial approach to treatment involves the use of parenteral drugs. Parenteral therapy provides guaranteed absorption with a relatively rapid onset of action. As such, this Antidotes in Depth focuses on the most commonly used parenteral benzodiazepines: diazepam, lorazepam, and midazolam. Clinically important pharmacologic parameters of these three drugs are listed in [Table A23–1](#). Of note, since the existing literature is insufficient to absolutely differentiate individual roles for specific benzodiazepines in particular disorders, these three drugs are often used interchangeably for a variety of indications based on availability within the hospital and regional historic preferences. Only through an understanding of the pharmacology can the clinician select the optimal drug, dose, route, and interval to ensure adequate response and limit adverse reactions. As discussed below, it is important to note that the onset and peak effects of sedative and anticonvulsant activity are distinctly different for each drug and among drugs, so pharmacodynamic data are an important adjunct to the interpretation of pharmacokinetic data.

TABLE A23–1. Pharmacologic Properties of Select Benzodiazepines

Parameter	Diazepam	Midazolam	Lorazepam
Lipid solubility (LogD; octanol/water at pH 7)	3.86	3.68	2.48
Volume of distribution (healthy adults) (L/kg)	0.89 ± 0.18	0.80 ± 0.19	1.28 ± 0.34
Protein binding (%)	97–99	96	85
Hepatic metabolism	Phase 1	Phase 1	Phase 2
Active metabolites	Yes (desmethyl-diazepam and others)	Yes: α-hydroxymidazolam (10% of parent, but accumulates with chronic dosing)	No
Average dose (mg) in 70 kg adult ^a			
Sedation	10 mg IV over 2 minutes Wait 2 minutes before redosing	2 mg IV over >2 minutes (not >1.5 mg in elderly or debilitated patients and over >2 minutes) Wait 2 minutes before titrating	2 mg IV over one minute (dilute with equal volume of NS or D ₅ W prior to injection) Wait 15 minutes before redosing
Status epilepticus (initial dose)	10 mg IV	10 mg IM	4 mg IV
Diluent	Alcohol 10% Benzyl alcohol 1.5% Propylene glycol 40%	Benzyl alcohol 1.0% Sodium edetate 1%	Benzyl alcohol 2% Propylene glycol 80%
Available	5 mg/mL Rectal gel 5 mg/mL	1 mg/mL 5 mg/mL	2 mg/mL 4 mg/mL

^aAvoid intra-arterial administration (since severe spasm may occur with resulting ischemia or gangrene). Also avoid extravasation.

D₅W = 5% dextrose in water; IV = intravenous; NS = 0.9% NaCl.

Intravenous administration guarantees complete and immediate absorption. When intravenous access is unavailable, intramuscular lorazepam or midazolam should be considered as they both have good absorptive profiles.^{33,39,40,43,56,78,88} Midazolam may offer added benefits as its role in synthesis of neurosteroids is experimentally defined.⁸¹ In contrast, the absorption following intramuscular diazepam is best described as slow, incomplete, erratic, and dependent on the site of administration and the skill of the person administering it.^{20,21,39,44,86} Intramuscular injection of diazepam should therefore not be considered unless no other alternatives exist.

Other routes of administration are used for rapid drug delivery when intravenous access is not available. For example, and especially in children, intranasal and rectal administration can be considered. When rectal diazepam was compared with intravenous diazepam in children with seizures, the peak concentration was more variable and was delayed by about 20 minutes.⁶⁶ Additionally, failure rates are higher when rectal diazepam is compared with intravenous diazepam.^{66,71} Similarly, although midazolam is more rapidly absorbed than diazepam following both nasal and rectal administration, the kinetic profile of nasal or rectal midazolam is still inferior to intravenous administration of either diazepam or midazolam.^{35,55,71} Recent evidence has supported a role for intramuscular midazolam for seizures and agitation.^{43,56,78}

Once absorbed, benzodiazepines must distribute into the central nervous system in order to produce their sedative and anticonvulsant effects. The differences among individual drugs can be evaluated in terms of their pharmacokinetics, such as cerebral drug concentrations, or pharmacodynamics, such as changes in either consciousness or electroencephalographic (EEG) findings. A cat model assessed cerebrospinal fluid (CSF) concentrations of benzodiazepines following intravenous administration along with their effects on the EEG.⁵ Diazepam, midazolam, and lorazepam all appeared rapidly in the CSF.⁵ However, the times to peak concentration, onset, and duration of EEG activities were remarkably different among the three drugs (Table A23–2).

TABLE A23–2. Selected Pharmacokinetic and Pharmacodynamic Properties of Benzodiazepines in Animals⁵

Parameter	Diazepam	Midazolam	Lorazepam
Time to peak CSF concentration (minutes)	3.7 ± 1.3	3.7 ± 1.3	7.0 ± 4.2
Onset of EEG activity (minutes)	0.89 ± 0.31	0.29 ± 0.04	3.8 ± 3.1
Duration of EEG activity (minutes)	7.5 ± 1.4	6.3 ± 1.9	28.3 ± 10.1

CSF = cerebrospinal fluid; EEG = electroencephalographic.

In a similar study, human volunteers were given a one minute intravenous infusion of either diazepam (0.15 mg/kg) or midazolam (0.1 mg/kg) and EEG analysis was used as a surrogate for the pharmacodynamic effects of sedation. Peak EEG

effects were present immediately at the end of the diazepam infusion, but were delayed for 5 to 10 minutes after the midazolam infusion.³² These EEG effects lasted for 5 hours in diazepam-treated volunteers in comparison to only 2 hours in midazolam-treated volunteers. The same investigators compared the EEG effects of either intravenous lorazepam (low dose, 0.0225 mg/kg; high dose, 0.045 mg/kg) or diazepam (0.15 mg/kg) in human volunteers.³¹ In comparison to diazepam, the EEG effects of lorazepam were slower in onset, delayed in peak (30 minutes), and prolonged in duration of effect. This may be related in part to a relatively long alpha distribution half-life for lorazepam.³⁰ When another group compared the EEG effects of intranasal to intravenous midazolam they demonstrated the onset of EEG effects within 1.2 minutes of a 5 mg intravenous dose.³⁵ The relative effects of diazepam, lorazepam, and midazolam are shown in [Table A23–3](#).

TABLE A23–3. Relative Pharmacodynamic Properties of Benzodiazepines in Humans

	<i>Diazepam</i>	<i>Midazolam</i>	<i>Lorazepam</i>
Anticonvulsant			
Onset of action			
IV	Rapid (minutes)	Rapid (minutes)	Rapid (minutes)
IM	Not advisable	~3 minutes	9 minutes
Duration of action			
IV	1–2 hours	30–80 minutes	Many hours
IM	Unpredictable	1–2 hours	Many hours
Sedative			
Onset of action			
IV	Rapid (minutes)	Rapid (minutes)	5–20 minutes
IM	Unpredictable	5–10 minutes	20–30 minutes
Relative duration of action			
Single dose	Short	Short	Long
Repeated doses	Long (secondary to active metabolites)	Intermediate (secondary to active metabolites)	Long

IV = intravenous; IM = intramuscular.

ROLE OF BENZODIAZEPINES IN SELECT POISONINGS: THEORETICAL ASPECTS SUPPORTING A TRYPTOPHAN-RICH SENSORY PROTEIN INTERACTION

Many chapters in this text discuss the use of benzodiazepines as GABA_A agonists in the management of poisoned patients ([Chaps. 14, 15, 75, 76, 78, 81, 82, and 86](#)). In contrast to the highly evidence-based support for GABA_A agonists in sympathomimetic overdose, xenobiotic-induced seizures, and sedative-hypnotic withdrawal, the use of benzodiazepines as modulators of TSPOs for the treatment of poisoned patients is highly speculative. However, as this field is rapidly evolving, discussions of two xenobiotics, chloroquine ([Chap. 59](#)) and cocaine ([Chap. 78](#)) are warranted.

Chloroquine

Although chloroquine overdose is uncommon, case fatality rates are extremely high, and ingestion of 5 g or more was once considered universally fatal. However, in 1988 a case series of patients with chloroquine overdose who survived with the use of an aggressive new regimen was described.⁷² The protocol, consisting of early endotracheal intubation, high-dose epinephrine infusion, and intravenous diazepam (2 mg/kg over 30 minutes), resulted in the survival of 10 of 11 patients who ingested at least 5 g of chloroquine. This regimen was based on a controlled trial where diazepam improved the hemodynamic and electrocardiographic manifestations of chloroquine poisoning in pigs.⁷³ Although the study was not designed to determine the mechanism of effect of diazepam, there was no difference in the chloroquine concentrations between the treated and control groups, suggesting that diazepam did not change the distribution of chloroquine.

In isolated perfused hearts, high-dose diazepam has positive inotropic effects that are suppressed by a TSPO antagonist.⁵⁰ Unfortunately, translation of these findings to use in human poisoning is not necessarily valid. Benzodiazepines, chloroquine, and experimental TSPO agonists share some structural elements, suggesting a receptor-

based mechanism (Fig. A23–4). Functional similarity is also suggested by evidence that both flurazepam and PK 11195 (a TSPO agonist) have antimalarial activity.²² Thus, one could speculate that it is possible that the beneficial effects of high-dose diazepam result from competitive inhibition between chloroquine and TSPOs.

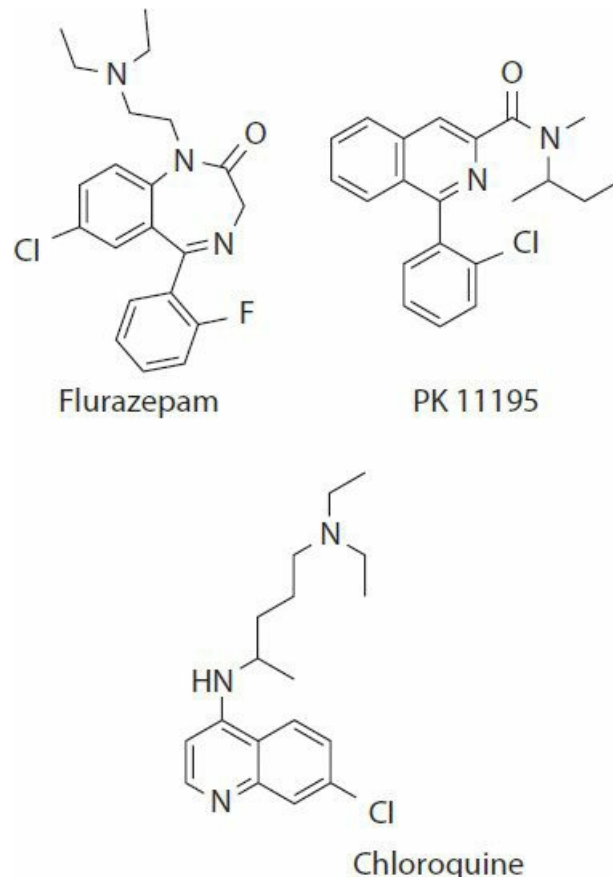


FIGURE A23–4. Comparative structures of flurazepam, PK 11195 (a PBR agonist), and chloroquine. Note the similarity and particularly the shared isoquinoline rings of chloroquine and PK 11195.

Cocaine

Patients who use cocaine frequently present to emergency departments with chest pain or signs or symptoms that could represent myocardial ischemia or infarction.¹² Unlike most patients with acute cocaine toxicity, however, these patients often present hours after their last drug use and without the classic sympathomimetic findings of acute cocaine toxicity.³⁶ While the pathophysiology of cocaine-induced myocardial ischemia is complex and multifactorial (Chap. 76), one component of delayed myocardial ischemia may result from the vasoconstrictive actions of benzoylecgonine, the principal metabolite of cocaine.⁵⁴ Benzoylecgonine is distinct from cocaine in that it has a much longer half-life,^{3,4} does not produce central nervous system stimulation,^{61,62} and directly vasoconstricts through modulation of calcium channels.⁵³

Limited research suggests that chronic cocaine use is associated with an increased number of TSPOs on human platelets.¹⁶ Also in humans, cocaine withdrawal is associated with a decrease in TSPOs on neutrophils. In the myocardium, TSPOs are either present on mitochondria or coupled to calcium channels.⁶⁰ Specifically, TSPO ligands have inhibitory effects on myocardial L-type calcium channels.¹⁴ Also in experimental models of cardiac ischemia and reperfusion injury, TSPO agonists limit myocardial infarction size and improve cardiac function.^{48,91} This effect most likely occurs through inhibition of the opening of the mitochondrial permeability transition pore,⁶⁵ the opening of which is a common final mechanism of cell death. Additionally, although the exact mechanism is unclear, TSPO agonists directly antagonize the vasoconstrictive effects of norepinephrine in rat aortic tissue.²⁹

Benzodiazepines are commonly used to treat the agitation associated with sympathomimetic overdose (Chaps. 76 and 78). While it is assumed that the normalization of vital signs results from a decrease in central nervous system stimulation and psychomotor agitation, effects on TSPOs may be contributory. In the same isolated perfused hearts described above, low-dose diazepam has a negative inotropic effect that results from an interaction with calcium currents.⁴⁹ As noted above, interpreting the implications of varied benzodiazepine doses in an isolated rat model with regard to human beings may not be valid. More importantly, two randomized controlled studies evaluated the use of benzodiazepines in patients with cocaine-associated chest pain.^{9,37} In the first study, patients were randomized to receive nitroglycerin, diazepam, or combined therapy.⁹ Both drugs were associated with an improvement in chest pain, and combined therapy appeared to offer no additional benefit. The second study randomized patients to nitroglycerin or combined nitroglycerin with lorazepam

therapy.³⁷ In this trial, combined therapy was better than either therapy alone, possibly suggesting that benzodiazepines and nitroglycerin relieve chest pain by different mechanisms.

ADVERSE EFFECTS AND SAFETY ISSUES

The most common adverse effect of benzodiazepines is central nervous system depression. While this is unavoidable in some cases, it can generally be limited by selecting the optimal drug and the proper dose and dosing interval for the drug being used. Extra caution is advised in elderly patients as they appear to be more sensitive, particularly to the sedative and respiratory depressant effects of midazolam.¹ In contrast, paradoxical reactions may occur where patients become more agitated following benzodiazepine administration.^{76,79,87} These infrequent reactions probably result from disinhibition and may respond to larger doses of benzodiazepines. Although paradoxical agitation also responds to flumazenil (Antidotes in Depth: A22), reversal would generally be inappropriate following the use of benzodiazepines for most toxicological indications.

Intravenous benzodiazepines produce a mild reduction in heart rate and both systolic and diastolic blood pressure. The effects of midazolam may be greater than diazepam,⁷⁰ but this may merely be based on an inability to determine an equivalent dosing regimen. While these reductions result in part from diminished sympathetic tone, direct myocardial effects are rarely severe and are often considered desirable in the overdose setting.⁷⁰

Whereas respiratory depression is generally not a concern with oral benzodiazepines, parenteral administration is documented to impair ventilation. Early investigations demonstrated that intramuscular diazepam (10 mg) blunted the hypoxic ventilatory drive in normal subjects.⁴⁶ Intravenous diazepam impaired the ventilatory response to a rising PCO₂ in normal volunteers.⁸ The impaired response to a rising PCO₂ was evident almost immediately and lasted for at least 25 minutes following injection of 0.4 mg/kg of diazepam in healthy volunteers.³⁴ Studies with midazolam demonstrate similar alterations in respiratory physiology²⁵ that are comparable in magnitude to those reported with diazepam.¹⁰ Apnea is reported following intravenous midazolam and appears to be dose and rate related, with doses greater than or equal to 0.15 mg/kg being of particular concern.⁴⁸ Individuals with preexisting pulmonary disorders, extremes of age, or other central nervous system or respiratory depressants may be more susceptible. When intramuscular midazolam is used for the treatment of agitation, some transient respiratory depression is noted, but the need for external ventilator support is uncommon.^{40,43,56}

Pregnancy and Lactation

Diazepam, lorazepam, and midazolam are all listed as category D drugs in pregnancy and are likely unsafe in lactation. These classifications are likely based on repetitive use and have little applicability to short-term benzodiazepine administration in emergent situations. However, the risks, benefits, and alternatives should always be considered prior to giving any xenobiotic to a pregnant woman. If a benzodiazepine is given to a lactating mother, “pumping and dumping” would be advised to prevent sedation in the child (Chap. 31).

DOSING AND ADMINISTRATION

In theory, an analysis of the pharmacokinetic and pharmacodynamic parameters presented in Tables A23–1 and A23–3 should allow clinicians to choose among the benzodiazepines based on the particular clinical situation. In reality, however, these choices may be difficult in patients with complex clinical presentations of uncertain etiologies. In addition, clinical studies seem to suggest less variability than might be predicted based on pharmacokinetic and pharmacodynamic modeling. For example, in an analysis of 28 studies of conscious sedation, 19 failed to demonstrate a significant difference in the times to recovery between diazepam and midazolam.⁶ Likewise, although multiple studies demonstrate that lorazepam is at least as effective and likely superior to diazepam in terminating status epilepticus, its onset of action does not appear to be delayed.^{2,51,82} In a double-blind trial of intravenous lorazepam versus intramuscular midazolam for patients with prehospital status epilepticus, patients who received intramuscular midazolam stopped seizing sooner and in greater numbers.⁷⁸

Some of the observed inability to translate controlled pharmacologic analyses into clinical practice may result from imprecision in determining equivalent doses of these drugs. We offer the following guidance. Each of these three benzodiazepines discussed will likely have some efficacy in all clinical scenarios for which a benzodiazepine is indicated. It may therefore be preferable for many clinicians to understand and master the pharmacology and limitations of a single drug rather than attempt to use all three drugs selectively and run the risk of an improper dose or suboptimal therapeutic interval leading to an adverse effect. For those who wish to use these drugs selectively, three variables should be considered: onset of effect, peak effect, and duration of effect. For example, in patients with extreme psychomotor agitation intravenous diazepam or midazolam would be preferred both for their rapid onset and rapid peak effects. The relatively

slow onset and delayed peak of lorazepam might lead to administration of multiple doses before the full effect of the first dose is appreciated, with resultant oversedation. When a short duration of sedation is anticipated, such as when treating a patient with toxicity following intravenous or inhaled use of cocaine, midazolam might be preferable over diazepam or lorazepam in that the duration of the effects of midazolam better matches the duration of effects of cocaine, thereby limiting oversedation after cocaine has been rapidly metabolized. For disorders where very long periods of agitation are expected, such as alcohol withdrawal, the choice of diazepam with its active metabolites (desmethyldiazepam and oxazepam) may be preferable over lorazepam and midazolam. With diazepam, less frequent dosing may be required and an auto-tapering effect may result at the end of therapy, because these metabolites persist longer than diazepam alone. When status epilepticus is present in the absence of substance use or withdrawal, midazolam in large doses seems to offer a clear advantage. It is important to note that switching from one benzodiazepine to another is rarely indicated and increases the risk of an adverse drug event from unpredictable peak effects or improper therapeutic doses or dosing intervals. Specific recommendations can be found in [Chaps. 15, 76, 78, and 81](#).

FORMULATION AND ACQUISITION

Parenteral benzodiazepines are available from multiple manufacturers in varying concentrations. It is essential to recognize that some formulations contain several significant and varied excipients ([Table A23–1](#)). Large doses or prolonged continuous infusions of benzodiazepines may result in toxicity from these excipients ([Chap. 55](#)).

SUMMARY

- Although benzodiazepines are commonly used in a variety of medical settings, subtle differences exist in their pharmacokinetics and pharmacodynamics. Optimal use of these drugs requires a thorough understanding of these differences.
- Clinicians should consider the desired onset of action, peak effect, and duration of action when choosing among different benzodiazepines.
- In general, intravenous administration is preferred in an emergency because of rapid and reliable absorption. Because of a rapid onset of action and short time to peak effect, sedation is best achieved with midazolam when a short duration of action is desirable, or diazepam for a longer duration of action.
- When intravenous access is not available, pharmacokinetic and pharmacodynamic parameters favor the use of midazolam for sedation.
- When used for sedation, the delayed peak effect of lorazepam (regardless of route of administration) is undesirable.
- Intravenous lorazepam is highly effective for seizures, but a continuous infusion of midazolam is preferred for status epilepticus.
- Although the use of benzodiazepines as TSPO (peripheral benzodiazepine receptor) agonists may explain some unique therapeutic effects of these drugs, existing research is too limited to offer guidance with regard to choice of drug, dose, or dosing interval required to optimize peripheral benzodiazepine receptor response.

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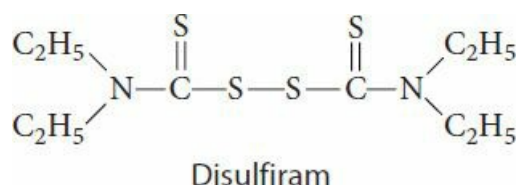
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79 DISULFIRAM AND DISULFIRAMLIKE REACTIONS

Amit K. Gupta



HISTORY AND EPIDEMIOLOGY

Disulfiram tetraethylthiuram disulfide (TETD) was synthesized from thiocarbamide in the 1880s to accelerate the vulcanization (stabilization) of rubber by the addition of sulfur.¹⁰⁴ Sixty years later it was the first western medication used to treat alcohol dependence. By the turn of the 20th century, most rubber factory workers exposed to disulfiram found that they were intolerant to alcohol.^{2,32} Williams, a rubber factory occupational physician, wrote, “If the chemical compound disulfiram is not harmful to man, one wonders if one has discovered a cure for alcoholism.” Apart from its use in the rubber industry, beginning in the early 1940s disulfiram was also used in medicine as a scabicide. Two scientists, Hald and Jacobsen, were exploring the antiparasitic effects of disulfiram when they made the rediscovery that ingesting alcohol after loading doses of disulfiram was quite unpleasant.³⁶ Subsequently, in 1951 the US Food and Drug Administration (FDA) approved disulfiram for the treatment for alcoholism. Disulfiram is typically prescribed at an initial dose of 500 mg/day for 1 to 2 weeks, followed by a maintenance dose of 125 to 500 mg/day.

Disulfiram was never widely used clinically, and its use further declined after the several studies revealed no significant difference in drinking outcomes between unsupervised disulfiram administration and placebo.³¹ Studies evaluating the efficacy of disulfiram span nearly 60 years and yield mixed results, with many studies having small sample sizes, nonrandomization, unblinded conditions, short follow-up periods, and no measurement of treatment adherence. With the worldwide approval of naltrexone in 1993, and later acamprosate, the clinical use of disulfiram declined. More recent interest in disulfiram for treating cocaine and other stimulant dependence has provided some renewed clinical interest.^{33,79,82,99}

Specific epidemiologic information about the three different forms of disulfiram toxicity is difficult to elucidate, even from an analysis of the American Association of Poison Control Centers (AAPCC). Data from the Annual Reports of the AAPCC National Poison Data System from 2007 to 2011 revealed 368 exposures to disulfiram, with the majority of cases being in adults and classified as unintentional. No deaths and only two major adverse outcomes were reported. Since 1982, 14 deaths associated with disulfiram have been reported to the AAPCC, most involving a disulfiram–ethanol reaction (Chap. 136). Serious adverse effects associated with both therapeutic use of disulfiram and with disulfiram overdose continue to be reported mostly in the form of case reports and case series. As such, these reports are difficult to interpret because of complications and comorbidities associated with alcohol use, the potential effects of polypharmacy, and the difficulty in relating the adverse effect to disulfiram, alcohol or a disulfiram–ethanol reaction.

In considering disulfiram toxicity, a distinction must be made between the clinical manifestations of a disulfiram–ethanol reaction and the toxic effects of disulfiram itself. Direct disulfiram toxicity can be further classified as acute or chronic poisoning. Although life-threatening effects associated with disulfiram are rare, clinicians should be aware of proper diagnosis and management of patients with disulfiram-associated toxicity.

PHARMACOLOGY AND PHARMACOKINETICS OF DISULFIRAM

Approximately 70% to 90% of disulfiram is absorbed from the gastrointestinal tract after oral administration.¹² Upon absorption, disulfiram is immediately converted to diethyldithiocarbamate (DDC), followed by rapid conversion to carbon disulfide and diethylamine.²² DDC can also chelate copper to form a bis(DDC)-copper complex.¹² Bis(DDC)-copper is absorbed from the small intestine. In one study, the mean serum disulfiram concentration in humans following a 250 mg

dose was reported to be $0.38 \pm 0.03 \mu\text{g/mL}$.²² Peak serum concentrations of disulfiram and DDC are achieved 8 to 10 hours following a 250 mg dose and 5 to 6 hours for carbon disulfide.²²

Disulfiram is highly lipid soluble and approximately 80% protein-bound.⁴³ An estimated 5% to 20% is not metabolized and is excreted unchanged in the feces. The volume of distribution has not been reported.

Within 5 to 10 minutes after absorption, disulfiram is rapidly reduced to DDC via glutathione reductase, which then can undergo nonenzymatic degradation to diethylamine and carbon disulfide or chelate copper to form a bis(DDC)-copper complex (Fig. 79–1).¹² As such, it may be difficult to detect the parent drug in blood concentrations. Metabolism of disulfiram occurs primarily in the liver and the erythrocyte. The oxidation of DDC in the liver is catalyzed by at least four isoenzymes of cytochrome P450 (CYP) and to a minor extent by human flavin monooxygenase.⁶⁰ DDC is also metabolized by glucuronidation, methylation, and oxidation. Methylation of DDC produces diethyldithiomethylcarbamate (MeDDC).¹⁵ MeDDC is oxidized primarily to the intermediate metabolite MeDDC sulfine, which is ultimately converted to MeDDC sulfoxide.⁶⁰ Genetic differences in various enzymatic activity between individuals can lead to fluctuating concentrations of the different metabolites.²² Carbon disulfide can undergo oxidation to carbonyl sulfide and further oxidation to carbon dioxide.

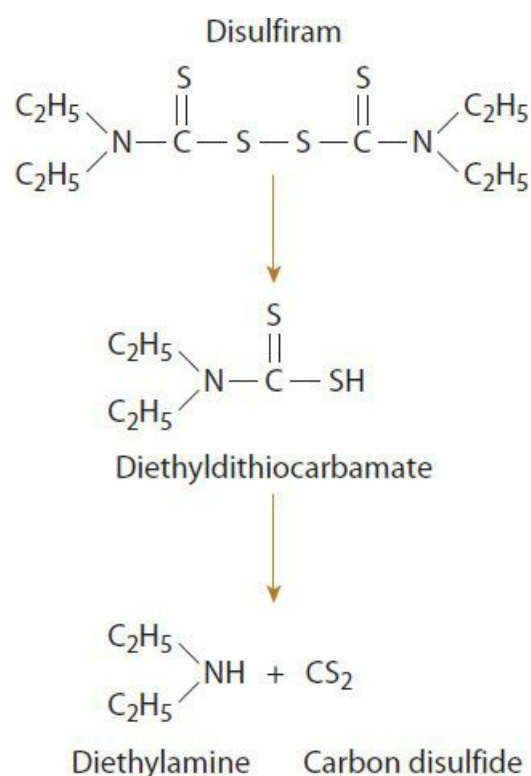


FIGURE 79–1 Disulfiram metabolism occurs in the liver and in the erythrocyte. The most consequential metabolites are diethyldithiocarbamate and carbon disulfide.

The hepatic metabolites of disulfiram are mostly excreted renally, although up to 20% of disulfiram can pass unchanged in the feces.²² Disulfiram has a half-life estimated at 60 to 120 hours. DDC is estimated to have a half-life of 13.9 hours and carbon disulfide 8.9 hours.⁴² With chronic dosing of disulfiram, carbon disulfide may also be excreted through the lungs, and this may explain the side effects of metallic taste and halitosis.²² Because of the long half-lives of disulfiram and its metabolites, 1 or 2 weeks may be needed before disulfiram is totally eliminated from the body following the last dose.²

DISULFIRAM–ETHANOL REACTION

Pharmacology and Pharmacokinetics

The primary indication for disulfiram is as an avoidant and aversive treatment for alcohol dependence. Either the fear of having a disulfiram–ethanol reaction or the memory of having one is a form of conditioned avoidance meant to deter the patient from using alcohol. Disulfiram inhibits both cytosolic and mitochondrial hepatic aldehyde–nicotinamide adenine dinucleotide (NAD) oxidoreductase, which is more commonly known as aldehyde dehydrogenase (ALDH), the enzyme that catalyzes the oxidation of acetaldehyde to acetate, resulting in an accumulation of acetaldehyde in the blood and tissues after ethanol ingestion (Fig. 79–2).² The increased concentration of acetaldehyde is responsible for the symptoms produced by the disulfiram–ethanol reaction.

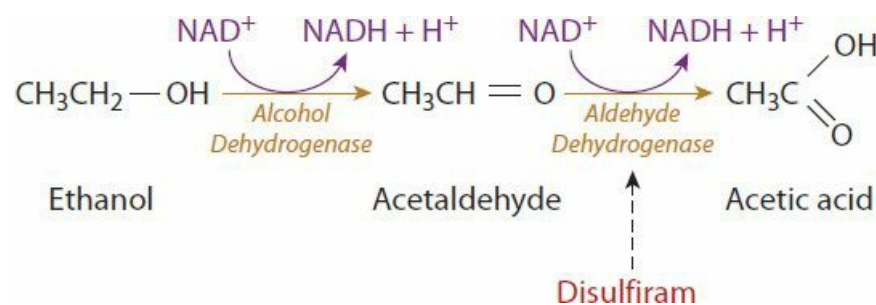


FIGURE 79–2 The site of action of disulfiram. The irreversible inactivation of aldehyde dehydrogenase results in an increased acetaldehyde concentration after ethanol is administered.

Elevations of blood acetaldehyde are largely determined by the extent of ALDH inhibition produced as well as the ethanol dose ingested.⁸⁰ After oral disulfiram administration, low-Km ALDH is inhibited with dosages greater than 150 mg/kg, but disulfiram does not inhibit high-Km ALDH even in high dosages (eg, 600 mg/kg).⁶⁴ ALDH will be inhibited by disulfiram at a more-or-less constant rate regardless of variations in the concentration of ALDH. ALDH inhibition with disulfiram develops over 12 hours and is mainly irreversible.⁴³ Recovery of enzymatic activity depends on de novo ALDH synthesis that takes place in 6 or more days.⁵⁰ The exact mechanism by which disulfiram and its metabolites inhibit ALDH is still unknown but may be due to oxidizing sulfhydryl groups or competition for NAD.⁹⁰ The metabolites of disulfiram, including DDC and its sulfoxide and sulfone metabolites, also inhibit ALDH.³⁶

The disulfiram–ethanol reaction may occur up to 3 weeks after the cessation of disulfiram therapy. There are also sustained-release and depot disulfiram preparations, but none are available in the United States. One patient developed a reaction 3 weeks after the subcutaneous injection of 2 g of disulfiram.⁸³

Disulfiram–ethanol reactions may follow exposure to the ethanol contained in many household products containing ethanol. [Table 79–1](#) lists some of these products.

TABLE 79–1. Common Household Products That Contain Ethanol and May Cause a Reaction with Disulfiram^{20,55,81,83,90}

Adhesives
Alcohols: denatured alcohol, rubbing alcohol
Detergents
Foods: liquor containing desserts, fermented vinegar, some sauces
Nonprescription xenobiotics: analgesics, antacids, antidiarrheals, cough and cold preparations, topical anesthetics, vitamins
Personal hygiene products: after shave lotions, colognes, contact lens solutions, deodorants, liquid soaps, mouthwashes, perfumes, shampoos, skin liniments, and lotions
Solvents

Clinical Manifestations

Symptoms of the disulfiram–ethanol reaction often begin within 15 minutes of ethanol ingestion, peak at 30 to 60 minutes, and gradually resolve over the next several hours. Symptoms are diverse and can include flushing, pruritus, diaphoresis, lightheadedness, headache, nausea, vomiting, and abdominal pain. Esophageal rupture due to forceful vomiting has been reported.²⁴ Electrocardiogram (ECG) changes, including ST-segment depressions and flattening of T waves, can occur along with dysrhythmias and myocardial infarction.^{67,71} Other rare complications include methemoglobinemia, hypertension, bronchospasm, and myoclonus.^{102,105,117} Severe shock and hypotension requiring vasopressor support is reported.^{10,70} Deaths attributed to the disulfiram–ethanol reaction are extremely rare and are associated with disulfiram doses in excess of current recommendations.^{4,44}

Disulfiramlike reactions can occur when ethanol is ingested with xenobiotics other than disulfiram. Symptoms are similar to those of disulfiram–ethanol reactions. Health care providers should warn patients of such reactions when prescribing certain medications that may cause this adverse effect. Unfortunately, these reactions are idiosyncratic and have not been studied extensively.¹¹¹ [Table 79–2](#) lists xenobiotics reported to cause disulfiramlike reactions.

TABLE 79–2. Xenobiotics Reported to Cause a Disulfiramlike Reaction with Ethanol^{7,1313,21,38,52,53,69,73,95,109,113,116}

Antimicrobials

Cephalosporins, especially those that contain an n-methylthiotetrazole (nMTT) side chain, such as cefotetan, cefoperazone, cefamandole, and cefmenoxime

Metronidazole

Moxalactam

Trimethoprim-sulfamethoxazole

Possible reactions with chloramphenicol, furazolidone, griseofulvin, nitrofurantoin, procarbazine quinacrine, sulfonamides

Calcium carbimide (citrated)

Carbon disulfide

Carbon tetrachloride

Chloral hydrate

Dimethylformamide

Mushrooms

Coprinus mushrooms including *C. atramentarius*, *C. insignis*, *C. variegatus*, and *C. quadrifidus*, *Boletus luridus*, *Clitocybe clavipes*, *Polyporus sulphureus*, *Pholiota squarosa*, *Tricholoma aurantium*, *Verpa bohemica*

Nitrefazole

Phentolamine

Sulfonylurea oral hypoglycemics

Chlorpropamide

Tolbutamide

Tacrolimus

Thiram analogs (fungicides)

Copper, mercuric, and sodium diethyldithiocarbamate

Zinc and ferric dimethyldithiocarbamate

Zinc and disodium ethylenebis [dithiocarbamate]

Thiuram analogs

Tetraethylthiuram monosulfide and disulfide (disulfiram)

Tetramethylthiuram disulfide (thiram)

Tolazoline

Trichloroethylene

Ingestion of ethanol following ingestion of various *Coprinus* species of mushrooms can cause a disulfiramlike reaction ([Chap. 120](#)).⁹²

MANAGEMENT OF DISULFIRAM-ETHANOL REACTIONS

The duration of the disulfiram-ethanol reaction varies from 30 to 60 minutes in mild cases to several hours and is largely dependent on the amount of alcohol that needs to be metabolized. Due to vomiting and volume depletion, serum glucose, electrolytes, and kidney function should be evaluated. Since only small amounts of ethanol can precipitate a disulfiram-ethanol reaction, it may be useful to confirm the presence of ethanol with a blood concentration. Patients with cardiovascular instability should have an ECG. Symptomatic and supportive care is the mainstay of treatment. Most patients with hypotension respond to intravenous 0.9% sodium chloride. Refractory hypotension is rare, but if necessary, a vasopressor can be administered. A direct-acting adrenergic agonist such as norepinephrine should be used since disulfiram inhibits dopamine β -hydroxylase (DBH), an enzyme necessary for norepinephrine synthesis. As such, indirect vasopressors, such as dopamine, that require functioning norepinephrine synthesis may be less effective.

For further symptomatic care, antiemetics can be administered, and for cutaneous flushing, a histamine (H_1) receptor antagonist, such as diphenhydramine, can be given.¹⁰¹ Most patients with a disulfiram-ethanol reaction have mild symptoms, are hemodynamically stable, and can be safely discharged following resolution of symptoms.

Fomepizole may halt the accumulation of acetaldehyde and thus cease severe disulfiram-ethanol reactions. Fomepizole, an inhibitor of alcohol dehydrogenase, may terminate the progression of the disulfiram reaction by blocking ethanol metabolism to acetaldehyde (Antidotes in Depth: A30). In a study of alcoholics, fomepizole decreased acetaldehyde concentrations and improved clinical symptoms in those experiencing a disulfiram-ethanol reaction.⁵⁹ A recent case series reported two patients who developed severe disulfiram-ethanol reactions with hypotension and tachycardia unresponsive to fluids who were treated successfully with a single dose of fomepizole.⁹⁷ One patient improved clinically 90 minutes after administration of fomepizole and the other within 30 minutes.

OTHER ENZYMES INHIBITED BY DISULFIRAM

Disulfiram and its active metabolites have many other targets besides ALDH. DDC is a potent metal chelator, which explains interest in the treatment of nickel and its effects on the activity of copper-dependent enzymes such as microsomal carboxylesterases, plasma cholinesterases, and cytochrome oxidase.⁶³ Inhibition of microsomal carboxylesterases and plasma cholinesterases are theorized to play a role in the pharmacokinetic increases in plasma cocaine concentrations caused by disulfiram.⁶⁵ Drugs metabolized by the cytochrome oxidase systems CYP450, specifically CYP2E1 (such as amitriptyline, warfarin, phenytoin, chlorthalidone, and diazepam) have increased serum concentrations and prolonged half-lives in patients taking disulfiram.³⁰

DDC also inhibits DBH, which converts dopamine to norepinephrine.^{34,72} Inhibition of DBH leads to increased concentrations of dopamine in the brain and periphery and decreased concentrations of norepinephrine and epinephrine.³⁴ The increased concentrations of dopamine from disulfiram may explain its possible therapeutic benefit in cocaine dependence and the potentiation of psychosis in psychotic individuals. Decreased urinary concentrations of vanillylmandelic acid, the metabolite of epinephrine and norepinephrine, are noted in individuals taking disulfiram, and this may explain the hypotension that occurs in patients with the disulfiram-ethanol reaction.³⁷

DISULFIRAM AND THE CYTOCHROME P450 OXIDATION SYSTEM

Disulfiram and its primary metabolite DDC are selective mechanism-based inhibitors of CYP2E1.⁴⁸ One study demonstrated in normal healthy volunteers that a single 500 mg dose of disulfiram markedly reduced by 93% the six-hydroxylation of chlorzoxazone, a putative index of CYP2E1 activity.⁴⁹ These same investigators showed, using probe drugs selectively metabolized by individual CYP enzymes, that 500 mg of disulfiram had no effect on the metabolism of coumarin (CYP2A6), tolbutamide (CYP2C9), mephenytoin (CYP2C19), dextromethorphan (CYP2D6), or intravenously administered midazolam (CYP3A).⁴⁸ Disulfiram does not significantly alter the metabolism of a therapeutic dose of acetaminophen, in either healthy patients or those with alcoholic liver disease.⁸⁴

DISULFIRAM AS AN ANTIDOTE

Disulfiram has been used for the treatment of nickel dermatitis. However, a small double-blind, placebo-controlled study of patients with hand eczema and nickel allergy did not find a clinically significant difference between those treated with disulfiram and those treated with placebo.⁴⁵ In fact, the conditions of some patients worsened after disulfiram therapy.⁵¹

DDC is available as the chelator dithiocarbamate. Although animal data and human case series suggest that DDC may be an effective chelator for the treatment of nickel-carbonyl poisoning, no well controlled human studies exist. Although animal studies suggest that DDC may be effective for nickel-carbonyl poisoning, there are no human studies to confirm this.^{11,103}

Since disulfiram increases nickel absorption in humans, it is recommended to consider use of disulfiram or DDC only for the treatment of nickel-carbonyl poisoning and not for elemental or inorganic nickel poisoning.

OTHER CLINICAL MANIFESTATIONS

Acute Disulfiram Toxicity

Reported cases of acute disulfiram overdose are rare and typically do not cause life-threatening toxicity. Most patients rapidly develop gastrointestinal symptoms within 1 to 2 hours that include nausea, vomiting, and abdominal pain. Neurologic symptoms may also be present after acute disulfiram overdose, including lethargy and coma.⁵⁸ Dysarthria and movement disorders, including myoclonus, ataxia, dystonia, and akinesia, occur rarely and may be related to direct effects of carbon disulfide on the basal ganglia.^{56,57,61} Symptoms can start as early as 3 days after ingestion. Hypotonia may be present in children.⁵ Persistent neurologic abnormalities, such as paresis, myoclonus, and neuropathy, lasting weeks to months, are reported in both children and adults but are rare.^{91,118}

Chronic Disulfiram Toxicity

The disulfiram-ethanol reaction, characterized by tachycardia, hypotension, diaphoresis, and facial erythema, is familiar to most physicians. However, the toxic effects of disulfiram alone, including depression, lethargy, loss of libido, psychosis, delirium, meningeal signs, unilateral weakness, optic neuritis, and peripheral neuropathy, are not well recognized by most clinicians, perhaps because the behavioral symptoms can be confused with manic-depressive or schizophrenic psychoses and the neurologic findings with the sequelae of alcoholism.^{17,21,25,54,77,89,96}

Two placebo-controlled trials showed no greater incidence of adverse effects with disulfiram 250 mg daily versus placebo other than drowsiness in the absence of alcohol.³¹ Over a 23 year period (1968–1991), 155 adverse drug reactions (ADR) were reported for disulfiram, giving it an ADR rate of 1 per 200 to 2000 patients per year (categorized as an “intermediate” rate of ADRs for a medication). Hepatic reactions were the most frequent ADR (34%), followed by neurologic (21%), cutaneous (15%), psychiatric (4%), and other (26%).²¹

Disulfiram-induced hepatitis was first reported in 1974.⁴⁷ In 1977, six additional cases were reported; five of the patients died.⁸⁸ Incidence of disulfiram-induced fatal hepatitis is reportedly 1 in 30,000 patients treated per year.¹⁴ The onset of symptoms of hepatotoxicity due to disulfiram occurs within 4 to 6 weeks (range, 2–24 weeks) after initiating treatment.^{14,27,88} Signs and symptoms include fatigue, headache, fever, pruritus, rash, myalgia, malaise, anorexia, nausea, vomiting, abdominal pain, jaundice, light stools, dark urine, and hepatomegaly. Symptoms usually resolve within 2 weeks of stopping disulfiram, but liver function may require up to 12 weeks to normalize.^{14,27,88} Liver biopsy may show predominantly hepatocellular degeneration with focal or extensive hepatocellular necrosis as well as portal and periportal eosinophilic infiltration.^{14,27} Although the exact mechanism of disulfiram-induced liver damage is unclear, most reports suggest an idiosyncratic hypersensitivity reaction as the primary mechanism involved.^{14,27,88} Alternatively, a carbon disulfide-induced hepatic injury resulting from covalent binding of electrophilic oxides or carbene derivatives of these oxides to macromolecules may be responsible.²⁸

Asymptomatic elevations in aminotransferase concentrations, up to three times the upper limit of normal, associated with disulfiram therapy are reported to range from 6% to 30% in alcoholics.^{35,106,115} Although hepatic effects have most commonly been reported with oral dosage forms, they also occur with implantable disulfiram.⁶⁶

Liver transplantation for disulfiram-induced liver failure was first reported in 1989.¹¹⁰ Since then, several case reports of liver transplantation for disulfiram-induced liver failure have been noted⁶⁸; the first North American case was performed in 1988.⁸⁶

Disulfiram may induce a peripheral neuropathy characterized by distal sensory impairment with loss of coordination, painful paresthesias, and distal weakness with foot drop.^{1,29} The severity of the neuropathy is directly related to dose and duration of exposure.^{78,112} If disulfiram is not discontinued, sensory and motor impairment can progress proximally.^{6,93} Wallerian-type axonal degeneration, intermediate filament accumulation, and marked loss of larger myelinated fibers have long been considered the pathological hallmarks of disulfiram toxicity.^{9,76} Experiments in animals showed that disulfiram causes Schwann cell damage and demyelination of peripheral nerves.^{107,108} In addition, isolated descriptions of both axonal and myelin involvement are reported.⁷⁵

The mechanisms underlying disulfiram-induced parkinsonism or catatonia are still controversial. One of the main hypotheses is that the lesions result from the toxicity of the disulfiram metabolite, carbon disulfide.^{46,87} Histopathological lesions of the globus pallidus and substantia nigra are observed after chronic exposure to carbon disulfide in animals.⁹³ Others have suggested involvement of brain dopaminergic transmission in disulfiram neurotoxicity.^{16,41} This is supported by an experiment in mice, where the toxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on nigrostriatal

dopaminergic systems were enhanced by pretreatment with disulfiram.¹⁶

The exact mechanism of disulfiram-mediated encephalopathy is not known. However, both DDC and carbon disulfide have been implicated, and both inhibit the activity of DBH, leading to the accumulation of dopamine, producing a relative deficiency of adrenaline and noradrenaline in the area of the basal ganglia.³⁹ Dopamine-mediated cellular injury may be related to its ability to induce excitatory toxic effects of glutamate and calcium-mediated cell death, as well as to impair the cellular ability to eliminate free oxygen radicals.⁹⁴

Disulfiram and Carbon Disulfide

Carbon disulfide is a colorless volatile liquid and a commonly used nonpolar chemical solvent. The principal industrial use of carbon disulfide is the manufacture of viscose rayon. In addition, carbon disulfide is used as an insecticide for the fumigation of grains, nursery stock, in fresh fruit conservation, and as a soil pesticide against insects and nematodes.¹⁹ The clinical, biochemical, and pathologic neurotoxic effects of disulfiram are similar to those of carbon disulfide. Both are associated with depression, lethargy, loss of libido, psychosis, ataxia, incoordination, and peripheral neuropathy.⁸⁷ Both inhibit DBH in vitro and produce increased brain dopamine and decreased brain norepinephrine, demyelination, and denervation in vivo.¹⁰⁰ Acute exposure to carbon disulfide causes rapid onset of headache, confusion, nausea, hallucinations, delirium, seizures, coma, and potentially death.³ Carbon disulfide may cause seizures by interacting with pyridoxal-5-phosphate, a cofactor in the production of γ -aminobutyric acid (GABA) from glutamate, thereby depleting GABA concentrations in the brain and leading to benzodiazepine-resistant seizures.⁸⁵

Although patients with occupational exposure to carbon disulfide have an increased risk of atherosclerosis and ischemic heart disease, this has not been proven for patients utilizing disulfiram.¹⁰⁴ Disulfiram therapy may increase serum cholesterol concentration.⁶²

Disulfiram and Pediatrics

The presence of this drug in the household makes it a potential xenobiotic encountered in unintentional poisonings; however, reports of significant toxicity are rare. One case report details a 5 year-old girl with exposure to 19 tablets of disulfiram, who subsequently developed dystonia, complete loss of developmental milestones, and spastic tetraparesis, over a 2-year follow-up period.⁶¹

Disulfiram and Pregnancy

There is a paucity of information regarding the teratogenic effects, if any, of disulfiram in humans or animals. Case reports have reported congenital defects, and one spontaneous miscarriage occurred.^{23,40,74} A confounder could be the combination of disulfiram and alcohol itself, which enhances the incidence of birth defects. The embryotoxic properties of disulfiram may also be due to its lead- and copper-chelating properties.¹⁸

DIAGNOSTIC TESTING

Acute Disulfiram Toxicity

Serum disulfiram concentrations are not useful when managing most patients with suspected acute or chronic disulfiram overdose, disulfiram toxicity, or a disulfiram-ethanol reaction. Because of rapid metabolism, only a small proportion of ingested disulfiram reaches the blood as the parent drug.⁴³ Metabolites of disulfiram, including diethyldithiomethylcarbamic acid and diethylmethylcarbamic acid, can be measured in the serum. Other markers of ingestion include carbon disulfide in the breath and diethylamine in the urine.²⁶ Leukocyte ALDH correlates most closely with hepatic mitochondrial ALDH. Decreased erythrocyte ALDH1 and leukocyte ALDH2 activity are markers of disulfiram exposure, but neither enzyme assay is commonly available. Elevated acetaldehyde concentrations in the blood will occur but are not readily available and therefore are not clinically useful in managing the majority of patients.

Chronic Disulfiram Toxicity

The development of hepatotoxicity is a potential concern with chronic disulfiram administration. Two common strategies employed for detecting and preventing severe hepatotoxicity include routine clinical monitoring for signs or symptoms of hepatic injury as well as periodic monitoring of biomarkers including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin.^{114,115}

There is no agreement on when disulfiram therapy should be modified or discontinued based on the finding of mildly elevated aminotransferase concentrations. There is much greater agreement that the development of an aminotransferase concentration greater than 3 times the upper limit of the reference range in combination with evidence of impaired hepatic

synthetic function, elevated total bilirubin greater than 2 times the upper limit of the reference range or international normalized ratio greater than 1.5 is suggestive of more severe drug-induced liver injury. In such situations, mortality may be 16% or higher and necessitate discontinuing disulfiram.^{8,98}

MANAGEMENT OF DISULFIRAM TOXICITY

Acute Disulfiram Toxicity

There is no antidote for acute disulfiram overdose. No specific studies have evaluated gastrointestinal decontamination for acute overdose. Unless otherwise contraindicated, activated charcoal at a dose of 1 g/kg can be administered. Forced emesis is not indicated, and orogastric lavage or whole-bowel irrigation is not required.

Chronic Disulfiram Toxicity

Most patients receiving disulfiram will not develop hepatotoxicity, but those who develop mild increase in their aminotransferases will likely normalize with continued disulfiram therapy.⁹⁸ Continued period monitoring of liver function tests should be performed, and therapy should be discontinued with symptoms of hepatic injury such as jaundice, abdominal pain, nausea, vomiting, or fever.

Treatment of hepatotoxicity is supportive and usually resolves following discontinuation of disulfiram therapy. Liver transplantation has been successfully performed for disulfiram-induced hepatic failure in both adults and children.^{68,86}

SUMMARY

- Even though the role of disulfiram in treating alcoholism is diminishing, its use for the treatment of cocaine dependence is gaining interest. It is critical to understand the distinction among the different forms of disulfiram toxicity, including toxicity from an acute overdose, from chronic therapy, and from a disulfiram–ethanol reaction.
- Disulfiram and its metabolites both irreversibly inhibit ALDH. This leads to accumulation of acetaldehyde and is responsible for many of the symptoms produced by the disulfiram–ethanol reaction. Symptoms are typically self-limiting and include facial and generalized body warmth and flushing, pruritus, urticaria, diaphoresis, lightheadedness, vertigo, headache, nausea, vomiting, and abdominal pain.
- Treatment for the disulfiram–ethanol reaction is mostly supportive and includes intravenous crystalloid administration, antiemetics, and histamine receptor antagonists. Fomepizole, an alcoholic dehydrogenase inhibitor, should be considered for more serious reactions.
- Disulfiram toxicity following an acute overdose is unlikely to be life threatening. Early symptoms are mostly gastrointestinal. Rarely, prolonged neurologic symptoms occur and include myopathy, movement disorders, ataxia, parkinsonism, and psychosis.
- Hepatotoxicity is the most common adverse drug reaction associated with chronic disulfiram therapy. Neurotoxicity is also reported with chronic disulfiram toxicity, and, symptoms are similar to those of acute disulfiram toxicity.

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80 ETHANOL

Luke Yip

HISTORY AND EPIDEMIOLOGY

Ethanol, or ethyl alcohol, is commonly referred to as “alcohol.” This term is somewhat misleading, because there are numerous other alcohols. However, ethanol is probably the most commonly used and abused xenobiotic in the world. Its use is pervasive among adolescents and adults of all ages, socioeconomic groups, and represents a tremendous financial and social cost.^{3,197} The ethanol content of alcoholic beverages is expressed by volume percent or by proof. Proof is a measure of the absolute ethanol content of distilled liquor, made by determining its specific gravity at an index temperature. In the United Kingdom, the Customs and Excise Act of 1952 declared proof spirits (100 proof) as those in which the weight of the spirits is 12/13 the weight of an equal volume of distilled water at 51°F (11°C). Thus, 100 proof spirits are 48.24% ethanol by weight or 57.06% by volume. Other spirits are designated over or under proof, with the percentage of variance noted. In the United States, a proof spirit (100 proof) is one containing 50% ethanol by volume.

The derivation of proof comes from the days when sailors in the British Navy suspected that the officers were diluting their rum (grog) ration and demanded “proof” that this was not the case. They achieved this by pouring a sample of grog on black granular gunpowder. If the gunpowder ignited by match or spark, the rum was up to standard, 100% proof that the liquor was at least 50% ethanol. This became shortened to 100 proof (Table 80–1).

TABLE 80–1. Basic Information and Calculations

Ethanol molecular weight (MW): 46 Da

$$\text{mmol} = \frac{\text{mg}}{\text{MW}} = \frac{\text{mg}}{46}$$

$$\text{mmol/L} = \frac{\text{mg/dL}}{4.6}$$

Specific gravity: 0.7939 (~0.8) g/mL

Volume of distribution (Vd): 0.6 L/kg

$$\text{Serum ethanol concentration (mg/dL)} = \frac{\text{dose (mg)}}{\text{Vd (L/kg)} \times \text{body weight (kg)} \times 10}$$

Average reduction in blood ethanol concentration (elimination phase):

Nontolerant adult: 3.26–4.35 mmol/L/h (15–20 mg/dL/h,
100–125 mg/kg/h)

Tolerant adult: 6.52–8.70 mmol/L/h (30–40 mg/dL/h, 175 mg/kg/h)

For a 70 kg individual:

<i>Dose of Ethanol</i>	<i>Estimated Serum Ethanol Concentration^a</i>
10 mL/kg of 10% (20 proof)	167 mg/dL (36.30 mmol/L)
3 mL/kg of 10% (20 proof)	50 mg/dL (10.87 mmol/L)
1.5 mL/kg of 10% (20 proof)	25 mg/dL (5.43 mmol/L)
150 mL (5 “shots”) of 40% (80 proof)	143 mg/dL (31.09 mmol/L)
30 mL (1 “shot”) of 40% (80 proof)	27 mg/dL (5.87 mmol/L)
A “standard drink,” defined as 1.5 fluid (fl) oz (eg, a single jigger or shot) of 80 proof spirits (“hard liquor”), 1.5 fl oz (eg, a single jigger or shot) of brandy, 2–3 fl oz of cordial, liqueur, or aperitif, 3–4 fl oz of fortified wine (eg, sherry or port), 5 fl oz of table wine, 8–9 fl oz of malt liquor, or 12 fl oz of regular beer ¹⁵⁸	43 mg/dL (9.35 mmol/L)

^aThis is the theoretical maximum concentration, based on instantaneous and complete ethanol absorption and no distribution or metabolism.

Blood concentration consistent with legal intoxication = 10.87–17.39 mmol/L (50–80 mg/dL or 0.05–0.08 g/dL)

The legal breath ethanol concentration to blood ethanol concentration ratio has been set at 1:2100; the amount of ethanol in 1 mL of blood is the same amount in 2100 mL of exhaled air: Measured breath ethanol concentration (mmol/L) x 2100 = (calculated) blood ethanol concentration (mmol/L).

In addition to beverages, ethanol is present in hundreds of medicinal preparations used as a diluent or solvent in concentrations ranging from 0.3% to 75%.^{28,44,52,145,152,196} Mouthwashes may contain up to 75% ethanol (150 proof), and colognes typically contain 40% to 60% ethanol (80 to 120 proof).^{15,96,152,166} These products occasionally cause intoxication, especially when unintentionally ingested by children.^{31,49,84,198}

Veisalgia, “alcohol hangover,” comes from the Norwegian kveis, “uneasiness following debauchery” and the Greek algia, “pain.” The “hangover” syndrome has been attributed to congeners, substances that appear in alcoholic beverages in addition to ethanol and water.^{26,33,34} Congeners contribute to the special characteristics of taste, flavor, aroma, and color of a beverage. The combinations and exact amounts of congeners vary with the type of beverage, ranging from 33 mg/L in vodka, to averages of 500 mg/L in some whiskies and as much as 29,000 mg/L in specially aged whiskies or brandies.^{26,33,34} The conventional listing of congeners includes fusel oil (a mixture containing amyl, butyl, propyl, and methyl alcohol), aldehydes, furfural, esters, low molecular weight organic acids, phenols, and other carbonyl compounds, tannins, solids, and a relatively large number of additional organic and inorganic compounds, usually in trace amounts.^{26,33}

Consumption of illicitly produced ethanol (“moonshine”) has resulted in methanol, lead or arsenic poisoning, and botulism.^{19,46,66,93,110,116,132,149} Incidental lead contamination is also reported in draught beers or wine contained in lead-capped bottles.^{173,174} Of historic interest is that the addition of cobalt salts to beer to stabilize the “head” (foam) led to

outbreaks of congestive cardiomyopathy among heavy beer drinkers in Canada and Belgium in the 1960s (Chap. 94). The clinical-pathological pattern of this disease is distinct from the classical alcoholic cardiomyopathy.^{126,128}

Alcoholism is the leading cause of morbidity and mortality in the United States. The prevalence of ethanol dependence in the United States has been relatively stable, at around 6% for men and 2% for women.²⁵ The overall estimated annual cost of US health expenses related to ethanol is \$185 billion.¹³⁸ More than 70% of the estimated costs were attributed to lost productivity, most of which resulted from ethanol-related illness or premature death. Most of the remaining estimated costs were expenditures for health care services to treat ethanol induced disorders (14.3%), property and administrative costs of ethanol-related motor vehicle crashes (8.5%), and criminal justice system costs of ethanol-related crime (3.4%). More than 200,000 Americans die annually of alcoholism, far more than those who die of all illicit drugs of abuse combined. Ethanol is the leading cause of mortality in people 15 to 45 years of age. In 2011, there were 9878 ethanol-related traffic fatalities in the United States, which accounted for 31% of total traffic fatalities; 66% of ethanol-impaired driving fatalities involved drivers with blood ethanol concentration 80 mg/dL or higher, 27% were passengers riding with the ethanol-impaired drivers, and 7% were nonoccupants of a motor vehicle.¹³⁷ Drivers aged 21 to 34 accounted for 44%, and drivers between 16 to 20 years accounted for 10% of all ethanol-impaired drivers in fatal crashes. Among 16 to 20 year-old male drivers, an increase of 20 mg/dL in blood ethanol concentration was estimated to more than double the relative risk of fatal single-vehicle crash injury compared with sober drivers of the same age and gender.²⁰⁹ When the blood ethanol concentration ranged from 80 to 100 mg/dL (17–22 mmol/L), 100 to 150 mg/dL (22–33 mmol/L), and greater than 150 mg/dL (33 mmol/L), the relative risk of fatal single-vehicle crash injury was 52, 241 and 15,560, respectively.

The Global Burden of Disease Study identified three effects of ethanol: harmful effects in relation to injuries, harmful effects in relation to disease, and the protective effect in relation to ischemic heart disease.¹³⁸ Overall ethanol accounted for 3.5% of mortality and disability, 1.5% of all deaths, 2.1% of all life years lost, and 6% of all the years lived with disability.¹³⁸ In the United States, according to National Highway Traffic Safety Administration (NHTSA) information, all jurisdictions have enacted per se blood ethanol concentration for adults operating noncommercial motor vehicles.¹³⁷ The term “illegal per se” refers to state laws that make it a criminal offense to operate a motor vehicle at or above a specified ethanol (or drug) concentration in the blood, breath, or urine, which may or may not reflect clinical intoxication (Special Considerations: SC6). For example, although ethanol-tolerant patients may not exhibit impairment even at serum ethanol concentrations greater than 300 mg/dL (65 mmol/L), they are still considered impaired with regard to the laws that governs motor vehicle operation.¹

There is a dose-response relationship between ethanol consumption and risk of death in men aged 16 to 34 and in women aged 16 to 54. Meta-analysis of aggregate data from epidemiologic dose-response ethanol and mortality cohort studies suggests that the level of ethanol consumption at which all-cause risk is lowest is approximately 5 g/d and that ethanol exerts a protective effect (J-shaped dose-response curve) up to a daily intake of approximately 45 g.⁹ It is suggested that sensible drinking of ethanol for men is 8 to 10 g/d up to age 34, 16 to 20 g/d between 34 and 44 years of age, 24 to 30 g/d between 44 and 54 years of age, 32 to 40 g/d up between 54 and 84 years of age, and 40 to 50 g/d over age 85. Women would be advised to limit their drinking to 8 to 10 g/d up to age 44, 16 to 20 g/d between 44 and 74 years of age, and 24 to 30 g/d over age 75.²⁰¹ However, no safe level of prenatal ethanol exposure has been established. The combination of a national tolerance of drinking and heavy advertising of ethanol makes it especially appealing to young people. In a society increasingly concerned with drug abuse, the excessive use of ethanol constitutes a serious and pervasive problem as well as a major health issue.

PHARMACOKINETICS/TOXICOKINETICS

Ethanol is rapidly absorbed from the gastrointestinal (GI) tract, with approximately 20% absorbed from the stomach and the remainder from the small intestine.¹⁴¹ Factors that enhance absorption include rapid gastric emptying, ethanol intake without food, the absence of congeners, dilution of ethanol (maximum absorption occurs at a concentration of 20%), and carbonation. Under optimal conditions for absorption, 80% to 90% of an ingested dose is fully absorbed within 60 minutes. Factors that delay or decrease ethanol absorption include high concentrations of ethanol (by causing pylorospasm), presence of food, coexistence of GI disease, coingestion of xenobiotics such as aspirin and N-butylscopolamine,^{94,146} time taken to ingest the drink, and individual variation. When any of these factors is present, absorption may be delayed for 2 to 6 hours. The relative amount of ethanol that is absorbed from the stomach is determined by the presence of alcohol dehydrogenase (ADH) in the gastric mucosa, which oxidizes a proportion of the ingested ethanol, thus reducing the amount available for absorption. This effect is more pronounced in men than in women and in nonalcoholics than in alcoholics.^{11,58} Histamine₂ (H₂) receptor antagonists such as cimetidine and ranitidine inhibit gastric ADH resulting in decreased first-pass metabolism and increase the bioavailability of imbibed ethanol.^{6,22,24,40,51}

Following complete distribution, ethanol is present in body tissues in a concentration proportional to that of the tissue water content. Ethanol freely passes through the placenta, exposing the fetus to ethanol concentrations comparable to that achieved in the mother.

Ethanol is primarily eliminated by the liver, with 2% to 5% excreted unchanged by the kidneys, lungs, and sweat.⁸⁸ Ethanol is metabolized via at least three different pathways: the aforementioned ADH pathway located in the cytosol of the hepatocytes, CYP2E1, a member of the cytochrome P450 mixed-function oxidase system, located on the endoplasmic reticulum, and the peroxidase-catalase system associated with the hepatic peroxisomes (Fig. 80–1).¹⁴¹

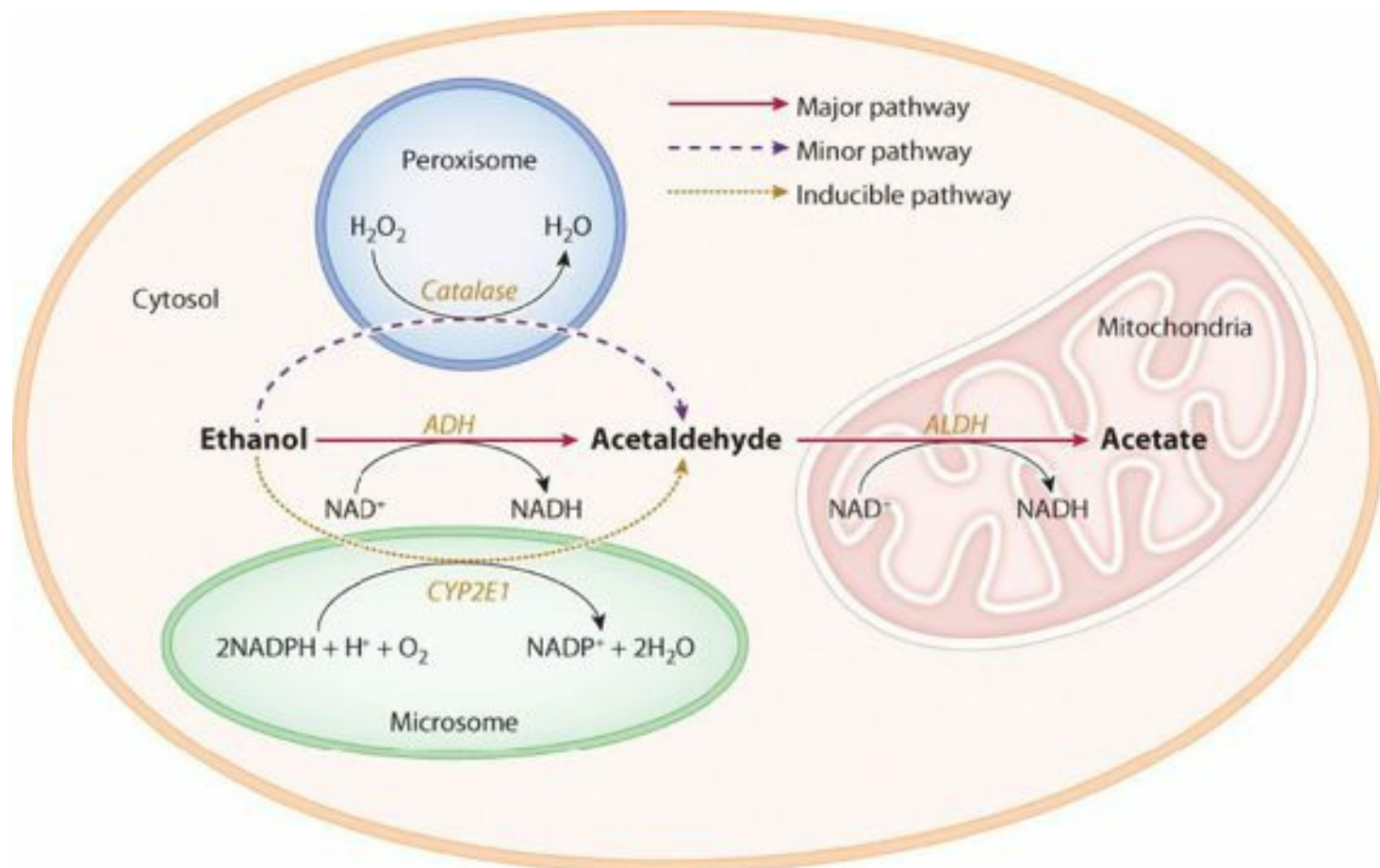


FIGURE 80–1 Ethanol is metabolized to acetaldehyde and then to acetate through major, minor, and inducible pathways. ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase.

For a given ethanol dose, 95% to 98% is metabolized in the liver, first to acetaldehyde by ADH and then further to acetate by aldehyde dehydrogenase (ALDH).⁸⁸ The end products of ethanol oxidation are carbon dioxide and water. The remaining 2% to 5% is excreted unchanged in urine, sweat, and expired air. In addition, less than 0.1% undergoes phase II conjugation reactions to produce ethyl glucuronide and ethyl sulfate, catalyzed by uridine diphosphate-glucuronosyltransferase and sulfotransferase, respectively.^{32,56,76,168,169}

The ADH system is the main pathway for ethanol metabolism and is also the rate-limiting step. ADH is a zinc metalloenzyme that uses oxidized nicotinamide adenine dinucleotide (NAD^+) as a hydrogen ion acceptor to oxidize ethanol to acetaldehyde. In this process, a hydrogen ion is transferred from ethanol to NAD^+ , converting it to its reduced form NADH . Subsequently, a hydrogen ion is transferred from acetaldehyde to NAD^+ . Under normal conditions acetate is converted to acetylcoenzyme A (acetyl-CoA), which enters the Krebs cycle and is metabolized to carbon dioxide and water. The entry of acetyl-CoA into the Krebs cycle is thiamine dependent (Antidotes in Depth: A24).

The ADH gene family encodes enzymes that metabolize a wide variety of substrates. There are at least seven genetic loci that code for human ADH arising from the association of different subunits, and there are more than 20 ADH isoenzymes.² These ADH forms are divided into five major classes (I–V) according to their subunit, isoenzyme composition, and physicochemical properties.⁸⁹ Two of these gene loci exhibit polymorphism and they both involve class I ADH genes; three alleles exist for ADH2 (ADH1B) [ADH2*1 (ADH1B*1), ADH2*2 (ADH1B*2), and ADH2*3 (ADH1B*3)] and three for ADH3 (ADH1C) [ADH3*1 (ADH1C*1), ADH3*2 (ADH1C*2), and ADH3*3 (ADH1C*3)].³⁰ Class I enzymes are inducible intracellular hepatic enzymes and are believed to play a major role in ethanol metabolism.¹¹³ Class IV ADH6 (σ -ADH) is the major ADH expressed in human gastric mucosa.^{11,58} σ -ADH is usually present in non-Asians, whereas in a majority of Pacific Rim Asians, the enzyme activity is either low or not detectable.^{11,12,42} The ADH1B*2 allele is present in 90% of Pacific Rim Asians but occurs infrequently in most Caucasians, except for people of Jewish and perhaps Hispanic descent.²⁰² This allele is responsible for the unusually rapid conversion of ethanol to acetaldehyde. People carrying ADH1B*2 alleles are about one-third as likely to be alcoholic compared with people without this allele.²⁰²

In the liver, ADH metabolizes ethanol to acetaldehyde, which is then converted to acetate by mitochondrial NAD-dependent ALDH. Human ALDH is divided into nine major gene families. There is a functional polymorphism of the mitochondrial ALDH2 gene and expression of an inactive form of the ALDH2, glutamate to lysine substitution at position 487 (E487K), results in impaired acetaldehyde metabolizing capacity. The variant allele ALDH2*2 encodes a protein subunit that confers low activity to the enzyme resulting in marked differences in the steady-state kinetic constants, which appears to be most prevalent in Pacific Rim Asians.^{2,30,68,182,183} These metabolic polymorphisms contribute to differences in ethanol and acetaldehyde elimination rate; high activity ADH variants are predicted to increase the rate of acetaldehyde generation, whereas the low activity ALDH2 variant is associated with limited capacity to metabolize this compound and may explain differences in ethanol-related behavior. Asians possessing an atypical ALDH2 gene are more sensitive to acute adverse responses to ethanol and tend to discourage ethanol consumption. Homozygous ALDH2*2 individuals are strikingly sensitive to small dose of ethanol (0.2 g/kg), as evidenced by the intense flushing, pronounced cardiovascular hemodynamic effects, and subjective perception of general discomfort.^{48,68,150,188,192} This effect may also be associated with the ADH2*2 and ADH3*1 allele and is similar to that induced by disulfiram (Chap. 79). The ethanol flushing response may involve prostaglandin and histamine release. Both prostaglandin antagonists (aspirin)¹⁸⁹ and antihistamines (H₁ and H₂)^{129,178,185} may attenuate this response.

CYP2E1 is responsible for very little ethanol metabolism in the non tolerant drinker, but becomes more important as the ethanol concentration rises or as ethanol use becomes chronic (Fig. 80–1). CYP2E1 uses reduced nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor in a complex process that ultimately oxidizes ethanol to acetaldehyde.¹⁰⁴ In this process, hydrogen is abstracted from ethanol and donated to molecular oxygen to form water. Subsequently, acetaldehyde is further oxidized to acetate as hydrogen ion is transferred from acetaldehyde to NADP⁺. The ability of ethanol to induce the CYP2E1 forms the basis for the well-established interactions between ethanol and a host of other xenobiotics metabolized by this system.^{41,57} In alcoholics and those with higher ethanol concentrations, cimetidine may also delay ethanol clearance by inhibiting CYP2E1.⁷² However, the increase in blood ethanol concentration from such an interaction is of questionable clinical significance.^{5,6,22,23}

ADH is saturated at relatively low blood ethanol concentrations. As the system is saturated, ethanol elimination changes from first-order to zero-order kinetics (Chap. 9). In adults, the average rate of ethanol metabolism is 100 to 125 mg/kg/h in occasional drinkers and up to 175 mg/kg/h in habitual drinkers.^{18,67} As a result, the average-sized adult metabolizes 7 to 10 g/h and the blood ethanol concentration falls 15 to 20 mg/dL/h (3.26–4.35 mmol/L/h). Tolerant drinkers, by recruiting CYP2E1, may increase their clearance of ethanol to 30 mg/dL/h (6.52 mmol/L/h) or even higher.^{18,67} Studies of ethanol-intoxicated patients indicate that although the average ethanol clearance rate is about 20 mg/dL/h (4.35 mmol/L/h), there is considerable individual variation (standard deviation of about 6 mg/dL/h (1.30 mmol/L/h)).^{18,67}

XENOBIOTIC INTERACTIONS

Ethanol interacts with a variety of xenobiotics (Table 80–2).^{92,196} The most frequent ethanol–drug interactions occur as a result of ethanol-induced increase in hepatic xenobiotic-metabolizing enzyme activity. In contrast, acute ethanol use may inhibit metabolism of other xenobiotics, and this may be due to competitive inhibition of hepatic enzyme activity or a reduction in hepatic blood flow. The interaction between ethanol and disulfiram (Antabuse) is well described, and it can be life threatening (Chap. 79).

TABLE 80–2. Ethanol Xenobiotic Interactions

<i>Xenobiotics</i>	<i>Adverse Effects</i>
Antihistamines (H ₁)	Additive sedative effect
Aspirin	Enhance antiplatelet effect
Carbamates	Disulfiramlike effect
Cephalosporins ^a	Disulfiramlike effect
Chloral hydrate	Additive sedative effect
Chloramphenicol	Disulfiramlike effect
Chlorpropamide	Disulfiramlike effect
<i>Coprinus</i> spp mushrooms	Disulfiramlike effect
Cyclic antidepressants	Additive sedative effect
Disulfiram (Antabuse)	Nausea, vomiting, abdominal pain, flushing, diaphoresis, chest pain, headache, vertigo, palpitations
Griseofulvin	Disulfiramlike effect
Isoniazid	Increased incidence of hepatitis; increased metabolism ^b
Methadone	Increased methadone metabolism ^b
Metronidazole	Disulfiramlike effect
Nitrofurantoin	Disulfiramlike effect
Opioids	Additive sedative effect
Oral hypoglycemics	Potentiates hypoglycemic effect
Phenothiazines	Additive sedative effect
Phenytoin	Increased phenytoin metabolism ^b
Ranitidine, cimetidine	Increased ethanol concentration
Sedative-hypnotics	Additive sedative effect/respiratory depression
Thiram derivatives	Disulfiramlike effect
Vasodilators	Potentiates vasodilator effect
Warfarin	Increased warfarin metabolism ^b

^aThose containing a *N*-methylthiotetrazole side chain. ^bEffect possibly associated with chronic alcohol consumption.

Concomitant use of cocaine and ethanol leads to the formation of an active metabolite, cocaethylene, through transesterification of cocaine by the liver.¹⁵⁶ Cocaethylene has a longer half-life than cocaine itself (2 hours vs. 48 minutes), and this may explain some of the delayed cardiovascular effects attributed to cocaine use.^{8,203} Both ethanol and cocaethylene inhibit the metabolism of cocaine, thereby prolonging the elimination of cocaine and enhancing its effect (Chap. 78).¹⁴⁷

Case reports and retrospective case series that suggest chronic ethanol consumption may predispose a person to acetaminophen (APAP) hepatotoxicity (Chap. 35),^{47,118,125,167,211} even when APAP has been taken according to the manufacturer's recommended dosage of not more than 4 g daily.²¹² Because ethanol induces CYP2E1, the enzyme involved in the metabolism of APAP to its hepatotoxic intermediate, N-acetyl-p-benzoquinone imine, a theoretical basis for this association exists. However, in randomized, placebo-controlled trials where confirmed alcoholics were given APAP 4 g

daily or placebo, there were no differences between the two groups with regard to liver enzymes or to their coagulation profile.¹⁶³ Recent fasting, common in alcoholics, was also associated with a predisposition to APAP hepatotoxicity, likely due to depletion of glutathione (Chap. 35).²⁰⁰ However, in a retrospective study, heavy drinkers did not develop more severe hepatotoxicity following APAP overdose than nondrinkers.¹¹⁹

PATHOPHYSIOLOGY

Despite the long history of ethanol use and study, no specific receptor for ethanol has been identified, and the mechanism of action leading to intoxication remains the subject of debate.¹⁵¹ Ethanol is known to affect a large number of membrane proteins that participate in signaling pathways such as neurotransmitter receptors, enzymes, and ion channels,^{136,194} and there is extensive evidence that ethanol interacts with a variety of neurotransmitters.^{50,190,191} The major actions of ethanol involve enhancing the inhibitory effects of γ -aminobutyric acid (GABA) at GABA_A receptors and blockade of the N-methyl-d-aspartate (NMDA) subtype of glutamate, an excitatory amino acid (EAA) receptor.^{37,102,103,194} Animal studies indicate that the acute effects of ethanol result from competitive inhibition of glycine binding to the NMDA receptor and disruption of glutamatergic neurotransmission by inhibiting the response of the NMDA receptor. Persistent glycine antagonism and attenuation of glutamatergic neurotransmission by chronic ethanol exposure results in tolerance to ethanol by enhancing EAA neurotransmission and NMDA receptor upregulation.^{85,135,187,190,191} The latter appears to involve selective increases in NMDA R2B subunit concentrations and other molecular changes in specific brain loci.⁴ The abrupt withdrawal of ethanol thus produces a hyperexcitable state that leads to the ethanol withdrawal syndrome and excitotoxic neuronal death.^{16,37,190} GABA-mediated inhibition, which normally acts to limit excitation, is eliminated during the ethanol withdrawal syndrome and further intensifies this excitation. In addition, NMDA receptors function to inhibit the release of dopamine in the nucleus accumbens and mesolimbic structures, which modulates the reinforcing action of addictive xenobiotics such as ethanol.^{20,21,177} By inhibiting NMDA receptor activity, ethanol could increase dopamine release from the nucleus accumbens and ventral tegmental area and could thus create dependence. Chronic ethanol administration also results in tolerance, dependence, and an ethanol withdrawal syndrome, mediated, in part, by desensitization and or downregulation of GABA_A receptors (Chaps. 14, 15, and 81).

Chronic alcoholism has multiorgan system effects (Table 80–3), and the relationships between ethanol use, nutrition, and liver disease have been reviewed elsewhere.¹¹⁴ In addition to the harmful effects of ethanol itself such as impairment of protein synthesis, its metabolite, acetaldehyde, is inherently toxic to biologic systems.^{108,112,193,210} Acetaldehyde directly impairs cardiac contractile function, disrupts cardiac excitation-contraction coupling, inhibits myocardial protein synthesis, interferes with phosphorylation, causes structural and functional alterations in mitochondria and hepatocytes, and inactivates acetyl-CoA. Acetaldehyde can also react with intracellular proteins to generate adducts. Acetaldehyde-protein and DNA adducts promote oxidative stress, lipid peroxidation, hepatic stellate cells activation-associated inflammation and fibrosis, and mutagenesis. Acetaldehyde adducts are believed to be important in the early phase of alcoholic liver disease, and in advanced liver disease they contribute to the development of hepatic fibrosis as well as hepatocellular carcinoma.¹⁷¹

TABLE 80–3. Systemic Effects Associated with Alcoholism

Cardiovascular	Esophagus	Genitourinary	Intoxication
Cardiomyopathy	Boerhaave syndrome	Hypogonadism	Korsakoff psychosis
"Holiday heart" (dysrhythmias)	Cancer of the esophagus	Impotence	Marchiafava-Bignami disease
"Wet" beriberi (thiamine deficiency)	Diffuse esophageal spasm	Infertility	Myopathy
Endocrine and metabolic	Esophagitis	Hematologic	Pellagra
Hypoglycemia	Mallory-Weiss tear	Coagulopathy	Polyneuropathy
Hypokalemia	Stomach and duodenum	Folate, B ₁₂ , iron-deficiency anemias	Wernicke encephalopathy
Hypomagnesemia	Gastritis	Hemolysis (Zieve syndrome, stomatocytosis, spur-cell anemia)	Ophthalmic
Hypophosphatemia	Chronic hypertrophic gastritis	Leukopenia	Tobacco-ethanol amblyopia
Hypothermia	Diarrhea	Thrombocytopenia	Psychiatric
Hypertriglyceridemia	Hematemesis	Neurologic	Animated behavior
Hyperuricemia	Malabsorption	Alcohol amnesic syndrome	Loss of self-restraint
Metabolic acidosis	Peptic ulcer	Alcoholic hallucinosis	Manic-depressive illness
Malnutrition	Liver	Alcohol withdrawal	Suicide and depression
Gastrointestinal	Cirrhosis	Central pontine myelinolysis	Respiratory
Mouth	Hepatitis	Cerebral atrophy (dementia)	Atelectasis
Cancer of the mouth, pharynx, larynx	Steatosis	Cerebellar degeneration	Pneumonia
Cheliosis	Pancreas	Cerebrovascular accident (subarachnoid hemorrhage, infarction)	Respiratory depression
Nutritional stomatitis	Pancreatitis (acute or chronic)		Respiratory acidosis

Ethanol metabolism through the CYP2E1 pathway generates highly reactive oxygen radicals, including the hydroxyethyl radical molecule. Elevated oxygen radical concentrations generate a state of oxidative stress, which leads to cell damage. Oxygen radicals can also initiate lipid peroxidation resulting in reactive molecules such as malondialdehyde and 4-hydroxy-2-nonenal. These reactive molecules react with proteins or acetaldehyde to form adducts, which contribute to the development of alcoholic liver injury.³⁸

Oxidation of ethanol generates an excess of reducing potential in the cytosol in the form of NADH with the ratio of NADH to NAD⁺ being dramatically increased. This ratio, also known as the redox potential, determines the ability of the cell to carry on various oxidative processes. The unfavorable change in redox potential due to ethanol metabolism contributes to the development of metabolic disorders, such as impaired gluconeogenesis, alterations in fatty acid metabolism, fatty liver, hyperlipidemia, hypoglycemia, elevated lactate concentration, hyperuricemia (gouty attacks), increased collagen and scar tissue formation associated with alcoholism, and a clinical syndrome of alcoholic ketoacidosis (AKA).

Studies in alcoholic liver disease have focused on Kupffer cell activation by endotoxin that is released by intestinal bacteria. When Kupffer cells are activated, they produce regulatory nuclear factor kappa β (NF κ B) and generate significant amounts of superoxide radicals (O₂⁻) and cytokines (tumor necrosis factor and interleukin-8), which is an essential factor in the injury to hepatocytes associated with alcoholic liver disease.^{124,199}

ACUTE CLINICAL FEATURES

Ethanol is a selective central nervous system (CNS) depressant at low doses and a general depressant at high doses. Initially it depresses those areas of the brain involved with highly integrated functions. Cortical release leads to animated behavior and the loss of restraint. This paradoxical CNS stimulation is due to disinhibition. In cases of mild intoxication, the signs of ethanol inebriation are quite variable. The patient may be energized and loquacious, expansive, emotionally labile, increasingly gregarious or may appear to have lost self-control, exhibit antisocial behavior, and be ill tempered. As the degree of intoxication increases, there is successive inhibition and impairment of neuronal activity. The patient may become irritable, abusive, aggressive, violent, dysarthric, confused, disoriented, or lethargic. With severe intoxication, there is loss of airway protective reflexes, coma, and increasing risk of death from respiratory depression. An ethanol-naive adult with a blood ethanol concentration of greater than 250 mg/dL (54 mmol/L) is usually comatose.¹

However, the acute effects of ethanol ingestion also depend on the habituation of the drinker. This is mainly due to the development of tolerance, which has both a metabolic (pharmacokinetic) and a functional (pharmacodynamic) component.¹⁸¹ Metabolic tolerance to ethanol is based on enhanced elimination by ADH, and to a greater extent, CYP2E1. Functional tolerance (resistance to the effects of ethanol at the cellular level) is a more important determinant of habituation and is mediated through alterations in GABA_A and NMDA receptors as well as serotonergic (eg, 5-HT_{1A}) and adrenergic

neurons.^{85,97,98,135,180–191} Acute ethanol tolerance is demonstrated by the Mellanby effect, which involves the comparison of physiologic responses or behavioral effects at the same blood ethanol concentration on the ascending and descending limbs of the blood ethanol concentration–versus–time curve. Impairment is greater at a given blood ethanol concentration when it is increasing than for the same blood ethanol concentration when it is falling.^{139,195} Although individuals who are acutely intoxicated move through a progressive sequence of events, the association of a particular aspect of intoxication with a specific blood ethanol concentration is not usually possible without knowing the pattern of ethanol use of the patient. Acute ethanol intoxication occurs in habitual drinkers when they raise their ethanol concentration an equivalent amount above baseline, and specific clinical manifestations of inebriation typically occur with significantly higher blood ethanol concentration than in nontolerant individuals. Regardless, the absolute change above baseline may be important.

A patient may present with obvious signs and symptoms consistent with ethanol intoxication that include flushed facies, diaphoresis, tachycardia, hypotension, hypothermia, hypoventilation, mydriasis, nystagmus, vomiting, dysarthria, muscular incoordination, ataxia, altered consciousness, and coma. However, an ethanol-intoxicated patient may present to the emergency department (ED) with a broad range of diagnostic possibilities and should prompt a careful evaluation for a variety of covert clinical and metabolic disorders. A meticulous and systematic approach to the evaluation and management of an inebriated patient will help avoid the potential pitfalls in such a situation.⁶¹ The presence or absence of an odor of ethanol on the breath is an unreliable means of ascertaining if a person is intoxicated or if ethanol was recently consumed.¹³⁴ Diplopia, visual disturbances, and nystagmus may be evident, which may be due to the toxic effects of ethanol or may represent Wernicke encephalopathy. Hypothermia may be exacerbated by environmental exposure, from malnutrition and loss of carbohydrate or energy substrate, and from ethanol-induced vasodilation. Ethanol intoxication can impair cardiac output in patients with preexisting cardiac disease⁶⁹ and induce dysrhythmias such as atrial fibrillation, atrioventricular block, and nonsustained ventricular tachycardia.^{45,70,71} The association between ethanol use and cardiac dysrhythmias, particularly supraventricular tachydysrhythmias, in apparently healthy people is called “holiday heart syndrome.”^{99,105,127} The syndrome was first described in people with heavy ethanol consumption, who typically presented on weekends or after holidays, and it may also occur in patients who binge but who usually drink little ethanol. The most common dysrhythmia is atrial fibrillation, which usually reverts to normal sinus rhythm within 24 hours. Although the syndrome may recur, the clinical course is benign in patients without anatomic cardiac pathology and specific antidysrhythmic therapy is usually not warranted.^{59,71} Acute heavy ethanol drinking may precipitate silent myocardial ischemia in patients with stable angina pectoris.¹⁶² Variant angina is reported to occur in patients following ethanol ingestion at a time when the blood ethanol concentration has decreased to almost zero.^{53,91,122,130,145,165,184} Ethanol-induced seizures are reported in adults but are more frequent in children with ethanol-induced hypoglycemia.^{31,84} Patients presenting with acute ethanol intoxication commonly have decreased serum ionized magnesium concentrations, while their total serum magnesium concentration is within the normal range.²⁰⁸ However, total body magnesium may be depleted due to poor dietary intake, decreased GI absorption secondary to ethanol, and renal wasting due to the ethanol-related diuresis.^{54,90,159,172,179}

DIAGNOSTIC TESTS

There are numerous qualitative and quantitative assays for ethanol in biological fluids and exhaled breath. Immunoassay or gas chromatography is commonly used for determination of ethanol in liquid specimens in most hospitals. Hospital laboratory analysis of blood samples for ethanol content is usually based upon serum (liquid portion of whole blood after the cellular components and clotting factors have been removed), or rarely plasma (acellular liquid portion of whole blood). In contrast, forensic casework expresses ethanol concentration in terms of ethanol concentration in whole blood (Special Considerations: SC6).

Ethanol saliva testing is a promising alternative to breath ethanol analysis in the rapid assessment of blood ethanol concentrations in patients regardless of their mental status.^{35,175} Fatty acid ethyl esters (FAEEs) may be a highly sensitive test for recent ethanol use.^{14,43,176} Because FAEEs remain in the body for at least 24 hours, they may have a role as a marker of recent ethanol use even after ethanol is completely metabolized. However, their availability is limited, and their place in patient management is undefined.

Ethyl glucuronide and ethyl sulfate are nonoxidative direct ethanol metabolites and are excreted for considerably longer time than ethanol.^{17,32,75,164,168} Testing for these metabolites in urine has gained popularity as a sensitive method to detect recent ethanol intake and is favored over tests such as γ -glutamyl transferase or carbohydrate-deficient transferrin, particularly by agencies concerned with monitoring an individual for recent ethanol consumption or relapse; confirming abstinence in treatment programs, workplaces, and schools; and providing legal proof of drinking.^{74,154} The presence of ethyl glucuronide and ethyl sulfate provides a strong indication of recent drinking even when ethanol is no longer detectable.⁷⁵ However, caution should be applied in the interpretation of ethyl glucuronide testing results. Ethyl glucuronide may be sensitive to degradation or may be synthesized by bacteria (eg, *Escherichia coli*) such that infected urine may result in either a false negative or false positive test, particularly when specimens have been improperly stored; ethyl sulfate

degradation or formation has not been detected under similar conditions.^{78,79} Detection windows for ethyl glucuronide and ethyl sulfate after drinking may be limited and dependent on the amount of ethanol consumed. For example, these metabolites are detectable in urine for ≤ 24 hours after intake of 0.25 g/kg ethanol and ≤ 48 hours after intake of 0.50 g/kg ethanol.^{32,73,75,81,82,206} Depending on the analytical cutoff limit, unintentional exposure to ethanol-based mouthwash and hand sanitizers may result in a urine positive for ethyl glucuronide or ethyl sulfate.^{29,161} There appears to be a marked interindividual variation in the concentration-time profiles for both metabolites. In situations where the times for ethanol intake and urine specimen collection between drinking and sampling are uncertain, it is not possible to link a single ethyl glucuronide and sulfate result to a specific ethanol dose taken at a specific time.⁷⁷ A common cutoff or reporting limit is yet to be determined for urinary ethyl glucuronide and ethyl sulfate when used as ethanol biomarkers.

Laboratory investigations that should be considered for patients with ethanol intoxication include a rapid reagent glucose test, complete blood count, electrolytes, blood urea nitrogen, creatinine, ketones, acetone, lipase, liver enzymes, ammonia, calcium, and magnesium. Patients with an anion gap metabolic acidosis should have urine ketones and a serum lactate concentration determined (Chaps. 19 and 109). High serum acetone concentrations may be indicative of isopropanol intoxication, whereas elevated serum or urinary ketones may be indicative of AKA, starvation ketosis, or diabetic ketoacidosis (DKA). Because the laboratory nitroprusside reaction detects only ketones (acetoacetate and acetone) and not β -hydroxybutyrate, the assay for urinary ketones may be only mildly positive in patients with AKA.

A blood ethanol concentration should be included in the initial laboratory studies.⁸³ If the blood ethanol concentration is inconsistent with the clinical condition of the patient, prompt reevaluation is indicated to elucidate the etiology of the altered mental status including toxic-metabolic (eg, hypoglycemia, electrolyte or acid-base disorder, toxic alcohols, therapeutic or illicit drug overdose, ethanol withdrawal, hepatic encephalopathy, and Wernicke-Korsakoff syndrome), trauma-related, neurologic (eg, postictal condition), and infectious etiologies. Comatose patients with concentrations below 300 mg/dL (65 mmol/L) and those with values in excess of 300 mg/dL (65 mmol/L) who fail to improve clinically during a limited period of close observation should have a head computed tomography (CT) scan, followed by a lumbar puncture if warranted. Because chronically ethanol-tolerant patients are prone to trauma and coagulopathies, both of which can cause intracerebral bleeding, the threshold for head CT scanning should be low.

MANAGEMENT OF THE INTOXICATED PATIENT

Ethanol is rapidly absorbed from the GI tract. In situations where recent ingestion (within one hour of presentation), delayed absorption, and concomitant ingestions are under consideration, GI decontamination may be considered. Occasionally, the extremely intoxicated or comatose patient may have severe respiratory depression necessitating endotracheal intubation and ventilatory support.

Any patient with an acute altered mental status mandates immediate investigation and treatment of reversible etiologies such as hypoxia, hypoglycemia, and opioid toxicity. In addition, Wernicke encephalopathy should be considered. Supplemental oxygen should be administered if the patient is hypoxic, and intravenous dextrose (0.5–1.0 g/kg), thiamine 100 mg, and naloxone 0.4 mg should be administered as clinically indicated. Abnormal vital signs should be addressed and stabilized. Patients who are combative and violent should be both physically and then chemically restrained. Randomized clinical trials suggest both benzodiazepine (ie, midazolam) and antipsychotics (ie, droperidol) are effective as “chemical restraints” in the ED setting.^{86,100,121,140} Midazolam has a more rapid onset of action and has a shorter duration of effect compared with droperidol.^{86,100,121,140} Patients receiving midazolam required more additional sedation and required airway management compared with patients receiving droperidol.^{86,100,121} Although the efficacy of midazolam and droperidol has been confirmed by multiple studies,^{86,100,121,140} they were not designed to inform about safety, equivalence, or superiority of midazolam and droperidol. Caution should be taken because of additive effects of ethanol and benzodiazepine on respiratory depression. Attempts by those who are significantly clinically intoxicated to sign out against medical advice or attempt to leave should also be prevented (Chap. 141). The fluid and electrolyte status of the patient should be assessed and abnormalities corrected. Multivitamins with folate, thiamine, and magnesium may be added to the maintenance intravenous solution.

A variety of therapies have been advocated either to reverse the intoxicating effects of ethanol or to enhance its elimination. Those proven to be either ineffective or unreliable include coffee, caffeine, naloxone, flumazenil, and rapid intravenous saline loading.^{55,111,142,143,160} Hemodialysis is an effective means of enhancing the systemic elimination of ethanol because of the small volume of distribution and low molecular weight of ethanol. In severe ethanol poisoning resulting in respiratory failure or coma, hemodialysis may be an adjunct treatment to supportive care. However, the risks and benefits of hemodialysis should be considered.

INDICATIONS FOR HOSPITALIZATION

A patient with uncomplicated ethanol intoxication can be safely discharged after a careful observation with social service

or psychiatric counseling. An individual should not be discharged while still clinically intoxicated. However, consideration may be given to a situation where the intoxicated patient is discharged to a protected environment under the supervision of a responsible not intoxicated adult. In all cases except allowing a person to drive, the clinical assessment of the patient is more important than the blood ethanol concentration. Indications for hospital admission include persistently abnormal vital signs, persistently abnormal mental status with or without an obvious cause, an overdose with intended self-harm, concomitant serious trauma, consequential ethanol withdrawal, and an associated serious disease process such as pancreatitis or GI hemorrhage.

Chronic alcoholism leads to an organic brain syndrome that is irreversible. The socioeconomic condition of the patient and the ability to comply with a treatment plan are critical in making a disposition. Alcoholics requesting ethanol detoxification can be admitted for rehabilitation. Inpatient detoxification programs differ substantially from outpatient programs, but their most consequential advantages may be that they enforce abstinence, provide more support and structure, and separate the patient from the social surroundings associated with drinking.¹³⁸ For patients who are not admitted, a referral should be offered to Alcoholics Anonymous or another suitable ethanol rehabilitation program.

ETHANOL-ASSOCIATED HYPOGLYCEMIA

Hypoglycemia associated with ethanol consumption occurs when ethanol metabolism increases the cellular redox ratio. The higher redox state favors the conversion of pyruvate to lactate, diverting pyruvate from gluconeogenesis (Fig. 80–2). Hypoglycemia typically occurs when there is a reduced caloric intake and only after the hepatic glycogen stores are depleted, as in an overnight fast. The mechanism by which hypoglycemia is associated with ethanol consumption in the well nourished individual is less well defined.

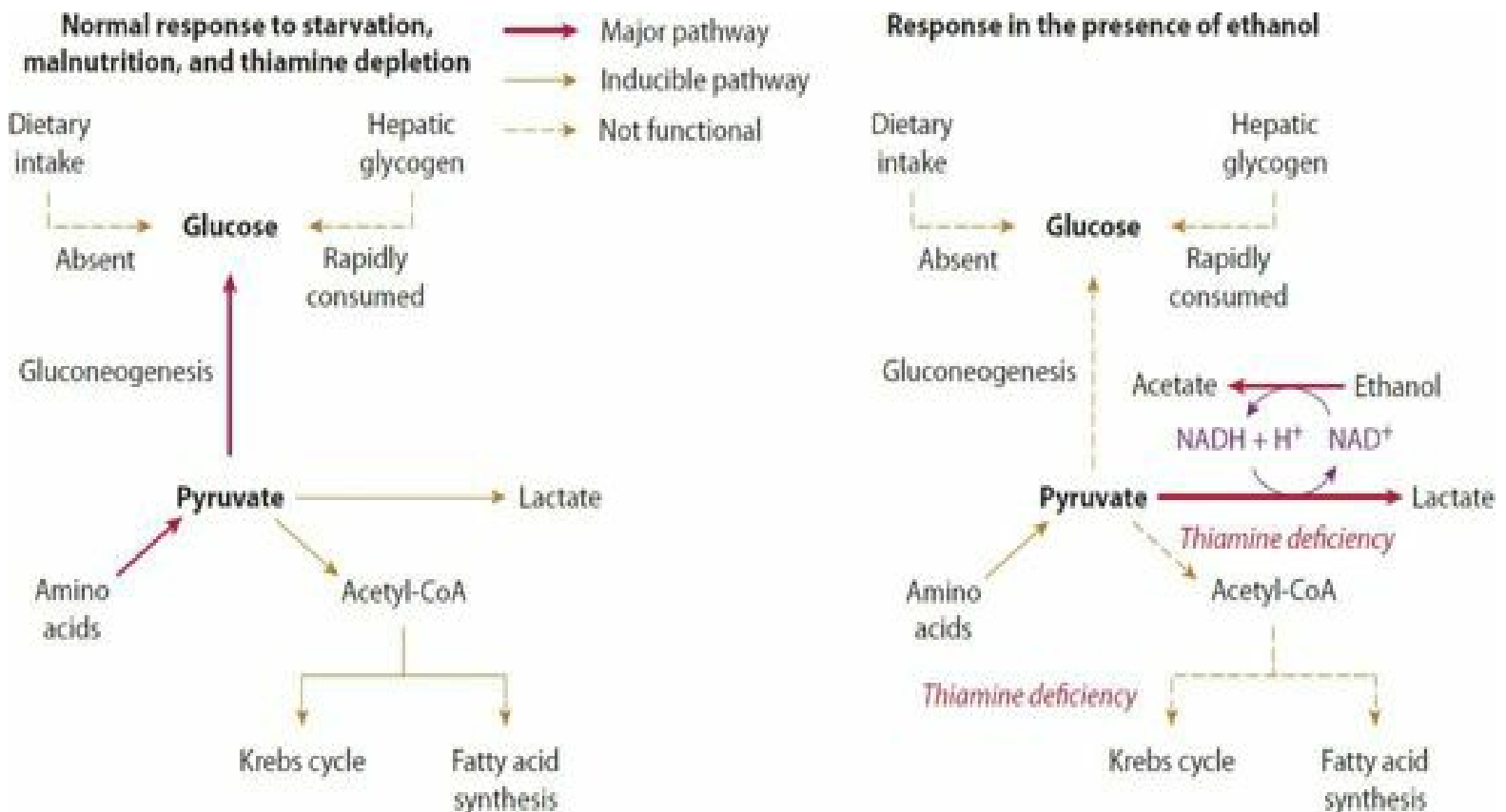


FIGURE 80–2 Central role of pyruvate in ethanol-induced hypoglycemia. Thiamine deficiency interrupts metabolism at the indicated steps.

Although the conditions associated with hypoglycemia in adults may also be present in infants and children, children, with their smaller liver, have less glycogen stores than adults and are more likely to develop hypoglycemia. Hypoglycemia associated with ethanol consumption usually occurs in malnourished chronic alcoholics and children. It may also occur in binge drinkers who do not eat. A 22% incidence of hypoglycemia was reported in one retrospective study of children with documented ethanol ingestion.¹⁰⁹ In another retrospective study of children and adolescents, there was a 3.4% incidence of hypoglycemia (serum glucose concentration less than 67 mg/dL {3.7 mmol/L})⁴⁹; children younger than 5 years of age have an increased risk of developing hypoglycemia, and it is the most common reported clinical abnormality related to ethanol ingestion in this age group.^{106,107}

Clinical Features

Patients with ethanol-associated hypoglycemia usually present with an altered consciousness 2 to 10 hours following ethanol ingestion. Other physical findings include hypothermia and tachypnea. Laboratory findings, in addition to hypoglycemia, usually include a positive blood ethanol concentration, ketonuria without glucosuria, and mild acidosis.

Management

Acute treatment of ethanol-associated hypoglycemia is similar to other causes of hypoglycemia ([Chap. 53](#) and Antidotes in Depth: A12) and should prompt a systematic evaluation for coexisting clinical and metabolic disorders. Hospital admission is indicated as this represents serious metabolic impairment.

ALCOHOLIC KETOACIDOSIS

The development of AKA requires that a combination of physical and physiologic events occur. The normal response to starvation and depletion of hepatic glycogen stores is for amino acids to be converted to pyruvate. Pyruvate can serve as a substrate for gluconeogenesis, be converted to acetyl-CoA, which can enter the Krebs cycle or can be utilized in various biosynthetic pathways (eg, fatty acids, ketone bodies, cholesterol, and acetylcholine). As described earlier, ethanol metabolism generates NADH, resulting in an excess of reducing potential. This high redox state favors the conversion of pyruvate to lactate, diverting pyruvate from being a substrate for gluconeogenesis. To compensate for the lack of normal metabolic substrates, the body mobilizes fat from adipose tissue and increases fatty acid metabolism as an alternative source of energy. This response is mediated by a decrease in insulin and an increased secretion of glucagon, catecholamines, growth hormone, and cortisol. Fatty acid metabolism results in the formation of acetyl-CoA, and it combines with the excess acetate that is generated from ethanol metabolism to form acetoacetate ([Fig. 80–3](#)).⁶⁰ Most of the acetoacetate is reduced to β -hydroxybutyrate due to the excess reducing potential or high redox state of the cell. Volume depletion interferes with the renal elimination of acetoacetate and β -hydroxybutyrate and contributes to the acidosis. An elevated lactate concentration may result from shunting from pyruvate or from hypoperfusion or infection that may coexist with the underlying ketoacidosis.

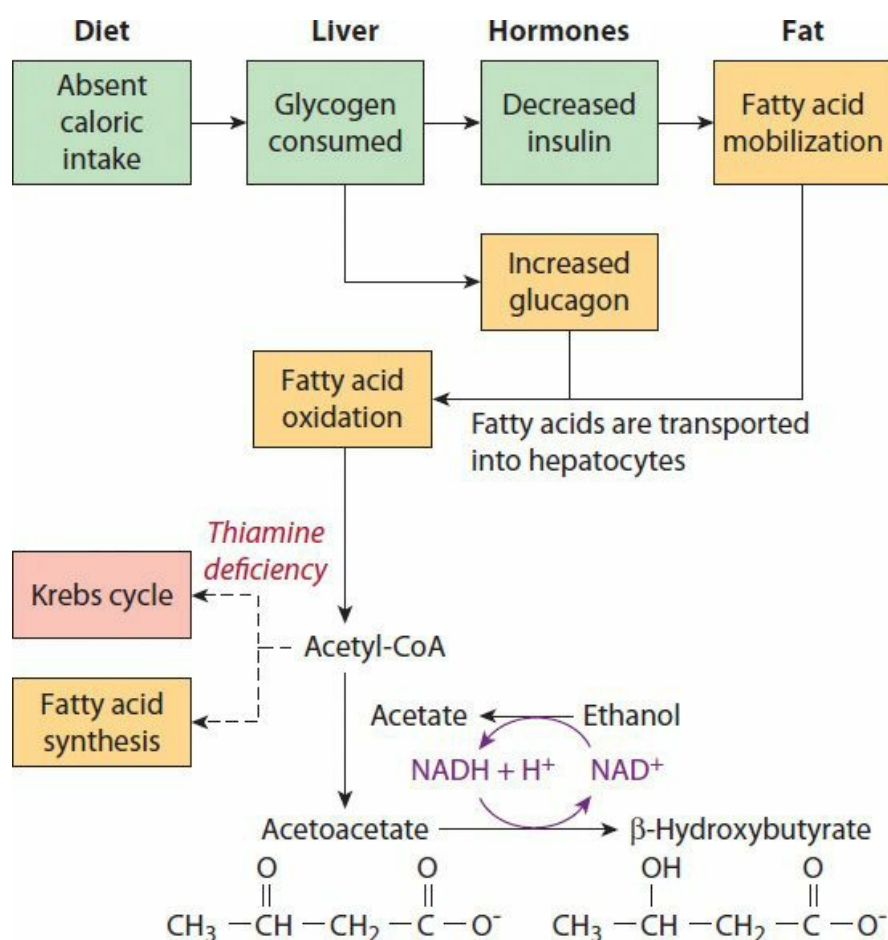


FIGURE 80–3 Mechanism of alcoholic ketoacidosis. Thiamine deficiency interrupts metabolism at the indicated steps.

Clinical Features

Patients with AKA are typically chronic ethanol users, presenting after a few days of “binge” drinking, who become acutely

starved because of cessation in oral intake due to bingeing itself or to nausea, vomiting, abdominal pain from gastritis, hepatitis, pancreatitis, or a concurrent acute illness.^{61–63} The patient may appear acutely ill with salt and water depletion, tachypnea, tachycardia, and hypotension. Underlying medical conditions such as sepsis, meningitis, pyelonephritis, or pneumonia may be present, and ethanol withdrawal may develop, all of which should be considered and systematically excluded. The diagnosis of AKA is a diagnosis of exclusion.

The blood ethanol concentration is usually low or undetectable because ethanol intake ceased substantially earlier in the clinical course. The hallmarks of AKA include an elevated anion gap metabolic acidosis with an elevated serum lactate concentration insufficient to account for the gap. However, some patients will have a normal blood pH or may be even alkalemic because of an associated primary metabolic alkalosis due to vomiting and a compensatory respiratory alkalosis (Chap. 19).⁶⁰ When patients with AKA are compared with patients with DKA, those with AKA tended to have a higher blood pH, lower serum potassium and chloride concentrations, and a higher serum bicarbonate concentration.⁶⁴ The etiology of anion gaps in patients with AKA and DKA is very similar, with β -hydroxybutyrate being the primary anion contributor and lactate having a less consequential role.⁶⁴

The nitroprusside test used to detect the presence of ketones in serum and urine may be negative or mildly positive in patients with AKA because the nitroprusside reaction detects only molecules containing ketone moieties. This includes acetone and acetoacetate but not β -hydroxybutyrate. Reliance on the nitroprusside test alone may underestimate the severity of ketoacidosis. Specific assays for β -hydroxybutyrate may be performed in some hospital laboratories and may be available as point-of-care testing at the bedside. The blood glucose may be low or mildly elevated. It is postulated that ethanol-induced hypoglycemia occurs first, causing increased levels of cortisol, growth hormone, glucagon, and epinephrine; this may correct the hypoglycemia and mobilize fatty acids, which are converted to ketones.³⁶ Therefore, alcoholic hypoglycemia and AKA may be sequential events of the same process, depending on the point in this process at which the patient is evaluated.

Management

Treatment should begin with adequate crystalloid fluid replacement, dextrose, thiamine, and folic acid. Supplemental multivitamins, potassium, and magnesium should be instituted on an individual basis. The administration of dextrose will stimulate the release of insulin, decrease the release of glucagon, and reduce the oxidation of fatty acids. Exogenous glucose also facilitates the synthesis of adenosine triphosphate (ATP), which reverses the pyruvate-to-lactate and NAD^+ -to-NADH ratios. The provision of thiamine facilitates pyruvate entry into the Krebs cycle, thus increasing ATP production. Volume replacement restores glomerular flow and improves excretion of ketones and organic acids. Administration of either insulin or sodium bicarbonate in the management of AKA is usually unnecessary.⁶³

During the recovery phase of AKA, β -hydroxybutyrate is converted to acetoacetate. As this process occurs, the nitroprusside test may become more positive because of higher concentrations of acetoacetate, resulting in hyperketonemia and ketonuria, which represents improvement of the metabolic status.

Patients presenting with AKA are manifesting serious metabolic impairment and require hospital admission. They may succumb to other precipitating or coexisting medical or surgical disorders⁶¹ such as occult trauma, pancreatitis, GI hemorrhage or hepatorenal dysfunction, and infections. However, mortality is rare from ethanol-induced ketoacidosis.

ALCOHOLISM

Alcoholism is traditionally defined as a chronic, progressive disease characterized by tolerance and physical dependence to ethanol and pathologic organ changes. Alcoholism is a multifactorial, genetically influenced disorder.^{30,80,138,150,157,170,186}

Screening is a preliminary procedure to assess the likelihood that an individual has a substance use disorder or is at risk of negative consequences from alcohol or other xenobiotics use. Whereas screening tools such as the Brief Michigan Alcoholism Screening Test (MAST)¹⁵³ and the CAGE questions¹²³ (Tables 80–4 and 80–5) were initially developed to identify people with active alcohol dependence for referral to treatment, the screening, brief intervention, and referral to treatment (SBIRT) was developed as a public health model designed to provide universal screening, secondary prevention in detecting risky or hazardous substance use before the onset of abuse or dependence, early intervention, and treatment for people who have problematic or hazardous alcohol problems within health care settings.⁷ Based on the Substance Abuse and Mental Health Services Administration (SAMHSA) model, SBIRT allows for universal screening of all patients regardless of an identified disorder, allowing health care professionals to address the spectrum of such behavioral health problems even when the patient is not actively seeking intervention or treatment.

TABLE 80–4. The Brief Michigan Alcoholism Screening Test

Question	Circle Correct Answer		Points
1. Do you feel you are a normal drinker?	Yes	No	N2
2. Do friends or relatives think you are a normal drinker?	Yes	No	N2
3. Have you ever attended a meeting of Alcoholics Anonymous?	Yes	No	Y5
4. Have you ever lost friends or girlfriends/boyfriends because of drinking?	Yes	No	Y2
5. Have you ever gotten into trouble at work because of drinking?	Yes	No	Y2
6. Have you ever neglected your obligations, your family, or your work for 2 or more days in a row because you were drinking?	Yes	No	Y2
7. Have you ever had delirium tremens (DTs) or severe shaking, or heard voices, or seen things that weren't there after heavy drinking?	Yes	No	Y2
8. Have you ever gone to anyone for help about your drinking?	Yes	No	Y5
9. Have you ever been in a hospital because of drinking?	Yes	No	Y5
10. Have you ever been arrested for drunk driving after drinking?	Yes	No	Y2
Score 6 = Probable diagnosis of alcoholism.			

Adapted with permission, from Pokorny AO, Miller BA, Kaplan HB: *Am J Psychiatry*. 1972;129:342–345. Copyright 1972, American Psychiatric Association.

TABLE 80–5. The CAGE Questions

1. Have you ever felt you should cut down on your drinking?
2. Have people annoyed you by criticizing your drinking?
3. Have you ever felt bad or guilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (eye-opener)?

Two or more affirmatives = probable diagnosis of alcoholism.

Data from Mayfield D, McLeod G, Hall P: The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatry*. 974;131:1121–1126.

The presence of tolerance and or dependence is not essential for a diagnosis of alcoholism. Emphasis instead is placed on the social and behavioral concomitants of heavy drinking.¹³³ In the ED setting, questions concerning the ability of the patient to function physically and psychologically are just as appropriate as quantifying the amount of ethanol consumed per day.

Alcoholism is commonly associated with affective disorders, especially depression.^{131,155} There is a higher rate of alcoholism among patients with bipolar disorder than in the general population, and there may be a genetic relationship between alcoholism and depression.^{95,144,204,205} Ethanol affects mood, judgment, and self-control; creates a clinical condition conducive to violence directed at self and others; and is an important risk factor for suicide. Although many people drink in an attempt to ameliorate their depression, all available evidence suggests that alcoholism adversely affects mood and cognitive ability. Research indicates alcoholism may be partly under genetic control.^{10,95,101,115} Chromosomal linkage analysis has implicated chromosomes 9, 15, and 16 in the genetic predisposition to alcoholism.^{13,39,117} Polymorphism in ADH and ALDH genes appears to be a marker for risk of alcoholism.^{27,30,48,186,188} The ADH1B*2, ADH1C*1, and ALDH2*2 alleles are associated with reduced risk of alcoholism. Genetic epidemiologic studies strongly correlate Asians with homozygous ADH1B*2 and ALDH2*2 alleles with reduced ethanol consumption and incidence of alcoholism.^{30,150,202} The incidence of both homozygous ADH1B*1 and ALDH2*1 alleles was significantly higher in patients with ethanol dependence and in patients with alcoholic liver disease.

Various strategies are employed to treat alcoholism, including psychosocial interventions, pharmacological interventions, or both. Pharmacologic treatment of ethanol dependence that is of potential collateral toxicologic

consequence include opioid antagonists naltrexone, acamprosate, disulfiram, serotonergic agents, and topiramate.^{65,87}

Although alcoholism is a serious disease with important health and economic consequences, it continues to be underdiagnosed and remains a treatment challenge.^{120,207}

SUMMARY

- Ethanol is widely used in society, and ethanol use problems impose a staggering personal, social, and economic burden on society.
- Domestic violence, child abuse, fires, falls, sexual assault, and other crimes such as robbery and assault, as well as medical consequences such as cancer, liver disease, and heart disease have all been associated with ethanol misuse.
- Ethanol research suggests that genetics may be an important determinant in vulnerability to ethanol dependence.
- Acute ethanol intoxication and alcoholism are among the most common and complex toxicologic and societal problems.
- Patients with acute ethanol intoxication or alcoholism may present with a diversity of clinical problems that challenge the clinician to be meticulous and systematic in the evaluation and management of these patients.

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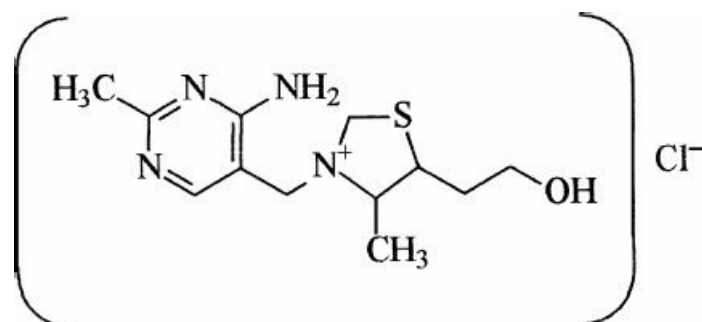
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A24 ANTIDOTES IN DEPTH

Thiamine Hydrochloride

Robert S. Hoffman



INTRODUCTION

Thiamine (vitamin B₁) is a water-soluble vitamin found in organ meats, yeast, eggs, and green leafy vegetables that is essential in the creation and utilization of cellular energy. While there is no toxicity associated with thiamine excess, thiamine deficiency is responsible for “wet” beriberi (congestive heart failure) and “dry” beriberi (Wernicke encephalopathy and the Wernicke-Korsakoff syndrome). Patients at risk include those with poor oral intake (HIV-AIDS, cancer, fad diets, anorexia nervosa, bulimia, hyperemesis gravidarum, and following bariatric surgery), those with impaired absorption (alcoholism and bariatric surgery), and those with enhanced elimination (high dose loop diuretic therapy). Typical signs of Wernicke encephalopathy include ataxia, altered mental status, and ophthalmoplegia. Although administration of 100 mg of parenteral thiamine hydrochloride will protect against thiamine deficiency for more than one week, patients with clinical deficiencies may require larger doses for a longer period of time.

HISTORY

Kanehiro Takaki, a physician in the Japanese navy, first established the relationship between a nutritional deficiency and beriberi in 1884. It was not until 1901 that Gerrit Grijns determined that the nutrient, as yet unnamed, was contained in the outer coat of rice and was lost during the polishing process. Ten years later, Casimir Funk isolated thiamine, and Williams finally determined its structure in 1934. Originally thiamine was called aneurin for “antineuritic vitamin”¹⁹ and was ultimately synthesized by Cline, Williams, and Finkelstein.²⁵ In 1936, Peters demonstrated that thiamine could reverse neurologic disease in nutritionally deprived pigeons and that improvement was coupled to an enhanced ability to metabolize pyruvate.⁸²

In 1881, Carl Wernicke reported three alcoholic patients who died after developing confusion, ataxia, and ophthalmoplegia.¹¹⁷ Autopsies showed characteristic hemorrhages surrounding the third and fourth ventricles. A few years later, Sergei Korsakoff reported amnesia and confabulation in 30 alcoholics that was preceded in many by the clinical findings reported by Wernicke.¹²⁵ Today, these two neurologic disorders are often combined and called the Wernicke-Korsakoff syndrome in recognition that they are likely a spectrum of the same disease.

PHARMACOLOGY

Biochemistry

As a coenzyme in the pyruvate dehydrogenase complex, thiamine diphosphate (thiamine pyrophosphate), the active form of thiamine, facilitates the conversion of pyruvate to acetylcoenzyme A (acetyl-CoA). This reaction occurs at the C2 atom of thiamine, which is located between the nitrogen and sulfur atoms on the thiazolium ring.³⁸ In the protein-rich environment of the enzyme complex, this C2 atom is deprotonated to form a carbanion that rapidly attaches to the carbonyl group of

pyruvate, thereby stabilizing it for decarboxylation.⁵⁴ In a series of subsequent reactions, the hydroxyethyl group that remains bound to thiamine diphosphate is transferred to lipoamide, where an acetyl group is later broken off and attached to coenzyme A (CoA). This overall process links anaerobic glycolysis to the Krebs cycle, where subsequent aerobic metabolism produces the equivalent of 36 moles of adenosine triphosphate (ATP) from each mole of glucose (Fig. A24-1). When pyruvate cannot be converted to acetyl-CoA because of thiamine deficiency, for example, only two moles of ATP can be generated by anaerobic metabolism from each mole of glucose. Within the Krebs cycle, thiamine is also required as a cofactor for the α -ketoglutarate dehydrogenase complex to catalyze the reaction of α -ketoglutarate to succinyl-CoA (Fig. A24-2), and for transketolase, an enzyme in the pentose phosphate pathway, in which nicotinamide adenine dinucleotide phosphate (NADPH) is formed for subsequent use in reductive biosynthesis.^{12,136} In addition to its metabolic effects, thiamine also has a role as a neuromodulator, influencing acetylcholine release.⁴⁸

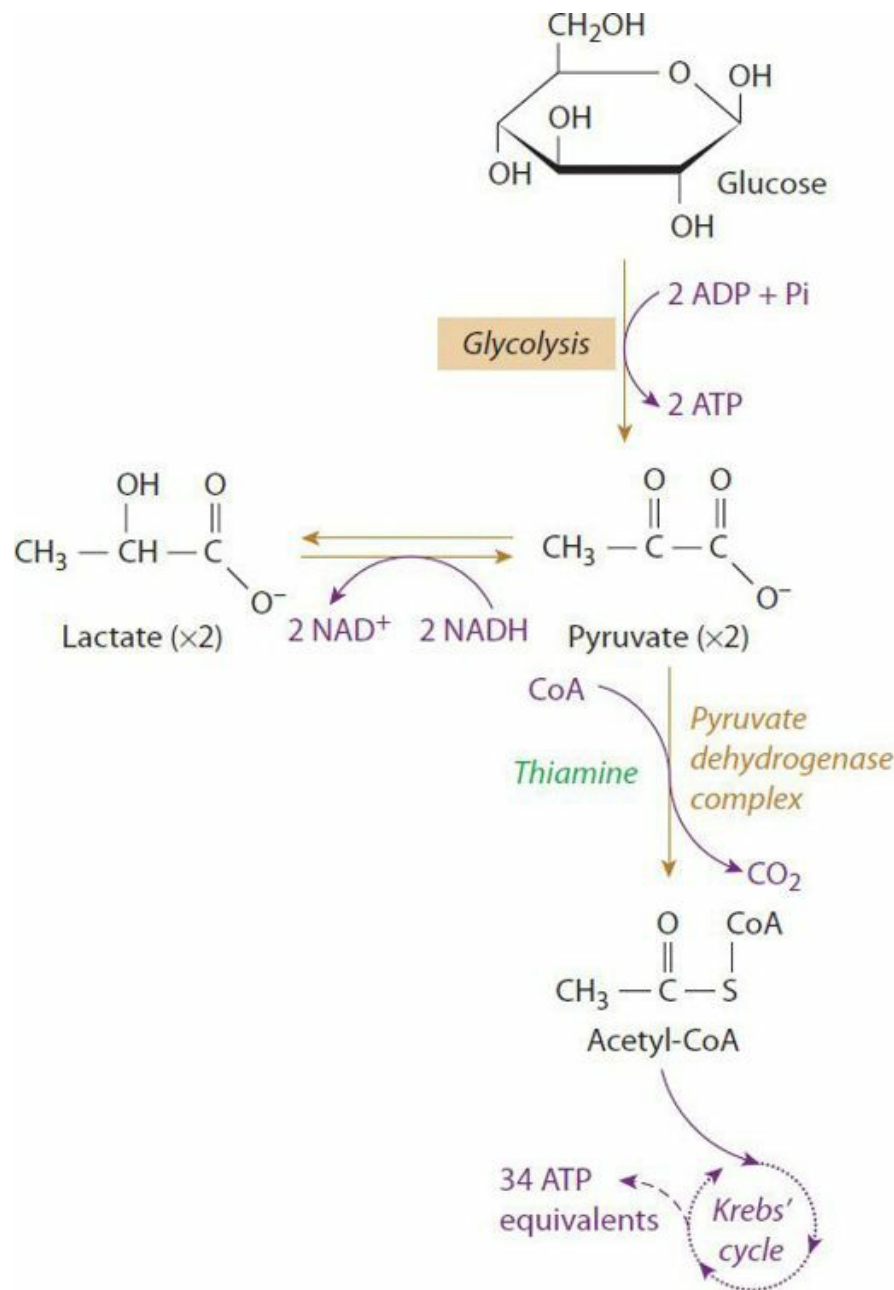


FIGURE A24-1 Thiamine links anaerobic glycolysis to the Krebs cycle. Anaerobic glycolysis only yields two moles of ATP as each mole of glucose is metabolized to two moles of pyruvate. To obtain the 34 additional ATP equivalents that can be derived as the Krebs cycle converts pyruvate to CO₂ and H₂O, pyruvate must first be combined with CoA to form acetyl-CoA and CO₂. This process is dependent on the thiamine-requiring enzyme system known as pyruvate dehydrogenase complex.

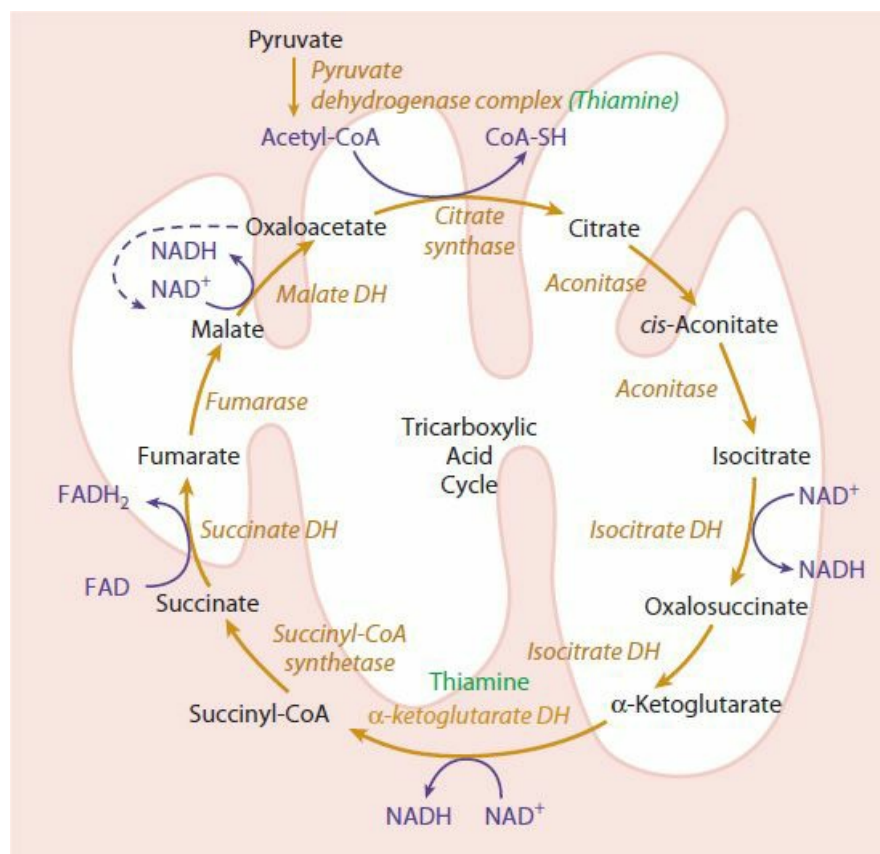


FIGURE A24-2. Thiamine is essential for α -ketoglutarate dehydrogenase activity, which is a rate-limiting step within the Krebs cycle. Thiamine deficiency leads to an accumulation of α -ketoglutarate, which is shunted to glutamate and causes excitatory neurotoxicity.

Naturally occurring thiamine is a base composed of a substituted pyrimidine ring and a substituted thiazole ring connected by a methylene bridge. This connection between the two rings is weak, and the molecule is unstable in an alkaline milieu and in a high temperature environment. In addition, thiamine is highly water soluble, allowing it to leach out of foods following prolonged washing or cooking in water. However, thiamine, which is synthesized as a hydrochloride salt, is usually quite stable. Thiamine requirements are determined by total caloric intake and energy demand, with 0.33 mg of thiamine required for every 4400 kJ (1000 kcal) of energy.¹⁰³ The recommended daily consumption is 0.5 mg/1000 kcal in order to provide a margin of safety.¹⁰²

Pharmacokinetics

Thiamine is well absorbed from the human gastrointestinal tract by a complex process.^{62,88} At low concentrations, thiamine absorption occurs through a saturable mechanism that is most effective in the duodenum, with absorption occurring to a lesser degree in the large bowel and stomach.⁶² As thiamine concentrations increase, however, the majority of absorption occurs through simple passive diffusion. A placebo-controlled human volunteer study evaluated the kinetics of oral administration of 100, 500, and 1500 mg in healthy subjects.¹⁰³ Following the 100 mg dose, peak concentrations occurred in whole blood in 3.43 hours. Although higher doses produced higher peak concentrations with a delay in time, the lack of linearity of the dose-response relationship confirmed complex absorption kinetics.¹⁰³ Synthesized analogs such as thiamine propyl disulfide, benfotiamine, and fursultiamine have enhanced bioavailability, but their use remains largely experimental.^{38,119} Chronic liver disease, folate deficiency, steatorrhea, and other forms of malabsorption all significantly decrease the absorption of thiamine.^{26,104} Recently, bariatric surgery was recognized to predispose patients to thiamine deficiency.^{1,3,34,96,97} Malabsorption has even greater clinical relevance in alcoholics.^{7,116} In experimental studies, when healthy volunteers were given small amounts of ethanol, a 50% reduction in gastrointestinal thiamine absorption resulted.¹¹⁶ A rat model confirmed that the simple presence of ethanol in the gut impairs thiamine absorption rather than the effects of chronic ethanol use alone.⁴⁹

Two genes are involved in the cellular transport of thiamine: a high affinity thiamine transporter known as THTR1 (SLC19A2) and a low affinity thiamine transporter known as THTR2 (SLC19A3).^{39,40} Variations or mutations in these genes may predispose to thiamine deficiency and cause thiamine-responsive megaloblastic anemia syndrome. Homozygous or compound heterozygous mutations in THTR2 can manifest two distinct clinical phenotypes, biotin-responsive basal ganglia disease and Wernicke-like encephalopathy.¹³⁴ Experimental evidence suggests that ethanol intake directly alters gene transcription, further increasing risk.¹²⁰ These models demonstrate ethanol-induced reductions in the expression of

intestinal thiamine transporters at the protein, mRNA, and transcriptional (promoter activity) levels.¹¹⁰

Thiamine is eliminated from the body largely by renal clearance, which consists of a combination of glomerular filtration, flow-dependent tubular secretion, and saturable tubular reabsorption.¹²⁹ In an animal model, furosemide, acetazolamide, chlorothiazide, amiloride, mannitol, and salt loading all significantly increased urinary elimination of thiamine.⁶⁹ This nonspecific flow-dependent elimination was confirmed in humans given small doses of furosemide.⁸⁷ Interestingly spironolactone use is associated with higher thiamine concentrations.⁸⁹ Additionally, both furosemide and digoxin appear to inhibit thiamine uptake into myocardial cells.¹³⁵

THIAMINE DEFICIENCY

Pathophysiology

Mice develop signs of encephalopathy 10 days after being rendered thiamine deficient. Immunohistochemistry in these animals demonstrates destruction of the blood–brain barrier with resultant extravasation of albumin.⁴³ Similarly, rats develop symptoms after 10 days of thiamine deficiency and subsequently demonstrate deterioration of the blood–brain barrier with hemorrhage into the mammillary bodies and other areas of the brain.¹⁷ This pattern is similar to findings described in humans with Wernicke encephalopathy.⁸⁴ Although there are no controlled trials of thiamine deprivation in humans, several unfortunate events support this time course. One report describes three patients who were given total parenteral nutrition without multivitamins; signs and symptoms developed in 7, 10, and 14 days, respectively.¹²⁴ Similar reports confirm this time course with some variability based on the nutritional status of the patients.^{4,61,74,80} Infants given a soy-based formula that lacked thiamine also developed findings consistent with Wernicke encephalopathy.³²

The proximate cause of Wernicke encephalopathy is unclear. In human autopsy studies, brain samples from alcoholic patients with Wernicke-Korsakoff syndrome demonstrate decreased function of pyruvate dehydrogenase, α -ketoglutarate dehydrogenase, and transketolase when compared with controls.¹⁵ However, a similar decrease in enzyme activity of neuronal tissue was demonstrated in alcoholics who died from hepatic coma without ever manifesting signs of Wernicke encephalopathy.⁶⁵ This finding is understandable given that high concentrations of ammonia inhibit α -ketoglutarate dehydrogenase.¹² Likewise, the activity of thiamine-requiring Krebs cycle enzymes is reduced in thiamine-replete patients with neurodegenerative diseases.¹¹ Thus, while thiamine deficiency produces deficits in critical enzymes in humans, many have argued that it is unclear whether these deficits are either necessary or sufficient to produce clinical disease.

Animal models offer insight into the mechanisms involved in developing thiamine-deficient neurologic injury. While the exact chain of events leading to these structural abnormalities is unclear, several models demonstrate key portions of the pathway. Thiamine deficiency in rats produces 200% to 640% increases in concentrations of glutamate,⁶⁴ which presumably results from blockade of α -ketoglutarate dehydrogenase. Excess α -ketoglutarate is shunted away from the Krebs cycle to form glutamate. Rats subsequently develop increases in lactate in vulnerable regions of the brain marked by the induction of the protooncogene c-fos. Both the histochemical lesions and the gene induction can be blocked by the administration of the calcium channel blocker nicardipine.⁷³ This suggests a strong role for excitatory amino acid–induced alterations in calcium transport in the genesis of thiamine-deficient encephalopathy.⁵² In other animal models of thiamine deficiency, neuronal tissues are also directly injured by oxidative stress and lipid peroxidation.^{18,45,46,52} Additional investigations demonstrate roles for triggered mast cell degranulation,³³ histamine,⁶⁴ and nitric oxide⁵⁸ in the generation of neuronal injury. The final common pathway is localized cerebral edema, which may result from altered expression of aquaporin.²³

In what may be the most important finding since Wernicke's original description, is that Kono and colleagues recently described two healthy nonalcoholic brothers who developed signs, symptoms, and neuroimaging findings consistent with Wernicke encephalopathy despite normal serum thiamine concentrations.⁵⁷ Both brothers were confirmed to have compound mutations of the SLC19A3 gene (K44E and E320Q) encoding for low-affinity thiamine transport (THTR2). High-dose thiamine (up to 600 mg) was clinically effective. The more severe E320Q homozygous THTR2 mutation manifests as impaired thiamine uptake, progressive brain atrophy, bilateral thalamic and basal ganglia lesions, and epileptic spasms beginning early in infancy.¹³⁴ Several other mutations (including G23V and T422A and those inducing premature termination codons) produce loss of thiamine THTR2 transport function and a spectrum of generalized dystonia; epilepsy; and bilateral striatal, caudate, putamen, and cortical lesions.^{27,99,109} Patients may respond to high-dose thiamine and/or biotin.⁹⁹ As demonstrated by magnetic resonance imaging, vasogenic edema is a characteristic finding during the acute crises.¹¹² When added to the cases where thiamine was excluded from total parenteral nutrition or infant formula, these findings definitively relate intracellular thiamine concentrations to clinical and anatomical manifestations of Wernicke encephalopathy and thiamine deficiency.

Clinical Manifestations

When thiamine is completely removed from the human diet, tachycardia is often the first sign of deficiency. The clinical symptoms of thiamine deficiency present as two distinct patterns: “wet” beriberi or cardiovascular disease and “dry” beriberi, the neurologic disease known as Wernicke-Korsakoff syndrome. Although some patients display symptoms consistent with both disorders, usually either the cardiovascular or the neurologic manifestations predominate. A genetic variant of transketolase activity, combined with low physical activity and low-carbohydrate diet, may predispose to neurologic symptoms, whereas high-carbohydrate diets and increased physical activity lead to cardiovascular symptoms.^{10,131} Thus, cardiovascular disease is more common in the Asian population, and neurologic disease predominates in the northern European population.

Wet beriberi results from high output cardiac failure induced by peripheral vasodilation and the formation of arteriovenous fistulae secondary to thiamine deficiency. These patients complain of fatigue, decreased exercise tolerance, shortness of breath, and peripheral edema. Myocardial edema may be demonstrated.³¹ The classic triad of oculomotor abnormalities, ataxia, and global confusion defines dry beriberi or Wernicke encephalopathy. Other manifestations include hypothermia and the absence of deep-tendon reflexes.¹²⁸ Vomiting and anorexia are common^{32,124} and may be related to increases in intracranial pressure. Additionally, patients develop a peripheral neuropathy with paresthesias, hypesthesias, and an associated myopathy, all related to axonal degeneration.¹⁰² Laboratory studies may reflect a metabolic acidosis with elevated lactate concentration brought on by excessive anaerobic glycolysis resulting from blocked entry of substrate into the Krebs cycle.^{22,24,55,56,63,81,90,128} Interestingly, a primary respiratory alkalosis of unclear etiology seems to be simultaneously present.²⁹ Korsakoff psychosis, an irreversible disorder of learning and processing of new information characterized by a deficit in short-term memory and confabulation, often occurs together with Wernicke encephalopathy.¹²⁵ A 10% to 20% mortality rate is associated with Wernicke encephalopathy, with survivors having an 80% risk of developing Korsakoff psychosis.⁸⁶

A clinical tool for identifying patients with Wernicke encephalopathy used four signs: dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction, and either an altered mental status or mild memory impairment. When two or more signs were present the tool was highly sensitive and specific.¹⁶

Epidemiology: Populations at Risk

In the United States, a healthy diet and mandatory thiamine supplementation of numerous food products protect most people from the manifestations of thiamine deficiency. Despite this, the prevalence of Wernicke encephalopathy in the general US population is estimated to be between 0.2% and 2.2%, although only 20% of these cases are estimated to be diagnosed during their lifetime.^{68,108} This is, unfortunately, not true in other countries. A survey of the 17 major public hospitals in the Sydney, Australia, area identified more than 1000 cases of either acute Wernicke encephalopathy or Korsakoff psychosis between 1978 and 1993.⁷⁰ Similarly, a single Australian hospital identified 32 cases of Wernicke encephalopathy during a 33-month period.¹³² In Australia, mandatory supplementation of flour with thiamine in 1991 resulted in a dramatic reduction in hospitalized cases during 1992 and 1993,⁷⁰ as well as of the percentage of cases diagnosed by postmortem studies.⁴⁴ Other countries at risk include Ireland and New Zealand, where lack of a mandatory thiamine supplementation program is correlated with a high prevalence of biochemical evidence of thiamine deficiency.⁷⁸

Alcoholic patients, whose consumption of ethanol is their major source of calories, are the best described and most easily recognized patients at risk for thiamine deficiency.⁸⁶ In Scotland, 21% of alcoholics requiring emergency admission to the hospital were thiamine deficient, as determined by erythrocyte transketolase.⁵⁰ The prevalence in US alcoholics is estimated to be 12.5%.¹⁰⁸

Consequential thiamine deficiency is also described in incarcerated prisoners,⁵¹ patients in drug rehabilitation,³⁵ patients receiving hemodialysis,²⁸ patients with hyperemesis gravidarum or anorexia nervosa,¹¹⁵ patients receiving parenteral nutrition,^{4,20,21,24,61,63,80,81,111,124,126} patients with acquired immunodeficiency syndrome (AIDS),^{5,13,14,95} patients with malignancies,^{9,59,91,123} the institutionalized elderly,^{60,77–79} critically ill children,^{53,66} patients with sepsis,²⁹ patients with congestive heart failure on furosemide therapy,⁶⁰ patients with malabsorption secondary to *Clostridium difficile* diarrhea,²⁶ patients with eating disorders,¹²⁷ and most recently, patients who had undergone bariatric surgery.^{1,3,34,37,96} Thus, despite routine dietary supplementation, many people are still at risk because of dietary limitations, alcohol abuse, or underlying medical or surgical conditions.

ROLE IN PREVENTION AND TREATMENT OF WERNICKE ENCEPHALOPATHY

Thiamine hydrochloride is included in the initial therapy for any patient with an altered mental status, potentially acting as

both treatment and prevention of Wernicke encephalopathy. Many patients with altered levels of consciousness have had or will have a poor nutritional status or will be hospitalized and deprived of oral intake for a number of days because of gastrointestinal disorders or altered mental status. Although thiamine concentrations can be either directly measured or functionally assessed by measuring erythrocyte transketolase activity at baseline and in response to thiamine diphosphate administration,⁴⁷ these determinations are unavailable for clinical use and do not correlate with disease severity.⁶⁸ Likewise, although clinical prediction models have been developed, they are cumbersome and unvalidated.¹⁰⁰ Glucose loading increases thiamine requirements, which can exacerbate marginal thiamine deficiencies, elevate lactate concentrations,⁷⁶ or even precipitate coma in the absence of parenteral thiamine supplementation.⁸⁶ Although it is commonly believed that acute glucose loading, in the form of a bolus of hypertonic dextrose, can precipitate Wernicke encephalopathy over several hours in normal individuals, there is evidence to support this effect only in patients who already have grave manifestations of thiamine deficiency or exaggerated delay in the provision of thiamine.^{71,92,128} Previously healthy patients require prolonged dextrose administration in the absence of thiamine in order to develop Wernicke encephalopathy. Because the morbidity and mortality associated with Wernicke encephalopathy are so severe and underdiagnosed, and treatment is both benign and inexpensive, thiamine hydrochloride should be included in the initial therapy for all patients who receive dextrose, all patients with altered consciousness, and every potential alcoholic or nutritionally deprived individual who presents to the emergency department or other clinical setting.

ROLE IN THE TREATMENT OF OTHER DISORDERS

A supplementary indication for the administration of thiamine hydrochloride occurs in patients with ethylene glycol poisoning. As shown in [Fig. 109–2](#), a minor pathway for the elimination of glyoxylic acid involves its conversion to α -hydroxy- β -ketoadipate by α -ketoglutarate: glyoxylate carboligase, a thiamine and magnesium-requiring enzyme. There are no data to support an increase in α -hydroxy- β -ketoadipate formation following thiamine administration in ethylene glycol-poisoned animals or humans. However, animal models of primary hyperoxaluria show increases in urinary oxalate during thiamine deficiency, suggesting at least a potential importance of this pathway.^{42,113} Because therapy is benign and inexpensive, it is prudent to administer standard doses of thiamine to patients with suspected or confirmed ethylene glycol poisoning.

Standard doses of thiamine should also be given to patients with alcoholic ketoacidosis (AKA). Glucose is required to stimulate insulin secretion, which subsequently terminates ketogenesis. Since by definition AKA occurs in malnourished alcoholics who are at risk for Wernicke encephalopathy, parenteral thiamine administration seems justified ([Chap. 80](#)).⁸

Routine thiamine administration should also be considered in patients with congestive heart failure and long-term use of diuretics. Diuretics enhance renal thiamine elimination.⁹⁸ In one randomized trial, 200 mg of daily intravenous thiamine was able to increase cardiac ejection fraction by 22% at 7 weeks.¹⁰¹ A more recent study showed that a daily oral dose of 300 mg of thiamine in patients with chronic heart failure was able to increase left ventricular ejection fraction by 10% over placebo.⁹⁴

ADVERSE EFFECTS

Very few complications are associated with the parenteral administration of thiamine. The older literature emphasized intramuscular administration because of numerous reports of anaphylactoid reactions associated with intravenous thiamine delivery.^{30,85,93,107,130} It is generally believed that these reactions resulted from responses to contaminants rather than thiamine itself. Despite the availability of purer, aqueous preparations of thiamine, rare adverse reports still occur.^{6,72,83,106} Although the intramuscular route is theoretically comparably efficacious in a healthy individual, many patients requiring thiamine may have diminished muscle mass or a coagulopathy, exacerbating the potential for pain and unpredictable absorption. The safety of thiamine use was evaluated in a large case series in which nearly 1000 patients received parenteral doses of up to 500 mg of thiamine without significant complications.¹³³ This study suggests that if anaphylaxis to thiamine exists, its occurrence is exceedingly rare, permitting the safe intravenous administration of thiamine to most patients.

PREGNANCY AND LACTATION

Thiamine hydrochloride is listed in pregnancy category A and is also considered safe for use in lactating mothers.

DOSING AND ADMINISTRATION

For prevention of Wernicke encephalopathy, initial therapy usually consists of the immediate parenteral administration of 100 mg of thiamine hydrochloride. This can be given either intramuscularly or intravenously, but the oral route should be

avoided because of its unpredictable absorption. In countries where thiamine propyl disulfide (a lipid soluble thiamine preparation) is available, the oral route may be considered equally efficacious for the replacement of serious thiamine deficiencies.^{7,119} Although there are no dose finding studies, some authorities recommend daily doses as high as 250 mg/d in high-risk patients without signs and symptoms of Wernicke encephalopathy.¹¹⁸ Current recommendations also exist for patients on total parenteral nutrition (3–3.5 mg/d), enteral feeding (2.2–2.9 mg/1500 kcal), and renal replacement therapy (100 mg/d).¹⁰⁵

The practice of requiring the administration of parenteral thiamine prior to hypertonic dextrose in patients with altered consciousness is illogical.⁴¹ Besides the fact that the first dose of dextrose is unlikely to cause thiamine deficiency, thiamine uptake into cells and activation of enzyme systems is slower than that of glucose uptake, which suggests that even pretreatment with thiamine offers little benefit over posttreatment.¹¹⁴ Despite these limitations, it is prudent to administer 100 mg of parenteral thiamine at the time of initial dextrose administration. The biochemical link between dextrose and thiamine is obvious, which demonstrates to the clinician the scientific basis for the administration of thiamine. Although thiamine is unlikely to offer immediate benefits for patients with altered consciousness, it will offer some long term protection for these individuals at risk and initiate therapy for a serious, insidious, and easily overlooked disorder.

For treatment of Wernicke encephalopathy, in some patients, symptoms such as ophthalmoplegia are reported to respond rapidly to as little as 2 mg of thiamine; however, the other neurologic and cardiovascular manifestations of thiamine deprivation may necessitate higher doses and may respond more slowly, if at all. Although many sources recommend that daily doses of 100 mg of thiamine are sufficient as in preventive therapy, others recommend initial doses as high as 200 or 250 mg,^{2,121} based on limited data. It is noteworthy that current guidelines recommended by the British National Formulary and the Royal College of Physicians, British Association for Psychopharmacology, the European Federation of Neurological Societies (EFNS), and the National Institute for Health and Clinical Excellence (NICE) guidelines all suggest that the initial thiamine regimen for patients with Wernicke encephalopathy is 500 mg intravenously three times daily for 2 to 3 days and 250 mg intravenously daily for the next 3 to 5 days.^{36,67} This increase over formerly recommended regimens is reflective of reports of patients' failing standard therapy and the safety of parenteral thiamine.

Because of the safety of thiamine hydrochloride, and the urgency to correct the manifestations of thiamine deficiency, up to 1000 mg of thiamine hydrochloride can be used in the first 12 hours if a patient demonstrates persistent neurologic abnormalities.⁷⁵

For ethylene glycol poisoning and AKA, 100 mg intravenously is recommended.

FORMULATION AND ACQUISITION

Multiple manufacturers formulate thiamine hydrochloride for intravenous or intramuscular administration. Typical concentrations are either 50 or 100 mg/mL. Although more concentrated solutions are available, their use is usually reserved for preparation of total parenteral nutrition solutions. Thiamine available in the United States is formulated in 0.5% (5 mg/mL) chlorobutanol. In the United Kingdom (UK), the formulation Pabrinex is chlorobutanol free. Chlorobutanol is a sedative with a long elimination half-life, but doses of 600 mg were given to human volunteers without complication.¹²² Thus UK and EFNS recommendations of 1500 mg/day of thiamine would only deliver 75 to 150 mg of chlorobutanol depending on which preparation was used. Even with the long elimination half-life, many days of high dose thiamine could be administered without delivering a single sedating dose.

SUMMARY

- Thiamine is an essential vitamin for cellular energy.
- Thiamine deficiency presents as either Wernicke encephalopathy or beriberi.
- Wernicke encephalopathy manifests as ataxia, ophthalmoplegia, altered mental status, decreased deep tendon reflexes, metabolic acidosis with elevated lactate, and hypothermia.
- Parenteral administration of 100 mg of thiamine will likely protect an individual for 1 to 2 weeks. When Wernicke encephalopathy is present or suspected, higher doses of thiamine are needed.
- Although thiamine requirements are based on caloric intake, there is no evidence that thiamine must be given prior to dextrose administration.

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SC7 SPECIAL CONSIDERATIONS

Assessment of Ethanol Induced Impairment

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INTRODUCTION

Myriad medical texts describe the medical consequences of acute and chronic ethanol use. The purpose of this discussion is to describe the history and use of assessments of ethanol induced impairment, primarily in a legal context. Some of the principles described may, however, be extrapolated from the legal to the medical setting. Throughout this chapter, the terms ethanol and alcohol are used interchangeably to retain the forensic, legislative, and medical contexts in which the terms are utilized.

HISTORY

Numerous well designed laboratory studies assessing alcohol induced impairment have been published. However, application of study results to actual cases of possible driving impairment or over service of alcohol in a drinking establishment may be inaccurate without an understanding of the origin of laws governing these activities. Although the intoxicating effects of ethanol have been known for centuries, the advent of mechanized transportation spawned increased public and legal scrutiny. Concern was expressed over the potential adverse safety implications of driving while intoxicated, not just for the impaired driver, but also for other persons (passengers, other drivers, pedestrians) and property. Although railroads had regulations against the operation of equipment while intoxicated dating back to the 19th century, the first arrest for drunk driving in an automobile was that of a London taxicab driver in 1897.²⁰ The realization that alcohol intoxicated motor vehicle operators were a public health issue worthy of legal scrutiny soon followed, and legislation was enacted to combat “drunken driving,” with New York being the first US state to enact such a law in 1910.²⁰

In early laws, “drunken driving” was poorly defined and relied heavily on observable signs of gross intoxication. Attempts at legislative clarification of language resulted in terms that were nearly as nebulous, such as “alcohol impaired” and “under the influence.” Prior to the landmark works in Sweden by Widmark and in the United States by Heise, evaluations of driver impairment were predominantly based on the “expert” testimony of an evaluating physician and the arresting police officer, as well as behaviors reported by witnesses. These evaluations were observational rather than scientifically based, and such nonsystematic and nonobjective testimony was often dubious and frequently plagued by exaggeration of behaviors (eg, staggering gait, incoherent speech).

The development of analytical technology capable of measuring the concentration of alcohol in blood gave rise to the idea that diagnosis of intoxication might be assisted by an objective chemical test result. The theory behind this idea being simply, the higher the blood alcohol concentration (BAC), the more drinks the individual must have consumed and therefore, the greater the degree of impairment. It was, therefore, reasoned that there may also exist a legally punishable limit of alcohol in blood or other biological matrix. Although the assignment of a specific clinical effect to a given BAC is not rigorously applicable to evaluation of an individual case, the general trends when examined across a population formed the foundation of many modern driving while intoxicated (DWI) laws.

Despite centuries’ worth of knowledge of the effects of alcohol and decades of efforts to articulate drunk driving standards, a single universal definition of “alcohol intoxicated” still does not exist. A typical medical definition may focus on altered mental status, ataxia, or the ability to care for oneself, whereas the focus of a legal definition may be on the ability to safely operate a motor vehicle or whether the patron of a bar or restaurant should be served additional alcohol. A lay public definition may include parts of both.

Although alcohol intoxication may be an important factor in a nearly infinite number of settings, two of the most common legal circumstances involving toxicology consultation for alcohol-related issues are (a) alcohol impaired operation of a motor vehicle and (b) so-called “dram-shop” cases when an already intoxicated individual is served alcohol. Discussion of alcohol use in the workplace and abstinence monitoring are beyond the scope of this discussion.

PER SE LIMITS

With the advent of analytical measurements capable of quantitatively determining BAC and the increasing public awareness

of the dangers associated with drinking and driving, legislation based on BAC began to appear. Although the initial laws did not define the specific BAC that established illegality in the operation of a motor vehicle, they did allow for the use of BAC results as supportive evidence of intoxication. The first states to incorporate BAC into drunk-driving statutes were Indiana and Maine, which did so in 1939.²⁷ The approach taken by the Indiana legislature resulted in a three-tiered statute, which stated that a BAC of less than 50 mg/dL was considered presumptive evidence of no intoxication, a BAC between 50 and 100 mg/dL was considered supportive evidence of intoxicated driving, and a BAC of greater than 150 mg/dL was considered *prima facie* (ie, obvious and evident without proof) evidence of guilt. From a legal perspective, *prima facie* evidence shifts the burden of proof from the accuser having to substantiate the charge to the defense to rebut the allegation. It is this legal perspective from which the so-called “per se” standards are derived—that is, an individual whose BAC exceeds a predetermined concentration is guilty “per se” of driving while impaired by alcohol, even without any other evidence of intoxication or impairment.

Early drunk-driving standards established in the Uniform Vehicle Code made reference to a BAC at which there was “no doubt of obvious intoxication”; this BAC was defined as 150 mg/dL. However, by 1960, as data regarding alcohol related motor vehicle crashes became available, most (but not all) states adopted a more rigorous per se BAC driving standard of 100 mg/dL.²⁷ This reduction in the per se legal BAC for a DWI charge was supported by powerful medical and political groups, including the American Medical Association (AMA). Interestingly, the AMA recommendation also noted that some persons were “under the influence” or impaired in their ability to safely operate a motor vehicle at BACs of 50 to 100 mg/dL. Despite newer drinking and driving laws defined on the basis of an objective chemical test, many state laws still contained older vague language such as “intoxicated,” “visibly intoxicated,” and “obviously intoxicated,” which forced legislators to define more clearly and objectively.

In 2000, the National Highway Traffic Safety Administration (NHTSA) reported that of 41,471 motor vehicle fatalities, 38.4% were alcohol related; this corresponded to an average of one alcohol-related traffic fatality every 31 minutes.⁵⁴ Although the NHTSA statistical methods likely overestimated the number of actual fatalities involved in alcohol-related crashes, there is little argument that alcohol use increases crash risk. Epidemiological assessments demonstrate that the probability of causing an alcohol-related motor vehicle crash increases slightly at a breath alcohol concentration (BrAC) of 50 mg/dL. The risk of causing a crash is increased by roughly four-fold at a BrAC of 80 mg/dL, seven-fold at a BrAC of 100 mg/dL, and 25-fold at a BrAC of 150 mg/dL.^{4,27} In 1994, a successful campaign vigorously supported by the AMA and Mothers Against Drunk Driving (MADD) encouraged all the states in the United States to lower the BAC used to define per se intoxicated driving to 80 mg/dL.²⁰ Although all states technically have the right to set drunk-driving statutes at their discretion, the anti-drunk-driving political lobby was successful in convincing the US government to require a minimum legal drinking age of 21 years and a mandatory per se BAC statute of 80 mg/dL in order to receive federal highway funding.²⁰ Consequently, as of July 2004, all states in the United States, the District of Columbia, and Puerto Rico conform with federal recommendations defining a BAC of 80 mg/dL as a violation of motor vehicle code. Lower per se BACs are applied to interstate commercial drivers (40 mg/dL) and pilots of aircraft (40 mg/dL, with no alcohol consumed within 8 hours prior to acting as pilot in command), as well as minors (10–20 mg/dL, depending on the state and 20–50 mg/dL in some European countries). Additionally, some states in the United States, such as Colorado, have lower per se statutes for the slightly lesser charge of driving while ability impaired (DWAI), which may be invoked when a driver’s BAC is between 50 and 80 mg/dL.

Laws addressing per se driving under the influence (DUI) limits are based on ethanol concentrations measured in whole blood. BrAC limits (which are arithmetically linked to BAC) are also frequently specified in per se statutes. As such, the use of appropriately conducted breath alcohol measurements eliminates the need to collect a blood specimen from a suspect. Per se limits, as described above, apply to the ability to safely accomplish specifically defined tasks such as driving an automobile or flying an aircraft. It is, however, imperative to understand that per se BACs do not define drunkenness or alcohol intoxication in nondriving situations, and their use in circumstances not involving motor vehicle operation is generally inappropriate.

The legal significance of a per se limit is that there is no requirement for behavioral evidence of intoxication, as long as the measured BAC exceeds that established by the legislature. Since their enactment, numerous legal arguments have challenged the constitutionality of per se drunk-driving laws. Issues including a lack of due process through application of the “void for vagueness” doctrine, reliability of breath testing results, and the distinction between blood alcohol and breath alcohol have all formed bases for legal challenges to per se laws.²⁰ However, despite such challenges, the courts have consistently upheld the laws.

ANALYTICAL CONSIDERATIONS

Accurate measurement of ethanol concentration in various biological matrices can be done using a number of analytical techniques. Historically, Widmark used wet chemical oxidation, using potassium dichromate and excess sulfuric acid followed by iodometric titration of the remaining amount of oxidizing agent. Although this method is effective, it is laborious and lacks specificity if other volatiles (eg, methanol, acetone, ether) are present, because they are also oxidized,

giving a falsely elevated ethanol result. Such wet chemical methods are obsolete and no longer used in forensic and clinical laboratories.

Enzymatic ethanol assays based on alcohol dehydrogenase (ADH) are commonly used, especially in high-throughput laboratories. The oxidation conditions of enzymatic methods are milder than wet chemical methods, and acetone, which was the most troublesome interference with wet chemical methods, is not oxidized by ADH. Interferences by other aliphatic low-molecular-weight alcohols such as methanol and isopropanol are known to occur with ADH isolated from humans and other animals; this interference is reduced by using yeast-derived ADH, which shows greater selectivity for ethanol.^{28,51} Specific enzymatic methods used for ethanol analysis in body fluids include enzyme multiplied immunoassay technique (EMIT), fluorescence polarization immunoassay (FPIA), and radiative energy attenuation (REA), which is related to FPIA (Chap. 6). Comparative study of ethanol determination by REA and gas chromatography shows excellent agreement in precision and accuracy between the two techniques.¹¹ Both high serum lactate and elevated lactate dehydrogenase concentrations interfere with ADH based methods of ethanol analysis, including providing false positive results in serum specimens from alcohol-free patients.^{2,36}

The greater selectivity for ethanol of gas chromatographic (GC) methods make this technique the mainstay for quantitative analysis in most forensic laboratories. Typically, the GC method involves head space sampling (HS-GC), which capitalizes on the volatility of ethanol, eliminates some potential interferences, and shortens run time. Samples to be run by HS-GC are first diluted (typically 1:5 or 1:10) with an aqueous solution of internal standard. This mixture is then sealed in a crimp-top vial with a rubber septum and gently heated to 122° to 140°F (50°–60°C) for 30 to 60 minutes in order to achieve equilibrium of volatiles between the gas and liquid phases. The vapor is then sampled with a syringe by puncturing the rubber septum and the withdrawn vapor injected into the instrument. Heating the sample for too long at a high temperature can result in oxidation from oxyhemoglobin.⁴³ This problem may be solved by the addition of sodium azide or sodium dithionite to block the oxidation or simply reducing the equilibrium temperature to 104° to 122°F (40–50°C).⁴³ Once chromatographic separation is achieved, various detection methods, including flame ionization (FID), electron capture (EC), and electrochemical sensing may be used (Chap. 6). Dual detection (eg, FID and EC) can also be useful in circumstances where a larger number of volatiles may need to be screened.⁴⁴

As ethanol distributes based on total body water, the water content of the matrix will affect the amount of ethanol present in a given volume or mass of biological sample. A common circumstance in which this is observed is in the difference between a whole blood ethanol determination and a plasma or serum ethanol determination. The water content of serum and plasma is 10% to 12% higher than whole blood, meaning that serum or plasma ethanol concentrations will be correspondingly higher than whole blood concentrations. Clinical laboratories most often use serum and plasma for analysis, whereas per se DUI statutes are written in terms of whole blood. Therefore, if a comparison is to be made between a serum or plasma analytical result and a legal standard, the result must be converted to an approximated whole blood ethanol concentration. Experimentally determined serum-to-whole blood ethanol ratios range from 1.12 to 1.17, whereas plasma-to-whole blood ethanol ratios range from 1.10 to 1.35.³⁷ Typically, a ratio of 1.16 is used for this conversion, and no significant difference appears to exist between the serum-to-whole blood and plasma-to-whole blood ratios.⁵⁴ Ratios between whole blood and other biological matrices such as urine, saliva, cerebrospinal fluid, vitreous humor, brain, liver, kidney, and bone marrow are published, and a table listing these ratios and the sources from which they are derived is available.¹⁰

Breath testing is commonly performed to assess BAC because of its relative simplicity and lack of invasiveness in its collection when compared with urine or blood. The analytical basis for sampling exhaled breath is that, at equilibrium, alcohol in expired air is present at a predictable ratio with blood. The gas exchange process in the lungs is complex, with significant theoretical variability.³⁴ In the United States, a blood-to-breath alcohol ratio of 2100:1 is commonly used in calibration of breath alcohol testing devices, although experimental evidence suggests that the ratio is actually closer to 2300:1.¹⁵ As such, a systematic underestimation of BAC is expected when breath alcohol results are converted to blood alcohol results. Several studies have documented this underestimation with data from suspected impaired drivers and evidential breath alcohol testing instruments.^{18,23} In 1983, Britain adopted a legal limit in breath of 35 µg/100 mL, which corresponds to a blood alcohol of 80 mg/dL, using a 2300:1 blood-to-breath ratio.²⁷ Legal statutes that include in their offense definition breath alcohol results expressed in units of g/210 L of exhaled air eliminate the need to convert breath alcohol to blood alcohol, largely mitigating arguments based on the breath-to-blood ratio.

BREATH TESTING DEVICES

Three general analytical detection principles have been extensively validated and are currently used in breath alcohol testing instruments. These are, infrared spectroscopy, electrochemical oxidation/fuel cell, and chemical oxidation/photometry.²⁴ Additionally, combination of multiple technologies is sometimes used, as in infrared/fuel cell dual detectors. Breath testing instruments may be generally divided into four broad categories: passive alcohol sensors (PASs), screening devices (preliminary breath testers, {PBTs}), breath alcohol ignition interlock devices (BAIIDs), and evidential

breath testers (EBTs).²⁴

A PAS device may be concealed in a device such as a modified police flashlight and is used to detect alcohol on or in the immediate vicinity of a subject through passive means (ie, with no requirement for subject cooperation). BAIDs are used to prevent drinking and driving by requiring the driver to blow into a sensor in order to start the ignition of the vehicle. The devices are typically installed on a court order designed to modify drinking and driving behavior in habitual DUI offenders, with the cost of installation typically borne by the offender. A number of mechanisms are employed to prevent substitution of breath samples, including preset patterns of exhalation or humming while blowing into the sampling tube. Additionally, random rolling retests may be required, failure of which may result in the vehicle's lights flashing or horn blowing. Neither PAS nor BAID results are useful for quantitative measurement of breath or blood alcohol for prosecution of a per se DUI case.

The PBT and EBT devices are the most common breath alcohol testing devices encountered in cases of DUI arrest. In this setting, PBT results are used in conjunction with observation and field sobriety tests to establish probable cause for DUI arrest. Although a measured BrAC is often provided as a digital readout on a PBT, these results are not admissible as evidence for proceedings other than probable cause hearings in most jurisdictions. Use of PBT devices is also common in nonlegal settings such as hospital emergency departments, alcohol detoxification units, homeless shelters, and workplaces. As with DUI prosecution, these results are generally used for screening for alcohol presence and not for establishing impairment.

In contrast to PBT results, measurements from an EBT device are admissible in court and administrative proceedings and can be used as the basis for establishment of per se DUI cases without the necessity of blood collection and analysis. Although mobile EBT devices are available, most often the EBT is maintained in a fixed location such as a police station. For the results to be considered valid and admissible, the operator of the EBT must be trained and certified, and the operation must be performed using an accepted testing protocol.

Required procedures for the use of EBT devices exist for the both the subject as well as the instrument. The subject must have a period of alcohol deprivation of at least 15 minutes in which trained personnel observe him or her for a minimum of 15 minutes to ensure not only that no additional ethanol is consumed, but also that no regurgitation, emesis, or eructation occurs, which could result in residual ethanol in the mouth prior to breath alcohol analysis. With respect to the instrument, both blank and control analyses must be performed prior to analysis of the subject sample. A blank analysis, typically done with room air, purges the instrument of contamination from previous samples and demonstrates a lack of environmental contamination. A control analysis is performed on a gaseous ethanol sample of known concentration, usually an ethanol gas canister or wet bath simulator, and demonstrates proper instrument calibration and maintenance. Certification of instrument maintenance of calibration must be documented, demonstrating compliance with applicable rules, regulations, laws, and standards for routine maintenance, troubleshooting, and corrective actions. These documents are then retained for a relevant time period after inspections are complete. Additional documentation for individual cases should include written verification that all steps in the accepted protocol were followed. This documentation may also include automated printouts from the analyzer used, and well as copies of manual checklists.²⁴

Beyond the required procedures, additional recommendations include the use of g/210 L as the reporting units, rather than reporting breath alcohol concentration as a converted blood alcohol concentration of %w/v, g/100 mL, or g/dL. Serial collection and analysis of at least two separate sequential breath samples taken 2 to 10 minutes apart should be done in order to demonstrate the absence of residual mouth alcohol, instrument artifacts, frequency interference, and spurious results. Agreement of the serial results must be within prescribed limits (usually, 0.02 g/210 L) to be considered acceptable.²⁴

STANDARDIZED FIELD SOBRIETY TESTS

A driver whose BAC exceeds the established legal standard is considered per se intoxicated and may be convicted without behavioral evidence of intoxication. However, some objective findings of impairment may be important in establishing probable cause to demand chemical testing, initiate a DUI arrest, or prosecute a charge of impairment, without invoking per se limits. In these settings, results of a specific group of behavioral tests may be of value in discriminating and prosecuting an impaired driving charge, although submitting to these behavioral tests is typically voluntary. Additionally, an objective measurement of alcohol effect may be helpful in assessing alcohol-related impairment in nondriving situations, where it is inappropriate to apply per se standards.

Under a contract with the NHTSA, a group of 15 candidate sobriety tests were evaluated in a laboratory study.⁹ From this original group, the investigators developed a series of three specific tests that have subsequently been standardized as a test battery, known as standardized "field sobriety tests" (FSTs), for assessing driver impairment in the United States. The three tests comprising the standardized FSTs are the one-leg stand (OLS), walk-and-turn (WAT), and horizontal gaze nystagmus (HGN). Descriptions of these tests are provided in [Table SC6-1](#).

TABLE SC6-1. Standardized Field Sobriety Tests³⁹

Test	Test Description	Test Scoring ("clues")
One-leg stand (OLS)	With the arms at sides, raise one foot at least 6 inches off the ground and stand on the other foot for at least 30 seconds.	4-point scale 1. Putting foot down 2. Hopping 3. Swaying 4. Raising arms Any two "clues" is failure.
Walk-and-turn (WAT)	Balance with feet heel-to-toe and listen to test instructions. Walk nine steps heel-to-toe in a straight line, turn 180 degrees, and walk nine more steps heel-to-toe, while counting steps, watching feet, and keeping hands at sides	8-point scale 1. Inability to maintain balance in the starting position 2. Starting too soon (eg, prior to completion of instructions) 3. Stepping off the line 4. Not touching toe to heel 5. Raising arms 6. Improper turn 7. Stopping 8. Wrong number of steps Any two "clues" is failure.
Horizontal gaze nystagmus (HGN)	Angle of onset of nystagmus is determined for each eye.	6-point scale (three points for each eye) 1. Lack of smooth pursuit 2. Distinct nystagmus at maximum deviation 3. Onset of nystagmus before 45 degrees Cutoff is 4 "clues."

Adapted with permission from Rubenzer SJ. The standardized field sobriety tests: a review of scientific and legal issues. *Law Hum Behav.* 2008;Aug;32(4):293–313.

A 1981 study of 297 drinking volunteers with BACs ranging from 0 to 180 mg/dL who were evaluated by trained police officers showed adequate interrater reliability (correlations, 0.6–0.8) and test-retest correlations (0.40–0.75).⁴⁶ Using all three field sobriety tests, the officers were able to distinguish whether BAC was above or below 100 mg/dL in 81% of participants. Test results were observed to correlate with BAC. However, the specificity and sensitivity of each individual test was not evaluated.

In the few studies evaluating the performance of individual FSTs, correlation between test performance and BAC is generally observed. Although the correlation magnitudes for the WAT and OLS tests are low, the HGN test showed excellent sensitivity and specificity across a range of BACs.³⁸ When the BAC was 0, using the WAT test, approximately 50% of the participants were judged to be impaired, and in the OLS test, 30% of the participants were rated as impaired. When the BAC was >150 mg/dL, sensitivity in the WAT and OLS tests improved to 78% and 88%, respectively. The rate of false positives (specificity; ie, those with a zero BAC who failed the HGN test) was only 3%. As seen with the other FSTs, the sensitivity of the HGN test increased with increasing BAC, being 81% for those with a BAC between 100 and 149 mg/dL and 100% for those with a BAC >150 mg/dL. The presence of horizontal gaze nystagmus, even in alcohol-tolerant drinkers, may give this test an advantage over the WAT and OLS tests in detecting the presence of alcohol.⁸ It is noteworthy that balance and coordination can be affected by factors unrelated to alcohol consumption, such as physical disability, age, and nervousness about potential arrest; however, chronic drinkers with substantial alcohol tolerance may be able to complete balance tests with few errors, even with moderate to high BACs.⁸

The three tests utilized for field sobriety assessment have some advantages, in that they are standardized and are easily understood by test takers; in addition, personnel administering the tests can be trained in a reasonable period of time.³³ However, because the test results are approximately correlated with BAC, their use is limited by the threshold BAC they are supposed to detect. Predictably, various scientific and legal challenges to the use of the FSTs have also been made. For example, the tests were designed and validated at a time when the per se DUI limit in most of the United States was 100 mg/dL; however, that threshold is now 80 mg/dL in every state (and 20–50 mg/dL in many European countries).³³ Due to the variability of psychomotor effects of alcohol as a result of individual tolerance, FST assessments are generally not

allowed as a means of estimating BAC in court proceedings. The effects of fear, fatigue, rehearsal of test performance, the arresting officer's knowledge of estimated BAC prior to administering the standardized FSTs, and various medical conditions have not been fully addressed. It has further been argued that the studies most strongly supporting use of standardized FSTs are those conducted by NHTSA-affiliated investigators and published in non-peer-reviewed government publications. So contentious has the debate been that in 2004 Booker openly leveled the charge that, "the United States Department of Transportation indulged in deliberate fraud in order to mislead the law enforcement and legal communities into believing the test (HGN) was scientifically meritorious and overvaluing its worth in the context of criminal evidence." A comprehensive review detailing this, and other, legal and scientific issues surrounding standardized FSTs was published by in 2008.³⁹

ESTIMATING THE AMOUNT OF ALCOHOL INGESTED

The kinetic profile of ethanol in the blood has been extensively studied. In general, it is known that when blood ethanol concentration is greater than 20 mg/dL, it follows a zero-order elimination profile and then converts to first-order elimination when the concentration drops below this threshold.²⁵ In the zero-order portion of the curve, typical elimination rates range from 10 to 20 mg/dL/h in social drinkers. In one study of adult patients in an urban hospital emergency department, nonchronic users of alcohol (n = 9) demonstrated a mean elimination rate of 18.7 mg/dL/h (range, 16.1–21.4), while chronic users (n = 15; defined as more than two drinks per day, history of delirium tremens, or prior detoxification) had a mean elimination rate of 20.3 mg/dL/h (range, 16.1–24.6).⁵ The difference in elimination rates between the populations was statistically significant. Other studies have reported elimination rates of 30 to 50 mg/dL/h in chronic alcoholics due, at least in part, to enzyme induction.^{5,6} Pharmacokinetic calculations in healthy nonalcoholic persons often employ a range of elimination rates of 10 to 20 mg/dL/h in order to best bracket individual differences.⁶

The estimation of the number of drinks ingested in order to achieve a given BAC has been extensively studied and is predicated on knowing several case-specific pieces of information. First, the specific definition of a "drink" in terms of alcohol content must be stated. According to the US Department of Agriculture, a standard drink consists of 12 ounces of beer (5% v/v), 5 ounces of wine (12% v/v), or 1.5 ounces of 80 proof spirits (40% v/v); each of these drinks contains approximately 14 g of ethanol.^{6,50} The time period over which the ingestion occurred, the time of the last drink, and time of blood alcohol specimen collection must be known. It is helpful to know whether the subject was fasting or had a full stomach at the time of drinking because the presence of food in the stomach alters ethanol absorption.^{29,52} Finally, the gender, age, height, and weight of the individual should be known and considered.

Using this information, estimation of the number of drinks is possible. The original work in which the prediction of ethanol concentrations from known doses was performed by Widmark in 1932 using 20 volunteer healthy moderate drinkers (10 of each gender). This research was translated from the original German into English by Baselt in 1981.^{6,25} The basis of Widmark's work was that the BAC in the body was directly proportional to the administered amount of alcohol ("dose"); the body weight of the subject; and a unitless scaling factor that Widmark referred to as "p" rho, which corrected the subject's body weight for water content. Of note, in present-day pharmacokinetics, Widmark's ρ represents the volume of distribution of ethanol. Due to the differences in body water content between sexes, ρ was determined to be approximately 0.6 in women and 0.7 in men. The original Widmark equation is therefore written as

$$A = C \times \rho \times p$$

where A represents the total amount of ethanol equilibrated in all fluids and tissues at the time of sampling (ie, total dose ingested), C is blood ethanol concentration in g/kg, ρ is the previously described Widmark ρ factor, and p is subject body weight in kilograms. Although the calculation has served well as an estimating tool for more than 70 years, it does have some limitations, principally in the ρ factor. As a result, refinement of Widmark's original ρ was undertaken by others.^{6,53} In his work, Watson derived a method for the estimation of total body water (TBW), which takes into account not only gender but also individual age, weight, and height. Watson's method for estimation of TBW (abbreviated ΣV_d) for men aged 17 to 86 years yields the following equation:

$$\Sigma V_d = 2.44 - (0.09516 \times \text{age}) + [0.1074 \times (\text{height} \times 2.54)] \\ + [0.3362 \times (\text{weight}/2.2045)]$$

For women aged 17 to 84 years, the TBW equation is:

$$\Sigma V_d = -2.097 + [0.1069 \times (\text{height} \times 2.54)] + [0.2466 \times (\text{weight}/2.2045)]$$

In all persons, the height is measured in inches and the weight is measured in pounds. Note that the equation for men includes a mathematical term derived from age, and the equation for women does not.⁵³ The significance of this calculation is its ability to be tailored to a specific person, rather than the broad extrapolation of the relatively few subjects in the original study. Inclusion of such individual information improves the accuracy of such calculations.⁴²

The need for a more standardized approach to calculations involving alcohol in forensic medicine has been known for some time. This challenge was largely undertaken in a 2006.⁶ In this paper, the author summarizes 20 of the most common calculations with respect to alcohol. As an example, the following equation is derived to calculate the estimated dose of ethanol necessary to achieve a specific blood alcohol concentration:

$$g \text{ EtOH} = \text{BAC}_{\text{target}} + [(\beta_{1-n} \times (t_s + t_p))] \times \Sigma V_d / \text{Bl}_{\text{H}_2\text{O}}$$

where g EtOH is the ingested dose of ethanol in grams; $\text{BAC}_{\text{target}}$ is the observed blood alcohol concentration in mg/dL; β_{1-n} is a range of alcohol elimination rates (typically, 10–20 mg/dL/h); t_s is the time from the start of drinking to the last drink; t_p is the range of times from the last drink to the peak PAC (typically, 30–90 minutes); ΣV_d is the Watson TBW, which is the volume of distribution based on age, weight, height and gender; and $\text{Bl}_{\text{H}_2\text{O}}$ is the approximate percentage of water in whole blood (80.65%).⁶ Noting the inherent variability in terms such as β_{1-n} and absent specific kinetic data from the individual in question, it can be seen that results of such equations should be presented as a range, rather than a discrete calculated value.

Some legal arguments have held that ethanol is odorless. This is, however, incorrect because ethanol has a characteristic pleasant smell, with an odor threshold of approximately 50 ppm.¹³ The presence or absence of breath alcohol odor is often used by police officers in the decision to proceed further with sobriety testing. In one study, 20 experienced police officers assessed alcohol odor on 14 subjects with BACs ranging from 0 to 130 mg/dL after drinking beer, wine, bourbon, or vodka.³⁵ Assessments were initiated 30 minutes after cessation of drinking. The strength of breath alcohol odor was determined to be an unreliable indicator of BAC. Correct detection of the presence of alcohol was 85% for BACs at or above 80 mg/dL but declined with decreasing BAC or the presence of food. The authors also noted that there were only small differences in odor intensity as a function of beverage type, meaning fusel oils and other constituents of alcoholic drinks are not the primary determinant of detectable odor after absorption of the beverage.

DRAM SHOP

Liquor liability or “dram shop” laws hold the server of alcoholic beverages liable for damages or injuries caused by an individual who was provided alcohol when such service should have been refused. For example, if a minor or an individual who was already intoxicated is served alcohol and crashes his or her car, the person and/or establishment who served the alcohol may be liable for damages or injuries sustained in the crash.

Interestingly, US dram shop laws were first enacted in the mid 1800s, although they were rarely used. The initial intent of these laws was to provide financial support to the families of persons who had become “habitual drunkards” through their patronage of a drinking establishment.⁴¹ Repeal of Prohibition in the United States in 1933 shifted laws governing alcohol sales from federal to state control, resulting in state-to-state variability in alcohol availability, criminal and administrative laws, and liquor liability. There was also a move from public focus on habitual drunkenness to the damage caused by drunk drivers, as well as a paradigm shift in the standard for irresponsible service away from serving a “drunkard” to serving an individual who was “visibly intoxicated.”⁴¹ The purpose of liquor liability laws has also changed over time. In the 19th century, laws were enacted to punish tavern owners who contributed to the downfall of patrons. In contrast, current application of the laws is typically as a means to compensate innocent victims injured by an intoxicated patron. This action on behalf of the innocent victim is why liquor liability law is sometimes referred to as “third party” liability.

Beginning in the late 1970s and early 1980s, political activists began to take note of dram shop laws as an effective means for prevention of drunk driving. Outreach began to bring attention to irresponsible commercial and social service of alcohol. Various drunk-driving prevention strategies emerged, including “server intervention” (ie, the practice of bar or restaurant workers intervening to prevent an intoxicated patron from driving). Interestingly, although the goal of keeping intoxicated patrons from “getting behind the wheel” is certainly praiseworthy, these programs put notably less emphasis on preventing intoxication in the first place. The 1983 Presidential Commission on Drunk Driving recommended dram shop liability and server intervention as drunk-driving prevention strategies, and federal grant funds for state drunk-driving initiatives also listed such programs as qualifying criteria.¹⁶

Alcoholic Beverage Control agencies in the various states are responsible for reviewing and approving liquor licenses of commercial establishments, collecting taxes, and enforcing criminal and administrative laws prohibiting service to minors and intoxicated persons. Largely as a tool to improve public perception of the industry, the alcoholic beverage producers have largely been responsible for development of training programs for servers in the retail community. Numerous programs offering Responsible Beverage Service (RBS) training for servers are administered at the state or regional level, or even sponsored by the server’s employer themselves. Calls for greater organization and standardization of RBS programs in the United States have been answered, at least in part, by the Responsibility Hospitality Council, whose work has focused on developing minimum training standards for legitimate RBS training.⁴¹ Although such standards

are often welcomed by regulators, some restaurant associations and owners have expressed concern over cost and compliance standards associated with RBS mandates. Nonetheless, the legal climate seems to dictate that alcoholic beverages be served in a “responsible” manner and that liability for “overservice” falls on the serving establishment. It is also noteworthy that cases putting liability onto individuals serving alcohol socially in their home have been successfully argued.

INTOXICATION AND ESTIMATION OF BLOOD ALCOHOL CONCENTRATION

Neither the characteristic odor of ethanol nor various markers of alcohol exposure (eg, ethyl glucuronide, ethyl sulfate, carbohydrate deficient transferrin, and so on) are useful in estimating BAC or degree of intoxication. The ability of an individual to estimate his or her own BAC accurately is poor.^{30,40} A lack of accuracy in estimating BAC is also observed in trained medical providers and police officers.^{3,12} A large confounding factor in these observations is tolerance. Greater tolerance, as occurs in heavy drinkers and alcoholics, imparts greater difficulty in detecting the clinical effects associated with alcohol intoxication.

Tolerance involves a central adaptation to the intoxicating effects of alcohol. As such, persons with significant tolerance to the effects of ethanol may not manifest signs of intoxication despite having a high BAC. Multiple case reports and case series in the medical literature describe alcoholic individuals with very high BACs but muted or absent clinical effects.^{14,22,26,32,45} As a result of tolerance in the alcoholic population, it may not be possible to detect clinical intoxication even though an individual has a high BAC. This circumstance does not, however, suggest that even in the clinically sober alcoholic that driving abilities are unaffected and the individual is necessarily capable of safely operating a motor vehicle.³ Furthermore, tolerance has no bearing on the potential prosecution of a DUI case on a per se BAC basis.

The circumstance is slightly more straight forward in the social drinker. The intensity of the effects of alcohol on the central nervous system (CNS) is generally proportional to the concentration of alcohol in the blood. Dubowski has tabulated the stages and effects of acute alcohol intoxication, and these tables are used in educational programs and some legal proceedings. In general, the greater the BAC, the greater the clinical effect observed.

However, while useful as a pedagogic tool for explaining the continuum of alcohol intoxication, the table must be used with care as the effects are defined only over a population, thereby making assignment of a specific effect or degree of effect in an individual impossible. The inherent individual variability in the table is apparent in the fact that the BAC ranges for the various stages of alcoholic influence overlap. Furthermore, the population and methods used to compile the table are not described, and the table itself has not been subjected to peer review.

The CNS effects of alcohol intoxication are typically more pronounced on the ascending portion of the blood alcohol kinetic curve than on the descending side due to acute tolerance.¹⁹ In other words, the clinical effect of intoxication is greater during the absorptive arm of the kinetic curve than on the elimination arm, even though the same blood alcohol concentration is measured in both kinetic phases. This principle is known as acute tolerance, or the Mellanby effect.

In a dram shop case, the ultimate question often becomes this—what is the typical BAC at which it is more likely than not that the average nontolerant individual will exhibit signs of intoxication (eg, the odor of alcohol on the breath, clumsiness, difficulty walking or maintaining balance, slurred speech, inappropriate behavior) that are apparent to a bystander or third party? A 1986 report by the Council on Scientific Affairs of the AMA examined a review of seven studies spanning 50 years that included more than 6500 participants for identification of BACs at which individuals appeared “drunk” (ie, clinically intoxicated).¹ BACs were stratified by increments of 50 mg/dL, beginning at 0.0 to 50 mg/dL and extending to 401 mg/dL. In the lowest BAC group (0.0–50 mg/dL), observer perceptions of subject drunkenness ranged from 0% to 10%, with an average of 4%. The percentage of individuals determined by observers to be drunk increased steadily from a mean of 32% (range, 14%–68%) at a BAC of 51 to 100 mg/dL to a mean of 62% (range, 47%–93%) at a BAC of 101 to 150 mg/dL. In this latter range, four of the seven studies indicated a perception of drunkenness by less than or equal to 50% of observers. However, in the next BAC increment of 151 to 200 mg/dL, observers judged a mean of 89% (range, 83%–97%) of the drinkers to be drunk. In each of the subsequent higher increments, the mean percentage of persons classified as drunk ranged from 95% to 100% with no individual study value less than 90%. Therefore, it can be reasonably concluded that, in a nontolerant individual, a BAC of 151 to 200 mg/dL will more likely than not result in observable signs of drunkenness.

The validity of a police officer detecting intoxication in drivers involved in motor vehicle crashes also increases with increasing BAC. A 1996 report examined a total of 1336 subjects over age 15 who were admitted or died at a level 1 trauma center in Seattle during a 5 year period from 1986 to 1993 and in whom both a recorded BAC and a police assessment of sobriety were conducted.²¹ The blood alcohol measurement was conducted in the hospital, and it is not expressly stated if the analytical matrix used was whole blood, serum, or plasma. Four categories of sobriety assessment were used by police: (a) had not been drinking, (b) had been drinking—not impaired, (c) had been drinking—sobriety unknown, and (d) had been drinking—impaired. Officers used a battery of specific criteria to judge whether a driver was

intoxicated, including odor on the breath, slurred speech, chemosis, poor coordination of motor function, and the ability to simultaneously perform multiple tasks. The greatest number of drivers were in the two extreme categories: had not been drinking ($n = 746$) and had been drinking—impaired ($n = 568$). A direct correlation between measured BAC and police officer assessment of sobriety was observed. The mean BAC associated with the “had been drinking—impaired” group was 190 mg/dL with a 95% confidence interval (CI) of 180 to 200 mg/dL. Those in the “had been drinking—sobriety unknown” group had a mean BAC of 130 mg/dL (95% CI, 110–150). Among all drivers, police field assessment of sobriety had a positive predictive value of 85% with sensitivity and specificity of 91% and 90%, respectively, demonstrating recognition of drunk driving by police with a high degree of accuracy, especially in the group with the highest BAC.

Another study designed to determine the ability of police officers, who have more training than the average lay person, to make assessments about alcohol intoxication in drinking target subjects without the aid of special testing normally available to them (eg, standardized field sobriety tests or the ability to smell the odor of alcohol on the subject’s breath).⁷ This study involved 39 police officers who viewed a series of videotaped interviews with six volunteer moderate drinkers having targeted BACs in three concentration ranges: low (80–90 mg/dL), medium (110–130 mg/dL), and high (150–160 mg/dL). Based on their observations of the taped interviews, the officers answered three questions:

1. Has the persons been drinking?
2. Was it OK to serve that person one additional drink?
3. Was the person able to drive a car?

Each of the three questions could be answered “yes,” “no,” or “not sure.” A fourth question assessed the officers’ confidence in their answers as “not sure,” “little uncertain,” or “positive.” Question 2 was to be answered from the perspective of a social host or bartender, not a police officer. None of the police officers had any formal training in the management or service of alcohol to intoxicated people, such as that offered by commercial seller/server training programs such as Techniques in Alcohol Management or Training for Intervention Procedures. With respect to their answers, the police officers were fairly certain that the subjects had been drinking only in the target groups with the highest BAC (150–160 mg/dL). Officers also answered in the affirmative to question 2 (ie, that it was OK to serve the target subject another drink) the majority of the time in the low- and medium-BAC target groups but not in the high BAC target group. The percentage of officers answering affirmatively to this question was 55%, 75%, and 41% for the low, medium, and high target groups, respectively.

Multiple studies have examined the likelihood of on-premise (bars and restaurants) and off-premise (liquor stores, grocery stores, and convenience stores) as well as outdoor events like festivals to sell alcohol to obviously intoxicated persons (typically, paid professional actors pretending to be drunk).^{17,31,47–49} The results are fairly uniform in that the majority of the time the alcohol was sold or served to the individual. Additionally, it was noted that male servers/clerks who appeared younger than age 31 were more likely to make such sales and the sales were more likely to occur in off-premise establishments.¹⁷

In a typical study, the authors employed 19 actors who were specifically hired based on their ability to feign intoxication. All actors were male and ranged in age from 31 to 59 years, with a mean of 42 years.⁴⁸ The actors used a standardized script to attempt to purchase either a single vodka drink after asking what beers were available on tap (on-premise) or a six-pack of beer (off-premise). Prior to entering the establishment, the actor received specific instructions to demonstrate multiple signs of intoxication, including disheveled hair and clothing, smelling of alcohol, lack of coordination, stumbling, fumbling with money, slurring words, repeating questions, appearing forgetful, and laughing inappropriately. If the actor was asked if he was driving, he responded “no” and if he was asked if he had been drinking, he responded, “I’ve had a few beers.” Attempts at alcohol purchase were made at 223 on-premise and 132 off-premise establishments.

Of the 355 attempts, actors were able to successfully make the alcohol purchase in 280 instances (79%). On-premise establishments served the actors 76% of the time, whereas off-premise establishments allowed the sale 83% of the time. Actors and a nondrinking observer also watched for clues that the server/clerk indicated an awareness or suspicion that the buyer was obviously intoxicated. Verbal indications, including asking the buyer to leave, suggesting a nonalcoholic drink, offering to call a cab, and so on, as well as nonverbal indications, such as staring or rolling of eyes, were recorded. A similar series of observations were made of security staff, other staff/bartenders/cashiers, and other customers. In 51% of the attempted purchases, there was an indication from the server of the recognition of the intoxication of the buyer. Even within the group that recognized signs of apparent intoxication, the alcohol was sold 61% of the time. When the server made no indication of the apparent intoxication, alcohol sales were completed 97% of the time. In 45% of purchase attempts, another staff member or customer made an indication that they believed the buyer was intoxicated. Still, alcohol purchases were completed in 66% of these cases. When no other staff member or customer indicating an awareness of the buyer’s behavior, the actor was served 89% of the time. The authors concluded that sales of alcohol to obviously intoxicated individuals in some US communities is very high and recommend additional study to identify effective training and tools to mitigate such illegal sales.

SUMMARY

- Alcohol use is associated with clinical effects, which adversely affect the ability to safely operate a motor vehicle.
- Impaired driving charges may be prosecuted based on BAC and application of a per se statute, and analytical techniques capable of accurately measuring alcohol concentration in a variety of biological matrices have been available for decades.
- The ability to accurately predict a BAC after drinking is poor, not only for the drinking individual, but also for trained personnel such as police officers and medical professionals.
- Clinically apparent signs of alcohol intoxication may be difficult to detect in individuals with significant tolerance, increasing the probability of driving when BAC exceeds a per se value, or “overservice” in a bar or restaurant. Tolerance also seriously limits the applicability of tables correlating BAC with specific clinical effects in an individual case.
- While the use of standardized FSTs has become the norm in the prosecution of impaired driving cases, this battery of tests has also received significant legal and scientific criticism.

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81 ETHANOL WITHDRAWAL

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HISTORY AND EPIDEMIOLOGY

The medical problems associated with alcoholism and alcohol withdrawal were initially described by Pliny the Elder in the first century B.C. In his work *Naturalis Historia*, the alcoholic and alcohol withdrawal were described as follows: "... drunkenness brings pallor and sagging cheeks, sore eyes, and trembling hands that spill a full cup, of which the immediate punishment is a haunted sleep and unrestful nights. ..." ⁵⁴ Initial treatments as described by Osler at the turn of the 20th century were focused on supportive care, including confinement to bed, cold baths to reduce fever, and judicious use of potassium bromide, chloral hydrate, hyoscine, and, possibly, opium. ²⁰

Some of the initial large series of alcohol related complications in the early 20th century describe alcohol use as a major public health concern. At Bellevue Hospital in New York City, there were 7000 to 10,000 admissions per year for alcohol-related problems from 1902 to 1935, with an estimated rate of 2.5 to 5 admissions per 1000 New York City residents. ³⁸ Many of these patients were described as suffering from "alcoholomania" or "acute alcoholic delirium."

A similar number of admissions to Boston City Hospital was also reported, with up to 10% of alcoholics admitted with evidence of delirium tremens (DTs). ⁵¹ The mortality at the beginning of the study among patients with DTs was 52% (1912), and DTs was the leading cause of death among admitted alcoholics. Over the ensuing 20 years, this rate declined to approximately 10% to 12%, a decrease believed to be secondary to improved supportive care and nursing.

Although alcoholics were widely recognized as having a high incidence of delirium and psychomotor agitation, whether this was caused by ethanol use, ethanol abstinence, or coexisting psychological disorders remained controversial. Isbell and colleagues, in 1955, proved that abstinence from alcohol was responsible when they subjected 9 male prisoners to chronic alcohol ingestion for a period of 6 to 12 weeks followed by 2 weeks of abstinence. ³⁶ Although they were ingesting alcohol daily, none of these prisoners developed signs and symptoms of DTs. However, during the abstinence phase, six of the nine men developed tremor, elevations in blood pressure and heart rate, diaphoresis, and varying degrees of either auditory or visual hallucinations, consistent with the diagnosis of DTs. In addition, two of the nine men developed convulsions, further linking alcohol abstinence to seizures. However, it should be noted that the high rate of development of DTs (67%) is atypical and does not represent the true prevalence found in later epidemiologic studies.

Alcoholism and the various manifestations of the alcohol withdrawal syndrome (AWS) still represent major problems in both the inpatient and outpatient setting. Ethanol is responsible for approximately 3.8% of all deaths worldwide (6.3% of men and 1.1% of women) and accounts for 4.6% of the global burden of disease (7.6% of men and 1.4% of women). ⁵⁸ The lifetime risk of alcohol use disorders in men is more than 20%, with a risk of about 15% for alcohol abuse and 10% for alcohol dependence. ⁶¹

Alcohol-related complications accounted for 21% of all medical intensive care unit (ICU) admissions, with alcohol withdrawal being the most common alcohol-related diagnosis. ⁴⁷ In other studies, 8% of all general hospital admissions, 16% of all postsurgical patients, and 31% of all trauma patients developed AWS. ²⁴ The development of AWS in postsurgical and trauma patients can increase the mortality in this population nearly threefold. ⁴

PATHOPHYSIOLOGY

Numerous studies over the past two decades provide valuable insight into the mechanism of alcohol withdrawal, allowing for better understanding of both the clinical spectrum of the disorder and potential therapeutic interventions. AWS is a neurologic disorder with a continuum of progressively worsening symptoms caused by the effects of chronic ethanol use on the central nervous system (CNS), and often exacerbated by the clinical manifestations of alcoholism (eg, nutritional depletion, impaired immunity, anemia, cirrhosis, and head trauma) (Table 81-1).

TABLE 81-1. Distinctions Among the Various Degrees of the Clinical Severity of Alcohol Withdrawal Syndrome (AWS)^a

Mild AWS

Symptoms

- Anorexia
- Anxiety
- Emotional lability
- Insomnia
- Irritability

Signs

- Diaphoresis
- Headache
- Hypertension
- Tachycardia
- Tremor (fine)

Moderate AWS (mild AWS, generally worse) plus:

- Agitation
- Tremor (coarse)

Severe AWS/Delirium Tremens (moderate AWS, generally worse) plus:

- Confusion/delirium progressing to tonic clonic seizures
- Hallucinations that may be visual, tactile, or auditory
- Hyperthermia

^aNote that alcohol withdrawal seizures and hallucinosis may occur with any degree of AWS.

The effects of chronic alcohol consumption on neurotransmitter function best explains the clinical findings. Persistent stimulation of the inhibitory γ -aminobutyric acid (GABA) receptor chloride channel complex by ethanol leads to downregulation of GABA receptor chloride channel complex.¹¹ This allows the alcohol user to maintain a relatively normal level of consciousness despite the presence of sedative concentrations of ethanol in the brain. A continued escalation of the steady-state ethanol concentration is required to achieve euphoria (ie, tolerance), which results in progressive desensitization of the GABA receptor chloride channel complex.⁴⁵ The exact mechanism by which this adaptive change occurs is incompletely understood but may involve substitution of an α_4 for an α_1 receptor subunit on the GABA_A receptor (Chaps. 14 and 15). A converse series of events occurs at the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor. Binding of ethanol to the glycine binding site of this receptor inhibits the NMDA receptor function, resulting in compensatory upregulation of these excitatory receptors.³⁰ Thus withdrawal of alcohol is associated with both a decrease in GABAergic activity and an increase in glutamatergic activity. This phenomenon of a concomitant increased excitation and loss of inhibition results in the clinical manifestations of autonomic excitability and psychomotor agitation.

Repeated episodes of alcohol withdrawal may lead to permanent alterations in neurotransmitters and their receptors. In rats, repeated episodes of alcohol withdrawal leads to persistent and progressive electroencephalographic abnormalities, with further episodes of withdrawal becoming increasingly resistant to benzodiazepines. Both clinical observation and in vitro data also suggest permanent dysregulation of GABA receptors. This understanding may be an explanation for the “kindling phenomena,” which is the clinical observation of increasing severity of alcohol withdrawal among individual subjects, and the development of benzodiazepine-resistant alcohol withdrawal.⁷⁸

CLINICAL MANIFESTATIONS

Alcohol withdrawal is defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) as the cessation of heavy or prolonged alcohol use resulting, within a period of a few hours to several days, in the development of two or more of the clinical findings listed in Table 81–1. Alcohol withdrawal syndromes can be classified both by timing (early vs. late) and severity (eg, complicated vs. uncomplicated) (Table 81–1). However, there are no adequate or fully accepted criteria by which to define these categories. Furthermore, the clinical course of AWS can vary widely among patients, and progression of individual patients through these different stages is variable.⁷⁰ In fact, some extensive alcohol users experience no withdrawal syndrome following the cessation of alcohol consumption. Recognizing these limitations, this conceptual framework still proves helpful in the clinical management of patients with alcohol withdrawal.

Early Uncomplicated Withdrawal

Alcohol withdrawal begins as early as 6 hours after the cessation of drinking. Early withdrawal is characterized by autonomic hyperactivity, including tachycardia, tremor, hypertension, and psychomotor agitation. This syndrome is sometimes called alcoholic tremulousness.⁶⁹ Although these symptoms are uncomfortable, they are not generally dangerous. Most patients who ultimately develop severe manifestations of AWS initially develop these findings, but this is not universal. At this “stage” of AWS, the symptoms are still readily amenable to treatment with ethanol, as is done daily by many heavy alcohol users.

Alcoholic Hallucinosis

Nearly 25% of patients with AWS will develop transient hallucinations, and a subset of these patients will develop alcoholic hallucinosis, a syndrome of vivid hallucinations that may last several weeks.^{26,71} Although classically these hallucinations are tactile or visual, other types of hallucinations are described. Tactile hallucinations include formication, or the sensation of ants crawling on the skin, which can result in repeated itching and excoriations. However, as opposed to what is observed with DTs, alcoholic hallucinosis is associated with a clear sensorium. The presence of alcoholic hallucinosis is neither a positive nor a negative predictor of the subsequent development of DTs.²⁷

Alcohol Withdrawal Seizures

Approximately 10% of patients with AWS develop alcohol withdrawal seizures, or “rum fits.” For many patients, a generalized alcohol withdrawal seizure may be the first manifestation of the AWS.⁶⁹ Approximately 40% of patients with alcohol withdrawal seizures have isolated seizures, and 3% develop status epilepticus.⁷⁰ Alcohol withdrawal seizures may occur in the absence of other signs of alcohol withdrawal and are characteristically brief, generalized, tonic–clonic events with a short postictal period. Rapid recovery and normal mental status belie the seriousness of an alcohol withdrawal seizure. However, for approximately one-third of patients with DTs, the sentinel event is an isolated alcohol withdrawal seizure.⁴⁹ Alcohol withdrawal seizures occurring in the presence of an elevated ethanol concentration may be a poor prognostic indicator for the development of DTs. Finally, clinicians should be cognizant that many alcoholics are prescribed anticonvulsant medications because they have a preexisting seizure disorder, often related to repetitive brain trauma.³⁵ Conversely, the use of anticonvulsants does not unequivocally indicate the presence of a preexisting seizure disorder because of the difficulty in differentiating these seizures from those of alcohol withdrawal.

Delirium Tremens

DTs is the most serious manifestation of the AWS and generally occurs between 48 and 96 hours after the cessation of drinking.⁶⁹ Many of the clinical characteristics of DTs are similar to those of uncomplicated early alcohol withdrawal, differing only in severity, and include tremors, autonomic instability (hypertension and tachycardia), and psychomotor agitation. However, unlike the other forms of AWS, DTs is associated with either (a) disturbance of consciousness (such as reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention, delirium, confusion, and frank psychosis, or (b) a change in cognition (such as memory deficit, disorientation, and language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.² Unlike the early manifestations of alcohol withdrawal, which typically last for 3 to 5 days, DT can last for up to 2 weeks (Table 81–2).

TABLE 81–2. Diagnostic Criteria for Substance Withdrawal Delirium²

- A.** Disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
- B.** A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
- C.** The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
- D.** There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after, a withdrawal syndrome.

Note: This diagnosis should be established instead of a diagnosis of substance withdrawal only when the cognitive symptoms are in excess of those usually associated with the withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

RISK FACTORS FOR THE DEVELOPMENT OF ALCOHOL WITHDRAWAL

Factors determining whether an individual will develop AWS and to what severity are not well identified. The strongest predictor for the development of AWS is a history of prior episodes of AWS/DTs and/or a family history.⁴² The influence of family history on the development of AWS suggests a strong role for genetic factors. A growing number of studies have identified associated polymorphisms, including genes involved in dopaminergic neurotransmission, glutamate signaling, cannabinoid receptors, serotonin signaling, and neuropeptide Y.⁶⁸ However, these findings must be interpreted with caution. First, whether these findings represent a predisposition to greater ethanol consumption because of an enhanced mesolimbic reward system, or some other underlying pathophysiologic effect, is unclear. Second, many of the studies do not systematically divide between AWS, withdrawal seizure, and DTs, all of which may be regulated by different pathways. Finally, almost uniformly these studies are small (fewer than 200 subjects) and are racially homogenous, making it imperative that these be replicated on a larger scale and among different racial groups. Larger and more varied patient cohorts that include both women and nonwhite ethnic groups are required before any definitive conclusions can be drawn. Racial predisposition to the development or severity of AWS is not definitive, but the experience at our institution suggests that African-American patients may be at lower risk of developing severe DTs than Caucasians.¹⁴

One of the more commonly used means for accurately assessing alcohol withdrawal is the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) score.⁶⁶ This scoring system contains 10 clinical categories and requires less than 5 minutes to complete. However, its use is limited by the requirement of subjective assessments by the patient; they cannot be adequately performed in highly agitated or sedated patients and are difficult to use in patients with language barriers. For these reasons, we prefer the Richmond Agitation Sedation Scale (RASS), which is observer based.⁶² Scoring systems are essential not only for symptom-triggered therapy, but they also provide a basis for comparative analysis of clinical trials in ethanol withdrawal. Greater use of CIWA-Ar, RASS, or a comparable validated scale will be essential for interpretation of both genetic and treatment trials in the future.

DIAGNOSTIC TESTING

Clinical and Biochemical Predictors

Numerous attempts have been made to develop biochemical predictors for the presence and/or severity of alcohol withdrawal. Although consistent abnormalities in readily obtained laboratory values are observed in patients with AWS (eg, aminotransferases, magnesium, mean corpuscular volume), their role in predicting the severity of AWS is poorly understood. In one study, an alanine aminotransferase of greater than 50 U/L, a serum chloride less than 96 mEq/L, and a serum potassium less than 3.6 mEq/L were all associated with the development of AWS in patients admitted to a detoxification center.⁷⁵ Another noted that risk factors for DTs included a lower serum potassium, thrombocytopenia, and prevalence of structural brain lesions.²³ However, the varied and generally low specificity of these derangements makes it difficult to assess their predictive value, especially when accounting for other clinical characteristics such as prior history, initial ethanol concentration, and admission CIWA-Ar or RASS score. In addition, there is a negative association between the presence of severe alcohol withdrawal and histopathologic cirrhosis, further clouding the usefulness of routine laboratory testing for prognostication.⁵

Other investigators have focused specifically on blood ethanol concentration as a predictor for the severity of AWS in at-risk subjects. In one study of patients entering a detoxification program, an admission blood ethanol concentration of greater than 150 mg/dL had a 100% sensitivity and a 57% specificity for the need for treatment of alcohol withdrawal.⁷² At a different treatment facility, an ethanol concentration of greater than 150 mg/dL had an 81% positive predictive value for the need to use more than a single dose of chlordiazepoxide for the treatment of AWS.⁷² In addition, admission blood ethanol concentrations in patients with alcohol withdrawal seizures were twofold higher than in those without seizures, irrespective of whether or not they had a history of prior withdrawal seizures. However, these results should be interpreted with caution and in the context of the clinical presentation, as other studies yield conflicting results. In one study, an admission ethanol concentration of less than 100 mg/dL was associated with an increased risk of recurrent alcohol withdrawal seizures, and in another study, admission ethanol concentrations failed to predict the development of DTs.^{15,56} There are many potential explanations, including differences in patient population, differences in cohort size, and the late onset of DTs, at a time when ethanol concentrations would be extremely low or nonexistent.

Homocysteine and B vitamin concentrations as well as hepatic function tests are associated with the development of AWS, although there are several contradictory study results.^{32,42} Because many studies are based on small numbers of often highly selected subjects, and some are promising but not prospectively validated,⁷⁶ their generalizability is typically poor. Numerous reports document hyperhomocysteinemia in alcoholism, presumably caused by a deficiency of dietary folic acid. Furthermore, homocysteine and its metabolites can act as excitatory neurotransmitters at the NMDA receptor and cause seizures and excitatory neuronal death. In one study, serum homocysteine concentrations were predictive of alcohol withdrawal seizures.⁸ However, in this study, there was very strong correlation ($r^2 = 0.7666$; $P < 0.001$) between admission blood ethanol concentrations and homocysteine concentrations and the development of seizures, raising doubts as to whether this holds any advantage over blood ethanol concentrations.

MANAGEMENT

Alcohol Withdrawal Seizures

Alcohol withdrawal seizures are perhaps the most rigorously studied complication of alcohol withdrawal. They are generally self-limited and if treatment is needed, benzodiazepines are the preferred agents. In a randomized, placebo-controlled trial of 229 subjects with alcohol withdrawal seizures, 2 mg of intramuscular lorazepam reduced the risk of recurrent seizure from 24% to 3% ($P < 0.001$) at 6 hours, and the need for hospital admission from 42% to 29% ($P = 0.0222$).¹⁸ However, whether this interrupts the natural history of progression to DTs is not known. There is no role for phenytoin in either treatment or prevention of alcohol withdrawal seizures. In multiple trials, phenytoin was ineffective in preventing recurrent seizures.^{1,55} The most likely explanation for the failure of phenytoin is its inability to regulate GABA or NMDA receptors, the principal mediators of seizures in alcohol withdrawal. One exception to this lack of usefulness occurs in the alcoholic patient with a non-alcohol withdrawal mediated seizure, or a history of underlying seizure disorders.

Alcohol Withdrawal

In the early stages of AWS, many patients are able to self-medicate with additional ethanol consumption. Among those who seek medical attention, many patients with AWS can be safely managed as outpatients. Outpatient management has significant cost savings with little effect on treatment outcome.⁶⁴ In one study, patients who were not clinically intoxicated, had no history of either DTs or alcohol withdrawal seizures, no comorbid psychiatric or medical disorders, and a CIWA-Ar score of less than 8 were safely managed as outpatients.³ Patients not meeting these criteria were referred to inpatient detoxification centers or medical units, depending on the severity of withdrawal and other comorbid conditions.

For all patients with AWS, the initial stages of therapy remain the same and should include a thorough assessment to identify a coexisting medical, psychiatric, or toxicologic disorder. In particular, an assessment for CNS trauma and infection should include the use of computed tomography and lumbar puncture as needed. Patients with altered cognition and an elevated body temperature should receive antibiotics, pending the results of a lumbar puncture. In concert with this approach, adequate supportive care should be instituted, including maneuvers to normalize any abnormal vital signs such as hyperthermia.

Chronic ethanol consumption leads to severe vitamin and nutritional deficiencies and electrolyte disturbances that should be corrected. Specifically, thiamine should be given to all patients to prevent the development of Wernicke encephalopathy.²¹ It was historically suggested that thiamine should be given prior to the administration of dextrose to prevent precipitation of Wernicke encephalopathy.^{48,73} Although there is no evidence for this approach, the administration of thiamine (Antidotes in Depth: A24) and dextrose together is a reasonable practice. In addition, there is a high incidence of intravascular volume depletion among alcoholics, so all patients should receive adequate volume resuscitation. Of 39 deaths between 1915 and 1936 attributed to DTs in which volume status was recorded, all subjects were volume depleted.⁵¹ Finally, for patients with AWS, prevention of nosocomial complications is paramount for reducing hospital stays. Currently, in addition to adequate volume replacement, we recommend that all patients (1) be kept with the head of the bed elevated to prevent aspiration and (2) that deep vein thrombosis prophylaxis be given if the patient is bed bound for an extended period.

The association of alcohol withdrawal with severe psychomotor agitation led to early use of sedative-hypnotics. One of the first randomized trials compared chlorpromazine to paraldehyde. In both arms there was a 0% mortality, suggesting equivalency of the two treatments.²⁵ Over the ensuing years, numerous trials documented similar efficacy between paraldehyde, benzodiazepines, and antipsychotics.^{13,25,67} However, in a landmark study, 547 patients were randomized to one of four drugs (chlordiazepoxide, chlorpromazine, hydroxyzine, and thiamine) or to placebo for the treatment of alcohol withdrawal.³⁹ Patients receiving chlordiazepoxide had the lowest incidence of both alcohol withdrawal seizures and DTs, establishing benzodiazepines as a first-line agent for treatment of alcohol withdrawal. Of note, use of chlorpromazine, an antipsychotic, is associated with a significant increase in the incidence of seizures in both humans and animal models.^{10,39}

Since this study, numerous trials have compared different routes of administration among various sedative-hypnotics, both to each other and to placebo. Because of the historical use noted above, chlordiazepoxide remains widely used in outpatient clinics and inpatient detoxification services. Oral benzodiazepine administration is generally effective in patients with early or mild AWS, although initial rapid titration with an intravenous regimen may be more efficient. Benzodiazepines administered intravenously have a rapid onset of action and have displaced paraldehyde as the preferred choice for acute control. Among the benzodiazepines, diazepam offers the most rapid time to peak clinical effects, which limits oversedation that may occur following the administration of lorazepam, which has a slower onset to the peak drug effect. Because of the delayed peak clinical effect of lorazepam of approximately 10 to 20 minutes, several doses may be administered in rapid succession with little clinical effect, followed by the appearance of the sedative effect of the cumulative doses. Midazolam may be administered intramuscularly if intravenous access is not available.⁶³ Although no significant differences are observed between benzodiazepines and barbiturates in terms of mortality or the duration of

delirium, the improved pharmacokinetic profile and ease of administration favor benzodiazepines over barbiturates when an intravenous medication is required.^{3,43}

Other pharmacokinetic factors and experience confirm that diazepam is the preferred benzodiazepine for initial intravenous use in patients with moderate to severe AWS. Diazepam has a long half-life and two active metabolites (desmethyldiazepam and oxazepam). The prolonged half-life (48–72 hours) of desmethyldiazepam further extends the effective duration of action of the initial dose of diazepam.⁸¹ A retrospective review reported that the use of a single benzodiazepine rather than multiple benzodiazepines was a marker for treatment success in surgical patients experiencing alcohol withdrawal during surgical admission.⁵³ These data suggest that it is more important to sedate the patient rapidly with adequate doses of a single benzodiazepine than to use multiple agents in hopes of finding an effective regimen. Finally, it should be noted that in patients with advanced liver disease, the use of diazepam may result in a very prolonged period of sedation because of impaired clearance of the parent compound and its metabolites. Consequently, in these patients, a benzodiazepine without active metabolites, such as lorazepam, may be a better drug.

The initial management of patients with AWS should include rapid titration with a benzodiazepine to achieve sedation.⁵² An oral benzodiazepine, such as chlordiazepoxide or diazepam may be sufficient, but certain patients will require intravenous medication. The goal of therapy is to have the patient sedated but breathing spontaneously, with normal vital signs. Although normalization of vital signs is not a mandatory therapeutic endpoint, abnormal vital signs despite adequate sedation should prompt a search for comorbidities. In many patients, attaining complete sedation using a loading protocol may allow for autotitration; that is, as the AWS resolves, the blood concentrations of the benzodiazepine decrease, allowing gradual clinical recovery.⁴⁶ In practicality, most patients need periodic symptom triggered redosing with benzodiazepines to maintain adequate sedation. This is particularly important in patients with AWS and a concomitantly elevated blood alcohol concentration. Their benzodiazepine requirements using symptom triggered therapy typically matches their decrease in blood alcohol concentration.

Multiple studies suggest that if additional doses are required, they should be administered based on symptoms (“symptom triggered”), as opposed to a fixed dosing schedule.¹² In two randomized controlled trials, administration of benzodiazepine in a symptom-triggered fashion reduced both the total amount of benzodiazepine and the duration of treatment.^{19,59} In these trials, benzodiazepines were administered every hour as long as the CIWA-Ar score remained greater than 8 to 10. In both trials, symptom-triggered therapy resulted in a four- to sixfold reduction in the duration of therapy and a four- to fivefold reduction in the total amount of benzodiazepine administered, with no increase in withdrawal seizures or adverse events. Symptom-triggered doses in patients with moderate or severe AWS should be diazepam 10 to 20 mg intravenously or lorazepam 2 to 4 mg. For less symptomatic patients, oral chlordiazepoxide 50 to 100 mg should be administered. However, it is important to note that the decision to treat in the symptom-triggered group was made based on CIWA-Ar score (usually >8), which demonstrates the usefulness of standardized scoring and evaluation tools. It should also be noted that in both these trials, patients had very mild withdrawal symptoms, with mean CIWA-Ar scores of 9 to 11. While experience suggests that this same regimen is also effective in patients with more severe withdrawal and/or DTs, it has not been validated in this population. Furthermore, it must be emphasized that protocolized use of the CIWA-Ar score is dependent upon a significant history of recent heavy drinking and a communicative subject. A prospective analysis of complex medical/surgical patients enrolled in a CIWA-Ar protocol suggested that more than 50% patients failed to have recent alcohol use and could not communicate, leading to unnecessary treatment.³¹

Resistant Alcohol Withdrawal and Delirium Tremens

There is a subgroup of patients with AWS who require very large doses of diazepam or another comparable drug to achieve initial sedation.²⁹ This same group often has exceedingly high benzodiazepine requirements to maintain this degree of sedation. Subjects with resistant AWS and DTs may have benzodiazepine requirements that exceed 2600 mg of diazepam within the first 24 hours and generally require admission to an intensive care or step-down unit.^{60,79} Patients admitted to the Bellevue hospital medical ICU for resistant alcohol withdrawal had very high diazepam requirements, with a mean of 234 mg (range, 10–1490 mg) required in the first 24 hours, and individual doses of diazepam that often exceeded 100 mg, to control their agitation. At Bellevue, these patients comprise approximately 5% of all ICU admissions, with nearly 40% of patients requiring mechanical ventilation and a mean ICU length of stay of 5.7 days.²⁸

The approach to the management of resistant AWS depends on several factors, including the availability of an ICU bed. In the ICU, despite the perception of failure of high benzodiazepine requirements, we favor administration of benzodiazepines in a symptom-triggered fashion. This approach was confirmed in a study of patients who developed AWS postoperatively in the ICU.⁶⁵ In this study, a symptom-triggered strategy resulted in a shorter length of stay and a lower incidence of mechanical ventilation than did continuous infusion of midazolam. Patients who receive this therapy generally respond to bolus doses of diazepam, which results in a brief period of sedation followed by recrudescence of their AWS. However, the dose range and other sedative-hypnotics required to achieve this may be dramatically different than what is observed in subjects with nonresistant AWS. In a recent study, use of escalating bolus doses of diazepam, up to 200 mg as an individual dose, combined with phenobarbital in subjects with continued benzodiazepine resistance (defined as the

requirement for bolus doses more frequently than every hour), reduced the need for mechanical ventilation by nearly 50%.²⁸ In non-ICU settings, the ability to administer frequent intravenous doses of diazepam is limited, and the use of intravenous infusions with a second sedative-hypnotic may be more practical.

In instances of extreme benzodiazepine resistance, patients often receive a second GABAergic drug because of “failure” of benzodiazepine therapy. Phenobarbital, given in combination with a benzodiazepine, in intravenous doses of up to 260 mg, is a reasonable choice.²⁸ Caution is required to avoid stacking doses of phenobarbital, as the onset of clinical effect takes approximately 20 to 40 minutes.³⁷ Alternatively, propofol in standard doses may be administered. Although propofol has a rapid onset, it is difficult to titrate, and high-dose or long-term use is associated with profound metabolic consequences.¹⁶ However, in an observational study, propofol was safely administered to 21 subjects intubated for severe benzodiazepine-resistant DTs.²⁸ The main drawback to the use of these drugs is their narrow therapeutic index, with the potential for profound respiratory depression. This is especially true for propofol, which should generally only be used in the setting of mechanical ventilation. Both these sedative-hypnotics can act synergistically with benzodiazepines to enhance GABA-induced chloride channel opening. In addition, propofol uniquely antagonizes NMDA receptors, thus reducing the excitatory component of AWS.

Ethanol

Ethanol consumption is a common and effective means by which alcoholics can self-medicate to treat and/or prevent mild alcohol withdrawal. Consequently, some hospitals still administer ethanol for either prophylaxis and/or treatment of AWS. In one survey, 72% of 122 hospitals surveyed had administered either intravenous or oral ethanol for these indications.⁹ Despite its widespread use, little randomized controlled data supports its use. In one trial, 39 trauma patients without hepatic or CNS disease were successfully treated with 10% ethanol infusion for treatment of presumed AWS.¹⁷ Conversely, intravenous ethanol was no more effective than flunitrazepam in one trial and inferior to diazepam in another in the prevention of AWS in postoperative surgical patients.^{22,74} Although the authors did not report any adverse effects in these trials, the necessity for frequent blood alcohol monitoring, unpredictable elimination kinetics, potential for significant hepatic complications, the postulated adverse effects of ethanol on wound healing, and the difficulty in safely administering this therapy makes it inappropriate to recommend this regimen.³³

Adrenergic Antagonists

Numerous studies have investigated the use of sympatholytics to control the autonomic symptoms of alcohol withdrawal. Both β -adrenergic antagonists and clonidine reduced blood pressure and heart rate in randomized, placebo-controlled trials.^{7,44} However, the inability of these xenobiotics to address the underlying pathophysiologic mechanism of AWS and subsequently control the neurologic manifestations makes them suboptimal as the sole therapeutic. There are additional concerns. By altering the physiologic parameters that serve as classic markers for AWS severity, there is a risk of underadministering necessary amounts of benzodiazepines.⁸⁰ This was observed in a randomized controlled trial of the central α -agonist lofexidine,⁴⁰ and it is particularly complicated if using the peripheral findings to assess severity as is done with CIWA. Finally, there are a growing number of reports documenting the use of the central α -adrenergic agonist, dexmedetomidine, for AWS in both animals and humans. A recent large, observational study demonstrates that dexmedetomidine is effective at reducing blood pressure and heart rate in patients with AWS, with a significant reduction in the amount of lorazepam required.⁵⁷ However, the study failed to document a change in overall treatment duration, and CIWA scores were not recorded. Consequently, given the high cost of dexmedetomidine, we do not recommend using this drug for the treatment of AWS until it becomes clear that other standard therapies have failed.

Magnesium

The theoretical benefits of magnesium supplementation are based both on the high prevalence of magnesium deficiency in alcoholics and its usefulness in preventing seizures in other disorders, including eclampsia.³⁴ Furthermore, magnesium deficiency has many clinical similarities to AWS, clouding the differential diagnosis. Numerous studies have evaluated the efficacy of magnesium supplementation. However, in a randomized, placebo-controlled trial, magnesium had no effect on either the incidence of withdrawal seizures or severity of alcohol withdrawal.⁷⁷ Consequently, aside from repletion of electrolyte abnormalities, there is no indication for routine administration of magnesium for the treatment of AWS. However, because hypomagnesemia is common and may worsen with glucose, water, and thiamine, it should be routinely screened with both blood and ECG (QT) and supplemented as needed.

Anticonvulsants

Carbamazepine has been used in multiple trials for treatment of mild AWS, more commonly in Europe where an intravenous preparation is available. In animal studies, carbamazepine increases both the CNS GABA concentrations and

the seizure threshold in alcohol withdrawal models. However, there are insufficient data to recommend the use of carbamazepine in humans.^{6,50} Valproic acid appears to have a benzodiazepine-sparing effect in patients with mild withdrawal, but the true clinical benefit is unclear.¹ In contrast, a recent randomized placebo-controlled study of the newer anticonvulsant, oxcarbazepine, showed no difference between this xenobiotic and placebo in inpatient detoxification.⁴¹ Consequently, while this class of drugs may be reasonably recommended as adjuncts, they should not be used as monotherapy for treatment of moderate or severe AWS.

SUMMARY

- Alcohol withdrawal is a complex physiologic process involving both enhanced neuronal excitation and reduced inhibition resulting in neuroexcitation.
- The manifestations of greatest concern are neurologic and include altered mental status and seizures, but the autonomic excess may be clinically consequential.
- Treatment includes supportive care and sedation with benzodiazepines in escalating doses.
- When benzodiazepines cannot produce adequate sedation, sedative-hypnotics such as phenobarbital or propofol should be added.

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82 HALLUCINOGENS

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HISTORY

A “hallucination” may be defined as a false perception that has no basis in the external environment. The term is derived from the Latin term meaning “to wander in mind.” While the term “psychedelic” has been used for years to refer to the recreational and nonmedical effects of hallucinogens, other terms, like entheogen and entactogen, frequently appear in Internet discussions. Entheogens are “substances which generate the god or spirit within,” while entactogens create an awareness of “the touch within.”⁴¹ These terms all refer to the same xenobiotics, used with differing intent or in varying settings. Hallucinations differ from illusions, which are distorted perceptions of objects based in reality.

Hallucinogens are a diverse group of xenobiotics that alter and distort perception, thought, and mood without clouding the sensorium. Hallucinogens can be categorized by their chemical structures, and further divided into natural and synthetic members of each family. The major structural classes of hallucinogens include the lysergamides, tryptamines (indolealkylamines), amphetamines (phenylethylamines), arylhexamines, cannabinoids, harmine alkaloids, belladonna alkaloids, and the tropane alkaloids. In addition, there are several unique hallucinogens, such as *Salvia divinorum*, nutmeg, kratom, and kava kava. This chapter focuses on lysergamides, tryptamines, phenylethylamines, and the unique hallucinogens. More on the other classes can be found in [Chaps. 76, 77, 78, and 86](#).

Hallucinogens have been used for thousands of years by many different cultures, largely during religious ceremonies. The ancient Indian holy book, *Rig-Veda*, written more than 3500 years ago, describes a sacramental substance called Soma both as a god and as an intoxicating substance. Although debated for many years, the source of Soma is now believed to be an extract of the mushroom *Amanita muscaria*.^{101,108} The Aztecs used the psilocybin-containing *teonanacatl* (flesh of the gods) and *Ololiuqui* (morning glory species) in their religious ceremonies. To this day, the Native American Church in the United States uses peyote in religious ceremonies.

From medieval times through recent years, several large-scale epidemics of vasospastic ischemia, gangrene, and hallucinations (collectively called ergotism) have resulted from *Claviceps purpurea* contamination of cereal crops.¹³⁶ The hallucinations from *Claviceps* ingestion are attributed to the ergot alkaloid lysergic acid amide from which lysergic acid diethylamide (LSD) was chemically synthesized. *Claviceps purpurea* has been suggested, but subsequently disproved, as the cause of the mass hysteria leading up to the Salem witch trials. Many of these adverse effects after ingestion of *C. purpurea* have been attributed to the serotonergic agonist effects of the ergot alkaloids ([Chap. 54](#)).³⁸

Synthetic hallucinogen use is often said to have begun in 1938 when Albert Hofmann, a Swiss chemist, synthesized LSD while performing extensive research on the medicinal uses of ergot alkaloids derived from the fungus, *C. purpurea*. Five years later, LSD was “tested” when Hofmann exposed himself in his laboratory and subsequently developed hallucinations.^{63,120} Soon thereafter, Sandoz Laboratories began marketing LSD under the trademark *Delysid* as an adjunct for analytic psychotherapy. In the 1950s, a small number of psychiatrists began using LSD to release the repressed memories of patients, and as an experimental model for schizophrenia.¹²⁷ The US Central Intelligence Agency reportedly experimented with the use of LSD as a tool for interrogating suspected communists and as a mind-control agent.^{23,120}

In the 1960s, the concept of the “fifth freedom” emerged. As individuals explored this “right” to alter their consciousness as they saw fit, LSD (also called acid) became a fashionable recreational drug. In one of the most famous slogans of the 1960s, Dr. Timothy Leary popularized LSD as a way to “Tune in, Turn on, Drop out.”¹²⁰ By 1966, US federal law banned the use of LSD.⁹⁴ Initial reports of LSD-induced chromosomal damage appeared in the 1960s.^{32,65,76} However, further studies of pregnant women who had taken LSD did not demonstrate an increased risk of abortions or birth defects.^{44,73}

LSD use diminished in the late 1970s and early 1980s, perhaps due to user concerns regarding potential health risks of brain damage, “bad trips” and flashbacks.¹⁰⁰ In the meantime, there was a rise in the use of the “designer” hallucinogens. Exploiting a loophole in drug enforcement laws, these designer synthetic tryptamine and amphetamine hallucinogens are chemically similar to, but legally distinct from, their outlawed counterparts and therefore not subjected to legislative drug control. These are often referred to as “legal highs.” The Internet has developed as a vehicle for the rapid and facile sharing of information on the synthesis of emerging drugs, user experiences, and adverse effects. Additionally, the Internet

marketplace has made many “herbal” hallucinogens widely available via unregulated Web sites.³⁶ All-night dance clubs host “rave parties,” at which emerging hallucinogens are popular.¹³ While the impact of these parties on the growth of hallucinogens in the United States is unclear, many of the newer hallucinogens have been christened “club drugs” because of this association.⁵³

Resurgence in LSD use was reported among high school teens in the late 1990s, with more prevalent use in the suburbs than the city.^{95,109} In 1997, two studies of adolescents showed a lifetime prevalence of LSD use at 13% and 14%.^{67,100} In 2000, US Drug Enforcement Agency (DEA) agents seized an LSD-production lab and apprehended two men involved in massive production of LSD in Kansas City. Their incarceration resulted in a more than 90% decrease in LSD availability nationwide.

While much of the research involving psychedelic drugs was halted in the 1960s, there has been a reemergence of clinical investigations since the late 1980s for the treatment of various psychiatric disorders, with emphasis on treatment of anxiety and addictions. Recently, psilocybin has been evaluated for the treatment of the existential anxiety associated with end-stage cancer and obsessive-compulsive disorders, while 3,4-methylenedioxymethamphetamine (MDMA) has been studied as an adjunct to psychotherapy for treatment-resistant posttraumatic stress disorder.^{57,89,90} The clinical or research use of psychedelic drugs remains highly controversial.

EPIDEMIOLOGY

The 2006 National Survey on Drug Use and Health (NSDUH) reported the following trends in hallucinogen use: more than 23 million Americans older than 12 years of age reported LSD use during their lifetime, 6.6 million had used phencyclidine (PCP), and 12 million reported previous MDMA use. Additionally, 2.3 million people reported prior use of ketamine, while only 700,000 reported use of α -methyltryptamine (AMT), dimethyltryptamine (DMT), or 5-methoxydimethyl tryptamine (5-MeO-DMT). About 1.8 million people reported use of *Salvia divinorum* during their lifetime. In the reported results, the 18 to 25 year-old age group was most likely to report use of any of these hallucinogens within the previous year (Table 82–1).¹²² In 2010 the NSDUH reported that 1.2 million Americans older than 12 years of age were current users of hallucinogens.¹²⁸

TABLE 82–1. Structural Classifications of Hallucinogens

Lysergamides

- D-Lysergic acid diethylamide

- Lysergic acid hydroxyethylamide

 - Morning glory (*Ipomoea violacea*)

 - South American morning glory (*Ololiuqui*)

- Ergine

 - Woodrose (*Argyrea nervosa*)

Indolealkylamines/tryptamines

- 5-Methoxy-*N,N*-dimethyltryptamine (5-MeO-DiPT, Foxy Methoxy)

- N,N*-dimethyltryptamine

- Psilocybin

Phenylethylamines

- Mescaline

- 3,4-Methylenedioxymethamphetamine (MDMA)

- 2C-B

- 2C-T-7

Tetrahydrocannabinoids

- Marijuana

- Hashish

Belladonna alkaloids

- Jimsonweed (*Datura stramonium*)

- Henbane (*Hyoscyamus niger*)

- Deadly nightshade (*Atropa belladonna*)

- Brugmansia* spp

Miscellaneous

- Kava kava

- Ketamine

- Kratom

- Nutmeg

- Phencyclidine (PCP)

- Salvia divinorum*

LYSERGAMIDES

Lysergamides are derivatives of lysergic acid, a substituted tetracyclic amine based on an indole nucleus (Fig. 82–1).

Naturally-occurring lysergamides are found in several species of morning glory (*Rivea corymbosa*, *Ipomoea violacea*) and Hawaiian baby woodrose (*Argyrea nervosa*).⁵⁹ Morning glory seeds contain multiple alkaloids, including lysergic acid, hydroxyethylamide, and ergonovine. Morning glory seeds were called *ololiuqui* in ancient Mexico, where Aztecs and other indigenous populations used them in religious rites.¹²⁴ However, in one volunteer study, *ololiuqui* caused sedation rather than hallucinations.⁶⁴ Hawaiian baby woodrose seeds contain ergine. Both morning glory and Hawaiian baby woodrose seeds can be legally purchased for planting in garden stores and on the Internet.

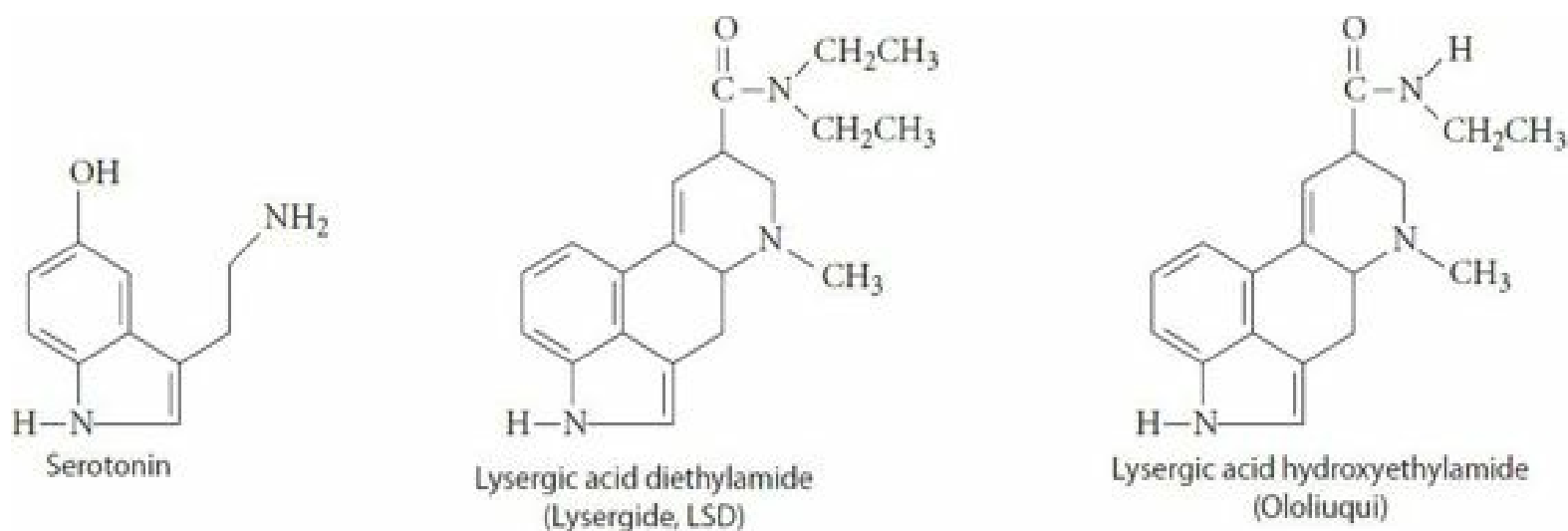


FIGURE 82–1. Hallucinogens of the lysergamide chemical class and their chemical similarity to serotonin.

The synthetic lysergamide, LSD, is derived from an ergot alkaloid of the fungus, *Claviceps purpurea*. Although four LSD isomers exist, only the d-isomer is active. Lysergic acid diethylamide is a water-soluble, colorless, tasteless, and odorless powder. Currently, LSD is typically sold as liquid-impregnated blotter paper, microdots, tiny tablets, “window pane” gelatin squares, liquid, powder, or tablets.¹⁰⁹ LSD users typically experience heightened awareness of auditory and visual stimuli with size, shape, and color distortions. Auditory and visual hallucinations may occur, as well as synesthesia, a confusion of the senses, where users may report “hearing colors, or seeing sounds.” Other more complex perceptual effects may include depersonalization and a sensation of enhanced insight or awareness. A “bad trip” is said to occur when LSD use produces anxiety, bizarre behaviors, and combativeness.

LSD is classified by the DEA as a Schedule I agent, with high abuse potential, lack of established safety even under medical supervision, and no known use in medical treatment.

INDOLEALKYLAMINES (TRYPTAMINES)

Indolealkylamines, or tryptamines, represent a class of natural and synthetic compounds that structurally share a substituted monoamine group (Fig. 82–2). Endogenous tryptamines include serotonin and melatonin. Naturally occurring exogenous tryptamines include psilocybin, bufotenine, and DMT. Psilocybin is found in three major genera of mushrooms: *Psilocyba*, *Panaeolus*, and *Conocybe*.¹⁰⁸ Other psychoactive mushrooms include *Amanita muscaria* and *Amanita pantherina*, which contain ibotenic acid, muscimol, and muscazone, which are unrelated to the tryptamines.⁵⁹ Hallucinogenic mushrooms are discussed at length in Chap. 120. Psilocybin-containing mushrooms, or “magic mushrooms,” grow in the Pacific Northwest and southern United States, usually in cow pastures. The mushroom may be recognized by a green-blue color that it assumes after bruising, but misidentification is common.¹¹

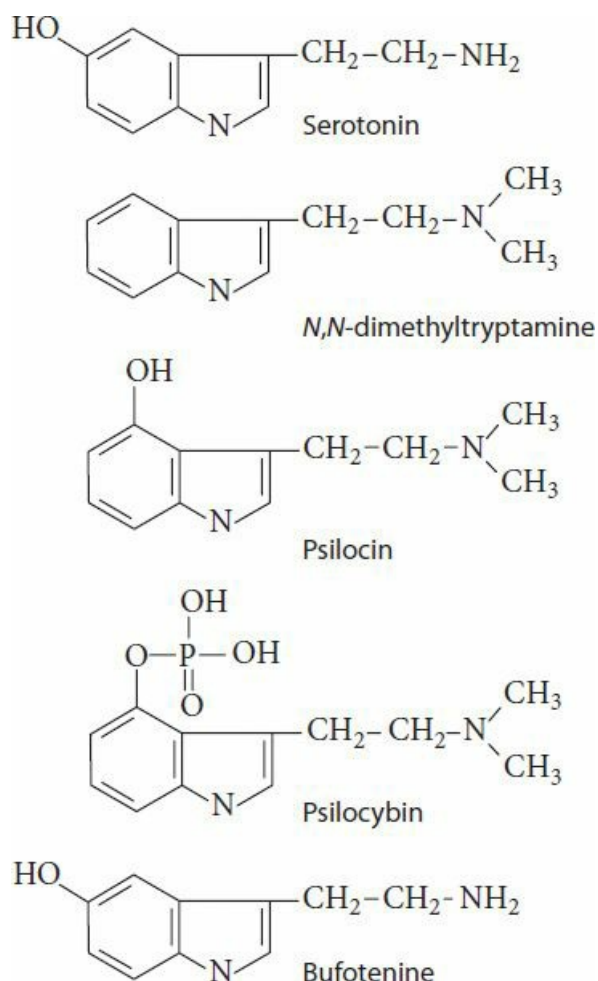


FIGURE 82–2. Hallucinogens of the indolealkylamine chemical class and their chemical similarity to serotonin.

N,N-dimethyltryptamine (DMT) is a potent short-acting hallucinogen found naturally in the bark of the Yakee plant (*Virola calophylla*), which grows in the Amazon basin. It is used by shamans as a hallucinogenic snuff to “communicate with the spirits.”¹⁰⁸ DMT is also found in the hallucinogenic tea, ayahuasca, which is used by indigenous healers in the Amazon Basin. In ayahuasca, DMT-containing plants (eg, *Psychotria viridis*) are combined with plants containing harmine alkaloids (eg, *Banisteriopsis caapi*), which inhibit hepatic monoamine oxidases to increase the oral bioavailability of DMT (Chap. 73).⁸⁵

The use of toads in religious ceremonies and witchcraft dates back thousands of years. All species of the toad genus *Bufo* have parotid glands on their backs that produce a variety of substances, including dopamine, epinephrine, and serotonin.⁷⁸ Some of these toads produce bufotenine, a tryptamine, which causes hypertension, but does not cross the blood–brain barrier. Interest in bufotenine grew out of reports of a toad-licking fad in the 1980s, in which individuals would reportedly lick toads for recreational purposes.⁷⁷ However, further review suggests that bufotenine is not the hallucinogenic substance found in toad secretions. Instead, 5-MeO-DMT has been identified as the psychoactive substance.¹³⁵ 5-MeO-DMT is only found in one species of toad, *Bufo alvarius* (Sonoran Desert toad or Colorado River toad).⁷⁷ Although bufotenine has been classified as a Schedule I substance by the DEA for many years, 5-MeO-DMT was not scheduled until 2009.⁹¹ Like DMT, 5-MeO-DMT is rapidly metabolized by intestinal monoamine oxidase enzymes; oral ingestion of toad venom or skins would thus have limited potential as a route of recreational use.²¹ Methods for extracting and drying *B. alvarius* secretions for smoking and insufflation are available on the Internet. Death has resulted from wrongful use of *Bufo* secretions for purposes of aphrodisia.^{30,55} The toad venom glands also produce cardioactive steroids, called bufadienolides, which cause digoxinlike cardiac toxicity, and in some species, can secrete tetrodotoxin.^{87,139}

Two of the more important synthetic tryptamines include N,N-diisopropyl-5-methoxytryptamine (5-MeO-DiPT, Foxy Methoxy) and α -methyltryptamine (AMT, IT-290). Since 2001, law enforcement authorities in more than 10 states have seized large amounts of 5-MeO-DiPT and AMT. These drugs are often sold surreptitiously as MDMA. 5-MeO-DiPT received Schedule I status in 2004.¹³⁰ α -Methyltryptamine (AMT or IT-290) is a monoamine oxidase inhibitor that was sold as an antidepressant in the former Soviet Union.¹¹⁴ AMT was placed into Schedule I status by the DEA in September 2004.¹³⁰

PHENYLETHYLAMINES (AMPHETAMINES)

Dopamine, norepinephrine, and tyrosine are endogenous phenylethylamines. Exogenous phenylethylamines stimulate catecholamine release and cause a variety of physiologic and psychiatric effects, including hallucinations. Substitution on the phenylalkylamine structure has important effects on both the hallucinogenic and stimulant potential of the drug. The presence of a methyl group in the side chain of the phenylethylamines is associated with a higher degree of hallucinogenic effect (Fig. 82–3).⁶⁹ MDMA, amphetamine, and methamphetamine are well known members of this family and are discussed in detail in Chap. 76.

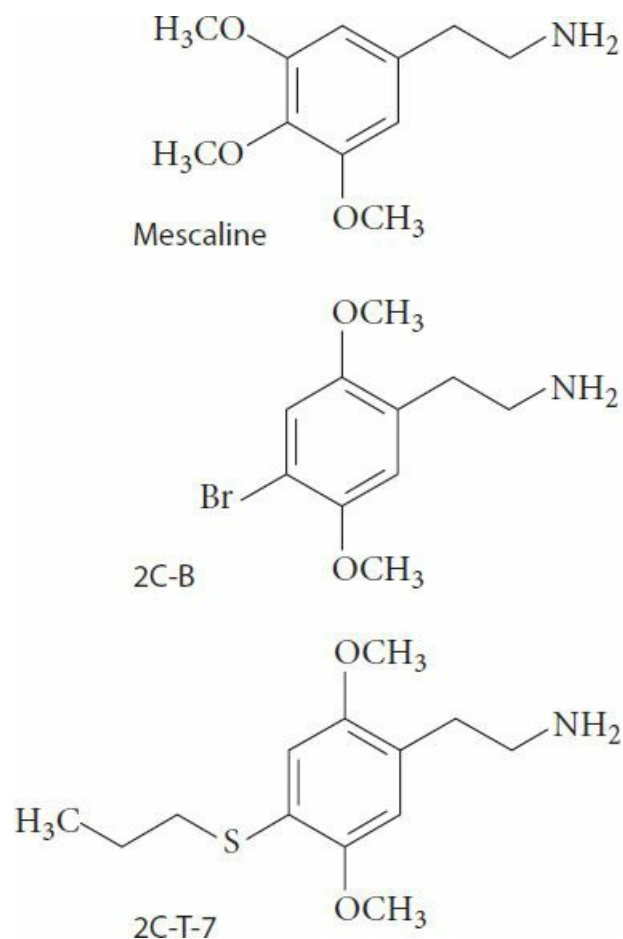


FIGURE 82–3. Hallucinogens of the phenylethylamine chemical class.

The best recognized of the naturally occurring psychoactive phenylethylamines is mescaline. Mescaline is found in Peyote (*Lophophora williamsii*), a small blue-green spineless cactus that grows in dry and rocky slopes throughout the southwestern United States and northern Mexico. Peyote buttons are the round, fleshy tops of the cactus that are sliced off and dried. The legal use of peyote in the United States is restricted to members of the Native American Church, for whom peyote buttons are used for both religious ceremonies and medical treatment for physical and psychological ailments.^{24,27}

Other nonindigenous cactus species containing significant amounts of mescaline include the San Pedro cactus (*Trichocereus pachanoi*) and Peruvian torch cactus (*Trichocereus peruvianus*). These plants can be purchased for ornamental purposes in garden stores and on the Internet.⁵⁹

The synthesis and effects of hundreds of other congeners of amphetamine is well described.¹¹³ Included are the synthetic hallucinogenic amphetamines 4-bromo-2,5-dimethoxyphenethylamine (2C-B, Nexus, Bromo, Spectrum) and 2,5-dimethoxy-4-N-propylthiopheneethylamine (2C-T-7, Blue Mystic).

During the 1980s, 2C-B gained popularity as a legal alternative to MDMA. When 2C-B was given Schedule I status in 1995, 2C-T-7 emerged as another legal designer amphetamine.⁹ In March 2004, 2C-T-7 also received Schedule I status.³⁴

SALVIA DIVINORUM

Salvia divinorum is a perennial herbaceous member of the mint family. While there are more than 500 species of *Salvia*, *S. divinorum* is most recognized for its hallucinogenic properties.¹³¹ *Salvia divinorum* is a native to areas of Oaxaca, Mexico, and grows well in sunny temperate climates. Plants, leaves, and extracts may be purchased online, and tips for cultivation of plants are easily accessible.

Since the sixteenth century, the Mazatec Indians have used *S. divinorum* as a hallucinogen in religious rites as a means of producing “visions.”¹³¹ The Mazatecs continue to revere *S. divinorum* as an incarnation of the Virgin Mary, referring to the plant as “ska Maria.” Currently, although the federal Controlled Substances Act does not prohibit use of *S. divinorum* or

its psychoactive extracts, the possession and sale of *S. divinorum* is illegal in several states, including Delaware, Florida, and Georgia. Nationwide regulation of this substance exists in Australia, and there is local regulation in some municipalities where *S. divinorum* use among teenagers is rampant.¹²⁹ There continues to be widespread marketing of this hallucinogen on the Internet as a “legal hallucinogen.”

KRATOM

Kratom, or *Mitragyna speciosa* Korth, is derived from the leaves of a tree native to Asia and Africa.¹¹² Kratom has dual properties, producing stimulant effects and opioidlike analgesic effects. It was used in Southeast Asia to enhance productivity in manual laborers. The Kratom alkaloids mitragynine and 7-hydroxymitragynine activate μ -, δ -, and δ -opioid receptors. It has been used as a substitute for opium, although hallucinogenic effects are uncommon, they are reported following heavy use.¹²³ Kratom has been illegal in Thailand since 1946 and in Australia since 2005. Kratom is currently legal to possess and use in the United States, where it has been adopted by some patients for self-treatment of chronic pain and to modulate opioid withdrawal symptoms.

NUTMEG

Nutmeg is derived from *Myristica fragrans*, an evergreen tree native to the Spice Islands. The fruits of the tree contain a central kernel called the nutmeg, while the surrounding red aril is used to produce a spice called mace.⁹⁹ While nutmeg is commonly available as a cooking spice, it has been used medicinally for centuries as an antidiarrheal and abortifacient.⁵⁸ It is a recreational herbal that has also been used to produce euphoria and hallucinations; it is more likely to be abused by adolescents due to its low cost and accessibility.^{35,99,105}

BELLADONNA ALKALOIDS

The belladonna alkaloids, including the tropane alkaloids atropine, hyoscyamine, and scopolamine, can be isolated from a number of plants. Deadly nightshade (*Atropa belladonna*), a perennial plant, grows throughout the United States, as well as in areas of Europe and Africa. Belladonna alkaloids can be isolated from both the leaves and berries of this perennial plant. Jimson weed (*Datura stramonium*), also called locoweed, grows throughout warm and moist areas of the world. This bush contains pods full of small black seeds that are ingested or brewed as a tea for their hallucinogenic properties. The common name Angel’s trumpet is used for plants of the Solanaceae family with large trumpet-shaped white flowers (*Brugmansia* or *Datura*). Given their wide availability, in the wild and over the Internet, these plants are frequently used as hallucinogens by adolescents.⁵⁴ Unfortunately, they produce significant morbidity from anticholinergic toxicity in unwary users. Moonflower, a common name given to several plants, including *Datura innoxia*, was responsible for anticholinergic poisoning of more than a dozen adolescents in one series.³¹ Additionally, epidemics of unintentional poisoning were reported among drug users who received heroin adulterated with scopolamine.⁶¹

TOXICOKINETICS

LSD is the most studied hallucinogen, and there is extensive information about its pharmacokinetics (Table 82–2). Ingestion is the most common route of exposure, and the gastrointestinal tract rapidly absorbs LSD. Other reported routes of administration include intravenous, intramuscular, intranasal, parenteral, sublingual, inhalation, and conjunctival instillation. Plasma protein binding is more than 80% and volume of distribution is 0.28 L/kg. It is concentrated within the visual cortex as well as the limbic and reticular activating systems. It is metabolized in the liver via hydroxylation and glucuronidation, and excreted predominantly as a pharmacologically inactive compound. LSD has an elimination half-life of about 2.5 hours. Only small amounts are eliminated unchanged in the urine. The minimum effective oral dose is 25 μ g.⁷⁰ The onset of effects may occur 30 to 60 minutes after exposure, with a duration of 10 to 12 hours.

TABLE 82–2. Pharmacology of Selected Hallucinogens

Drug Name or Source	Psychoactive Component (if Different)	Typical Oral Dose	Onset	Duration
Bufo species toads	5-MeO-DMT	5–15 mg (smoked)	Immediate (smoked)	5–20 minutes (smoked)
DMT	–	15–60 mg	5–20 minutes	30–60 minutes
"Foxy Methoxy"	5-MeO-DiPT	6–10 mg	20–30 minutes	3–6 hours
Woodrose (<i>Argyreia nervosa</i>)	Ecgonine	5–10 seeds	minutes	6–8 hours
Jimson weed (<i>Datura stramonium</i>)	Atropine, hyoscyamine, scopolamine	10 seeds	20–30 minutes	2–3 hours
Kratom (<i>Mitragyna speciosa</i> Korth)	Mitragynine, 7-Hydroxy-mitragynine	2–6 g (stimulant); >7 g (sedative)	10–15 minutes	4–6 hours
Lysergic acid diethylamide (LSD)	Lysergic acid diethylamide	50–100 µg	30–60 minutes	10–12 hours
"Magic mushrooms" (<i>Psilocybe</i> species)	Psilocybin, psilocin	5 g mushrooms	30 minutes–2 hours	4 hours
Nutmeg (<i>Myristica fragrans</i>)	Myristicin, elemicin	20 g	1 hour	24 hours
Peyote (<i>Lophophora williamsii</i>)	Mescaline	6–12 buttons, 270–540 mg mescaline	1–3 hours	10–12 hours
<i>Salvia divinorum</i>	Salvinorin A	–	30 minutes (inhaled); 1 hour (oral)	15–20 minutes (inhaled); 2 hours (oral)
2C-B	–	16–30 mg	1 hour	6–10 hours

Ingestion of 200 to 300 morning glory seeds is required to achieve hallucinogenic effects. Only 5 to 10 seeds of Hawaiian baby woodrose are required to produce hallucinations. After ingestion of woodrose seeds, the effects typically last for 6 to 8 hours and produce tranquility without marked euphoria.⁴

Peyote buttons are very bitter, and can be eaten whole or dried and crushed into a powder, which is reconstituted as tea.⁵⁹ Nausea, vomiting, and diaphoresis often precede the onset of hallucinations, which begin at 1 to 3 hours postingestion, and last for up to 12 hours.⁹⁹ Six to twelve peyote buttons, or 270 to 540 mg of mescaline, are commonly required to produce hallucinogenic effects.¹⁰⁷ Ingestion of up to 5 g of psilocybin-containing mushrooms may be required to produce hallucinogenic effects. After ingestion of *Psilocybe* mushrooms, psilocybin is converted to psilocin, the active hallucinogen in the gastrointestinal tract.⁵⁶ The effects of psilocin are similar to LSD, but with a shorter duration of action of about 4 hours.

For recreational purposes, DMT is typically smoked, snorted, or injected. Hallucinogenic effects peak in 5 to 20 minutes, with a duration of 30 to 60 minutes, earned DMT the nickname the "businessman's trip." 5-MeO-DiPT is most commonly ingested, but may be smoked or insufflated. Effects begin 20 to 30 minutes after ingestion, and include disinhibition and relaxation. There is a dose-dependent response and at higher ranges, symptoms include mydriasis, euphoria, auditory and visual hallucinations, nausea, diarrhea, and jaw clenching.^{93,115} The hallucinogenic effects are reported to last from 3 to 6 hours.^{86,115} Other substances may be used to heighten or prolong the hallucinogenic effects of 5-MeO-DiPT. These include sildenafil, γ -hydroxybutyrate, benzodiazepines, and marijuana. AMT is available as a white powder, which may be ingested, smoked, or insufflated. Hallucinations typically occur within 30 minutes, but may last 12 to 16 hours.⁷⁵

Amphetamine, methamphetamine, and MDMA are well absorbed through the gastrointestinal tract. The elimination half-life ranges from 8 to 30 hours for members of this class and is dependent on urine pH.^{12,33} Amphetamines are weak bases and undergo more rapid elimination in acidic urine.¹¹⁰ The volume of distribution ranges from 3 to 5 L/kg for amphetamine, 3–4 L/kg for methamphetamine, and likely more than 5 L/kg for MDMA.^{12,33,74,110} Elimination of other amphetamines occurs through multiple mechanisms including aromatic hydroxylation, aliphatic hydroxylation, and N-dealkylation.⁷⁴ Tolerance occurs with chronic amphetamine use.⁷¹

There is little information about 2C-B and 2C-T-7 in the medical literature. Both drugs may be used via oral, intranasal, and intrarectal routes. Both 2C-B and 2C-T-7 exert their hallucinogenic effects within one hour of use, and physiologic and psychologic effects may persist for 6 to 10 hours. Additional information on the kinetics of amphetamine and congeners may be found in [Chap. 76](#).

Salvia divinorum may be chewed, smoked, or ingested as tea. Hallucinations occur immediately after exposure to the

drug and are typically quite vivid. Synesthesia is reported among *Salvia* users. Hallucinogenic effects after *S. divinorum* use are typically brief, lasting only 1 to 2 hours. Pharmacokinetic data for *S. divinorum*, and its primary psychoactive, Salvinorin A, were described in one volunteer study.¹¹⁶ Psychoactive effects were typically experienced 5 to 10 minutes after absorption of Salvinorin A via the buccal mucosa, reaching a plateau during the first hour after exposure and resolving within 2 hours. Vaporization and inhalation of Salvinorin A led to more rapid effects beginning at 30 seconds after exposure. These effects would plateau at 5 to 10 minutes and typically subside after 20 to 30 minutes. In this study, ingestion of *S. divinorum* leaves did not produce the same effects as buccal or inhalational administration, leading to the theory that gastrointestinal deactivation of Salvinorin A occurs after ingestion.¹¹⁶

Kratom leaves can be decocted into tea, chewed, or smoked.⁶⁶ Kratom leaves contain approximately 0.8% mitragynine by weight, but can vary by geographic origin of trees, as well as season.¹¹¹ Neuropsychiatric effects are dose dependent and occur within 5 to 10 minutes of exposure, with effects lasting 4 to 6 hours.¹²³ Stimulant effects predominate at doses of 2 to 6 g, while sedation becomes more pronounced at doses above 7 g.

Nutmeg is usually ingested as a paste, or mixed in a beverage; 15 to 20 g of the substance is required for clinical effects.⁹⁹ This dose is often unpalatable, and a case report of recreational use of encapsulated nutmeg has been described.¹⁰⁵ Clinical effects can begin 1 hour after nutmeg ingestion; nausea and vomiting precede the onset of hallucinations, and effects can persist for more than 24 hours after exposure.⁹⁹

The belladonna alkaloids are most concentrated in the seeds of Jimson weed; each seed contains approximately 0.1 mg of atropine.¹¹⁸ Ingestion of as few as 10 seeds can produce hallucinations within 20 to 30 minutes; these effects can last for 2 to 3 hours. While the roots and seeds of Angel's trumpet contain the highest alkaloid concentrations, users most often brew the blossom into a tea. Each blossom contains approximately 0.3 mg of atropine and 0.65 mg of scopolamine.⁵⁴ The elimination half-lives of atropine and hyoscyamine are 2.5 and 3.5 hours, respectively, while the elimination half-life of scopolamine is considerably longer, at 8 hours.¹⁵

PHARMACOLOGY

Although the lysergamide, indolealkylamine, and phenylethylamine hallucinogens are structurally distinct, the similarities in their effects on cognition support a common site of action on central serotonin receptors.^{3,20,26,62,126} Serotonin (5-HT) modulates many psychological and physiologic processes, including mood, personality, affect, appetite, motor function, sexual activity, temperature regulation, pain perception, sleep induction, and ADH release. There are more than 14 known 5-HT receptor subtypes (Chap. 14); differing affinity for these subtypes occurs based on the structure of the hallucinogen, and may account for the subtle differences between their effects.

The lysergamide, indolealkylamine, and phenylethylamine hallucinogens all bind to the 5-HT₂ class of receptors. There is good correlation between the affinity of both indolealkylamine and phenylethylamine hallucinogens for 5-HT₂ receptors in vitro and hallucinogenic potency in humans.^{3,52,98,126} The 5-HT_{2A} receptor subtype appears to have the highest density in the cerebral cortex and may represent the binding site for hallucinogens.⁸⁰ This is bolstered by an animal study that shows that a selective 5-HT_{2A} antagonist can inhibit the effects of LSD and a phenylethylamine, 2,5-dimethoxy-4-iodo-amphetamine (DOI). The response to high doses of LSD and DOI suggest that both lysergamides and phenylethylamines are partial agonists at cortical 5-HT_{2A} receptors.^{51,80,104}

Although most investigations have focused on the role of serotonin for drug-induced hallucinations, other neurotransmitters are also involved. Stimulation of 5-HT_{2A} receptors enhances release of glutamate in the cortical layer V pyramidal cells.^{3,8} LSD and other lysergamides stimulate both D₁ and D₂ dopamine receptors.^{7,50,134} In animal models, LSD and phenylethylamine hallucinogens modulate NMDA receptor-mediated effects and may have a protective effect against neurotoxicity secondary to PCP and ketamine.^{8,43}

Another theory that incorporates these other neurotransmitters involves the concept of "thalamic filtering."⁴⁹ The thalamus receives input and output from the cortex and reticular activating system, and functions to filter relevant sensory input. This theory has been explored as an explanation for organic psychosis and the effects of hallucinogenic drugs. Multiple neurotransmitters, including dopamine, acetylcholine, GABA, and glutamate, exert their actions on the thalamus. Increased excitatory or decreased inhibitory neurotransmitter in this region of the brain may lead to "sensory overload," which manifests itself clinically as symptoms of psychosis.⁴⁹ Experimental evidence also demonstrates EEG abnormalities after administration of hallucinogens, confirming a cortical, rather than the ophthalmologic, etiology for hallucinations.⁴²

Salvinorin A, the psychoactive component of *Salvia divinorum*, is one of the most potent natural hallucinogens. The effect of Salvinorin A occurs via binding at the δ -opioid receptor, making it structurally and mechanistically unique (Fig. 82-4).¹³⁸ The δ -opioid receptor is distinct from the μ opioid receptor, a stimulation that generally causes euphoria and analgesia (Chap. 38). Salvinorin A does not demonstrate any known serotonergic activity.¹³⁸

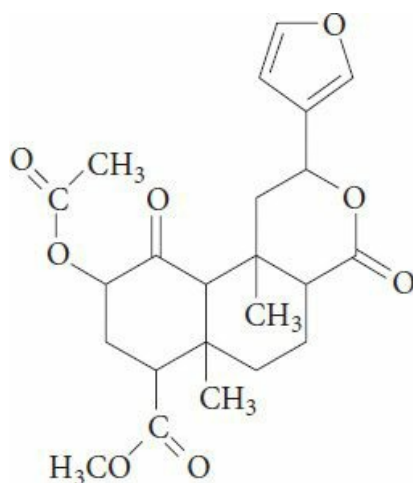


FIGURE 82–4. Structure of Salvinorin A.

The opioid effects of Kratom have been attributed to mitragynine.^{111,137} The most prevalent of the Kratom alkaloids, mitragynine shares a structural similarity with yohimbine.¹⁰ In vitro, mitragynine is active at both supraspinal opioid δ - and μ -receptors.¹²⁵ This μ -receptor activity results in analgesia and efficacy in treating opioid withdrawal symptoms. Additionally, mitragynine activates noradrenergic and serotonergic pathways.⁸³ Another Kratom alkaloid, 7-hydroxymitragynine, also demonstrates antinociceptive effects and high affinity for opioid receptors.⁸⁴ In animal studies, 7-hydroxymitragynine has more analgesic potency than morphine, even after oral administration.⁸²

Nutmeg contains a number of purportedly psychoactive compounds, including myristicin, elemicin, and safrole (Fig. 82–5). The psychoactive components of nutmeg include terpenes and alkyl benzyl derivatives (myristicin, elemicin, and safrole).⁹⁹

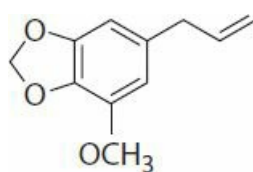


FIGURE 82–5. Structure of myristicin.

It is theorized that the aromatics found in nutmeg are metabolized to amphetaminelike compounds that create hallucinogenic effects.⁹⁹ However, this mechanism is unsupported by both theory and animal data.¹⁰⁵ Nutmeg contains myristicin and elemicin, both weak monoamine oxidase inhibitors that also demonstrate serotonergic activity, which may account for the clinical effects of nutmeg.¹⁰⁵

The pharmacology of atropine, a competitive central and peripheral antimuscarinic, and the most well studied belladonna alkaloid, is discussed in detail in Antidotes in Depth: A32. Like atropine, scopolamine and hyoscyamine are tertiary amines, which can cross the blood–brain barrier. Scopolamine causes more sedation than atropine, and its transdermal availability has led to its use in motion sickness patches. Hyoscyamine is more potent than atropine; it has traditionally been used as an antispasmodic for gastrointestinal conditions.

CLINICAL EFFECTS

Physiologic changes accompany and often precede the perceptual changes induced by lysergamides, tryptamines, and phenylethylamines. The physical effects may be caused by direct drug effect or by a response to the disturbing or enjoyable hallucinogenic experience. Sympathetic effects mediated by the locus coeruleus include mydriasis, tachycardia, hypertension, tachypnea, hyperthermia, and diaphoresis. They may occur shortly after ingestion and often precede the hallucinogenic effects. Other clinical findings that are reported include piloerection, dizziness, hyperactivity, muscle weakness, ataxia, altered mental status, coma, and rhythmic, pupillary dilation, and constriction.⁷² Nausea and vomiting often precede the psychedelic effects produced by psilocybin and mescaline. Potentially life-threatening complications, such as hyperthermia, coma, respiratory arrest, hypertension, tachycardia, and coagulopathy, were described in a report of eight patients with a massive LSD overdose.⁶⁸ Sympathomimetic effects are generally less prominent in LSD toxicity than in phenylethylamine toxicity. Similar sympathetic symptoms are described after the use of 2C-B and 2C-T-7. Low doses of 2C-B and 2C-T-7 may produce hypertension, tachycardia, and visual hallucinations, while elevated doses are associated with shifts in color perception, enhanced auditory, and visual stimulation. Three deaths are associated with 2C-T-7 use; in one case, death may have resulted from seizures or aspiration.^{34,39} An analog of 2C-B, called 2C-B-FLY, or Bromo-

dragonFLY, is implicated in finger necrosis that requires amputation secondary to potent peripheral vasospastic activity as well as sudden cardiac death.⁹⁶ Similar vasoconstrictive effects resulting in limb ischemia may be induced by exposure to ergot containing alkaloids.

The psychological effects of hallucinogens seem to represent a complex and elusive interaction between different neurotransmitters, including the serotonergic and dopaminergic systems. Based on this serotonergic mechanism, serotonin toxicity could theoretically occur after the use of any of the lysergamide, indolealkylamine or phenylethylamine hallucinogens. Animal studies have documented LSD and tryptamine-induced serotonin toxicity.^{117,132} Case reports have linked phenylethylamine use to fatal serotonin toxicity in recreational users.^{92,133}

Tolerance to the psychological effects of LSD occurs within 2 to 3 days with daily dosing, but rapidly dissipates if the drug is withheld for two days. Psychological cross-tolerance among mescaline, psilocybin, and LSD is reported in humans.¹⁴ There is no evidence for physiologic tolerance, physiologic dependence, or a withdrawal syndrome with LSD. Limited cross-tolerance is demonstrated between psilocybin and cannabinoids such as marijuana.²²

Salvia divinorum use results in vivid hallucinations and synesthesia.¹¹⁶ Additionally, its use may cause diuresis, nausea, and dysphoria. These aversive effects may limit its long-term recurrent use.¹⁰

The dual stimulant and sedative properties of Kratom contributed to its traditional use among manual laborers. However, its opioidlike activity has led to a surge in contemporary use as an herbal treatment for opioid withdrawal among patients with chronic pain.^{18,19} Anorexia, weight loss, and insomnia are reported among Kratom addicts. Hyperpigmentation of the cheeks is also described among chronic users.¹²³

Recreational nutmeg use results in the desired effects of euphoria and hallucinations, as well as the adverse effects of nausea, vomiting, dizziness, flushing, tachycardia, and hypotension. Two case reports of fatalities from nutmeg ingestion are reported; however, it is unclear if these deaths truly represent nutmeg toxicity.^{29,119}

The belladonna alkaloids produce classic signs of anticholinergic toxicity, including hyperthermia, tachycardia, mydriasis, flushing, anhidrosis, urinary retention, and ileus. The central effects can include restlessness, hallucinations, agitation, delirium, seizures, and coma.³¹ The psychosis produced by belladonna alkaloids can be profound; in one case, a young man autoamputated his tongue and penis after ingestion of tea made from Angel's trumpet.⁸¹

The vast majority of morbidity from hallucinogen use stems from trauma. Hallucinogen users frequently report lacerations and bruises sustained during their "high." Additionally, dysphoria may drive patients to react to stimuli with unpredictable, and occasionally, aggressive behaviors. Many Internet sites regarding hallucinogen use advise readers to take hallucinogens only while under the supervision of a "sitter."⁴⁰

The psychological effects of hallucinogens are dose related and affect changes in arousal, emotion, perception, thought process, and self-image. The response to the drug is related to the person's mindset, emotions, or expectations at the time of exposure and can be altered by the group or setting.¹ The person experiencing the effects of a hallucinogen is usually fully alert, oriented, and aware that he or she is under the influence of a drug. Euphoria, dysphoria, and emotional lability may occur.

Illusions are common, typically involving distortion of body image and alteration in visual perceptions. Hallucinogen users may display acute attention to details with excessive attachment of meaning to ordinary objects and events. Usual thoughts seem novel and profound. Many people report an intensification of their sensory perceptions such as sound magnification and distortion. Colors often seem brighter with halolike lights around objects. Frequently, hallucinogen users relate a sense of depersonalization and separation from the environment, commonly called an "out-of-body" experience. Synesthesias, or sensory misperceptions, such as "hearing colors," or "seeing sounds" are commonly described. Hallucinations may be visual, auditory, tactile, or olfactory.

Acute adverse psychiatric effects of hallucinogens include panic reactions, psychosis, and major depressive dysphoric reactions. Acute panic reactions, the most common adverse effect, present with frightening illusions, tremendous anxiety, apprehension, and a terrifying sense of loss of self-control.⁴⁶ These psychiatric effects may cause patients to seek care in the emergency department.

LABORATORY

Routine urine drug-of-abuse immunoassay screens do not detect LSD or other hallucinogens. Although LSD can be detected by radioimmunoassay of the urine, confirmation by high-performance liquid chromatography (HPLC) or gas chromatography is necessary. These tests are rarely used in the clinical setting but are commonly available for forensic purposes.^{14,37} False-positive urine immunoassay testing for LSD is reported after exposure to several medications, including fentanyl, sertraline, haloperidol, or verapamil.^{47,102}

Depending on their structure, phenylethylamines may cause positive qualitative urine testing by immunoassay for amphetamines. However, amphetamine drug screening is associated with numerous false positive results, particularly after

the use of cold medications that contain ephedrine, pseudoephedrine, or phenylpropanolamine.¹²¹ Urine immunoassays do not detect 5-Meo-DiPT, DMT, AMT, 2C-T-7, and 2CB, but gas chromatography/mass spectrometry (GC/MS) testing methods for detection of these compounds has been described.¹³⁷

Routine urine drug immunoassay screens do not detect Salvinorin A, mitragynine, or myrsitacin. HPLC and liquid chromatography/mass spectrometry (LC/MS) protocols have been applied to the quantitative analysis of Salvinorin A and B in plant matter and in ex vivo animal studies. GC/MS identified Salvinorin A in urine and saliva obtained after two human volunteers smoked *S. divinorum*.⁹⁷ Myristicin testing is not widely available, but it can be obtained.¹¹⁹

TREATMENT

Most hallucinogen users rarely seek medical attention because they experience only the desired effect of the drug. For any hallucinogen user who does present to the emergency department, initial treatment must begin with attention to airway, breathing, circulation, level of consciousness, and abnormal vital signs. Even in those in whom exposure to a hallucinogen is suspected, the basic approach for altered mental status should include dextrose, naloxone, and oxygen therapy as indicated, as is the vigorous search for other etiologies. Hallucinogens rarely produce life-threatening toxicity. Due to their rapid absorption, gastrointestinal decontamination with activated charcoal is of little value after clinical symptoms appear, and attempts may lead to further agitation. Sedation with benzodiazepines is usually sufficient to treat hypertension, tachycardia, and hyperthermia. The patient with a dysphoric reaction can be placed in a quiet location with minimal stimuli. A nonjudgmental advocate should attempt to reduce patient anxiety, provide reality testing, and remind the individual that a drug was ingested and the effect will wear off in a couple of hours. Physical restraint (without chemical restraint) should be avoided to prevent hyperthermia and rhabdomyolysis. Benzodiazepines remain the cornerstone of therapy for both autonomic instability and dysphoria, as the sedating effect can diminish both endogenous and exogenous sympathetic effects.⁸⁸ Autonomic instability and hyperthermia may be a feature of phenylethylamine use as well as tryptamine use or massive LSD overdose.^{46,68,88} Hyperthermia resulting from agitation or muscle rigidity requires urgent sedation with benzodiazepines and rapid cooling. While central nervous system depression is unlikely to be severe enough to require endotracheal intubation in a patient with a pure hallucinogen exposure, intubation and paralysis may be required in the patient with intractable hyperthermia.¹⁶ Seizures may occur with tryptamine or phenylethylamine use and can be initially treated with benzodiazepines. Seizures may also result from hyponatremia in MDMA users and would necessitate treatment with 3% hypertonic saline (Chaps. 19 and 76).

The treatment of anticholinergic toxicity from the belladonna alkaloids involves several critical components: correction of abnormal vital signs, management of delirium, and rapid intervention for seizures or dysrhythmias. The mainstays of therapy are fluid resuscitation and benzodiazepines; however, physostigmine should be considered as antidotal therapy in cases of belladonna alkaloid poisoning. Conflicting data exist regarding the efficacy of physostigmine in decreasing morbidity and length of hospital stay when compared with benzodiazepines alone.^{25,103} Based on the strength of evidence, physostigmine should be considered in patients with evidence of anticholinergic delirium or agitation if there are no contraindications. More information on physostigmine can be found in Antidotes in Depth: A9.

Morbidity and mortality typically result from the complications of hyperthermia, including rhabdomyolysis and myoglobinuric acute kidney injury, hepatic necrosis, and disseminated intravascular coagulopathy. However, for the most part, hydration, sedation, a quiet environment, and meticulous supportive care will prove adequate to prevent morbidity or mortality in recreational use or overdose.²⁸ Treatment of serotonin toxicity from phenylethylamine use is largely supportive and includes the avoidance of further administration of serotonergic medications. Specific therapy with agents like cyproheptadine may be warranted¹⁷ (Chap. 75).

The role of antipsychotics in controlling hallucinogen-induced agitation is unclear. Haloperidol, risperidone, and ziprasidone may have utility in controlling the acutely agitated patient. However, haloperidol and risperidone may worsen panic and visual symptoms, increasing the incidence of hallucinogen persisting perception disorder (HPPD; see below).² The safety of ziprasidone in hallucinogen users has not yet been reported. While further study on these agents is required, prolonged psychosis may require treatment with long-term antipsychotic therapy.

LONG-TERM EFFECTS

Long-term consequences of LSD use include prolonged psychotic reactions, severe depression, and exacerbation of preexisting psychiatric illness.^{60,106} When LSD was initially popularized, some patients were noted to behave in a manner similar to schizophrenia and required admission to psychiatric facilities. In volunteer studies, panic reactions, HPPD, and extended psychoses were noted. When the drug was used for alleviation of anxiety and personality abnormalities, flashbacks and extended psychosis were reported.⁴⁵ It is suggested that these individuals had preexisting compensated psychological disturbances.^{3,79}

Flashbacks are reported in up to 15% to 80% of LSD users.⁵ Anesthesia, alcohol intake, and medication use may precipitate flashbacks.⁴⁸ These perceptions can be triggered during times of stress, illness, and exercise, and are often a virtual recurrence of the initial hallucinations. HPPD is a chronic disorder where flashbacks lead to impairment in social or occupational function. According to the Diagnostic and Statistical Manual V, the diagnosis of HPPD requires the recurrence of perceptual symptoms that were experienced while intoxicated with the hallucinogen that causes functional impairment and is not due to a medical condition.⁶ The etiology of HPPD is still unknown, and the reported incidence varies widely. Symptoms are primarily visual, and reality testing is typically intact in HPPD. Common perceptual and visual disturbances in HPPD include geometric forms, false and fleeting perceptions in the peripheral fields, flashes of color, intensified color, and halos around objects.⁷⁹ One finding described after LSD use is palinopsia, or “trailing,” which refers to the continued visual perception of an object after it has left the field of vision. These visual perceptions are associated with normal ophthalmologic examinations and abnormal EEG evaluations, suggesting a cortical etiology for the visual symptoms.

SUMMARY

- Hallucinogens are a diverse group of drugs that alter and distort perception, thought, and mood without clouding the sensorium.
- The lysergamide, phenylethylamine, and tryptamine hallucinogens share a serotonergic mechanism of action; however, other neurotransmitters may be responsible for the complex effects of these hallucinogens.
- Acute adverse psychiatric effects of hallucinogens include panic reactions, true hallucinations, psychosis, and major depressive dysphoric reactions.
- Hallucinogens rarely produce life-threatening problems, but can cause autonomic instability, seizures, and hyperthermia, particularly in large overdose.
- Meticulous supportive care with attention to abnormal vital signs and sedation with a benzodiazepine is often the only therapy required.

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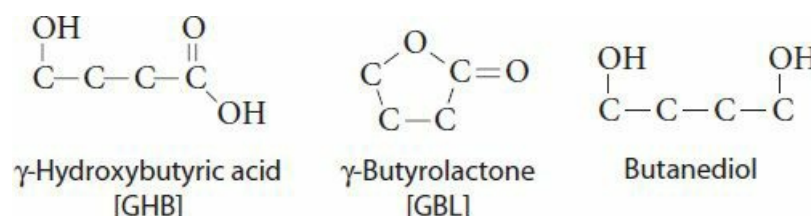
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83 γ -HYDROXYBUTYRIC ACID (γ -HYDROXYBUTYRATE)

Brenna M. Farmer



HISTORY AND EPIDEMIOLOGY

GHB was discovered in 1960 while searching for an analog for γ -aminobutyric acid (GABA).³¹ Due to its central nervous system (CNS) depressive and amnestic properties, GHB was initially used as an anesthetic adjunct, especially in Europe but never gained favor in the United States for this indication. Outside the United States, GHB is still used for anesthesia or as an adjunct sedative for therapeutic hypothermia and wound care in children.^{43,44,53} During the 1970s, an investigational new drug protocol was submitted to the US Food and Drug Administration (FDA) to test the use of GHB as a treatment for sleep disturbances. In the 1980s and 1990s, body builders popularized GHB as an anabolic dietary supplement due to its release of growth hormone. Its euphoric effects were recognized at this time, and it rapidly gained favor as a “club drug.” Because it can cause coma and profound amnesia, GHB has been used in drug-facilitated sexual assault, and in 1990 the FDA banned all use of nonprescription GHB due to this concern.⁶¹

Following the FDA ban, the analogs GBL and 1,4-BD were quickly substituted for GHB in dietary supplements. After the Samantha Reid and Hillory J. Farias Date-Rape Prevention Act of 1999 was passed in 2000, the US Drug Enforcement Agency (DEA) classified GHB and its analogs as Schedule I substances claiming that GHB was a hazard to public safety.⁶⁸ Also in 2000, a new drug application was submitted to the FDA for GHB—under the generic name sodium oxybate and the trade name Xyrem—to reduce the incidence of cataplexy and improve the symptoms of daytime sleepiness in patients with narcolepsy.²⁹ This latter indication was approved in 2002 and given a Schedule III designation by the DEA,²⁹ which was expanded in 2005 to include the treatment of excessive daytime sleepiness in patients with narcolepsy. It is now also used “off-label” for fibromyalgia, chronic fatigue syndrome, and depressive disorders.^{6,56,65} However, in 2010, the FDA declined to approve GHB for fibromyalgia.

In 2007, during an epidemic of toxicity from toy beads, marketed under the names Bindeez or Aquadots, 1,4-BD was identified in the sticky surface material that allowed the beads to reversibly adhere to one another. Multiple cases of toxicity were reported, largely in England and Australia.^{25,55}

National statistics demonstrated a trend of escalating GHB abuse and poisoning throughout the 1990s. However, a decline has occurred in exposures reported to poison control centers and the Drug Abuse Warning Network in recent years. In 2002, there were 1386 exposures with GHB and its analogs and precursors reported to the American Association of Poison Control Centers (AAPCC)—Toxic Exposure Surveillance System, representing more than a twofold increase from approximately 600 GHB cases reported in 1996. Among these, 1181 exposures (85%) required treatment in a health care facility and resulted in 272 major outcomes and three deaths (Chap. 136).⁷⁴ From the 2011 AAPCC NPDS report, 464 cases mentioned exposure to GHB, its analogs, and precursors. In 303 of those cases, GHB, its analogs, and precursors were the single xenobiotic of exposure. Of the reported cases, 224 were treated in a health care facility and 144 of those cases had moderate or major outcomes.⁸ The Drug Abuse Warning Network’s 2010 estimates revealed 1787 emergency department visits for GHB exposures, similar to the number of visits from 2004 to 2009, with a range of 1036 to 2207 visits to the emergency department.⁶⁶ A recent retrospective review of deaths related to GHB, GBL, and 1,4-BD showed that men in their 20s were more likely to die from GHB poisoning. Thirty-four percent of these deaths were due to GHB alone.⁷⁸

The apparent trend of decreased GHB exposures in the United States after 2000 contrasts with the increased use reported in some European countries and Australia.^{12,15,30} In Melbourne, Australia, a retrospective study showed a 4%

increase per month in the number of ambulance calls related to GHB and its analogs from March 2001 to October 2005.¹² In Spain, a study of 505 consecutive GHB-poisoned patients presenting to one hospital, from 2001 to 2007, revealed that these patients come to the hospital on the weekends, in the early morning hours, and will likely require more treatment if ethanol, amphetamines or their derivatives, and/or cocaine are concomitantly used.²¹

PHARMACOLOGY

GHB is both a precursor and degradation product of GABA.⁶³ It has a dual pharmacologic profile, with the neuropharmacology of endogenous GHB being distinct and divergent from that of exogenously administered GHB. The principal difference is that the activity of endogenous GHB appears to be mediated by the GHB receptor, whereas the activity of exogenously administered GHB is most likely mediated by intrinsic activity at the GABA_B receptor.

Endogeneous GHB

GHB is formed from GABA by the enzymes GABA transaminase and succinic semialdehyde reductase³⁹ (Fig. 83–1). GHB is also endogenously transformed from GBL by lactonases and from 1,4-BD by alcohol and aldehyde dehydrogenases. Endogenous GHB acts as a putative neurotransmitter and is found in highest concentrations in the hippocampus, basal ganglia, hypothalamus, striatum, and substantia nigra.^{39,41,72} It has subcellular systems for synthesis, vesicular uptake, and storage in presynaptic terminals. It is released in a Ca²⁺-dependent manner following depolarization of neurons.

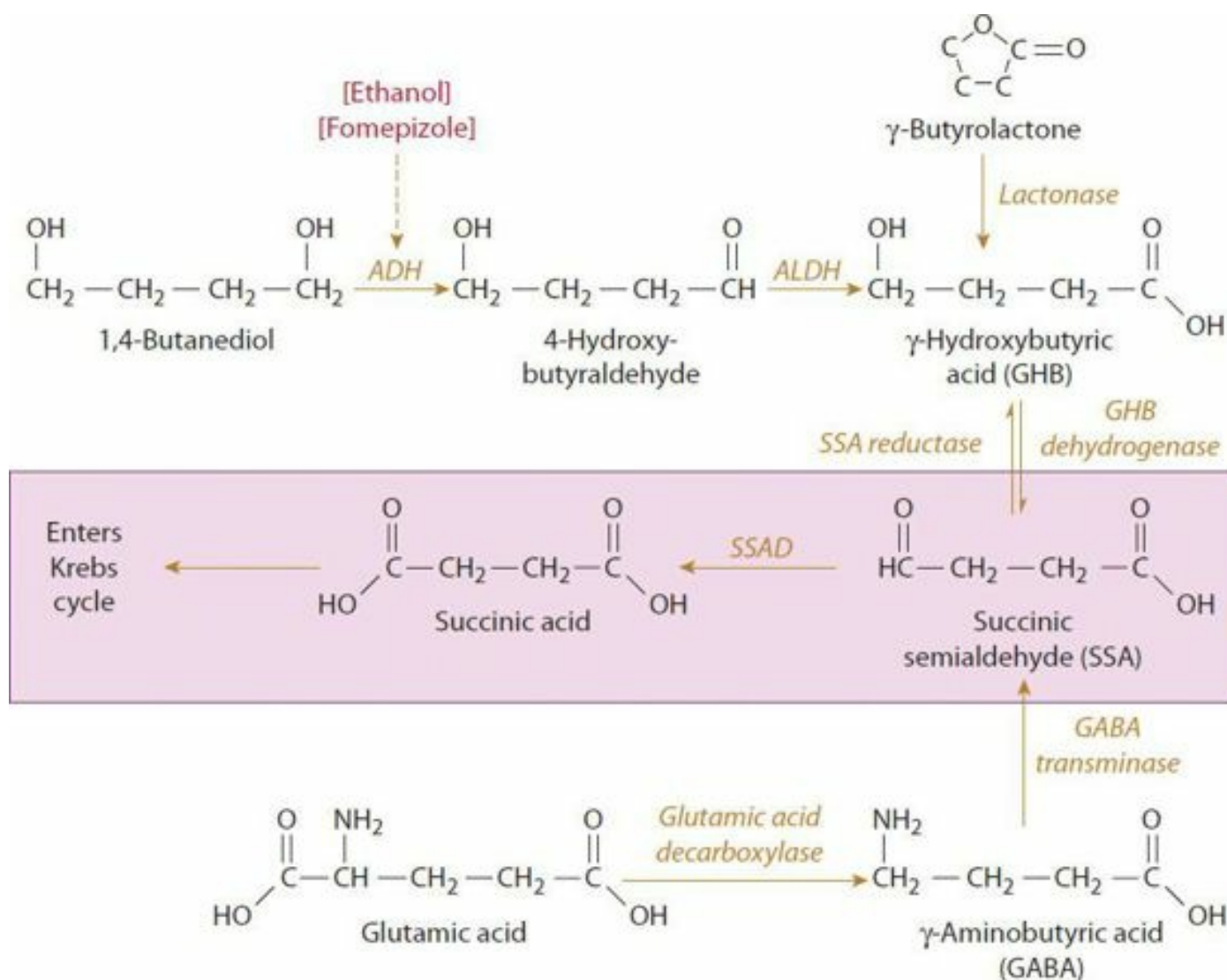


FIGURE 83–1. The synthesis and metabolism of γ -hydroxybutyric acid. ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase; SSA reductase = succinic semialdehyde reductase; SSAD = succinic semialdehyde dehydrogenase.

After release, GHB binds to GHB-specific receptors that modulate other neurotransmitter systems. Endogenous GHB acts predominantly on the GHB receptor, which is a G protein linked receptor located presynaptically.^{13,39,62} The GHB receptor is located in the synaptosomal membranes of neuronal cells most highly concentrated in the pons and hippocampus followed by the cerebral cortex and caudate. The GHB receptor has no affinity for typical GABA_A or GABA_B agonists such as GABA and baclofen, respectively. Localized application of GHB can produce a response that mimics the action of

endogenous GHB released by nerve stimulation.^{4,44} GHB receptors are highly associated with dopaminergic neurons and increase the concentration of dopamine by stimulating tyrosine hydroxylase to synthesize dopamine.^{39,64,69} GHB is also a neuromodulator of dopamine, acetylcholine, endogenous opioids, and glutamate.³⁹ It either increases (concentrations below 1 mM) or decreases (at higher concentrations) the release of dopamine throughout the mesolimbic system.¹¹ By contrast, GHB increases dopamine concentrations in the striatum and cortex in a dose-dependent manner by stimulating tyrosine hydroxylase to synthesize dopamine.^{39,40,64} GHB also increases the turnover of serotonin in the brain by stimulating both serotonin synthesis and breakdown.^{24,27} Furthermore, GHB decreases acetylcholine in the brainstem and corpus striatum, as well as in the hippocampus (via GABA_B receptors).^{45,64} GBL, but not GHB itself, increases total brain acetylcholine concentrations by decreasing firing of cholinergic neurons.^{23,32,58}

Through an unclear mechanism, GHB increases the release of growth hormone by promoting slow wave sleep without effecting total sleep time and GHB release is enhanced.^{71,73} Although GHB has no effect on total sleep time, it decreases latency to slow wave sleep while also decreasing the time spent in stages 1 and 2 of the sleep cycle.³³ GHB activity is terminated by active uptake from the synaptic cleft for metabolism by specific cytosolic and mitochondrial enzymes.

Exogenous GHB

Exogenous GHB, which produces supraphysiologic GHB concentrations, acts predominantly on the GABA_B receptor, which is found throughout the cerebral cortex, cerebellum, and thalamus.^{22,54,75} Presynaptically and postsynaptically, these receptors signal the adenylate cyclase system to activate calcium channels and G protein–coupled inwardly rectifying K⁺ channels.⁵ Through these GABA_B receptor signaling pathways, both dopamine and acetylcholine pathways are altered leading to decreased dopamine release and decreased acetylcholine concentrations.^{11,45} These effects of GHB are potentiated by baclofen, a GABA_B receptor agonist. Further discussion of these receptors and pathways is found in Chap. 14.

GHB ANALOGS

GBL, like GHB, exists in the mammalian brain.¹⁴ Its pharmacologic properties are only evident after conversion to its active metabolite, GHB. Like GBL, 1,4-BD occurs naturally in the brain and exerts its pharmacologic and toxicologic properties only when converted to GHB by alcohol dehydrogenase.⁵¹

Table 83–1 lists other GHB analogs known to result in similar toxicity and lists synonyms for GHB, GBL, and 1,4-BD that are often found on the labels of commercial and illicit products.

TABLE 83–1. Common Synonyms for GHB and Analogs					
GHB	GBL	1,4-BD	GHV	GVL	THF
γ-Hydroxybutyrate	γ-Butyrolactone	1,4-Butanediol	γ-Hydroxyvaleric Acid	γ-Valerolactone	Tetrahydrofuran
γ-Hydroxybutyric acid	2(3H)-Furanone dihydro	1,4-Butylene glycol	γ-Methyl-GHB	4-Hydroxypentanoic acid lactone	No other synonyms
4-Hydroxybutyric acid	Butyrolactone	1,4-Dihydroxybutane		4,5-Dihydro-5-methyl-2(3H)-furanone	
sodium salt	4-Butyrolactone	1,4-Tetramethylene glycol		γ-Methyl-GHB	
γ-Hydroxybutyric acid	Dihydro-2(3H)-Furanone				
Sodium salt	2(3H)-Furanone				
Sodium oxybate	Tetrahydro-2-furanone				
Sodium 4-hydroxybutyrate	4-Deoxtetronic acid				
4-Hydroxybutanoic acid	Butyryl lactone				
	Butyric acid lactone				
	Butyrolactone-γ				
	4-Hydroxybutyric acid lactone				
	γ-Hydroxybutyric acid lactone				
	4-Butanolide				
	1,4-Butanolide				
	1,4-Lactone				

PHARMACOKINETICS AND TOXICOKINETICS

The endogenous production and metabolism of GHB are both shown in Fig. 83–1. Exogenous GHB is typically ingested in its sodium salt form. Oral bioavailability of exogenous GHB is approximately 60% in rats.^{34,35} It is rapidly absorbed from the gastrointestinal tract in 15 to 45 minutes and displays two-compartment distribution in animals with an initial volume of distribution of 0.4 L/kg and final volume of distribution 0.6 L/kg.^{16,34–36} It is lipid soluble and crosses the blood–brain barrier rapidly. It does not bind significantly to any plasma proteins.⁴⁷ GHB is metabolized mainly by succinic semialdehyde reductase (also known as GHB dehydrogenase) to succinic semialdehyde, which is subsequently metabolized to succinate and enters the Krebs cycle (Fig. 83–1). GHB is also metabolized directly to succinate via β oxidation in the liver.⁴⁹ GHB is subject to first-pass metabolism by the cytochrome P450 system; however, the specific isozyme is not known.³⁴ In adult volunteers, the elimination half-life is 20 to 53 minutes. Less than 5% of GHB is excreted unchanged in the urine.⁴⁷

GBL undergoes conversion to GHB by a lactonase.^{51,52} In comparison with GHB, GBL is more rapidly absorbed from the gastrointestinal tract and has a longer duration of action, both of which result from higher lipid solubility. 1,4-BD exerts its effects after conversion to GHB by alcohol dehydrogenase (ADH).^{9,50} Therefore, coingestion with ethanol can prolong the onset of clinical effects because of competitive inhibition of ADH.^{46,57}

In patients with HIV taking protease inhibitors, GHB first-pass metabolism is altered such that low doses of GHB can produce toxic manifestations. This results from the interactions of the protease inhibitors on the cytochrome P450 system.^{1,26}

CLINICAL MANIFESTATIONS

The clinical manifestations of GHB are mainly due to its effects on the CNS. Initial clinical effects of ingested GHB occur in 15 to 20 minutes and peak in 30 to 60 minutes.⁷ The clinical manifestations of GHB follow a steep dose–response curve. Doses of 20 to 30 mg/kg create euphoria, memory loss, and drowsiness, while doses of 40 to 60 mg/kg result in coma.^{19,41} Doses of 25 mg/kg given to naïve healthy volunteers result in mean serum GHB concentrations of 39.4 ± 25.2 $\mu\text{g/mL}$ (range, 4.7–76.3 $\mu\text{g/mL}$).⁷ Vital sign changes include bradycardia, hypotension, bradypnea, and hypothermia. Pupils may be miotic and poorly responsive to light. Acute toxicity typically results in CNS depression/coma, respiratory depression, salivation, vomiting, and sometimes myoclonus.^{16,38} Of these findings, the most concerning is respiratory depression, as apnea and death may ensue.^{10,37,77} Salivation and vomiting can complicate the respiratory depression leading to pulmonary aspiration in patients with a depressed level of consciousness. Case series also report aggressive and combative behavior, which may be exacerbated when assessing the airway and initiating endotracheal intubation in those patients with compromised consciousness.^{16,76} Motor manifestations can be confusing. Although GHB induces seizures (EEG changes and convulsions) in animal models, this has never been demonstrated in humans. More commonly, in humans GHB induces myoclonus that can be confused with seizures.¹⁸

Other findings reported in patients taking prescribed therapeutic doses for narcolepsy include confusion, abnormal thought processes, and depression.²⁹ The most common adverse effects reported in these patients using prescribed GHB include nausea, dizziness, headache, vomiting, and urinary incontinence.²⁹

Recovery from overdose occurs rapidly, typically in less than 6 to 8 hours, and patients often extubate themselves following rapid improvement of their level of consciousness. No sequelae should be expected if hypoxia or aspiration did not occur.

Frequent GHB users can develop both tolerance and dependence to GHB.^{20,61} Such patients typically use GHB or one of its analogs every 2 to 4 hours over a prolonged period of time, with cumulative daily doses in the range of 10 g or more.⁴² In rats receiving doses of GHB every 3 hours for up to 6 days tolerance was observed.² In patients with dependence, withdrawal symptoms can occur.

DIAGNOSTIC TESTING

Routine “screens” for drugs of abuse do not typically include analysis for GHB. Specific testing for GHB and its related analogs usually is not requested unless there is suspicion of its use associated with drug-facilitated sexual assault. However, urine and serum testing can also be performed if needed for forensic purposes. Gas chromatography–mass spectrometry is the test of choice for both urine and serum. GHB can be detected in the urine up to 12 hours after use.⁷ Interpretation of these tests must include cutoff concentrations as GHB, GBL, and 1,4-BD also occur naturally. These cutoff concentrations must be able to distinguish endogenous production and therapeutic use (as in patients using prescribed GHB for narcolepsy) from abuse or misuse. However, attempts to correlate concentrations with clinical effects in any individual may not be valid when used chronically and when tolerance develops. Due to rapid metabolism and elimination,

concentrations return to baseline shortly after drug naïve patients become clinically normal. Urinary concentrations of endogenous GHB are usually less than 5 to 10 µg/mL, while serum concentrations of endogenous GHB are usually less than 5 µg/mL.⁷ In patients receiving a 25 mg/kg dose of GHB, serum GHB concentrations ranged from 4.7 to 76.3 µg/mL 20 to 45 minutes after administration and urine concentrations from below the detection limit to 840 µg/mL. In general, loss of consciousness occurs when serum concentrations reach 50 µg/mL, and deep coma occurs when concentrations rise above 260 µg/mL.⁵⁹

Screening for GHB may also routinely be performed when specific genetic or metabolic disorders are of concern. In particular, elevated GHB concentrations on a urinary organic acid screen in a child may indicate a succinic semialdehyde dehydrogenase deficiency. These children have developmental delay, seizures, hypotonia, and elevated GHB concentrations in the blood, urine, and cerebrospinal fluid.⁴⁸ One case report describes a child with a serum GHB concentration of 775 µg/mL, significantly higher than most patients with exogenous GHB poisoning.²⁸

Other routine tests in patients with depressed levels of consciousness include a rapid evaluation of blood glucose, an ethanol concentration as clinically indicated, and electrocardiography. Electrocardiographic findings may include sinus bradycardia and prominent U waves, which may be related to the sinus bradycardia. Other standard laboratory tests are typically normal.¹⁰ When intentional overdose or self-harm is suspected, a determination of serum acetaminophen concentration is also indicated. Other studies should be obtained based on the clinical condition of the patient.

MANAGEMENT

Supportive care is the mainstay of therapy for patients with GHB toxicity. All patients presenting to the hospital should have their airway, breathing, and circulation assessed immediately. Patients with GHB toxicity may require airway protection in the presence of profound coma and respiratory depression or apnea. However, many become combative during the intubation process. Supportive care with a nasal airway may suffice in the snoring patient who has an appropriate gag and respiratory function. The need for endotracheal intubation is a bedside clinical decision and should be based on the ability of the patient to oxygenate and ventilate, especially when the diagnosis is known or highly suspected as recovery is expected shortly. Atropine may be given as needed for severe bradycardia. However, in most instances, the bradycardia will not necessitate treatment in otherwise healthy patients. An intravenous catheter should be established and intravenous fluids infused as necessary for hypotension. Patients should be warmed if they are hypothermic.

There is no role for gastric decontamination in patients with GHB toxicity as GHB is rapidly absorbed from the gastrointestinal tract. The increased risk of vomiting and aspiration also limits any beneficial role of gastric decontamination. If a coingestant is present, then appropriate decontamination methods may be employed if there are no contraindications to their use.

Other therapies such as dextrose and thiamine should be administered as clinically indicated. Some proposed antidotes include physostigmine, naloxone, and flumazenil. All these antidotes lack a pharmacologic basis for use and may place the patient at increased risk as other drugs of abuse commonly used with GHB may interact with these xenobiotics. An animal model did not support the use of physostigmine in GHB toxicity,³ nor did a systematic literature review.⁷⁰ Naloxone can be administered to the patient with respiratory and CNS depression in the setting of unknown or presumed overdose. In GHB toxic patients, naloxone administration is largely unsuccessful at improving clinical status.³⁷

Those patients whose symptoms resolve may be discharged from the hospital following appropriate psychosocial evaluation for abuse and dependency. All patients who do not follow the expected course of resolution of their clinical manifestations (approximately 6 hours) should be admitted to the hospital and investigated for other potential etiologies.

GHB WITHDRAWAL

Patients who use GHB or its analogs daily in large quantities can develop tolerance and dependence.²⁰ Such patients are prone to withdrawal if they abruptly cease or decrease their daily dose. In patients prescribed GHB for narcolepsy, withdrawal rarely develops when the GHB is used as prescribed as the recommended doses are low and given only at night.^{29,67} Most patients with GHB withdrawal are body builders.

GHB withdrawal is similar to ethanol and benzodiazepine withdrawal ([Chap. 15](#)). It can be severe and potentially life threatening. The onset of withdrawal typically occurs 1 to 6 hours after last use. Men appear to be more commonly affected than women.⁴² Manifestations of withdrawal include tachycardia, hypertension, tremors, agitation, dysphoria, nausea, vomiting, auditory and visual hallucinations, and seizures.^{17,20,42,67}

For acute withdrawal symptoms, benzodiazepines and supportive care are the mainstays of therapy.^{42,67} Rapid cooling, intravenous fluids, and evaluation for other medical or traumatic illnesses should be performed. These patients may require large doses of benzodiazepines to control symptoms. In patients with withdrawal symptoms refractory to benzodiazepines, barbiturates and propofol can be considered.^{42,60,67} Baclofen, a GABA_B receptor agonist, is also a reasonable

consideration in severe GHB withdrawal, although research must be done to determine appropriate dosing and escalation of dosing. In these refractory patients, endotracheal intubation may be required ([Chap. 15](#)).

SUMMARY

- GHB is a unique xenobiotic because it occurs naturally as an endogenous neurotransmitter, it is a licensed pharmaceutical, and it is a drug of abuse.
- GHB, GBL, and 1,4-BD result in GHB toxicity through complex neuropharmacologic effects to rapidly produce CNS and respiratory depression that is characteristically of short duration.
- GHB toxicity rarely results in death when patients are treated with supportive care.
- A life threatening withdrawal syndrome can occur with cessation or decreased use of the drug and its related analogs. This withdrawal syndrome should be treated in a manner similar to ethanol withdrawal or sedative-hypnotic withdrawal.
- With appropriate care of both acute intoxication and withdrawal, patients can recover without sequelae, but psychosocial care and referral for management of abuse or dependency are essential.

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84 INHALANTS

Heather Long

HISTORY AND EPIDEMIOLOGY

Inhalant abuse is defined as the deliberate inhalation of vapors for the purpose of changing consciousness or becoming “high.” It is also referred to as volatile substance abuse and was first described in medical literature in 1951.³⁷ Inhalants are appealing to adolescents because they are inexpensive, readily available, and sold legally. Initially, inhalant abuse was viewed as physically harmless, but reports of “sudden sniffing death” began to appear in the 1960s.¹¹ Shortly thereafter, evidence surfaced of other significant morbidities, including organic brain syndromes, peripheral neuropathy, and withdrawal.

The demographics of inhalant abuse differ markedly from those of other traditional substances of abuse. According to the 2011 National Survey on Drug Use and Health, inhalants continued to be the most frequently reported illicit xenobiotics used by 12 and 13 year-olds. The age at initiation of illicit drug use is youngest for those choosing inhalants, and the reported usage of inhalants peaked at age 14.¹⁴⁰ A worrisome trend reported by the 2011 Monitoring the Future study is that although the perceived risk of even one-time use of an inhalant has fallen steadily since 2001, and a study of 279 youths who were lifetime inhalant users found 37% perceived experimental inhalant use of slight or no risk.^{100,116}

In the United States, the problem is greatest among children of lower socioeconomic groups. Non-Hispanic white adolescents are the most likely and black adolescents the least likely to use inhalants.^{14,96} Although inhalant use is a problem in both urban and rural communities, it is more prevalent in rural settings.^{96,134} This may relate to the easier access that teens in urban areas have to other drugs of abuse.

Inhalant abuse includes the practices of sniffing, huffing, and bagging. Sniffing entails the inhalation of a volatile substance directly from a container, as occurs with modeling glue or rubber cement. Huffing involves pouring a volatile liquid onto fabric, such as a rag or sock, and placing it over the mouth, nose, or both while inhaling and is the method used by more than 60% of volatile-substance abusers.⁹⁶ Bagging refers to instilling a solvent into a plastic or paper bag and rebreathing from the bag several times; spray paint is among the xenobiotics commonly used with this method.

XENOBIOTICS COMMONLY USED

There are myriad xenobiotics abused as inhalants (Table 84–1), most of which are volatile hydrocarbons. Hydrocarbons are organic compounds comprised of carbon and hydrogen atoms and are divided into two basic categories: aliphatic (straight, branched, or cyclic chains) and aromatic. Most of the commercially available hydrocarbon products are mixtures of hydrocarbons; for example, gasoline is a mixture of aliphatic and aromatic hydrocarbons that may consist of more than 1500 compounds. Substituted hydrocarbons contain halogens or other functional groups such as hydroxyl or nitrite that are substituted for hydrogen atoms in the parent structure. Solvents are themselves a heterogeneous group of xenobiotics that are used to dissolve other chemical compounds or provide a vehicle for their delivery.

TABLE 84–1. Common Inhalants and the Constituent Xenobiotics

<i>Inhalant</i>	<i>Chemical</i>
Glues/adhesives	Toluene, <i>n</i> -hexane, benzene, xylene, trichloroethane, trichloroethylene, tetrachloroethylene, ethyl acetate, methylethyl ketone, methyl chloride
Spray paint	Toluene, butane, propane
Computer keyboard duster	Difluoroethane, tetrafluoroethane
Hair spray, deodorants, air fresheners	Butane, propane, fluorocarbons
Cigarette lighter fluid	Butane
Paint thinner	Toluene, methylene chloride, methanol
Gasoline	Aliphatic and aromatic hydrocarbons
Carburetor cleaner	Methanol, methylene chloride, toluene, propane
Dry cleaning agents, spot removers, degreasing agents	Tetrachloroethylene, trichloroethane, trichloroethylene
Typewriter correction fluid	Trichloroethane, trichloroethylene
Nail polish remover	Acetone
Paints, lacquers, varnishes	Trichloroethylene, toluene, <i>n</i> -hexane
"Poppers"	Amyl nitrite, isobutyl nitrite
Room deodorizers	Butyl nitrite, isobutyl nitrite, cyclohexyl nitrite
Whipped cream dispensers, "whippits"	Nitrous oxide

The most commonly inhaled volatile hydrocarbons are fuels, such as gasoline, and solvents, such as toluene.¹³⁴ Other commonly inhaled hydrocarbon-containing products include spray paints, lighter fluid, air fresheners, and glue. In most reported cases of inhalant use, the inhalant is identified not by its chemical name (eg, butane and toluene) but rather by its intended use (eg, lighter fluid and paint thinner). Because exact components may vary between products, identification by the intended commercial use of the product is inaccurate and imprecise. The choice of xenobiotic used likely reflects their availability: cases from the 1970s frequently reported abuse of antiperspirants and typewriter correction fluid; computer and electronics cleaners have replaced these products. Dusting refers to the inhalation of compressed air cleaners containing halogenated hydrocarbons (eg, CRC Dust Off), marketed for cleaning computer keyboards and electronics equipment. Reports of exposures to these products, including death and ventricular dysrhythmias, doubled in 2005 and tripled in 2006.⁹⁵ Of the 30 deaths attributed to recreational inhalant use in North Carolina between 2000 and 2008, one-third involved compressed-air products; yet, dusting is not perceived to be harmful by users and, surprisingly, many users do not consider it a form of inhalant abuse.^{64,95}

Although volatile alkyl nitrites are technically substituted hydrocarbons, they have pharmacologic and behavioral effects, as well as patterns of abuse, distinct from the other volatile hydrocarbons. For this reason, researchers usually classify them as a separate category among abused inhalants. Amyl nitrite is the prototypical volatile alkyl nitrite.⁹ Amyl nitrite became popular in the 1960s with the appearance of "poppers," small glass capsules containing the chemical in a plastic sheath or gauze. When crushed, the ampules release the amyl nitrite. When nonprescription sales of amyl nitrite were restricted in 1968, sex and drug paraphernalia shops began selling small vials of butyl and isobutyl nitrites marketed as room deodorizers or liquid incense.^{9,91} Because of further restrictions on sales of alkyl nitrites, most of these products now contain chemicals not technically alkyl nitrites, such as cyclohexyl nitrite.⁹

The most commonly used non-hydrocarbon inhalant is nitrous oxide. Nitrous oxide, or "laughing gas," is used medically as an inhalational anesthetic (Chap. 68). It is the propellant in supermarket-bought whipped cream canisters, and cartridges of the compressed gas are sold for home use in whipped cream dispensers. These battery-sized metal containers of compressed gas may be used as "whippits," in which the container is punctured using a device known as a "cracker," and the escaping gas is either inhaled directly or collected in a balloon and then rebreathed.

PHARMACOLOGY

Although chemically heterogeneous, inhalants are generally highly lipophilic and gain rapid entrance into the central nervous system (CNS). Little is known about the cellular basis of the effects of inhalants. Evidence to date shows that the most commonly abused hydrocarbons have molecular mechanisms similar to those of other classic CNS depressants, frequently with common cellular sites of action. Their effects are probably best represented by the model for ethanol in which multiple different cellular mechanisms explain diverse pharmacologic and toxicologic effects.⁹

Volatile Hydrocarbons

The clinical effects of the volatile hydrocarbons are likely mediated through stimulation of inhibitory neurotransmission and antagonism of excitatory neurotransmission within the CNS. Like ethanol, toluene, trichloroethane (TCE), and trichloroethylene enhance γ -aminobutyric acid type A (GABA_A) receptor-mediated synaptic currents as well as glycine-receptor-activated ion function. Stimulation of these receptors acts to increase chloride permeability, hyperpolarizing the neuronal cell membrane and inhibiting excitability.^{16,70,136} Like inhaled anesthetics, these abused inhalants appear to act presynaptically on the GABA_A nerve terminals. Toluene-induced increase in inhibitory synaptic current is blocked by dantrolene and ryanodine, suggesting toluene effects release of calcium from intracellular nerve terminal stores.⁹⁰ Despite very different molecular structures, ethanol, enflurane, chloroform, toluene, and TCE compete for binding sites at α_1 glycine receptors.¹⁵ Like ethanol and subanesthetic concentrations of isoflurane, toluene, TCE, and benzene all interfere with glutamate-mediated excitatory neurotransmission by inhibiting N-methyl-D-aspartate (NMDA) receptor-mediated currents in a concentration dependent manner.^{8,39,118,129} Furthermore, repeated toluene exposure increases NMDA receptors, suggesting that chronic exposure can lead to upregulation of excitatory neurotransmission as occurs with ethanol.^{8,157}

Toluene is the prototypical volatile hydrocarbon and the best studied. In animal models, differences in pharmacologic action are demonstrated between toluene and other alkylbenzenes, and halogenated hydrocarbons such as TCE, and acetone.^{22,39,85,130,144} These differences may represent evidence that specific cellular sites for their actions exist. In addition, these differences may explain the variation in their abuse potential or their clinical effects.^{9,85} Despite these distinctions, there are marked similarities in the behavioral and pharmacologic effects of the volatile hydrocarbons. Moreover, the clinical effect profile shared by the volatile hydrocarbons, subanesthetic concentrations of general anesthetics, ethanol, and benzodiazepines suggests that they share cellular mechanisms. Shared clinical effects include anxiolysis,²⁷ anticonvulsant effects,¹⁵⁹ impaired motor coordination,¹⁰³ and evidence of physical dependence on withdrawal.^{47,48}

Most research on inhalants has focused on the neural basis of their effects, yet it is the cardiotoxicity that is responsible for the majority of their lethal effects. In vivo, toluene reversibly inhibits myocardial voltage-activated sodium channels.⁴⁰ Similarly, it inhibits muscle sodium channels but with less potency.⁵⁵ Ethanol and toluene have opposite effects on potassium channels in vivo; ethanol potentiates the large conductance, calcium-activated potassium channels as well as certain G protein-coupled inwardly rectifying potassium channels, while toluene inhibits them.⁴² The combined inhibition of the sodium channels and the inwardly rectifying potassium channels is postulated to play a role in cardiac dysrhythmias and sudden sniffing death associated with the aromatic and halogenated hydrocarbons. Animal studies show toluene and 1,1,1-trichloroethane produce biphasic dose-response curves for motor activity: low concentrations yield motor excitation, while high concentrations produce sedation, motor impairment, and anesthesia.^{23,152} Molecular mechanisms underlying both the neural and cardiac effects may maximize the risk effects and explain the observed clinical phenomenon described in sudden sniffing deaths (see below).

Scant data exist on the pharmacokinetics of the inhalants. Most data are derived from studies on occupational and environmental exposures and have limited applicability to intentional inhalation. More relevant to the understanding of inhalants are the similarities with the inhalational anesthetics, many of which are also halogenated hydrocarbons. Factors determining pharmacokinetic and pharmacodynamic effects of a given inhalational anesthetic include its concentration in inspired air; partition coefficient; interaction with other inhaled substances, ethanol, and drugs; the patient's respiratory rate and blood flow; percent body fat; and individual variation in drug metabolism (Chap. 68).⁵⁹

Partition coefficients measure the relative affinity of a gas for two different substances at equilibrium and are used to predict the rate and extent of uptake of an inhaled substance. The blood:gas partition coefficient is most commonly referenced. The higher the number, the more soluble the substance is in blood. Substances with a low blood:gas partition coefficient, like nitrous oxide, are rapidly taken up by the brain and, conversely, are rapidly eliminated from the brain once exposure is ended (Table 84-2).

TABLE 84-2. Blood:Gas Partition Coefficients, Routes of Elimination, and Important Metabolites of Selected Inhalants

<i>Xenobiotic</i>	<i>Blood:Gas Partition Coefficient (98.6°F (37°C))</i>	<i>Routes of Elimination</i>	<i>Important Metabolites</i>
Acetone	243–300	Largely unchanged via exhalation 95% and urine 5%	None
n-Butane	0.019	Largely unchanged via exhalation	None
Carbon tetrachloride	1.6	50% unchanged via exhalation; 50% hepatic metabolism and urinary excretion	CYP2E1 to trichloromethyl radical, trichloromethyl peroxy radical, phosgene
n-Hexane	2	10%–20% exhaled unchanged; hepatic metabolism and urinary excretion	CYP2E1 to 2-hexanol, 2,5-hexanedione, γ -valerolactone
Methylene chloride	5–10	92% exhaled unchanged; hepatic metabolism and urinary excretion	1. CYP2E1 to CO and CO ₂ 2. Glutathione transferase to CO ₂ , formaldehyde, and formic acid
Nitrous oxide	0.47	> 99% exhaled unchanged	None
Toluene	8–16	< 20% exhaled unchanged; > 80% hepatic metabolism and urinary excretion	CYP2E1 to benzoic acid, then 1. Glycine conjugation to form hippuric acid (68%) 2. Glucuronic acid conjugation to benzoyl glucuronide (insignificant pathway except following large exposure)
1,1,1-Trichloroethane	1–3	91% exhaled unchanged; hepatic metabolism and urinary excretion	CYP2E1 to trichloroethanol, then 1. Conjugated with glucuronic acid (urochloralic acid) or 2. Further oxidized to trichloroacetic acid
Trichloroethylene	9	16% exhaled unchanged; 84% hepatic metabolism and urinary excretion	CYP2E1 to epoxide intermediate (transient); chloral hydrate (transient); trichloroethanol (45%), trichloroacetic acid (32%). Urinary trichloroacetic acid peaks 2–3 days postexposure
1,2-Dichloro-1,1-difluoroethane	NA	NA	CYP2E1 to 2-chloro-2,2-difluoroethyl glucuronide, 2-chloro-2,2-difluoroethyl sulfate, chlorodifluoroacetic acid, chlorodifluoroacetaldehyde hydrate, chlorodifluoroacetaldehyde-urea adduct, and inorganic fluoride. No covalently bound metabolites to liver proteins.

In a rodent model of inhalation abuse of toluene and acetone, the rapidity of onset and the extent of CNS depression were dependent on the concentration of the solvent inhaled.³⁰ There was a parallel relationship between brain concentration and pharmacologic effect during induction (inhalation) and postexposure. Brain and liver concentrations dropped rapidly after exposure; concentration in blood decreased at the slowest rate. Elimination was biphasic: rapid elimination during the first step was a result of tissue redistribution, alveolar ventilation, and metabolic clearance. During the second phase, there was a slow decrease in tissue concentrations as a result of the gradual mobilization from adipose tissue with subsequent exhalation or metabolism. Acetone, which is more water soluble than toluene, is less potent and slower acting than toluene, but is eliminated much more slowly than toluene and has a much longer duration of action.³⁰ Positron emission tomography (PET) studies using (¹¹C) radiolabeled toluene, butane, and acetone in nonhuman primates showed rapid uptake of radioactivity in striatal and frontal regions of the cortex followed by rapid clearance from the brain.⁵⁶ Whole-body PET scans in mice showed excretion through the kidneys and liver.⁵⁷

The inhalants are eliminated unchanged by the lungs, they undergo hepatic metabolism, or both (Table 84–2). For some, the percentage that is metabolized versus eliminated unchanged varies with the exposure dose. Nitrous oxide and the aliphatic hydrocarbons are frequently eliminated unchanged in the expired air. The aromatic and halogenated hydrocarbons are metabolized extensively via the cytochrome P450 (CYP) system, particularly CYP2E1, which has a substrate spectrum that includes a number of aliphatic, aromatic, and halogenated hydrocarbons.^{20,65,66,160} Extrahepatic expression of CYP2E1 occurs to a lesser extent but may be of toxicologic significance, particularly in the kidneys and the dopaminergic cells of the substantia nigra.^{21,71,148} In humans, there appears to be no significant gender difference in CYP2E1 activity; however, it is polymorphic and, as such, allelic distributions vary among different human populations.^{21,132} Moreover, this polymorphism may explain the varying degrees of toxicity exhibited following inhalant abuse.

Reward and reinforcement effects of inhalants are readily demonstrated. While the mechanisms underlying their reinforcement behavior remain poorly studied, activation of the mesolimbic dopamine system is thought to play an important role in solvent abuse, similar to more commonly studied drugs of abuse.^{57,121} Interestingly, the reward and

reinforcement effects of toluene appear to vary with age of exposure, suggesting that physiologic as well as psychosocial factors play a role in the prevalence of inhalant abuse among adolescents compared with adults.^{12,25,109} Furthermore, age at exposure differentially affects dendritic growth in the brain suggesting that the adolescent brain is more at risk for cognitive impairment following inhalant use.¹¹¹

Volatile Alkyl Nitrites

Unlike other volatile hydrocarbons, the volatile alkyl nitrites do not have any demonstrable direct effects on the CNS. Their effects are mediated through smooth muscle relaxation in the central and peripheral vasculature, and they share a common cellular pathway with other nitric oxide (NO) donors similar to nitroglycerin and sodium nitroprusside.⁷⁹ A rat model of inhalation of isobutyl nitrite found a half-life of 1.4 minutes with almost 100% biotransformation to isobutyl alcohol. Bioavailability following inhalation was estimated to be 43%.⁷⁸

Nitrous Oxide

The pharmacokinetics and pharmacodynamics of nitrous oxide (N₂O) abuse are derived from its use as an inhalational anesthetic. Anesthetic uptake or induction, as well as emergence with N₂O, is rapid because of its low solubility in blood, muscle, and fat.¹³⁷ No appreciable metabolism of N₂O is present in human tissue. An animal study found N₂O significantly inhibited excitatory NMDA-activated currents and had no effect on GABA-activated currents.⁷² N₂O also stimulates dopaminergic neurons, but the significance of this in mediating its anesthetic effects remains unclear.^{76,104}

Animal studies suggest the analgesic effects (or more accurately the antinociceptive effects because it refers to animals) of N₂O appear to be mediated through opioid peptide release in the midbrain. These antinociceptive effects can be reversed by the opioid antagonist naloxone.¹⁸ However, in humans the anesthetic effects are not attenuated by naloxone, and the subjective and psychomotor effects of N₂O are not extinguished by even high doses of naloxone.^{133,161}

CLINICAL MANIFESTATIONS

Signs and symptoms of inhalant use may be subtle, tend to vary widely among individuals, and generally resolve within several hours of exposure. Following acute exposure, there may be a distinct odor of the abused inhalant on the patient's breath or clothing. Depending on the inhalant used and the method, there may be discoloration of skin around the nose and mouth. Mucous membrane irritation may cause sneezing, coughing, and tearing. Patients may complain of dyspnea and palpitations. Gastrointestinal complaints include nausea, vomiting, and abdominal pain. After an initial period of euphoria, patients may have residual headache and dizziness.

Volatile Hydrocarbons

The CNS is the intended target of the inhalants and is most susceptible to its adverse effects. Initial CNS effects include euphoria and hallucinations, both visual and auditory, as well as headache and dizziness. As toxicity progresses, CNS depression worsens and patients may develop slurred speech, confusion, tremor, and weakness. Transient cranial nerve palsies are reported.¹⁴² Further CNS depression is marked by ataxia, lethargy, seizures, coma, and respiratory depression. These acute encephalopathic effects generally resolve spontaneously and associated neuroimaging abnormalities are not reported.⁵⁰

As can be expected, given the high lipophilicity of most inhalants, toxicity from chronic use is manifested most strikingly in the CNS. Toluene leukoencephalopathy, characterized by dementia, ataxia, eye movement disorders, and anosmia, is the prototypical manifestation of chronic inhalant neurotoxicity. Patients with toluene leukoencephalopathy display characteristic neurobehavioral deficits reflecting white matter involvement, including inattention, apathy, impaired memory, and visuospatial skills, with relative preservation of language.⁵⁰ Autopsy studies reveal white-matter degeneration including cerebral and cerebellar atrophy and thinning of the corpus callosum.^{2,80,122} On microscopy, there is diffuse demyelination with relative sparing of the axons. Abundant perivascular macrophages containing coarse or laminar myelin debris found in areas of the greatest myelin loss is a characteristic pathologic feature.^{2,50} This targeting of myelin, which is 70% lipid, may be explained by the lipophilicity of toluene.⁵⁰ As myelination continues at least through the second decade of life, the typical toluene abuser who begins inhaling during adolescence may be particularly susceptible to its toxic CNS effects.⁴⁹ Advances in magnetic resonance imaging (MRI) with gadolinium, which allow enhanced visualization of the cerebral white matter, demonstrate that the extent of white matter injury in the brain directly corresponds to the clinical severity of toluene leukoencephalopathy.⁵⁰ It is postulated that reactive oxygen species generated either by toluene or its metabolite benzaldehyde induce lipid peroxidation in the brain.^{93,120} Genetic polymorphisms and host susceptibility among chronic abusers are also hypothesized to play a role.⁶¹

Acute cardiotoxicity associated with hydrocarbon inhalation is manifested most dramatically in “sudden sniffing death.” In witnessed cases, sudden death frequently occurred when sniffing was followed by some physical activity. Examples include running or wrestling or a stressful situation like being caught sniffing by parents or police.¹¹ It is thought that the inhalant “sensitizes the myocardium” by blocking the potassium current (I_{KR}), thereby prolonging repolarization.¹⁰⁶ This produces a substrate for dysrhythmia propagation; the activity or stress then causes a catecholamine surge that initiates the dysrhythmia (Chap. 16).¹⁰⁶ Cardiac dysrhythmias following the inhalation of hydrocarbons were documented with the halogenated inhalational anesthetics in the early 1900s, and this association was subsequently confirmed in both animal and human studies.^{51,143}

More typically, the clinical presentation of a patient with hydrocarbon cardiotoxicity may include palpitations, shortness of breath, syncope, and abnormalities on electrocardiography, including atrial fibrillation, premature ventricular contractions, QT interval prolongation, and U waves.

Multiple case reports of ventricular fibrillation follow intentional inhalation of other hydrocarbons such as butane fuel,^{63,156} fluorinated hydrocarbons, and Glade Air Freshener (SC Johnson), which contains a mixture of short-chain aliphatic hydrocarbons.⁸⁷ Among 44 patients with a history of inhalant abuse, specifically toluene exposure, the QT interval and corrected QT dispersion were significantly greater than in healthy controls. Furthermore, the QT interval and corrected QT dispersion were significantly greater in the 20 toluene abusers with a history of unexplained syncope than in asymptomatic abusers and controls.³ Although cardiotoxic effects of inhalant abuse are generally acute, dilated cardiomyopathy is reported with chronic abuse of toluene and trichloroethylene.^{97,158} Microscopy reveals evidence of chronic myocarditis with fibrosis.¹⁵⁸

The most significant respiratory complication of inhalational abuse is hypoxia, which is either caused by displacement of inspired oxygen with the inhalant, reducing the fraction of inspired oxygen (FiO_2), or by rebreathing of exhaled air, as occurs with bagging. Direct pulmonary toxicity associated with inhalants is most often a result of inadvertent aspiration of a liquid hydrocarbon (Chap. 108). Aspiration injury is associated with the acute respiratory distress syndrome, a continuum of lung injury characterized by increased permeability of the alveolar–capillary barrier and the resulting influx of edema into the alveoli, neutrophilic inflammation, and an imbalance of cytokines and other inflammatory mediators.¹⁵¹ Reports of asphyxiation initially ascribed to inhalant abuse were later found caused by suffocation by a plastic bag, mask, or container pressed firmly to the face, and not specifically by toxicity of the inhaled vapor.^{11,34,150}

Irritant effects on the respiratory system are frequently transient, but patients may develop chemical pneumonitis. This syndrome is characterized by tachypnea, fever, tachycardia, crackles, rhonchi, leukocytosis, and radiographic abnormalities, including perihilar densities, bronchovascular markings, increased interstitial markings, infiltrates, and consolidation. Acute eosinophilic pneumonia following abuse of a fabric protector containing 1,1,1-trichloroethane is also reported.⁷⁷ Barotrauma, from deep inhalation or breath holding, presents as pneumothorax, pneumomediastinum, or subcutaneous emphysema.¹²⁵

Hepatotoxicity is associated with exposure to halogenated hydrocarbons, particularly carbon tetrachloride (CCl_4), as well as chloroform, trichloroethane, trichloroethylene, and toluene.⁹² Intentional inhalation of CCl_4 is rarely reported, but its toxic metabolite, the trichloromethyl radical, created by the cytochrome CYP2E1, can covalently bind to hepatocyte macromolecules and cause lipid peroxidation.¹¹⁹ This has led to a postulated antidotal role for hyperoxia and hyperbaric oxygen supported by some rat studies and human case reports.^{32,146} Histologically, the potentially fatal centrilobular necrosis that occurs with CCl_4 mimics acetaminophen toxicity and antidotal N-acetylcysteine (NAC) therapy has been explored. Animal studies on the efficacy of NAC in preventing CCl_4 –induced hepatotoxicity have yielded mixed results.^{38,41} There are no clinical trials in humans, but a case series suggest a protective role for NAC.¹²³ Two cases of centrilobular hepatic necrosis following inhalation of trichloroethylene are reported. In a case series of 34 serum-confirmed inhalant deaths, two of the three who died from trichloroethane and trichloroethylene inhalation had cirrhosis of the liver at autopsy. None of the victims of other inhalants had cirrhosis.⁵⁴ Inhalation of either toluene or one of the many halogenated hydrocarbons is associated with elevated liver enzymes and hepatomegaly that generally return to pre-exposure condition within 2 weeks of abstinence.^{7,69,74,86,105,108}

Most reported kidney toxicity is associated with toluene inhalation. Prolonged toluene inhalation was said to cause a distal renal tubular acidosis (RTA), resulting in hypokalemia. However, distal RTA is typically associated with a hyperchloremic metabolic acidosis and a normal anion gap, whereas toluene abuse may be associated with an increased anion gap. Production of hippuric acid, a toluene metabolite, plays an important role in the genesis of the metabolic acidosis.³⁵ Hippurate excretion, usually expressed as a ratio to creatinine, rises dramatically with toluene inhalation.⁹⁸ The excretion of abundant hippurate in the urine unmatched by ammonium mandates an enhanced rate of excretion of sodium and potassium cations. Continued loss of potassium in the urine leads to hypokalemia. Toluene is rapidly metabolized to hippuric acid and the hippurate anion is swiftly cleared by the kidneys, thus leaving the hydrogen ion behind. This prevents the rise in the anion gap that would normally occur with an acid anion other than chloride, resulting in a normal anion gap.

In some cases, the loss of sodium causes extracellular fluid volume contraction and a fall in the glomerular filtration rate, which may transform the metabolic acidosis with a normal anion gap into one with a high anion gap caused by the accumulation of hippurate and other anions.³⁵ Other renal abnormalities of uncertain etiology are associated with toluene inhalation, including hematuria, albuminuria, and pyuria. Glomerulonephritis associated with hydrocarbon inhalation is also reported and is a result of antglomerular basement membrane antibody-mediated immune complex deposition.^{17,147,162}

Toluene-abusing patients may present with profound hypokalemic muscle weakness. In a study of 25 patients admitted to the hospital following inhalant abuse, nine presented with muscle weakness.¹³⁸ The mean serum potassium concentration was 1.7 mEq/L, and six of these patients also had rhabdomyolysis. Four patients were quadriplegic on presentation; of these, two were initially diagnosed erroneously with Guillain-Barré syndrome. The patients had inhaled toluene 6 to 7 hours per day for 4 to 14 days prior to presentation.¹³⁸

Acute dermatologic and upper airway toxicity is associated with the inhalation of fluorinated hydrocarbons. First- and second-degree burns of the face, neck, shoulder, and chest are reported in a 12 year-old girl inhaling a computer cleaner containing difluoroethane.¹⁰¹ Pyrolysis of difluoroethane may yield hydrofluoric acid burns.⁵² Vesicular lesions resembling frostbite and massive, potentially life-threatening edema of the oropharyngeal, glottic, epiglottic, and paratracheal structures are also reported.^{1,81,95} This is caused by the cooling of the gas associated with its rapid expansion once it is released from its pressurized container. With chronic abuse of volatile hydrocarbons, patients may develop severe drying and cracking around the mouth and nose as a consequence of a defatting dermatitis known as “huffer’s eczema.” Other manifestations of chronic irritation include recurrent epistaxis, chronic rhinitis, conjunctivitis, halitosis, and ulceration of the nasal and oral mucosa.⁹⁸

Bone mineral density was significantly lower in 25 adolescent chronic glue sniffers compared with that of healthy controls.⁴⁵ In a mouse model, chronic exposure to toluene significantly reduced bone mineral density.⁵ Methylene chloride (dichloromethane), most commonly found in paint removers and degreasers, is unique among the halogenated hydrocarbons in that it undergoes metabolism in the liver by CYP2E1 to carbon monoxide.¹¹⁰ In addition to acute CNS and cardiac manifestations, inhalation of methylene chloride is associated with delayed onset and prolonged duration of signs and symptoms of carbon monoxide (CO) poisoning. The CO metabolite is generated 4 to 8 hours after exposure and its apparent half-life is 13 hours, significantly longer than that of CO following inhalation (Chap. 125).^{10,139} Methanol toxicity is reported following intentional inhalation of methanol-containing carburetor cleaners.^{53,88,94} Significant findings may include hyperemic optic discs on funduscopic examination, metabolic acidosis, and CNS and respiratory depression (Chap. 109). Methanol-containing carburetor cleaners may also contain significant amounts of toluene (43.8%), methylene chloride (20.5%), and propane (12.5%). These xenobiotics may potentiate CNS depression and contribute to the toxicity associated with these products.

Chronic inhalation of the solvent n-hexane, a petroleum distillate and a simple aliphatic hydrocarbon found, for example, in rubber cement, can cause a sensorimotor peripheral neuropathy. Toxicity is mediated via a metabolite, 2,5-hexanedione, which interferes with glyceraldehyde-3-phosphate dehydrogenase-dependent axonal transport, resulting in axonal death.⁴⁴ Numbness and tingling of the fingers and toes is the most common initial complaint; progressive, ascending loss of motor function with frank quadriparesis may ensue.³⁶ Sural nerve biopsy shows axonal swelling and axonal loss, with secondary loss of myelin, probably as a result of retraction by axonal swelling, and accumulation of neurofilaments.⁸² Nerve conduction studies show marked slowing and blockade (Chap. 24).^{36,82}

Reports of polyneuropathy associated with chronic gasoline inhalation date to the 1960s and describe a symmetric, progressive, sensorimotor neuropathy with occasional superimposed mononeuropathies.^{31,75} Initially, these deficits were attributed to the presence of tetraethyl lead as an “anti-knocking” agent in gasoline, but cases following abuse of unleaded gasoline are also reported.^{31,126} n-Hexane is present in gasoline in concentrations of up to 3% and is thought to be the likely mediator of gasoline neuropathy.¹⁵³

Teratogenicity. Fetal solvent syndrome (FSS) was first reported in 1979.¹⁴⁵ The authors described a 20 year-old primigravida woman with a 14 year history of solvent abuse defined as “daily” and “heavy” who gave birth to an infant exhibiting facial dysmorphism, growth retardation, and microcephaly, a constellation of findings that resembles fetal alcohol syndrome (FAS). Since then, many cases and case series have been reported.^{4,68,124,155} A general limitation of these case series is their reliance on self-reporting of substance abuse. In a number of cases included for analysis of teratogenic effects, mothers admit to use during pregnancy of other potential teratogens, including ethanol, cocaine, heroin, and phenobarbital.^{4,155} Cases purported to represent inhalant abuse in the absence of other drug abuse, particularly ethanol, are not verified by laboratory testing. A small study of infants born to mothers with a self-reported history of chronic solvent abuse found 16% had major anomalies, 12.5% had facial features resembling FAS, and 3.6% had cleft palate.¹²⁴ Craniofacial abnormalities common to both FAS and FSS include small palpebral fissures, thin upper lip, and midfacial hypoplasia. Features of FSS that distinguish it from FAS include micrognathia, low-set ears, abnormal scalp hair pattern, large anterior fontanelle, and downturned corners of the mouth.¹⁴⁵ Hypoplasia of the philtrum and nose are more characteristic of FAS.¹¹³ Compared with matched controls, infants born to mothers who report inhalant abuse are more

likely to be premature, have low birth weight, have smaller birth length, and have small head circumference.^{4,155} Follow-up studies of these infants show developmental delay when compared with children matched for age, race, sex, and socioeconomic status.^{4,68} A rat model of toluene abuse embryopathy found a significant reduction in the number of neurons within each cortical layer, as well as abnormal neural migration.⁶⁰ In animal models of inhalant abuse, exposure to brief, repeated, high concentrations of toluene significantly increases rates of growth restriction, minor malformations, and impaired motor development.^{24,73} In another rat model of maternal inhalant abuse, toluene concentrations in fetal brain tissue, the placenta, and amniotic fluid increased in a concentration-dependent manner.²⁶

Withdrawal. Observed similarities in the acute effects of inhalants compared with other CNS depressants have suggested similar patterns of tolerance and withdrawal. Rodent models of inhalant abuse with toluene and TCE show evidence of physical dependence that manifests as an increase in handling-induced seizures on cessation of inhalation.^{48,154} In addition, these studies demonstrate cross-tolerance of the benzodiazepine diazepam with the motor-stimulating effects of TCE and, to a lesser degree, with toluene. Inhalant abusers have themselves described tolerance with weekly usage in as little as 3 months.⁶² Withdrawal symptoms, including irritability, insomnia, craving, nausea, tremor, and dry mouth lasting 2 to 5 days after last use, are described.¹²⁸

VOLATILE ALKYL NITRITES

Methemoglobinemia caused by inhalation of amyl, butyl, and isobutyl nitrites is well reported.^{28,89} Nitrites are strong oxidants that may induce hemoglobin oxidation from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. Patients may present with signs and symptoms of methemoglobinemia, including shortness of breath, cyanosis, tachycardia, and tachypnea (**Chap. 127**). Eye pain, transient increased intraocular pressure, and progressive bilateral visual loss are reported following use of amyl nitrite.^{6,112,114}

Nitrous Oxide

Reported deaths associated with abuse of nitrous oxide (N_2O) appear to be caused by secondary effects of N_2O , including asphyxiation and motor vehicle collisions while under the influence, and not a direct toxic effect.^{141,150} Investigations following deaths associated with N_2O have found that many of the people who died were discovered with plastic bags over their heads, in an apparent attempt to both prolong the duration of effect and increase the concentration of the inhalant.¹⁵⁰ Autopsy findings in these cases were consistent with asphyxiation: acute respiratory distress syndrome, cardiac petechiae, and generalized visceral congestion.^{141,150} Laboratory simulation of a reported death in which the victim was found with a plastic bag over his head with a belt fastened loosely around his neck and a spent whipped cream canister within the plastic bag showed that N_2O displaces oxygen in a closed space.¹⁵⁰ In addition, N_2O concentrations in this simulation were above 60%; at concentrations of N_2O above 50%, the normal hypoxic response is diminished.¹⁵⁰ The combined effects of displaced oxygen and a blunted hypoxic drive may increase the risk of asphyxia.

Chronic abuse of N_2O is associated with neurologic toxicity mediated via irreversible oxidation of the cobalt ion of cyanocobalamin (vitamin B_{12}). Oxidation blocks formation of methylcobalamin, a coenzyme in the production of methionine and S-adenosylmethionine, required for methylation of the phospholipids of the myelin sheaths. In addition, cobalamin oxidation inhibits the conversion of methylmalonyl to succinyl coenzyme A. The resultant accumulation of methylmalonate and propionate can result in synthesis of abnormal fatty acids and their subsequent incorporation into the myelin sheath (**Chap. 68**).¹¹⁵ Case reports and small case series in humans following self-reported chronic, heavy abuse of N_2O describe the development of a myeloneuropathy resembling the subacute combined degeneration of the dorsal columns of the spinal cord of classic vitamin B_{12} deficiency.^{19,84,149} Presenting signs and symptoms reflect varying involvement of the posterior columns, the corticospinal tracts, and the peripheral nerves. Numbness and tingling of the distal extremities is the most common presenting complaint. Physical examination may reveal diminished sensation to pinprick and light touch, vibratory sensation and proprioception, gait disturbances, the Lhermitte sign (electric shock sensation from the back into the limbs with neck flexion), hyperreflexia, spasticity, urinary and fecal incontinence, and extensor plantar response.^{33,115} Among reported patients with N_2O -associated neurotoxicity who had documented concentrations of vitamin B_{12} , approximately 50% were low.^{19,33,84,135,149} In the few patients who underwent Schilling tests to evaluate for potential vitamin B_{12} deficiency results were normal.^{84,149} MRI of the spinal column may reveal enhancement and edema of the central and dorsal aspects of the spinal cord.¹¹⁷ Nerve conduction studies and electromyography typically revealed a distal, axonal sensorimotor polyneuropathy.^{33,84,149}

LABORATORY AND DIAGNOSTIC TESTING

Routine urine toxicology screens are unable to detect inhalants or their metabolites. Although most volatile inhalants can be detected using gas chromatography, the likelihood of detection is limited by the dose, time to sampling, and method of specimen storage. Blood is the preferred specimen, but urinalysis for metabolites, including hippuric acid (the toluene metabolite) and methyl hippuric acid (the xylene metabolite), may extend the time until the limit of detection is reached.^{29,83} Specimens should be stored at a temperature between 23°F (−5°C) and 39.2°F (4°C).²⁵ Testing is not readily available at most institutions and the need to send the specimen to a reference laboratory limits the clinical utility in most situations. A thorough history and physical examination and careful questioning of the friends and family of the patient are probably more helpful in cases of suspected inhalant abuse.

Depending on the patient's signs and symptoms, additional diagnostic testing may be indicated, including electrocardiography, chest radiography, and laboratory studies (electrolytes, liver enzymes, and blood pH). Inhalation of some xenobiotics presents unique diagnostic considerations (Table 84–3). Routine laboratory testing, including cerebrospinal fluid analysis, is unremarkable in patients with inhalant-induced leukoencephalopathy. Computed tomography of the head is generally normal until late in the disease when diffuse hypodensity of white matter becomes evident. T2-weighted MRI with its superior resolution of white matter is the diagnostic study of choice. Standard MRI does not detect initial changes caused by toluene leukoencephalopathy; measurement of N-acetyl aspartate (NAA), a marker of CNS axonal damage, with magnetic resonance spectroscopy may assist with earlier detection. A decrease in NAA concentration, usually expressed as the ratio of NAA to creatinine (NAA:Cr), may serve as a marker of axonal damage.⁵⁰

TABLE 84–3. Inhalants with Unique Clinical Manifestations

<i>Inhalant</i>	<i>Clinical Manifestations</i>
Toluene	Hypokalemia Hepatotoxicity Leukoencephalopathy (chronic)
1,1,1-Trichloroethane, trichloroethylene	Hepatotoxicity
Methylene chloride	Carbon monoxide poisoning
Carburetor cleaner	Methanol poisoning
Alkyl nitrites (amyl, butyl, isobutyl)	Methemoglobinemia Vision loss
<i>n</i> -Hexane	Peripheral neuropathy (chronic)
Nitrous oxide	Myeloneuropathy (chronic)

MANAGEMENT

Management begins with assessment and stabilization of the patient's airway, breathing, and circulation (the “ABCs”). The patient should be attached to a pulse oximeter and cardiac monitor. Oxygen should be administered and the patient should be treated with nebulized β -adrenergic agonists if wheezing is present. Early consultation with a regional poison center or medical toxicologist may assist with identification of the xenobiotic and patient management.

Cardiac dysrhythmias associated with inhalant abuse carry a poor prognosis. Sudden death following use is not limited to novices and there appears to be no premonitory signal to the user.^{8,11,105} Life-threatening electrolyte abnormalities must be considered and corrected in the patient presenting with dysrhythmia. Patients with nonperfusing rhythms should be managed following standard management with defibrillation. There are no evidence-based treatment guidelines for the management of inhalant-induced cardiac dysrhythmias, but β -adrenergic antagonists are thought to offer some cardioprotective effects to the sensitized myocardium.¹⁰⁶ Propranolol and esmolol both have been used successfully in treatment of ventricular dysrhythmias following inhalant abuse.^{58,102}

Fluid and electrolyte abnormalities should be sought and corrected early. In the course of management, other complications, including methemoglobinemia, elevated carboxyhemoglobin, and methanol toxicity, should be managed with the appropriate antidotal therapy. Patients with respiratory symptoms persisting beyond the initial complaints of gagging and choking should be evaluated for hydrocarbon pneumonitis and treated supportively (Chap. 108).

With abstinence, cognitive and neuroimaging changes associated with toluene-induced leukoencephalopathy may initially be partially reversible; beyond a poorly defined period, these changes are irreversible.^{43,50} Cessation of abuse is the most important therapeutic intervention in patients with *n*-hexane–induced neuropathy. In N₂O-induced myeloneuropathy limited anecdotal evidence supports the coadministration of vitamin B₁₂ (1000 μ g intramuscularly) and methionine (1 g

orally).^{33,127,135}

Agitation, either from acute effects of the inhalant or from withdrawal, is safely managed with a benzodiazepine. In the vast majority of patients, symptoms resolve quickly and hospitalization is not required. The potential toxicity of inhalants should be reinforced and patients should be referred for counseling. Subsets of users who meet the criteria for inhalant dependence and inhalant-induced psychosis require inpatient psychiatric care. Pharmacotherapy with carbamazepine or the antipsychotics haloperidol, risperidone, and aripiprazole appears beneficial to some patients with an inhalant-induced psychotic disorder.^{46,67,99} Case reports describe successful treatment of inhalant dependence with lamotrigine, which inhibits excitatory glutamatergic tone, and with buspirone, an atypical anxiolytic.^{107,131} Drug use treatment programs for inhalant abuse are scarce and few providers have special training in this area.¹³

SUMMARY

- Inhalants are a heterogeneous group of xenobiotics that include the volatile hydrocarbons, alkyl nitrites, and nitrous oxide.
- The incidence of inhalant abuse is greatest among adolescents.
- The CNS is the intended target for the inhalant users; early effects include euphoria, hallucinations, headache, and dizziness.
- Acute cardiotoxicity is manifested most dramatically in “sudden sniffing death.”
- The diagnosis is largely clinical; further diagnostic testing should be guided by the patient’s presenting complaint.
- Management begins with basic life support and care is generally supportive.
- Cessation of use is the only known treatment for many manifestations of chronic toxicity.

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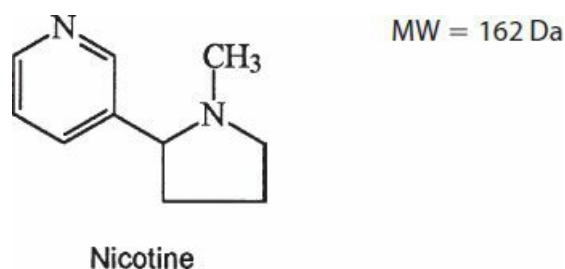
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85 NICOTINE

Sari Soghoian



HISTORY AND EPIDEMIOLOGY

The tobacco plant is native to the Americas, and its use most likely predates the Mayan empire. In 1492 Christopher Columbus and his crew were given tobacco by the Arawaks, but reportedly threw it away not knowing any use for it. Ramon Pane, a monk who accompanied Columbus on his second voyage to America, is credited with introducing tobacco to Europe.⁸³

The principal alkaloid, nicotine, is still primarily derived from members of the genus *Nicotiana*, collectively known as the tobacco plant, in the family Solanaceae. The most important species in human use today is *Nicotiana tabacum* and the primary method of nicotine exposure is cigarette smoking. Because of the highly addictive properties of nicotine, the global disease burden related to cigarette use is staggering. Cigarette smoking increases rates of chronic obstructive pulmonary disease (COPD), cardiovascular disease, pulmonary infections, macular degeneration, and cancers, and causes more than 5 million deaths worldwide per year. Chronic nicotine exposure causes cardiovascular damage related to catecholamine release and vasoconstriction, and directly promotes angiogenesis, neuroteratogenicity, and possibly some cancers.⁵¹ However, there are more than 3000 components to tobacco smoke and nicotine per se may not be the crucial determinant of the total health burden associated with its use.

Although the long-term effects of cigarette smoking and tobacco dependency are significant, this chapter is concerned with the sources, effects, and management of acute toxicity referable to nicotinic receptor stimulation and cholinergic activation. Reviews of case data from the National Poison Data System suggest that cigarettes are by far the most common vehicle implicated in acute nicotine exposures and poisoning in the United States.² Smoking cessation products containing nicotine are increasingly available and some of the more novel smokeless tobacco products have the appearance of candy, raising concern about the potential for unintentional poisoning of young children, in particular.²¹

Compared with other xenobiotics, exposure to nicotine containing products is nonetheless a relatively rare cause of acute poisoning. For example, over a period of 27 years from 1983 to 2009, tobacco products accounted for 217,340 calls, or 0.37%, of all pediatric exposures reported to poison centers in the United States,² and accounted for 0.7% of all unintentional poisoning cases in children treated in US hospital emergency departments in one national estimate.³¹ Although fatalities are reported, most patients with nicotine exposure have a benign course, with only mild to moderate symptoms and an infrequent need for hospitalization.

Nicotine receptor partial agonists/antagonists are a relatively new class of drug mimicking the physiologic effects of nicotine. A 2-year review of poison center data from the California Poison Control System found 36 calls regarding human exposures to varenicline (Chantix), which was approved in 2006 by the US Food and Drug Administration (FDA) as a smoking cessation aid.⁴⁶ Of these, 17 cases had no outcome data or involved coingestions. Nine of the remaining cases involved unintentional exposure in children younger than 6 years of age, one of whom was hospitalized; none experienced major adverse events.

Use of nicotine as an insecticide is no longer in widespread use in the United States, but are still used in other countries and can be purchased from some online retailers. The neonicotinoids are a relatively new class of insecticide developed in the last quarter century, and epidemiologic data about their role in acute pesticide poisoning are still limited. A retrospective review of poison center data from Thailand found no reports of neonicotinoid exposures before 1993.⁷¹ Between 1993 and 2007 there were a total of 70 cases, including two deaths. The number of exposures reported annually increased dramatically after 2002, suggesting that neonicotinoid insecticides may still be an emerging cause of acute

pesticide poisoning. However, in the year with the highest case incidence, these insecticides still represented less than 3% of all pesticide exposures reported.

Dermal exposure to tobacco plants during harvest remains an important source of occupational nicotine toxicity known as green tobacco sickness (GTS). GTS was first reported in 1970 among tobacco workers in Florida.⁸⁷ In 1992, the US Centers Disease and Control and Prevention estimated the crude 2-month incidence rate of hospital treated GTS was 10 per 1000 workers in a five-county area in Kentucky.⁶² Overall prevalence estimates among seasonal and migrant farmworkers are as high as 25% to 40% of workers.^{3,5,73}

PHARMACOLOGY/PHARMACOKINETICS

The pharmacologic characteristics of nicotine are listed in Table 85–1. Nicotine is well absorbed from the respiratory tract, mucosal surfaces, skin, and the intestines. Nicotine is a weak base (pKa = 8.0) and is more readily absorbed in an alkaline environment. Many tobacco and nicotine replacement products are therefore buffered to alkaline pH to facilitate absorption.

TABLE 85–1. Pharmacologic Characteristics of Nicotine

Absorption	Lungs, oral mucosa, skin, intestinal tract; increased in more alkaline environment
Volume of distribution	Approximately 2.6 L/kg
Protein binding	About 5%
Metabolism	80%–90% hepatic; remainder in lung, kidney; principal (inactive) metabolite is cotinine
Half-life	Nicotine: 1–4 hours, decreases with repeated exposure Cotinine: ~ 20 hours
Elimination	2%–35% excreted unchanged in urine

Nicotine from cigarette or cigar smoke is carried on inhaled tar particles into the lungs where a large alveolar surface area allows rapid absorption into the pulmonary circulation. In the bloodstream, nicotine is about 69% ionized at pH 7.4 and less than 5% is bound to plasma proteins. Distribution to body tissues is rapid and extensive, with an average volume of distribution of about 2.6 L/kg.⁶ Nicotine readily crosses the placental barrier and is secreted in breast milk. Metabolism occurs primarily in the liver via P450 cytochrome oxidases CYP2A6 and CYP2D6, aldehyde oxidase, flavin monooxygenase, and by glycosylation. About 70% of circulating nicotine is metabolized to cotinine, and much smaller amounts to nornicotine, nicotine-1-N-oxide, nicotine glucuronide, and 2'-hydroxynicotine.

Peak plasma concentrations of nicotine and cotinine are influenced most strongly by individual variations in clearance.^{10,11} Hepatic nicotine metabolism is inducible and nicotine-dependent individuals metabolize the drug more rapidly than naïve ones.⁴⁰ Nicotine metabolism may also be linked to race and sex. Asians and African Americans metabolize nicotine more slowly than Caucasians, and they have prolonged cotinine clearance in the urine.^{10,52,68} Women metabolize nicotine faster than men, which is further accelerated by oral contraceptive use and pregnancy, and is most likely mediated by an influence of estrogen on CYP2A6 activity.⁴⁰

Renal excretion of unchanged nicotine accounts for 2% to 35% of total nicotine elimination,¹⁵ and this is pH dependent. Nicotine is reabsorbed in the proximal tubule and acidification of the urine enhances elimination. The half-life of nicotine in the body is 1 to 4 hours and it decreases with repeated nicotine exposure such as with habitual cigarette smoking. Cotinine and trans-3'-hydroxycotinine are eliminated in the urine as glucuronide esters independent of urine pH. The elimination half-life of cotinine is approximately 20 hours and therefore urinary cotinine is a more useful marker of nicotine exposure. The apparent elimination half-life of nicotine after transdermal patch removal is longer than that noted with nicotine exposure by other routes,⁴³ but this is most likely because a dermal reservoir of drug is established during patch use, from which absorption continues after removal.

Cigarette smoking modulates the bioavailability and effectiveness of numerous medications through effects on drug absorption, metabolism, or pharmacodynamics. Cigarette smoking induces CYP1A2 and accelerates the metabolism of caffeine, clozapine, olanzapine, tacrine, theophylline, and erlotinib.^{39,42} This may not be an effect of nicotine. For example, intravenous nicotine administration does not affect theophylline metabolism.¹² Smokers also have diminished effectiveness

of opioids, benzodiazepines, β -adrenergic antagonists, and nifedipine,¹⁹ and are more likely to fail antacid and H₂-blocker therapy for peptic ulcer disease.¹² However, these interactions have also not been clearly linked to an effect of nicotine per se.

The LD₅₀ of nicotine has been estimated at about 0.5 to 1 mg/kg in adults.^{33,35,54} Severe toxicity is reported with ingestion of less than 2 mg in a child,^{59,80} and this dose is sufficient to produce mild symptoms in an unhabituated adult. Children younger than 6 years of age who ingest one or more cigarettes, or three or more cigarette butts, generally develop symptoms of nicotine toxicity.⁸⁰ A retrospective review of 10 pediatric cigarette ingestions found that all four patients with symptoms requiring medical evaluation and treatment had ingested at least two entire cigarettes.⁵⁴

Acute tolerance to nicotine develops in smokers who take in small doses of nicotine regularly throughout the day. Sensitization to the effects of nicotine is restored with overnight abstinence.^{9,40} Tolerance may also develop in tobacco workers with regular exposure to tobacco plant leaves. However, the phenomenon of acute tolerance, along with considerable genetic variability in nicotine metabolism, implies a range of susceptibility to drug effect.

SOURCES AND USES OF NICOTINE

Cigarettes and Cigars

The amount of nicotine contained in a single cigarette is highly variable, ranging from less than 10 mg in a “low nicotine” cigarette to 30 mg in some European cigarettes (Table 85–2). Since most nicotine is either lost in the sidestream (secondhand) smoke, or left in the filter, the absorbed nicotine yield from a smoked cigarette is much less than this, on the order of 0.05 to 3 mg/cigarette.³⁰ The amount of nicotine absorbed by a particular individual from a single smoked cigarette is highly variable among smokers and depends on the puff rate, volume, the depth and duration of inhalation, and the size of the residual.⁵⁵ Cigars have higher nicotine content than cigarettes (Table 85–2) and potentially greater absorption since cigar and pipe tobacco is typically air cured to achieve a high pH.

TABLE 85–2. Sources of Nicotine

Source	Content (mg)	Delivered (mg)
1 cigarette	10–30	0.05–3
1 cigarette butt	5–7	—
1 cigar	15–40	0.2–1
1g snuff (wet)	12–16	2–3.5
1g chewing tobacco	6–8	2–4
1 piece nicotine gum	2 or 4	1–2
1 nicotine patch	8.3–114	5–22 over 16–24 hours
1 nicotine lozenge	2 or 4	2–4
1 nicotine nasal spray	0.5	0.2–0.4
30-mL bottle of nicotine liquid refill for e-cigarette cartridges (30, 50, 100 mL bottles also sold)	0–<36 mg/mL	<43.2 μ g/100mL “puff” of nicotine mist

The potential for nicotine toxicity from smoking is limited since peak effects by this route will occur within seconds and tend to limit further intake of drug. Most reports of acute nicotine toxicity referable to cigarette exposure are associated with cigarette and cigarette butt ingestion, usually by young children.^{61,70,79} Although uncommon, severe toxicity from cigarette^{14,80} ingestion is well reported. Ingesting cigarette soakage water has been recommended on the Internet as a “safe and effective” means of suicide, and several cases are reported.^{23,76} Intravenous injection of cigarette soakage is also reported.³⁸

Oral Tobacco

Snuff and chewing tobacco are still widely employed by users of smokeless tobacco products,²¹ despite clear associations

with periodontal disease, dental cavities, and up to a 48 times greater risk of oropharyngeal cancers compared with people who do not use tobacco products.²² Snuff, or dip, is a finely ground and sometimes flavored tobacco preparation often sold in small teabaglike pouches that users insert between their lower lips and gums. Chewing tobacco consists of shredded, twisted, or “bricked” dried tobacco leaves. Because nicotine is a weak base, smokeless tobacco is buffered to facilitate buccal absorption. In one survey of major US brands, the pH of marketed oral tobacco products ranged from 5.24 to 8.35, and the nicotine content ranged from 3.37 to 11.04 mg/g.⁶⁰ Acute nicotine toxicity from smokeless tobacco is rarely reported in adults. A 14 month-old boy had muscle fasciculations and lethargy after ingesting material out of his father’s spittoon, but recovered within 24 hours with supportive care.³⁵ Rectal administration of moist snuff as a treatment for migraine headache resulted in significant toxicity in one patient.⁴⁴ Presumably the relatively alkaline environment of the rectum facilitated absorption of a high dose.

Gum

Nicotine gum has been available without a prescription as an aid to smoking cessation in the United States since 1996. It is sold in 2 mg and 4 mg strengths per piece. Approximately 53% to 72% of the nicotine in the gum is absorbed. It is buffered to an alkaline pH to facilitate buccal absorption. The gum is supposed to be chewed until mouth and throat tingling and a peppery taste develops, signaling nicotine release. The gum is then “parked” in the cheek until the sensation subsides, at which time it may be chewed again to release more drug.⁶⁵ If used correctly, serum nicotine concentrations rise gradually to a level slightly lower than normally achieved by cigarette smoking.⁶⁵ If the gum is swallowed whole, then serum concentrations rise even more slowly because the acidic environment of the stomach delays absorption.¹² Conversely, if the gum is chewed vigorously and saliva is swallowed, then nicotine concentrations may rise rapidly and adverse reactions may occur.⁸⁰

Lozenges

Nicotine lozenges containing 2 and 4 mg of nicotine are available for purchase without a prescription in the United States. The potential for rapid absorption of nicotine as a bolus dose from chewing the lozenge is a concern.

Transdermal Patches

Nicotine patches have been FDA approved for purchase without prescription in the United States since 1996. Most nicotine transdermal delivery systems are designed to deliver 7, 14, or 21 mg of nicotine over 24 hours.³⁷ Because many patch users have difficulty sleeping, experience vivid dreams, or have nightmares if they wear the patch overnight, systems designed to be applied for only 16 hours are now made. Several reports document consequential nicotine toxicity related to nicotine patch misuse. Toxicity may occur in people who continue to smoke cigarettes after beginning therapy with the nicotine patch. Children have developed symptoms after exploratory self-application of one or more patches to the skin,^{85,88} and concurrent use of multiple patches has been used as a means of suicide.^{47,81,87} Severe toxicity may also occur if patches are punctured—for example, by biting or tearing—thus allowing delivery of excess content.⁸⁸ The patch reservoirs contain an estimated 36 to 114 mg per patch.⁶⁴ This amount exceeds the estimated LD₅₀ for nicotine in humans of 1 mg/kg for most children and many adults.

Spray/Inhaler

A nicotine spray has been available since 1996 to aid efforts at smoking cessation. The most commonly reported adverse effects during initiation of therapy are due to local irritation and include rhinorrhea, lacrimation, sneezing, and nasal and throat irritation.⁴¹ One spray delivers 0.5 mg of nicotine and the recommended dose is two sprays every 30 to 60 minutes as needed. The absorption is about 50% of the delivered dose and may be diminished or delayed by rhinitis or by α -adrenergic agonist decongestants.⁵⁰ No report of acute nicotine toxicity from nicotine inhalers has been published to date.

Electronic Cigarettes

Electronic cigarettes, or e-cigarettes, are a relatively new nicotine delivery product now widely available in various strengths and flavors.⁹¹ The devices resemble cigarettes and contain a rechargeable battery pack along with a small heating element attached to a reservoir of liquid nicotine. An electronic airflow sensor activates the heating element when the user inhales, allowing release of a “puff” of nicotine-containing vapor. An FDA analysis of cartridges found that identically labeled products contained variable amounts of nicotine and a number of potentially harmful contaminants.⁸² The potential for harm is evident, particularly since e-cigarette sales are still unrestricted in many states and large-volume liquid nicotine replacement fluid bottles (used to refill e-cigarette cartridges) are increasingly available. The nicotine content of these bottles is substantial. Formulations of different strengths are sold; the highest strength preparations may contain over a gram

of nicotine per 30mL bottle, raising serious concerns about the risk of both unintentional and intentional toxic exposures. Analysis of calls to US poison centers about e-cigarette exposures has shown substantial increase between the years 2010 and 2014, with significantly greater adverse effects reported compared to calls about cigarette exposures.^{16a}

Nicotine Receptor Partial Agonists (Varenicline, Cytisine)

Nicotine receptor partial agonists are used to aid smoking cessation. Theoretically, they work by reducing smoking satisfaction (agonist antagonism effect) while helping to maintain moderate levels of central dopamine release (partial agonist effect). Cytisine is a plant-derived xenobiotic with a chemical structure similar to nicotine that has been used in East and Central Europe as a smoking cessation drug since the 1960s under the trade name Tabex (Sopharma Pharmaceuticals). Despite its widespread use, it has not been well studied for its safety, efficacy, pharmacokinetics, and pharmacodynamics in humans.²⁹ Varenicline (marketed as Chantix in the United States and Champix in Europe) was approved as a prescription-only aid to smoking cessation in 2006. Several randomized controlled trials demonstrated efficacy in controlling nicotine cravings and evidence suggests that varenicline increases the probability of successful abstinence from smoking.¹⁶ In 2009, the FDA mandated a black box warning due to an association with increased risk of depression or suicidal behavior. There is still limited experience with effects or outcomes after acute overdose.

Plants/Leaves

Residual moisture or dew drops on tobacco leaves may contain as much as 9 mg of nicotine per 100 mL.³⁴ Sweat wrung out of the shirts worn by workers during tobacco harvest in one study contained up to 98 mg/mL of nicotine.³⁴ Risk factors for GTS include younger age, working in wet tobacco, and a relative lack of work experience.^{3,5,58,62} These factors may all be related to a lack of nicotine tolerance. The use of impermeable garments or other barrier protection is the only protective factor consistently noted to be useful across multiple studies.^{4,58,62}

Salts (Pesticides)

Nicotine in the form of tobacco extracts was first reported as effective for pest control in 1690. In 1886 a mixture of tobacco and soapsuds was advocated for aphid control, but it was not until 1912 that the first commercial nicotine insecticides were developed. Crop dusting with nicotine sulfate began in 1917, although at the time this was mostly accomplished by horse-drawn carriage.⁶⁹ The most widely known application of 40% nicotine sulfate, BlackLeaf 40, was discontinued in 1992. Nicotine is still available as a restricted use pesticide, and a 14% preparation of nicotine is still marketed as a greenhouse smoke fumigator.⁶⁶ Because nicotine pesticides are highly concentrated, the ingestion of even small amounts may produce serious toxicity, including catastrophic brain injury⁷⁵ and death.⁴⁸

Neonicotinoids

The neonicotinoids are a relatively new class of insecticides with theoretical safety by markedly reducing the affinity for vertebrate nicotinic receptors as compared with those in insects.⁸⁴ Neonicotinoid compounds include the heterocyclics nithiazine, imidacloprid, thiacloprid, and thiamethoxam; and the acyclics nitenpyram, acetamiprid, clothianidin, and dinotefuran. Experience with human poisoning is still limited.

Miscellaneous

Tobacco has been used for medicinal and therapeutic purposes in many societies for some time. Tobacco extract and tobacco smoke enemas were used in the pre-Columbian Americas by many tribes for both medicinal and spiritual purposes. They are still recommended by some naturopaths and folk healers as a remedy for constipation, urinary retention, pin worm and “hysterical convulsions.” Nicotine has also been recommended as a treatment for migraine, on the basis of its vasoconstrictive properties.³⁶ Nicotine poisoning has resulted from “therapeutic misadventure” in several documented cases.^{33,44,45} For example, acute nicotine toxicity occurred in an 8 year-old boy after application of a homemade remedy for eczema made from a mixture of tobacco leaves, lime juice, and freeze dried coffee.²⁶

PATHOPHYSIOLOGY

Nicotine mimics the effects of acetylcholine release by binding to nicotinic receptors (nAChR) in the brain, spinal cord, autonomic ganglia, adrenal medulla, neuromuscular junctions, and chemoreceptors of the carotid and aortic bodies (Chap. 14). Activation of nAChR in the CNS directly stimulates neurotransmitter release. When nicotine binds to this receptor, an ion channel opens allowing an influx of cations, mostly sodium and calcium. Voltage-gated calcium channels are then activated leading to further influx of calcium, and a variety of downstream effects, including depolarization.

At doses generally produced by cigarette smoking there is stimulation of the reticular activating system and an alerting pattern on electroencephalogram.⁹² Nicotine-stimulated release of dopamine occurs in the mesolimbic area, the corpus striatum, the prefrontal cortex, and in the nucleus accumbens; it is an important mediator of nicotine addiction.⁵⁶ Nicotine also stimulates glutaminergic activation and the GABAergic inhibition of dopaminergic neurons in the hippocampus, basal forebrain, and ventral tegmental area of the midbrain.^{8,28} These pathways, along with endogenous cannabinoid and opioid systems, are also thought to be important neuromodulatory pathways for drug-induced reward, dependence, and withdrawal.^{53,56,67} Norepinephrine, acetylcholine, GABA, serotonin, glutamate, and endorphins are all released by nicotine and are associated with cognitive and mood enhancement as well as appetite suppression, increased basal energy expenditures and anxiety reduction.⁸

Nicotine's clinical effects are dose-dependent. Low doses of nicotine and related compounds stimulate nicotinic receptors centrally and in autonomic and somatic motor nerve fibers, resulting in sympathetic agonism. At toxic concentrations, prolonged or excessive nicotinic stimulation ultimately leads to receptor blockade ([Chap. 69](#)), with parasympathetic and neuromuscular-blocking effects.

At very high doses nicotine induces seizures. In a mouse model, nicotine-induced seizures are blocked by the nicotine-receptor antagonists mecamylamine, methyllycaconitine citrate, and hexamethonium.²⁴ However, when given to mice at slightly higher doses, these nicotine receptor antagonists are epileptogenic. The specific mechanisms by which nicotine produces seizures are unknown. A disinhibition model has been proposed in which desensitization or antagonism of central nicotinic cholinergic neurons blocks excitatory input to GABAergic neurons and a reduction of inhibitory GABAergic input to pyramidal cells then results in increased excitability and seizures.^{1,17,27,32} An alternative hypothesis is that synchronous depolarization from activation of $\alpha 7^*$ -subtype nicotinic receptors promotes kindling-induced seizures.²⁷

CLINICAL MANIFESTATIONS

Exposure to nicotine in low doses comparable to cigarette smoking in nicotine naïve patients produces fine tremor, cutaneous vasoconstriction, increased gastrointestinal motility, nausea, and increases in heart rate, respiratory rate, and blood pressure. Low-dose nicotine also increases mental alertness and produces euphoria. Because nicotine is poorly absorbed in the acid environment of the stomach, symptom onset may not occur until 30 to 90 minutes after ingestion of nicotine-containing products.

Early signs and symptoms of consequential nicotine toxicity are referable to nicotinic cholinergic excess: increased salivation, nausea, vomiting, diaphoresis, and diarrhea may all occur within minutes of systemic absorption. Vasoconstriction may manifest with pallor and hypertension. Tachycardia may also occur, and nicotine gum chewing has been implicated in the development of atrial fibrillation in several cases.^{18,74} Neurologic signs and symptoms include headache, dizziness, ataxia, confusion, and perceptual distortions. Nicotine is an irritant and ingestion of nicotine, including use of nicotine gum, may cause burning and pain in the mouth, and constriction of the throat muscles. Similarly, application of nicotine patches generally results in dermal irritation.

Data from poison centers in the United States suggests that most patients with nicotine exposure rarely display more than mild symptoms and typically have a benign course. Vomiting is the most common adverse effect reported, although agitation also occurs. The relative rarity of life-threatening symptoms may be due to autodecontamination from vomiting, or may reflect selection bias since most reported cases involve unintentional tobacco ingestion by young children. Although less common, ingestion of novel smokeless tobacco preparations, such as gums and lozenges, may be more likely to produce symptoms compared to cigarette ingestion, possibly because these are buffered to promote more rapid nicotine release.⁸⁰

Because nicotine is rapidly metabolized, patients who develop only mild symptoms are expected to recover quickly. Most patients recover fully within 12 hours. An important exception to this rule is patients with symptoms of nicotine toxicity after transdermal nicotine patch application, because a reservoir of drug may persist in the skin after patch removal and can serve as a source of ongoing absorption.

Clinical manifestations of severe poisoning are classically biphasic, reflecting early central stimulation followed by depression. Initial signs may include cardiac dysrhythmias, seizures, and muscle fasciculations in addition to the cholinergic features described above. Bradycardia, hypotension, coma, and neuromuscular blockade with respiratory failure from muscular paralysis may develop later on ([Table 85–3](#)).

TABLE 85–3. Signs and Symptoms of Acute Nicotine Poisoning

	<i>Gastrointestinal</i>	<i>Respiratory</i>	<i>Cardiovascular</i>	<i>Neurologic</i>
Early (0.25–1 hour)	Nausea Vomiting Salivation Abdominal pain	Bronchorrhea Hyperpnea	Hypertension Tachycardia Pallor	Agitation Anxiety Dizziness Blurred vision Headache Hyperactivity Confusion Tremors Fasciculations Seizures
Late (0.5–4 hours)	Diarrhea	Hypoventilation Apnea	Bradycardia Hypotension Dysrhythmias Shock	Lethargy Weakness Paralysis

Exposure to fresh tobacco leaves may produce GTS, which has been likened to the experience of seasickness. The syndrome is characterized by dizziness, headache, nausea, weakness, vomiting, diarrhea, abdominal cramps, and chills. Signs of autonomic instability may also be present in severe cases. Onset of toxicity is typically within 3 to 17 hours after exposure and the duration of illness may be several days.⁵⁷

A limited number of case reports describe the clinical course of patients poisoned by imidacloprid or other neonicotinoid pesticides. Many of the clinical manifestations may actually be attributable to the solvent N-methyl-2-pyrrolidone, which is used to formulate the pesticide and has irritant effects on skin and mucosae.⁹⁰ Published case reports of intentional imidacloprid ingestions describe an initial period of drowsiness, disorientation, dizziness, and tachycardia, with subsequent development of fever, vomiting, and leukocytosis.^{71,90} Oral, esophageal, and gastric erosions are demonstrated by upper endoscopy in several patients.^{71,72} Late-presenting bradycardia and electrolyte abnormalities have also been reported.^{71,77}

DIAGNOSTIC TESTING

Determination of serum or urinary concentrations of nicotine or its metabolites is unlikely to be helpful in the management of the acutely poisoned patient. Measurement can be made for confirmation purposes using various chromatographic techniques. Cigarette smokers typically maintain serum nicotine concentrations around 30 to 50 ng/mL during the day, but may achieve concentrations as high as 100 ng/mL.⁶³ Postmortem analyses of nicotine concentrations in blood after fatal acute intoxication range from 5.5 to 800 mg/L.²³

The presence of measurable concentrations of nicotine or cotinine in biologic samples may reflect coincidental or chronic exposure, and does not necessarily imply acute toxicity. Urinary cotinine has a longer detection window than nicotine, and is often used to document exposure to nicotine containing products, including exposure to second-hand smoke, or to guide dosage adjustments in nicotine replacement therapy.^{8,49,63} Conversely, the absence of cotinine in the urine may be used to document abstinence from tobacco products.

MANAGEMENT

Most patients with unintentional or low-dose nicotine exposures will not require medical treatment. Patients should be immediately referred for evaluation if they are symptomatic or have ingested any amount of nicotine- or neonicotinoid-containing insecticide or fluid. Children who ingest one or more cigarettes or three or more cigarette butts should also be referred for evaluation without delay. Patients with mild or no symptoms can be observed for several hours and safely discharged home if there are no complicating circumstances such as significant comorbid cardiovascular illness or intent to self-harm.

Patients with dermal exposure to wet tobacco leaves or pesticides should be undressed completely and the skin washed thoroughly with soap and copious amounts of water. Personal protective gear should be worn by medical staff charged with handling both clothes and patients prior to decontamination. Symptomatic patients should have any nicotine patches removed immediately and the skin washed with soap and water.

Vomiting is the most commonly reported adverse effect in patients with acute nicotine toxicity, and may limit absorption in some cases. Induction of emesis should be avoided since it is unlikely to be of added benefit and has the potential for harm. Orogastric lavage may be considered in patients who present immediately after large intentional ingestions of

nicotine-containing products. Activated charcoal adsorbs nicotine and can reduce absorption, but the risks of pulmonary aspiration in case of vomiting, seizure, or depressed level of consciousness tend to outweigh the potential benefit.

There is no specific antidote for nicotine toxicity. Treatment of acute nicotine toxicity is symptomatic and supportive. The first priority is to ensure airway protection and respiratory support. Atropine may be used to treat symptoms associated with parasympathetic stimulation such as excess salivation, wheezing, or bradycardia. Endotracheal intubation may be required for airway protection or to assist ventilation in severely poisoned patients. Seizures may be treated with a benzodiazepine. Hypotension should be treated with fluid boluses and an infusion 0.9% NaCl initially. Patients who fail to respond to volume infusion may require treatment with a vasopressor such as norepinephrine. Dysrhythmias should be treated according to standard protocols. Nicotine elimination is enhanced in acidic urine,¹³ but the potential risks outweigh the benefits of this elimination strategy.

SUMMARY

- The primary source of nicotine is tobacco made from the leaves of *Nicotiana* species, but chemically related tobacco substitutes and pesticides are becoming increasingly available.
- Nicotine is well absorbed after inhalation, mucosal, or dermal exposure. It is rapidly distributed to the brain where it activates nicotinic acetylcholinergic receptors, stimulates the reticular activating system, and facilitates neurotransmitter release.
- Metabolism via the hepatic cytochrome oxidase system produces pharmacologically inactive metabolites slowly excreted in urine. The half-life of nicotine in the body is about 1 to 4 hours, with more rapid clearance in individuals who are chronically exposed.
- Clinical manifestations of nicotine toxicity are those of nicotinic cholinergic excess, most commonly including vomiting and agitation. Severe poisoning may cause seizures, cardiac dysrhythmias, hypotension, and neuromuscular blockade with respiratory failure from muscular paralysis.
- There are no antidotes for nicotine, and acute toxicity should be managed with symptom directed, supportive care.

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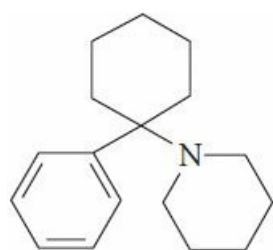
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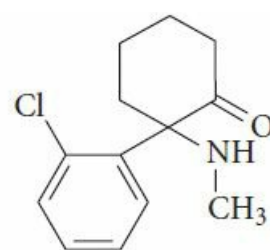
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86 PHENCYCLIDINE AND KETAMINE

Ruben E. Olmedo



Phencyclidine (PCP)



Ketamine



Dextromethorphan

HISTORY AND EPIDEMIOLOGY

Phencyclidine (PCP) was discovered in 1926 but was not developed as a general anesthetic until the 1950s. At that time, the Parke Davis drug company was searching for an ideal intravenous (IV) anesthetic to rapidly achieve analgesia and anesthesia with minimal cardiovascular and respiratory depression.³⁷ PCP was marketed under the name Sernyl because it rendered an apparent state of serenity when administered to laboratory monkeys. Its surgical use began in 1963, but was rapidly discontinued when a 10% to 30% incidence of postoperative psychoses and dysphoria was documented over the subsequent 2-year period.⁸⁶ By 1967 the use of PCP was limited exclusively to veterinary medicine as a tranquilizer marketed under the name Sernylan.

Simultaneously, in the 1960s, PCP emerged as a street drug in San Francisco called “the PeaCe Pill.”⁷⁰ Numerous street names have been given to phencyclidine; on the West Coast, it was called “angel dust,” PCP, “crystal,” and “crystal joints” (CJs); in Chicago it was called “THC” or “TAC”; and those on the East Coast opted for “the sheets,” “Hog,” or “elephant tranquilizer.”¹³² Ironically, PCP was initially unpopular with drug users because of its dysphoric effects and unpredictable oral absorption.¹⁷³ However, with time its use spread in a similar geographic pattern to that of marijuana and lysergic acid diethylamide (LSD), from the coastal United States to the Midwest region.⁷⁰

PCP abuse became widespread during the 1970s.^{26,200} The relatively easy and inexpensive synthesis coupled with the common marketing of PCP as LSD, mescaline, psilocybin, cocaine, amphetamine, and/or “synthetic THC” (tetrahydrocannabinol) added to its allure and consumption.¹³² By the late 1970s PCP abuse had reached epidemic proportions.⁸ The Drug Abuse Warning Network (DAWN) reported that the number of PCP-related emergencies and deaths had more than doubled from 1975 to 1977. In 1978 the National Institute of Drug Abuse reported that 13.9% of young adults (18–25 years old) had used PCP.⁵³ The manufacture of PCP was ultimately prohibited in 1978 when it was added to the list of federally controlled substances. Classifying PCP as a Schedule II drug led to its decrease in availability and, consequently, a decrease in its use. Although the 1980s brought about a cocaine epidemic that eclipsed PCP, PCP has remained consistently available, primarily regionalized to large cities in the northeastern United States and in the Los Angeles area,¹¹¹ where PCP use continues to rise and fall with societal trends. Because many of the PCP congeners made during the manufacturing process were being abused in place of PCP, the Controlled Substance Act of 1986 made these

derivatives illegal and established that the use of the precursor of PCP, piperidine, necessitated mandatory reporting. With this new law in place, those possessing similar but not identical illegal substances could be prosecuted. This led to a further decline in the popularity of PCP. Beginning in 1984, the overall use of PCP declined sharply, reaching a nadir in 1994.²⁰³ However, during the 8 years that followed, there was a small resurgence in reported PCP use, but never reaching the epidemic proportions of the 1970s. Peak use reached an annual prevalence rate of 2.6% in 1996 among 12th graders. DAWN reported that the highest number of PCP related emergencies occurred in Washington, DC, Philadelphia, Los Angeles, Chicago, and Newark, NJ.^{204,207,208} Since 2003, the use of PCP has declined and its prevalence has remained low. During these years the National Survey on Drug Use and Health reports that the annual prevalence rate for the use of PCP for young adults has fluctuated between 0.6% and 0.1% with the latest report of 0.3% in 2011. Lifetime prevalence use of PCP is highest among adults aged 23 to 30 years (3.3%).¹¹³

Laboratory investigation of phencyclidine derivatives led to the discovery of ketamine, a chloroketone analog. Ketamine was introduced for general clinical practice in 1970 and was marketed as Ketalar, Ketaject, and, for veterinary use, Ketavet. Because ketamine has approximately 5% to 10% of the potency of PCP and a much shorter duration of action, it provides greater control in clinical use. Thirty-five years of clinical experience have established that ketamine provides adequate surgical anesthesia, a rapid recovery, and less prominent emergence reactions than PCP.^{60,83,176,222} Because of the simplicity and efficacy of its use, it is regularly used in operating rooms, emergency departments (EDs), and throughout the developing world where little clinical monitoring is available during surgical and emergency procedures.^{57,82,83,85,86,177,221}

Abuse of ketamine was first noted on the West Coast in 1971.¹⁸⁹ During the 1980s there were reports of its abuse internationally, including physicians.^{4,72} The nonmedical use of dissociative anesthetics has continued to increase throughout the 1990s and into the 2000s, in spite of the common complications associated with their use.²⁰² Unfortunately, it is those same pharmacologic qualities that make ketamine more popular than PCP clinically that are responsible for its nonmedical popularity. Ketamine is regularly consumed at all-night “rave parties” and in nightclubs because of its “hallucinatory” and “out-of-body” effects, relatively inexpensive price, and short duration of effect: a single insufflation lasts between 15 and 20 minutes.^{12,47,100,104,223}

The use of ketamine is not limited to the inner city. In the past decade, the media reported police arrests in affluent suburban communities for possession and sale of ketamine, which is coupled to more in-depth and frequent reporting of its toxicity among users.^{47,100,174,223} By contrast to PCP, ketamine is not manufactured illegally, but rather, it is diverted from legitimate medical, dental, and veterinary sources. Additionally, with the advent of the Internet, its availability has dangerously grown nationwide; a sham “biotech” Internet company was seized by the New York City Police Department in 2000 for selling so-called date rape drugs, including ketamine.¹⁴⁵

Adverse reactions do occur, although there are few reports of fatalities secondary to ketamine, even during this period of increased use.^{76,122,126,151} Because of its abuse potential, ketamine was placed in Schedule III of the Controlled Substance Act in 1999.¹⁷⁶ DAWN reported that there was a more than 2000% increase of ketamine related ED visits between 1994 and 2001. Despite any clear reason, after peaking in 2001, there was a decline in ketamine related ED visits in 2002.²⁰⁵ The use of ketamine has remained very low since 2006,¹⁸⁸ with an annual prevalence rate at or below 1.3% for high school students and 0.8% for young adults.^{112,113,206}

PHARMACOLOGY

Chemistry

The chemical name, 1-(1-phenylcyclohexyl)piperidine, provided the basis for its street abbreviation, PCP. During its unlawful chemical synthesis, numerous analogs are made that have similar effects on the central nervous system (CNS) and have been used as PCP substitutes. These “designer” arylcyclohexylamines are aliphatic- or aromatic-substituted amines, ketones, or halides, and appear similar to the parent compound. More than 60 psychoactive analogs are known. The following salient points of the five most prevalent compounds are worth mentioning: 1-[1-(2-thienyl)cyclohexyl] piperidine (TCP) and 1-piperidino-cyclohexanecarbonitrile (PCC) are piperidine derivatives. Piperidine, the synthetic precursor, was formerly easily purchased for the manufacture of PCP and its derivatives. TCP, a thiophene analog, produces even more intense effects than PCP. An intermediate of PCP synthesis, PCC was a constituent of up to 22% of illicit xenobiotic preparations analyzed for phencyclidine. This most likely resulted from a poor manufacturing process.^{15,188} PCC degrades to piperidine, which is recognizable by its strong fishy odor. The presence of its carbonitrile group adds to its toxicity by generating cyanide when smoked.^{13,15,195,196} The pyrrolidine derivative, phencyclohexylpyrrolidine (PHP), is clinically comparable to PCP and is not detected by many of the available drug-screening methods.^{28,95} More potent than PCP, 1-phenyl-cyclohexylethylamine (PCE) was commonly available on the street as a white powder indistinguishable from PCP.¹⁸⁸ TCP, PCE, and PHP are classified as Schedule I drugs, and PCC is classified as Schedule II drug.

Ketamine and tiletamine, two legal analogs of PCP, are used clinically for sedation and anesthesia. In larger quantities, both are also used in veterinary medicine for animal sedation. Tiletamine, in combination with zolazepam (Telazol), is

commonly used for animal procedures in veterinary medicine. Ketamine is the only dissociative anesthetic product manufactured for human use for the purpose of anesthesia, conscious sedation, and the treatment of bronchospasm. The development of a mechanistic approach to pain therapy in the last 20 years has brought a renewed interest in the use of ketamine as an adjuvant to multimodal pain treatment. Ketamine is used prophylactically and therapeutically in children and adults in the management of postoperative pain. For the treatment of pain ketamine is administered intravenously (median dose: 0.4 mg/kg; range: 0.1–1.6), orally, intramuscularly, rectally, subcutaneously, intraarticularly, caudally, epidurally, transdermally, intranasally, or added to a patient-controlled analgesia device.^{65,87,96,117,179} Currently, the rapid antidepressant effect of ketamine is being studied clinically. A common single study dose of 0.5 mg/kg administered intravenously (IV) for 40 to 60 minutes to patients with refractory major depressive disorder provides a 14% to 70% antidepressant response lasting 72 hours postinfusion. Presently randomized control trials are underway to explore dosing, maintenance of response, mode of delivery, and adverse effects.¹

The molecular structure of ketamine [2-(ortho-chlorophenyl)-2-methylaminocyclohexanone] contains a chiral center, producing a racemic mixture of two resolvable optical isomers or enantiomers, the D(+)-isomer and L(–)-isomer. Commercially available preparations of ketamine contain equal concentrations of the two enantiomers. These two molecules differ in their pharmacodynamic effects. In a randomized, double-blind evaluation of patients undergoing surgery, the D(+)-isomer of ketamine was a more effective anesthetic but manifested a higher incidence of psychotic emergence reactions than the L(–)-isomer. In other studies, the D(+)-isomer caused a greater increase in both blood pressure and pulse than the L(–)-isomer, and also had more bronchodilatory effects.^{177,222}

Pharmacokinetics and Toxicokinetics

Phencyclidine is a white, stable solid readily soluble in both water and ethanol. It is a weak base with a pK_a between 8.6 and 9.4 and a high lipid-to-water-partition coefficient. It is rapidly absorbed from the respiratory and the gastrointestinal tracts; as such, it is typically self administered by oral ingestion, nasal insufflation, smoking, or intravenous and subcutaneous injection.

The effects of PCP are dependent on routes of delivery and dose. Its onset of action is most rapid from the IV and inhalational routes (2–5 minutes) and slowest (30–60 minutes) following gastrointestinal absorption.^{45,46} Sedation is commonly produced by doses of 0.25 mg intravenously, whereas oral ingestion typically requires 1 to 5 mg to produce similar sedation. Signs and symptoms of toxicity usually last 4 to 6 hours, and large overdoses generally resolve within 24 to 48 hours, but effects may persist in a chronic user.^{17,58,61,131,158,173} However, in the PCP-poisoned patient, the relationships between dose, clinical effects, and serum concentrations are not reliable or predictable.

There are several explanations for the protracted CNS effects of PCP. Its large volume of distribution of 6.2 L/kg^{45,229} and high lipid solubility account for its entry and storage in adipose and brain tissue. Also, on reaching the acidic cerebrospinal fluid (CSF), PCP becomes ionized, producing CSF concentrations approximately six to nine times greater than those of serum.¹⁴⁸

PCP undergoes first-order elimination over a wide range of doses. It has an apparent terminal half-life of 21 ± 3 hours under both control and overdose settings.^{45,103} Ninety percent of PCP is metabolized in the liver and 10% is excreted in the urine unchanged. PCP undergoes hepatic oxidative hydroxylation into two monohydroxylated and one dihydroxylated metabolites.⁴⁶ All three compounds are subsequently conjugated to form the more water-soluble glucuronide derivatives and then excreted in the urine.

Urine pH is an important determinant of renal elimination of PCP. In acidic urine, PCP becomes ionized and then cannot be reabsorbed. Acidification of the urine increased renal clearance of PCP from 1.98 ± 0.48 L/h to 2.4 ± 0.78 L/h.⁴⁵ If the urine pH is decreased to less than 5.0, then even higher renal clearance (8.04 ± 1.56 L/h) is noted.¹¹ Although this may account for a 23% increase in the renal clearance, it only represents a 1.1% increase of the total clearance.

Similarly, ketamine is water soluble but also has a high lipid solubility ($\text{Log } D = 2.01$) that enables it to distribute to the CNS readily. It has a pK_a of 7.5 and a volume of distribution of 1.8 ± 0.7 L/kg. Ketamine has approximately 10% of the potency of PCP.^{83,105} Human trials demonstrate that, similar to PCP, the clinical effects of ketamine are both route and dose dependent.^{49,52,60,197} Peak concentrations occur within 1 minute of IV administration and within 5 minutes of a 5 mg/kg intramuscular (IM) injection.^{222,233} Ketamine distributes immediately into the CNS with the duration of its hypnotic and anesthetic effects decreased by its redistribution from the brain to other tissues.²²² Recovery time averages 15 minutes for IV administration, but may require 30 to 120 minutes following IM administration. Oral or rectal doses are not well absorbed and undergo substantial first-pass metabolism.^{177,222} In contrast to oral administration of ketamine where effects last 4 to 8 hours, after nasal administration they last for 45 to 90 minutes.

Ketamine is extensively metabolized in the liver by the cytochrome P450 (CYP) isoenzyme CYP2B6 and to a lesser extent by CYP3A4 and CYP2C9.²³¹ Its biotransformation is complex with numerous metabolites described.^{3,177,222} The major pathway involves its N-demethylation to norketamine, a metabolite with one-third the anesthetic potency of ketamine.

Norketamine is hydroxylated at different sites within its hexanone ring, producing varying second chiral centers. Most of these diastereoisomers are glucuronidated to more water-soluble derivatives that are then excreted in the urine.^{83,177} Ketamine also undergoes ring hydroxylation prior to N-demethylation as a minor metabolic pathway. The elimination half-life, which reflects both metabolic and excretory phases, is 2.3 ± 0.5 hours and is prolonged when xenobiotics requiring hepatic metabolism are coadministered.¹²⁸ Because of the enzymatic metabolism, both tolerance and enzyme induction are reported following chronic administration.^{83,177}

Available Forms

PCP is available on the street in a variety of forms, including powder, liquid, tablets, leaf mixtures, and rock crystal. Because of its uncontrolled illegal manufacture, the contents of PCP vary considerably, with powder often the purest form. A typical dose consumed contains approximately 5 mg.¹⁷² Leaf mixtures are made by sprinkling approximately 1 to 10 mg of phencyclidine onto parsley, oregano, mint, tobacco, or marijuana. A typical PCP joint (known as “crystal joint,” “KJ,” or “supergrass”) is developed for smoking and contains about 1 mg per 150 mg of plant product.⁷ Mentholated cigarettes dipped into liquid PCP are known as “supercools.”

PCP is included in the US Federal Controlled Substance Act of 1970, reducing its availability for incorporation into marijuana cigarettes. There are reports of marijuana cigarettes being adulterated with PCP and sold on the street under varying names like “Illy” in Connecticut, “Hydro” in New York City, “Dip” in New Jersey, “Wet” in Philadelphia, and “Fry” in Texas.⁹⁸

The cigarettes are purportedly treated with “embalming fluid,” which allegedly enhances the euphoric effects of the drug. Rather, the embalming fluid, or another organic solvent, is used as a medium to allow a uniform distribution of PCP in these cigarettes.⁹⁸ Furthermore, the organic solvent may be the remnant of the organic solvent used in the synthesis of PCP or one of its analogs. In either case, the ability to smoke the cigarette prior to drying after dipping in the solvent/PCP (nonaqueous) mixture accounts for its various names. In most cases, this “enhanced” mixture appears to be purchased intentionally rather than having the PCP placed in these cigarettes surreptitiously.

On the street and on the Internet, ketamine is known as “vitamin K,” “Special K,” “Super K,” “Ket,” or simply “K.” It is available in a liquid form that is dried into a pure-white crystalline powder and is typically self-administered by ingestion or insufflation in a fashion similar to PCP. It is rarely injected IV or IM in aqueous form.

When used by injection, there is an observed demographic and behavioral difference among those who initiate drug injection use with ketamine and those who initiate injection use with another xenobiotic and later transition into ketamine injection.¹²⁵

Ketamine is primarily sold as tablets, capsules, or powder. These formulations are often adulterated with caffeine, methylenedioxymethamphetamine (MDMA), ephedrine, methamphetamine, heroin, and cocaine (a mixture known as CK or Calvin Klein).^{63,180} In fact, in addition to alcohol, MDMA (39%), heroin (17%), and cocaine (14%) are the most frequently mentioned xenobiotics used with ketamine.²¹¹ Exemplifying the commercial growth of ketamine, some of the tablets are even found to contain a “K” logo.⁶³ Common sedating doses are 75 to 300 mg orally (30–75 mg for insufflation). Higher doses, ranging between 300 and 450 mg orally (100–250 mg for insufflation), result in substantial CNS adverse effects. These manifestations are similar to the clinical “emergence reactions” that patients experience during ketamine anesthesia.

More recently, abuse of a ketamine analogue, methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino) cyclohexanone) is reported. This designer drug is a means of evading drug enforcement. Sold through the Internet internationally as a white powder, it may be ingested, insufflated, or injected. Its market is mostly in the United Kingdom and is referred to by various names, including M-ket, Kmax, and Mexxy. Case reports indicate that the clinical symptoms of patients with methoxetamine toxicity are similar to those reported from ketamine.^{97,218,228}

PATHOPHYSIOLOGY

The arylcyclohexylamines, of which PCP and ketamine are prototypes, are a group of anesthetics that functionally and electrophysiologically “dissociate” the somatosensory cortex from higher centers.^{49,221} The precise mechanisms by which PCP and ketamine achieve these effects are complex and not fully understood; however, investigation of the nature of PCP-induced psychosis has led to a substantial identification of the various sites of PCP activity.

Most studies demonstrate that PCP and ketamine bind with high affinity to sites located in the cortex and limbic structures of the brain.¹³⁴ They block the NMDA receptors at serum concentrations encountered clinically.^{215,234} Analogs of PCP (TCP, PCE, PHP, and ketamine) and dizocilpine (MK-801) also interact with the NMDA receptor in a dose-response manner that corresponds appropriately to their neurobehavioral effect.^{27,185,224} These xenobiotics bind to the NMDA receptor at a site independent of glutamate.^{105,110,134,226} As such, they antagonize the action of glutamate on this channel and noncompetitively block Ca^{2+} influx (Fig. 14–14).

PCP and ketamine bind to the biogenic amine reuptake complex with 10% to 20% of the affinity to which they bind to the NMDA receptor. Binding occurs at physiologic concentrations that normally take place after subanesthetic doses.^{5,168} This weak inhibition of the catecholamine reuptake accounts for the respective sympathomimetic and psychomotor effects. An increase in blood pressure and heart rate is induced. Rapid IV infusion produces a more pronounced effect than by IM injection, with the D(+)-isomer having a greater effect than the L(-)-isomer.²²²

In significant overdoses, PCP and ketamine also stimulate sigma receptors at concentrations generally associated with coma, although with lower affinity than NMDA receptors.^{198,225} Both D₂ and sigma receptors have an inhibitory effect on the cholinergic receptor pathways.²²⁵ At the higher concentrations, typically associated with death, PCP and ketamine also bind to the nicotinic, opioid, and muscarinic cholinergic receptors.²¹⁴

NMDA antagonists produce effects on behavior, sensation, and cognition that resemble aspects of endogenous psychoses, particularly schizophrenia.^{106,165} These behavioral abnormalities were first observed in studies in the late 1950s when PCP, administered to healthy volunteers, generated a form of organic psychosis that mimicked schizophrenia. When PCP was administered to schizophrenic patients, it uniformly intensified their primary symptoms of profound disorganization, and some of these symptoms lasted for weeks.¹³¹ PCP psychosis is so similar to schizophrenia that many psychiatrists cannot distinguish them without a prior indication of drug abuse history.¹⁹⁴ The multireceptor action of PCP and its link to schizophrenia is made more intriguing as various antipsychotics (eg, phenothiazines, thioxanthenes, butyrophenones) are also α receptor agonists.⁸⁰

Current interest in the role of excitatory neurotransmitter systems in the pathophysiology of schizophrenia has led to similar observations in patients after ketamine administration. Subanesthetic doses of ketamine administered to both healthy and schizophrenic volunteers induced a mild, dose-related, short-lasting increase in psychotic symptoms. Although the normal and schizophrenic volunteers had different levels of baseline psychosis, the magnitude, time course, and dose-response changes in positive symptoms were similar across the two populations. Both groups experienced thought disorganization, such as concreteness and loose association, hallucinations, and delusions of varying intensity.^{120,122–124}

There is a connection between PCP psychosis and sensory processing. PCP and ketamine inhibit sensory perception in a dose-dependent manner. This processing in sensory information corresponds to their relative affinities to the NMDA receptor and not to the sigma receptor.^{7,168} Clinically, the impairment of sensory input produced by PCP resembles that of patients who are deprived of sensory stimulation.¹⁴¹ When external stimulation was reduced by environmental sensory deprivation, the psychotomimetic effects of PCP were diminished,⁴³ giving credence to the theory that it may not be anxiety that causes perceptual dysfunction in schizophrenia, but the converse.

Many of the NMDA antagonists, including PCP and ketamine, have a negative effect on cognition and memory. Repeated administration of PCP and ketamine in many animal models results in cognitive and memory impairment.^{93,108} Both impair concentration, recall, learning, and retention of new information.^{14,31,56,58,77,92–94,120,138,150,161} In human volunteers, ketamine selectively impairs explicit,⁷⁶ episodic,^{55,154} and procedural memory,¹⁵⁴ and disrupts frontal cortical function, as measured by the Wisconsin Card Sorting Task and verbal fluency,^{120,138} in a dose-dependent manner. Learning and memory impairments in volunteers who were administered subanesthetic doses of ketamine (0.65 mg/kg) are independent of the user's attention and related psychosis.¹³⁸ Testing performed on chronic ketamine users produces similar results that are long lasting and have more marked effects on semantic and episodic memory.^{55,56,156,157} Accordingly, it is presumed that the acute and repeated NMDA receptor antagonism interferes with those functions that integrate interoceptive and exteroceptive input in which goal-directed action becomes possible, similar to the organic psychosis in schizophrenia. Because the rapid antidepressant effects of ketamine have the potential for either continuous and/or repeated dosing, current research may attend to its long-term adverse effects.

Hypofunction of the NMDA receptor causes neuroanatomic and neurobehavioral effects. Animals exposed to NMDA antagonists such as PCP and dizocilpine transiently demonstrated neuronal vacuolar degeneration in the retrosplenial cortex and the posterior cingulate areas of the brain.^{163,164} The major function of cingulate cortical neurons is to mediate affective responses to pain.²¹⁶ Single high doses or repeated exposures to NMDA receptor antagonists are associated with a higher incidence of cellular death.^{48,66,67,163} This injury seems to be related to the induction of selective expression of individual heat shock proteins in this anatomical area.¹⁸⁷ Excitatory amino acids are neurotransmitters responsible for mediating seizure activity in the brain. Although NMDA inhibitors, the anticonvulsant properties of PCP and ketamine are not demonstrated. Animals administered PCP or PCP analogs progress through dose-related clonic activity followed by tonic-clonic convulsions, as is typical of classic convulsant compounds.¹⁶⁸ Animal research also demonstrates wide interspecies variability of the electroencephalographic (EEG) effects of PCP.⁶¹ In a murine seizure model, ketamine possessed selective anticonvulsant properties.³² In addition, ketamine preserves learning proficiency in rats when administered shortly after onset of status epilepticus, an effect that may prove useful in the clinical setting when combined with conventional antiepileptic medications.¹⁹⁹

In humans, although these dissociative xenobiotics induce excitatory activity in the thalamus and limbic areas, they do

not affect cortical regions.^{51,52,60,73} Excitation, muscle twitching, posturing,¹⁴⁹ and tonic–clonic motor activity with or without EEG changes are reported with these subcortical EEG alterations.^{35,50,73,149} In the clinical setting, many report ketamine to possess anticonvulsant properties at clinically relevant doses and may be explained by an NMDA inhibitory effect.^{35,50} This effect was employed to treat patients with refractory status epilepticus in the critical care setting.²¹⁰

The NMDA receptor is also responsible for the development of the neuronal organization of the central nervous system.^{101,102,190,191} It is linked to hypoxic–ischemic brain injury by mediating calcium influx, a final pathway in cell death. The uninhibited firing of NMDA afferent neurons secondary to brain injury causes their death, as well as the death of efferent neurons downstream. In neonatal rats, ketamine increases the rate of neuronal apoptosis.¹⁸⁵ NMDA antagonists such as PCP block hypoxic brain injury from stroke and trauma.^{18,130} In a rat model of ischemic stroke, PCP had a protective effect on the brain, demonstrated by a decreased rate of seizure activity.¹⁸ This effect is transient and has not been studied in humans.

PCP induces modest tolerance in rats and squirrel monkeys. The development of tolerance is mostly secondary to the pharmacologic effects of PCP rather than to biodispositional changes. Dependence was also observed in monkeys who self-administered PCP (10 mg/kg/d to serum concentrations of 100–300 ng/mL) over one month by the appearance of dramatic withdrawal signs when access was denied. Signs included vocalizations, bruxism, oculomotor hyperactivity, diarrhea, piloerection, difficulty remaining awake, tremors, and in one case convulsions.¹⁶ These signs appeared within 8 hours of abstinence and were most severe at about 24 hours. When either PCP or ketamine (2.5 mg/kg/h) was readministered to the animals, PCP withdrawal symptoms were reversed, indicating cross-dependence from PCP to ketamine.^{21,107,193}

Physiologic dependence in humans has not been formally studied. It is implied to occur by the observation that chronic PCP users developed depression, anxiety, irritability, lack of energy, sleep disturbance, and disturbed thoughts after one day of abstinence from drug use.¹⁷⁵ In addition, neonates whose mothers used PCP developed jitteriness, vomiting, and hypertonicity that lasted for at least 2 weeks.²⁰¹ These symptoms may represent PCP withdrawal or intrinsic teratogenic effects on neurologic development.^{81,101} Although there are no controlled studies observing the physiologic symptoms of withdrawal in humans who chronically use PCP or ketamine, there is a definite psychological dependence on the sensations experienced during recreational use of the drugs.¹⁸⁹ There are a few cases of ketamine tolerance where patients report a need to use an increased quantity of drug to get the same effect.^{54,152,169} In a study of ketamine abstinence, patients characterized their withdrawal symptoms as anxiety, shaking, sweating, and palpitations.¹⁵⁵ In addition, ketamine impairs response inhibition, which is found to be related to increases in subjective ratings of desire for the drug.¹⁵⁴

CLINICAL MANIFESTATIONS

The reported signs and symptoms of patients presenting to the ED with PCP and ketamine toxicity are variable. The variations are a result of differences in dosage, the multiple routes of administration, concomitant xenobiotic use, and other associated medical conditions. In accordance with their pharmacologic effect, ketamine toxicity produces signs and symptoms similar to PCP with a shorter duration of action. In addition, individual differences in xenobiotic susceptibility, the development of tolerance in chronic users, as well as contaminants in the drug manufacture, may account for erratic clinical findings.

Vital Signs

Body temperature is rarely affected directly by PCP and ketamine. In one large series, only 2.6% of patients demonstrated hyperthermia ($> 101.8^{\circ}\text{F}$ [38.8°C]).¹⁴² In an experimental animal model, PCP failed to increase body temperature.^{37,61} When hyperthermia does occur, all the known complications, including encephalopathy, rhabdomyolysis, myoglobinuria, acute kidney failure, electrolyte abnormalities, and liver failure, occur (Chap. 30).^{9,20,42,170}

Most PCP and ketamine toxic patients demonstrate mild sympathomimetic effects. PCP consistently increases both the systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a dose-dependent fashion.^{37,61} Doses of 0.06 mg/kg of IV PCP increase the SBP and DBP by 8 mm Hg, whereas 0.25 mg/kg produce a 26 and 19 mm Hg increase in SBP and DBP, respectively. PCP also increases the heart rate, although it does so inconsistently.⁹⁰ Likewise, ketamine produces mild increases in blood pressure, heart rate, and cardiac output via this same mechanism.^{52,133,197,212,222} In fact, tachycardia was the most common finding on physical examination in a case series of ketamine abusers presenting to the ED.²²⁰

Cardiopulmonary

Cardiovascular catastrophes are rarely encountered in PCP toxicity.^{64,143} These complications may result from direct vasospasm,^{6,36} causing severe systemic hypertension, pulmonary edema, hypertensive encephalopathy,⁶⁵ and cerebral

hemorrhage.²³ Hypertension, along with abnormal behavior, miosis, and nystagmus in children, strongly suggest toxicity due to a dissociative anesthetic.¹¹⁵

The effect of PCP and ketamine on cardiac rhythm is controversial. Dysrhythmias are only observed in animals poisoned with very large doses of PCP. Ketamine both enhances and diminishes epinephrine-induced dysrhythmias in animals.^{22,62,91,116} The considerable experience in the use of ketamine anesthesia on humans undergoing surgery or cardiac catheterization has not demonstrated prodysrhythmic effects.^{69,159}

As these dissociative anesthetics were designed to maintain normal ventilation, hypoventilation is uncommon. In clinical studies, PCP increased the minute ventilation, tidal volume, and respiratory rate of volunteers.⁹⁰ Clinically, in PCP-toxic patients, irregular respiratory patterns develop as tachypnea much more often than as bradypnea.^{9,142} Hypoventilation, when present, is usually secondary to the use of particularly high doses of PCP. Acute respiratory distress syndrome secondary to respiratory depression is also a rare occurrence. Large doses of PCP (20 mg/kg) administered to laboratory animals produced respiratory depression.³⁷ Although respiratory depression in humans is an extremely rare event, it has been reported with fast or high-dose infusions of ketamine.^{84,222} In fact, ketamine has been successfully used to prevent intubation in patients with refractory asthma. Ketamine relaxes bronchial smooth muscles, decreases mean airway pressure and $P_{a_{CO_2}}$, and increases $P_{a_{O_2}}$.^{75,178,202,222}

Neuropsychiatric

Most patients with PCP and ketamine toxicity brought to medical attention manifest diverse psychomotor abnormalities.^{13,19,29,72,108,220} As dissociative anesthetics, these xenobiotics impair response to external stimuli by separating various elements of the mind. Consciousness, memory, perception, and motor activity appear dissociated from each other. This dissociation prevents the user from attaining cognition and properly assembling all this information to construct a reality. Clinically, the person may appear inebriated, either calm or agitated, and sometimes violent. In large overdoses, the anesthetic effect causes patients to develop stupor or coma. In recreational use, “dissociatives” are not taken for these effects, but rather for so-called out-of-body experiences. In addition patients often have disordered thought processes (including disorientation as to time, place, and person) or amnesia, paranoia, and dysphoria.⁷¹

The manifestations of PCP and ketamine toxicity are better illustrated by the results of their effects in controlled human studies. Volunteers who took oral doses of up to 7.5 mg/day of PCP or 0.1 mg/kg of ketamine exhibited clinical inebriation, but higher doses (PCP > 10 mg/day; ketamine 0.5 mg/kg) generally caused a more severe impairment of mental function.^{61,120} IV doses of 0.1 mg/kg of PCP^{17,58,131,158,181} and 0.5 mg/kg of ketamine^{120,168} cause diminution in all sensory modalities (pain, touch, proprioception, hearing, taste, and visual acuity) in a dose-dependent fashion. Both xenobiotics also cause feelings of apathy, depersonalization, hostility, isolation, and alterations in body image.^{17,58,74,109,137,156} The deficits in sensory modalities are evident prior to the development of the psychological effects of PCP, with pain perception disappearing first. This alteration in analgesic perception is caused by a blocking action on the thalamus and midbrain (Fig. 86–1).¹⁵⁸

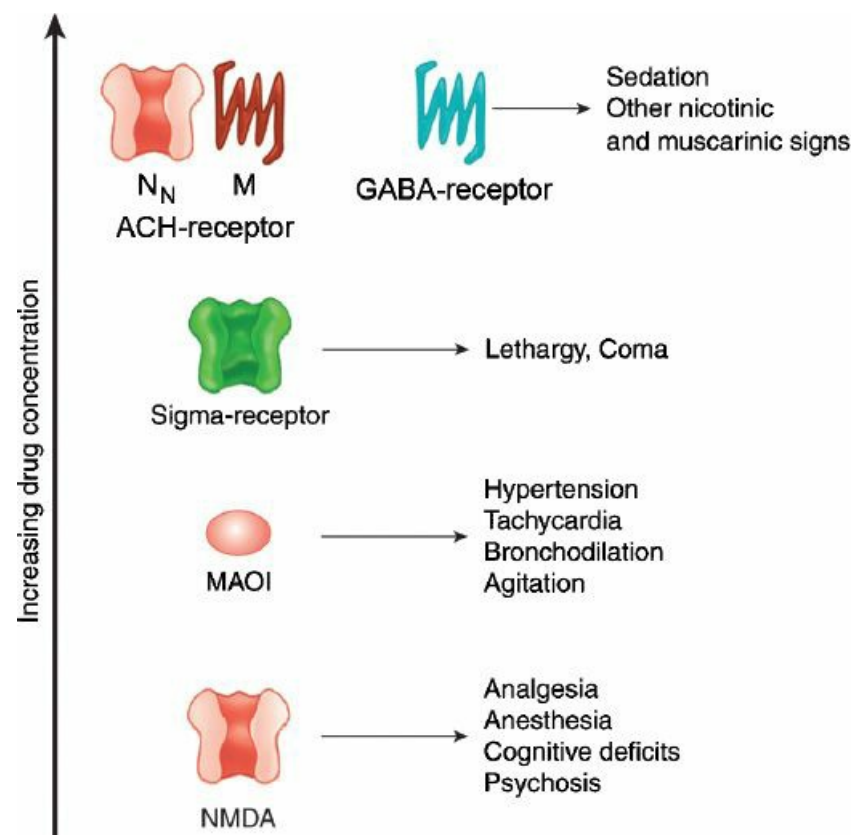


FIGURE 86–1. Clinical effects of phencyclidine and ketamine. Phencyclidine and ketamine bind to different receptors in the CNS with varying degrees of affinity; ie, an increasing concentration is necessary to achieve the various clinical effects. ACh = acetylcholine; CNS = central nervous system; GABA = γ -aminobutyric acid; M = muscarinic receptor; MAOI = monoamine oxidase inhibitor; NMDA = N-methyl-d-aspartate; N_N = nicotinic receptor.

Abnormal stereognosis and proprioception occur in a dose-dependent manner. This disturbed perception results in body image distortions described as “numbness,” “sheer nothingness,” and “depersonalization.” The decrease of proprioceptive sensation to gravity probably gives the sensation of “tripping” or “flying.” Because all sensory modalities are affected, visual, auditory, and tactile illusions and delusions are common. Hallucinations are typically auditory rather than visual, which are more common with LSD use. The hallucinogenic effects of ketamine on healthy human volunteers are linearly related to steady-state concentrations between 50 and 200 ng/mL.²⁴ Most ketamine users report experiencing a “k-hole,” a slang term for the intense psychological and somatic state experienced while under the influence of ketamine. This experience varies with the individual, but can include buzzing, ringing or whistling sounds, traveling through a dark tunnel, intense visions, and out-of-body or near-death sensations.⁵⁹

The reaction to the misperceived or disconnected reality may result in unintentional actions and violent behavior. The hallmark of PCP toxicity is the recurring delusion of superhuman strength and invulnerability resulting from both its anesthetic and dissociative properties. There are case reports of patients presenting with trauma either from jumping from high altitudes, fighting large crowds or the police, or self-mutilation. The true extent and incidence of violence is probably less than previously suggested.²⁵

Typically, neurologic signs include horizontal, vertical, and/or rotatory nystagmus, ataxia, and altered gait. Initially, except for ataxia, motor movement is not impaired until the patient becomes unconscious. On physical examination, use of dissociative anesthetics typically produces relatively small pupils, nystagmus, and diplopia. In the largest case series reported to date, nystagmus and hypertension were noted in 57% of patients who had taken PCP.¹⁴² Smaller and more limited studies have found an incidence of nystagmus approximating 89%.¹⁹ In comparison, nystagmus was only found in 15% of patients with ketamine abuse.²⁰⁰ Other cerebellar manifestations were also encountered, most notably dizziness, ataxia, dysarthria, and nausea. A pooled data compilation of 35 reports demonstrated that emesis occurred 8.5% of the time.⁸⁴ In fact, Internet chat groups devoted to substance abuse commonly direct users to “mix dissociatives with marijuana” for its antiemetic effect.

Larger doses of PCP produce loss of balance and confusion, the latter characterized by inability to repeat a set of objects, frequent loss of ideas, blocking, lack of concreteness, and disordered linguistic expression.^{55,61,120,131,181} Similarly, ketamine users report a high incidence of incoordination, confusion, unusual thought content, and an inability to speak.⁵⁹ In general, dissociative anesthetics stimulate the CNS but seizures rarely occur, except at high doses. The largest case series of PCP-toxic patients detected a 3.1% incidence of seizures.¹⁴²

Although PCP and ketamine toxic patients also present with motor disturbances, it is unclear to what extent PCP and

ketamine are actually responsible for these manifestations. The most common of the reported disturbances are dystonic reactions: opisthotonos, torticollis, tortipelvis, and risus sardonius (facial grimacing). Myoclonic movements, tremor, hyperactivity, athetosis, stereotypies, and catalepsy also occur.^{13,30,72,142} A slight increase in muscle tone results from a dopaminergic effect.¹³¹ Laryngospasm requiring intubation has been reported after the use of ketamine anesthesia. The incidence of this complication is less than 0.017%.⁸³ By comparison, the incidence of laryngospasm following traditional general anesthesia is 2%.¹⁵⁰

Urological and Hepatobiliary

Intense abdominal and pelvic pain is regularly reported in habitual ketamine users.^{160,232} In the majority of cases, the etiology is urologic. The first case series describing ketamine-associated urological dysfunction was reported in 2007. The patients' symptoms consisted of severe lower urinary tract syndrome (LUTS): dysuria, frequency, urgency, urge incontinence, and painful hematuria (Fig. 86–2). When investigated by cystoscopy, patients with hematuria were frequently found to have ulcerative cystitis.¹⁸⁴



FIGURE 86–2. Ketamine-associated lower urinary tract syndrome. This abdominal-pelvic computed tomographic (CT) scan was obtained in an 18 year-old girl who presented to the hospital with complaints of severe abdominal pain and hematuria. The image demonstrates a small bladder volume with an irregular thickened mucosal surface that enhances with contrast. (Used with permission of The Division of Medical Toxicology, Department of Emergency Medicine, NYU School of Medicine, Bellevue Hospital Center.)

Subsequent reports have established LUTS as a complication in both recreational ketamine users as well as in a patient receiving ketamine therapeutically for chronic regional pain syndrome.^{39,89,103} The incidence of ketamine-induced urologic dysfunction is not well established. Studies from the United Kingdom report an incidence of 20%, whereas a study from Hong Kong reports the incidence of 32% and 92% in acute and chronic ketamine users respectively.^{139,227,232}

The symptoms of ketamine-induced urologic dysfunction are secondary to an inflammatory process that reduces bladder size. Initial urinalyses are typically sterile. Patients develop diminished voiding capacity of 20 to 200 mL, decreased bladder compliance, and detrusor overactivity as measured by urodynamic testing. A thickened bladder wall, a small bladder volume, and perivesicular stranding are usually detected by ultrasonography and computerized tomography (CT) of the lower urologic tract.¹³⁹ Cystoscopy demonstrates an erythematous bladder mucosa with various degrees of ulcerations. Bladder biopsies confer epithelium denudation and ulcerative cystitis. There is a marked lymphocytic infiltration with a variable number of eosinophils and fibrosis as well as squamous metaplasia and nephrogenic metaplasia. The exact mechanism by which ketamine or one of its metabolites causes the destruction of the urinary tract remains unknown.^{39,40,227,232}

The pathology of ketamine-induced urologic dysfunction is not confined to the lower urinary tract. Upper urinary tract involvement is variable. A lower incidence of 13% has been reported in the United Kingdom compared with 51% in Hong Kong. The lower incidence is thought to be due to patients in the United Kingdom seeking medical attention earlier than those living in Hong Kong. IV urography and urography by CT reveal unilateral or bilateral ureteric narrowing. Bilateral hydronephrosis was reported in 44% to 50% of patients, and renal impairment has also been described.^{139,147} Biopsy of the ureter in a patient who underwent right nephrectomy with an ileal conduit anastomosis to the left renal pelvis demonstrated nephrogenic metaplasia throughout the ureter extending to the renal pelvis as well as ulceration with associated inflammatory changes, as described the bladder biopsies.⁹⁹

Intense abdominal pain in frequent ketamine users is also suggested to be hepatobiliary in nature. Case series of patients who used ketamine illicitly or therapeutically report abnormal liver function tests and biliary tract abnormalities.^{129,162,183} CT revealed common bile duct dilation with a smooth tapered end, a condition that mimics benign cystic dilation of the bile ducts. Endoscopic retrograde cholangiopancreatography and hepatobiliary iminodiacetic acid studies concur with these findings, suggesting gallbladder wall dyskinesia. These biliary abnormalities are noted to subside with cessation of ketamine use.¹²⁸

Emergence Reaction

The acute psychosis observed during the recovery phase of PCP anesthesia limits its clinical use. This bizarre behavior, characterized by confusion, vivid dreaming, and hallucinations, is termed an “emergence reaction.” These reactions occur most frequently in middle-aged men, with a reported incidence of 17% to 30%.^{90,114} The most violent emergence reactions follow an IV dose of approximately 0.25 mg/kg of phencyclidine.⁶¹ The mildest degrees of agitation produced by PCP resemble the effects of ethanol intoxication.

These same postanesthetic reactions also limit the clinical use of ketamine. The incidence of emergence reactions following ketamine administration may approximate 50% in adults and 10% in children.⁸³ Patients older than 10 years of age, women, persons who normally dream frequently, have a prior personality disorder, or both, premorbid denial of presence of illness or anosognosia (denial of the presence of an illness), and paranoia incur the greatest risk.^{83,144} The incidence of the occurrence of emergence reactions appears to be exacerbated when dissociative anesthetics are rapidly IV administered, as well as in patients exposed to excessive stimuli during recovery. Although it has not been proved in a controlled study, reducing external stimuli during the recovery phase might reduce emergence reactions.

Ironically, the very characteristics thought to make PCP ideal for anesthesia—the preservation of muscle tone and cardiopulmonary function—magnify the difficulties in managing an individual who manifests dysphoria after an overdose. The course of delirium, stupor, and coma associated with PCP and ketamine is extremely variable, although the manifestations are much milder and shorter acting following ketamine use.

Cholinergic and Anticholinergic Effects

Both cholinergic and anticholinergic clinical manifestations occur in the PCP- or ketamine-toxic patient. Miosis or mydriasis, blurred vision, profuse diaphoresis, hypersalivation, bronchospasm, bronchorrhea, and urinary retention may occur.^{13,19,127,141,142} Clinically, ketamine stimulates salivary and tracheobronchial secretions, both of which are equally and effectively inhibited by atropine and glycopyrrolate.¹⁵² Furthermore, in a randomized, double-blind trial, after infusion of 1.5 mg/kg of ketamine in healthy volunteers, physostigmine decreased nystagmus, blurred vision, and the time to recovery. However, nausea and vomiting were more frequent.²¹¹

DIAGNOSTIC TESTING

If it is necessary to confirm the suspicion of PCP usage, then urine is most commonly used as a matrix for analysis, although serum, and possibly gastric contents, can also be used. Rarely is it essential to make this determination. Most hospital laboratories do not perform quantitative analysis of PCP, but many can perform a qualitative urine test for the presence of the drug. Qualitative testing is more important than a quantitative determination as serum concentrations do not correlate closely with the clinical effects. PCP is qualitatively detected by an enzyme immunoassay at a sensitivity of 10 ng/mL. High-affinity antibodies were once studied as specific PCP antagonists to reverse PCP-induced toxicity.^{167,213} Thus, the detection of PCP is dependent on the concentration of PCP in the body fluid tested and the affinity of the antibody for the PCP molecule. As such, the immunoassay antibody binding to a molecule similar to PCP can produce false-positive reactions. Metabolites of PCP, such as PCE, PHP, TCP, and its pyrrolizidine derivative TCPy, cross-react with the immunoassay at concentrations 30 times higher than those used to detect PCP. Because of its similar structure to PCP, dextromethorphan and its metabolite dextrorphan also cross-react with Syva enzyme-multiplied immunoassay and fluorescence polarization PCP assays (Chap. 6).^{100,219}

Although nonspecific, laboratory findings resulting from PCP use can include leukocytosis, hypoglycemia, and elevated

concentrations of muscle enzymes, myoglobin, BUN, and creatinine.¹⁴² The EEG reveals diffuse slowing with θ and δ waves, which may return to normal before the patient improves clinically.

There is no commercially available quantitative immunoassay for ketamine. When necessary, ketamine is detected by gas chromatography/mass spectroscopy. The increase in popularity in ketamine use in certain parts of the world has led to the development of rapid-detection urine assays that are sensitive, specific, and accurate.^{38,217} There is anecdotal evidence that ketamine also cross-reacts with the urine PCP immunoassay because of their structural similarity.¹⁸⁶ Other authors, including the manufacturer that tests the reactivity of the commercially available PCP immunoassay with ketamine, do not find such results.^{33,220}

MANAGEMENT

Agitation

Conservative management is indicated for PCP and ketamine toxicity and includes maintaining adequate respiration, circulation, and thermoregulation. The psychobehavioral symptoms observed during acute dissociative reactions and during the emergence reaction are similar. To treat the symptoms of agitation and alteration of mental status of acutely toxic PCP patients, it is helpful to recognize that both pharmacologic^{2,34,41,44,68,82,83,135,140} and behavioral^{43,44,83,121} modalities have been used to diminish agitation and emergence phenomena during conscious sedation with ketamine. To prevent self-injury, a common form of PCP-induced morbidity and mortality, the patient must be safely restrained, initially physically, and then chemically. An IV line should be inserted and blood drawn for electrolytes, glucose, BUN, and creatinine concentrations. The use of 0.5 to 1.0 g/kg of body weight of dextrose and 100 mg IV thiamine HCl should be considered as clinically indicated.

Although body temperature is directly affected by PCP and ketamine, hyperthermia may occur secondary to psychomotor agitation and should be rapidly identified. Treatment should be accomplished immediately with adequate sedation to control motor activity. At presentation, placing the patient in a quiet room with low sensory stimuli will help achieve this goal. Physical restraint should only be used temporarily, if necessary, until chemical sedation is achieved. Rapid immersion in an ice water bath may be necessary because body temperatures greater than 106°F (41.1°C) place the patient at a great risk for end-organ injury. These patients will need volume repletion and electrolyte supplementation because hyperthermia increases fluid loss from sweat.

In the pharmacologic treatment of emergence reactions, benzodiazepines have been used with great success. A benzodiazepine such as diazepam, administered in titrated doses of up to 10 mg intravenously every 5 to 10 minutes until agitation is controlled, is usually safe and effective. Numerous studies demonstrate the benefits of benzodiazepines, although under certain conditions^{41,83} they may prolong recovery time. Midazolam may be more effective than diazepam under certain circumstances.^{34,140} Additionally, in a double-blind placebo-controlled study, lorazepam reduced the anxiety associated with ketamine without antagonizing the cognitive or psychotomimetic effects of ketamine.¹¹⁹ By contrast, phenothiazines may lower the seizure threshold, and both phenothiazines and butyrophenones may cause acute dystonic reactions. Phenothiazines may also cause significant hypotension due to their α -adrenergic blocking effects on the vasculature, worsen hyperthermia, and exacerbate any anticholinergic effects from these drugs.

Some behavioral modalities have also been implemented in the treatment. Early studies demonstrated that the psychotomimetic effects of PCP were diminished when external stimulation was reduced by environmental sensory deprivation.⁴³ The practice of placing patients in a quiet room with minimal sensory stimulation is recommended by many, but has never been formally studied in a double-blind, controlled trial, nor is it functionally feasible in most clinical settings. Conversely, it is observed in patients undergoing ketamine anesthesia that emergence reactions are less violent when patients are talked to or when music is played.^{121,192}

Although it is always important to ask the patient the names, quantities, times, and route of all xenobiotics taken, the information obtained may be unreliable. Even when the patient is trying to cooperate and give an accurate history, many street psychoactive xenobiotics are mixtures whose contents are unknown to the patient. Consequently, pharmacologic management is complex and often sign or symptom dependent. Although some authors have attempted to define the appropriate therapy for specific PCP congeners and for ketamine-induced psychosis, no single approach has been consistently efficacious.^{77,78,118,136}

Cystitis

The objectives of the management of ketamine-induced cystitis are in making the diagnosis, decreasing symptoms and in maintaining kidney function. Urinalysis should be obtained on all symptomatic patients in order to exclude urinary tract infection and a serum creatinine should be obtained to evaluate kidney function. For patients whose symptoms are mild, abstinence from ketamine use may be sufficient to reverse symptoms and pathology. Several therapeutic regimens have been tried with little success. They include antibiotics, nonsteroidal antiinflammatory drugs (NSAIDs), steroids,

anticholinergics. Urologic evaluation and follow-up will be necessary.¹⁴⁷

Moderate and severe symptoms of LUTS are defined as a daytime frequency of more than six, nighttime frequency of one or more than one, regular urgency on voiding, and moderate bladder or pelvic pain. For those patients with these symptoms, urologic consultation and repeated kidney function monitoring are essential. Ultrasonography and urography by CT assist in detecting lower and upper tract abnormalities. Urodynamic studies may further quantify bladder voiding capacity and detrusor activity. Invasive procedures may need to be undertaken in patients with impaired kidney function and deterioration. Cystoscopy will aid in visualizing the bladder and excluding other causes of hematuria and LUTS. During this procedure, a bladder biopsy may be performed. Injury to the upper urologic tract may be imaged with urography by CT. Nephrostomy insertions may be necessary in patients who present with impaired kidney function secondary to ureteric narrowing. Refractory cases may need to undergo urinary diversion.^{40,99,139}

Decontamination

Patients with a history of recent oral use of PCP or ketamine are candidates for gastrointestinal decontamination. Although there is rarely, if ever, an indication for orogastric lavage, aggressive decontamination may be indicated if potentially lethal coingestants are suspected. Activated charcoal (1 g/kg) should be administered as soon as possible and may be repeated every 4 hours for several doses. Activated charcoal will effectively adsorb PCP and increase its nonrenal clearance; even without prior gastric evacuation this approach is usually adequate.¹⁷⁴

Theoretically, xenobiotics that are weak bases, such as PCP, can be eliminated more rapidly if the urine is acidified. Although urinary acidification with ammonium chloride was previously recommended,¹⁰ we do not recommend this approach. The risks associated with acidifying the urine—simultaneously inducing a systemic acidosis, thereby potentially increasing urinary myoglobin precipitation—outweigh any perceived benefits (Chap. 10).

As opposed to the problems in applying ion trapping to renal excretion, ion trapping results in the active mobilization of PCP into gastric secretions. PCP is in a substantially ionized (and therefore non-lipid-soluble) form in the acid of the stomach and can be absorbed only when it reaches the more alkaline intestine. As a result, gastric suction can remove a significant amount of the drug, as well as interrupt the gastroenteric circulation by which the xenobiotic is secreted into the acid environment of the stomach only to be reabsorbed again in the small intestine.¹⁰ However, continuous gastric suction is unnecessary and can also be dangerous. It should be considered only in comatose patients. Continuous suction may result in trauma to the patient as well as in fluid and electrolyte loss, which can further complicate management and possibly interfere with the efficacy of activated charcoal. For these reasons, the administration of single- or multiple-dose activated charcoal rather than continuous nasogastric suction appears to be the safest and most effective way of removing ion-trapped drug from the stomach in severely poisoned patients.

Most patients rapidly regain normal CNS function anywhere from 45 minutes to several hours after its use. However, those who have taken exceedingly high doses or who have an underlying psychiatric disorder may remain comatose or may exhibit bizarre behavior for days, or even weeks, before returning to normal. Those who rapidly regain normal function should be monitored for several hours and then, after a psychiatric consultation, should receive drug counseling and any additional social support available. Patients whose recovery is delayed should be treated supportively and monitored carefully in an intensive care unit.

Many patients become depressed and anxious during the “post-high” period, and chronic users may manifest a variety of psychiatric disturbances.²³⁰ These individuals typically present with repeated drug use, hospitalizations, and poor psychosocial functioning in the long term.

The major toxicity of PCP appears to be behaviorally related: self-inflicted injuries, injuries resulting from exceptional physical exertion, and injuries sustained as a result of resisting the application of physical restraints are frequent. Patients appear to be unaware of their surroundings and sometimes even oblivious to pain because of the dissociative anesthetic effects. In addition to major trauma, rhabdomyolysis and resultant myoglobinuric acute kidney injury account in large measure for the high morbidity and mortality associated with PCP intoxication. If significant rhabdomyolysis^{42,170} has occurred, early fluid therapy should be used to avoid deposition of myoglobin to the kidneys. Urinary alkalization as part of the treatment regimen for rhabdomyolysis would potentially increase PCP reabsorption and deposition in fat stores, but this is only theoretical.

Although the clinical experience with recreational use of ketamine is limited, toxic manifestations appear to be similar yet milder and shorter lived when compared with PCP. In a study of 20 patients who presented with acute ketamine toxicity, all were treated conservatively and successfully with intravenous hydration, and sedation with benzodiazepines.²²⁰

SUMMARY

- PCP and ketamine produce an “out-of-body experience” with seemingly hallucinatory effects.
- The action of these xenobiotics is largely mediated by the NMDA receptor.

- The neuropsychiatric toxicity is managed by supportive care.
- The popularity of ketamine may be related to its lesser toxicity and milder distortion of the personality.
- A chronic effect of ketamine abuse is cystitis and bladder dysfunction.

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I. METALS

CASE STUDY 7

History A 45 year-old man presented to the hospital complaining of hand and foot pain so severe that he was unable to drive his car. The man had been well until several weeks earlier, when he began having gastrointestinal distress that he thought was “heartburn” and mild weight loss, which he attributed to his dyspepsia. He denied fever, chills, nausea, vomiting, or diarrhea. He also related that on the day prior to admission he was unable to eat a meal because he thought it was spoiled after taking a few bites. The next morning, while driving, he pulled off the road and phoned emergency medical services. He was taking no medications and had no allergies.

Physical Examination In the emergency department, the patient appeared well developed and well nourished, but was complaining of severe pain in his hands and feet. Vital signs were: blood pressure, 124/68 mm Hg; pulse, 92 beats/min; respiratory rate, 14 breaths/min; oral temperature, 98.6°F (37.0°C); oxygen saturation, 99% on room air; and a rapid reagent glucose of 128 mg/dL. Physical examination was notable for pupils that were equal, round (4 mm), and reactive to light; normal extraocular movements; and the absence of nuchal rigidity. His chest was clear to auscultation, and his heart sounds were normal. His abdomen was soft and nontender, with normal bowel sounds and no organomegaly. He was awake, alert, and oriented with normal symmetrical strength and brisk reflexes. Although he complained of pain in his hands and feet, his two-point discrimination, proprioception, and vibration sensation appeared normal. His gait was slightly wide based and slow, but this was thought to be secondary to pain. Cranial nerves II through XII appeared intact, and cerebellar testing was normal.

Immediate Assessment and Management Although the patient appeared uncomfortable, there was no perception of an immediate life threat. An intravenous line was inserted, and blood was obtained for a complete blood count, electrolytes, and liver function testing. A urinalysis was requested as was an electrocardiogram and a chest radiograph. Acetaminophen was given for analgesia, without relief. The patient required parenteral opioids to diminish his pain, although he noted that the distribution had spread to include most of his legs and arms. He also became somnolent, and it was unclear if the ensuing somnolence was opioid related.

What Is the Differential Diagnosis? The major presenting symptom in this case is a painful sensory peripheral neuropathy (an uncommon clinical manifestation) associated with gastrointestinal symptoms (a common manifestation). Considerations include a variety of metabolic and endocrine disorders, infections, medications, and toxins. Severely painful symmetrical paresthesias are fairly uncommon and the differential diagnosis is limited. Considerations include freezing injury such as frostbite ([Chap. 30](#)), proximity to radioactive materials ([Chap. 134](#)), and topical exposure to hydrofluoric acid ([Chap. 107](#)). A list of xenobiotics that can cause such findings following ingestion is found in ([Table CS7-1](#)).

TABLE CS7-1. Differential Diagnosis of Sensory Peripheral Neuropathy with Gastrointestinal Complaints

Endocrine

Diabetes mellitus

Hypothyroidism

Nutritional

Alcoholism

B₁₂ deficiency

Thiamine deficiency

Xenobiotics

Alcohol

Acrylamide

Hexane derivatives

Metals (arsenic, gold, mercury, thallium)

Nitrous oxide

Organic phosphorus compounds

Medications

Cisplatin

Disulfiram

Isoniazid

Metronidazole

Phenytoin

Pyridoxine

Taxol

Vinca alkaloids

Connective tissue diseases

What Immediate Diagnostic and Therapeutic Interventions Are Indicated? In addition to the above evaluation, a diagnosis of encephalitis was considered when the patient became somnolent, and a computed tomography (CT) scan of the head was obtained without intravenous contrast. A lumbar puncture was performed after the CT scan was interpreted as normal. The lumbar puncture showed: 2 red blood cells/mm³; 0 white blood cells/mm³; glucose, 85 mg/dL; and protein, 45 mg/dL.

Unfortunately, over the next 48 hours, the patient's condition deteriorated and was characterized by encephalopathy with cranial nerve dysfunction and weakness with loss of deep tendon reflexes. A repeat lumbar puncture demonstrated elevated protein without abnormal cells or findings on the Gram stain.

Further Diagnosis and Treatment A diagnosis of poisoning was considered, and a toxicology consult was obtained. The combination of gastrointestinal symptoms without significant diarrhea, severely painful ascending peripheral neuropathy and progression to encephalopathy with motor and cranial nerve findings strongly suggested metal poisoning, specifically thallium ([Chap. 102](#)). Treatment with Prussian Blue (Antidotes in Depth: A28) was recommended, and the original blood urine and cerebrospinal fluid were sent for thallium concentrations. Unfortunately, the patient's illness progressed rapidly, and he suffered a cardiac arrest shortly after the diagnosis was considered. Ultimately, a spot urine thallium concentration was reported as 50,000 µg/L (normal <5 µg/L), and his serum was 8700 µg/L (normal <2 µg/L).

Acknowledgment Postmortem findings and cerebrospinal fluid results of this case were reported in the following article: Sharma AN, Nelson LS, Hoffman RS: Cerebrospinal fluid analysis in fatal thallium poisoning: evidence for delayed distribution into the central nervous system. *Am J Forensic Med Pathol.* 2004;25:156–158.

87 ALUMINUM

Brenna M. Farmer

Aluminum (Al)

Atomic number	=	113
Atomic weight	=	26.98 Da
Normal concentrations		
Serum	<	2 µg/L (0.074 µmol/L)
Whole blood concentration	<	12 µg/L (4.43 µmol/L)
Urine (24 hour)	<	4–12 µg/g creatinine (1.48–4.45 µmol/g creatinine)

CHEMISTRY

Aluminum (Al) is the most abundant metal in the crust of the earth, where it is found in many types of ores: bauxite, gibbsite, boehmite, as alumina, and in gems such as ruby, sapphire, and turquoise. The most naturally occurring isotope is ²⁷Al. Aluminum is a nonessential element and a trace metal with a single oxidation state, Al³⁺.

The aluminum industry is one of the largest industries in the world. Aluminum ores are converted to alumina and then reduced to aluminum metal. The first step usually involves refining bauxite at high temperature and pressure in a caustic soda to form alumina (aluminum oxide, Al₂O₃). The second step occurs by a special method, the Hall-Heroult process, in potrooms and uses electrolytic reduction to form aluminum. Aluminum is then used alone or is processed into alloys to build a variety of products that are anticorrosive.¹⁶ Aluminum is found in cookware, infant formula,²¹ foil, vaccines as an adjuvant to boost immune response,²⁸ antiperspirants, antacids, and previously, in phosphate binders. It also contaminates hemodialysis (HD) fluids, intravenous (IV) fluids, total parenteral nutrition (TPN),³⁸ albumin,³⁹ and as alum solution (potassium aluminum sulfate or ammonium aluminum sulfate)—an astringent for bladder irrigation.⁹⁶ In this chapter, aluminum metal is discussed as an occupational toxin with mainly lung manifestations. Aluminum salts, the more common form discussed in aluminum toxicity, primarily act as neurotoxins, with both acute and chronic toxicity.

HISTORY AND EPIDEMIOLOGY

The first case of aluminum toxicity with neurologic findings was reported in 1921. This patient had memory loss, tremor, and impaired coordination.⁸⁶ Subsequently, a case series described occupational asthma in Norwegian aluminum (potroom) workers (“potroom asthma”).²² In 1947, 26% of German potroom workers exposed to high concentrations of aluminum dust mixed with mineral oil–based lubricants developed pulmonary fibrosis, “aluminosis”.²⁴ Some potroom workers also developed neurologic findings described as a progressive encephalopathy and termed “potroom palsy,” with balance problems, intention tremors, decreased cognitive ability, and impaired memory, initially described in 1962.^{45,51,71}

In the 1970s, encephalopathy in patients with chronic kidney disease (CKD) was attributed to using aluminum salt–containing phosphate binders or, more rarely, to aluminum contaminated dialysis fluid. This clinical syndrome, known as “dialysis dementia,” develop after years of HD.⁷⁷ By 1976, elevated serum aluminum concentrations were reported in encephalopathic HD patients.⁶⁶ Both the relationship between aluminum and microcytic anemia as well as the connection between aluminum and osteomalacia in dialysis patients were recognized in 1978.^{17,88}

In 1982, alum (potassium aluminum sulfate or ammonium aluminum sulfate) was first used in the treatment of hemorrhagic cystitis.⁶⁴ Neurotoxicity can develop if patients absorb alum systemically, especially if kidney insufficiency is present.

More recently, aluminum has been linked to the spongiform leukoencephalopathy that rarely develops in heroin abusers “chasing the dragon.” These patients inhale the pyrolysate of heroin heated on aluminum or tin foil. A 2007 study showed elevated urinary aluminum concentrations in patients using heroin in this manner.¹⁸ They then can develop bizarre behavior, slowed speech and movements, as well as cognitive abnormalities.⁴⁴

There is also a concern over the relationship between aluminum and Alzheimer disease. This linkage was studied because of the dialysis encephalopathy syndrome (dialysis dementia) and the association of aluminum with neuropsychiatric deficits and electroencephalographic (EEG) changes that occur in aluminum welders.⁷² Although aluminum is a component of neurofibrillary tangles in senile plaques associated with Alzheimer disease, to date no studies have proven that aluminum is the cause of the disease.^{56,66} Regardless, this association has led several agencies in the United States and Canada to decrease the amount of aluminum contamination allowable in food and water products.⁹²

ALUMINUM-CONTAINING XENOBIOTICS

Antacids

Aluminum-containing products are rarely prescribed. However, patients may take antacids containing aluminum hydroxide for symptomatic control of dyspepsia and gastroesophageal reflux disease. Aluminum hydroxide is usually packaged with magnesium hydroxide to counteract the induced delay of gastric emptying and constipation caused by aluminum hydroxide. These antacids are poorly absorbed and exit the stomach in about 30 minutes. The neutralizing effects of antacids last for 2 to 3 hours, especially in the presence of food.

Sucralfate

Sucralfate, an aluminum-containing salt with sucrose sulfate, is used for symptomatic control of ulcer disease, to accelerate healing of peptic ulcer disease, and as a protectant against stress ulcer formation. This sucrose aluminum complex is poorly absorbed from the gastrointestinal (GI) tract, and the little that is absorbed is excreted by the kidney without undergoing any metabolic changes. Although not approved by the US Food and Drug Administration as a phosphate binder, it does have phosphate binding properties.⁹

Alum

Alum is usually a potassium aluminum sulfate salt $[KAl(SO_4)_2 \cdot 12H_2O]$ or an ammonium aluminum sulfate salt $[NH_4Al(SO_4)_2 \cdot 12H_2O]$, as a 1% solution, and is typically used as an astringent during bladder irrigation for hemorrhagic cystitis, although use is rare. It is poorly absorbed unless there is a defect in the bladder wall.

TOXICOKINETICS

Aluminum toxicokinetics are difficult to comprehend as many mechanisms have not been elucidated. It is known that daily intake occurs, that absorption is limited, but that the concentrations of aluminum in urine and feces do not equal 100% of the intake.²⁵ More research is necessary to determine the full extent of toxicokinetics.

Absorption

Aluminum is ubiquitous in the food we eat and water we drink.⁶⁵ The daily intake of aluminum in the United States is estimated to be 2 to 25 mg from food and beverages, depending on the diet studied.²⁵ GI absorption mainly occurs in the proximal small bowel with uptake by the intestinal mucosal cells. Uptake occurs through both passive transport methods such as diffusion and active transport methods via transferrin as well as active methods shared by calcium.²⁵ Transferrin may also mediate absorption into the blood from the mucosal cells.²⁵ The exact amount of aluminum absorption in humans is difficult to quantify due to the short half-lives of isotopes and lack of sensitive analysis techniques.²⁵ However, GI absorption increases in the presence of citrate, other small organic acids, and in uremia, based on increases in serum aluminum concentrations.^{25,29,62,83} The GI absorption of aluminum is decreased in the presence of phosphorus and silicon.²⁹ There is negligible dermal absorption from the use of antiperspirants containing aluminum.^{19,25} Pulmonary absorption of inhaled aluminum particulates is 1.5% to 2%, based on increased urinary aluminum excretion in workers exposed to aluminum containing metal fumes.^{25,57,81}

Distribution

The initial distribution of aluminum is consistent with blood volume 0.06 L/kg with equal distribution between plasma and red blood cells in the blood.⁸⁹ Aluminum then becomes 90% bound to transferrin, with approximately 10% bound to citrate.^{87,91} From the blood, it distributes to many tissues, including 50% to the bone, where it is concentrated at the mineralization front,⁹⁵ and approximately 1% to the brain, primarily in the gray matter.⁶⁶ The remainder of the aluminum appears to distribute variably to the heart, liver, kidney, and other organ systems. The primary carrier in the cerebrospinal fluid (CSF) is citrate.⁹¹ Intracellularly, aluminum localizes in the lysosomes of brain neurons, liver (not the Kupffer cells),

spleen, kidney epithelial tubules and glomerular mesangium cells, cardiac myocytes,^{5,75} and in the mitochondria of osteoblasts.¹⁵

Metabolism/Excretion

Aluminum is not metabolized in the body and is considered to be greater than 95% excreted unchanged in the urine with a normal daily urinary excretion of less than 50 µg.²⁵ Citrate in the blood may enhance the excretion of aluminum.⁴⁸ Less than 2% of aluminum is excreted by the bile.^{40,69,93} Because of the primary renal excretion of aluminum, patients with severe CKD have decreased aluminum excretion. The elimination half-life for aluminum is approximately 85 days in dialysis patients.⁷⁶ Based on urinary excretion in workers (with preserved kidney function) with prolonged occupational exposure, the apparent half-life is extended to years.⁴³ This prolonged half-life may be related to deposits of aluminum metal dust in the lungs of those workers (such as in those patients with pulmonary fibrosis from exposure to the aluminum dust). There is no normal reference point for elimination half-life.

PATHOPHYSIOLOGY

Little is known about the pathophysiology of aluminum toxicity. The information that follows is based on a summary of limited research. Some animal studies provide insight into mechanisms that may be responsible for the toxicity of aluminum, but the studies should not be considered to form a comprehensive understanding of aluminum toxicity as the basic science studies raise more questions. There remain many gaps in our knowledge of aluminum toxicity for different organ systems.

Pulmonary System

In rats exposed to alumina and aluminum through intratracheal injection, fibrosis develops.^{35,36} These animals develop epithelialization of alveoli, with focal fibrosis occurring in the respiratory bronchioles and alveolar ducts with alveolar proteinosis.^{27,68}

Central Nervous System

Aluminum is associated with acute encephalopathy, dialysis encephalopathy, seizures, and Alzheimer disease. The primary site of aluminum entry into the brain appears to be the cerebral microvasculature. Following IV administration in rats and rabbits, aluminum concentrations are higher in the frontal cortex than in the lateral ventricles. The cortex concentrations should result from blood supply, while lateral ventricle concentration may represent blood supply or be CSF derived as the lateral ventricles are bathed in CSF.^{94,95} The mechanisms of entry are postulated to be transferrin mediated, endocytosis and other active processes.²² Aluminum interacts with the acetylcholine pathways in the brain and decreases acetylcholine activity. It decreases the amount of high-affinity choline uptake in the brains of rats and also decreases the activity of choline acetyltransferase in rabbit brains.^{30,42} Rabbits treated with aluminum have significantly decreased acetylcholine outflow compared with controls; this does not improve with potassium addition to the neurons. This finding suggests that aluminum may attenuate the response of neurons to potassium-induced depolarization.⁹⁴ Adult rabbits exposed to aluminum also have a significant reduction in conditioned responses compared with rabbits exposed in utero or in the first or second month postpartum.

Hematologic System

Prior to alterations in the central nervous system, aluminum affects hematopoiesis. A microcytic hypochromic anemia results. In rats, aluminum inhibits cell growth, while in humans hematopoietic cells are inhibited. In mice, aluminum decreases cell proliferation and hemoglobin synthesis.^{3,55} It inhibits δ-aminolevulinic acid dehydrogenase in the heme synthesis pathway,^{1,52} leading to the accumulation of erythrocyte protoporphyrins (Fig. 22–3). This effect is most noted in HD patients with aluminum overload.¹⁰

Musculoskeletal System

Vitamin D resistant osteomalacia and osteopathy occurs in patients with aluminum toxicity. It is characterized by hyperosteoidosis, minimal osteoblastic activity, and decreased mineralization. The metabolism and kinetics of calcium, magnesium, and phosphate do not appear to be affected in these patients.¹³ Aluminum concentrates in the mitochondria of the osteoblasts at the mineralization front.¹⁵ It is theorized that aluminum competes and replaces other cations in the bone, leading to osteopathy.²⁶ The osteomalacia is not caused solely by CKD but develops in the presence of aluminum exposure.⁷³ In rat studies, exogenous parathyroid hormone enhanced aluminum deposition into bone, leading to

osteopathy.^{49,50}

MANIFESTATIONS

Acute Toxicity

Regardless of etiology, patients with acute aluminum toxicity develop encephalopathy, myoclonus, and seizures. The encephalopathy manifests as disorientation, confusion, and coma. All symptoms appear to develop within days to a few weeks of receiving massive systemic aluminum exposure (usually to an aluminum salt). Serum concentrations range from barely elevated to extremely elevated. Most patients who manifest toxicity have systemically absorbed aluminum, usually in the presence of CKD. In several case reports of acute aluminum toxicity, the initial exposure to aluminum was associated with alum bladder irrigations for hemorrhagic cystitis.^{34,59,67} In two patients, these symptoms developed after only weeks of exposure to aluminum containing phosphate binders in the presence of citrate.³⁷ Two neonates with uremia developed neurotoxicity after exposure over a 1 to 2 month period to infant formula with high aluminum content.²⁰ Recovery occurs in patients treated with deferoxamine and or HD.^{34,58,59} Patients in whom aluminum toxicity is not recognized and or treated late usually die (despite supportive care in the intensive care unit, never recovering a normal mental status).^{37,77,80}

Chronic Toxicity

Two distinct types of chronic aluminum toxicity are reported: occupationally related lung problems, such as asthma and pulmonary fibrosis, and a multisystem syndrome most often noted in HD patients, which was initially described as dialysis encephalopathy syndrome or “dialysis dementia.” As these names only describe one organ system involvement, they should not be used.

Pulmonary. Potroom asthma consists of dyspnea, cough, wheezing, bronchitis, and chest tightness.⁵³ These symptoms may present after only a few months of exposure to the metal fumes of aluminum and aluminum dust. The asthma may improve upon cessation of work in the potroom, although some workers never fully improve.⁶³ These symptoms may be a cause for high turnover in potroom workers and appear to have made long-term follow-up difficult.^{32,85}

Pulmonary fibrosis from aluminum, termed aluminosis, is very similar to the other pneumoconiosis, like silicosis, and appears to progress in a similar manner. This manifestation develops in workers exposed to aluminum dust. Patients experience cough, shortness of breath, and dyspnea on exertion, and they eventually develop restrictive lung disease.^{41,54} Abnormal chest radiograph findings include increased pulmonary markings, distortion of pleura and diaphragms, and irregular opacities.^{23,30,78} Recovery of lung function does not occur, and several patients have died from complications of pulmonary disease such as pneumonia.

Multisystem Toxicity. The other form of chronic aluminum toxicity has multisystem manifestations. It primarily affects three organ systems: hematopoietic, nervous, and musculoskeletal. In patients with CKD, the toxicity appears to occur after months to years of exposure to aluminum salt–contaminated dialysate and or aluminum salt–containing phosphate binders such as aluminum hydroxide and sucralfate. A similar presentation has been reported in a patient using aluminum-coated cookware to boil methadone for IV abuse. The patient experienced 3 months of chronic aluminum toxicity (prior to presentation) after 4 years of processing his methadone this way.^{21,96} Three industrial workers exposed to aluminum metal powder were reported to have encephalopathy. One of these workers had a brain aluminum concentration 20 times normal.⁴⁵ One infant with kidney insufficiency developed focal seizures, which eventually progressed to generalized seizures, hypotonia, poor head control, ataxia, and developmental delay in the presence of elevated serum aluminum concentration after 10 months of exposure to aluminum salt–containing phosphate binders.⁷⁰

The microcytic hypochromic anemia of aluminum poisoning is unresponsive to iron replacement therapy.³¹ This clinical finding usually precedes encephalopathy and osteomalacia.⁷⁹ The encephalopathy is characterized by speech disturbances, EEG abnormalities, myoclonic jerks, and dementia.⁸⁴ The typical speech disturbances include dyspraxia, dysphasia, stuttering, and possibly mutism.^{46,74,84} EEG abnormalities include slowing of the normal rhythm and high voltage biphasic or triphasic spikes.^{47,84} The myoclonic activity can include uncontrolled twitching movements, myoclonus, or seizures.⁸⁴ The osteopathy and osteomalacia can lead to bone pain and fractures.^{14,92} Death is common in these patients when aluminum toxicity is not recognized and treated.

DIAGNOSTIC TESTS

A normal serum aluminum concentration should be less than or equal to 2 µg/L,²⁵ while a whole blood aluminum concentration should be less than 12 µg/L.⁸² Daily urinary excretion less than 50 µg aluminum is considered normal.^{25,61} Toxicity has occurred in a wide range of serum and urine concentrations, with patients dying who had severe manifestations

and concentrations only slightly above normal.

Pulmonary function testing can be performed to evaluate for restrictive lung function, as occurs with aluminosis.

MANAGEMENT

Patients should be removed from any aluminum exposure if identified. Exposure to aluminum in industry and exposure to antacids containing aluminum salts should also be limited. Patients with occupational asthma from aluminum exposure should be symptomatically treated with bronchodilators and steroids.

The only chelator with proven benefit is deferoxamine (DFO). Chelation therapy is recommended for both acute and chronic toxicity from aluminum salts. Chelation appears to limit and improve manifestations of neurotoxicity, anemia, and osteomalacia (Antidotes in Depth: A7). Other chelators such as D-penicillamine and 2,3-dimercapto-1-propanol (BAL) have been tried in chronic HD patients without any improvement in their manifestations or aluminum concentrations.¹² A review of numerous chelator studies revealed that no other chelator has been found as an alternative to DFO.⁹⁰

Acute Toxicity

A DFO dose of 15 mg/kg/d intravenously is recommended. Adults have received doses ranging from 1 to 2 g for aluminum toxicity. DFO chelates the aluminum to form aluminoxamine, which is excreted in the urine or removed by HD.⁹¹ Chelation mobilizes aluminum from its storage sites in blood and increases its renal elimination.

In patients with stage 5 CKD, chelation therapy is usually followed 6 to 8 hours later by HD with a high-flux membrane in order to clear the aluminoxamine (the aluminum-DFO product).⁵⁸ Patients with normal kidney function may not require HD, as the aluminoxamine is excreted in the urine.

Chronic Toxicity

Chelation therapy with DFO reverses encephalopathy, osteomalacia, and anemia. Numerous case reports demonstrate the reversal of the neurotoxicity, vitamin D-resistant bone disease, and iron-resistant anemia.^{4,8,11} The National Kidney Foundation has issued complicated guidelines for the treatment of dialysis encephalopathy. It consists of 4 months of once weekly DFO 5 mg/kg over 1 hour given 5 hours before a regularly scheduled HD session in patients with an aluminum concentration greater than 300 µg/L. In patients with aluminum concentrations between 50 and 300 µg/L, DFO 5 mg/kg is given the last hour of HD, once a week for 2 months. Serum aluminum concentrations are then monitored, and this therapy is repeated as needed.⁶⁰ Recent studies have evaluated the effect of lower doses of DFO (2.5 mg/kg/week) for treatment of chronic toxicity in dialysis patients.³³

SUMMARY

- Inhalational exposure to aluminum metal causes pulmonary toxicity, primarily manifested as bronchospasm, but progresses to restrictive lung disease.
- Acutely, aluminum salts are neurotoxins with manifestations of encephalopathy and seizures.
- Chronically, aluminum salts affect at least three systems with manifestations of anemia, encephalopathy, dementia, and osteomalacia.
- Treatment involves limiting or terminating exposure, chelation with DFO, and HD in patients with CKD.

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88 ANTIMONY

Asim F. Tarabar

Antimony (Sb)

Atomic number	=	51
Atomic weight	=	121.75 Da
Normal concentrations		
Serum	<	3 µg/L (24.6 nmol/L)
Urine (24 hour)	<	6.2 µg/L (50.1 nmol/L)
	<	3.5 µg/g creatinine (28.7 nmol/g creatinine)

HISTORY AND EPIDEMIOLOGY

Antimony (Sb) and its compounds are among the oldest known remedies in the practice of medicine.^{102,154} Because of a strong chemical similarity to arsenic, the features of antimony poisoning closely resemble arsenic poisoning (Chap. 89). Antimony poisoning also shares features common with other metal poisonings in the chapters that follow. Although relatively uncommon, antimony toxicity still occurs, usually as a complication of the treatment of visceral leishmaniasis.⁹² Acute overdose represents an even more rare, but potentially lethal event, often as a result of a nonconventional alcohol aversion treatment.^{99,139}

Objects discovered during exploration of ancient Mesopotamian life (third and fourth millennium B.C.) suggested that both the Sumerians and the Chaldeans were able to produce pure antimony.^{102,154} The reference to eye paint in the Old Testament suggested the use of antimony.¹⁰² For several thousand years, Asian and Middle Eastern countries used antimony sulfide in the production of cosmetics, including rouge and black paint for eyebrows, also known as kohl or surma.^{97,103} Because of the scarcity of antimony sulfide, lead replaced antimony as a main component in more modern cosmetic preparations.

One of the first monographs on metals, written in the 16th century, included a description of antimony.¹⁴⁶ The medicinal use of antimony for the treatment of syphilis, whooping cough, and gout dates to the medieval period. Paracelsus was credited with establishing antimony compounds as therapeutic agents and increasing their popularity. In spite of being aware of its toxic potential, many of the disciples of Paracelsus enthusiastically continued the use of antimony.¹⁰² Various antimony compounds were also used as topical preparations for the treatment of herpes, leprosy, mania, and epilepsy.¹⁵⁴ Orally administered tartar emetic (antimony potassium tartrate) was used for treatment of fever, pneumonia, inflammatory conditions, and as a decongestant, emetic, and sedative, but it was abandoned because of its significant toxicity.^{22,47,66,81} The use of antimony as a homicidal agent¹⁴⁰ continued well into the 20th century (Chap. 1).

The current medical use of antimony is limited to the treatments of leishmaniasis and schistosomiasis, and to sporadic use as aversive therapy for substance abuse.^{99,139} Pentavalent compounds are used because they are better tolerated. In the endemic regions of the world, generic pentavalent antimonials remain the mainstay of therapy because of their efficacy and low cost; however, the growing incidence of resistance may reduce future use.¹⁰⁷

Some contemporary homeopathic⁶⁰ and anthroposophical¹³³ practices still recommend use of antimonial compounds as home remedies; however, these practices are rare.^{102,154} In spite of its anticancer effects in vitro⁴⁷ and remarkable therapeutic efficacy in patients with acute promyelocytic leukemia,¹²⁹ there is no current accepted oncologic use of antimony. When compared to suramin, a well-known antineoplastic compound, sodium stibogluconate appears to be a better inhibitor, giving a foundation for future research of antimony-based antineoplastics.¹²⁹

The elemental form of antimony has very few industrial uses because of its physical limitations, particularly the fact that it is not malleable. In contrast, its alloys with copper, lead, and tin have important applications. Various antimony compounds can be used in the production of textiles, enamels, ceramics, fireworks, and pigments, and as catalysts in chemical reactions. Industrial and occupational exposure to antimony occurs mainly by the inhalation of dust or fumes during the processing or packaging of antimony compounds.^{14,71} Smelters can have occupational exposure to antimony as it

is often present in arsenic-containing ore.⁵⁹ A time-weighted average over an 8 hour shift of permissible exposure limit for antimony and its compounds is established at 0.5 mg per cubic meter of air (mg/m^3) by the Occupational Safety and Health Administration.¹⁴⁵ Antimony concentrations in cigarette smoke range from 10 to 60 mg/kg ,^{59,110} which may be responsible for a substantial percentage of antimony found in the lungs of smokers.⁵⁹

In developed countries, antimony poisoning rarely occurs following intentional ingestion of antimony preparations.^{99,154} Most recent descriptions of antimony toxicity result from parenteral exposures during the treatment of schistosomiasis and leishmaniasis. Because of the infrequent use of therapeutic antimony preparations, health care providers in the United States may not be familiar with the standard dosing and administration procedures, placing their patients at risk for therapeutic misadventures.⁸⁷ One can expect an increase in cases of domestically treated leishmaniasis as a result of deployment of US troops to the Middle East.¹⁵⁵

Oral exposures usually occur following the use of antimony potassium tartrate-containing compounds.^{99,139} Several cases were described after the use of old porcelain houseware or after use of antimony compounds as home remedies.^{4,90,106,139}

CHEMISTRY

Antimony is located in the same group on the periodic table as arsenic (As), and as such it has many similar chemical, physical, and toxicologic properties. Because it can react as both a metal and a nonmetal, antimony is classified as a metalloid (Chap. 12).^{14,135} Pure antimony is a lustrous, silver-white, brittle, hard metal that is easily pulverized.^{105,154} It is extremely rare to find elemental antimony in nature because of its ability to rapidly convert to either antimony oxide or antimony trioxide.¹⁴ It has been suggested that even its name originates from anti monon (enmity to solitude) because antimony is almost always found with some other metal.¹⁰² Thus, for the purposes of this chapter, the term antimony refers to antimony ions.

In nature, antimony can be found in more than 100 different minerals,^{83,102} including stibnite, cervantite, valentine, and kermesite.⁵³ The sulfide ore (stibnite) is the most abundant form,¹⁰² and Bolivia and South Africa are among the leading producers.¹⁵⁴ Like arsenic, antimony forms both organic and inorganic compounds with trivalent (3^+) and pentavalent (5^+) oxidation states. Common inorganic trivalent antimony compounds include antimony potassium tartrate ($\text{C}_8\text{H}_4\text{K}_2\text{O}_{12}\text{Sb}_2$), antimony trichloride (SbCl_3), antimony trioxide (Sb_2O_3), antimony trisulfide (Sb_2S_3), and stibine (SbH_3). Antimony pentasulfide (Sb_2S_5) and pentoxide (Sb_2O_5) are inorganic compounds that can act as oxidizing agents.⁶⁸ Antimony pentachloride (SbCl_5) is used as a chemical reagent with acidic properties. It reacts with water, forming hydrochloric acid that causes a direct corrosive effect on skin and mucous membranes.³⁷

Standard treatment of cutaneous leishmaniasis, recommended by the World Health Organization (WHO) and the Centers for Disease Control (CDC), is a 20 day course of 20 $\text{mg}/\text{kg}/\text{d}$ of sodium stibogluconate.¹⁵⁵ Use of higher doses is associated with more side effects.¹⁵⁵ A recent new analytical approach measured a higher presence of trivalent antimony than previously reported in the pentavalent antimonial drug, suggesting that the pentavalent form acts as a carrier. It is postulated that trivalent antimony is released specifically in the acidic intracellular compartment targeting the Leishmania parasites. Released trivalent antimony could be responsible for the toxic effects of antiparasitic treatment.¹²⁸ The proposed mechanism of antimonial activity against the Leishmania parasites is inhibition of trypanothione reductase that is essential for the parasite survival and virulence.⁸

From an industrial perspective, the most important application of antimony is the use of antimony oxychloride ($\text{Sb}_2\text{O}_3\text{Cl}_2$) as a flame retardant.¹⁰² Investigation by the CDC of a possible antimony toxicity outbreak in US firefighters concluded that wearing uniforms made from fabric that contains antimony is safe.²⁹

Analysis of soil around firing ranges⁹⁵ and environmental examination around mines revealed elevated concentrations of antimony that can pose significant health risk.^{70,157} A public health concern was raised after reports of elevated antimony concentrations in water containers and commercial juices due to leaching from the packaging material or flawed manufacturing process.^{67,130}

Tartar emetic (antimony potassium tartrate) is an odorless trivalent antimony compound with a sweet metallic taste⁶⁹ and a potent emetic effect.⁶⁸ Antimony potassium tartrate is considered to be one of the most toxic antimony compounds, with minimal lethal doses reported between 200 mg ¹⁰⁶ and 1200 mg .¹⁰² There are large species variations of the LD_{50} in experimental animals, with a reported range of 115 mg/kg in rabbits and rats to 600 mg/kg in mice. In comparison, because of low water solubility, antimony trioxide is considered to be nontoxic, with an LD_{50} greater than 20,000 mg/kg .⁵⁷

PHARMACOLOGY

The antiparasitic mechanisms action of antimony may result from the inhibition of phosphofructokinase, which is the rate-limiting step in the glycolytic pathway of schistosoma.³¹ Trivalent antimony compounds inhibit phosphofructokinase, leading to energy failure from impaired adenosine triphosphate (ATP) synthesis.^{27,154} It is speculated that antimonial preparations exert their antiparasitic effect through selective targeting of guanosine diphosphate–mannose pyrophosphorylase, which interferes with nucleoside and mannose metabolism.⁵⁴ The result is that the parasites cannot synthesize purines and cannot survive without these mannose-containing glycoconjugates. The most recently proposed mechanism involves inhibition of trypanothione reductase.⁸ Even less is known about the effects of antimony in humans. It has been proposed that, like other metals, antimony inactivates thiol containing proteins and enzymes by binding to sulfhydryl groups.⁴² Pentavalent antimony may act as a prodrug that is converted in acidic intracellular compartment into active and more toxic trivalent antimony.¹²⁸

TOXICOKINETICS

Absorption

Antimony is absorbed by inhalation, ingestion, or transcutaneously. Absorption from the gastrointestinal tract begins immediately following ingestion, and the oral bioavailability of antimony ranges from 15% to 50%.^{58,147} It is suggested that antimony absorption might be a saturable process, given that several studies failed to demonstrate a dose-response relationship for absorption.^{2,136} In fact, after a lethal ingestion of antimony tartrate, the total body antimony burden was only 5% of the ingested dose.⁹⁶ This poor gastrointestinal absorption in humans, in addition to the concomitant emesis, necessitates parenteral administration of many antimony based pharmaceuticals.

Pulmonary absorption of many inorganic antimony compounds is very slow and limited by low solubility.¹⁰² In contrast, animal data suggest that inhaled trivalent antimony is well absorbed from the lung, distributed to various organs, and subsequently excreted in the feces and urine.⁴⁶

Transcutaneous absorption of antimony trioxide and pentoxide was documented in studies with rabbits,¹⁰⁹ however, dermal absorption in humans of antimony trioxide is considered negligible.¹²⁵ The CDC, in its investigation of possible outbreak of antimony exposure in firefighters, did not measure significant transcutaneous absorption from the antimony containing uniforms.²⁹

Distribution

Distribution depends on the oxidation state of antimony. In animals, more than 95% of trivalent antimony is incorporated into the red blood cells within 2 hours of exposure, whereas in a similar time frame, 90% of pentavalent antimony remains in the serum.⁴⁸

When administered intravenously or orally, antimony is predominantly distributed among highly vascular organs, including the liver, kidneys, thyroid, and adrenals.^{115,154} The antimony that is detected in the liver and spleen is predominantly in the pentavalent form, whereas the thyroid accumulates trivalent forms.¹³ Uptake by the liver occurs through the mechanisms of diffusion and saturable binding.¹³² In a hamster model, following a single injection of organic antimonials, the greatest concentration of antimony was found in the liver.⁵⁸ After inhalation, antimony accumulates predominantly in red blood cells and to a significantly lesser extent in liver and spleen.^{46,48} It is possible that inhaled antimony is retained in the lungs for a prolonged period of time without significant systemic absorption and distribution.⁵⁹ Animal data also reported accumulation of antimony in the skeletal system and in fur.^{50,51}

After intramuscular (IM) administration of sodium stibogluconate, the antimony concentration time profile suggested the two-compartment open model, with rapid distribution phase and slower elimination half-life in the range of 10 hours.¹⁵⁹

Metabolism

Although antimony and arsenic share many toxicokinetic properties, unlike arsenic, inorganic trivalent antimony is not methylated in vivo.⁷ Some microorganisms, however, are capable of biomethylation of antimony.¹⁷ Instead, in humans, antimony is converted by binding to macromolecules, by incorporation into lipids,¹⁶ and by covalent interactions with sulfhydryl groups and phosphates. Pentavalent antimony may be converted to trivalent compounds in the liver¹⁵⁴ or it can release trivalent form into acidic intracellular environment of Leishmania infected cells.¹²⁸

Excretion

Trivalent antimony is excreted in the bile after conjugation with glutathione. A significant proportion of excreted antimony undergoes enterohepatic recirculation.⁷ The remainder is excreted in urine. The overall elimination is very slow, with only 10% of a given dose cleared in the first 24 hours and 30% in the first week;¹¹ some urinary antimony is still detected in the urine 100 days after administration.^{98,154} Pentavalent antimony is much more rapidly excreted by the kidneys than trivalent antimony (50%–60% versus 10% over the first 24 hours).¹⁵⁴ In actuality, renal excretion of sodium stibogluconate can be as high as 90% within 6 hours of an IM administration.¹²² However, urine and serum antimony concentrations remain elevated for several years following therapeutic use.¹⁰¹ In workers, urine concentrations of pentavalent antimony correlate well with the extent of exposure.⁷

The clearance of tartar emetic has a biphasic pattern, with 90% being excreted within 24 hours after acute exposure, followed by a second slower phase with an estimated half-life of approximately 16 days.⁵⁰

The renal elimination half-life of inhaled stibine was estimated at approximately 4 days following occupational exposure.⁹¹

PATHOPHYSIOLOGY

Antimony has no known biological functions and is considered to be potentially toxic even at very low concentrations.¹³¹ Like other toxic metals, antimony binds to sulfhydryl groups to inhibit a variety of metabolic functions.^{32,42} Trivalent antimony compounds are more toxic than the pentavalent compounds because of their higher affinity for erythrocytes and sulfhydryl groups.⁹³ Tartar emetic and other antimony salts are also considered gastrointestinal irritants. One proposed mechanism for this local effect is the activation of enterochromaffin cells, which produce and secrete serotonin (5-HT₃). Released serotonin acts on the 5-HT₃ receptors, stimulating vagal sensory fibers and activating the vomiting center.^{65,149} In addition, there is apparent direct central medullary action, particularly after administration of higher doses of antimony.¹⁵⁴

CLINICAL MANIFESTATIONS

Data on human toxicity of antimony are very limited. They are largely extrapolated from occupationally exposed patients, adverse effects that have occurred during treatment of leishmaniasis and schistosomiasis, and very few case reports of intentional antimony exposures.¹⁰⁶ Serious adverse events and deaths resulting from the treatment with sodium stibogluconate are very rare, and if they occur, they are most often resulting from cardiac dysrhythmias or pancreatitis.¹⁵⁵ Patients older than 50 years may be at increased risk for more serious reactions to meglumine antimonate used for the treatment of visceral leishmaniasis.^{45,112}

Workers with occupational exposures usually present with subtle clinical symptoms as chronic toxicity develops slowly over time. It is important to recognize that antimony ore contains a small concentration of arsenic, making it difficult to determine whether the effects on workers are caused by contaminants such as arsenic or by the antimony. Therapeutic side effects of antiparasitic treatment may have acute and subacute clinical manifestations, as some patients with leishmaniasis require prolonged antimonial treatment to achieve cure,¹⁴³ exposing them, over time, to very large cumulative doses. Therapeutic misadventures are possible, particularly in the setting where antimony preparations are rarely used and health care providers are not familiar with the dosing regimen.⁸⁶

Patients with acute ingestions usually present with symptoms mimicking the toxicity of arsenic and other metal and metalloid salts.

Local Irritation

The most common manifestations of antimony toxicity involve local irritation. In sufficient concentration, antimony acts as an irritant to the eyes, skin, and mucosa. Ophthalmic exposure can cause conjunctivitis.^{19,53,123} Irritation of the upper respiratory tract can lead to pharyngitis and frequent epistaxis.¹⁵²

Antimony pentachloride is very irritating and can cause local dermal and mucosal burns. It reacts with water, releasing hydrochloric acid, heat, and antimony pentoxide (Sb₂O₅). Following ingestion, contact with the water in saliva produces sufficient hydrochloric acid with the potential to result in consequential gastrointestinal burns.

Ocular exposure to Sb₂O₅ can cause typical caustic injury, resulting in blepharospasm, lacrimation, photophobia, and even corneal burns. Exposure to antimony trichloride fumes can cause similar ocular symptoms.⁶¹

Following systemic exposure ocular toxicity can manifest in optic atrophy, uveitis, and retinal hemorrhage with exudates resulting with diminished visual acuity.^{34,89} Some of these changes can be permanent.⁸⁹

Thrombophlebitis is common after intravenous (IV) use of antimony but is also reported when poisoning occurs

orally.⁹⁶

Gastrointestinal. Following acute exposures, antimony can rapidly produce anorexia, nausea, vomiting, abdominal pain, and diarrhea.^{96,99,150} Some patients may report a metallic taste in the mouth.^{7,40} It is possible to sense a garlic odor on the breath, but this might be due to concomitant arsenic exposure. In severe overdose, gastrointestinal irritation can progress to hemorrhagic gastritis.⁹⁶ Workers chronically exposed to antimony dusts have a much higher incidence of gastrointestinal ulcers in comparison to controls (63 per 1000 versus 15 per 1000).²³ Many patients develop pancreatitis following treatment with pentavalent antimonial salts.^{41,56,104} Because most cases improved despite continuation of treatment, a mechanism other than direct pancreatic toxicity is presumed. In another series, several patients with human immunodeficiency virus (HIV) who were treated with high doses of meglumine antimonate developed severe pancreatitis and died.⁴³

Cardiovascular. In animals, antimony decreases myocardial contraction; lowers coronary vasomotor tone, producing decreased systolic pressure; and causes bradycardia.^{39,154} The majority of reported human cardiac effects are related to the electrocardiographic (ECG) changes. Prolongation of the QT interval, inversion or flattening of T waves, and ST segment changes are frequently described during treatment of visceral leishmaniasis with pentavalent antimonial compounds (sodium stibogluconate and meglumine antimonate).^{33,126,153} Torsade de pointes was described in patients treated with pentavalent antimonial preparations.^{114,142} Prolongation of the cardiac action potential may be due to an increase in cardiac calcium currents.⁹⁴

In patients with underlying myocardial disease such as a cardiomyopathy, ECG changes can occur even at subtherapeutic antimony doses.⁶⁴ These changes are not necessarily associated with deterioration in cardiac function.^{73,75} However, it is important to recognize that pentavalent antimonial drugs used for the treatment of leishmaniasis are associated with sudden death, probably as a result of the development of ventricular dysrhythmias.^{30,138} Cardiomyopathy followed by congestive heart failure and death is rare but is a reported adverse effect attributed to antimony.^{112,137} Pericarditis can present with chest pain and typical ECG changes during the treatment with antimony.⁴⁹

In regard to chronic antimony exposure, it appears that elevated concentrations of antimony in urine are associated with an increase in composite cardiovascular and cerebrovascular disease.¹

Respiratory. Local irritation from antimony trioxide can produce laryngitis, tracheitis, and pneumonitis.^{59,123,141} Pneumonitis is usually reversible after exposure ceases and can be followed radiologically.¹²³ Acute respiratory distress syndrome was reported after acute exposure to antimony pentachloride.^{37,38}

Although antimony oxides are capable of causing metal fume fever,^{6,52} this is much less common in comparison to exposure to zinc oxide (**Chaps. 103 and 124**).^{6,52} Antimony metal fume fever is reported to occur even with air concentrations below 5 mg/m³.³⁶

Workers chronically exposed to antimony compounds for many years may develop “antimony pneumoconiosis.”^{35,103} Patients present with cough, wheezing, and exertional dyspnea that can progress to obstructive lung disease. Radiologically, antimony pneumoconiosis appears as diffuse, dense, punctate nonconfluent opacities with a predominant distribution in middle and lower lung lobes with or without pleural adhesions.¹¹⁹

Renal. Patients treated with sodium stibogluconate can develop varied manifestations of nephrotoxicity ranging from renal cell casts, proteinuria, and increased blood urea nitrogen concentration³⁴ to acute kidney injury (AKI).^{9,121} Some patients can also develop renal tubular acidosis⁸⁰ and acute tubular necrosis.¹²⁰ Older age and underlying chronic kidney disease are risk factors for development of AKI that can progress to death.¹¹² Hemodialysis may be helpful during oliguric phase in acute overdose.⁹⁹

Hepatic. Acute exposure to antimony can result in severe acute liver injury.⁹⁹ Chronic therapeutic use of antimony compounds for the treatment of leishmaniasis can cause liver toxicity that can range from reversible elevations of aminotransferase concentrations to hepatic necrosis.^{76,78,127,154} Elderly patients are at an increased risk for development of significant hepatic failure.¹¹² Pediatric patients treated for leishmaniasis may develop fulminant hepatic failure after an initial positive response to antimony. The mechanism is unknown, but may be due to a direct antimony effect in combination with immunologically mediated liver injury.^{10,44}

Hematologic. Severe anemia was reported in HIV positive patients during treatment with sodium stibogluconate. Bone marrow biopsy documented transient severe marrow dyserythropoiesis, followed by complete recovery on discontinuation of the therapy.^{77,100}

Patients treated with sodium stibogluconate for visceral leishmaniasis occasionally develop thrombocytopenia.^{20,74,86} Rare cases of epistaxis are described during the treatment, and it is unclear if they are associated with thrombocytopenia.⁸⁸ Visceral leishmaniasis itself is known to be associated with pancytopenia, probably as a result of increased destruction of peripheral blood cells.¹¹⁸ It may be difficult to determine whether this phenomenon is caused by disease itself or is

secondary to the treatment, although some authors suggested a drug-induced immune thrombocytopenia.¹¹⁸

Leukopenia is frequently observed in patients treated with antimonial compounds.^{43,154,156} Some authors speculate that antimony-induced lymphopenia is associated with an increased frequency of herpes zoster in HIV infected patients.¹⁵⁶ It is suggested that pentavalent antimony can theoretically precipitate sickle cell crisis via common glutathione pathway.⁵⁵ A study with homeopathic antimony indicated procoagulant effect, and even some homeopathic practitioners use it in the treatment of bleeding disorder.⁷⁹

Dermatologic. Antimony spots¹³⁴ are papules and pustules that develop around sweat and sebaceous glands and may resemble varicella. Chronically exposed patients can develop areas of eczema and lichenification that typically occur in the summer and are usually found on the arms, legs, and in the joint creases with sparing of the face, hands, and feet.^{103,123} A similar skin rash was described in the 18th century after external application of antimony tartrate for medicinal use.¹⁰² Interestingly, these eruptions were usually interpreted as a sign of cure.⁶⁶ It is also suggested that antimony trioxide can cause contact dermatitis.¹⁰⁸ A very high incidence of severe cutaneous reactions (37%) was reported in patients who were treated with meglumine antimonate at 20 mg/kg/d.¹¹³ This high incidence was associated with high concentrations of other metals in the one particular drug lot. Herpes zoster was reported as a complication of antileishmaniasis treatment and it may be resulting from leukopenia.^{113,156}

Neurologic. A patient with cutaneous leishmaniasis who was treated with sodium stibogluconate (pentavalent antimony) developed a reversible, peripheral sensory neuropathy in temporal association with treatment.²⁵

Musculoskeletal. Therapeutic use of parenteral antimonials can be associated with diffuse muscle and joint pain.^{28,40,127,154} One of the most frequently reported clinical adverse effects of pentavalent antimonials was musculoskeletal pain.¹¹³ The symptoms can be so severe that they will require treatment interruption in about one third of the patients. Patients that are not candidates for the treatment with nonsteroidal antiinflammatory drug treatment can be managed with glucocorticoids.²⁴

Reproductive. In animal studies, antimony causes ovarian atrophy, uterine metaplasia, and impaired conception.¹⁵ An association between spontaneous abortion and premature births reported in women who were occupationally exposed to antimony salts. Antimony was found in the blood, urine, placenta, amniotic fluid, and breast milk of these women.¹⁵

Carcinogenicity. Female rats developed lung tumors after inhalation of antimony trioxide and antimony trisulfide.^{18,63,148} A survey among antimony smelters suggested an excess of lung cancer, with a latency of 20 years, in comparison to a nonexposed population. However, concomitant exposure to arsenic and its effects could not be excluded, and the data were poorly or inadequately controlled for smoking habits.⁸⁵ In one group of workers who were exposed to antimony oxide over 9 to 31 years, there was no increased incidence of lung cancer.¹¹⁹ Patients with schistosomiasis have an increased incidence of bladder tumors, and antimony compounds are considered to be one potential cause.¹⁵⁴ The International Agency for Research on Cancer classified antimony trioxide as possibly carcinogenic to humans (group 2B).⁶²

Genotoxicity. Both stibine and trimethylstibine are capable of damaging DNA, presumably by the generation of reactive oxygen species. Other forms of antimony tested, including potassium antimony tartrate, potassium hexahydroxyantimonate, and trimethylantimony dichloride, were found to not be genotoxic.⁵ Trivalent antimony interferes with proteins involved in nucleotide excision repair and partly impairs this pathway, pointing to an indirect mechanism in the genotoxicity of trivalent antimony.⁶²

STIBINE

Antimony compounds can react with nascent hydrogen, forming an extremely toxic gas, stibine (SbH_3), which resembles arsine (AsH_3) (Chap. 89). Stibine is probably the most toxic antimony compound. It is a colorless gas with a very unpleasant smell that rapidly decomposes at temperatures above 302°F (150°C).^{72,154} Historically, stibine release was reported during charging of lead storage batteries.¹⁵⁴ In addition to gastrointestinal symptoms that include nausea, vomiting, and abdominal pain, stibine has strong oxidative properties that may result in massive hemolysis (Chap. 22). Similar to arsine,¹²⁴ severe stibine exposure may result in hematuria, rhabdomyolysis, and death. Maintenance workers are advised to avoid use of drain cleaners containing sodium hydroxide, which is capable of releasing hydrogen in situations where antimony may be present.¹¹⁶

DIAGNOSTIC TESTING

Standard laboratory testing to help identify volume depletion and AKI is indicated for patients with acute antimony toxicity. A complete blood count, electrolytes, renal function studies, and a urinalysis should be obtained. When there is a known or suspected exposure to stibine, additional studies should include tests for hemolysis, such as determinations of bilirubin and

haptoglobin. Blood should also be obtained for a blood type and cross-match, as transfusions are likely to be required.

An ECG should be obtained to evaluate for QT interval prolongation and dysrhythmias. Patients with known myocardial disease should have frequent evaluations of cardiac function,⁶⁴ and continuous ECG monitoring is recommended for all patients with significant symptoms or abnormal cardiovascular status. A chest radiograph should be performed in patients with respiratory symptoms and evidence of hypoxia after significant inhalation exposure. In addition, an abdominal radiograph should be considered in patients with ingestion to evaluate gastrointestinal antimony load and help guide decontamination.²⁶

Antimony concentration in a 24-hour urine collection can be used for assessment of the intensity of exposure to either trivalent or pentavalent antimony.⁷ A normal urinary antimony concentration in nonexposed patients is reported in the range of < 6.2 µg/L.^{117,151} A serum antimony concentration cannot be determined in a timely fashion. The normal serum concentration of antimony is in the range of < 3 µg/L,¹⁰¹ although some laboratories use higher values.¹¹¹

TREATMENT

Decontamination

Following a significant acute ingestion, the majority of patients develop vomiting. Induction of emesis is unlikely to offer any additional benefit. In contrast, gastric lavage may be beneficial, especially if performed before the onset of spontaneous emesis. Although it is unknown whether antimony is adsorbed to activated charcoal, based on experience with salts of arsenic, thallium, and mercury, administration of activated charcoal is appropriate. Additionally, because antimony has a documented enterohepatic circulation, multiple-dose activated charcoal may be of value.⁷ Limited data on arsenic decontamination suggested effectiveness of this method.⁸⁴ Based on experience with arsenic poisoning, the whole bowel irrigation (WBI) should be attempted in severe ingestions in patients who are able to tolerate it, especially if radiographs confirm radiopaque material.^{3,26} One author suggested that WBI has no effectiveness after 48 hours from arsenic exposure.⁸⁴

For patients exposed to stibine, removal from the exposure should be followed by the administration of high-flow oxygen. Theoretically, patients with severe stibine exposures may require exchange transfusion for removal of the stibine–hemoglobin complex.¹²⁴ Dermal exposures, particularly to antimony tri- or pentachloride, may require decontamination with soap and water. Prompt removal from the contaminated area is important for patients exposed to stibine. Rescuers need to take appropriate precautions to ensure their own safety ([Chap. 131](#)).

Supportive Care

The mainstay of treatment for antimony poisoning is good supportive care. Clinicians should anticipate massive volume depletion and begin rehydration with isotonic crystalloid solutions. Electrolytes, urine output, and renal and liver function⁹⁹ should be followed closely. A central venous pressure monitor may be required in patients with cardiovascular instability. Antiemetics are indicated both for patient comfort and to facilitate the administration of activated charcoal. Following stibine exposure, the hemoglobin concentration should be followed closely and blood should be transfused based on standard criteria.

Chelation

Human experience with regard to chelation of antimony is rather limited because of the scarcity of serious toxicity and the rarity of instances when patients have received chelation. Most of the available data are based on animal experimentation. Dimercaprol, succimer, and dimercaptopropane–sulfonic acid (DMPS) all improve survival of experimental animals.^{12,21,82,144} A group from Shanghai demonstrated the ability of the sodium salt of succimer to increase the murine LD₅₀ of tartar emetic 16-fold.¹⁵⁸ One animal study that compared survival after treatment with multiple chelators concluded that the most effective antidotes were DMPS and succimer.¹²

A single case series documented survival in three of four patients exposed to tartar emetic who were treated with intramuscular dimercaprol at a dose of 200 to 600 mg/d. All four patients had increased urinary excretion of antimony.⁹⁶ In another case report, a patient survived after chelation with dimercaprol but without evidence of enhanced urinary excretion of antimony.⁷ Although specific recommendations are difficult to make, it is reasonable to begin therapy with IM dimercaprol until it is certain that antimony is removed from the gastrointestinal tract, at which time the patient can be switched to oral succimer. If the patient experiences cardiac or respiratory symptoms with associated ECG changes during administration of dimercaprol, treatment should be stopped.⁹⁹ Because chelation doses for antimony poisoning are not established, chelators should be administered in doses and regimens that are determined to be safe and effective for other metals (Antidotes in Depth: A25 and A26).

SUMMARY

- Antimony toxicity should be suspected in patients with unexplained profuse nausea, vomiting, diarrhea, and abdominal pain, particularly in the setting of alcohol aversion treatment.
- Most of the patients will require only supportive therapy with decontamination.
- Multiple doses of activated charcoal should be administered.
- WBI should be administered in the first 48 hours following oral exposure.
- Symptomatic patients should be admitted to telemetry for monitoring for cardiac dysrhythmias.
- Chelation should be considered in severe cases of acute overdose.
- Serious complications from treatment of leishmaniasis antimonial preparations are rare; they are mostly related to the heart and pancreas, with age and underlying diseases constituting known risk factors.

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89 ARSENIC

Stephen W. Munday

Arsenic (As)

Atomic number = 33

Atomic weight = 74.92 Da

Normal concentrations

Whole blood < 5 µg/L (0.067 µmol/L)

Urine (24 hour) < 50 µg/L (0.67 µmol/L)

< 1.33 µmol/g creatinine (13.3 µmol/g creatinine)

HISTORY AND EPIDEMIOLOGY

Arsenic poisoning can be unintentional, suicidal, homicidal, occupational, environmental, or iatrogenic.^{108,109,141,165} Mass poisonings have occurred. Nearly 400 residents of Hong Kong fell ill after eating contaminated bread from the Esing Bakery in 1857; two bakery foremen were thought to have tampered with the recipe.⁸⁹ The 1900 Staffordshire beer epidemic in England saw 6000 beer drinkers fall ill and 70 die from beer brewed with sugar made with arsenic-contaminated sulfuric acid.¹⁰⁸ In Wakayama, Japan, 67 people were poisoned by eating intentionally contaminated curry at a festival in 1998.²²³ In 2003, the largest recent outbreak of arsenic poisoning in the United States occurred in New Sweden, Maine, when intentionally adulterated church coffee resulted in the death of one parishioner and the hospitalization of an additional 15 victims.¹⁹ Arsenic trioxide (As₂O₃) reemerged as a treatment for acute promyelocytic leukemia (APML) in the 1990s after physicians in Harbin, China, found a high remission rate in patients given, a crude As₂O₃ infusion.^{126,259}

Contaminated soil, water, and food are the primary sources of arsenic for the general population. Pentavalent arsenic (As⁵⁺) is the most common inorganic form in the environment.⁵⁷ Inorganic arsenic exposure from food is generally low and usually occurs from soil-derived foods such as rice and produce.^{32,199,250,258} Exposure to organic arsenic compounds of low toxicity occurs from consumption of algae, fish, and shellfish. In the past two decades, consumption of contaminated water has emerged as the primary cause of large-scale outbreaks of chronic arsenic toxicity. Arsenic leaches from certain minerals and ores, as well as from industrial waste.¹⁴⁸ In Bangladesh, millions of people have been poisoned by drinking water from wells contaminated with arsenic leached from ground minerals.¹⁷⁰ Ironically, the wells were dug to obtain safer groundwater. Hydroarsenicism is also reported in Chile, Taiwan, Brazil, India, Mexico, and Argentina.^{35,51,57,102,148,170,239} In 2001, the US Environmental Protection Agency decreased the maximum contaminant concentration of arsenic in drinking water to 10 parts per billion (ppb), or 10 µg/L, after statistical modeling indicated an increased risk of lung and bladder cancer from water contaminated with arsenic at the formerly acceptable concentration of 50 ppb.⁶⁶ The World Health Organization also recommends a maximum concentration of 10 ppb.

CHEMISTRY

Arsenic is a metalloid that exists in multiple forms: elemental, gaseous (arsine), organic, and inorganic [As³⁺ (trivalent, or arsenite) and As⁵⁺ (pentavalent, or arsenate)]. Tables 89–1 and 89–2 list sources of arsenic and regulatory standards about arsenic, respectively. Arsenic metal is considered nonpoisonous because of its insolubility in water and, therefore, bodily fluids.¹⁹⁸ Arsine, which is highly toxic, is discussed in Chap. 124. Trivalent arsenicals include arsenic trioxide (As₂O₃), tetra-arsenic tetrasulfide (realgar; As₄S₄), and diarsenic trisulfide (orpiment; As₂S₃). Realgar and orpiment were used by the Chinese to treat malignancies, diarrhea, and infections of the chest and liver.¹³⁹ Organic arsenicals vary in toxicity. Arsenobetaine, which is synthesized from inorganic arsenic by fish and crustaceans, and arsenosugars, which are synthesized by fish, crustaceans, and algae, have very low toxicity.^{12,63,131} In contrast, the organoarsenical medication melarsoprol, used to treat the meningoencephalitic stage of African trypanosomiasis, is highly toxic and similar to inorganic

arsenite.^{27,187}

TABLE 89–1. Sources of Exposure to Arsenic

Inorganic

Occupational/manufacturing

Animal feed (additive)

Brass/bronze

Ceramics/glass

Computer chips (same as semiconductors)

Dyes/paints

Electron microscopy

Fireworks (Chinese)

Fossil fuel combustion—coal

Herbicides

Insecticides/pesticides

Metallurgy

Mining

Rodenticides

Semiconductors (gallium arsenide)

Smelting—copper, lead, zinc, sulfide minerals

Soldering

Wood preservatives

Medicines/contaminated xenobiotics

Chemotherapy (acute promyelocytic leukemia)

Depilatory

Herbals/alternative medicines

Homeopathic remedies

Kelp

“Moonshine” ethanol

Opium

Other

Contaminated well water

Contaminated foods/candies, eg, licorice

Organic

Melarsoprol (trypanocidal)

Thiacetarsamide (heartworm therapy in dogs)

Seafood (arsenobetaine)

TABLE 89–2. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds			
Agency	Guideline Description	Concentration	Source
Air			
ACGIH	TLV (TWA) for arsenic and inorganic arsenic compounds	0.01 mg/m ³	ACGIH 2004
NIOSH	REL (15-min ceiling limit) for arsenic and inorganic compounds	0.002 mg/m ³	NIOSH 2005
	IDLH for arsenic and inorganic compounds	5 mg/m ³	
OSHA	PEL (8-hour TWA) for arsenic organic compounds (general industry, construction, and shipyard)	0.5 mg/m ³	OSHA 2005 29 CFR 1910.1000; 1926.55; 1915.1000
	PEL (8-hour TWA) for general industry for arsenic inorganic compounds	10 µg/m ³	OSHA 2005 29 CFR 1910.1018
Water			
EPA	National primary drinking water standards for arsenic		EPA 2002
	MCL	10 µg/L (10 ppb)	
	MCLG	Zero	
FDA	Bottled drinking water	10 µg/L	FDA 2005 21 CFR 165.110
WHO	Drinking water quality guidelines for arsenic	10 µg/L	WHO 2004
ACGIH			ACGIH 2004
Confirmed human carcinogen			
EPA/NTP			IRIS 2007 / NTP 2005
IARC			IARC 2007

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; MW = molecular weight; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization.

PHARMACOLOGY/PHYSIOLOGY

As₂O₃ has been used successfully to treat APLM. The role of arsenic in our pharmacopeia is expanding; its efficacy in treating various other leukemias, lymphomas, and multiple myeloma, as well as a variety of solid tumors such as breast cancer, colon cancer, lung cancer, hepatocellular carcinoma, colorectal cancer, renal cell carcinoma, and osteosarcoma is being studied.^{38,122,159}

As₂O₃ is administered therapeutically for treating APLM in doses of 0.15 to 0.16 mg/kg/d by either the intravenous or oral route.^{124,126,201,202,205} At this dose its beneficial effects occur predominantly by initiating cellular apoptosis when arsenic concentrations reach 0.5 to 2.0 µmol/L. Apoptosis is triggered by several mechanisms. The trivalent arsenic (As³⁺) ion binds to mitochondrial membrane sulfhydryl (SH) groups, damaging mitochondrial membranes and collapsing membrane potentials. Cytochrome c is released from the damaged mitochondria, with subsequent activation of caspases 9, 3, and 8 and initiation of apoptosis. Cells may be more susceptible if the intracellular concentrations of catalase and glutathione peroxidase (H₂O₂ scavenging enzymes) and glutathione-S-transferase (responsible for conjugating glutathione to xenobiotics) are reduced.^{44,65,79,110,191} As₂O₃ also facilitates apoptosis by down-regulating gene expression of BCL2, a prosurvival protein that protects against apoptosis.³⁶ Finally, As₂O₃ can arrest cells early in mitosis, subsequently leading to apoptosis.⁹²

Low-dose As₂O₃ treatment (0.08 mg/kg/d) beneficially promotes cell differentiation of APL cells when arsenic concentrations reach 0.1 to 2.0 µmol/L. This differentiation is impaired by the promyelocytic leukemia-retinoic acid receptor α (PML-RARα) oncoprotein. This oncoprotein results from the APLM-defining translocation of chromosomes 15 and 17. The PML portion of this oncoprotein plays a key role in leukemogenesis by interfering with RARα activity that is

essential for normal myeloid cellular development. As^{3+} degrades this PML portion, freeing $\text{RAR}\alpha$ to facilitate cell differentiation.^{44,154,161}

Melarsoprol is a trivalent organic arsenical compound used in Africa and parts of Europe to treat the meningoencephalitic stages of both species of African trypanosomes. It is ineffective against American trypanosomiasis and is available in the United States only directly from the Centers for Disease Control and Prevention (CDC), as it is not approved by the US Food and Drug Administration (FDA). The mechanism of action is still poorly understood but may be related to inhibition of glycolysis and oxidation-reduction reactions. The pharmaceutical compound also contains dimercaprol (BAL), which seems to reduce toxicity without diminishing effectiveness. The therapeutic use of melarsoprol can produce many of the toxic effects that occur with inorganic arsenic, including fever, encephalopathy, and acute cerebral edema with seizures and coma. Whether these effects are caused by drug toxicity or by an immune reaction elicited by trypanosomal antigens is unknown.^{27,171,187} Other adverse effects include vomiting, abdominal pain, peripheral neuropathy with hypersensitivity reactions, hypertension, myocardial damage, and albuminuria. Hemolysis can occur in patients with glucose-6-phosphate dehydrogenase deficiency, and erythema nodosum can occur in patients with leprosy.^{27,171} In a study of the usefulness of melarsoprol as a treatment for refractory or advanced leukemia, efficacy was very limited, and reported adverse effects included fatigue, vomiting, diarrhea, vertigo, fever, seizures, headache, back pain, and injection site pain.²⁰⁶

TOXICOLOGY/PATHOPHYSIOLOGY

Investigations of the pathophysiologic effects induced by toxic doses of arsenic are discussed below. The apoptotic mechanisms³⁰ thought to be responsible for some therapeutic effects of As_2O_3 have not been well studied in toxicity models, but limited evidence suggests that cell necrosis may be more important.

Trivalent Arsenic

The primary biochemical effect of As^{3+} is inhibition of the pyruvate dehydrogenase (PDH) complex (Fig. 89–1). Normally, dihydrolipoamide is recycled to lipoamide, a necessary cofactor in the conversion of pyruvate to acetylcoenzyme A (acetyl-CoA). As^{3+} binds the sulfhydryl groups of dihydrolipoamide, blocking lipoamide regeneration.¹⁸⁶ Acetyl-CoA is a central molecule in metabolism, and the resulting decrease leads to several deleterious effects:

- Decreased citric acid cycle activity and thus decreased adenosine triphosphate (ATP) production.
- Disruption of oxidative phosphorylation, which leads to production of hydrogen peroxide and oxygen radicals.
- Decreased gluconeogenesis that can worsen hypoglycemia. Pyruvate carboxylase catalyzes the conversion of pyruvate to oxaloacetate (initial step in gluconeogenesis), and this reaction requires the carboxylation of biotin, a CO_2 carrier attached to pyruvate carboxylase. Biotin cannot be carboxylated unless acetyl-CoA is attached to the enzyme.^{187,211}

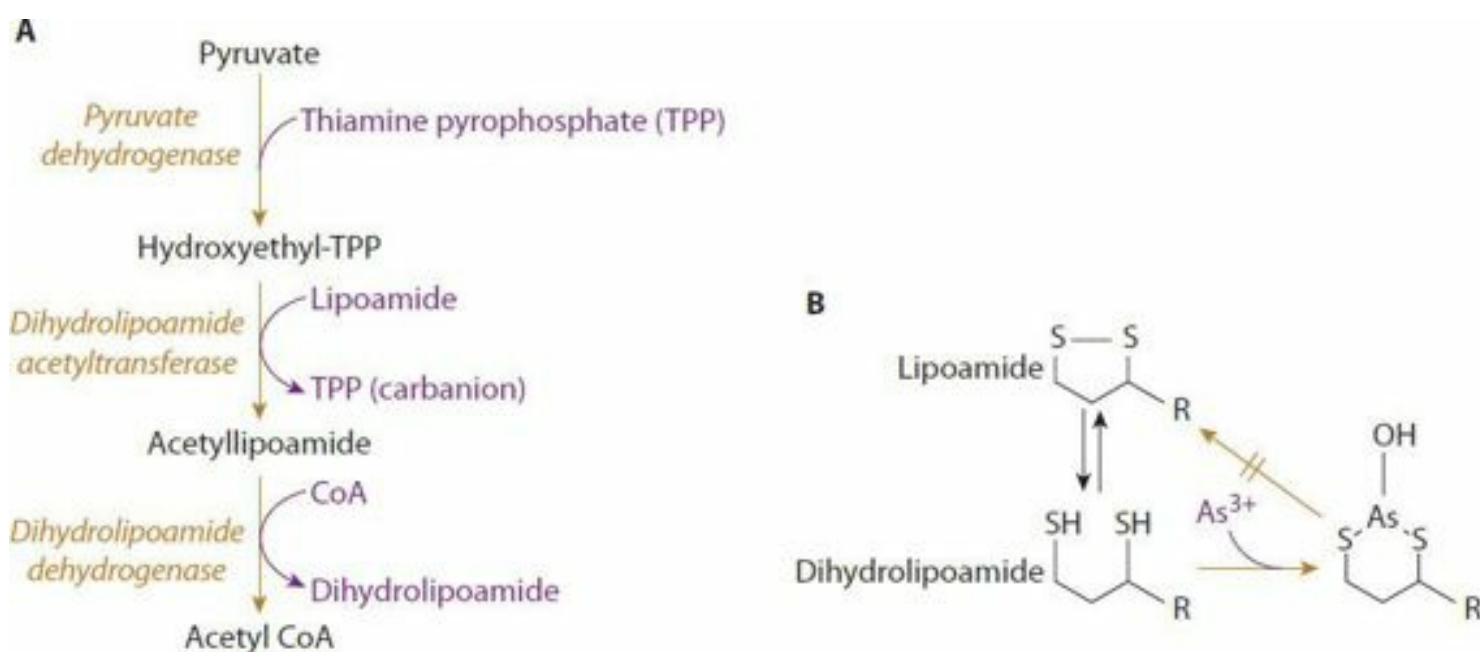


FIGURE 89–1. Effect of trivalent arsenicals (As^{3+}) on pyruvate dehydrogenase (PDH) complex. (A) The PDH complex is composed of the three enzymes, which use thiamine pyrophosphate (TPP) and lipoamide as cofactors to decarboxylate pyruvate and form acetyl CoA. (B) Arsenic interferes with the regeneration of lipoamide from dihydrolipoamide, thereby altering the function of the PDH complex.

In the citric acid cycle, oxidation of α -ketoglutarate to succinyl-CoA uses an α -ketoglutarate dehydrogenase complex that contains the same cofactors as the PDH complex, including lipoamide. Succinyl-CoA is necessary for production of porphyrins and amino acids, and deficiency may contribute to the anemia and wasting that occurs with chronic arsenic poisoning. Arsenic inhibition of thiolase, the catalyst for the final step in fatty acid oxidation, also impairs ATP production. Diminished fatty acid oxidation results in decreased acetyl-CoA, in the loss of the reduced form of nicotinamide adenine dinucleotide (NADH) and the reduced form of flavin adenine dinucleotide (FADH₂) (electron carriers reduced during fatty acid breakdown whose subsequent oxidation yields ATP). As³⁺ also inhibits glutathione synthetase, glucose-6-phosphate dehydrogenase (required to produce nicotinamide adenine dinucleotide phosphate {NADPH}), and glutathione reductase.⁸ These inhibitions result in decreased concentrations of reduced glutathione, which is required to facilitate arsenic metabolism, protect red blood cells (RBCs) from oxidative damage, maintain hemoglobin in the ferrous state, and scavenge hydrogen peroxide and other organic peroxides.

Arsenic affects cardiac repolarization currents. When toxicity occurs, the result is ventricular dysrhythmias, including torsade de pointes. An in vitro study of cells exposed to As³⁺ demonstrated blockade of the delayed rectifier channels I_{Ks} and I_{Kr}. Interestingly, activation of I_{K-ATP}, a weak inward rectifier channel, also occurred; this activation could potentially counteract some of the effects of As³⁺ on the I_{Ks} and I_{Kr} channels.⁶⁰

Animal experiments with phenylarsine oxide, a trivalent arsenical, demonstrate inhibition of insulin-induced glucose transport involving vicinal (adjacent) sulfhydryl groups, as well as β cell damage in pancreatic islets attributed to inhibition of the α -ketoglutarate dehydrogenase complex.²⁵ The impaired glucose transport, plus the inhibited gluconeogenesis, can lead to glycogen depletion and hypoglycemia.¹⁸⁸ Several animal experiments indicate improved central nervous system (CNS) glucose content¹⁸⁷ and increased in survival time with glucose treatment.¹⁸⁷

Effects on RBCs include decreased membrane fluidity and ATP depletion.²⁴⁶ Chronic arsenic exposure is associated with vascular disease; in vitro studies demonstrate inhibition of endothelial cell proliferation and glycoprotein synthesis in addition to lipid peroxidation.³⁷ A study on rodent and human platelets demonstrates increased platelet aggregation and arterial thrombosis.¹³³ Noncirrhotic hepatic portal fibrosis can develop. In a controlled study where mice chronically ingested water containing equal parts As³⁺ and As⁵⁺ for up to 15 months, the development of portal fibrosis was preceded by decreased hepatic glutathione (GSH) concentration, increased lipid peroxidation, and diminished concentrations or activities of numerous enzymes involved in regenerating GSH or scavenging free radicals.¹⁹⁶ Proposed mechanisms by which arsenic induces cancer include DNA damage induced by a dimethyl sulfide (DMS)-derived peroxy radical, gene amplification, replacing phosphate in DNA during replication, increased cell proliferation, and decreased DNA repair efficiency.^{17,115,249} Experimental evidence and human studies support a number of etiologic or contributing factors for skin keratosis and cancer,¹ including chronic stimulation of keratinocyte-derived growth factors such as transforming growth factor- α (TGF- α), impaired methylation, mutation in the p53 tumor-suppressor gene, inhibition of poly(adenosine diphosphate {ADP}-ribose) polymerase vital for DNA repair, and interference with mitotic spindle and microtubular function.^{7,81,105,137,248} Pigmentary changes also occur, and hyperpigmentation is attributed to increased melanin.

Pentavalent Arsenic

Several mechanisms contribute to the toxicity of As⁵⁺. As⁵⁺ can be reduced to As³⁺.^{106,231} As⁵⁺ also resembles phosphate chemically and structurally, may share a common transport system for cellular uptake with phosphate,¹⁰⁶ and can inhibit oxidative phosphorylation by substituting for inorganic phosphate (P_i) in the glycolysis reaction catalyzed by glyceraldehyde 3-phosphate dehydrogenase (Fig. 89–2).^{34,189} The resulting unstable product, 1-arseno-3-phosphoglycerate, spontaneously hydrolyzes to 3-phosphoglycerate, so glycolysis continues but the ATP normally produced during conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate is lost. Uncoupling may also occur if ADP forms ADP-arsenate, instead of ATP, in the presence of As⁵⁺. The ADP-arsenate rapidly hydrolyzes, thus uncoupling oxidative phosphorylation.

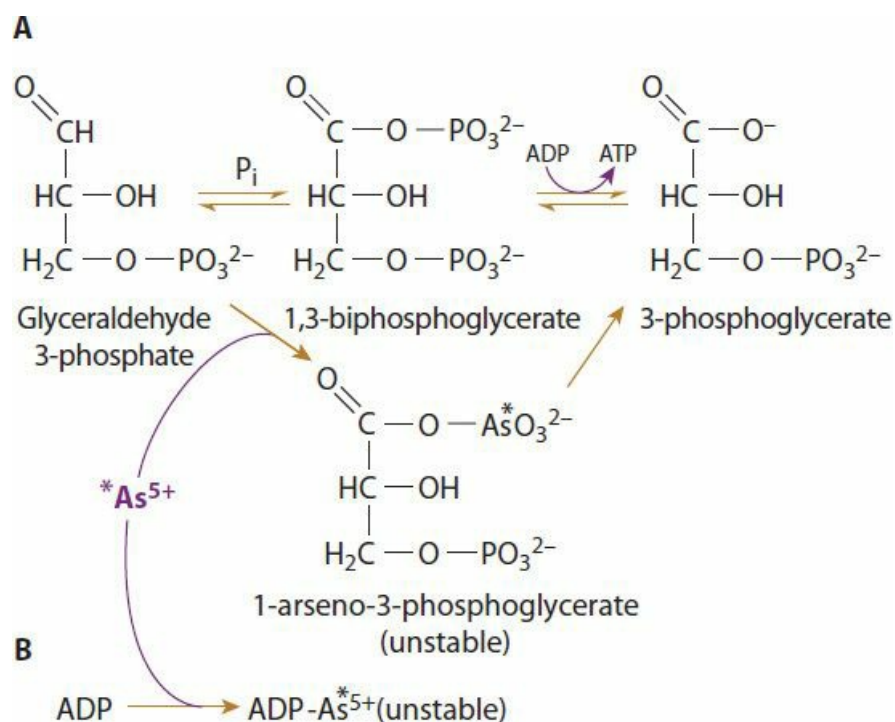


FIGURE 89–2. Pathophysiologic effects of As^{5+} (As^{5+} ; arsenate). (A) Arsenate (chemical formula AsO_4^{3-}) substitutes for inorganic phosphate (P_i ; * indicates substitutions), bypassing the formation of 1,3-bisphosphoglycerate (1,3-BPG), and thus losing the ATP formation that occurs when 1,3-BPG is metabolized to 3-phosphoglycerate. (B) Energy loss also occurs if arsenate substitutes for P_i and blocks the formation of ATP from ADP. ADP = adenosine diphosphate; ATP = adenosine triphosphate.

PHARMACOKINETICS AND TOXICOKINETICS

Absorption

Inorganic arsenic is tasteless and odorless and can be absorbed by the gastrointestinal (GI), respiratory, intravenous, and mucosal routes. GI absorption is facilitated by increased solubility and smaller particle size, and it occurs predominantly in the small intestine, followed by the colon. Poorly soluble trivalent compounds such as As_2O_3 are less well absorbed than more soluble trivalent and pentavalent compounds that, in aqueous solution, have an oral bioavailability greater than 90%. Therefore, when placed in an aqueous solution, As_2O_3 is more toxic than an identical dose of undissolved As_2O_3 eaten in food because of its failure to dissolve, thereby limiting absorption.²²⁸ Organic arsenicals tend to be well absorbed; for example, a rodent study demonstrated approximately 70% GI absorption of the commonly used organic arsenical herbicide, dimethylarsinic acid (cacodylic acid).²⁰⁸ Systemic absorption via the respiratory tract depends on the particulate size, as well as the arsenic compound and its solubility. Large, nonrespirable particles are cleared from the airways by ciliary action and swallowed, allowing GI absorption to occur. Respirable particles lodging in the lungs can be absorbed over days to weeks or remain unabsorbed for years.^{28,243} Dermal penetration of arsenic through intact skin does not pose a risk for acute toxicity but potentially may be problematic with chronic application. Arsenic acid (H_3AsO_4) applied to intact skin in rhesus monkeys resulted in absorption of a mean of 2.0% to 6.4% of the applied dose.²⁴¹ Skin irritation and damage may increase systemic absorption.^{78,190}

Pharmacokinetics of Arsenic Trioxide

Intravenous administration of a single 10-mg dose of As_2O_3 to eight patients showed mean pharmacokinetic values as follows: maximum plasma concentration (Cp_{max}) of $6.85 \mu\text{mol/L}$, α elimination half-life ($t_{1/2 \alpha}$) of 0.89 ± 0.29 hours, and β elimination half-life ($t_{1/2 \beta}$) of 12.13 ± 3.31 hours.²⁰² In six patients, only 1% to 8% of the daily dose was eliminated in a 24-hour urine. Repeat pharmacokinetic studies on day 30 of treatment were not statistically different.²⁰² Another study of patients receiving a single dose of 5 mg of As_2O_3 intravenously demonstrated mean pharmacokinetic values as follows: Cp_{max} of $2.6 \mu\text{mol/L}$, $t_{1/2 \alpha}$ of 1.41 hours, $t_{1/2 \beta}$ of 9.41 hours, serum clearance of 1.98 L/h , and area under the plasma drug concentration versus time curve (AUC) of $12.7 \mu\text{mol/L/h}$. A single dose of 10 mg intravenously showed a Cp_{max} of $6.7 \pm 0.3 \mu\text{mol/L}$.²⁰¹ As_2O_3 10 mg given orally for APL demonstrated total plasma and blood AUC values that were 99% and 87%, respectively, of the corresponding values reported for a 10-mg intravenous dose administered in the same nine patients.¹²⁴

A study in humans receiving intravenous radioarsenic isotope (^{74}As) showed arsenic clearing from the blood in three phases:

- Phase 1 (2 to 3 hours)—Arsenic is rapidly cleared from the plasma with a $t_{1/2}$ of 1 to 2 hours; more than 90% may be cleared during this phase because of redistribution to tissue and renal elimination.
- Phase 2 (3 hours to 7 days)—A more gradual plasma decline occurs, with an estimated $t_{1/2}$ of 30 hours.
- Phase 3 (10 or more days)—Clearance continues from the plasma slowly with an estimated $t_{1/2}$ of 300 hours.¹⁵⁰

The rapid clearance in phase 1 explains why blood testing for arsenic is unreliable, except early in acute poisoning.

Initial distribution is predominantly to liver, kidney, muscle, and skin. The skin is rich in sulfhydryl groups; the elimination $t_{1/2}$ of arsenic by the skin was estimated to be one month in a rabbit study.⁶¹ Distribution to brain also occurs quickly. In the ^{74}As study, 0.30% of the administered dose was found in brain biopsy samples in the first hour postinfusion. This peak declined to 0.16% by day 7.¹⁵⁰ Ultimately, arsenic distributes to all tissues. In the single patient in this study who was followed for 18 days, 96.6% of the total injected arsenic dose was recovered in the urine. Fecal arsenic recovery was less than 1% of the total dose.¹⁵⁰ Other studies in humans demonstrate renal arsenic elimination of 46% to 68.9% within the first 5 days postingestion.^{29,32,111,179} Approximately 30% is eliminated with a half-life of greater than one week, while the remainder is slowly excreted with a half-life of greater than one month.^{29,149} Fecal elimination is considerably less, with reported amounts as much as 6.1% in humans.²¹³ Canine studies have revealed that the mechanisms of urinary elimination of unchanged arsenic and its methylated metabolites are via glomerular filtration and tubular secretion; active reabsorption also occurs.²²¹

Arsenic crosses the placenta and accumulates in the fetus,¹⁴⁰ but three studies of breast milk excretion from women exposed to drinking water with arsenic concentrations of approximately 200 $\mu\text{g/L}$ came to disparate conclusions. Breast milk arsenic concentrations were low in these studies, and only one of them demonstrated a correlation between maternal arsenic concentrations and concentrations in breast milk.^{52,67,195} The authors of one of the two negative studies suggest that breast feeding actually protects the infant from arsenic exposure.⁶⁷

Metabolism, by adding methyl groups, occurs primarily in the liver, as well as in the kidneys, testes, and lungs (Fig. 89–3). If the arsenic is pentavalent, approximately 50% to 70% of As^{5+} will first be reduced to As^{3+} .^{51,209,229} This bioactivation step requires the oxidation of glutathione⁵⁸ and can begin within 15 minutes of exposure.²²⁹ S-adenosylmethionine (SAM) is the primary methyl donor. Nonenzymatic methylation is also demonstrated in an in vitro study using human liver cytosol; here, methylcobalamin (methyl B_{12}) was the methyl donor.²⁵⁵ Dietary and vitamin deficiencies, as well as high doses of inorganic arsenic, may diminish the ability to methylate arsenic, and folate supplementation lowers blood arsenic concentrations in a folate-deficient population.^{15,75–77,93,97,98,176,178,230} However, a study in pregnant Bangladeshi women showed efficient arsenic methylation despite nutritional deficiencies.¹³⁶ Addition of one methyl group produces monomethyl-arsenic acid (MMA^{5+}); adding a second methyl group produces dimethylarsinic acid (DMA^{5+}). Production of a trivalent intermediate in this reaction, monomethylarsonous acid (MMA^{3+}), is catalyzed by MMA^{5+} reductase. In rabbits this is the rate-limiting enzyme in the biotransformation pathway; however, no data exist to confirm a similar role in human metabolism.^{227,256} Conversion of MMA^{5+} to DMA^{5+} is catalyzed by a methyltransferase. Genomic studies have begun to identify gene polymorphisms in these pathways that are associated with variations in arsenic metabolism and toxicity.^{3,175}

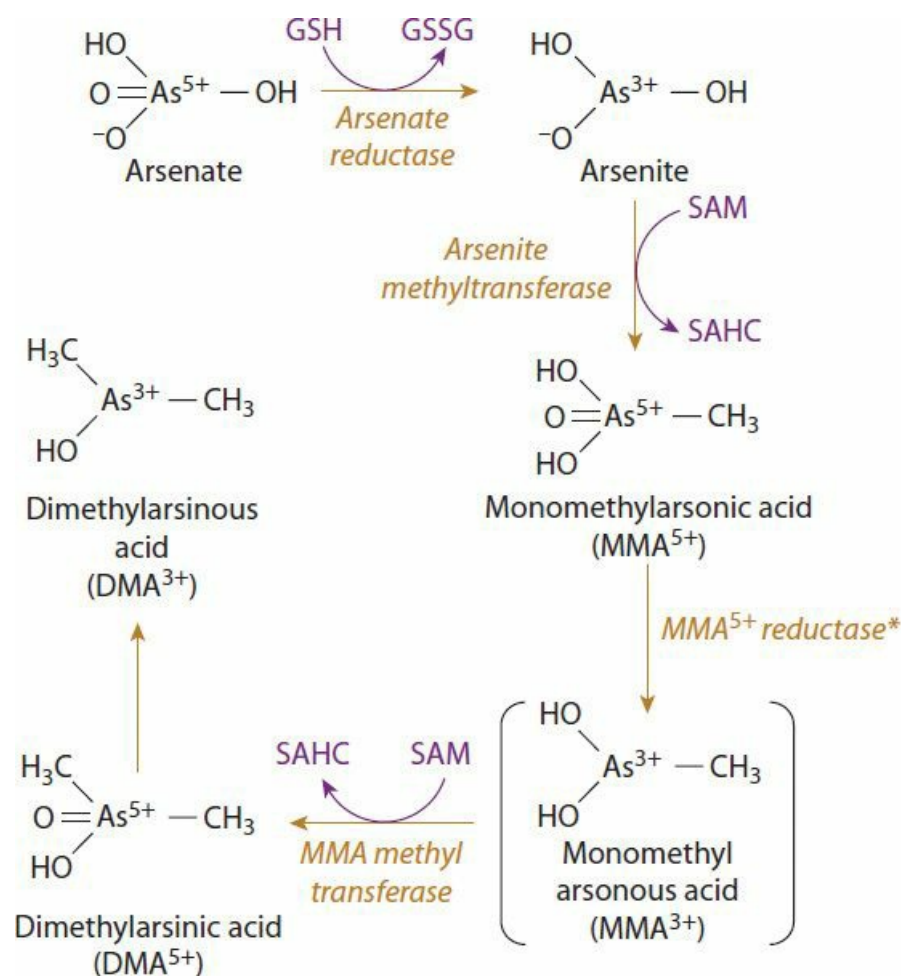


FIGURE 89–3. Metabolism of arsenate [As^{5+}] and arsenite [As^{3+}]. DMA, dimethylarsinic acid; GSH = glutathione; MMA = monomethylarsonic acid; SAHC = S-adenosylhomocysteine; SAM = S-adenosylmethionine. The asterisk (*) denotes MMA^{5+} reductase, the rate-limiting enzyme in rabbit studies of arsenic metabolism; the analogy to humans is unknown.

These monomethylation and dimethylation steps were previously thought to detoxify arsenic, but this has been questioned because of the generation of these trivalent intermediates, which are more toxic than the parent compounds.²²⁵ Estimated human LD_{50} (median lethal dose for 50% of test subjects) doses were reported to be As_2O_3 , 1.43 mg/kg; MMA^{5+} , 50 mg/kg; and DMA^{5+} , 500 mg/kg. However, it is important to note that the doses cited for MMA and DMA apply to arsenic existing in the pentavalent form (As^{5+}). Studies in animals and cell cultures indicate that MMA^{3+} may be more toxic than As^{3+} .^{144,173,174} Cytotoxicity studies in human hepatocytes revealed descending toxicity of arsenic and its metabolites as follows: $\text{MMA}^{3+} > \text{arsenite} > \text{arsenate} > \text{MMA}^{5+} = \text{DMA}^{5+}$.¹⁷³ Thus, toxicity increases with the formation of MMA^{3+} .

There is some evidence that these findings have clinical relevance. In a study from a blackfoot disease–hyperendemic area of Taiwan, lower capacity to methylate inorganic arsenic to DMA^{5+} was associated with increased risk of blackfoot disease. The capacity to methylate arsenic to DMA^{5+} was measured as the ratio of DMA^{5+} to MMA^{5+} and the ratio of MMA^{5+} to the sum of As^{3+} and As^{5+} .²¹⁹ In addition, a cohort study found that the odds of premalignant skin lesions increased with increasing urinary MMA^{5+} and decreasing urinary DMA^{5+} .³ They also found that there was an increased risk of skin lesions associated with genetic polymorphisms of glutathione S-transferase and borderline increased risk with polymorphisms of methylenetetrahydrofolate reductase. The authors suggested that the conversion of MMA^{5+} to DMA^{5+} may be saturable and that arsenic metabolism and toxicity are affected by genetics.³ An additional nested case-controlled study of this cohort confirmed that folate deficiency and DNA hypomethylation were risk factors for skin lesions.¹⁷⁷

Arsenobetaine (AsB) is also well absorbed orally and is excreted unchanged in the urine.²²⁸ Elimination occurs more rapidly than with inorganic arsenic. In a study involving human volunteers, 25% was excreted within 2 to 4 hours, 50% by 20 hours, and 70% to 83.7% after 166 hours. A two-compartment exponential model shows nearly 50% of the AsB eliminated, with a first compartment $t_{1/2}$ of 6.9 to 11.0 hours and a second compartment $t_{1/2}$ of 75.7 hours.¹¹¹

CLINICAL MANIFESTATIONS

Inorganic Arsenicals

Toxic manifestations vary, depending on the amount and form, route, and chronicity of arsenic exposure. Other influencing factors include individual variations in methylation and excretion. Larger doses of a potent compound, such as As_2O_3 , will rapidly produce manifestations of acute toxicity, whereas chronic ingestion of substantially lower amounts of As^{5+} in groundwater will result in different clinical findings over time. Manifestations of subacute toxicity can develop in patients who survive acute poisoning, as well as in patients who are slowly poisoned environmentally.

Acute Toxicity. GI signs and symptoms of nausea, vomiting, abdominal pain, and diarrhea, which occur 10 minutes to several hours following ingestion, are the earliest manifestations of acute poisoning by the oral route. The diarrhea has been compared to cholera in that it may resemble “rice water.” Severe multisystem illness can ensue with extensive exposure. Cardiovascular signs, ranging from sinus tachycardia and orthostatic hypotension to shock, can develop. Reported cases have mimicked myocardial infarction or systemic inflammatory response syndrome, with intravascular volume depletion, capillary leak, myocardial dysfunction, and diminished systemic vascular resistance.^{16,22,24,85,112,200} Acute encephalopathy can develop and progress over several days, with delirium, coma, and seizures attributed to cerebral edema and microhemorrhages.^{71,200} Seizures may be secondary to dysrhythmias, and the underlying cardiac rhythm should be assessed. Seizures apparently secondary to torsade de pointes associated with a prolonged QT interval developed 4 days to 5 weeks after acute arsenic ingestion.^{22,83,207} Acute respiratory distress syndrome (ARDS) and respiratory failure, hepatitis, hemolytic anemia, acute kidney injury (AKI), rhabdomyolysis, other ventricular dysrhythmias, and death can occur.^{24,69,88,156,222} Death may occur after suddenly developing bradycardia, followed by asystole.^{24,112,141} Fever may develop, misleading the practitioner to diagnose sepsis.^{62,112} Hepatitis can occur and may be a result of altered intrahepatic heme metabolism causing an increased synthesis of bilirubin or a result of altered protein transport between hepatocytes.⁶ AKI failure may be secondary to ischemia caused by hypotension, tubular deposition of myoglobin or hemoglobin, renal cortical necrosis, and direct renal tubular toxicity.^{26,80,197,222} Glutathione depletion may be contributory.¹⁰³ Unusual complications include phrenic nerve paralysis, unilateral facial nerve palsy, pancreatitis, pericarditis, and pleuritis.^{18,256} Fetal demise has been reported, with toxic arsenic concentrations found in the fetal organs.^{24,140}

Acutely poisoned patients with less severe illness may experience gastroenteritis and mild hypotension that persist despite antiemetic and intravenous crystalloid therapies. Hospitalization and continued intravenous fluids may be required for several days.¹³² The prolonged character of the GI symptoms is atypical for most viral and bacterial enteric illnesses and should alert the physician to consider arsenic poisoning, especially if there is a history of repetitive GI illnesses. A metallic taste or oropharyngeal irritation, mimicking pharyngitis, can occur.^{24,100} GI ulcerative lesions and hemorrhage are reported.^{71,85} Toxic erythroderma and exfoliative dermatitis result from a hypersensitivity reaction to arsenic.²¹⁴

In the days and weeks following an acute exposure, prolonged or additional signs and symptoms in the nervous, GI, hematologic, dermatologic, pulmonary, and cardiovascular systems can occur. Encephalopathic findings of headache, confusion, decreased memory, personality change, irritability, hallucinations, delirium, and seizures may develop and persist.^{62,74,192} Sixth cranial nerve palsy and bilateral sensorineural hearing loss are reported.^{50,83} Peripheral neuropathy typically develops 1 to 3 weeks after acute poisoning, although in one series nine patients developed maximal neuropathy within 24 hours of exposure.^{50,100,132,241} Sensory symptoms develop first, and diminished to absent vibratory sense may be present. Progressive signs and symptoms include numbness, tingling, and formication with physical findings of diminished to absent pain, touch, temperature, and deep-tendon reflexes in a stocking-glove distribution. Superficial touch of the extremities may elicit severe or deep aching pains, a finding that also occurs with thallium poisoning (**Chap. 102**). Motor weakness may then develop. The most severely affected patients manifest an ascending flaccid paralysis that mimics Guillain-Barré syndrome.^{50,100,132} Respiratory findings can include dry cough, crackles, hemoptysis, chest pain, and patchy interstitial infiltrates.^{100,172} These findings may be misinterpreted as viral or bronchitic disease. Leukopenia, and less commonly anemia and thrombocytopenia, occur from days to 3 weeks after an acute exposure, but resolve as bone marrow function returns.^{108,135}

Dermatologic lesions can include patchy alopecia, oral herpetiform lesions, a diffuse pruritic macular rash, and a brawny nonpruritic desquamation (**Chap. 18**). Diaphoresis and edema of the face and extremities can develop.¹ Mees’ lines (transverse striate leuconychia of the nails) are 1- to 2-mm wide horizontal nail bands that represent disturbed nail matrix keratinization (**Fig. 89–4**). They are uncommon in arsenic poisoning. A minimum of 30 days after exposure is required for the lines to extend visibly beyond the nail lunulae.^{100,248} Contact dermatitis has been reported from topical exposure in an occupational setting. Other possible toxic manifestations of subacute inorganic arsenic toxicity include nephropathy, fatigue, anorexia with weight loss, torsade de pointes, and persistence of GI symptoms.^{16,145}



FIGURE 89-4. Mees' lines, parallel white bands across the nails result from exposures to metals, radiation, and chemotherapeutic agents, among others. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Chronic Toxicity. Malignant and nonmalignant skin changes, hypertension, diabetes mellitus (DM), and peripheral and cerebral vascular disease, as well as lung, bladder, and hepatic malignancies are associated with drinking water containing arsenic that is consumed by study populations.^{47,152,170,180,252} The skin is very susceptible to the toxic effects of arsenic; multiple dermatologic lesions have been reported in populations suffering from hydroarsenicism.^{148,252} Alterations in pigmentation occur first, with hyperpigmentation being the most common. Hypopigmentation ("raindrop" pattern) can also occur (Fig. 89-5). Hyperkeratoses typically develop on the palms and soles, but can be diffuse (Fig. 89-6). Squamous and basal cell carcinomas and Bowen's disease (intraepidermal squamous cell carcinoma) may occur. Bowen's disease usually proliferates in multiple sites, especially on the trunk, and is noted for developing on sun-protected areas. Latency periods for developing keratoses, Bowen's disease, and squamous cell carcinoma were 28, 39, and 41 years, respectively, in 17 patients chronically exposed to environmental or medicinal arsenic.^{56,247} GI symptoms of nausea, vomiting, and diarrhea are less likely but can occur. Hepatomegaly was present in 120 of 156 patients with hydroarsenicism; liver biopsy in 45 cases revealed a noncirrhotic portal fibrosis in 91.1%.¹⁴⁸ Rodent studies also demonstrate hepatic fibrosis from inorganic arsenic exposure.¹⁹⁶ Portal hypertension and hypersplenism have occurred.^{148,196} Hepatic angiosarcomas are linked to arsenic exposure.^{48,114,130}



FIGURE 89-5. Characteristic hemorrhagic vesicles of arsenical dermatitis is shown. (Used with permission of New York University Department of Dermatology.)



FIGURE 89–6. Characteristic vesicular xerotic arsenical dermatitis is shown. (Used with permission of New York University Department of Dermatology.)

Some, but not all, population studies in areas of Bangladesh, Taiwan, and the United States with arsenic-contaminated water show an increased prevalence of DM, pulmonary fibrosis, and other organ system effects.^{39,117,182,183,220} A cross-sectional drinking water study from the United States revealed an odds ratio of 3.58 for prevalence of type 2 DM among those at the 80th percentile, as compared to those at the 20th percentile, despite a median total arsenic concentration of only 7.1 ppb.^{129,160} However, a cross-sectional study in Bangladesh did not find a relationship between arsenic exposure and DM.³⁹ Animal studies demonstrate that arsenic can decrease insulin-mediated uptake of glucose by cells and can also disrupt insulin transcription factor signal transduction.^{169,236} In a study from West Bengal, restrictive lung disease was reported in 9 of 17 patients, and a restrictive plus obstructive pattern occurred in another 7 cases.¹⁴⁸ Lung disease has also been noted in other populations.⁹⁰ Proposed mechanisms include arsenic-induced inflammation and oxidative stress.¹⁶⁶ Aplastic anemia and agranulocytosis are documented in patients exposed to arsenic.⁶² A dose-response relationship between arsenic exposure and vascular disease is reported in several populations.²³⁸ After adjusting for age, sex, hypertension, DM, cigarette smoking, and alcohol consumption, a significant relationship was observed with cerebrovascular disease in a region of Taiwan.⁴⁷ Blackfoot disease, an obliterative arterial disease of the lower extremities, occurring in Taiwan, is linked to chronic arsenic exposure,^{35,218} as is ischemic heart disease.³³ The incidence of Raynaud's phenomenon and vasospasm was reported to be increased in smelter workers exposed to arsenic, compared with a control group.¹²⁸ Encephalopathy and peripheral neuropathy are the neurologic manifestations most commonly reported.^{21,99} Electromyographic studies of 33 patients with chronic ingestion of arsenic-contaminated water revealed 10 patients with findings consistent with sensory neuropathy. The minimum duration of exposure was 2 years. Interestingly, three of these patients consumed water with an arsenic concentration that only slightly exceeded the contaminant concentration of 50 ppb previously permissible in the United States.¹⁰²

Arsenic is classified as a definite carcinogen by the International Agency for Research on Cancer (IARC, Group 1) and the National Toxicology Program (NTP). Cancers known to develop include lung, skin, and bladder.^{12,49,107,195,204} Transitional cell bladder carcinoma was the most common type in one large epidemiologic study.⁴⁶ However, the exposure threshold of concern remains controversial.¹⁵¹ A critical literature review of animal and human studies found that exposure to environmental arsenic was unlikely to cause reproductive or developmental toxicity.⁵⁹ However, a more recent rodent study revealed fetal growth retardation and neurotoxicity at doses relevant to human exposure and in the absence of maternal toxicity.²³⁷ More concerning, two recent drinking water cohort studies from Bangladesh showed small but statistically significant increases in birth defects and fetal loss.^{125,182,226} In addition to possibly increasing the risk of birth defects, there is also cohort and cross-sectional evidence that in utero or early childhood exposure may be associated with persistent neurocognitive effects in children.^{31,39,54,94,95,117,217,234,239,240} Finally, there is evidence that in utero or early childhood exposure to arsenic in drinking water increases the risk of malignant and nonmalignant lung diseases in young adults.²⁰⁴ In summary, there is accumulating evidence of persistent adverse effects from in utero or early childhood exposure, but additional prospective studies are needed to confirm these findings by decreasing the effects of confounding and bias that may explain the results.

Many of the questions regarding the chronic health effects of exposure to arsenic in drinking water are currently being investigated in the Health Effects of Arsenic Longitudinal Study (HEALS). This study was designed to evaluate the health effects of a full range of drinking water arsenic exposures, including mortality, premalignant and malignant skin tumors,

pregnancy outcomes, and children's cognitive development.⁵

This study is a prospective cohort study in Araihaazar, Bangladesh. Participants were between the ages of 18 and 75 years and married, although both members of a couple were not required to enroll. A total of 11,764 subjects enrolled, 6704 women and 5042 men. The participation rate in the initial enrollment was 97.5% of those approached.⁵ Of those who agreed to participate, 98% completed an extensive questionnaire that included demographic and lifestyle components and a validated food-frequency questionnaire. They also participated in a clinical examination with an extensive skin evaluation. More than 90% of this group also provided blood and spot urine arsenic samples.⁵

Approximately one third of the participants consumed water in each of three groups: greater than 100 µg/L, 25 to 100 µg/L, and less than 25 µg/L. Average urinary concentrations of arsenic were approximately 140 µg/L.

Many studies from this cohort have been published. Studies of persons with arsenic-induced skin lesions have shown increasing risk of disease as exposure increases.^{4,13} Modification of risk was noted in relationship to nutritional status, sunlight exposure, smoking, and some occupational exposures such as fertilizers and pesticides.^{41,42,153} A dose-response relationship was also found for other health effects, including total mortality,¹⁴ cardiovascular disease,⁴⁰ respiratory symptoms,¹⁶⁷ proteinuria,⁴³ oral cavity lesions,²¹⁰ and neurologic effects.^{91,168} Biannual follow-up of this cohort continues.

Adverse Drug Effects: Arsenic Trioxide

The most common adverse effects are dermatologic (skin dryness, pigmentary changes, maculopapular eruptions with or without pruritus); GI (nausea, vomiting, anorexia, diarrhea, and dyspepsia); hematologic (leukemoid reactions); hepatic (elevation of aminotransferase concentrations typically less than or equal to 10 times the upper limit of normal values, with a reported incidence of 20% with low-dose and 31.9% with conventional-dose therapy²⁰¹); cardiac (prolonged QT interval in 40%–63% of patients, first-degree atrioventricular block, ventricular ectopy, monomorphic nonsustained ventricular tachycardia, torsade de pointes, asystole, and death);^{194,201,205,224,245} facial edema; and neurologic (paresthesias, peripheral neuropathy, and headache). All of these effects occurred more commonly in one case series with conventional-dose therapy (0.16 mg/kg/d) when compared to low-dose therapy. The majority of patients are treated symptomatically without discontinuing As₂O₃ treatment. Leukemoid reactions, defined as white blood cell counts greater than $50 \times 10^9/L$, develop in nearly 50% of patients between 14 and 42 days of beginning treatment. Such patients are at risk for intracerebral hemorrhage or infarction and for the APML syndrome. This syndrome is similar to the differentiation syndrome (DS), which was formerly known as the retinoic acid syndrome.¹⁵⁵ The remission induction treatment phase is the period of greatest risk.²⁰² Common clinical findings in this syndrome include pulmonary interstitial infiltrates and/or pleural effusions, dyspnea, tachypnea, fluid retention, myalgias, arthralgias, fever, and weight gain; approximately 20% to 25% of patients treated with arsenic trioxide will develop one or more signs or symptoms of this syndrome.^{146,159,194,201,202}

Although a theoretical concern, there is currently no evidence of increased risk of secondary malignancies in treated patients. Continued close follow-up will be necessary to evaluate whether secondary malignancy risk will increase over time.⁶⁵

DIAGNOSTIC TESTING

Timing of testing for arsenic must be correlated with the clinical course of the patient and whether the poisoning is acute, subacute, chronic, or remote with residual clinical effects. To properly interpret laboratory measurements, confounding factors, such as food-derived organic arsenicals or accumulated arsenic (DMA and arsenobetaine) in patients with chronic kidney disease, must be considered.^{55,260,261} Failure to understand potential confounders, as well as the time course of arsenic metabolism, clearance, and effect on laboratory parameters, can cause erroneous assessment of possible arsenic poisoning.

Urine and Blood

Diagnosis ultimately depends on finding an elevated urinary arsenic concentration. In an emergency, a spot urine may be sent prior to beginning chelation therapy. A markedly elevated arsenic concentration verifies the diagnosis in a patient with characteristic history and clinical findings, but a low concentration does not exclude arsenic toxicity.²³⁵ In nine acutely symptomatic patients, initial spot urine arsenic concentrations ranged from 192 to 198,450 µg/L.¹¹⁶ Definitive diagnosis of arsenic exposure hinges on finding a 24-hour urinary concentration equal to or greater than 50 µg/L, 100 µg/g creatinine, or 100 µg total arsenic. A study on arsenic exposure from drinking water showed excellent correlations between spot and 24-hour urine arsenic concentrations. There are not enough data to determine if this relationship holds true in acutely poisoned patients, so a 24-hour collection is still preferred.³² Challenge testing with dimercaptopropane sulfonate (DMPS) has been performed in individuals exposed to arsenic in drinking water and clearly increases arsenic excretion; however, it also alters the percentages of the arsenic species recovered compared with controls and has not been correlated with clinical

effects.¹¹ All urine should be collected in metal-free polyethylene containers; acid-rinsed containers are not recommended since the acid alters the arsenic species.⁶⁸ If testing is performed by an outside reference laboratory, specimens from acutely ill patients should be sent via express transportation with a request for a rapid result.

When interpreting slightly elevated urinary arsenic concentrations, laboratory findings must also be correlated with the history and clinical findings, because seafood ingestion is reported to transiently elevate urinary total arsenic excretion up to 1700 µg/L.¹² When seafood arsenic is a consideration, speciation of arsenic can be accomplished by high-performance liquid chromatography (HPLC) separation, followed by inductively coupled plasma-mass spectrometry (ICPMS), HPLC via ion-pair chromatography coupled with hydride-generation atomic-fluorescence spectrometry (HGAFS), or by hydride generation coupled with cold-trap gas chromatography-atomic absorption spectrometry. These techniques separate AsB, As³⁺, As⁵⁺, MMA, and DMA.⁶⁸ Arsenobetaine can also be directly measured by silica-based cation-exchange separation, followed by atomic absorption spectrometry.¹⁶² Two other methods, selective hydride-generation atomic-absorption spectrometry (HGAAS) and resin-based ion-exchange chromatography, do not directly measure AsB; instead, they indirectly derive this value by subtracting the sum of all measured arsenic species from the total arsenic concentration.¹⁶² If arsenic speciation cannot be done, the patient can be retested after a one-week abstinence from fish, shellfish, and algae food products.

Conditions under which urine is stored can affect total arsenic recovery, as well as proportionality of the species. The various arsenic species—arsenate (As⁵⁺), arsenite (As³⁺), MMA, DMA, and AsB—remain stable for 2 months in urine stored without preservatives at either -4°F (-20°C; freezer) or 39.2°F (4°C; refrigerator); AsB is stable for 8 months under these conditions. Storage for longer than 2 months can alter the recovery of various species. Addition of 0.1% hydrochloric acid (HCl) facilitates reduction of arsenate to arsenite and also decreases MMA and DMA concentrations. Acid-washed collection containers should not be used if measurement of the various arsenic species is planned. Total arsenic recovery can be diminished by any of the following: specimen storage for greater than 2 months, acidification, or testing using HPLC-ICPMS and HPLC-HGAFS, since all these methods usually require that the samples be filtered prior to undergoing HPLC separation.⁶⁸

Diagnostic evaluation of chronic toxicity should include laboratory parameters that may become abnormal within days to weeks following an acute exposure. Tests should include a complete blood count, renal and liver function tests, urinalysis, and 24-hour urinary arsenic determinations. Complete blood count findings can include a normocytic, normochromic, or megaloblastic anemia; an initial leukocytosis followed by development of leukopenia, with neutrophils depressed more than lymphocytes, and a relative eosinophilia; thrombocytopenia; and a rapidly declining hemoglobin, indicative of hemolysis or a GI hemorrhage.¹²⁷ Basophilic stippling of RBCs can be seen; this can occur in other toxic and clinical disorders. Karyorrhexis, a rupture of the RBC cell nucleus with chromatin disintegration into granules that are extruded from the cell, and dyserythropoiesis are reported in both lead- and arsenic-toxic patients. Both findings are caused by arsenic-induced inhibition of DNA synthesis and damage to the nuclear envelope.⁶⁴ The karyorrhexis can occur within 4 days and resolve by 2 weeks after poisoning, and may be an early indication of arsenic toxicity.¹²⁷ Elevated serum creatinine, aminotransferases, and bilirubin, as well as depressed haptoglobin concentrations, may develop. Urinalysis may reveal proteinuria, hematuria, and pyuria. Cerebrospinal fluid examination in patients with CNS findings can be normal or exhibit mild protein concentration elevation, measured at 26.5 mg/dL in one case.¹⁰⁰ Urinary arsenic excretion in subacute and chronic cases varies inversely with the postexposure time period, but low-concentration excretion can continue for months after exposure. In a study of 41 cases of arsenic-induced peripheral neuropathy, most patients with a neuropathy of 4 to 8 weeks duration had total 24-hour urinary arsenic measurements of 100 to 400 µg.¹⁰⁰

Hair and Nail Testing

In cases of suspected arsenic toxicity, in which the urinary arsenic measurements fall to less than toxic concentrations, analysis of hair and nails may yield the diagnosis. Arsenic can be detected in the proximal portions of hair within 30 hours of ingestion.²⁵³ Inorganic arsenic is the form best absorbed by these tissues and the form most commonly found in human poisoning cases; small amounts of methylated metabolites may also be detected.¹⁸¹ Arsenobetaine has not been found in hair and tissues in human and animal studies.^{250,251} Hair grows at rates varying from 0.7 to 3.6 cm per month, with a mean rate of 1 cm per month.²⁴² The Society of Hair Testing has made the following recommendations for collection of hair specimens, although they are only validated for testing drugs of abuse: (a) collect approximately 200 mg of hair from the posterior vertex region of the scalp using scissors to cut as close to the scalp as possible, and (b) tie the hairs together, wrap in aluminum foil to protect from environmental contamination, and store at room temperature.²⁴² Nails grow approximately 0.1 mm per day. Total replacement of a fingernail requires 3 to 4 months, whereas toenails require 6 to 9 months of growth. These facts, plus the frequency of hair cutting, should be considered when estimating the usefulness of measuring arsenic levels in these tissues. The normal values of the testing laboratory should be used to determine whether arsenic concentrations are elevated. In cases of remote toxicity, hair and nail arsenic measurements may or may not be elevated, depending on the time elapsed since exposure. Sequential hair analysis to assess the time(s) of exposure can be

performed by solid sampling graphite furnace atomic absorption spectrophotometry or by x-ray fluorescence spectrometry.^{118,215,216}

Other Tests

Abdominal radiographs might demonstrate radiopaque material in the GI tract soon after an ingestion.^{2,45,85,86,101} However, even after an acute ingestion, the absence of radiopaque materials on abdominal radiographs is reported.⁵³ The incidence of positive radiographs after an ingestion is unknown, and a negative radiograph should not eliminate arsenic as a diagnostic consideration. Electrocardiographic changes reported include QRS widening, QT prolongation, ST-segment depression, T-wave flattening, ventricular premature contractions, nonsustained monomorphic ventricular tachycardia, and torsade de pointes.^{20,164,205,224} Nerve conduction studies (NCS) can confirm or diagnose clinical or subclinical axonopathy. Both the sensory nerve action potential (SNAP) and the motor compound muscle action potential (CMAP) measure the number of axons that are available to conduct impulses. Since the sensory studies are more sensitive than motor studies in detecting axonal degeneration and demyelination, decreased SNAP measurements better indicate subclinical neuropathy. In motor nerve studies, the amplitude (height of the CMAP) is a more sensitive measure of the number of axons that can conduct impulses than is the conduction velocity; this can be explained by the pattern of axonal destruction as opposed to myelin injury (which mainly affects conduction velocity). Nerve biopsies have confirmed disintegration of both axons and myelin in patients with arsenic-induced peripheral neuropathy; the axonal loss begins distally in the lower extremities and is initially scattered. Thus, conduction along the remaining functional axons can be sufficient to produce normal or only slightly decreased conduction measurements on NCS.^{82,100,119,132,158,163}

MANAGEMENT

General

Acute arsenical toxicity is life threatening and mandates aggressive treatment. Advanced life support monitoring and therapies should be initiated when necessary, but with a few caveats. Careful attention to fluid balance is important because cerebral and pulmonary edema may be present. Xenobiotics that prolong the QT interval, such as the class IA, class IC, and class III antidysrhythmics, should be avoided whenever possible ([Chaps. 16 and 64](#)). Potassium, magnesium, and calcium concentrations should be maintained within normal range to avoid exacerbating a prolonged QT interval. Glucose concentrations and glycogen stores should be maintained parenterally with dextrose and hyperalimentation solutions or with enteral feedings, in view of their beneficial effects in experimental models of arsenic poisoning.^{138,187,188,211}

GI decontamination of patients acutely poisoned with arsenic is controversial. Arsenic poorly adsorbs to activated charcoal, cholestyramine, and bentonite.¹⁸⁵ Moreover, significantly poisoned patients usually have nausea and vomiting and may have altered mental status, which make activated charcoal administration difficult. Despite these concerns, activated charcoal in conjunction with airway protection if necessary is recommended because of the relatively low likelihood of harming the patient and the hope that preventing even a small amount of absorption might prevent or lessen the potentially disastrous consequences of arsenic poisoning. If radiopaque material is visualized in the GI tract, whole bowel irrigation can be administered until the radiopaque material is no longer visualized on repeat abdominal radiograph. Continuing nasogastric suction may be important in removing arsenic resecreted in the gastric or biliary tract. Arsenite was still detectable in the gastric aspirate in three patients 5 to 7 days following an ingestion.¹⁴³ There is no clinical experience with the use of N-acetylcysteine to increase glutathione concentrations, although an animal model suggested a protective effect.¹⁸⁴

In cases of chronic toxicity, patients should be removed from the arsenic source, and gastric decontamination should be performed if there is evidence of arsenic in the GI tract. Arsenic can be readily removed from skin with soap, water, and vigorous scrubbing. In this situation, when homicidal intent is suspected, all hospital visitors should be closely monitored, and outside nutritional products should be forbidden.

Chelation Therapy

Chelators. Dimercaprol (BAL) and 2,3-dimercaptosuccinic acid (succimer) are the two chelators available in the United States. A third drug, DMPS, is distributed by Heyl, a German pharmaceutical company, as Dimaval, but it is not approved or marketed in the United States ([Antidotes in Depth: A25 and A26](#)). All contain vicinal dithiol moieties that bind arsenic to form stable 1,2,5-arsadithiolanes ([Fig. 89–7](#)), and all are most effective when administered in doses equimolar to the arsenic burden.¹⁵⁷ Dosing regimens and adverse effects are listed in [Table 89–3](#).

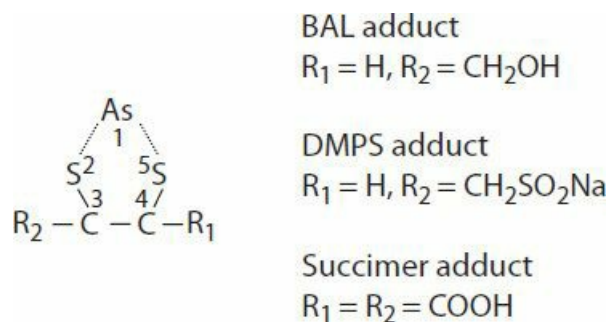


FIGURE 89–7. 1,2,5-Arsadithiolane adducts with BAL, DMPS, and DMSA.

TABLE 89–3. Chelators for Arsenical Poisoning

<i>Dosage</i>	<i>Adverse Effects</i>
BAL 3–5 mg/kg IM every 4–6 hours	Hypertension, febrile reaction, diaphoresis, nausea, vomiting, salivation, lacrimation, rhinorrhea, headache, painful injection, injection site sterile abscess, hemolysis in G6PD-deficient patients, chelation of essential metals (prolonged course)
SUCCIMER 10 mg/kg/dose orally every 8 hours for 5 days, then 10 mg/kg/dose every 12 hours	Nausea, vomiting, diarrhea, abdominal gas and pain, transient elevations of hepatic aminotransferases and alkaline phosphatase concentrations, rash, pruritus, sore throat, rhinorrhea, drowsiness, paresthesias, thrombocytosis, eosinophilia
DMPS (not FDA approved) Dose: 5 mg/kg/dose IM, administered as a 5% solution Day 1: q6–8h Day 2: q8–12h Day 3 and thereafter: q12–24h End point: for chelation is a 24 hour urinary arsenic concentration of <50 µg/L	Allergic reactions, increased copper and zinc excretion, nausea, pruritus, vertigo, weakness, toxic epidermal necrolysis

G6PD = glucose-6-phosphate dehydrogenase; IM = intramuscularly.

The decision to initiate chelation therapy should depend on the clinical condition of the patient as well as the laboratory results for arsenic in urine, hair, or nails. A severely ill patient with known or suspected acute arsenic poisoning should be chelated immediately, prior to laboratory confirmation. In the United States, BAL remains the initial chelating drug for acute arsenical toxicity.¹⁵⁷ In a series of 33 patients who had coma, seizures, or both, 24 patients were treated with BAL within 6 hours (mean, 1 hour) and 75% survived, compared with a survival rate of 45% of nine patients who were treated later (range, 9–72 hours; mean, 30 hours).⁶² Cases of subacute and chronic toxicity can await rapid laboratory confirmation prior to beginning chelation, unless the clinical condition deteriorates.

In a cellular study of glucose uptake impaired by a lipophilic arsenical, BAL was superior to succimer and DMPS in restoring cellular equilibrium.¹⁵⁷ A human case series found increased survival with early use of BAL and improvement in encephalopathy within 24 hours of initiating therapy.⁶² However, other acute cases treated promptly with BAL developed peripheral neuropathy.¹³² In a study of subacute cases with peripheral neuropathy, BAL accelerated neurologic recovery but did not affect the overall recovery rate.⁵⁰ Despite starting BAL therapy 8 hours postexposure, a man who had ingested 2.15 g of arsenic developed severe toxicity and neurologic deficits.⁷⁰ Most concerning are the animal experiments indicating that BAL shifts arsenic into the brain and testes, two organs that have blood–organ barriers susceptible to this lipophilic drug.^{10,104,121} It is clear that BAL has limitations, and that a safer, more effective intracellular/extracellular parenteral chelator is needed.

Succimer is an oral hydrophilic analog of BAL and is the chelator of choice for subacute and chronic toxicity. It has proven effective in animal studies and in reported human cases.^{10,120,134,142,203} In mice exposed to sodium arsenite, succimer

was more effective than either DMPS or BAL in decreasing lethality and more potent than BAL in restoring activity in the pyruvate dehydrogenase complex.¹⁰ It is equal or superior to BAL in speeding arsenic elimination.¹⁵⁷ Liver function tests and essential metal concentrations should be monitored in patients requiring prolonged therapy.^{73,87}

DMPS is also a water-soluble analog of BAL. It is not approved for use in the United States. It can be administered by the oral, intravenous, and intramuscular routes. It is eliminated from the body more slowly than succimer and has the advantage of intracellular as well as extracellular distribution.⁷ It predominantly binds MMA^{3+} and possibly removes the MMA^{3+} from endogenous ligands. The DMPS– MMA^{3+} complex is eliminated in the urine.^{9,11,84} It may also work by synergistically increasing the nonenzymatic methylation of As^{3+} .²⁵⁵ Two brothers ingested nearly pure arsenic trioxide (1 and 4 g each) and were treated with intravenous and oral DMPS. The brother who ingested 4 g developed hypotension, AKI, respiratory insufficiency, and asystolic cardiac arrest. DMPS was started 32 hours postingestion, and the patient survived with normal renal function and no neurologic dysfunction. His sibling had a milder course; DMPS was started 48 hours postingestion, and there were no neurologic sequelae on follow-up examination.¹⁵⁶ DMPS significantly increased biliary excretion of arsenic in a guinea pig model but did not increase fecal excretion. The latter is most likely a result of enterohepatic recirculation of the DMPS–As complex.¹⁸⁵ However, in another guinea pig model, the addition of oral cholestyramine to either DMPS or DMSA but not to BAL increased fecal arsenic excretion.¹⁵⁷

D-Penicillamine has not demonstrated efficacy in chelating or reversing the biochemical lesions of arsenic and should not be used. Its previous advantage of oral administration is no longer relevant with the availability of succimer.

Because of the limitations of currently available chelators, research is ongoing to find better chelators to treat arsenic toxicity. For example, some analogs of succimer, especially its monoisoamyl ester, have increased intracellular penetration relative to the parent compound and increase survival in arsenic-poisoned rats.^{72,113} In addition to improved chelators, other treatments for arsenic toxicity are being investigated. Some rodent studies have suggested that certain micronutrients, such as zinc or selenium, can decrease arsenic toxicity.⁷² However, early findings from the HEALS cohort are mixed. A cross-sectional substudy from this group revealed an inverse relationship between the severity of skin lesions and dietary intake of folate; pyridoxine; riboflavin; and vitamins A, C, and E.²⁵⁴ In contrast, another study from the same cohort did not find a statistically significant relationship between the severity of skin lesions and supplementation with vitamin E, selenium, or both.²³³ Until more data are available, nutritional supplementation, in the absence of dietary deficiency, remains controversial.

Hemodialysis. Hemodialysis removes negligible amounts of arsenic, with or without concomitant BAL therapy, and is not indicated in patients with normal kidney function.^{23,96,147} In patients with AKI, hemodialysis clearance rates have ranged from 76 to 87.5 mL/min, with or without concomitant BAL therapy.²³² In two acutely toxic patients with AKI, total arsenic removed during a 4 hour dialysis measured 4.68 mg in one and 3.36 mg in the other. Concomitant 24 hour urinary arsenic excretions were 3.12 mg and 2.03 mg, respectively. When renal function returned, however, the 24 hour urinary excretion of arsenic far exceeded that recovered with dialysis, with reported amounts of 18.99 mg in the first patient and 75 mg in the second patient.²³² There are no published rigorous data regarding hemodialysis removal of a water-soluble complex such as DMPS–As.¹²³

SUMMARY

- Environmental contamination of water sources has become a major health problem in many countries, including the United States.
- Arsenicals produce multisystem toxicity by a variety of pathophysiologic mechanisms.
- A thorough understanding of inorganic arsenic metabolism and excretion as well as the different clinical manifestations of acute, subacute, and chronic toxicity are necessary to avoid misdiagnosis.
- Chelation therapy with BAL in the United States, or with DMPS elsewhere, if available, should be started immediately in the severely ill patient.
- Treatment can await laboratory results for patients with subacute or chronic toxicity, unless clinical deterioration intervenes.

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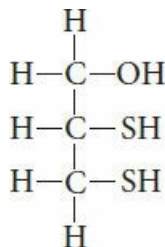
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A25 ANTIDOTES IN DEPTH

Dimercaprol (British Anti-Lewisite or BAL)

Mary Ann Howland



INTRODUCTION

British anti-Lewisite (BAL) (2,3-dimercaptopropanol; dimercaprol) is a metal chelator used clinically in conjunction with edetate calcium disodium (CaNa₂EDTA) for lead encephalopathy and severe lead toxicity.^{23,30} In this, BAL should precede the first dose of CaNa₂EDTA by 4 hours to prevent redistribution of lead to the central nervous system (CNS). BAL has a narrow therapeutic index, BAL must be administered intramuscularly (IM) because it is formulated in peanut oil. Oral succimer is used for patients with less severe lead toxicity. The roles for BAL in arsenic and mercury poisoning have diminished since the development of succimer and the investigational chelator 2,3-dimercaptopropane sulfonate (DMPS). BAL is still indicated when the gastrointestinal tract is compromised.

HISTORY

Investigation into the use of sulfur donors as antidotes was precipitated by the World War II threat of chemical warfare with lewisite (dichloro[2-chlorovinyl]arsine) and mustard gas (dichlorodiethyl sulfide [ClCH₂CH₂]₂S).^{1,31,32} Both are vesicants that cause tissue damage when combined with protein sulfhydryl groups (Chap. 132).³⁵ The investigations of Stocken and Thompson at Oxford led to the discovery of the dithiol 2,3-dimercaptopropanol (or BAL) that combines with lewisite to form a stable five-membered ring.^{40,42}

PHARMACOLOGY

Chemistry

BAL has a molecular weight of 124.2 Da and a specific gravity of 1.21.³³ It is an oily liquid with only 6% weight/volume water solubility, 5% weight/volume peanut oil solubility, and a disagreeable odor. Aqueous solutions are easily oxidized and therefore unstable. Peanut oil stabilizes BAL and benzyl benzoate (in the ratio of one part BAL to two parts of benzyl benzoate) renders the BAL miscible in peanut oil.³⁶

Mechanism of Action

The sulfhydryl groups of dimercaprol form chelates with certain metals, which are then excreted in the urine. Lead, arsenic, and inorganic mercury salts are the metals most amenable to chelation with BAL.

Pharmacokinetics

There are no recent studies of the pharmacokinetics of BAL. The limited information available was first described in the late 1940s.^{1,24} Serum concentrations of BAL peak about 30 minutes after IM administration, and distribution occurs rapidly.^{36,39} Within 2 hours after IM administration to rabbits, serum concentrations rapidly fall. Urinary excretion of BAL

metabolites, perhaps partially as glucuronic acid conjugates, accounted for nearly 45% of the dose within 6 hours and 81% of the dose within 24 hours.^{36,38} Very little is excreted unchanged in the urine.³⁶ BAL is concentrated in the kidney, liver, and small intestine.³⁴ BAL can also be found in the feces, suggesting that enterohepatic circulation exists. Hemodialysis may be useful in removing the BAL–metal chelate in cases of kidney failure.^{23,29,41}

ROLE OF DIMERCAPROL IN ARSENIC EXPOSURE

Animal Studies

The fear of lewisite attack causing skin lesions led researchers to investigate the potential for cutaneous application of BAL.⁴⁰ This was based on the limited water solubility and high lipid solubility of BAL. In a rodent model, low concentrations of topical BAL were very effective both in preventing lewisite-induced toxicity and in reversing toxicity when administered within one hour of skin exposure.^{33,35} In rabbits, ophthalmic application of BAL proved effective in preventing corneal destruction if applied within 20 minutes of exposure.²³ Additionally, urinary arsenic concentrations were significantly increased after the application of BAL.³⁵

The effectiveness of both parenteral single-dose and multiple-dose BAL against lewisite and other arsenicals was studied in rabbits. When begun within 2 hours of lewisite exposure, BAL injections of 4 mg/kg every 4 hours led to a 50% survival of exposed rabbits. This dosing regimen was demonstrated to be one-seventh of the maximum tolerated dose of BAL.¹⁷

The most recent animal studies demonstrate that although BAL increases the LD₅₀ (median lethal dose for 50% of test subjects) of sodium arsenite, the therapeutic index of BAL is low and arsenic redistribution to the brain occurs.^{4,6,7,20,37} In these same animal models, succimer and DMPS also increased the LD₅₀ but with a better therapeutic index and without causing redistribution to the brain.^{3,4}

Ophthalmic damage caused by lewisite is partly a result of the liberation of hydrochloric acid, which results in an acid injury causing localized superficial opacity of the cornea and deep penetration of lewisite into the cornea and aqueous humor with resultant rapid necrosis. In an experimental model, a 5% BAL ointment or solution applied within 2 minutes of exposure prevented the development of a significant reaction; application at 30 minutes limited the reaction, but did not prevent permanent damage.²¹

Human Studies

Experiments in human volunteers who were given minute amounts of arsenic demonstrated that BAL increased urinary arsenic concentration by approximately 40%, with maximum excretion occurring 2 to 4 hours after BAL administration.⁴⁴ BAL was subsequently used in the treatment of arsenical dermatitis resulting from organic arsenicals used to treat syphilis. When applied to affected skin, topical BAL produced erythema, pruritus, and dysesthesias, but it had no adverse effects on unaffected skin. IM BAL produced both subjective and objective improvement, limited the duration of the arsenical dermatitis, and increased urinary arsenic elimination.^{13,27,28}

In a study of 227 patients with inorganic arsenic poisoning, maximal efficacy and minimal toxicity were achieved when 3 mg/kg of BAL was administered IM every 4 hours for 48 hours and then twice daily for 7 to 10 days. This regimen resulted in complete recovery in six of seven patients with severe arsenic-induced encephalopathy and demonstrated the importance of administering BAL as soon as possible after the exposure. Of 33 patients with severe arsenic-induced encephalopathy, 18 of 24 (75%) treated within 6 hours survived, versus only four of nine (44%) treated after a delay of at least 72 hours.¹⁶ Furthermore, the effectiveness of BAL was also demonstrated in three patients who were treated successfully after mistakenly receiving 10 to 20 times the therapeutic dose of oxophenarsine hydrochloride (Mapharsen). A fourth patient, treated with inadequate doses of BAL, died.¹⁶ These cases support the effectiveness of BAL in treating arsenic-induced agranulocytosis, encephalopathy, dermatitis, and probably arsenical fever.¹⁵

When BAL first became more widely available, 42 children were treated following arsenic ingestions, and their results were compared with a historical group of 111 untreated children who had also ingested arsenic.⁴⁵ The percentage of children exhibiting symptoms on presentation were similar between groups (46%), but in the group of children treated with BAL there were fewer deaths (zero versus three), a shorter average hospital stay (1.6 versus 4.2 days), and fewer cases of persistent symptoms at 12 hours (0% versus 29.3%).

ROLE OF DIMERCAPROL IN MERCURY EXPOSURE

Because mercury also reacts with sulfhydryl groups, animal studies were performed to assess the affinity and ability of thiols to competitively chelate inorganic mercury and prevent toxicity. As in the case of arsenic, the dithiol BAL was more

effective than the monothiol 1-thiosorbitol in preventing mercury-induced death and uremia.¹⁹ The clinical efficacy of BAL in treating inorganic mercury poisoning was substantiated in patients who ingested mercuric chloride.^{25,26} Thirty-eight patients ingesting more than 1 g of mercuric chloride who were treated with BAL within 4 hours of exposure were compared with historical controls.²⁵ There were no deaths in the 38 patients treated with BAL as compared to 27 deaths in the 86 untreated patients. Death typically resulted from hemorrhagic gastritis and kidney failure.²⁵ BAL is particularly useful for patients who have ingested a mercuric salt, as the associated gastrointestinal toxicity of the mercuric salt limits the potential of an orally administered antidote such as succimer.⁴³

Animal models demonstrate that when BAL is administered following poisoning from elemental mercury vapor or exposure to short-chain organic mercury compounds, brain concentrations of mercury may increase.^{9,12} As a result BAL therapy is not recommended in these circumstances.^{2,5,23} (Chap. 98).

ROLE OF DIMERCAPROL IN LEAD EXPOSURE

BAL may be used in combination with CaNa_2EDTA to treat patients with severe lead poisoning. In all other cases, succimer has become the chelator of choice. When treating patients with lead encephalopathy, it is essential to administer the BAL first, followed 4 hours later by CaNa_2EDTA with a second dose of BAL. This regimen prevents the CaNa_2EDTA from redistributing lead into the brain.^{14,15} Providing two different chelators also reduces the blood lead concentration significantly faster than either one alone, and maintains a better molar ratio of chelator to lead.¹⁴ Once the mobilization of lead has begun, it is important to provide uninterrupted therapy to prevent redistribution of lead to the brain (Chap. 96).¹⁴

ADVERSE EFFECTS AND SAFETY ISSUES

BAL has an LD_{50} in mice via intraperitoneal administration of 90 to 180 mg/kg, which is significantly lower than that of CaNa_2EDTA at 4000 to 6000 mg/kg, succimer at 2480 mg/kg, and DMPS at 1100 to 1400 mg/kg.²

Less than 1% of 700 IM injections resulted in minor reactions, such as pain at the injection site, among patients who received 2.5 mg/kg of BAL every 4 to 6 hours for 4 doses.¹³ When doses of 4 mg/kg and 5 mg/kg were given, the incidence of adverse effects rose to 14% and 65%, respectively.¹⁶ At these higher doses, the following symptoms were reported in decreasing order of frequency: nausea, vomiting, headache, burning sensation of lips, mouth, throat, and eyes, lacrimation, rhinorrhea, salivation, muscle aches, burning and tingling of extremities, tooth pain, diaphoresis, chest pain, anxiety, and agitation.²⁷ These effects were maximal within 10 to 30 minutes of exposure and usually subsided within 30 to 50 minutes.¹⁶ Elevations in systolic and diastolic blood pressure and tachycardia commonly occurred and correlated with increasing doses.^{23,30} Thirty percent of children given BAL may develop a fever that can persist throughout the therapeutic period.²³ In addition, in children, a transient reduction in the percentage of polymorphonuclear leukocytes may also occur.²³ Doses above 5 mg/kg should not be administered because of the high risk of adverse reactions. Doses above 25 mg/kg can be expected to produce a hypertensive encephalopathy with convulsions and coma.⁴⁵

BAL is not very effective in the presence of arsenic-induced hepatotoxicity.²⁸ Moreover, in rats, preexistent hepatotoxicity was exacerbated when BAL was used for treatment of arsenic poisoning. Therefore, unless the hepatotoxicity is considered to be arsenic induced, hepatic dysfunction is a contraindication to BAL use.³⁵ BAL should not be used for patients poisoned by methylmercury because animal studies demonstrate a redistribution of mercury to the brain.^{5,23}

Because dissociation of the BAL-metal chelate will occur in acidic urine, the urine of patients receiving BAL should be alkalinized with hypertonic sodium bicarbonate to a pH of 7.5 to 8.0 to prevent kidney liberation of the metal.²³ BAL should be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as it may cause hemolysis²²; a risk-to-benefit analysis must be made because G6PD-deficiency syndromes are variably expressed. In addition, chelators are relatively nonspecific and may bind metals other than those desired, thus causing deficiency of an essential metal. For example, BAL given to mice increased copper elimination to three times normal.¹¹ BAL is formulated in peanut oil; therefore, the patient should be questioned regarding any known peanut allergy and a risk-benefit analysis undertaken. Limited evidence suggests that iron supplements should not be given to patients who are receiving BAL because the BAL-iron complex appears to cause severe vomiting and decreases metal chelation.^{14,15,18}

Unintentional intravenous (IV) infusion of BAL could theoretically produce fat embolism (peanut oil), lipid pneumonia, chylothorax, and associated hypoxia.³⁸

Pregnancy and Lactation

Dimercaprol is pregnancy category C.⁸ There have not been any animal studies evaluating the effects of BAL on reproduction. It is not known whether BAL is harmful to a fetus or is capable of affecting reproduction capability.⁸ There are no data in human poisoning in pregnancy, and BAL should only be administered to a pregnant woman if clearly indicated.⁸

No data address whether BAL or its chelates are excreted in human breast milk.

DOSING AND ADMINISTRATION

No clinical trial has been performed to identify the appropriate dose of BAL. The dosing for BAL is expressed in both mg/m² and mg/kg. BAL should be administered only by deep IM injection. The dose of BAL for lead encephalopathy is 75 mg/m² IM every 4 hours for 5 days in children.^{14,15} As noted earlier, the first dose of BAL should precede the first dose of CaNa₂EDTA by 4 hours. Thereafter, IV CaNa₂EDTA, in a dose of 1500 mg/m²/d (up to a maximum of 2–3 g) as a continuous infusion, or divided into two to four doses, should be administered. These daily doses are equimolar. For adults, the dose of BAL is 4 mg/kg every 4 hours.⁸

The dose of BAL for severe inorganic arsenic poisoning has not been established. One regimen suggests the use of 3 mg/kg IM every 4 hours for 48 hours and then twice daily for 7 to 10 days.¹⁶ Another regimen uses 3 to 5 mg/kg IM every 4 to 6 hours on the first day and then tapers the dose and frequency, depending on the patient’s symptomatology. A third regimen reduces the number of injections by day 2 and terminates therapy within 5 to 7 days⁴⁵ (Table A25–1).

TABLE A25–1. Calculations for Average Deep Intramuscular (IM) BAL Use When Using Body Surface Area (m²)

Child	Average Height (in)	Average Weight (lbs)	m ²	75 mg/m ² Every 4 hours IM ^a	50 mg/m ² Every 4 hours IM ^b
2 year-old boy	36	30.5	0.593	44.5 mg	30 mg
2 year-old girl	35	29	0.57	43 mg	28.5 mg
4 year-old boy	42	39.75	0.73	55 mg	36.5 mg
4 year-old girl	41.75	38.75	0.72	54 mg	36 mg

^aapproximately 4 mg/kg ^bapproximately 3 mg/kg

The dose of BAL for patients exposed to inorganic mercury salts is 5 mg/kg IM initially, followed by 2.5 mg/kg every 12 to 24 hours until the patient appears clinically improved, up to a total of 10 days.⁸

As noted above, the urine should be kept alkaline to avoid dissociation of the BAL–metal chelate.^{10,23}

FORMULATION AND ACQUISITION

Commercially available BAL is a yellow, viscous liquid with a sulfur odor. It is available in 3 mL ampules containing 100 mg/mL of BAL, 200 mg/mL of benzyl benzoate, and 700 mg/mL of peanut oil.⁸ BAL is for deep IM use only.

SUMMARY

- BAL is a metal chelator used clinically in conjunction with CaNa₂EDTA for lead encephalopathy and severe lead toxicity.^{23,30}
- In this instance, BAL should precede the first dose of CaNa₂EDTA by 4 hours.
- The roles of BAL in arsenic and mercury poisonings are being supplanted by oral succimer and the investigational chelator DMPS, which is indicated unless the gastrointestinal tract is compromised.

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90 BISMUTH

Rama B. Rao

Bismuth (Bi)		
Atomic number	=	83
Atomic weight	=	208.98 Da
Normal concentrations		
Blood	<	5 µg/dL (239.5 nmol/L)
Serum	<	1 µg/dL (<47.9 nmol/L)
Urine	<	20 µg/L (<95.7 nmol/L)

HISTORY AND EPIDEMIOLOGY

Elemental bismuth is nontoxic. Bismuth salts have therapeutic uses and are responsible for the toxicities described in this chapter. Thus, the term “bismuth” in this chapter refers to bismuth salts. Nearly 300 years ago, bismuth was recognized as medically valuable. It was included in topical salves and oral preparations for various GI disorders. Nephrotoxicity was described as early as 1802. In the early 20th century, acute kidney injury was reported in children administered intramuscular bismuth salts for the treatment of gingivostomatitis.^{7,25,47,48} Administration of bismuth thioglycollate and its related water soluble compounds, triglycollamate and trithioglycollamate, were responsible for the kidney failure, which occurred with as little as one or two treatments.^{8,12,29,34,38,39,55} Children with kidney failure would typically present with abdominal pain, oliguria, anuria, malaise, depressed mental status, and vomiting. Alterations in consciousness usually abated with treatment or resolution of the uremia. After the use of intramuscular injections was abandoned, this form of bismuth-induced kidney failure became uncommon. Syphilis was previously treated with intramuscular bismuth. A rash known as “erythema of the 9th day,” consisting of a diffuse macular rash of the trunk and extremities, occasionally occurred and resolved without intervention.¹⁶

In patients administered “Analbis” antipyretic rectal suppositories, hepatic failure was described histopathologically as yellow atrophy with vacuolization.^{3,22} An investigation of the suppositories suggested that diallylacetic acid, a xenobiotic that is no longer marketed in the United States, and not bismuth, was the hepatotoxin.

Today, bismuth is one of many xenobiotics commonly used in prescription and nonprescription oral preparations for treatment of traveler’s diarrhea, nausea, and vomiting. In addition bismuth-impregnated surgical packing paste is used for the treatment of the flatus and odor associated with ileostomies and colostomies,^{9,57} and as an adjunct in the treatment of ulcers.¹⁴ In the gastrointestinal (GI) tract, bismuth binds to sulfhydryl groups and decreases fecal odor through formation of bismuth sulfide.⁵⁰ Sulfhydryl binding is also the proposed mechanism for the antimicrobial effect of bismuth, causing lysis of *Helicobacter pylori*, the causative bacteria in peptic ulcer formation. Bismuth may also inhibit bacterial enzyme function, as well as prevent adhesion of *H. pylori* to the gastric mucosa.⁵⁶

Epidemics of bismuth-induced encephalopathy, particularly among patients with ileostomies or colostomies, were reported from France, Britain, and Australia. As a result, some countries banned or restricted bismuth preparations to prescription only. Bismuth subsalicylate, which is currently available in the United States as a nonprescription remedy, is still periodically responsible for cases of encephalopathy.^{15,17,30} Other reported causes of bismuth-induced encephalopathy include systemic absorption from bismuth-impregnated surgical packing paste and transdermal absorption from chronic application of a bismuth-containing skin cream.²⁴

In 2006, the Food and Drug Administration (FDA) of the United States issued a warning on an alternative health product known as “bismacine” or “chromacine.” This nonpharmaceutical product is not FDA approved, but was used by some practitioners as an injectable treatment for Lyme disease, for which efficacy data are lacking. The product contains bismuth citrate and was associated with at least one death and other adverse events.²

CHEMISTRY AND TOXICOLOGY

Bismuth is present in nature in both the trivalent and pentavalent forms. The trivalent form of bismuth is used for all medicinal uses, usually as the bismuthyl (BiO) moiety generated by hydrolysis of trivalent bismuth compounds to yield a low solubility alkaline salt. Bismuth salts are divided into four groups based on their water or lipid solubility. Most orally administered bismuth remains in the GI tract, and is subsequently excreted in the feces, with only 0.2% is systemically absorbed.¹⁹ Absorption of some bismuth preparations such as colloidal bismuth subcitrate may increase as gastric pH increases.³⁶ The time to peak absorption ranges between 15 and 60 minutes with high intra- and interindividual variation.^{23,25} The serum-to-blood ratio of bismuth is 1.55.⁴ The distribution and elimination of orally administered bismuth follows a complex, multicompartmental model. The volume of distribution in humans is unknown.^{5,44}

Once in the circulation, bismuth binds to α_2 -macroglobulin, IgM, β -lipoprotein, and haptoglobin. Bismuth rapidly enters liver, kidney, lungs, and bone.⁵¹ Bismuth can cross the placenta and enter the amniotic fluid and fetal circulation.⁵³ It also readily crosses the blood–brain barrier.³⁵ Evidence in a rat model suggests that, when administered intramuscularly, bismuth can enter the central nervous system (CNS) via retrograde axonal transport.⁴⁹ In both animal models and human reports bismuth is identified in the fenestrated membranes of synaptosomes,^{38,41} localizing in the thalamus and cerebellum with diffuse cortical uptake as well.^{25,35} Ninety percent of absorbed bismuth is eliminated through the kidneys, where it induces the production of its own metal-binding protein.⁵¹

Some authors propose three different half-lives to describe the pharmacokinetics of orally administered therapeutic doses of bismuth.^{5,44} The first, a distribution half-life, is approximately 1 to 4 hours. The second, the apparent plasma half-life, lasts 5 to 11 days. The third is the apparent half-life of urinary excretion lasting between 21 and 72 days⁴ with urinary bismuth detected as late as 5 months after the last oral dose.²³

PATHOPHYSIOLOGY

Like other metals, bismuth toxicity involves multiple organ systems. The effect of different bismuth salts can be categorized into four groups based on solubility and GI absorption (Table 90–1).⁴³ The highly lipid soluble compounds such as bismuth subsalicylate or bismuth subgallate are most commonly associated with neurotoxicity.

TABLE 90–1. The Physicochemical Characteristics of Bismuth Salts

Group	Chemistry	Toxicity	Examples
I	Insoluble in water Inorganic	Minimal	Bismuth subnitrate Bismuth subcarbonate
II	Lipid soluble Organic	Neurologic	Bismuth subsalicylate Bismuth subgallate
III	Water soluble Organic	Renal	Bismuth triglycollamate
IV	Hydrolyzable Water soluble Organic	Minimal	Bismuth bicitropeptide

The mechanism of bismuth-induced encephalopathy is thought to be related to neuronal sulfhydryl binding. In patients who die of bismuth encephalopathy, the gray-matter concentration of bismuth is nearly twice that of white matter.²⁵ In a bismuth encephalopathic patient dying from concomitant sepsis, the autopsy revealed loss of cerebellar purkinje cells, which is not expected from sepsis alone.²⁶ The factors predisposing some individuals to encephalopathy from group II bismuth salts, however, are not well defined. Age, gender, and duration of therapeutic use do not predict the likelihood of developing encephalopathy, but typically patients are on chronic bismuth therapy with a lipid soluble (group II) xenobiotic.

CLINICAL MANIFESTATIONS

Acute

Acutely, massive overdoses of bismuth may result in abdominal pain and oliguria or anuria. Acute kidney failure can occur and is not limited to exposure to the water soluble bismuth salts (group III).^{34,39} In reported cases, overdoses of colloidal bismuth subsalicylate or tripotassium dicitratobismuthate (TDC) caused acute tubular necrosis.^{1,18,20,48,52}

Histopathologically, bismuth causes degeneration of the proximal tubule, similar to other metals. While these substances are potentially neurotoxic, signs of encephalopathy are generally absent.^{11,17} In one case, a patient with bismuth-induced kidney failure was described as having diminished deep-tendon reflexes, muscle weakness, and myoclonus, without an alteration in consciousness.¹⁸

Chronic

The most common toxicologic finding associated with repeated therapeutic doses of oral bismuth compounds is a diffuse, progressive encephalopathy.^{11,17} Affected patients exhibit neurobehavioral changes, such as apathy and irritability. With continued exposure, these patients may develop difficulty concentrating, diminished short-term memory, and occasionally, visual hallucinations.^{27,28} A movement disorder characterized by muscle twitching, myoclonus, ataxia, and tremors may ensue.¹¹ This is often described as a myoclonic encephalopathy. Weakness and, rarely, seizures may advance to immobility.^{30,32} With continued bismuth administration these patients can develop coma and die.

Rarely, patients recovering from severe encephalopathy may complain of scapular, humeral, or vertebral pain because of fractures caused by severe neuromuscular manifestations such as myoclonus.¹³

Like several other metals, bismuth can cause a generalized pigmentation of skin. Deposition of bismuth sulfide into the mucosa causes a blue-black discoloration of gums.⁵⁸ This can occur in the absence of toxic effects. Formation of the same compound in the GI tract causes blackening of the stool. Liver failure is rarely reported, except in patients with multisystem organ failure from fatal neurotoxicity.

DIAGNOSIS

The clinician must have an index of suspicion based on the acute or chronic nature of the exposure and the class of bismuth salt ingested. Patients with acute massive overdoses should be evaluated for acute kidney injury, the earliest findings suggestive of which are hematuria and proteinuria on urinalysis. Formation of nuclear inclusion bodies can be identified on renal biopsy or on postmortem examination of the kidney.^{12,40}

The diagnosis of bismuth-induced encephalopathy is based on a history of exposure coupled with diffuse neuropsychiatric and motor findings.²⁸ Other causes of encephalopathy should be entertained and excluded (Table 90–2). An abdominal radiograph will likely demonstrate radiopacities of bismuth in the intestines. Stool likely will be black and test negative for occult blood.

TABLE 90–2. Differential Diagnosis of Bismuth Encephalopathy

- Creutzfeld-Jacob disease
- Ethanol withdrawal
- Lithium toxicity
- Neurodegenerative leukoencephalopathies
- Nonketotic hyperosmolar coma
- Postanoxic and posthypoglycemic encephalopathies
- Progressive multifocal ataxia
- Viral encephalopathies

The presence of bismuth in the blood is confirmatory of exposure, but absolute concentrations correlate poorly with morbidity.⁵ In a review of 310 patients with bismuth-induced encephalopathy, 288 patients (93%) had a blood concentration greater than 10 µg/dL, with the majority of these blood concentrations between 10 and 100 µg/dL.²⁷ Twenty-two patients suffered encephalopathy at blood concentrations below 10 µg/dL.²⁷ In another report, two patients with encephalopathy had blood concentrations of 90 and 250 µg/dL, both of whom recovered when the concentration fell below 50 µg/dL.⁶ Just as blood concentrations do not reflect severity of illness, tissue concentrations also correlate poorly with severity of illness. An example was noted in a patient who recovered from severe encephalopathy. On discharge, he had a low blood bismuth concentration and died 3 months later of unrelated trauma. At autopsy he was found to have an elevated CNS bismuth burden but no reported symptoms at the time of the trauma.¹⁰

The electroencephalographic (EEG) findings of patients with bismuth encephalopathy generally demonstrate nonspecific slow wave changes.^{15,18} In one study, the EEG findings were described in association with blood concentrations. At less than 5 µg/dL, the EEG was normal or demonstrated diffuse slowing. In patients with blood concentrations of less than 150 µg/dL, the findings of sharp wave abnormalities were noted. At higher concentrations (greater than 200 µg/dL), some patients with neurological events, such as myoclonic jerks, did not have corresponding EEG changes. The authors proposed that an elevated body burden might have an inhibitory effect on the cerebral cortex.¹⁰

In encephalopathic patients with blood concentrations greater than 200 µg/dL, diagnostic imaging such as computed tomography may demonstrate a diffuse cortical hyperdensity of the gray matter. These findings tend to resolve with recovery. Magnetic resonance imaging was normal in another encephalopathic patient.¹⁵

TREATMENT

Typically, supportive care results in a complete recovery. Some authors suggest GI decontamination with activated charcoal and polyethylene glycol solution.⁴⁵ Although evidence for this approach is lacking, it appears to be a reasonable initial intervention, especially in patients with severe encephalopathy. In patients with kidney failure, resolution is generally observed with supportive care. The use of chelators in patients with acute overdose without neurotoxicity is probably not indicated.

It is uncertain whether different chelators affect the clinical course of encephalopathic patients. Withdrawal of the source of bismuth results in complete reversal of effects within days to weeks, even in severely ill patients. The precise timing, dosage, indications, and choice of chelator is not known; however, chelation with succimer has few side effects and may potentially limit the potentially fatal complications associated with prolonged immobilization. British anti-Lewisite (BAL), which has more side effects, can be considered in encephalopathic patients with kidney failure in whom no neurological improvement is noted within 48 hours of whole-bowel irrigation and bismuth withdrawal (see Chelation below).

Prevention is the most effective means of avoiding neurotoxicity. Blood concentrations of bismuth are not routinely performed, but a bismuth concentration above 100 ng/mL or symptoms at lower concentrations warrant withdrawal of bismuth therapy.

CHELATION

In general, the data regarding chelation are limited and in vitro and animal models are not clearly predictive of human response. Chelation therapy with BAL is beneficial in experimental models,^{45,48} reportedly beneficial in humans,³¹ and often recommended, although clear evidence of efficacy is lacking. BAL undergoes biliary elimination, offering a major advantage over other chelators in patients who may develop acute kidney injury. One study advocated the addition of dimercaptopropane sulfonate (DMPS), as BAL did not affect hemodialysis clearance, but the addition of DMPS to patients needing hemodialysis was effective in enhancing elimination.⁴⁸ It is uncertain whether the clinical course of the patients was improved. In human volunteers given colloidal bismuth subcitrate, succimer and DMPS, both at a dose of 30 mg/kg, increased urinary elimination of bismuth by 50 fold.⁴⁶

In an animal model, D-penicillamine was most efficacious in enhancing elimination of bismuth. In a human volunteer model using therapeutic doses of tripotassium-dicitrato-bismuthate, however, a single dose of D-penicillamine did not enhance urinary excretion.³³ Based on the above information we would recommend withdrawal of bismuth therapy and whole bowel irrigation as a first intervention. While data on chelation efficacy is lacking, BAL may be used in patients with life threatening encephalopathy unresponsive to initial measures after 48 hours.

BISMUTH DRUG INTERACTIONS AND REACTIONS

The coadministration of proton pump inhibitors (PPIs) may increase the absorption of some bismuth preparations. In a prospective evaluation of patients receiving different treatment regimens for *H. pylori*-induced dyspepsia or peptic ulcer disease, individuals taking PPIs had a statistically significant elevation in their blood bismuth concentrations with three patients exceeding 5000 µg/dL, compared with a similar group administered bismuth without PPIs. The authors suggest that the bismuth preparation used, colloidal bismuth subcitrate, is more soluble and absorbable at the higher gastric pH of patients on PPIs.¹⁹ All these patients received short courses of therapy (2 weeks). While the investigators did not attempt to follow neurobehavioral or neuropsychiatric changes, none of the patients had clinically evident bismuth toxicity.³⁶

Based on this investigation, coadministration of PPIs with longer courses of colloidal bismuth subcitrate should be avoided or only offered with extreme caution. Ranitidine, which is frequently prescribed with a bismuth compound for dyspepsia or ulcer disease, does not affect the pharmacokinetics of bismuth absorption.²³

In the United States, where bismuth subsalicylate is the most common oral bismuth-containing compound, up to 90% of the salicylate is absorbed.^{37,42} Salicylate toxicity has been reported, and salicylate concentrations should be determined in both acute and chronic exposures.^{42,47} Methemoglobinemia from subnitrate salt of bismuth is uncommonly described.²¹

SUMMARY

- Bismuth toxicity may manifest as nephrotoxicity from group III water soluble bismuth salts.
- Encephalopathy, myoclonic jerks, and coma may occur with chronic toxicity of Type II lipophilic bismuth salts.
- Supportive care, WBI, and withdrawal of the bismuth containing compound are the mainstays of treatment.
- The role of chelators is under investigation.
- Salicylate concentrations may be elevated in some cases of chronic bismuth subsalicylate poisoning.

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91 CADMIUM

Stephen J. Traub and Robert S. Hoffman

Cadmium (Cd)	
Atomic number	= 48
Atomic weight	= 112.40 Da
Normal concentrations	< 5 µg/L (44.5 nmol/L)
Whole blood	< 3 µg/g creatinine
Urine (24 hour)	< 26.7 nmol/g creatinine

HISTORY AND EPIDEMIOLOGY

Cadmium, atomic number 48, is a transition metal in group IIB of the periodic table. In its pure atomic form, it is a bluish solid at room temperature. It is readily oxidized to a divalent ion, Cd^{2+} . Naturally occurring cadmium commonly exists as cadmium sulfide (CdS), a trace contaminant of zinc-containing ores.³⁶

Cadmium sulfide, cadmium oxide, and other cadmium-containing compounds are refined to produce elemental cadmium, which is used for industrial purposes. When combined with other metals, cadmium forms alloys of relatively low melting points, which accounts for its extensive use in solders and brazing rods. Today, cadmium is primarily used as a reagent in electroplating and in the production of nickel-cadmium batteries. Other uses of cadmium include as a pigment and as a neutron absorber in nuclear reactors. Cadmium salts have also been used as veterinary antihelminthics.¹²

As cadmium processing has increased, so has the incidence of cadmium toxicity. Cadmium toxicity usually occurs after environmental, occupational, or hobby work exposure.

Environmental Exposure

Environmental exposure to cadmium generally occurs through the consumption of foods grown in cadmium contaminated areas. Because cadmium is fairly common as an impurity in ores, areas where mining or refining of ores takes place are the most likely to contain cadmium contamination.

In the 1950s, a mine near the Jinzu River basin in Japan discharged large amounts of cadmium into the environment, contaminating the rice that was a staple of the local food supply. An epidemic of painful osteomalacia followed, affecting hundreds of people, with postmenopausal multiparous women being most affected.⁶⁷ The afflicted were prone to develop pathologic fractures, and were reported to call out “itai-itai” (“ouch-ouch”) as they walked, because of the severity of their pain.²⁸ These symptoms were ultimately linked to the cadmium. Less consequential environmental cadmium exposures have also occurred in Sweden,⁴⁶ Belgium,¹⁰ and China.⁴⁸ Additionally, smokers have higher blood cadmium concentrations than nonsmokers,⁹¹ probably as a result of contamination of soil where the tobacco is grown. This is noteworthy, in that cadmium and tobacco may be synergistic causes of chronic pulmonary disease.⁶³

Occupational and Hobby Exposure

Welders, solderers, and jewelry workers who use cadmium-containing alloys are at risk for developing acute cadmium toxicity due to inhalation of cadmium oxide fumes. Other workers who do not work with metals per se may develop significant chronic cadmium toxicity through exposure to cadmium-containing dust.

Hobbyists who work with cadmium solders have exposures similar to occupational metalworkers. Significant cadmium toxicity in this population is usually the result of metalworking in a closed space with inadequate ventilation and or improper respiratory precautions.

TOXICOKINETICS

There is no known biologic role for cadmium or its salts. Orally ingested cadmium salts are poorly bioavailable (5%–

20%); however, inhaled cadmium fumes (cadmium oxide) are readily bioavailable (up to 90%).⁹⁹ As the only data on cadmium toxicokinetics are derived from work with cadmium salts and oxides, the term “cadmium” in the following discussion refers to these species unless otherwise noted.

After exposure, cadmium is absorbed into the bloodstream, where it is bound to α_2 -macroglobulin and albumin.¹⁰⁰ It is then quickly and preferentially redistributed to the liver and kidney, and to a lesser extent to other organs such as the pancreas, spleen, heart, lung, and testes.²⁵ Cadmium may enter target organs via three mechanisms: zinc and calcium transporters, uptake of cadmium–glutathione or cadmium–cysteine complexes by transport proteins, or endocytosis of cadmium–protein complexes.¹⁰⁶

After incorporation into the liver and kidney, cadmium is complexed with metallothionein, an endogenous thiol-rich protein that is produced in both organs. Metallothionein binds and sequesters cadmium. Slowly, hepatic stores of the cadmium–metallothionein complex (Cd-MT) are released. Circulating Cd-MT is then filtered by the glomerulus. A significant amount is reabsorbed and concentrated in proximal tubular cells,^{19,86,87} explaining why the kidney is a principal target organ in cadmium toxicity.

There is no evidence that cadmium ions are oxidized, reduced, methylated, or otherwise biotransformed in vivo. The volume of distribution (Vd) of cadmium is unknown, but is presumably quite large as a consequence of significant hepatic sequestration. Cadmium distribution and elimination are complex, and an eight-compartment kinetic model has been proposed.⁵⁴ The slow release of cadmium from metallothionein-complexed hepatic stores accounts for its very long biologic half-life of 10 or more years.

PATHOPHYSIOLOGY

Cellular Pathophysiology

Cadmium toxicity results from interaction of the free cation with target cells.^{25,35,61,66,87} Complexation with metallothionein is cytoprotective,^{22,61} and metallothionein functions as a natural chelator with a strong affinity for cadmium.^{18,55} Although metallothionein may play a role in proximal tubular concentration of cadmium, kidney damage is attenuated by metallothionein, as metallothionein-deficient mice are more susceptible to cadmium toxicity than controls.⁶¹

There are several mechanisms by which cadmium interferes with cellular function. Cadmium binds to sulfhydryl groups, denaturing proteins and or inactivating enzymes. The mitochondria are severely affected by this process,¹ which may result in an increased susceptibility to oxidative stress.⁴⁷ Cadmium also interferes with mediators of cell adhesion such as E-cadherin, N-cadherin, and β -catenin.^{72–74} Finally, the demonstrated interference of cadmium with calcium transport mechanisms^{96,97} might lead to intracellular hypercalcemia and, ultimately, apoptosis (Table 91–1).

TABLE 91–1. Chronic and Acute Organ System Effects of Cadmium

Organ	Acute	Chronic
Kidney		Proteinuria Nephrolithiasis
Bone		Osteomalacia
Lung	Pneumonitis	Cancer
Gastrointestinal system	Caustic injury	

Specific Organ System Injury

Kidney. The kidney damage caused by cadmium develops over years. Proteinuria is the most common clinical finding and correlates with proximal tubular dysfunction, which manifests as urinary loss of low-molecular-weight proteins such as β_2 -microglobulin and retinol-binding protein. Cadmium also produces hypercalciuria,⁸³ possibly also via damage to the proximal tubule.

Bone. Cadmium-induced osteomalacia is a result of abnormalities in calcium and phosphate homeostasis, which, in turn, result from renal proximal tubular dysfunction. In one autopsy study, the severity of osteomalacia in cadmium exposed subjects correlated with a decline in the serum calcium-phosphate product.⁹⁰

Lung. Acute cadmium pneumonitis is characterized by infiltrates on chest radiograph and hypoxia. Human autopsy studies^{32,71,84,101} generally show degeneration and or loss of bronchial and bronchiolar epithelial cells.

Gastrointestinal Tract. Based on case reports,^{11,102} ingested cadmium salts are caustic with the potential to induce

significant nausea, vomiting, and abdominal pain, and result in GI hemorrhage, necrosis, and perforation. With respect to their effect on the GI mucosa, cadmium salts act similar to mercuric salts (Chap. 98).

CLINICAL MANIFESTATIONS

Acute Poisoning

Pulmonary/Cadmium Fumes. Cadmium pneumonitis results from inhalation of cadmium oxide fumes. The acute phase of cadmium pneumonitis may mimic metal fume fever (Chap. 124), but in fact, the two entities are distinctly different, with regard to both mechanism and clinical consequences. Whereas metal fume fever is benign and self-limited, acute cadmium pneumonitis can progress to hypoxia, respiratory insufficiency, and death.

Published case reports of patients who develop acute cadmium pneumonitis^{4,5,32,71,84,93,101,105} are strikingly similar in their presentation. Within 6 to 12 hours of soldering or brazing with cadmium alloys in a closed space, patients typically develop constitutional symptoms, such as fever and chills, as well as a cough and respiratory distress.

On initial presentation these patients may have a normal physical examination, oxygenation, and chest radiograph. This relatively benign presentation may lead both to the misdiagnosis of metal fume fever and the underestimation of the severity of illness. As the pneumonitis progresses to acute respiratory distress syndrome (ARDS) (Chap. 124), crackles and rhonchi develop, oxygenation becomes impaired, and the chest radiograph develops a pattern consistent with alveolar filling. Despite aggressive supportive care, death may occur, usually within 3 to 5 days.^{32,71,84,101}

Patients who survive an episode of acute cadmium pneumonitis may develop chronic pulmonary disorders, including restrictive lung disease,^{4,5} diffusion abnormalities,⁴ and pulmonary fibrosis,⁹³ although recovery without sequelae is also reported.¹⁰⁵

Oral/Cadmium Salts. Most acute cadmium exposures are inhalational, and acute ingestions are rare. Based on case report data, GI injury is likely to be the most significant clinical finding after acute ingestion, although other presentations are possible.

In one case,¹¹ a 17 year-old student ingested approximately 150 g of cadmium chloride that she obtained from her school science stockroom. She presented to the emergency department with hypotension and edema of the face, pharynx, and neck. Her condition quickly deteriorated, and she suffered a respiratory arrest. She was intubated and underwent orogastric lavage, chelation with an unspecified agent, and charcoal hemoperfusion. Multisystem organ failure ensued, and she died within 30 hours of presentation. At autopsy, the most significant finding was hemorrhagic necrosis of the upper GI tract. Her blood cadmium concentration was more than 2000 times normal.

In a second reported case a 23 year-old man ingested approximately 5 g of cadmium iodide in a suicide attempt and presented with acute hemorrhagic gastroenteritis.¹⁰² His condition deteriorated, and despite treatment with calcium disodium ethylenediaminetetraacetic acid (CaNa₂EDTA) and supportive measures, he died on hospital day 7. Autopsy did not reveal a specific cause of death.

A 51 year-old man taking multiple nutritional supplements who had no history to suggest cadmium exposure presented with a one month history of fatigue, with laboratory findings suggestive of autoimmune hemolytic anemia. He was treated aggressively for that condition, but developed progressive multisystem organ failure and expired one week after presentation. His blood cadmium concentrations were extraordinarily high, suggesting an acute ingestion, although the source of the cadmium was never determined.⁷⁶

Chronic Poisoning

Nephrotoxicity. The most common finding in chronic cadmium poisoning is proteinuria. Low-molecular-weight proteinuria is usually more significant than, and generally precedes, glomerular dysfunction, although some cadmium exposed workers manifest predominantly glomerular proteinuria.⁷ There is a dose–response relationship between total body cadmium burden and kidney dysfunction,^{10,44,46,67,95} although this relationship may not be as strong at low doses.³⁹ Patients with diabetes mellitus may be particularly susceptible to the nephrotoxic effects of cadmium.³⁷ In most cases, proteinuria is generally considered to be irreversible even after removal from exposure,^{38,52,79} but improvement is sometimes reported.^{60,94} Less clear is the question of whether kidney dysfunction progresses after removal from exposure, with studies showing both stable³⁸ and deteriorating^{42,78,79} function in cadmium exposed workers who are removed from exposure. The routes and duration of exposure, as well as blood and urine cadmium concentrations, differ markedly among these studies, limiting wider applicability of any analysis.

Occupational cadmium exposure is also associated with nephrolithiasis,^{45,82} likely as a result of hypercalciuria.⁸³

Pulmonary Toxicity. Large studies of workers chronically exposed to relatively low concentrations of cadmium fail to demonstrate consistent effects on the lung. In one study of 57 workers with sufficient exposure to cadmium oxide to produce kidney dysfunction, there was no evidence of pulmonary dysfunction, even in those with the greatest cumulative cadmium

exposure.²⁷ In contrast, other studies have reported both restrictive¹⁷ and obstructive^{21,81} changes on pulmonary function tests. Interestingly, a follow-up study of the group with restrictive lung disease showed improvements after cadmium exposure was reduced.¹⁶ The discrepancies in these results may be partly a result of markedly different doses and durations of exposure among the various groups.

Cadmium is associated with pulmonary neoplasia; the carcinogenicity of cadmium is discussed separately (see Cancer below).

Musculoskeletal Toxicity. Cadmium-induced osteomalacia usually occurs in the setting of environmental exposure, as was true in Japan and Sweden.⁴³ Although mentioned in case reports,^{8,52} osteomalacia is generally not a prominent feature of occupational exposure to cadmium. Gender and age differences may explain part of this apparent difference: victims of the original Itai-Itai epidemic were mostly older women, whereas occupational cadmium exposures typically occur in younger men. In addition, differences in cumulative dosing and in route of exposure (oral vs. pulmonary) may partly account for the unique prominence of osteomalacia in patients with environmental exposures. Cadmium exposure is associated with osteopenia and osteoporosis even in areas (such as the United States) where widespread environmental exposure is unlikely.¹⁰³

Hepatotoxicity. Although the liver stores as much cadmium as any other organ, hepatotoxicity is not a prominent feature in humans with cadmium exposure, probably because hepatic cadmium is usually complexed to metallothionein.⁴⁰ The liver is a potential target organ, however, as hepatotoxicity is easily inducible in animals.^{1,25,26,77}

Neurologic Toxicity. Cadmium exposure is linked to olfactory disturbances,^{64,80,89} impaired higher cortical function,⁹⁸ and parkinsonism.^{68,98}

Other Organ Systems. Cadmium induces hypertension in rats,⁵⁹ but human studies have only yielded unconvincing and conflicting results.^{31,58,69,92} Although there is evidence that cadmium may cause immunosuppression affecting both humoral and cell-mediated immunity in animals,²⁴ a single human study showed no overt immunopathology in an occupationally exposed cohort.⁵¹ The testes are clearly a target organ in animal exposures,⁵⁷ but they are not considered a major target organ in humans.

Cancer. Cadmium induces tumors in multiple animal organs, an effect that is exacerbated by zinc deficiency.⁹⁹ In humans, cadmium exposure is associated with lung cancer.⁷⁰ The strength of this association has been questioned because most studies have methodologic problems, such as coexposure to arsenic, a known pulmonary carcinogen.^{9,53} Despite these confounding coexposures, cadmium is officially designated as a human carcinogen by the International Agency for Research on Cancer.⁴¹

DIAGNOSTIC TESTING

Other than to confirm exposure, cadmium concentrations have limited usefulness in the management of the acutely exposed patient. Diagnosis and treatment are based on the history, physical examination, and symptoms. In a patient exposed to cadmium oxide fumes, ancillary tests, such as pulse oximetry and chest radiography, are more useful than actual cadmium concentrations.

In the patient chronically exposed to cadmium, both cadmium concentrations and ancillary testing may prove helpful. Urinary cadmium concentrations, which reflect the slow, steady-state turnover and release of metallothionein-bound cadmium from the liver, are a better reflection of the total body cadmium burden than are whole blood concentrations. In a 22-year follow up study, mortality was higher in those with elevated urine cadmium concentrations, although it was impossible to determine if the cadmium was causative or served as a marker for another process.⁷⁵

Workers at high risk for cadmium toxicity should routinely have urinary protein testing, supplemented with urine and or blood cadmium testing when urinary protein testing is abnormal. Workers with a urinary cadmium concentration greater than 7 µg/g urinary creatinine or a whole blood cadmium concentration greater than 10 µg/L require immediate reassignment to a cadmium-free area. Workers with significant proteinuria (β₂-microglobulin concentrations of 750 µg/g urinary creatinine) should also be reassigned if additional testing confirms cadmium exposure (as defined by a urinary cadmium concentration greater than 3 µg/g urinary creatinine or a whole blood cadmium concentration greater than 5 µg/L). These numbers are reasonable in light of the fact that kidney dysfunction can occur at cadmium concentrations as low as 5 µg/g urinary creatinine,^{20,44} a concentration significantly higher than that of the general US population, 95% of whom have concentrations that are less than 2 µg/g urinary creatinine.¹⁵

MANAGEMENT

Acute Exposure

Oral Exposure/Cadmium Salts. After the patient's airway, breathing, and circulation are secured, attention can be given

to GI decontamination. Although large ingestions of soluble cadmium salts are rare, they frequently prove fatal.^{11,102} The lowest reported human lethal dose is 5 g. In light of this, if a significant ingestion occurs but emesis has not occurred, gastric lavage is appropriate. In this situation, a small nasogastric tube should suffice, as inorganic cadmium salts are powders, not pills.

Given the relative lack of experience with acute oral cadmium poisoning, all patients with known exposures and/or abnormal findings consistent with cadmium toxicity or exposure should be admitted to the hospital for supportive care, monitoring of renal and hepatic function, and possibly evaluation of the GI tract for injury.

Although it seems logical to use chelation therapy in any patient with an acute life-threatening ingestion of a metal compound, the benefit of chelation in acute cadmium exposure is unproven. Multiple chelators have been used, all in animal models, with inconsistent results.

The ideal chelator for treatment of oral cadmium toxicity would be well tolerated, and would decrease GI absorption of cadmium and decrease the concentration of cadmium in organs such as the kidney and liver, while not increasing cadmium concentrations in other critical organs such as the brain. Of the chelators studied for cadmium toxicity, succimer comes closest to fulfilling these criteria. In models of acute oral cadmium toxicity, succimer decreases the GI absorption of cadmium,^{3,6} without increasing cadmium burdens in target organs, and improves survival.^{2,6,50}

In a patient thought to have ingested potentially lethal amounts of cadmium, treatment with succimer is reasonable. Succimer should be given as soon as possible after the ingestion, as the effectiveness of chelators decreases dramatically over time in experimental models of cadmium poisoning.¹⁴

It must be stressed, however, that supporting data for chelation are promising, but not definitive, and are only derived from animal models. Succimer dosing in human cadmium poisoning is unstudied. Doses that are well tolerated (10 mg/kg/dose three times a day) are reasonable.

Other chelators that may be beneficial, but for which further investigation is needed, include diethylenetriaminepentaacetic acid (DTPA)^{6,13} and 2,3-dimercaptopropane sulfonate (DMPS),^{13,50} both of which reduce tissue burdens and increase survival.

Most other chelators are either ineffective or detrimental, including 2,3-dimercaptopropanol (British anti-Lewisite, BAL),^{13,19,49} penicillamine,^{13,62} cyclic tetramines (such as cyclam and tACPD),⁸⁸ detergent formula chelators (such as sodium tripolyphosphate {STPP} and nitrilotriacetic acid {NTA}),^{29,30} CaNa₂EDTA,⁶⁵ and dithiocarbamates.^{3,33}

Pulmonary/Cadmium Fumes. The patient who is ill after exposure to cadmium fumes (generally cadmium oxide) presents with predominantly respiratory complaints and possibly also with constitutional symptoms. The patient's airway should be assessed and appropriate oxygenation ensured, although hypoxia may not be a problem acutely. Steroids are used in most reported cases (although there are no studies to support their efficacy), and a standard dose of methylprednisolone (1 mg/kg up to 60 mg) is reasonable. Because cadmium inhalation injuries are neither benign nor self-limited, all patients with acute inhalational exposures to cadmium should be admitted to the hospital for observation and supportive care until respiratory symptoms have resolved. All such patients should have long-term follow-up arranged with a pulmonologist to assess the possibility of chronic lung injury, even following a single exposure.

Chelation should not be entertained as an option for patients with single acute exposures to cadmium fumes, as these patients do not appear to develop extrapulmonary injury.^{4,5,93,105}

Chronic Exposure

Patients chronically exposed to cadmium frequently come to attention during routine screening, as those who work with cadmium are under close medical surveillance ([Chap. 123](#)). These patients may have developed proteinuria or, less commonly, chronic pulmonary complaints.

Management is challenging. Cessation of cadmium exposure is the first intervention. However, as mentioned earlier, chronic cadmium-induced kidney and lung changes are largely irreversible.

Chelation for chronic cadmium toxicity is not currently recommended. There is no evidence that chelation of chronically poisoned animals improves long term outcomes, and one study in humans found no improvement in cadmium-induced kidney dysfunction with periodic CaNa₂EDTA chelation.¹⁰⁴ Furthermore, in a chronically exposed patient, the majority of cadmium is bound to intracellular metallothionein, which greatly reduces its toxicity. Any attempt to remove cadmium from these deposits risks redistributing cadmium to other organs, possibly exacerbating toxicity, as is known to occur with BAL therapy.²³

Of all the chelators tested thus far in animal models of chronic cadmium toxicity, the dithiocarbamates have shown the most success in reducing total body cadmium burdens. Unfortunately, these chelators tend to cause redistribution of cadmium to the brain; the lipophilicity that allows them to cross cell membranes into hepatocytes (to access stored cadmium) also promotes their uptake into the lipid-rich central nervous system (CNS).³⁴ Numerous dithiocarbamates have been synthesized and studied with regard to cadmium decorporation, however, and several species effectively reduce

whole-body, kidney, and liver cadmium concentrations without an increase in CNS cadmium.^{56,85}

At present, there is insufficient evidence to justify the use of any chelator in the treatment of chronic cadmium toxicity.

SUMMARY

- Cadmium toxicity is largely dependent on route of and chronicity of exposure.
- After acute oral exposure, GI injury predominates.
- After acute inhalation, a severe chemical pneumonitis may ensue.
- With chronic environmental or occupational exposure, nephrotoxicity (usually manifested by proteinuria) is the most significant finding, although other organ systems, such as the lungs, can be affected.
- Treatment for all patients with suspected cadmium poisoning consists of removal from the source, decontamination if possible, and supportive care.
- In the rare instance of exposure from acute cadmium salt ingestion, treatment with succimer may be warranted.
- At this time there is insufficient evidence to recommend chelation in the patient with chronic cadmium poisoning.

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92 CESIUM

Zhanna Livshits

Cesium (Cs)	
Atomic number	= 55
Atomic weight	= 132.91 Da
Normal concentrations	
Whole blood	= <10 µg/L (75.42 nmol/L)
Urine	= <20 µg/L (150.48 nmol/L)

HISTORY AND EPIDEMIOLOGY

The name “cesium” derives from Latin word for “sky” (caelum). Gustav Kirchhoff and Robert Bunsen first identified cesium spectrophotometrically in the mineral water of Dürkheim, Germany in 1860.⁸¹ Cesium (Cs) is among the most rare and reactive alkali metals. Elemental cesium (Cs⁰) is silvery white, soft, and malleable. It has a relatively low melting point of 82.4°F (28°C) and thus may exist as both solid and liquid at room temperature. Cs⁰ ignites violently when exposed to moist air or water but forms stable salt complexes. The greatest concentration of naturally occurring cesium (32%), the compound cesium oxide (Cs₂O), is found in the ore pollucite.^{1,78,80} Since Cs⁰ is so highly reactive and short lived, the name “cesium” will refer to cesium salts in the following discussion, unless specifically noted otherwise.

Radionuclides of cesium were identified in the 1940s by the American scientist and Nobel Prize winner Glenn Seaborg and his student Margaret Melhase.⁶⁰ Radioactive cesium isotopes are products of nuclear fission of uranium and plutonium.⁸¹ Both ¹³⁴Cs and ¹³⁷Cs decay via β particle emission; however, only ¹³⁷Cs emits γ rays.⁷⁸ ¹³⁷Cs has a long half-life of 30 years, and it serves not only as an “atomic clock” but also poses potential radiological hazard as it deposits and complexes in earth and water. Of the numerous cesium radioisotopes have been identified to date, only ¹³³Cs is stable.⁹

Several releases of radioactive cesium have occurred in the past century, resulting in large-scale contamination and human exposure. Examples include the nuclear weapons use in Hiroshima and Nagasaki, nuclear weapons testing in Bikini Atoll¹¹ and Republic of Georgia,²⁷ poor nuclear waste management in Goiânia,^{36,57,65} Tammiku,³⁷ and Camp Lilo²⁷ in the Republic of Georgia, as well as critical nuclear power plant malfunctions in Chernobyl⁶⁸ and Fukushima Daiichi.

Whereas nuclear disasters are associated with release of numerous radioactive isotopes, isolated exposure to ¹³⁷Cs was implicated in the events that took place in Goiânia, Tammiku, and Camp Lilo. In September 1987, two men removed a large cylinder that contained ¹³⁷Cs from an abandoned apparatus in Goiânia Institute of Radiotherapy. Several weeks passed between the incident and discovery of the source, with resultant ¹³⁷Cs contamination of the community. Approximately 112,000 people required monitoring and 249 people suffered from internal and external contamination.^{36,65}

On October 21, 1994, three brothers entered a waste repository in Tammiku, Estonia. One of the brothers picked up a metal vessel that unknowingly contained ¹³⁷Cs. Although he died of a syndrome similar to radiation-induced illness, acute radiation contamination was not recognized until his stepson was hospitalized with radiation-induced hand burns a month later.³⁷

Three years later, 11 soldiers undergoing military exercises in Camp Lilo, situated near Tbilisi in the Republic of Georgia, all developed cutaneous radiation syndrome from inadvertent exposure to ¹³⁷Cs capsules at the campsite.²⁷

Occupational exposure to radiocesium occurs routinely in nuclear power plant employees and people who live and work in close proximity to a nuclear facility. Both ¹³⁷Cs and ¹³¹Cs are used as sources of external and internal radiation for treatment of numerous malignancies. Internal radiotherapy with ¹³¹Cs seed implantation, called brachytherapy, is approved by the Food and Drug Administration (FDA).²³ Medical occupational exposure may occur in physicians, patients, and staff working with these isotopes.^{24,58}

Cesium compounds are employed in scintillation counters, photoelectric cells, vacuum tubes, optical instruments, and semiconductors.¹ They serve as catalysts for organic synthesis and are utilized for physiologic laboratory experiments in animal models of ventricular dysrhythmias. Nonradioactive cesium chloride is promoted as a supplement and alternative

treatment for cancer, despite any scientific support for this claim. Its increasing popularity in cancer treatment stems from a theory that cesium chloride increases intracellular pH of tumor cells, resulting in cell death.^{7,70} Cesium chloride was also proposed, but not implemented, as a preventive therapy for potential radiocesium exposure.⁶

PHARMACOLOGY

Like thallium (Chap. 102), cesium has a molecular structure that resembles potassium and similarly, it either mimics or antagonizes potassium in cellular processes.⁴² Since cesium blocks the delayed rectifier (I_{KR}) channel in the cardiac myocyte and prolongs repolarization (Chap. 16), it has been used in animal models to induce QT interval prolongation and subsequent ventricular ectopy and ventricular dysrhythmias.^{54,71}

Although radiocesium is indistinguishable from nonradioactive cesium in biological and chemical reactions, radiocesium damages tissues via emission of β and γ particles during its decay (Chap. 134). ^{134}Cs decays to a stable isotope by emission of β particles. ^{137}Cs initially emits β particles to form the unstable intermediate barium isotope $^{137\text{m}}\text{Ba}$, which then further emits γ rays to form stable ^{137}Ba .¹⁰ Radiocesium is such a potent emitter that lethal doses of radiation are delivered following exposures that are too small to cause cardiac effects.

Pharmacokinetics and Toxicokinetics

Pharmacokinetic data following radiocesium injection and ingestion is derived from radiotracer studies in animals and a few reports in human volunteers. The data are limited and challenging to translate to a human model.

Exposure to cesium occurs through ingestion, inhalation,⁵² injection, and dermal contact. Animal studies with a guinea pig model demonstrate rapid absorption via inhalation, intraperitoneal injection, and ingestion.⁷³ Human volunteer studies demonstrate 98% to 99% absorption of ingested cesium salts.^{66,67} Absorption through intact skin is minimal. One case estimated 20% dermal absorption of radiocesium through burned skin.⁸²

Once absorbed, cesium is rapidly distributed to the blood compartment, followed by subsequent distribution to various organs and eventual accumulation in the skeletal muscle. Animal studies with rat, dog, and guinea pig models demonstrate that cesium is initially distributed to the myocardial, renal, lung, and liver tissue followed by subsequent accumulation in the skeletal muscle.^{41,48,73,77}

Data from human volunteers suggest that once ingested, cesium is absorbed from the small intestine,^{33,42} distributes to the blood compartment and various organs, and eventually accumulates in the skeletal muscle. Volunteer radiotracer studies demonstrate rapid initial accumulation in the liver both following ingestion and injection of radiocesium; and accumulation in the salivary glands following ingestion; subsequent distribution to the myocardium, spleen, adrenals, gastrointestinal (GI) tract, bone, and lungs, with elevated concentration in the skeletal muscle approximately 10 days postexposure.^{35,66} A human biokinetic model suggests that the myocardium, GI tract, and kidneys have the highest extraction ratios of cesium.⁴² Postmortem studies demonstrate elevated concentrations in the skeletal muscle, bone, liver, spleen, and adrenal glands.^{9,46,66}

Cesium undergoes enterohepatic circulation limiting fecal elimination. As such, urinary excretion accounts for 80% to 90% and fecal excretion for 2% to 10% of elimination of an ingested dose.^{44,46,62} Some elimination occurs in the feces independent of whether cesium is injected or ingested, likely due to hepatic elimination.⁶⁶ Only a small amount of cesium is eliminated through sweat or respiratory secretions.^{22,46,83}

Biological elimination $t_{1/2}$ ranges from 50 to 150 days.⁹ Volunteer studies report the biologic elimination half-life of radiocesium from 45 to 150 days,^{32-35,46,49,64,67,79} with few cases up to 200 days³⁵ following ingestion. The biological half-life likely increases with age^{4,8} and male sex⁴ and decreases with pregnancy.⁹⁰ The half-life in children and infants is significantly shorter than that of adults.⁴⁹

^{137}Cs elimination follows first-order kinetics.⁴⁴ Pharmacokinetic analysis in a woman who developed cardiac toxicity from nonradioactive cesium suggested first-order elimination using a two-compartment model.⁸⁸

Radiocesium transfers to placenta and maternal breast milk.^{3,26,31,50,75,86} Modeling based on estimates and human studies demonstrates approximately 0.5%, 10%, and 24% transfer of ^{137}Cs through maternal milk during the stages of early pregnancy, late pregnancy, and lactation.³¹

PATHOPHYSIOLOGY

^{137}Cs undergoes radioactive decay by emission of β particles and γ rays. β Particles have very limited dermal penetration and effects from external exposure are limited to dermal irritation and burns (Chap. 134). Release of β particles within the

body, as typically occurs after inhalation, ingestion, or dermal absorption, may harm internal organs. γ Rays can penetrate the skin with external exposure and cause organ toxicity.

As noted above, cardiotoxicity is the principal and most dangerous clinical effect of nonradioactive cesium. QT prolongation occurs rapidly and predisposes individuals to torsade de pointes (TdP) and ventricular dysrhythmias. In animal models, especially in canines, cesium is one of the more reliable methods to induce and study nonischemic ventricular dysrhythmias. Prolongation of the QT interval in the cardiac myocyte results from antagonism at the delayed rectifier I_{KR} channel.⁸⁹ This delays the repolarization phase of the cardiac action potential, thus prolonging the action potential duration.³⁰ Additionally, it promotes early after-depolarizations (EADs), which are cellular depolarizations that occur during phases 2 and 3 of the cardiac action potential prior to completion of repolarization.^{19,30,43} This generation of EADs is thought to lead to TdP,^{13,19,20,28,74} as cesium chloride-induced EADs precede the development of dysrhythmias in a canine model.^{43,59}

Cesium-induced ventricular dysrhythmias are furthermore potentiated by bradycardia.^{5,38,59} This may be explained by either potentiation of EAD formation³⁸ or increase in temporal variability of the refractory period throughout the cardiac muscle.²⁹ Overdrive pacing abolishes both EADs and ventricular dysrhythmias in an isolated canine cardiac tissue.^{17,43,59} In addition to bradycardia, EADs are induced by hypokalemia²¹ and metabolic acidosis¹² (Chaps. 16 and 17). These EADs are modulated by L-type calcium channel currents,^{2,38} and calcium channel blockers, such as verapamil, suppress cesium-induced ventricular dysrhythmias in dogs.^{16,54}

Sodium channel modulation also may be contributory in cesium-induced ventricular dysrhythmias. Low concentrations of tetrodotoxin, a sodium channel antagonist, terminates EADs induced by cesium chloride.^{5,40} Lidocaine abolishes cesium-induced ventricular dysrhythmias in a canine model.⁵⁴

CLINICAL MANIFESTATIONS

Radiation injuries are discussed in detail in Chap. 134. The following discussion focuses on nonradioactive cesium toxicity.

Cardiovascular Toxicity

Exposure to cesium chloride is associated with QT interval prolongation and predisposes to the development of ventricular dysrhythmias such as TdP. According to case reports, the most common cumulative ingested dose was 3 g/d,^{45,69,87} with only one case reporting 9 g/d.¹⁵ Time from cesium exposure to development of dysrhythmia ranged from 1 week to 3 months. Most patients with ventricular ectopy, TdP, or ventricular dysrhythmias reported a chief complaint of syncope or “seizurelike” activity. Prolonged QT interval was universally present and did not correct with potassium repletion. Serum and urine cesium concentrations were markedly elevated in all case reports. Serum concentrations ranged from 2400 $\mu\text{g/dL}$ ⁵⁶ to 13,973 $\mu\text{g/dL}$ ⁶¹ (reference range, $<10 \mu\text{g/L}$ or $<1 \mu\text{g/dL}$), and urine cesium concentration 750 mg/L ⁸⁷ to 3600 mg/L ⁵⁶ (reference range, $<20 \mu\text{g/L}$). Dalal et al reported whole blood cesium concentration of 160,000 $\mu\text{g/L}$ (reference range, $<10 \mu\text{g/L}$).¹⁵ The QT interval normalized and dysrhythmias ceased after termination of cesium chloride exposure.^{10,14,15,45,56,61,69,87,88}

Intravenous injection of cesium chloride in two end-stage patients with metastatic cancer resulted in death. Forensic records indicate that the first patient had chills and seizures during the first session and went into cardiac arrest during the second session. The second patient collapsed during the infusion.⁹ Postmortem whole blood concentration of cesium was 84.0 $\mu\text{g/mL}$ for first patient and 28.1 $\mu\text{g/mL}$ for second patient (reference range, 0.041–0.138 $\mu\text{g/mL}$ in nonexposed controls). Another case report described an 8 year-old boy who developed bradycardia, premature ventricular depolarizations, and TdP with resultant cardiac arrest that terminated without intervention.¹⁴ Cesium concentrations were not obtained.

Gastrointestinal Effects

Nausea, vomiting, diarrhea, and abdominal cramping are described in case reports of patients ingesting from 3 to 9 g of cesium chloride per day.^{10,15,45,56,69} Although patients experienced GI symptoms during oral therapy with cesium chloride, time course from exposure to onset of symptoms is not described.

Electrolyte Abnormalities

Patients taking cesium chloride supplementation may develop hypokalemia and hypomagnesemia. Serum potassium concentration ranged from 2.8 mEq/L ^{10,61} to 3.2 mmol/L ^{45,69} (reference range, 3.5–5.1 mmol/L), and serum magnesium concentrations were reported as low as 1.4 mg/dL .⁸⁷ Both corrected with electrolyte repletion. Electrolyte imbalance likely

reflects GI loss through vomiting and/or diarrhea.^{10,15,45,61,69,87}

Neurologic Effects

A heightened sense of perception as well as facial and acral tingling are described following self-administration of 6 g of cesium chloride daily for 36 consecutive days.⁵⁵ Reports of syncope^{10,45,56,61,87,88} and “seizures”^{9,15} should be interpreted with caution since a nonperfusing cardiac rhythm is the most likely etiology.

DIAGNOSTIC TESTING

Radioactive cesium may be detected by whole-body counters using γ ray spectrometry and β counting.⁷⁸ Shielding of the room where testing is performed is sometimes necessary to reduce background radiation. Urine and feces may be analyzed for ^{137}Cs and/or ^{134}Cs in a similar manner.

Analysis of nonradioactive cesium in blood, urine, feces, or tissue samples is performed by spectrometric methods such as flame atomic emission spectrometry, inductively coupled plasma mass spectrometry (ICP-MS), or instrumental neutron activation analysis. Cesium concentration following exposure to a nonradioactive cesium salt may also be determined by similar methods such as flame atomic emission spectrometry or ICP-MS.¹

MANAGEMENT

Radiocesium

Patient management following radiation exposure is outlined in detail in [Chap. 134](#) and Antidotes in Depth: A28. Although most data are obtained following radiocesium exposures in both animals and humans, the treatment of patients with cesium-induced toxicity is similar. Recognition and cessation of cesium exposure is critical in all cases of exposure and toxicity.

GI decontamination is likely of limited value and is not recommended following cesium ingestion. Cesium does not adsorb to activated charcoal,⁸⁵ and patients who present with significant cesium toxicity may have vomiting or altered mental status. Administration of antiemetics and repletion of volume loss with intravenous fluids is central to supportive management of patients who present with nausea and vomiting. Serum potassium and magnesium concentrations should be carefully monitored and supplemented as needed.

All patients with suspected cesium salt ingestion should have an electrocardiogram (ECG) and be attached to a continuous cardiac monitor. QT intervals should be monitored closely and documented often with serial ECGs. TdP is an unstable rhythm requiring cardioversion, but recurrent episodes may be prevented with intravenous magnesium infusion and/or overdrive pacing. Cesium chloride-associated cardiac dysrhythmias may be treated with lidocaine and/or synchronous cardioversion. Amiodarone should be used with caution given its propensity to prolong the QT interval.

Since isolated seizures have not been reported, syncope and “seizurelike activity” should heighten concern for hypoperfusion or potential cardiac dysrhythmia.

The following therapies have been attempted after radiocesium exposure and have not been effective: activated charcoal, diuretics, enhanced sweating, and disodium ethylenediaminetetraacetate (EDTA).^{22,84} The paucity of literature makes it challenging to conclusively recommend or reject hemodialysis as a modality for enhanced cesium elimination.^{39,84}

Prussian Blue

Prussian blue, ferric hexacyanoferrate (II), is a blue crystal lattice composed of iron and cyanide molecules. In 2003, the insoluble form of Prussian blue (Radiogardase) was approved by the FDA for oral treatment of thallium and cesium toxicity (Antidotes in Depth: A28).⁶³ The insoluble crystal lattice adsorbs cesium¹⁸ in the intestinal lumen, and enhances both elimination and gut dialysis.⁵³ A systematic analysis of published literature on the use of Prussian blue in the treatment of radiocesium poisoning suggests that it may reduce the half-life of radiocesium by as much as 43%.⁷⁶

Although the majority of Prussian blue literature focuses on radiocesium elimination,^{44,47,51,72,76} there is one case report that described Prussian blue administration in a patient with cesium chloride toxicity. Prussian blue was started on hospital day 7 in a patient with cardiac toxicity following cesium ingestion. She received 3 g three times per day for duration of 4 weeks. Cesium half-life was decreased by 47.7% (from 61.7 days to 29.4 days).¹⁰

Since laboratory confirmation will be substantially delayed, Prussian blue should be administered upon suspicion of cesium toxicity. Although the optimal dose and interval are unknown, the package insert for Radiogardase recommends 3 g orally three times per day, for a total daily dose of 9 g in adults and adolescents. A dose of 1 g orally three times per day is recommended in children for a total daily dose of 3 g. Duration of therapy should be 30 days.⁶³

SUMMARY

- Radioactive cesium is a strong β - and γ -ray emitter that is released following normal operation of power plants and/or nuclear incidents.
- Because of the availability of commercial and therapeutic sources of radioactive cesium, human exposure is also likely either through unintentional exposure to discarded equipment or through acts of terrorism.
- Exposure to nonradioactive cesium salts occurs through intentional use as an alternative therapy for cancer.
- The principal toxicity of nonradioactive cesium is ventricular dysrhythmias and TdP that result from blockade of cardiac potassium channels.
- In addition to supportive care, Prussian blue is indicated for both radioactive and nonradioactive cesium toxicity.

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93 CHROMIUM

Steven B. Bird

Chromium (Cr)	
Atomic number	= 24
Atomic weight	= 51.99 Da
Normal concentrations	
Whole blood	= 20–30 µg/L (380–580 nmol/L)
Serum	= 0.05–2.86 µg/L (1–56 nmol/L)
Urine	< 1 µg/g creatinine (19.2 nmol/g creatinine)

HISTORY AND EPIDEMIOLOGY

Chromium (from the Greek word for color, chroma) is a naturally occurring element that may be found in oxidation states of –2 to +6 but primarily exists in the trivalent (Cr^{3+}) and hexavalent (Cr^{6+}) forms. It was first discovered in 1797 in the form of Siberian red lead (crocoite: PbCrO_4), and it occurs only in combination with other elements, primarily as halides, oxides, or sulfides (Table 93–1).

TABLE 93–1. Common Forms of Chromium

Name	Chemical Formula	Oxidation State	Uses
Barium chromate	BaCrH_2O_4	6+	Safety matches, anticorrosive, paint pigment
Calcium chromate	CaCrO_4	6+	Batteries, metallurgy
Chromic acid	H_2CrO_4	6+	Electroplating, oxidizer
Chromic chloride	CrCl_3	3+	Supplement in total parenteral nutrition
Chromic fluoride	CrF_3	3+	Mordant in dye industry, moth-proofing agent for wool
Chromic oxide	Cr_2O_3	3+	Metal plating, wood treatment
Chromite ore	FeCr_2O_4	3+	Water tower treatment
Chromium picolinate	$\text{C}_{18}\text{H}_{12}\text{CrN}_3\text{O}_6$	3+	Nutritional
Lead chromate	PbCrO_4	6+	Yellow pigment for paints and dyes
Potassium dichromate	$\text{K}_2\text{Cr}_2\text{O}_7$	6+	Oxidizer of organic compounds, leather tanning, porcelain painting

Elemental chromium (Cr^0) does not occur naturally but is extracted commercially from ore. Chromium is found most abundantly in chromite ore (FeCr_2O_4).⁹ Elemental chromium is a blue-white metal that is hard and brittle. It can be polished to a fine, shiny surface, affords significant protection against corrosion, and can be added to steel in order to form stainless steel (an alloy of chromium, nickel, and iron). One of the most important uses of chrome plating is to apply a hard, smooth surface to machine parts such as crankshafts, printing rollers, ball bearings, and cutting tools. This is known as “hard” chrome plating. Elemental chromium is also used in armor plating, safes, and is used in forming brick molds due to its high melting point and limited thermal expansion.

The carcinogenic potential of hexavalent chromium was first recognized as a cause of nasal tumors in Scottish chrome pigment workers in the late 1800s. In the 1930s, the pulmonary carcinogenicity of hexavalent chromium was first described in German chromate workers.¹³ Chromium toxicity may result from occupational exposure, environmental exposure, or a combination of both routes. Like many metals, the clinical manifestations of chromium toxicity depend upon whether the exposure is acute or chronic and on the chemical form of chromium.

PHARMACOLOGY

Chromium is an essential element involved in glucose metabolism. This may be through facilitation of insulin binding to insulin receptors or by amplification of the effects of insulin on carbohydrate and lipid metabolism. Chromium deficiency may have a causal link to diabetes mellitus and arteriosclerosis. Cr³⁺ is an essential trace metal required for the metabolism of glucose and fats. The complex nutritional interactions of trivalent chromium with numerous metabolic pathways are not understood and remain the subject of much debate among researchers. However, it is clear that dietary chromium deficiency leads to elevated insulin concentrations, hypercholesterolemia, hyperglycemia, increased body fat, and the attendant risks of these metabolic derangements. Cr³⁺ enhances insulin sensitivity and glucose disappearance concomitantly with lower insulin concentrations in a obese rat models, with no difference in lean controls.¹²

The chemical properties and health risks of chromium depend mostly on its oxidative state and on the solubility of the chromium compound. Chromium in the Cr⁶⁺ and Cr³⁺ oxidation states has very different properties. The relationship between these oxidative states is described by the following equation:



This difference of 1.33 eV in electric potential between the Cr⁶⁺ (in Cr₂O₇²⁻) and Cr³⁺ states reflects both the significant oxidizing potential of Cr⁶⁺ and the high energy required for the oxidation of Cr³⁺ to Cr⁶⁺. Reduction of Cr⁶⁺ to Cr³⁺ occurs in vivo by abstraction of electrons from cellular constituents such as proteins, lipids, DNA, RNA, and plasma transferrin and accounts for the toxicity of Cr⁶⁺.³⁷

The rapidity and completeness of the reduction of Cr⁶⁺ is the subject of considerable scientific debate. Hexavalent chromium is reduced to Cr³⁺ in saliva, the gastrointestinal tract, the respiratory tract epithelium and pulmonary macrophages, and in blood.^{4,34} During this reduction, several other oxidative states transiently occur (namely Cr⁴⁺ and Cr⁵⁺) and contribute to the cytotoxicity, genotoxicity, and carcinogenicity of Cr⁶⁺ chromium compounds.⁴⁶

Although most Cr⁶⁺ is rapidly reduced upon entering the stomach before it can be absorbed, ingestion of Cr⁶⁺ in drinking water does lead to measurable Cr⁶⁺ concentrations in plasma, red blood cells, and urine. Hexavalent chromium can accumulate in most body tissues, raising concerns that chromium-induced toxicity and carcinogenesis may be more widespread than is currently appreciated.¹³

Environmental Exposure

The processing of chromium ores primarily releases Cr³⁺ into the environment. However, some hexavalent chromium is released from chromate manufacturing and coal-based power plants. The most significant environmental sources of Cr⁶⁺ are chromate production, ferrochrome pigment manufacturing, chrome plating, and certain types of welding.

The general population may be exposed to chromium via drinking water, food and food supplements (eg, chromium picolinate), joint arthroplasty, coronary artery stents, and cigarettes. Hexavalent chromium salts are used extensively to prevent equipment and piping corrosion in industrial cooling towers and air conditioning and malfunctions or corrosion may lead to cross contamination with drinking water. Dermal exposure may occur from use of tanned leather products or wood treated with copper, chromate, and arsenate (CCA), which contains hexavalent chromium. This form of chromium is reduced to trivalent chromium by natural organic compounds found in wood. CCA-treated lumber was voluntarily removed from the US consumer market in December 2003 because of possible health concerns as a result of exposure to the arsenic and chromium. No specific adverse health effects related to CCA-treated lumber were reported by the Environmental Protection Agency prior to the voluntary withdrawal. A recent reanalysis of cancer mortality and hexavalent chromium-contaminated drinking water from Liaoning Province, China, demonstrated an increase in stomach cancer rate in communities with chromium-contaminated drinking water from ferrochromium factories.⁷ Significant exposure from more than 160 chromate production waste sites within Hudson County, New Jersey was discovered in the late 1980s.²⁰ A final report published by the Agency for Toxic Substances and Disease Registry in 2008 found an increased risk of lung cancer incidence in populations living in close proximity to historic chromium ore processing residue sites, although the increases were not statistically significant.²

Occupational Exposure

Workers in industries that use chromium may be exposed to 100 times greater concentrations of chromium than the general population. Chromium pigmentation production and leather tanning use significantly more Cr^{6+} compounds, whereas metal finishing and wood preservation use Cr^{3+} compounds (Table 93–2).

TABLE 93–2. Occupations at Risk for Chromium Exposure

Cement workers
Chromite ore workers
Electroplaters
Foundry workers
Galvanized steel workers
Glass polishers and glazers
Lithographers
Machinists
Painters
Photograph developers
Tanners
Textile dyers
Welders
Wood preservers

Several studies have focused on the risk of chromium exposure in welders.^{41,42} Stainless steel welding liberates significantly more hexavalent chromium than do other types of welding. Although the lung cancer rate of chromium containing stainless steel welders does not differ from that of regular steel welders, in 2006 the Occupational Safety and Health Administration (OSHA) lowered the permissive exposure limit of hexavalent chromium by 10-fold for welders.

Medical Device Exposure

Ongoing concerns and media attention have been directed to the use of metal-on-metal (MoM) implants for total hip arthroplasty and surface refinishing. Unlike non-MoM implants made of ceramic or polyethylene, these metal implants contain chromium and cobalt. As early as 1997, it was demonstrated that blood concentrations of metal ions increase in patients with MoM hip arthroplasty.¹⁰ One-year postoperative blood chromium concentrations increased by 21 times over the preoperative concentrations in patients with MoM implants.²³ Metal release will cause some tiny metal particles to wear off the device around the implant, which may damage to bone and/or soft tissue surrounding the implant and joint. Although some patients with failed MoM hip implants have complained of memory difficulties, chronic pain, and pain in the implanted hip, the true incidence and nature of adverse health outcomes due to release of chromium ions and particles from these implants has not yet been established. Currently, there is insufficient evidence to conclusively demonstrate that MoM hip implants produce side effects beyond those that may occur at the site of implantation. The significance of elevated blood chromium concentrations is unknown.¹⁹ (See Chap. 94 for further discussion of arthroprosthetic cobaltism.)

PHARMACOKINETICS AND TOXICOKINETICS

Because they possess significantly different properties, Cr^{3+} and Cr^{6+} must be evaluated separately.

Absorption

Trivalent Chromium Compounds. Oral absorption of Cr^{3+} salts is limited. Approximately 98% of an ingested dose is recovered in the feces, just 0.1% is excreted in the bile, and 0.5% to 2.0% is excreted in the urine.^{17,33} Human case reports and animal studies also corroborate the generally poor absorption of Cr^{3+} salts by the oral, inhalational, and dermal routes, except through burns and other disrupted mucosal or epithelial surfaces.²⁹

Hexavalent Chromium Compounds. Cr^{6+} is modestly absorbed after ingestion partly as a result of the structural similarity between hexavalent chromium compounds and phosphate and sulfate.¹⁴ These three chemicals undergo both facilitated diffusion through nonspecific anion channels and active transport. In human volunteers, approximately 10% of an orally ingested dose of sodium chromate was absorbed; duodenal administration increased this to roughly 50%.¹⁷ This difference likely relates to the reduction of the hexavalent chromium to trivalent chromium in the acidic environment of the

stomach. Similarly, 3 hours after a lethal ingestion of potassium dichromate (hexavalent), greater than 80% of the chromium was reduced to the trivalent state in the blood.²² Hexavalent chromium compounds are generally not well absorbed after dermal exposure. Whatever the route of exposure, Cr^{6+} is absorbed much more readily than Cr^{3+} , but the Cr^{6+} is then rapidly reduced to Cr^{3+} after absorption.

Epidemiologically, inhalational of Cr^{6+} is the most consequential route of exposure. However, the greatest health consequences from Cr^{6+} exposure are due to inhalation. The exact rate of absorption is unknown but is dependent on the solubility of the specific Cr^{6+} compound, the size of the particles, the phagocytic activity of the pulmonary macrophages, and general health of the lungs. Animal studies suggest that roughly 50% to 85% of small ($<5\ \mu\text{m}$) Cr^{6+} potassium dichromate particles are absorbed.²

Distribution

Because most of the Cr^{6+} is rapidly reduced before absorption by the stomach, proximal gastrointestinal tract, and by red blood cells (RBCs), Cr^{3+} accounts for virtually the entire body burden of chromium. Trivalent chromium accumulates to the greatest extent in the kidneys, bone marrow, lungs, lymph nodes, liver, spleen, and testes. The kidneys and liver alone account for approximately 50% of the total body burden.¹⁴

Elimination

Urinary excretion of trivalent chromium occurs rapidly. Roughly 80% of parenterally administered Cr^{6+} is excreted as Cr^{3+} in the urine and 2% to 20% in the feces.³³ The urinary excretion half-life of Cr^{6+} ranges from 15 to 41 hours.²⁴ Because Cr^{6+} undergoes reduction to Cr^{3+} following uptake by RBCs, an apparent slow compartment is created, with the elimination half-life dependent on the life span of RBCs. Small amounts of chromium are detectable in sweat, breast milk, nails, and hair.

PATHOPHYSIOLOGY

Trivalent Chromium

Chromium picolinate is a popular Cr^{3+} dietary supplement. There is a dearth of rigorous science concerning the efficacy or safety of chromium picolinate. However, it appears that organ deposition of Cr^{3+} occurs.⁴⁰ There is no strong evidence of any significant end-organ toxicity due to exposure to Cr^{3+} , perhaps because Cr^{3+} is so poorly absorbed. There is little or no rigorous evidence that exposure to Cr^{3+} compounds increases cancer risk. Animal work and epidemiological studies of workers exposed to Cr^{3+} compounds have failed to demonstrate a statistically significant increased incidence of cancer.⁵

Hexavalent Chromium

Cr^{6+} is a powerful oxidizing agent that has corrosive and irritant effects. The greatest toxicity from Cr^{6+} lies in its ability to produce oxidative DNA damage. DNA strand breaks, DNA-DNA and DNA-protein cross-links, and nucleotide modifications all occur.¹⁵ Although the exact mechanisms of how Cr^{6+} affects the genome are unknown, transient toxic chromium intermediates such as Cr^{4+} and Cr^{5+} are probably responsible.³⁹

Inconsistent data suggest that either immunostimulation and immunosuppression result from chronic chromium exposure. At least one study suggests that chromium-induced immunosuppression may be responsible for implant-associated infections in patients after hip or knee arthroplasty.⁴⁷ In limited human studies, no adverse developmental toxicity has been demonstrated. In animals, adverse developmental effects, including cleft palate, hydrocephalus, and neural tube defects, are described.¹⁶

CLINICAL MANIFESTATIONS

The clinical manifestations of chromium poisoning depend on the valence of the element, the source and route of exposure, and the duration of exposure. The clinical manifestations of chromium exposure are best divided into acute and chronic (low-level exposure) effects.

Acute

Manifestations of acute, massive Cr^{6+} ingestions are similar to other corrosive metal ingestions. Gastrointestinal hemorrhage, with or without bowel perforation, may occur acutely.⁵⁰ Because of the strong oxidative properties of Cr^{6+} ,

intravascular hemolysis with disseminated intravascular coagulation may also develop. Renal effects include acute tubular necrosis leading to acute kidney injury.⁴⁹ Metabolic abnormalities after acute, massive exposure include lactic acidosis, hyperkalemia, and uremia. Acute respiratory distress syndrome may develop up to 3 days after exposure. Although Cr^{6+} is generally not well absorbed after dermal exposure, it is a corrosive that causes skin inflammation and ulceration, which can lead to increased dermal absorption. Dermal chromic acid (H_2CrO_4) burns may lead to severe systemic toxicity with as little as 10% body surface area involvement.

Chronic

Because most chronic exposures are inhalational, the respiratory tract is the organ most affected after chronic chromium exposure. When inhaled, Cr^{6+} is a respiratory tract irritant that causes inflammation and, with continued exposure, ulceration (including nasal septum perforation).²⁵ Furthermore, the sensitizing effects of Cr^{6+} may lead to chronic cough, shortness of breath, occupational asthma, bronchospasm, and anaphylactoidlike reactions. Chronic deposition of chromium dust may also lead to pneumoconiosis.³⁸

Epidemiological studies of chromate workers in the 1980s indicated a significantly increased risk of lung cancer in individuals exposed to Cr^{6+} compounds.^{26,35} Small-cell and poorly differentiated carcinomas are the most common types, although nearly all pathologic types of lung cancer are associated with inhalational Cr^{6+} exposure.¹ The latency between exposure and development of lung cancer ranges from 13 to 30 years, although cases have been reported after as few as 2 years.⁸

Although conclusive evidence is missing, it appears that chronic exposure to Cr^{6+} via all routes may cause mild-to-moderate elevation in hepatic aminotransferases and abnormal liver architecture, visible on histologic specimens.⁵⁰ Unlike acute exposures, low-dose chronic chromium exposure occasionally causes only transiently elevated urinary β -microglobulin concentrations, with no obvious lasting effects.⁴⁹

Type IV (delayed-type) hypersensitivity reactions may occur after acute exposure to hexavalent chromium compounds. Chronic hexavalent chromium exposures also occur via dermal contact. Up to 24% of cement workers who have frequent contact with wet cement (which contains Cr^{6+}), automobile part handlers, and locksmiths develop skin sensitivity to chromium compounds.^{28,30}

Occupational chromium exposure may also lead to contact dermatitis (dermatitis toxicosis) in as many as 10% to 20% of chromium workers.⁴⁴ There remains considerable debate over the relative sensitization abilities of Cr^{3+} and Cr^{6+} . Furthermore, what was initially thought to be sensitization to Cr^{3+} exposure may in fact have been exposure to Cr^{6+} with subsequent in vivo reduction to Cr^{3+} . It appears, however, that the Cr^{6+} is a more potent sensitizer than Cr^{3+} and that there may be limited cross-reactivity between the two forms of chromium.¹⁸ Similarly, chromium-containing gaming table felt has led to hand dermatitis referred to as “blackjack disease,” and virtually all occupations that involve exposure to chromium can lead to painless skin and nasal septum ulcerations referred to as “chrome holes.”²⁷

DIAGNOSTIC TESTING

Chromium may be detected in blood, urine, and hair of exposed individuals. Because of the great difficulty in speciation, differentiation between Cr^{3+} and Cr^{6+} is generally not performed; instead the total chromium concentration is usually reported. Needles used for phlebotomy and plastic containers used for sample storage may all contain significant amounts of chromium. Unfortunately, there are no commercially available chromium-free needles. Modern, highly sensitive assay equipment such as graphite furnace atomic absorption spectrometry, neutron activation analysis, and graphite spark atomic emission spectrometry requires diligence in sample handling to ensure that biological samples are not contaminated.

Because of the inherent difficulties in quantifying trace elements such as chromium, and the lack of standard chromium reference materials, the reported normal serum and urine chromium concentrations in unexposed people have varied by more than 5000-fold over the past 50 years.³ Consequently, older reference ranges should be interpreted with caution. Lastly, although cigarette smoke contains chromium, no studies have quantified the effect of smoking on serum, blood, or urinary chromium concentrations.

Blood or Serum

Chromium is distributed evenly between the serum and erythrocytes. Serum chromium concentrations are reflective of recent exposure to both Cr^{3+} and Cr^{6+} . Serum concentrations in people without occupational exposure to chromium range from 0.05 $\mu\text{g/L}$ (1 nmol/L)¹¹ up to more than 2.8 $\mu\text{g/L}$ (56 nmol/L).³ It is not certain whether concentrations above these values should be considered potentially toxic, as no clear correlation has been found between serum or blood concentrations and physiologic effects.

Urine

Although urine chromium concentrations reflect the acute absorption of chromium over the previous 1 to 2 days, wide individual variation in metabolism and total body burden limit the value of urinary chromium monitoring. Urine should be collected in acid-washed plastic (polypropylene) containers over a 24-hour period due to diurnal variation in excretion. Data from the third National Health and Nutrition Examination Survey (NHANES III) demonstrated mean and median urinary chromium concentrations in approximately 500 individuals without known exposure to chromium of 0.22 µg/L (4.4 nmol/L) and 0.13 µg/L (2.6 nmol/L). When corrected for creatinine, the values were 0.21 and 0.12 µg/g creatinine, respectively.³²

Hair and Nails

Hair and nail samples are not reliable indicators of exposure to chromium because of the difficulty distinguishing between chromium contamination of the hair sample from chromium incorporated into the hair during normal hair protein synthesis. Chromium found in hair is not due to contamination or exposure to shampoo or tap water.²¹ Chromium concentrations in hair may be up to 1000 times higher than those found in serum.

Ancillary Tests

After confirmed or suspected acute chromium exposure, complete blood count, serum electrolytes, blood urea nitrogen, creatinine, urinalysis, and liver enzymes testing should be performed. If signs of systemic toxicity are evident, serial determination of coagulation function and disseminated intravascular coagulation may be useful to guide therapy.

MANAGEMENT

Patients with acute chromium ingestions are infrequent but often become severely ill, with significant morbidity and mortality. Consequently, after adequate airway, breathing, and circulatory support have been addressed, attention should be given to decontamination.

Decontamination

As a consequence of its very limited toxicity, Cr³⁺ compounds should require limited decontamination measures. However, as coingestants could be present, standard gut decontamination with activated charcoal should be considered as clinically indicated. Like with most other dermal exposures, decontamination with soap and water should be performed after skin contact. No specific pulmonary decontamination is required.

Hexavalent chromium is corrosive, and profuse vomiting and hematemesis usually follow acute ingestions. Nasogastric lavage may be beneficial after Cr⁶⁺ ingestions if the patient presents to the emergency department within 1 to 2 hours of exposure and no vomiting has occurred. There are no data regarding the use of activated charcoal in acute chromium ingestions. Endoscopic visualization may be difficult after administration of activated charcoal, and the relative benefits of these two modalities need to be considered. If there is a low likelihood of a coingestion, it is better to forego activated charcoal in order to obtain adequate endoscopic visualization. Known or suspected perforation is an absolute contraindication to activated charcoal.

Oral N-acetylcysteine increases the renal excretion of chromium in rats,⁶ but there are no human data to support this therapy. Years of clinical experience using N-acetylcysteine for other indications and the very low incidence of adverse effects, however, favor the administration of oral N-acetylcysteine in the setting of acute chromium toxicity.

Although ascorbic acid facilitates reduction of Cr⁶⁺ to Cr³⁺ in vitro, there are no data to substantiate decreased absorption.⁴⁴ There is some evidence that topical ascorbic acid may reduce dermal Cr⁶⁺ exposure, but this has not been demonstrated in controlled trials.³⁹ Therefore, the routine use of ascorbic acid cannot be advocated at this time.

Chelation Therapy

Currently available chelating agents do not appear efficacious at either lowering serum or blood chromium concentrations or ameliorating chromium toxicity in experimental models. Specifically, ethylenediaminetetraacetic acid (EDTA) has no effect on urinary chromium excretion in human subjects,⁴⁸ and dimercaprol (British anti-Lewisite, BAL) was not beneficial in an animal model of chromium poisoning.³¹

In a single study, dimercaptopropane sulfonate (DMPS) had no effect on urinary chromium excretion in humans.⁴⁵ D-Penicillamine also failed to increase urinary excretion of chromium.³¹ There are no studies of chromium chelation with 2,3-dimercaptosuccinic acid (succimer). Therefore, at this time, there is no evidence to support the use of chelation therapy after acute Cr⁶⁺ or Cr³⁺ poisoning.

Extracorporeal Elimination

Hemodialysis, hemofiltration, and peritoneal dialysis do not efficiently remove chromium. Studies in animals and human case reports indicate that as little as 1% of chromium is removed by hemodialysis or hemofiltration after acute dichromate (a hexavalent compound) exposure.^{22,43} Exchange transfusions may rapidly reduce blood chromium concentrations, but there are no data suggesting that clinical outcomes are positively affected. Limited data in dialysis patients have demonstrated some ability of peritoneal dialysis and hemodialysis to remove intravenously administered chromium.³⁶ Therefore, in the setting of normal kidney function, extracorporeal means of eliminated chromium are not likely to be of benefit. In the setting of acute or chronic kidney failure, peritoneal dialysis or hemodialysis may be beneficial in reducing serum chromium concentrations, although there are no data that clinical outcomes are affected.

SUMMARY

- Hexavalent (Cr^{6+}) chromium remains an uncommon but serious cause of acute metal salt poisoning, while trivalent (Cr^{3+}) chromium lacks toxicity.
- The acute exposure to Cr^{6+} chromium salts by ingestion causes gastrointestinal hemorrhage, hepatic necrosis, and acute kidney injury.
- Chronic Cr^{6+} chromium exposure includes ulcerations of the skin and nasopharynx (“chrome holes”), and more significantly, lung and stomach cancer.
- Regardless of the time course of the poisoning, treatment for chromium exposure includes removal of the patient from the source of exposure, gastrointestinal decontamination, and supportive care. There is insufficient evidence to support the use of chelators in either acute or chronic chromium poisoning.

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94 COBALT

Gar Ming Chan

Cobalt (Co)	
Atomic number	= 27
Atomic weight	= 58.9 Da
Normal concentrations	
Serum	= 0.1–1.2 µg/L (1.7–20.4 nmol/L)
Urine	= 0.1–2.2 µg/L (1.7–37.3 nmol/L)

HISTORY AND EPIDEMIOLOGY

The name cobalt (Co) originates from kobold, German for “goblin,” and was given to the cobalt containing ore, cobaltite (CoAsS), because it made exposed miners ill. However, the miners’ illness was more likely a result of exposure to arsenic rather than cobalt. Brandt discovered cobalt in 1753 during an attempt to prove that an element other than bismuth gave glass a blue hue.

With an atomic number of 27 and a molecular weight of 58.93 Da, cobalt is a light metal with a melting point of 1768.2°K and a boiling point of 3373°K. These attributes make elemental cobalt (Co⁰) very useful in industry, where it is primarily incorporated into hard, high-speed, high-temperature cutting tools. When aluminum and nickel are blended with cobalt, an alloy (Alnico) with magnetic properties is formed. Other uses for cobalt include electroplating because of its resistance to oxidation and as an artist’s pigment due to its bright blue color.

A Co³⁺ ion is at the center of cyanocobalamin (vitamin B₁₂), which is synthesized only by microorganisms and is not found in plants. Common dietary sources are fish, eggs, chicken, pork, and seafood. A diet deficient in cyanocobalamin results in pernicious anemia. Hydroxocobalamin, a Co³⁺ containing precursor to cyanocobalamin, is used as an antidote for cyanide poisoning (Antidotes in Depth: A41).

Medicinally, cobalt chloride was combined with iron salts and marketed in the 1950s as “Roncovite”—for the treatment of anemia due to its ability to stimulate erythropoiesis. As recently as 1976, physicians still used cobalt salts to reduce transfusion requirements in anemic patients, despite well-known adverse effects.⁴³ The other common medical use of cobalt is as a radioactive isotope, cobalt-60 (⁶⁰Co). This γ emitter was formerly used in the radiotherapy of cancers but has been largely replaced by linear accelerators in the Western world. Radiotherapy machines may be targeted by terrorist groups as a source of radioactive material.

Epidemics of cardiomyopathy and goiter termed “beer drinker’s cardiomyopathy”¹⁶ and “cobalt-induced goiter”⁶⁹ occurred between the 1960s and the 1970s. During this period, cobalt sulfate was added to beer as a foam stabilizer. In the 1970s, these epidemics were halted with the discontinued use of cobalt sulfate for this purely esthetic purpose.¹⁰⁶

Current sources of cobalt exposure include chemistry kits,⁷⁴ weather indicators,⁷⁴ antiquated anemia therapies,⁷⁴ cement,⁸¹ fly ash,⁸¹ dyes,⁵³ mineral wool,⁸¹ asbestos,⁸¹ molds for ceramic tiles,⁴⁹ the production of Widia-steel (utilized in the wood industry),¹⁴² mining,⁷⁵ porcelain paint,¹²⁶ orthopedic implants,⁷³ and dental hardware.⁷ A recent area of attention is “arthroprosthetic cobaltism,”^{97,115,130,156,157} which results from cobalt-containing orthopedic implants.¹⁵⁸

The most significant source, however, arises through the formation of cemented tungsten carbide, a “hard metal.” In tungsten carbide factories, powdered cobalt and tungsten are combined through an intense sintering process that exposes the metals to hydrogen that has been heated to 1832°F (1000°C). The first published investigation of these factories reported a 10-fold increase in workspace cobalt concentrations compared to atmospheric concentrations.⁴⁶ These respiratory exposures result in pulmonary toxicity, known as “hard metal disease.” As a result of the original report, occupational studies and preventive measures have greatly reduced the acceptable cobalt exposure concentration in the workplace.

CHEMISTRY

Like other metals, cobalt occurs in elemental, inorganic, and organic forms. The clinical effects of each form are less well defined than more common transition metals such as lead, mercury, or arsenic. Elemental cobalt (Co^0) toxicity is reported through both inhalational¹⁵⁵ and oral exposures.^{68,69} Inorganic cobalt salts typically occur in one of two oxidation states: cobaltous (Co^{2+}) or cobaltic (Co^{3+}). Inorganic cobalt salts, such as cobaltous chloride (CoCl_2) and cobaltous sulfate (CoSO_4), were historically used for the treatment of anemias^{17,58,64,125,166} and were implicated in the “beer drinker’s cardiomyopathy” epidemics, respectively.^{2,101,108}

Organic cobalt exposure results from cyanocobalamin (vitamin B_{12}) ingestion, but due to its limited oral absorption and its rapid renal elimination it is considered of low toxicity.¹²² Comparing organic and inorganic forms of cobalt in animal models, cobalt salts are more toxic than the organic forms such as cobalt stearate.²¹

TOXICOKINETICS

Based on animal studies, oral absorption of cobalt oxides, salts, and metal is highly variable with a reported bioavailability of 5% to 45%.^{82,93} In human studies, both iron deficiency and iron overload (hemochromatosis) enhance radiolabeled ⁵⁷ CoCl_2 absorption in the small bowel.¹¹⁴ Similarly, inhaled cobalt oxide is about 30% bioavailable,⁹³ but the volume of distribution and elimination half-life are not well defined.

The distribution of cobalt is influenced by plasma proteins, mainly albumin^{22,23} and is the basis of the recently Food and Drug Administration (FDA)–approved albumin cobalt binding test (ACB test) for myocardial ischemia. Transferrin, another plasma protein, which normally binds iron can also bind cobalt and may help explain its erythropoietic effect.⁷⁶ Following distribution, cellular uptake is mediated by P2X7 transporter¹⁶⁰ and the active divalent metal transporter 1 (DMT1).²³

Most (50%–88%) absorbed cobalt (organic and inorganic) is eliminated renally, and the remainder is eliminated in the feces.¹⁴⁰ Acutely, an increase in inorganic cobalt concentrations will result in an increased renal elimination.⁷⁹ However, this initial increased elimination decreases rapidly in spite of a large body burden.^{3,114}

The elimination of cobalt correlates with the patterns of occupational exposure.¹⁵⁵ For example, a worker with a standard work week will have much higher urine cobalt concentrations on Friday morning compared to Monday morning.¹⁵⁵ However, Monday afternoon urine cobalt concentrations may be higher than Friday morning concentrations, which is due to the rapid elimination that occurs following an initial exposure.^{3,155} Based on these findings, the exposure over time must be considered when interpreting urinary cobalt concentrations in occupationally exposed individuals.¹²

PATHOPHYSIOLOGY

Like other transition metals, cobalt is a multiorgan toxin. Co^{2+} inhibits several key enzyme systems and interferes with the initiation of protein synthesis.¹³ Polynucleotide phosphorylase, an essential enzyme in RNA synthesis, requires Mg^{2+} to function normally. In vitro, this enzyme only functions at 50% that of normal in the presence of Co^{2+} .¹³ It is hypothesized that Co^{2+} is capable of displacing Mg^{2+} from its cofactor site of this enzyme.¹³

Cobalt salts interfere with the Krebs cycle mitochondrial enzyme, α -ketoglutarate dehydrogenase. Due to this inhibition, Co^{2+} increases the rate of anaerobic glycolysis and at the same time decreases oxygen consumption³¹ and thus inhibits aerobic metabolism. In vitro studies demonstrate that other divalent cations, Zn^{2+} , Cd^{2+} , Cu^{2+} , and Ni^{2+} , also inhibit α -ketoglutarate dehydrogenase (Chap. 13).¹⁶³ When compared to these other divalent cations, Co^{2+} is not considered a potent inhibitor.¹⁶³ However, this in vitro model demonstrates that Co^{2+} is capable of almost entirely inhibiting the reaction when nicotinamide adenine dinucleotide (NADH) is added.¹⁶³ This study suggests that NADH abundance, such as occurs with chronic ethanol use, may potentiate the inhibition of α -ketoglutarate dehydrogenase.¹⁶⁴

Moreover, cobalt salts are capable of inhibiting α lipoic acid and dihydrolipoic acid by complexing with its sulfhydryl groups.^{34,163} These reactions result in the inability to convert both pyruvate into acetyl-CoA and α -ketoglutarate into succinyl-CoA (Chap. 13 and Antidotes in Depth: A24). These combined interactions may explain why chronic ethanol use and cobalt exposure result in cardiomyopathy (see Clinical Manifestations, Cardiovascular).¹⁶³

In addition to enzyme inhibition, CoCl_2 induces oxidant-mediated pulmonary toxicity (see Clinical Manifestations, Pulmonary)¹¹² and neurotoxicity.²³ Xenobiotics implicated in free radical–mediated pulmonary injury are capable of accepting an electron from a reductant and subsequently transferring the electron to oxygen, forming a superoxide free radical (Chap. 12). Cobalt is then capable of accepting another electron, which starts the cycle over again, a process known as redox cycling. This leads to an accumulation of free radicals in the lung due to the abundance of oxygen ready to receive electrons and results in injury.

Within the endocrine system, CoCl_2 is capable of inhibiting tyrosine iodinase.⁸⁵ This enzyme is responsible for combining iodine (I_2) with tyrosine to form monoiodotyrosine and serves as the first step in the synthesis of thyroid hormone (Chap. 56). Inhibition of tyrosine iodinase leads in a decrease of circulating T_3 and T_4 which may result in hypothyroidism (see Clinical Manifestations, Endocrine).

The hematopoietic system is also affected by cobalt salts. Multiple animal models demonstrate that CoCl_2 administration results in reticulocytosis, polycythemia, and erythropoiesis.^{52,83,105,116,117,166} These events occur in both the bone marrow and extramedullary locations.^{17,55} Although the pathogenesis remains largely unknown,³⁴ one theory is that cobalt ion binds to iron binding sites such as transferrin,⁷⁶ resulting in impaired oxygen transport to renal cells, which in turn induces erythropoietin production. A second theory in which cobalt is thought to stimulate erythropoiesis is through improving iron availability. In an animal model of anemia, a greater degree of gastrointestinal iron uptake occurs in cobalt-treated rats compared to rats with either hypoxia or nephrectomy.⁵⁵ A similar study of injected cobalt chloride in mice suggested that the increase in iron uptake exceeded that following exogenous erythropoietin.⁴

Finally, within the nervous system, CoCl_2 inhibits neuromuscular transmission by competing with Ca^{2+} , another divalent ion. Co^{2+} is 20 times more potent than magnesium with regard to its ability to compete with calcium for a site on the motor nerve terminal.¹⁶² Additionally, the formation of free radicals is theorized as a cause of cobalt associated neurotoxicity.²³

TOXICITY

The single acute minimal toxic dose of cobalt salts is not well defined. In fact, varying effects have occurred at variable doses in different patients. Patients with “beer drinker’s cardiomyopathy” received an average daily dose of 6 to 8 mg of CoSO_4 (over weeks to months) and developed toxic effects of acidemia, cardiomyopathy, shock, and death,^{80,108} whereas infants being treated for anemia who received much higher daily cobalt doses of an iron-cobalt preparation (40 mg of CoCl_2 and 75 mg of FeSO_4) for 3 months did not develop toxicity.¹³¹ The inconsistency of these findings suggests that multiple factors are responsible for the development of the clinical manifestations of toxicity; in this case the role of ethanol metabolism may be an important variable.⁷⁴

CLINICAL MANIFESTATIONS

Organ systems affected by acute cobalt poisoning include endocrine,⁶⁸ gastrointestinal,^{43,58} central^{58,139} and peripheral nervous system,¹³⁹ hematologic,^{52,83,105,166} cardiovascular,⁶⁹ and metabolic.⁶⁹ Chronic inhalational exposures affect the pulmonary system^{26,32,46,87,88,128,147} and dermatologic system.^{50,134,165} Radioactive ^{60}Co used for radiation therapy is associated with radiation burns (Chap. 134). Unlike acute toxicity, chronic cobalt exposure is not associated with an increased mortality; a cohort study evaluating more than 1100 persons with pulmonary exposures to cobalt salts and oxides over a 30-year period was unable to show an increased mortality rate.¹¹⁰

Acute Exposure

Cardiovascular. “Beer drinker’s cardiomyopathy.” In 1966, a Veterans Affairs (VA) Hospital in Nebraska cared for 28 white men with a history of beer drinking who presented with tachycardia, dyspnea, metabolic acidosis with elevated lactate concentration, and congestive heart failure.¹⁰¹ The mortality rate for these cases was 38%, and death occurred rapidly within 72 hours of presentation, due to severe acute metabolic acidosis and cardiac failure.¹⁰¹ Of the survivors, most responded immediately to supportive care and thiamine supplementation and a lack of response was found to be secondary to complications—most commonly, symptomatic pericardial effusions or embolic events.¹⁰¹ Epidemiologic evaluation of this case series revealed that these men habitually drank large quantities of beer.

Ultimately, 64 cases and 30 fatalities were reported from Nebraska.¹⁵⁴ Of the reported 30 deaths, 26 decedents received autopsies. Common postmortem findings were dilated cardiomyopathy and cellular degeneration with vacuolization and edema with a lack of inflammation or fibrosis.¹⁰¹ When cobalt was implicated in the pathogenesis of these deaths, preserved cardiac tissue of eight decedents revealed cobalt concentrations ten times greater than that of controls.¹⁵⁴

Within a year of the Nebraska cases, reports began to emerge from Quebec.¹⁰⁸ Forty-eight beer drinkers (only two of whom were women) developed unexplained cardiomyopathy with a mortality rate of 46%.¹⁰⁸ The only association between these patients was the common consumption of “brand XXX beer”.¹⁰⁸ The producers of this beer had factories in Quebec City and Montreal. The only difference between the Nebraska brewery and the one in Quebec was that the latter added ten times the amount of CoSO_4 to the beer as a foam stabilizer.¹⁰⁶ Clinical findings in these cases included tachycardia,

tachypnea, polycythemia, and low voltage electrocardiograms (ECGs).¹⁰⁷ Cases began to appear one month after beer with the higher amount of CoSO₄ was released onto the market, and no new cases were reported in Quebec after this beer with more CoSO₄ was removed from the market.¹⁰⁶

In 1972, 20 additional cases occurred in Minneapolis with similar findings of tachycardia, dyspnea, pericardial effusion, polycythemia, and metabolic acidosis with elevated lactate concentration, and there was a mortality rate of 18% acutely and 43% over a 3-year period.⁸⁰ Similar to the previous cases, all were associated with the addition of CoSO₄ as a foam stabilizer in beer.

Since the clinical findings resemble the cardiomyopathy associated with chronic alcoholism⁴⁸ and infantile malnutrition,¹²³ a debate persists as to whether cobalt is the sole cause of this syndrome. Cardiomyopathies due to poor protein intake, vitamin deficiency, and cobalt toxicity have similar histological findings. For example, myocardial biopsy of dogs with cobalt-induced cardiac failure revealed diffuse cytosolic vacuolization, loss of cross striations, and interstitial edema,¹³⁷ all of which are similar to findings of malnutrition.^{48,123} However, some other findings may be specific to cobalt-associated cardiomyopathy. For example, a small retrospective analysis revealed myocyte atrophy and myofibril loss to be present in people with cobalt-associated cardiomyopathy significantly more often than in those with idiopathic dilated cardiomyopathy.²⁴

Some animal models of cobalt cardiomyopathy were only able to reproduce pathologic and ECG findings if cobalt and ethanol⁸ were administered, while others required protein deficiency.¹³² Contrary to these studies, several murine and canine models of cobalt poisoning demonstrated cardiac lesions,^{62,136,137} cardiac failure,^{65,136,137} and ECG abnormalities while receiving nutritional supplementation.^{63,136}

Despite the implication that cobalt-induced cardiomyopathy requires malnutrition or alcoholism, a case of cardiac toxicity following acute cobalt poisoning is reported.^{68,69} However, it is difficult to identify other cases reported outside of the aforementioned small epidemics in beer drinkers. In a controlled study of occupationally exposed subjects evaluated with echocardiograms, significantly more cobalt exposed workers had diastolic dysfunction when compared to controls.⁹¹ However, none of these subjects under study developed congestive heart failure.⁹¹ Of the few reported cases of cardiomyopathy associated with arthroplastic cobaltism, patients are typically older than those with the “beer drinker’s cardiomyopathy” cohort and their nutritional status and ethanol use are unreported.^{115,121} There are rare reports of cardiomyopathy in chronically exposed workers,^{15,30,78} which suggests that the cardiomyopathy reported in the “beer drinkers” cohort is multifactorial and not solely due to cobalt.

Another source of criticism of the role of cobalt in the development of cardiomyopathy is the relatively low dose of cobalt needed to induce heart failure in these patients.⁸⁰ In patients receiving 20 to 75 mg/d of CoCl₂ for various red cell dysplasias, there were no reports of heart failure,⁸⁰ whereas the “beer drinker’s cardiomyopathy” group reportedly consumed only 6 to 8 mg/d of CoSO₄ while drinking 24 pints of cobalt-containing beer.^{80,106} All patients who developed cardiomyopathies were malnourished, which supports the theory that a multifactorial nutritional deficiency in the presence of excessive cobalt may be necessary for the development of cardiomyopathy.⁸⁰

Endocrine. Both acute and chronic cobalt exposures are associated with thyroid hyperplasia and goiter. A series of patients with severe sickle cell anemia treated with cobalt salts developed goiter with varying degrees of thyroid dysfunction.^{64,84} including clinical hypothyroidism.⁸⁵ In one patient, the goiter was so severe that airway obstruction developed.⁸⁴

Older occupational data suggest that inhalational exposure to cobalt metals, salts, and oxides may result in abnormalities in thyroid function studies.¹⁵⁵ When 82 workers in a cobalt refinery were compared to age- and sex-matched controls, exposed workers had significantly lower T₃ concentrations.¹⁵⁵ However, more recent studies of cobalt-exposed workers in environments that limit exposure do not demonstrate any changes in serum thyroid markers.⁹⁰

Within the previously mentioned beer drinker’s cardiomyopathy cohort, 11 of 14 decedents had abnormal thyroid histology.¹³³ Among them, the most common findings were follicular cell abnormalities and colloid depletion, which did not exist on thyroid analysis from 11 randomly selected autopsies that served as controls.¹³³ Of the patients with arthroprosthetic cobaltism, one patient developed clinical hypothyroidism,¹¹⁵ and another developed subclinical hypothyroidism.¹²¹

Hematologic. Anemias of the newborn,^{28,77,125} erythrocyte hypoplasia,¹⁴¹ red cell aplasia,¹⁶¹ and kidney failure associated anemia⁵⁸ have all been successfully treated with cobalt salts. Patients undergoing CoCl₂ therapy for these diseases had increased hemoglobin,^{58,125} hematocrit,^{58,125} and red cell counts.⁵⁸ Unfortunately, the effects did not persist after cessation of therapy.^{58,125}

A published series of Peruvian cobalt miners working in an open pit at 4300 meters (2.7 miles) elevation developed various clinical effects, including headache, dizziness, weakness, mental fatigue, dyspnea, insomnia, tinnitus, anorexia,

cyanosis, polycythemia, and conjunctival hyperemia consistent with acute mountain sickness.⁷⁵ When the study group was compared to age-, height-, and weight-matched high-altitude controls, the study group was noted to have higher chronic mountain sickness scores.⁷⁵ The only difference detected was elevated serum cobalt concentrations in the study group.⁷⁵

In addition to effects on red cells, recent work demonstrates transient hemolysis, methemoglobinemia, and methemoglobinuria from subcutaneous CoCl_2 exposure in mice.⁷⁰ These findings may explain reports of dark urine following cobalt exposure in other animal models.^{60,149} However, similar human cases have not been reported.

Other. Gastrointestinal distress following the ingestion of “therapeutic” doses of cobalt salts¹³⁹ and elemental cobalt are reported.⁷⁴ Decreased proprioception, impaired VIII cranial nerve function, and nonspecific peripheral nerve findings are reported with acute oral CoCl_2 exposures.¹³⁹ Patients with arthroprosthetic cobaltism are reported to have seizures, cerebellar deficits, retinopathy, hearing loss, cognitive deficits, and peripheral neuropathy; some of which had concomitant elevations of cerebrospinal fluid (CSF) cobalt concentrations.^{23,97,115,156,157}

Chronic Exposure

Pulmonary. Both asthma and “hard metal disease” are associated with cobalt exposure. Occupational asthma is reported in hard metal workers with a prevalence of 2% to 5%^{26,87,88} at exposure concentrations as low as $50 \mu\text{g}/\text{m}^3$.³⁸⁸ As is the case with most causes of occupational asthma, cobalt hypersensitivity-induced asthma is most likely immune mediated rather than toxicologic.^{29,87,147} Most hard metal workers are exposed to other metals, such as tungsten (W) and nickel (Ni), in addition to Co, and these other metals may account for some of the occupational asthma that is attributed to cobalt.^{144,146} However, in a small but well-performed study in patients with cobalt-associated asthma, intradermal cobalt chloride (CoCl_2) resulted in a positive wheal response in all subjects, and 50% of patients had a positive radioallergosorbent test (RAST) scores, which correlated to the wheal size¹⁴⁵ and suggests Co salts can illicit an immune response independent of the other metals.

Cobalt-associated pulmonary toxicity was first noted in tungsten-carbide workers^{46,66} and was subsequently referred to as “hard metal disease.” Exposures result from the process by which tungsten-carbide is sintered with cobalt. Signs and symptoms of hard metal disease may include upper respiratory tract irritation, exertional dyspnea, severe dry cough, wheezing, and interstitial lung disease ranging from alveolitis to progressive fibrosis. The prevalence of hard metal disease is largely unknown. In one study, 11 of 290 (3.8%) exposed workers were diagnosed with interstitial infiltrates on chest radiographs, but only 2 (0.7%) had a decrease in predicted total lung capacity.¹⁵⁰

Certain individuals who are exposed to large doses of hard metals for prolonged periods never develop disease, which suggests that a susceptible population exists. A glutamate substitution for lysine in position 69 of the β unit HLA-DP has a strong association with hard metal disease, similar to chronic beryllium disease.¹²⁴ Clinically, hard metal disease is difficult to distinguish from berylliosis, although an occupational history should be helpful.

Histopathologic findings of hard metal disease include multinucleated giant cells and interstitial pneumonitis with bronchiolitis.⁹ Elevated concentrations of cobalt in lung tissue can be detected,^{129,148} even as long as 4 years after exposure.¹²⁹ In patients with interstitial lung disease, bronchioalveolar lavage (BAL) commonly reveals multinucleated giant cells, type II alveolar cells, and alveolar macrophages.³² The finding of multinucleated giant cells from BAL washing is characteristic of hard metal disease.^{29,35,36,102,159}

A cross-sectional study of more than a 1000 tungsten carbide-exposed workers found an increased odds ratio of 2.1 for having a work-related wheeze when exposed to greater than $50 \mu\text{g}/\text{m}^3$ of Co.¹⁵¹ In the same study, workers with exposures recorded at greater than $100 \mu\text{g}/\text{m}^3$ had higher odds (OR 5.0) of having a chest radiograph profusion score of greater than or equal to 1/0.¹⁵¹ This profusion score, established by the United Nations agency, the International Labor Organization (ILO), is a grading system for pneumoconioses. When used to grade radiographs of asbestosis, this score correlates strongly with mortality risk,¹⁰⁰ reduced diffusing capacity, and decreased ventilatory capacity.^{67,111} A score of 0/1 is suggestive but not diagnostic (“negative”), and a score of 1/0 is presumptively diagnostic but not unequivocal (“positive”).⁵ Additional studies have similarly concluded that pulmonary disease occurs when individuals are exposed to concentrations of cobalt that approach $100 \mu\text{g}/\text{m}^3$.⁸⁶ Thus, with a margin of safety, the current threshold limit value is less than $50 \mu\text{g}/\text{m}^3$.

Until 1984, all reported cases of hard metal disease were associated with the combination of cobalt and other metals, such as nickel, cadmium and tungsten.^{9,66,88,151} When diamond polishers initiated the use of high-speed grinding disks coated with abrasive microdiamonds embedded in a matrix of cobalt powder, case reports ensued demonstrating similar clinical⁸⁹ and pathologic findings to hard metal disease, strengthening the association with cobalt.^{29,35,113} Some authors still contend that the presence of other metals^{9,66,88,151} and diamond dust^{35,59,113} are confounding factors.¹⁵⁵ Like hard metal disease, most reported cases show resolution of symptoms upon removal from the exposure,³⁵ although this is not always sufficient.¹¹³

There are very few reports of isolated cobalt exposures. In an age- and sex-matched study of 82 workers with respiratory exposures to cobalt oxides, cobalt salts, cobalt metal, and no other metal, researchers were unable to detect a difference between exposed (mean of 8 years, time weighted average = $125 \mu\text{g}/\text{m}^3$, 25% $>500 \mu\text{g}/\text{m}^3$) and unexposed workers with any objective measured pulmonary tests.¹⁵⁵ Neither group had any abnormality in chest radiography that would suggest pulmonary fibrosis.¹⁵⁵ The only significant pulmonary differences detected were a higher reported rate of dyspnea both on exertion and at rest and the presence of wheezing in the exposed group.¹⁵⁵ These authors concluded that cobalt contributes to the development of pulmonary disease but is not independently responsible for the development of pulmonary fibrosis.¹⁵⁵

Despite the progressive and debilitating nature of hard metal disease, most signs and symptoms improve with cessation of exposure.^{98,103,168} Moreover, the length and dose of exposure do not appear to correlate with the presence or severity of illness suggesting that individual susceptibility is the key determinant for developing illness.^{98,135}

Arthroprosthetic Cobaltism. It has been known for some time that metal-on-metal alloy orthopedic implants result in elevation of the associated metals in blood, urine, and hair.²⁷ Serum concentrations of cobalt become elevated 3 weeks after surgery and remain elevated through a 5-year study period, which contradicts earlier theories of elevated concentrations being related to the life of the implant.²⁰ Despite the elevation of both chromium and cobalt in measured samples, it appears that the constellation of findings is more consistent with cobalt rather than chromium.¹ However, chromium's toxicity may present in a more delayed fashion relative to cobalt.¹ Reported cases of toxicity can follow revisions, dislocations, or first-time arthroplasties of cobalt-containing prosthetics.^{97,156,157} Since these findings have been reported, the association of having a cobalt-containing prosthetic, an elevated marker of cobalt burden, and findings of end-organ toxicity has been coined "arthroprosthetic cobaltism."

Of the reported cases, some of arthroplasties have had excessive wear¹¹⁵ or have been placed following a ceramic arthroplasty resulting in metallosis.¹⁰⁰ In one case, a patient developed hypothyroidism, seizures, peripheral neuropathy, and cardiomyopathy.¹¹⁵ Unfortunately, the diagnosis was not established initially, and the hip revision resulted in improvement of serum cobalt concentrations and thyroid markers but the patient had permanent neurologic sequelae.¹¹⁵ Furthermore, one patient with cobaltism with evidence of cardiac tamponade, hypothyroidism, hearing loss, and polycythemia underwent implant removal and chelation with 2,3-dimercaptopropane-1-sulfonate, which resulted in decreased blood cobalt concentrations but permanent hearing loss.¹²¹ However, other case reports of metallosis from cobalt arthroplasties suggest clinical manifestations of cobaltism improve following revision.^{156,157} It appears that lumbar metal-on-metal total disk replacements are associated with smaller elevations in serum cobalt concentrations when compared to hip resurfacing or total hip arthroplasties,¹⁹ but there are no reported cases of clinical cobaltism with lumbar implants. Finally, within this cohort, retinal effects have been noted in at least two case reports.^{10,11} The pathophysiology of these cases is poorly understood and confounded by comorbidities typical in this cohort of patients.

Renal. A single report associates reversible acute kidney injury with the chronic administration of CoCl_2 as treatment for anemia.¹³⁹ Some animal models of cobalt cardiomyopathy demonstrate cellular changes in renal tissue.⁶¹ However, when 26 exposed hard metal workers were evaluated for urinary albumin, retinol binding protein, β_2 -microglobulin, and tubular brush border antigens no detectable differences could be found between the study group and controls.⁵⁴ Additionally, patients with cobalt-containing total hip arthroplasties were followed over 2 years with elevated serum cobalt concentrations without any significant effect on serum creatinine over this study period.¹⁴ Based on these few reports, it appears that acute and chronic exposure to cobalt has little effect on the kidneys.

Dermatology. In a study of 1782 construction workers, 23.6% developed dermatitis and 11.2% developed oil acne while using cobalt-containing cement, fly ash, or asbestos.⁸¹ As in hard metal disease, it is difficult to isolate cobalt as the sole contributor to the development of dermatitis. Nickel (Chap. 99) is the classic toxicant causing dermatitis. Commonly found in some of these construction occupations, it may be implicated in the development of cutaneous manifestations.^{50,134} However, consumer products such as piercings, tattoo ink, plastics, clothing dye, makeup, and dental treatments are implicated in cobalt-induced allergic contact dermatitis.⁵³ Furthermore, in vitro studies demonstrate that cobalt can induce production of both Th1- and Th2-type cytokines in peripheral blood mononuclear cells—the same pathway implicated in nickel contact dermatitis.¹⁰⁴ Thus, it appears that cobalt can independently induce a hypersensitivity reaction independent of the presence of nickel.

Reproduction. In pregnant rats, CoCl_2 exposure neither results in teratogenicity nor fetal toxicity.¹¹⁹ In a case report of a pregnant woman with hard metal disease, the woman was able to bring the pregnancy to term and deliver without complication.¹²⁷ In another case report, a woman with a cobalt-containing hip arthroplasty had repeated joint aspirations, dislocations, and revisions before and during her pregnancy.⁵⁶ Cobalt concentrations of this mother were 138 to $143 \mu\text{g}/\text{L}$ throughout the pregnancy, cord blood concentration was $75 \mu\text{g}/\text{L}$, and infant blood concentration at 8 weeks was $13 \mu\text{g}/\text{L}$. Despite these elevated concentrations, there was no clinical evidence of toxicity.⁵⁶ It is hypothesized that only exposures

toxic to the mother result in fetal toxicity.⁴²

In mice, chronic exposure to cobalt results in impaired spermatogenesis and decreased fertility without affecting follicular stimulating hormone or leuteinizing hormone, whereas acute exposures did not demonstrate similar reproductive effects.¹²⁰ Additional murine studies discuss the possible interactions between cobalt with iron and zinc, which are both essential elements for spermatogenesis.⁶ Despite these findings, there are no reported human cases that associate cobalt exposure with teratogenicity or impaired fertility.

Carcinogenesis. Animal experiments with injection of CoCl_2 into soft tissue resulted in soft tissue sarcomas, leading the International Agency for Research on Cancer (IARC) to consider cobalt metal without tungsten carbide and cobalt sulfate and other soluble cobalt (II) salts possibly carcinogenic to humans (group 2B).^{18,33,44,152,167} It was suggested that cobalt metal associated with tungsten carbide was probably carcinogenic to humans (group 2A).¹⁶⁷ There are case reports and cohort studies that suggest that pulmonary exposure to Co^{2+} increases the risk of lung cancer. However, these studies were unable to control for other known carcinogens such as arsenic.³³ In the largest cohort study to date, which followed more than 1100 workers for more than 38 years, there was no increase in the prevalence of lung cancer.¹⁰⁹

DIAGNOSTIC TESTING

Body fluid cobalt concentrations are not readily available and therefore cannot be used to direct emergent clinical care. Some adjunctive testing that may support a clinical diagnosis of cobalt toxicity should include a complete blood count (CBC), reticulocyte count, erythropoietin (EPO) concentration, and thyroid-stimulating hormone (TSH) concentration. The results of these tests may reflect the level of exposure or potential toxic manifestations.

Cardiac Studies

ECG, echocardiogram, and radionuclide angiocardigraphy with ⁹⁹Tc(RNA) are useful screening tests for detecting abnormalities associated with cobalt cardiomyopathy and/or pulmonary hypertension due to hard metal disease.³⁰ It is important to remember that these cardiac tests are neither specific nor diagnostic of cobalt-induced cardiomyopathy.

Pulmonary Testing

Patients with hard metal lung disease may demonstrate bilateral upper lobe interstitial lung disease on chest radiograph. However, patients may have signs and symptoms of disease without specific radiographic findings.¹²⁷ Pulmonary function testing in occupationally exposed workers may show decreased vital capacity¹²⁷ and a decrease in transfer factor for carbon monoxide, both of which may be useful in identifying patients at risk for developing pulmonary fibrosis.¹⁵⁴ Some authors suggest an inversion of CD4/CD8 ratio in BAL washings as a useful tool for diagnosis and evaluation of progression of illness and that normalization is a marker for improvement.¹²⁸ Despite these available tests, a definitive diagnosis of hard metal disease requires a tissue sample with findings of multinucleated giant cells in the setting of interstitial pulmonary fibrosis.

Cobalt Testing

Cobalt, as stated above, is primarily eliminated in the urine and to a lesser extent in the feces making urine cobalt evaluation most appropriate.⁹³ The difficulty lies in the interpretation of the result. Cobalt is detectable in the urine after inhalational exposure and reflects elimination kinetics that are rapid during an initial exposure but slow after prolonged exposure.^{93,138} Due to this variable elimination pattern, it is difficult to interpret both urine and blood concentrations unless the dose and length of exposure are precisely known. Furthermore, the defined patterns may be applicable only to shift workers utilizing soluble forms of cobalt.⁹³

Further complicating the interpretation of urinary cobalt concentrations is the abundance of organic cobalt in the form of vitamin B₁₂. A detailed vitamin supplementation history is required prior to the interpretation of a urine or blood cobalt concentration, as a diet regimen high in vitamin B₁₂ may increase urine cobalt concentrations. For this reason, speciation of cobalt has been investigated. The ratio of inorganic to organic cobalt is higher in occupationally exposed workers (2.3) when compared to controls (1.01), independent of the wide variations of urinary cobalt concentrations.⁵⁷ This is a promising area of study for the evaluation of cobalt exposed workers.

Toxic concentrations of cobalt in serum and urine are poorly defined. Published literature on “normal values” is fraught with variability, which may reflect differences in the population under study techniques for measurement. Normal serum concentrations of cobalt are frequently reported as 0.1 to 1.2 $\mu\text{g/L}$.^{3,16,68,69,72,143} In comparison, a single acutely poisoned patient had a reported serum concentration of 41 $\mu\text{g/L}$.⁶⁸ In the “arthroprosthetic cobaltism” group, serum cobalt concentrations ranged from 24 to 625 $\mu\text{g/L}$.^{56,98,116,122,157} In contrast, several case series of metal-on-metal hip arthroplasties and resurfacings demonstrate peak serum cobalt concentration not to exceed that of 11.5 $\mu\text{g/L}$ barring one outlier of 35 $\mu\text{g/L}$ at 1 year postprocedure.^{14,19,20} Based on this data, some recommend that the risk of “arthroprosthetic

cobaltism” be suspected when serum cobalt concentrations exceed 10 µg/L.¹⁵⁷

Normal reference urine cobalt concentrations are between 0.1 and 2.2 µg/L.^{3,16,68,69,72,118,143} In contrast, an acute elemental cobalt ingestion resulted in a concentration of 1700 µg/L on a spot urinalysis several days after the exposure.⁶⁹ In the “arthroprosthetic cobaltism” cases, one patient had a urine cobalt concentration of 16,500 µg/L.¹¹⁵

Chronic exposures should be evaluated differently as discussed above (see Toxicokinetics). Exposed workers, without clinical disease, have reported spot urine concentrations that range from 10 µg/L to several hundred µg/L.⁷¹

TREATMENT

Acute Management

Patients with acute cobalt poisoning require aggressive therapy. It is reasonable to conclude that the same decontamination principles used for other metals apply to cobalt. There have been no studies examining the benefit of gastric emptying, activated charcoal, or whole bowel irrigation. An attempt of whole-bowel irrigation for radiopaque solid forms of cobalt should be made prior to endoscopic or surgical removal. Regardless of the decontamination procedure utilized, chelation therapy should not be initiated until the gastrointestinal cobalt source has been removed. If there is a large stomach burden in solid form, endoscopic or surgical removal may be of benefit,⁶⁹ keeping in mind that the administration of activated charcoal prior to surgical removal may obscure visualization of the surgical field (Chap. 8). After decontamination, reduction of tissue burden and prevention of end-organ toxicity is the next crucial step.

The data on chelation therapy is unfortunately limited to animal models^{37–42,94–96} and human case reports.^{69,121} The basis of chelation therapy originates from the mid 1900s when oral protein intake was found to result in a reduction of cobalt toxicity in calves⁴⁵ and rats.⁶² Certain sulfur containing proteins serve as good chelators for some transition metals.

In a series of animal models of acute cobalt toxicity, several agents N-acetylcysteine (NAC), succimer, ethylenediaminetetraacetic acid (EDTA), glutathione, and diethylenetriaminopentaacetic acid (DTPA) were evaluated for their ability to enhance urinary and fecal elimination of cobalt.⁹⁶ Succimer and EDTA were able to enhance fecal elimination.⁹⁶ Glutathione and DTPA were able to enhance urinary elimination, and NAC was able to enhance elimination by both routes.⁹⁶

In two separate animal studies, NAC reduced tissue burden and injury due to cobalt in the liver and spleen.^{41,96} Glutathione, another sulfur-containing protein, also reduced tissue concentrations of cobalt but only in the spleen.⁹⁶

The sulfur-containing proteins, NAC,^{38,41} L-cysteine,^{37,38} L-methionine,³⁸ and L-histidine,⁴² were studied for their ability to reduce mortality in rats that were administered an LD₅₀ of CoCl₂ orally and intraperitoneally. Therapies with NAC, L-cysteine, and L-histidine⁴² are more effective than L-methionine in protecting against mortality, upward of 100% protection. In a similar fashion, Na₂EDTA effectively reduced mortality.⁴⁰ In all these therapies, the successful reduction in mortality from these therapies is predicated on its early administration.^{37,38,40–42}

In a murine model, L-cysteine, NAC, glutathione, L-histidine, sodium salicylate, D,L-penicillamine, succimer, N-acetylpenicillamine (NAPA), diethyldithiocarbamate (DDC), BAL, 4,5-dihydroxy-1,3-benzene disulfonic acid, Na₃CaDTPA, Na₂CaEDTA, and deferoxamine mesylate were each evaluated for exposures to an LD₅₀ and an LD₉₉ of CoCl₂.⁹⁵ Sodium salicylate, NAPA, DDC, BAL, 4,5-dihydroxy-1,3-benzene disulfonic acid, and deferoxamine mesylate were all ineffective at improving survival following an LD₅₀.⁹⁵ Chelators that were seemingly effective at an LD₅₀ and not at an LD₉₉ were L-histidine and D,L penicillamine.⁹⁴ NAC, L-cysteine, and succimer were able to improve survival by 40% to 50%.⁹⁵ The most effective chelators at LD₉₉ were EDTA and DTPA.^{94,95} An expanded analysis of these data revealed that EDTA and DTPA had a better therapeutic index when compared to succimer.⁹⁵ In this study, BAL was ineffective as is suggested in an in vitro study where BAL was unable to chelate Co²⁺ that is already bound to α-ketoglutarate.¹⁶³

Human chelation data are available from two case reports.^{69,121} In the first, a child ingested multiple elemental cobalt containing magnets yielding a serum cobalt concentration of 41 µg/L.⁶⁹ Five days of 50 mg/kg/d of intravenous CaNa₂EDTA enhanced renal elimination of cobalt, and the patient’s metabolic acidosis and the cardiac dysfunction also resolved simultaneously.⁶⁹ In the second, a 56 year-old man developed “arthroprosthetic cobaltism” with elevated serum (506 µg/L) and CSF concentrations (8.5 µg/L) of cobalt and evidence of hypothyroidism, cardiomyopathy with pericardial effusion, polycythemia, and both central and peripheral neuropathy.¹²¹ Unlike the previous case report, this patient was treated 2,3-dimercaptopropane-1-sulfonate (DMPS) at a dose of 14 mg/kg for 6 days and followed by 4 mg/kg for 5 days for a total of 10 g of antidote. The authors were able to demonstrate a 26% reduction in serum cobalt concentrations 1 month following treatment.¹²¹ However, despite removal of the prosthesis and chelation therapy, the patient had permanent

hearing loss and a persistently elevated serum concentration.¹²¹ This permanent hearing loss and persistently elevated serum concentration are most likely due to a delay of 7 months from onset of symptoms and metallosis of tissue to treatments.

In conclusion, based on a single human case report, several animal studies and safety profiles, CaNa_2EDTA and NAC can be used as antidotal therapy. Indications for treatment should include patients who demonstrate end-organ manifestations of toxicity. This includes metabolic acidosis and cardiac failure. Other manifestations of severe cobalt toxicity such as pericardial effusion, clinically significant goiter, and hyperviscosity syndrome should be treated aggressively with pericardiocentesis, airway protection, and phlebotomy, respectively. Based on years of experience with lead, CaNa_2EDTA should be administered as doses of 1000 mg/m²/d by continuous infusion for 5 days. If the diagnosis is confirmed and signs of cardiac failure and metabolic acidosis persist after 5 days, an alternate chelator (succimer or DTPA) can be started. Similarly, NAC dosing should be based on the acetaminophen (APAP) experience. The 20 hour intravenous NAC protocol should be initiated and continued as in the case of fulminant hepatic failure (Antidotes in Depth: A3) for as long as the patient can tolerate therapy or continued if cardiac failure or acidemia persists. If there are contraindications to intravenous NAC, oral NAC can be administered using one of the APAP treatment regimens. Thiamine hydrochloride should be administered to all patients presenting with or without overt cardiomyopathy independent of whether the patient is alcoholic or malnourished. The dose of thiamine is not well defined but should be based on its safety and clinical experience with the treatment of Wernicke encephalopathy. The daily administration of 100 mg of parenteral thiamine can be initiated with increasing doses to 100 mg every hour for life threatening manifestations (cardiac failure and metabolic acidosis) (Antidotes in Depth: A24).

Arthroplasty Cobaltism

It appears that clinical symptoms and serum cobalt reduction respond well to arthroplasty revision^{115,121,156} and potentially chelation therapy.¹²¹ The key to treatment of this entity is early clinical suspicion with the constellation of findings of cardiomyopathy, hypothyroidism, polycythemia, and peripheral and central nervous system impairment. Early arthroplastic revision supports the decontamination tenets within this text and published in case reports,^{115,121,156} however, emergent revisions may not be practical in an acutely ill patient. Therefore, the only modality of treatment other than supportive may be chelation. However, based on limited literature, it is unclear if chelation in the presence of a large reservoir of metal can mobilize cobalt. However, the single case report of DMPS treatment for a patient with “arthroprosthetic cobaltism” (including cardiomyopathy, neurologic derangements, hypothyroidism, and polycythemia) was able to demonstrate a decrease in serum cobalt concentration and an increase in urinary cobalt concentration postchelation.¹²¹

Occupational/Chronic Exposure

As is always the case of occupational poisonings, prevention is of paramount importance. The utilization of skin and respiratory protection and improvement of personal hygiene has reduced exposure and subsequently the amount of urinary cobalt in occupationally exposed workers.⁹² Barrier and emollient creams cannot prevent the dermatitis associated with cobalt metal exposures.⁵¹

Large statistically significant reductions in urinary cobalt concentrations were demonstrated after the implementation of aspirator systems over machines in the production of Widia-steel.²⁵ These aspirators were found to reduce ambient cobalt concentrations by as much as a factor of six.⁴⁷

SUMMARY

- Acute cobalt toxicity results in multiorgan system toxicity, including the cardiac, endocrine, hematopoietic, gastrointestinal, and neurologic systems.
- Arthroprosthetic cobaltism is unique in that there is a large reservoir of metal, and the clinical presentation may be subacute and mistaken for other disease processes.
- The evaluation and treatment of all patients will be determined by the cobalt source and type (elemental, inorganic, or organic), route of poisoning, and time and duration of exposure.
- Treatment of patients with chronic occupational exposures to cobalt is mainly symptomatic and is often dependent on improved industrial hygiene and removal from the source.
- Acute poisoning with end organ manifestations may require aggressive gastrointestinal decontamination and chelation therapy utilizing CaNa_2EDTA and NAC, and at times, succimer.

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95 COPPER

Lewis S. Nelson

Copper (Cu)

Atomic number = 29

Atomic weight = 63.5 Da

Normal concentrations

Whole blood = 70–140 µg/dL (11–22 µmol/L)

Total serum = 120–145 µg/dL (18.8–22.8 µmol/L)

Free serum = 4–7 µg/dL (0.63–1.1 µmol/L)

Ceruloplasmin = 25–50 µg/dL (3.9–7.8 µmol/L)

Urine = 5–25 µg/24 h (0.078–3.9 nmol/L)

HISTORY AND EPIDEMIOLOGY

Copper exists naturally, either as native copper (elemental copper, Cu⁰) or as one of its sulfide or oxide ores. Important ores include malachite (CuCO₃·(OH)₂), chalcocite (Cu₂S), cuprite (Cu₂O), and chalcopyrite (CuFeS₂ or Cu₂S·Fe₂S₃).

Chalcopyrite, a yellow sulfide ore, is the source of 80% of the world's copper production. The smelting, or separation, of copper ores began about 7000 years ago; copper gradually assumed its current level of importance at the start of the Bronze Age, around 3000 BC. Smelting begins with roasting to dry the ore concentrate, which, in more modern times, is further purified by electrolysis to a 99.5% level of purity. The sulfide ores have a naturally high arsenic content, which is released during the extraction process, posing a risk to smelters.

Although acute copper poisoning is uncommon in the United States, the historical therapeutic role of copper remains noteworthy. Copper sulfate was used in burn wound débridement until cases of systemic copper poisoning were reported.⁵¹ Interestingly, in one report, each wound débridement procedure was associated with an 8% to 10% fall in the patient's hematocrit. In the 1960s, copper sulfate (250-mg dose, containing 100 mg copper ion) ironically was recommended as an emetic agent, typically for use in children following potentially toxic exposures.⁶⁰ It was recognized for its rapidity of onset and effectiveness, and it compared favorably with syrup of ipecac. However, copper-induced emesis was rapidly identified as a highly dangerous practice, and this use was generally discontinued,^{68,111} although fatal cases still occur. Copper salts are administered in religious rituals as a green-colored “spiritual water,” containing 100 to 150 g/L of copper sulfate as an emetic to “expel one's sins.”^{5,110}

There is a growing body of knowledge linking copper to the promotion of both physiologic and malignant angiogenesis.⁴⁷ In this latter case, copper may enable tumor expansion, invasion, and metastasis. Additionally, copper binding to amyloid fibers in the brains of patients with Alzheimer disease may lead to local oxidative damage and cause the characteristic neurodegeneration.¹⁹ Copper is also similarly implicated in the pathogenesis of both Parkinson disease and autism.^{22,126}

Acute or chronic copper poisoning can occur when the metal is leached from copper pipes or copper containers. This occurs frequently when carbon dioxide gas, used for postmix soft drink carbonation, backflows into the tubing transporting water to the soda dispensers, creating an acidic solution of carbonic acid that leaches copper from the equipment pipes.¹²² Similarly, storage of acidic potable substances, such as orange or lemon juice, in copper vessels may cause copper poisoning. A particularly dangerous situation occurs when acidic water is inadvertently used for hemodialysis.^{35,74} In this circumstance, the leached copper avoids the normal gastrointestinal barrier and is delivered parenterally to the patient's circulation. In one reported series, the copper concentration in the dialysis water was 650 µg/L, causing several poisonings and the death of a patient with a whole-blood copper concentration of 2095 µg/L.³⁶ Similarly, stagnant water or hot water,¹⁰⁰ even if not highly acidic,¹⁰⁴ can accumulate copper ions from pipes and cause poisoning.^{7,36}

Although most natural water contains a small quantity of copper (4–10 µg/L), it is tightly bound to organic matter and therefore not orally bioavailable. Copper pipes typically add about 1 mg of copper to the daily intake of an adult. The

Environmental Protection Agency guidelines permit up to 1.3 mg/L of copper in drinking water,²⁹ although in some areas intermittent concentrations may rise as high as 60 mg/L.

Metallic copper is ideal for electrical wiring because it is highly malleable and can be drawn into fine wire. Its electrical conductivity is only exceeded by silver. Similarly, its excellent heat conductivity accounts for its widespread use in cookware. Although the metal is reactive with air, it forms a resistant layer of insoluble copper carbonate on its surface. It is this water-and air-resistant compound that accounts for the green coloration of ornamental roofing and statues. Because copper is a soft metal, it must be strengthened prior to use in structural applications or as a coinage metal. This is most commonly done by the creation of copper alloys. Brass is an alloy of copper compounded with as much as 35% zinc. Similarly, bronze contains copper combined with up to 14% tin. Gun metal is an alloy that contains 88% copper, 10% tin, and 2% zinc. Sterling silver and white gold also contain copper.

CHEMICAL PRINCIPLES

Metallic copper (Cu^0), although not in itself poisonous, may react in acidic environments to release copper ions. The metallic copper contraceptive intrauterine device derives its efficacy from the local release of copper ions.¹⁴ Metallic copper bracelets, worn by patients with rheumatoid arthritis and other ailments, purportedly derive their far-reaching antiinflammatory effect through dermal copper ion absorption and distribution to affected tissues.¹¹⁹ Local copper ion release is responsible for the occasional case of dermatitis that occurs following skin exposure to copper metal.⁵² Ingestion of large amounts of metallic copper (eg, as coins) may rarely produce acute copper poisoning.^{95,125} Poisoning under these circumstances is a result of the release of large amounts of copper ion from copper alloy by the acidic gastric contents. Also, inhalation of finely divided metallic copper dust or bronze powder, used in industry and for gilding, may produce life-threatening bronchopulmonary irritation, presumably as a consequence of the local release of ions.^{34,45}

The majority of patients suffering from acute copper poisoning are exposed to ionic copper. In copper sulfate, also known as cupric sulfate, the copper atom is in the +2 oxidation state. Copper sulfate is used as a fungicide and algicide, and to eradicate tree roots that invade septic, sewage, and drinking water systems.⁹³ Copper sulfate is the most readily available form and is the form involved in the majority of nonindustrial copper salt exposures. Copper sulfate was a favorite ingredient in many home chemistry sets because of its brilliant blue color when dissolved in water. Although serious poisoning, particularly in children, led regulatory agencies in the United States to restrict its use, it accounts for the most consequential chemistry set-related toxic exposures reported in other countries.⁷⁹ Similarly, homegrown copper sulfate crystals from kits are occasionally responsible for fatal poisonings.⁴³

Cuprous salts, containing copper in the +1 oxidation state, are unstable in water and readily oxidize to the cupric form. There are numerous copper salts with varying oxidation states used in industry and agriculture (Table 95–1), many of which are not poisonous. Because those salts that are water soluble are more likely to be toxic, it is important to determine the nature of the copper product implicated in an exposure. Analogously, when examining the medical literature, it is critical to discern which form of copper is involved in the scientific experiment or case report before applying the results to clinical practice.

TABLE 95–1. Important Copper Products

Chemical Name	Chemical Structure	Common Name	Notes
Chalcopyrite	CuFeS_2	Copper iron sulfide	Copper ore; source of 80% of world's copper
Chromated cupric arsenate	35% CuO 20% CrO_3 45% As_2O_3	CCA	Wood preservative ^a
Copper octanoate	$\text{Cu}[(\text{CH}_3(\text{CH}_2)_6\text{COO})_2]$	Copper soap	Fungicide in home garden products, paint, rot-proof rope, and roofing
Copper triethanolamine complex	$\text{Cu}[(\text{HOCH}_2\text{CH}_2)_3\text{N}]_2$	Chelated copper	Algicide
Cupric acetoarsenite	$\text{Cu}(\text{C}_2\text{H}_3\text{O}_2)_3 \cdot 3\text{Cu}(\text{AsO}_2)_2$	Paris or Vienna green	Insecticide, wood preservative, pigment ^a
Cupric arsenite	CuHAsO_3	Swedish or Scheele's green	Wood preservative, insecticide ^a
Cupric hydroxide	$\text{Cu}(\text{OH})_2$	Copper hydroxide	Fungicide
Cupric chloride	CuCl_2		Catalyst in petrochemical industry
Cupric chloride, basic	$\text{CuCl}_2 \cdot 3\text{Cu}(\text{OH})_2$	Basic copper chloride; copper oxychloride	Fungicide
Cupric oxide	CuO	Black copper oxide; tenorite	Glass pigment, flux, polishing agent
Cupric sulfate	CuSO_4	Roman vitriol, blue vitriol, bluestone, hydrocyanite	Fungicide, plant growth regulator, white-wash, homegrown crystals
Cupric sulfate, basic	$\text{CuSO}_4 \cdot 3\text{Cu}(\text{OH})_2 \cdot 3\text{CaSO}_4$	Bordeaux solution	Fungicide
Cuprous cyanide	CuCN	Cupridin	Electroplating solutions
Cuprous oxide	Cu_2O	Red copper oxide, cuprite	Antifouling paint

^aNo longer used in the United States.

PHARMACOLOGY AND PHYSIOLOGY

Copper is an essential metal that our body stores in milligram amounts (100–150 mg). Daily requirements of copper are approximately 50 µg/kg in infants and 30 µg/kg in adults. The average daily intake of copper in the United States noted in NHANES III is about 1.2 mg.³⁷

The daily requirement is satisfied by nuts, fish, and green vegetables such as legumes, although our largest source is generally from drinking water. Copper deficiency is exceedingly rare even in the poorest communities and is most frequently acquired through the excessive zinc intake.⁸³ There are genetic aberrations, such as Menkes “kinky-hair” syndrome, in which intestinal copper uptake is impaired. Menkes syndrome is characterized by mental retardation, thermoregulatory dysfunction, hypopigmentation, connective tissue abnormalities, and pili torti (kinky hair). Interestingly, with the increased focus on the role of copper in neurodegenerative disorders and cancer, some authors suggest intentionally depleting patients of their copper stores with tetrathiomolybdate, an experimental copper chelator.⁴⁰

Copper is absorbed by an active process involving a copper adenosine triphosphatase (CuATPase, also known as the Menkes ATPase) in the small intestinal mucosal cell membrane (see below). The gastrointestinal absorption varies with the copper intake and the food source,⁴⁸ and is as low as 12% in patients with high copper intake. In the presence of damaged mucosa, such as following acute overdose, the fractional absorption is likely to be significantly higher.⁶⁹ Once absorbed, copper is rapidly bound to high-affinity carriers, such as ceruloplasmin, and low-affinity carriers, such as albumin, for transport to the liver and other tissues.¹²⁰ Under normal circumstances the amount of unbound copper in the blood is well below 1%. After being released locally in the reduced form from its carrier, copper uptake by the hepatic cells occurs via a specific uptake pump.⁹⁷ This process, which is facilitated by the reducing agent ascorbic acid, provides a potential window, however brief, for detoxification of the ion by chelating agents. In acute overdose, a high fraction of the plasma copper remains bound to low-affinity proteins, such as albumin, and thus is biologically active.

In the hepatocyte, complex trafficking systems exist (involving ceruloplasmin, metallothionein, and other metallochaperones within the cytoplasm) to prevent copper toxicity and to aid delivery to the appropriate enzymes.⁹⁴ A distinct Cu-ATPase, located on certain subcellular organelles such as the trans-Golgi network or pericanalicular lysosomes, assists in the appropriate localization and elimination, respectively, of the metal.¹²¹ By this mechanism, copper

is either incorporated into enzymes or released, as a metallothionein–copper complex, directly into the biliary system for fecal elimination.

Some copper released from the liver is bound primarily to ceruloplasmin, an α_2 -sialoglycoprotein with a molecular weight of 132,000 Da. Ceruloplasmin-bound copper accounts for approximately 90% to 95% of serum copper. Ceruloplasmin is a multifunctional protein that binds 6 atoms of copper per molecule. Copper bound to this carrier has a plasma half-life of approximately 24 hours. Ceruloplasmin is also involved in the mobilization of iron from its storage sites, and it serves an analogous role as a ferroxidase during the ferrous–ferric conversion. Cu^+ is oxidized directly by ceruloplasmin, thereby avoiding the generation of reactive oxygen species.

There are several important copper-containing enzymes in humans (Table 95–2). The common link among these enzymes is their participation in reduction-oxidation (redox) reactions in which a molecule, typically oxygen, donates or shares its electrons with another compound. In this respect, the physiology, chemistry, and toxicology of copper are most similar to that of iron. In fact, “blue-blooded” animals, such as octopi and spiders, use copper in hemocyanin, a blue pigment, in an analogous manner that “red-blooded” animals use iron in hemoglobin.

TABLE 95–2. Important Copper-Containing Enzymes and Proteins and Their Functions

<i>Enzyme or Protein</i>	<i>Function</i>
Alcohol dehydrogenase	Metabolism of alcohols
Catalase	Detoxifies peroxide
Ceruloplasmin enzymes	Copper transport, ferroxidase
Cytochrome C oxidase	Electron transport chain
Dopamine β -hydroxylase	Converts dopamine to norepinephrine
Factor V	Coagulation cascade
Lysyl oxidase	Cross links collagen and elastin
Monoamine oxidase	Deamination of primary amines
Superoxide dismutase	Detoxifies free radicals
Tyrosinase	Melanin production

The volume of distribution of copper is 2 L/kg and the $t_{1/2}$ of erythrocyte copper is 26 days. The elimination of copper occurs predominantly through biliary excretion following complexation with ceruloplasmin. Biliary excretion approximates gastrointestinal absorption and averages 2000 $\mu\text{g}/24\text{ h}$.⁹⁴ Renal elimination under normal conditions is trivial, accounting for approximately 5 to 25 $\mu\text{g}/24\text{ h}$.

Copper in water may be tasted at concentrations of 1 to 5 mg/L, and a blue-green discoloration is imparted when the concentrations are greater than 5 mg/L.³³ Acute gastrointestinal effects occurs when drinking water contains more than 25 mg/L,⁵³ although concentrations as low as 3 mg/L are associated with abdominal pain and vomiting in many, without a rise in the serum copper concentrations.⁹² In one blinded, randomized study comparing copper-adulterated water to pure water, women appeared more sensitive than men to copper, but both groups were symptomatic when the copper concentration in the water was 6 mg/L.⁶

TOXICOLOGY AND PATHOPHYSIOLOGY

Redox Chemistry

Because copper is a transition metal, it is capable of assuming one of several different oxidation (or valence) states, and it is an active participant in redox reactions. In particular, participation in the Fenton reaction and Haber-Weiss cycle explains the toxicologic effects of copper as a generator of oxidative stress and inhibitor of several key metabolic enzymes (Fig. 12–2).⁵⁷ In the presence of sulfhydryl-rich cell membranes, such as those on erythrocytes, cupric ions are reduced to cuprous ions, which are capable of generating superoxide radicals in the presence of oxygen.⁶⁴ This one-electron reduction of oxygen regenerates the cupric ion, allowing redox cycling and continuous generation of reactive oxygen species (Fig. 95–1). In particular, the mitochondrial electron transport chain and lipid membranes serve as ready sources of electrons for copper reduction, establishing a chain of events that ultimately leads to mitochondrial or membrane dysfunction,

respectively.⁸²

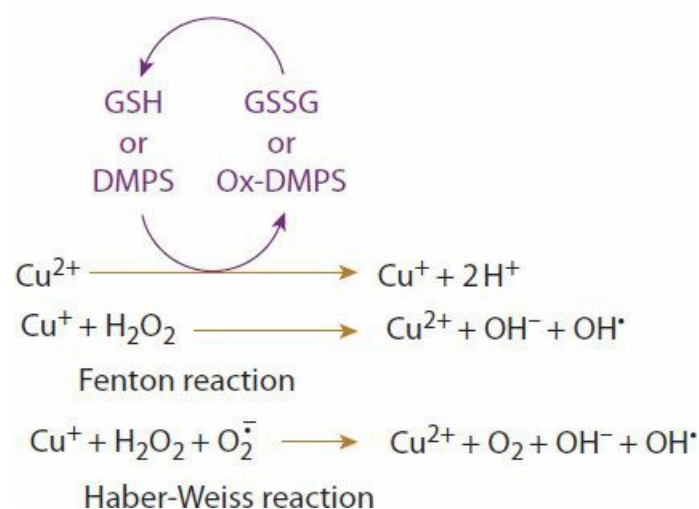


FIGURE 95–1. In the cupric or Cu²⁺ state, copper is reduced by sulfhydryl-containing compounds such as glutathione (GSH) or dimercaptopropane sulfonate (DMPS) to its cuprous form (Cu⁺), forming disulfide links in the process. Oxidized glutathione (GSSG) is subsequently enzymatically reduced by glutathione reductase to regenerate GSH. Superoxide anions (O₂⁻), formed when molecular oxygen (O₂) acquires an additional electron, are continually generated by mitochondria. Both the Fenton and the Haber-Weiss reactions use the cuprous form of copper as a catalyst to convert hydrogen peroxide or superoxide radical into the more biologically consequential hydroxyl radical (OH[•]).

Erythrocytes

Cupric ion inhibits sulfhydryl groups on enzymes in important antioxidant systems, including glucose-6-phosphate dehydrogenase and glutathione reductase.¹⁰¹ However, while support for these effects is only indirect, intraerythrocyte concentrations of reduced glutathione fall demonstrably following copper exposure. This effect is presumably part of the protective role that glutathione, a nucleophile or reducing agent, normally has on oxidants, such as either cupric ions or the reactive oxygen species they generate.^{76,77} Thus, in the setting of copper poisoning, in which excessive quantities of oxidants are produced, the depletion of glutathione presumably augments peroxidative membrane damage.

The importance of hemoglobin-derived reactive oxygen species is demonstrated by the lack of hemolysis in the presence of copper under anaerobic conditions or in an environment saturated with carbon monoxide.¹¹ The in vitro hemolytic activity of copper sulfate is reduced by albumin and several sulfhydryl containing compounds, including D-penicillamine and succimer.¹ Interestingly, dimercaptopropane sulfonate (DMPS), another sulfhydryl containing compound often used as a chelator, exacerbates copper-induced hemolysis. This paradoxical effect is variably attributed to concomitant inhibition of superoxide dismutase, an important antioxidant enzyme, or to the ability of DMPS to efficiently reduce either membrane dithiols or cupric ions, in either case increasing the generation of superoxide.²

Hemolysis frequently occurs within the first 24 hours following with acute copper poisoning.^{26,110,124} This rapidity of hemolysis differs markedly from most other oxidant stressors, which may take several days, and is likely a result of the differing nature of the erythrocyte insult. That is, the hemolysis following most oxidant exposures is caused by precipitation of hemoglobin as Heinz bodies and subsequent erythrocyte destruction by the reticuloendothelial system. Hemoglobin precipitation may also occur in the setting of acute copper poisoning, particularly following less substantial exposure. Additionally, and accounting for the early hemolysis, copper also directly oxidizes the erythrocyte membrane, thereby initiating red cell lysis independently of the reticuloendothelial system.⁹⁹ Oxidant-induced disulfide cross-links in the erythrocyte membrane reduce its stability and flexibility, thereby predisposing to early cell rupture.³

Copper-induced oxidation of the heme iron within the erythrocyte produces methemoglobinemia.⁸⁰ Given the high incidence of hemolysis, the methemoglobin is commonly released within the plasma. In this situation, methylene blue may not reliably reduce the ferric iron.

Liver

Although most of the accumulated copper in hepatocytes is rapidly complexed with metallothionein or otherwise used, unsequestered copper ions participate in redox reactions. Hepatic cells are protected from copper toxicity in vitro by induction of metallothionein with zinc or cadmium salts or by the infusion of metallothionein prior to exposure. These interventions demonstrate the toxicologic significance of free intracellular copper. These findings also explain the therapeutic use of zinc acetate in patients suffering from Wilson disease, because copper itself is not a good inducer of

metallothionein in humans.

Copper ions also generate hydroxyl radicals, which are potent inducers of both lipid peroxidation, and other reactive oxygen species. The peroxidative effect on biologic membranes is more significant in animals deficient in vitamin E and is prevented by vitamin E replacement, presumably because of the role of vitamin E as a free radical scavenger.¹⁰⁸ These effects are most pronounced in mitochondria, perhaps as a consequence of the reduction of cupric to cuprous ion in these organelles.^{42,109} Copper also accumulates in the cellular nuclei, where localized production of hydroxyl radicals may form DNA adducts and cause apoptosis.⁹⁸ Histologically, liver damage follows a centrilobular pattern of necrosis ([Chap. 23](#)).

The sequelae of the potent hepatotoxic effects of copper are not isolated to the liver. Once liver necrosis occurs, typically at liver copper concentrations greater than 50 mg/g dry weight, massive release of copper into the blood occurs, which may be of sufficient magnitude to cause hemolysis. This sequence of events is common during the crises of Wilson disease and may allow for an understanding of the delayed secondary episode of hemolysis that occurs in some copper-poisoned patients.

Kidney

The kidneys bioaccumulate copper, where it is bound primarily to metallothionein. Reactive oxygen species are probably also responsible for the nephrotoxic effects of unbound copper. Pathologic analyses of the kidneys of oliguric or anuric patients typically reveal acute tubular necrosis that may demonstrate hemoglobin casts. These findings suggest that kidney failure may result indirectly from the hemoglobinuria induced by the massive release of free extracellular hemoglobin. The urinary hemoglobin, like myoglobin, may undergo conversion to ferriheme or release its iron, either of which results in oxidative stress on the renal tubular epithelial cell. Additionally, free extracellular hemoglobin may cause renal vasoconstriction through the local scavenging of nitric oxide within the renal arterioles.

Central Nervous System

Although charged entities such as copper ions do not readily cross the blood–brain barrier, elevated cerebrospinal fluid copper concentrations are characteristic of chronic copper overload conditions such as Wilson disease.¹¹² This accumulation is accomplished through carrier-mediated transport of albumin-bound, not ceruloplasmin-bound, copper into the central nervous system.

CLINICAL MANIFESTATIONS

Acute Copper Salt Poisoning

The acutely lethal dose of ingested copper sulfate is suggested to be 0.15 to 0.3 g/kg, but this is unverified. Gastrointestinal irritation is the most common initial manifestation of copper salt poisoning. This syndrome includes the rapid onset of emesis, abdominal pain, and less frequently gastroduodenal hemorrhage, ulceration, or perforation.^{6,28} Blue coloration of the vomitus may occur following the ingestion of certain copper salts, particularly copper sulfate.⁸¹ Blue vomitus is not, however, pathognomonic for copper poisoning and also occurs in patients who ingest boric acid, methylene blue, or food dyes. Other common symptoms include retrosternal chest pain and a metallic taste.

Given its location within the gastrointestinal tract, the liver receives the initial and most substantial exposure to any ingested copper. In the patients with more severe acute copper sulfate poisoning, hepatotoxicity is a frequent, although rarely an isolated,⁵⁵ manifestation. Jaundice, while among the most common clinical and biochemical findings following overdose, can be due to hepatocellular injury or hemolysis.⁸

Hemolysis is more common than hepatotoxicity, and occurs invariably in those patients with liver damage.¹⁰⁶ As noted, copper-induced hemolysis often occurs rapidly following exposure and may be severe (see Toxicology and Pathophysiology above and [Chap. 22](#)). In most reported cases, the discovery of significant methemoglobinemia occurs early in the clinical course and is rapidly followed by hemolysis. Because free methemoglobin is filterable, methemoglobinuria may occur, although it cannot be differentiated from other heme forms in the urine without specialized testing.

Kidney and lung toxicities occur occasionally and represent extraerythrocytic manifestations of the oxidative effects of the copper ions. In spite of massive intravascular hemolysis, hemoglobinuric kidney failure is uncommon in patients who receive adequate volume-replacement therapy.²⁶

Hypotension and cardiovascular collapse occur in patients with the most severe poisoning and is likely multifactorial in origin.¹⁰⁵ Undoubtedly, intravascular volume depletion from vomiting and diarrhea is involved. However, the severity and poor patient outcome despite appropriate volume repletion suggests that the direct effects of copper on vascular and cardiac cells are also involved. Sepsis, as a result of transmucosal bacterial invasion from the gastrointestinal tract, may also be partially responsible.⁶⁹

Depressed mental status, which ranges from lethargy to coma, or seizures following acute poisoning is likely an

epiphenomenon related to damage to other organ systems. An altered level of consciousness is particularly common in patients with hepatic failure, and the presentation is comparable to that of hepatic encephalopathy from other causes. In patients with chronic copper poisoning, such as Wilson disease, neurologic manifestations are prominent and typically involve movement disorders (see Chronic Copper Poisoning below).

Intravenous injection of copper sulfate reportedly produces a clinical syndrome identical to that which occurs following ingestion, although the gastrointestinal findings may be less pronounced.^{13,16,86} Subcutaneous administration of a veterinary copper glycinate solution produced skin necrosis in the area of the injection.^{9,87}

Although not strictly a form of copper poisoning, inhalation of copper oxide fumes generated during welding or other industrial processes may produce metal fume fever, a syndrome historically called “brass chills” or “foundry workers’ ague.” Patients with this syndrome present with cough, chills, chest pain, or fever that is most likely immunologic, and not toxicologic, in origin (Chap. 124). However, copper oxide formation, unlike zinc oxide, only occurs at extremely high temperatures, accounting for the relative infrequency of the copper-induced metal fume fever.

Chronic Copper Poisoning

Although hepatolenticular degeneration, known as Wilson disease, is a condition of chronic copper overload, there are qualitative similarities to acute copper poisoning. Wilson disease is an inherited, autosomal recessive disorder of copper metabolism affecting approximately 1 in 40,000 persons. The gene implicated in this disease (ATP7B) codes for a hepatocyte membrane-bound, copper-binding protein that is required for the maturation of ceruloplasmin and the biliary excretion of copper. Transgenic replacement models, in which human ATP7B is expressed in deficient animals, demonstrate normalization of copper excretion.⁷⁵ The absence of this gene, and the resultant increase in hepatic copper concentrations, produces continuing oxidative stress on the hepatocyte and cellular necrosis with the inevitable development of cirrhosis. Patients undergo periodic fluctuations in the extent of their copper-induced hepatotoxicity, and episodes of severe hepatotoxicity are frequently associated with hemolysis as stored copper is released from dying hepatocytes.

The adverse effects of copper on the lenticular nucleus in the basal ganglia cause movement disorders such as ataxia, tremor, parkinsonism, dysphagia, and dystonia.^{70,85} No other forms of copper poisoning are associated with substantial or direct neurotoxicity. Psychiatric manifestations, such as behavioral changes or mood disorders, may also occur. Accumulation of copper within the cornea accounts for the characteristic green-brown Kayser-Fleischer rings. Although the affected patient’s serum copper concentrations are decreased, the individuals typically have a reduced ceruloplasmin concentration and an elevated urinary copper concentration. Treatment involves lifelong therapy with D-penicillamine, trientine (triethylenetetramine), or molybdenum salts if the patient is D-penicillamine sensitive. Zinc acetate, approved by the US Food and Drug Administration (FDA) as a maintenance therapy, induces the formation of intestinal metallothionein and thereby blocks copper absorption by enhancing intestinal mucosal cell sequestration. Orthotopic liver transplantation results in improvement in nearly all aspects of the disease, including the central nervous system and ophthalmic manifestations.⁹⁶

Chronic exogenous copper poisoning is uncommon in adults but is reported following the use of copper-containing dietary supplements.⁸⁴ However, subacute or chronic exposure is common in children in some parts of the world. This condition, commonly called childhood cirrhosis in India or idiopathic copper toxicosis elsewhere, generally occurs following excessive dietary intake of copper due to copper contamination of milk from brass storage vessels. The affected children may have a genetic predisposition to copper accumulation, as signs of chronic liver disease develop by several months of age and progress rapidly thereafter.^{56,103} Both serum copper and ceruloplasmin concentrations are markedly elevated, which differentiates this disease from Wilson disease. The incidence of the disease has fallen dramatically, probably as a result of improved nutrition and replacement of utensils and storage containers containing copper with those made of steel. A family of four developed abdominal pain, malaise, tachycardia, and anemia after approximately one month of eating homegrown vegetables treated with copper oxychloride pesticide.⁴⁴ Each patient had anemia and a high normal or slightly elevated serum copper concentration.

“Vineyard sprayer’s lung,” first described in 1969, refers to the occupational pulmonary disease that occurred among Portuguese vineyard workers applying Bordeaux solution, a 1% to 2% copper sulfate solution neutralized with hydrated lime ($\text{Ca}(\text{OH})_2$).⁸⁹ The patients developed interstitial pulmonary fibrosis and histiocytic granulomas containing copper. Many of these workers also developed pulmonary adenocarcinoma, hepatic angiosarcoma, and micronodular cirrhosis, raising the possibility of a carcinogenic effect of chronic copper exposure.⁹⁰ There is also a suggestion of an increased incidence of pulmonary adenocarcinoma among smelters, who are, however, exposed to many other xenobiotics, including arsenic, a known carcinogen.⁷¹ Copper is not on the list of suspected carcinogens compiled by the International Agency of Research on Cancer.

Ophthalmic effects of copper salts, primarily following occupational exposure, include irritation of the corneal, conjunctival, or adnexal structures. Chronic ophthalmic exposure to particulate elemental copper or one of its alloys may result in chalcosis lentis, from the Greek word chalkos, or copper. This chronic exposure manifests as a green-brown

discoloration of the lens or cornea, similar to Kayser-Fleischer rings.

DIAGNOSTIC TESTING

Real-time testing for copper is impractical, and almost all management decisions must be based on clinical criteria. Copper concentrations are often obtained for confirmatory or investigative purposes. Although never adequately studied, whole-blood copper concentrations may correlate better with clinical findings than serum copper concentrations.²⁸ The rapid movement of copper from the serum into the erythrocyte presumably explains this finding. However, although there is a statistical relationship between the whole-blood copper concentrations and the severity of poisoning,^{28,118} there is little correlation between clinical findings at any given copper concentration, regardless of which biologic tissue is measured. Similarly, other than at extremely high or low concentrations, there is no defined concentration at which the prognosis may be established with certainty. Reported serum copper concentrations in patients with hemolysis range from 96 to 747 $\mu\text{g/dL}$, and reported concentrations in patients with severe poisoning are 6600 $\mu\text{g/dL}$ ⁴³ and 8267 $\mu\text{g/dL}$.²⁷ Serum copper concentrations in 11 patients with copper-induced acute kidney failure ranged from 115 to 390 $\mu\text{g/dL}$.²⁵ The urinary copper excretion per 24 hours is up to approximately 25 μg under normal circumstances and is reportedly as high as 628 $\mu\text{g}/24\text{ h}$ in patients with copper poisoning.

Occasionally, there is a secondary rise in serum copper concentrations, which likely results from release during hepatocellular necrosis. This secondary rise typically occurs in patients with life-threatening poisoning, and clinical evaluation is far more important and relevant than serial copper concentrations.¹⁰⁶

Elevated copper concentrations are also noted in patients with inflammatory conditions, biliary cirrhosis, pregnancy, and estrogenic oral contraceptive use.²¹ These conditions are associated with an elevated ceruloplasmin, and while the serum copper concentrations rise, the fraction of bound copper in the serum remains normal. Copper concentrations in the erythrocyte remain normal. Patients with Wilson disease have elevated hepatocyte copper content, but their serum copper concentrations are generally below normal unless hepatic necrosis is occurring.⁷²

Although serum ceruloplasmin concentrations rise in patients with acute copper poisoning,¹¹⁸ presumably reflecting increased hepatic synthesis, the ceruloplasmin concentration cannot be used to define prognosis. Tissue metallothionein concentrations may also rise following copper poisoning, but the implications of this finding, which is limited by the inability to rapidly obtain tissue samples, are unknown.⁶⁶ Ceruloplasmin concentrations are low in patients with Wilson disease, reflecting aberrant enzymatic activity.

Routine laboratory testing following acute copper salt poisoning should include an assessment for both intravascular hemolysis and hepatotoxicity. Differentiation of these etiologies as a cause for jaundice is made using standard methodologies, such as comparison of the bilirubin fractions and an assessment of the hepatic enzymes and hemoglobin; that is, indirect bilirubin is proportionally elevated in patients with hemolysis, whereas the direct fraction rises in patients with hepatocellular necrosis. The determination of intravascular hemolysis can be aided with the identification of a low serum haptoglobin or an elevated lactate dehydrogenase. An assessment of the patient's electrolyte and hydration status is warranted. The prothrombin time may be prolonged in the absence of liver injury or disseminated intravascular coagulopathy as a direct effect of free copper ions on the coagulation cascade.⁸⁰ In addition, many reports document an abnormal glucose 6-phosphate dehydrogenase (G6PD) activity, suggesting causation for hemolysis. However, interpretation of G6PD activity is difficult, because copper poisoning interferes with the measurement of G6PD.

Although copper metal embedded in the skin is clearly visible on radiography, topically applied copper salts are not visualized.¹⁵ The clinical usefulness of radiographs to identify ingested copper solutions has not been studied. Obtaining an abdominal radiograph, while probably of limited benefit, may be justified, because it occasionally demonstrates the presence of radiopaque material in the gastrointestinal tract. Early efforts to use magnetic resonance imaging to identify Wilson disease are underway.^{23,107}

MANAGEMENT

Supportive care is the cornerstone to the effective management of patients with acute copper poisoning, emphasizing antiemetic therapy, fluid and electrolyte correction, and normalization of vital signs prior to the consideration of chelation therapy. Gastrointestinal decontamination is of limited concern because the onset of emesis generally occurs within minutes of ingestion and is often protracted. In patients who present shortly after the ingestion of a liquid copper solution and who have not yet vomited, aspiration with a nasogastric tube may remove copper ions in solution or suspended in gastric materials. In one case, even after extensive vomiting, nasogastric aspiration still removed a blue solution, but removing this remaining volume is unlikely to provide significant clinical benefit.¹⁷ Although oral activated charcoal is unlikely to be harmful, it is of unproved benefit, and it may hinder the ability to perform gastrointestinal endoscopy to evaluate the corrosive effects of a copper salt on the mucosal surface.¹⁷ For this reason, even though activated charcoal may adsorb the

remaining copper in the proximal gastrointestinal tract, it is relatively contraindicated in most situations. Advanced therapy for patients with kidney failure may include hemodialysis, and for patients with life-threatening hepatic failure, liver transplantation may be needed.

Chelation Therapy

Chelation therapy should be initiated when hepatic, hematologic complications, or other concerning or severe manifestations of poisoning are present. Studies on the efficacy of chelation therapy following acute copper salt poisoning are limited. Even when administered early and appropriately, organ damage and death still occur. Application of the data from the existing literature is complex because of the lack of controlled studies of human copper poisoning. Although animal models and uncontrolled human data exist, the results are frequently contradictory. Three chelators are clinically available, and most data regarding dosing and efficacy data are derived either from chelator use in the treatment of patients with Wilson disease or from their effects on copper elimination during chelation of patients manifesting toxicity from other metals.

Most patients with copper poisoning are initially treated with intramuscular British anti-Lewisite (BAL).¹¹³ Although BAL may be less effective, its use is appropriate in patients in whom vomiting or gastrointestinal injury prevents oral D-penicillamine administration. Furthermore, because the BAL–copper complex primarily undergoes biliary elimination, whereas D-penicillamine undergoes renal elimination, BAL proves useful in patients with kidney failure. When tolerated, D-penicillamine therapy should be started simultaneously or shortly after the initiation of therapy with BAL (Antidotes in Depth: A25).

Calcium disodium ethylenediaminetetraacetate (CaNa_2EDTA) reduces the oxidative damage induced by copper ions in experimental models.¹²³ However, it does not greatly enhance the elimination of copper when used for the chelation of other metals.¹¹⁴ In addition, short-term use of CaNa_2EDTA inactivates dopamine β -hydroxylase in humans, presumably by chelating the copper moiety from its active site.³² However, because the *in vivo* activity of this enzyme is restored following the addition of exogenous copper, the potential for inhibition of the formation of neuronal norepinephrine during the treatment of acute poisoning is unknown. Successful clinical use of CaNa_2EDTA is reported.^{38,86,113} Interestingly, CuCaEDTA is used as a copper supplement in animals, and overdose of this formulation results in copper poisoning suggesting that its chelating ability is limited.³⁹ (See Antidotes in Depth: A27).

D-Penicillamine (Cuprimine), a structurally distinct metabolite of penicillin, is an orally bioavailable monothiol chelator. It is used in the treatment of lead, mercury, and copper toxicity, as well as in the management of rheumatoid arthritis and scleroderma. It has also more recently been investigated for its antiangiogenesis effects in cancer therapy, which occur by chelation of copper that serves as a cofactor for growth factors, such as fibroblast growth factor.¹¹⁵ D-Penicillamine is effective in preventing copper-induced hemolysis in patients with Wilson disease. Its protective mechanism is primarily mediated through chelation of unbound copper ions, rendering them unable to participate in redox reactions.⁶² The D-penicillamine–copper complex undergoes rapid renal clearance in patients with competent kidneys. The use of D-penicillamine is not formally studied in patients with acute copper salt poisoning, but case studies and animal models suggest that copper elimination is enhanced.^{18,41,51} In patients with Wilson disease, it dramatically increases the urinary elimination.¹¹⁷ The recommended adult dose is 1 to 1.5 g/d given orally in four divided doses, and although formal pediatric dosing recommendations are not available, some recommend the adult dose and others suggest 20 mg/kg/d orally every 12 hours.⁴⁹ D-Penicillamine is also indicated for the treatment of chronic exogenous copper poisoning, such as Indian childhood cirrhosis. Initiation early in the course of disease and discontinuation of the exposure to copper are associated with hepatic recovery and dramatically improved survival rates.¹²

Although D-penicillamine appears to be effective, it is associated with several significant complications. In nearly 50% of patients treated with D-penicillamine for Wilson disease, there is worsening of the neurologic findings.²⁰ Subacute toxicities of D-penicillamine include aplastic anemia, agranulocytosis, kidney and lung toxicity, and loss of trace metals.⁵⁴ Long-term use of D-penicillamine is also associated with the development of cutaneous lesions and immunologic dysfunction. However, in the brief treatment necessary for acutely poisoned patients, the major risk is the potential for hypersensitivity reactions that occur in 25% of patients who are allergic to penicillin. This hypersensitivity reaction is likely related to contamination of the pharmaceutical preparation with penicillin, rather than immunologic cross-reactivity.^{50,59} The use of D-penicillamine during pregnancy is associated with congenital abnormalities, although all of the data are derived from women with Wilson disease who were receiving long-term therapy.⁹¹

Succimer is sometimes described as an ineffective copper chelator, although it is able to triple the baseline copper elimination in a murine model. Given its ease of use, relative safety, and benefit in experimental models,¹ succimer may be used in lieu of D-penicillamine in patients with mild or moderate poisoning. Under these circumstances, the use of standard lead poisoning dosing regimens is warranted (Chap. 96 and Antidotes in Depth: A26).

DMPS, an experimental chelator that is gaining popularity for the treatment of arsenic poisoning, prevents acute tubular

necrosis in copper-poisoned mice.⁷⁸ DMPS also proved to be the most effective of a panel of chelators in a murine model of copper sulfate poisoning,⁵⁸ and it substantially increased urinary copper elimination in nonpoisoned, healthy individuals.¹¹⁶ However, DMPS, unlike D-penicillamine, forms intramolecular disulfide bridges, which liberates an electron. Although this accounts for its potency as a reducing agent, it also probably explains its propensity to worsen copper-induced hemolysis in vitro.² Because an adequate analysis of risk versus benefit is unavailable, DMPS should not be used to chelate copper-poisoned patients at this time.

Trientine (triethylenetetramine), an orally bioavailable chelator, is the second-line therapy for patients with Wilson disease, but its use in patients with acute copper poisoning is unreported. It has recently been studied for its role as a copper chelator in patients with Alzheimer disease.³¹ Zinc therapy to induce metallothionein synthesis, which is also of proven efficacy in Wilson disease, has an unknown role in the treatment of acute copper poisoning. The need for several weeks of zinc therapy prior to realizing full efficacy makes its therapeutic use in acutely poisoned patients questionable. Although large oral doses of zinc salts may limit the absorption of copper ion, the concomitant gastrointestinal irritant effects of zinc ion make this therapy impractical.

Tetrathiomolybdate, an FDA-recognized chelator with orphan drug status although not marketed, may be available through compounding pharmacies, typically as ammonium tetrathiomolybdate. In uncontrolled studies, tetrathiomolybdate is suggested to benefit copper-poisoned animals,⁸⁸ but its use in acute copper poisoning in humans is unstudied. Tetrathiomolybdate depleted the copper stores in a patient with cancer who purchased the compound over the Internet as an “alternative” antiangiogenesis therapy.⁶⁷

Clioquinol, a xenobiotic used 50 years ago as an antiparasitic, was discontinued due to epidemic optic neuropathy that may have been associated with its ability to chelate copper ions.¹⁰² Clioquinol is currently under investigation as a therapy for Alzheimer disease,¹⁰ but it has not been studied for patients with acute or chronic copper poisoning.

Extracorporeal Elimination

Limited data exist regarding the elimination of copper ions by various extracorporeal means. Hemodialysis membranes undoubtedly allow copper ions to cross, based on the epidemics in which hemodialysis using copper-rich water inadvertently resulted in copper poisoning.³⁵ Although copper should be similarly cleared by hemodialysis, its relatively large volume of distribution limits the potential clinical usefulness of this technique. Furthermore, copper ions are highly protein bound, and the dialyzable concentration is typically less than 1 pmol/L, suggesting that hemodialysis would have little clinical usefulness. This fact is supported by case reports in which serum, tissue, or dialysate concentrations of copper are assessed.^{4,86} Furthermore, given the propensity of hemodialysis to lyse erythrocytes, which may release stored copper and worsen toxicity, hemodialysis is not recommended except as indicated for kidney failure.

Molecular adsorbents recirculating system (MARS) and single-pass albumin dialysis (SPAD), modified forms of hemodialysis in which albumin is included in the dialysate, are reported to rapidly and substantially lower the serum copper concentrations in patients with fulminant Wilson disease, allowing a bridge to hepatic transplantation.^{24,30} A single patient with Wilson disease was treated with albumin dialysis using a 44 g/L albumin-containing dialysate and a slow dialysate flow rate (1–2 L/h) in a manner similar to routine continuous venovenous hemodiafiltration; this reportedly removed 105 mg of copper and normalized the serum copper concentration.⁶³ The risk associated with hemolysis likely remains, and caution should be used when extrapolating therapy from Wilson disease to exogenous copper poisoning.

Exchange transfusion is of undefined, but probably limited, benefit in acute copper sulfate poisoning.^{73,124} Plasma exchange enhanced the elimination of copper in patients with fulminant Wilson disease.^{61,63} Copper removal ranged from 3 to 12 mg per treatment, but it is unclear if either of these removal techniques would be beneficial following an ingestion of gram quantities of copper sulfate. The same warning as above about inadvertent red cell lysis applies.

Peritoneal dialysis is not useful in patients with fulminant Wilson disease.⁶⁵ Peritoneal dialysis removed less than 700 µg in a copper sulfate–poisoned child whose copper concentration was 207 µg/dL.⁴⁶ However, in the same patient, the addition of albumin to the dialysate removed 9 mg of copper at a time when the child’s serum copper concentration had already fallen substantially.

Management of the hepatic toxicity requires little more than standard supportive care. The potential benefit of N-acetylcysteine has not been studied, although it is useful in many forms of fulminant hepatic failure and is warranted in most hepatotoxic patients. Liver transplantation should be considered, but specific criteria for transfer to a specialized liver unit or for transplant, other than those that are applicable for Wilson disease or other more common etiologies of fulminant hepatic failure, are undefined.

There are no controlled data on the treatment of acute copper poisoning in pregnancy. The available data on pregnant women with Wilson disease document that D-penicillamine is teratogenic and that zinc may be the preferred therapy.

SUMMARY

- The toxic effects of copper are primarily mediated by oxidative stress on the erythrocyte and hepatocyte, and this similarity to iron salt poisoning adds a framework for the conceptual understanding of the disease.
- Chelation is most commonly performed with BAL and D-penicillamine.
- Succimer is more familiar to most clinicians and has fewer associated adverse effects; therefore, it is an acceptable alternative.
- Extracorporeal elimination is unlikely to be of benefit. Fortunately, exhaustive research into diseases of copper metabolism, particularly Wilson disease, which has periodic exacerbations similar to acute copper poisoning, has provided insight into managing patients with acute copper salt poisoning.

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96 LEAD

Diane P. Calello and Fred M. Henretig

Lead (Pb)	
Atomic number	= 82
Atomic weight	= 207 Da
Normal concentration	
Whole blood	< 10 µg/dL (0.48 mmol/L)

HISTORY AND EPIDEMIOLOGY

Industrial Applications

The low melting point and high malleability of lead made it one of the first metals smelted and used by humans. Ancient Egyptians and Hebrews used lead, and the Phoenicians established lead mines in Spain circa 2000 B.C. The Greeks and Romans released lead during the process of extracting silver from ore. Roman society found many uses for lead, including pipes, cooking utensils, and ceramic glazes, and a common practice was to use sapa, a grape syrup simmered down in lead vessels, as a sweetener and preservative.¹¹⁸ Post-industrial lead use increased dramatically, and today lead is the most widely used nonferrous metal, with global extraction on the order of 9 million tons annually.⁸² Lead is used widely for its waterproofing and electrical-and radiation-shielding properties. Use of both lead-based paint for house paint and leaded gasoline has been essentially eliminated by regulation in the United States since the 1980s, but is still a concern in many nations, and persistence of lead paint in older US homes still constitutes an enormous environmental challenge.³

History of Lead-Related Health Effects

Dioscorides, a Greek physician in the second century B.C., observed adverse cognitive effects, and Pliny cautioned the Romans of the danger of inhaled fumes from lead smelting.¹¹⁴ Modern authors have suggested that extensive use of sapa in Roman aristocratic society contributed to the downfall of Roman dominance.¹¹⁸ Lead poisoning was also recognized in American colonial times. Benjamin Franklin observed in 1763 the “dry gripes” (abdominal colic) and “dangles” (wristdrop) that afflicted tinkers, painters, and typesetters, as well as the “gripes” caused by rum distillation in leaden condensing coils.¹⁰⁵ Lead salts, particularly lead acetate (sugar of lead), were used medicinally in the early 19th century to control bleeding and diarrhea. With the 19th century Industrial Revolution, lead poisoning became a common occupational disease. The reproductive effects of lead poisoning were recognized by the turn of the 20th century, including the high rate of stillbirths, infertility, and abortions among women in the pottery industry or who were married to pottery workers.

The modern history of childhood plumbism can be traced to the recognition of lead-paint poisoning in Brisbane, Australia, in 1897.¹¹⁴ Lead poisoning was reported in American children in 1917, and by 1943, it was established that children who recovered from clinical plumbism were frequently left with neurologic sequelae and intellectual impairment. Symptomatic childhood lead poisoning was a frequent occurrence in American pediatric medical centers throughout the 1950s and 1960s, a period during which research established effective chelation therapy protocols with British anti-Lewisite (BAL) and edetate calcium disodium (CaNa₂EDTA).³⁴ From the 1970s to the present, the research thrust in childhood lead poisoning has centered on the recognition and quantification of more subtle neurocognitive impairment caused by subclinical lead poisoning.^{16,115} Over this time period, the US Centers for Disease Control and Prevention (CDC) has steadily revised downward the definitions of a normal blood lead concentration (BLL) in children. The CDC definition of childhood lead poisoning was 60 µg/dL in the early 1960s, was reduced to 10 µg/dL in 1991,²² and in recent years has been further revised in light of evidence suggesting adverse cognitive effects in young children at BLLs below 10 µg/dL.²⁰ The most recent CDC Advisory Council on Childhood Lead Poisoning recommendations lower the “level of concern” to 5 µg/dL and eliminate the term “threshold,” in response to emerging data demonstrating a supralinear dose-response curve for intelligence quotient (IQ) decrement at even the lowest detectable BLLs.^{8,27,79,88}

Sources of Human Exposure

Numerous sources of lead exposure exist and can be generally classified as environmental, occupational, or additional (some what “exotic”) sources. Environmental exposures affect the entire population, particularly young children. These occur primarily by exposure to lead paint in the United States (Table 96–1). Because of its continuing impact in the United States today, lead paint exposure is further detailed here.

TABLE 96–1. Environmental Lead Sources

Source	Comment
Paint	Especially pre-1978 homes
Dust	House dust from deteriorated lead paint
Soil	From yards contaminated by deteriorated lead paint, lead industry emissions, roadways with high leaded gasoline usage
Water	Leached from leaded plumbing (pipes, solder), cooking utensils, water coolers
Air	Leaded gasoline (pre-1976 United States; still prevalent worldwide), industrial emissions
Food	Lead solder in cans (pre-1991 United States; still prevalent in imported canned foods); “natural” dietary supplements; “moonshine” whiskey and lead foil–covered wines; contaminated flour, paprika, other imported foods and candy; lead leached from leaded crystal, ceramics, vinyl lunch boxes
Other	Complementary and alternative medicines, children’s toys and jewelry (especially imported products), cosmetics, leaded ink, vinyl mini-blinds

Lead pigments (typically lead carbonate) account for 50% by weight of many white house paints from the pre–World War II era. Since 1978, paint intended for interior or exterior residential surfaces, toys, or furniture in the United States may contain, by law, no more than 0.06% lead. However, an estimated 3 million tons of lead remain in 57 million US homes built before 1980 and painted with lead-based paint. This aging housing stock has created an enormous environmental hazard of lead exposure to children and to adult homeowners, house painters, and construction workers who become involved in sanding, scraping, and restoration of painted surfaces in these homes. Furthermore, lead-based paint is still allowed for industrial, military, marine, and some outdoor uses, such as structural components of bridges and highways; occasionally, some of this paint is inadvertently used in homes.²³ Attempts to abate lead-painted outdoor structures can pollute entire communities.⁸⁷

Although paint-derived lead exposure may result from pica in some children, most lead paint exposure in childhood relates to the crumbling, peeling, flaking, or chalking of aging paint.²² These fine paint particles are incorporated into household dust and yard soil, where ordinary childhood hand–mouth activity results in ingestion.²⁹ Seasonal variations in house dust contamination occur, with higher house dust lead concentrations and increased BLLs in exposed preschool children noted during the summer.

Adults with occupational exposures to lead constitute another large group of persons at risk. It is estimated that more than 1 million workers in the United States, employed in more than 100 occupations, are exposed to lead.¹⁴⁰ The most important route of absorption in occupational settings is inhalation of lead dust and fumes. In addition, ingestion may result when workers eat, drink, or smoke in lead dust–contaminated areas. However, the presence of lead in the workplace, per se, does not imply a significant risk of poisoning. Some types of lead-related work are more hazardous than others (Table 96–2).^{140,147} For example, lead smelting can be categorized as primary (from raw ore) and secondary (reclamation, such as from used car batteries). Secondary lead production workers may be at higher risk of poisoning because this job more typically involves small, sometimes “backyard” operations that are less likely to adhere to industry safety regulations than large, well regulated primary smelters.⁴¹

TABLE 96–2. Occupational and Recreational Lead Sources

High Risk Occupations

Automobile radiator repairers

Crystal glass makers

Firing range instructors, bullet salvagers

Lead smelters, refiners

Metal welders, cutters (includes bridge and highway reconstruction workers)

Painters, construction workers (sanding, scraping, or spraying of lead paint; demolition of lead-painted sites)

Polyvinyl chloride plastic manufacturers

Shipbreakers

Storage battery manufacturers, repairers, recyclers

Moderate Risk Occupations

Automobile factory workers and mechanics

Enamellers

Glass blowers

Lead miners

Plumbers

Pottery glazers

Ship repairers

Shot makers

Solderers

Type founders

Varnish makers

Wire and cable workers

Possible Increased Risk Occupations

Electronics manufacturers

Jewelers

Pipefitters

Printers

Rubber product manufacturers

Traffic police officers, taxi drivers, garage workers, turnpike tollbooth operators, gas station attendants (exposed to leaded gasoline exhaust fumes; unlikely now in the United States but still a hazard in developing countries)

Recreational and Hobby Sources

Ceramic crafts

Furniture refinishing, restoring

Home remodeling, refinishing

Painting (fine artist's pigments)

Repair of automobiles, boats

Stained glass making

Target shooting, recasting lead for bullets

Additional sources

Ingested lead foreign bodies and retained lead bullets

Illicit substance abuse (heroin, methamphetamine, leaded gasoline "huffing")

Burning batteries, leaded paper, or wood for fuel

Hand-mouth contact with pool cue chalk, glazes, leaded ink

For convenience, environmental and occupational or recreational lead exposures are discussed separately, although there is considerable overlap. For example, workers who fail to change lead dust-covered work clothes or shoes may bring this occupational lead hazard home and secondarily contaminate their children's environment.¹⁴⁰

Finally, numerous additional sources of lead exposure are also reported, including contaminated folk medications or cosmetics,^{19,21,89,143} imported food,⁶⁶ ingested lead foreign bodies,^{102,106,172} and retained bullets.^{50,94,148} Since 2010, an outbreak of lead encephalopathy from artisanal gold mining in Nigeria has claimed hundreds of lives, with the toll still growing.^{11,44}

Some potential exposures have raised considerable community concern and media coverage in recent years—for example, the discovery of lead contamination of some artificial turfs²³ and imported toys coated with lead paint.⁹⁵ These, too, are highlighted separately in [Table 96–2](#).

Prevalence

Several recent national and regional surveys have evaluated current US population-based trends in BLLs and sociodemographic correlates. The CDC estimates that approximately 450,000 children aged 1 to 5 years have BLLs greater than 5 µg/dL,²⁷ the 2012 revised reference value representing primarily excessive household exposure, and that approximately 8000 adults are reported each year with BLLs greater than 24 µg/dL (typically reflecting excessive occupational exposure).¹⁷ Although such numbers are impressive, they represent a considerable decrease from prevalence rates reported in prior decades (eg, from 8.6% of children with elevated BLLs from 1988 to 1991 to 1.4% from 1999 to 2004),⁷⁷ and it is certainly the observed clinical experience that symptomatic lead poisoning in children, in particular, is far less common than it was a generation ago. Nevertheless, for young minority children and poor people who reside in the deteriorating central cities of the United States, the battle is far from won. For example, the CDC reported in 2000 that children enrolled in Medicaid had a prevalence of elevated BLLs three times greater than those not enrolled.²⁵ Refugee, immigrant, and foreign-born adopted children remain at particularly high risk,^{18,89} and remarkable cases of extremely elevated BLLs (>100 µg/dL) may still be detected on routine screening.⁴⁰

PHYSICAL PROPERTIES

Lead is a silvery-gray, soft metal ubiquitous element in the earth's crust, with an atomic weight of 207.21 Da and an atomic number of 82. It has a low melting point, 621.3°F (327.4°C), and boils at 2948°F (1620°C) at atmospheric pressure.¹⁷¹ It occurs principally as two isotopes: ²⁰⁶Pb and ²⁰⁸Pb. Metallic lead is relatively insoluble in water and dilute acids but dissolves in nitric, acetic, and hot, concentrated sulfuric acids. In compounds, lead assumes valence states of +2 and +4. Inorganic lead compounds may be brightly colored and vary widely in water solubility; several are used extensively as pigments in paints such as lead chromate (yellow) and lead oxide (red). Lead also forms organic compounds, of which two, tetramethyl and tetraethyl lead (TEL), were used commercially as gasoline additives.⁸² These are essentially insoluble in water but readily soluble in organic solvents.¹⁴⁴ Lead complexes with ligands containing sulfur, oxygen, or nitrogen as electron donors. It thus forms stable complexes with several ligands common to biologic molecules, including –OH, –SH, and –NH₂. Complexes with endogenous sulfhydryl (–SH) groups are thought to be the most toxicologically important. There is no known physiologic role for lead, and thus any lead presence in human tissue represents contamination.

TOXICOLOGY

Toxicokinetics

Inorganic and Metallic Lead. Absorption. Gastrointestinal (GI) absorption is less efficient than pulmonary absorption. Adults absorb an estimated 10% to 15% of ingested lead in food, and children have a higher GI absorption rate, averaging 40% to 50%.^{1,58} In animal studies, this varies by type of lead compound studied.⁶ However, it should be noted that fasting and diets deficient in iron, calcium, and zinc—factors that are frequent among groups of young children—enhance GI absorption of lead.^{58,97} The role of essential trace elements in decreasing lead absorption is assumed to be a consequence of competitive absorption processes. Metallic lead is also absorbed, albeit less readily than most lead compounds.⁶ The rate of absorption of metallic lead appears to be related to particle size, total surface area, and GI tract location; whereas gastric acidity favors dissolution, the small bowel is likely the site of maximal absorption.^{102,106,172}

The overall absorption of inhaled lead averages 30% to 40%. Of note, both minute ventilation and the concentration of lead in air determine airborne lead exposure, so a worker engaged in vigorous physical activity will absorb considerably more lead than a person in the same atmosphere at rest. Likewise, children, having a relatively greater volume of inhaled air per unit of body size because of higher metabolic rates, are proportionally at greater risk in a given degree of atmospheric lead pollution. It is estimated that children have a 2.7-fold higher lung deposition rate of lead than do adults.¹

Cutaneous absorption of inorganic lead is low; one study found an average absorption of 0.06% through intact skin.¹⁰⁹ Soft tissue absorption of metallic lead follows exposure to retained bullets, and similar to ingested lead foreign bodies, also depends on particle size, total surface area, and location; multiple small shot and location in which particles are bathed by synovial, serosal, or spinal fluid favor a more rapid increase in BLL.^{50,94,148} This is thought to be due to increased solvency of lead in organic acids, such as hyaluronic acid in synovial fluid, as well as mechanical forces from joint motion.

Transplacental lead transfer is critical in fetal and neonatal lead exposure. Lead readily crosses the placental barrier throughout gestation, and lead uptake is cumulative until birth.¹³¹

Distribution. Absorbed lead enters the bloodstream, where at least 99% is bound to erythrocytes.⁵⁹ From blood, lead is distributed into both a relatively labile soft tissue pool and into a more stable bone compartment. This classic three-compartment model may be some what of an oversimplification. Currently, at least two bone compartments are recognized: a more labile pool in trabecular bone and a more stable pool in cortical bone. In adults, approximately 95% of the body lead burden is stored in bone versus only 70% for children. The remainder is distributed to the major soft tissue lead-storage sites, including the liver, kidney, bone marrow, and brain. Lead uptake into soft tissues occurs in a complex fashion that depends on numerous factors, including blood lead concentrations, external exposure factors, and specific tissue kinetics. Most of the toxicity associated with lead is a result of soft tissue uptake, so that the relative decrease in bone storage is another comparative disadvantage for children.

Lead in the central nervous system (CNS) is of particular toxicologic importance. Lead preferentially concentrates in gray matter and certain nuclei.⁵⁹ Fetal brain uptake is relatively higher than with postnatal exposure in animal models. The highest brain concentrations are found in the hippocampus, cerebellum, cerebral cortex, and medulla.

Unlike soft tissue storage, bone lead accumulates throughout life. Bone storage begins in utero and occurs across all ranges of exposure, so that there is no threshold for bone lead uptake.¹ Total body accumulation of lead may range from 200 to 500 mg in workers with heavy occupational exposure.⁵⁹ Bone lead is thought to be relatively metabolically inert, but it can be mobilized from the more labile compartments and contributes as much as 50% of the blood lead content. This may be of particular importance during times of rapid bone turnover such as pregnancy and lactation, in elderly persons with osteoporosis,¹⁵⁶ and in children with immobilization.¹⁰³ Lead also accumulates in the teeth, particularly the dentine of children's teeth, a phenomenon that has been used to quantify cumulative lead exposure in young children.¹¹⁵

Excretion. Absorbed lead that is not retained is primarily excreted in urine (approximately 65%) and bile (approximately 35%).¹ A miniscule amount is lost via sweat, hair, and nails. Children excrete less of their daily uptake than adults, with an average retention of 33% versus 1% to 4%, respectively.¹⁸² Biologic half-lives for lead are estimated as follows: blood (adults, short-term experiments), 25 days; blood (children, natural exposure), 10 months; soft tissues (adults, short-term exposure), 40 days; bone (labile, trabecular pool), 90 days; and bone (cortical, stable pool), 10 to 20 years.^{1,99,132} Trace amounts of lead are also excreted in breast milk.⁷

Organic Lead. Alkyl lead compounds are lipid soluble and have unique pharmacokinetics that are less well characterized than those of inorganic lead.⁹ Animal studies and human clinical experience with acute ingestions and leaded gasoline sniffing demonstrate TEL absorption through ingestion; inhalation; and intact skin and subsequent distribution to lipophilic tissues, including the brain.^{144,164,180} TEL is metabolized to triethyl lead, which is believed to be the major toxic compound. Alkyl leads may slowly release lead as the inorganic form, with subsequent kinetics as noted above.⁹

PATHOPHYSIOLOGY

General Mechanisms

Similar to many metals, lead is a complex xenobiotic exerting numerous pathophysiologic effects in many organ systems.⁵⁹ Furthermore, genetic polymorphism may impact on individual susceptibility to lead.¹¹⁹ Recently identified examples of such include the genes for apolipoprotein E, the vitamin D receptor, Na⁺-K⁺-ATPase, δ -aminolevulinic acid, and protein kinase C.¹⁴⁶ At the biomolecular level, lead functions in three general ways. First, its affinity for biologic electron-donor ligands, especially sulfhydryl groups, allows it to bind and impact numerous enzymatic, receptor, and structural proteins. Second, lead is chemically similar to the divalent cations calcium and zinc and interferes with numerous calcium-(and perhaps zinc-) mediated metabolic pathways, particularly in mitochondria and in second-messenger systems regulating cellular energy metabolism.⁹⁰ Lead-induced mitochondrial injury may result in apoptosis, a phenomenon particularly well studied in animal models of retinal cells.⁹⁰ Lead may function as an inhibitor or agonist of calcium-dependent processes. For example, lead inhibits neuronal voltage-sensitive calcium channels⁶ and membrane-bound Na⁺-K⁺-ATPase (adenosine triphosphatase)¹⁵⁸ but activates calcium-dependent protein kinase C.¹⁰¹ These effects adversely impact neurotransmitter function.¹⁷⁶ Third, lead exhibits mutagenic and mitogenic effects in mammalian cells in vitro and is carcinogenic in rats and mice.⁴⁵ There is mechanistic plausibility and some epidemiologic evidence for at least a facilitative role of lead in human carcinogenesis,⁷¹ and the International Agency for Research on Cancer (IARC) has assigned inorganic lead compounds a group 2A (probably carcinogenic to humans) classification.^{72,155}

Neurotoxicity

The neurotoxicity of lead involves multiple targets, including cerebrovascular endothelium, mitochondria, neural cell adhesion molecules, neurotransmitter and second-messenger function, regulation of apoptosis, and myelin formation.^{90,133,176} Lead-induced dysfunction in several neurotransmitter systems is linked to its calcium-mimetic properties. Through blockade of calcium influx at voltage-sensitive calcium channels, lead inhibits depolarization-triggered release of acetylcholine, dopamine, and γ -amino butyric acid (GABA) but augments the background rate of spontaneous release.^{36,59,76,90,176} The dampening of the evoked neurotransmitter response in conjunction with enhanced background release results in a decreased “signal-to-noise” ratio.^{56,76} In addition, lead decreases calcium currents at the N-methyl-D-aspartate (NMDA) glutamate receptor and directly activates the intracellular second-messenger protein kinase C.⁷⁶ These effects on neurotransmitter release, receptor activity, and intracellular signaling adversely affect “synaptic pruning” in the developing brain, a process by which the volume of excessive synaptic connections is selectively reduced. This disruption results in suboptimal cortical microarchitecture and function, and it particularly affects the hippocampus, an important locus of learning and memory.^{56,76,176}

Lead also interferes with the 78-kDa chaperone glucose-regulated protein (GRP78) in astrocytes, which may result in adverse protein conformational effects that are thought to be associated with conditions such as Alzheimer disease.¹⁷⁶ In severe cases, pathologic changes in cerebral microvasculature may result in cerebral edema and increased intracranial pressure (ICP), which are associated with the clinical syndrome of acute lead encephalopathy (Fig. 96–1). Peripheral neuropathy is a classic effect of lead poisoning in adults. The neuropathology in humans is poorly characterized. In animal models, it is associated with Schwann cell destruction, segmental demyelination, and axonal degeneration.⁵⁹ Sensory nerves are less affected than motor nerves.

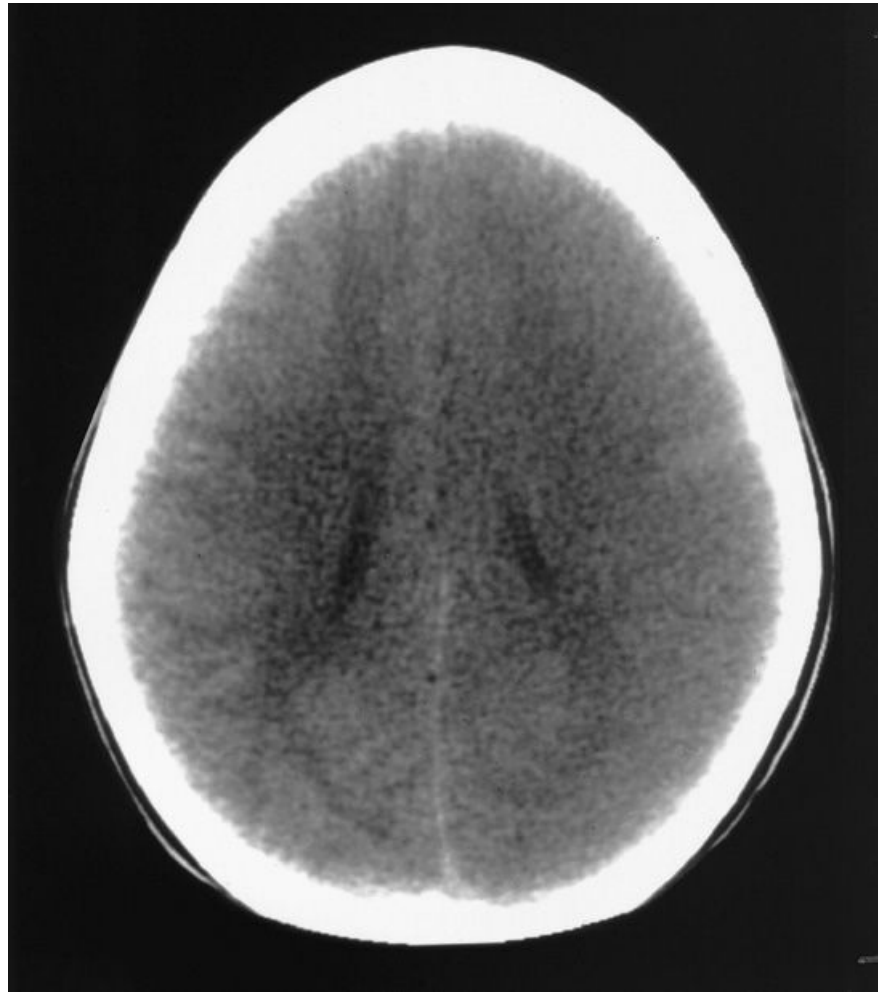


FIGURE 96–1. Computed tomography scan of the brain reveals diffuse cerebral edema and loss of gray-white matter differentiation on day 1 of hospitalization of a 3 year-old boy. He had presented with a brief prodrome of vomiting and altered mental status followed by status epilepticus, characteristic of acute lead encephalopathy. His blood lead concentration was 220 $\mu\text{g/dL}$. (Used with permission of Department of Radiology, St. Christopher’s Hospital for Children, Philadelphia, PA.)

Hematologic Toxicity

Lead is hematotoxic in several ways, including via potent inhibition of several enzymes in the heme biosynthetic pathway (Chap. 22 and Fig. 22–3). It also induces a defect in erythropoietin function secondary to associated kidney damage.^{64,139} A shortened erythrocyte life span is caused by increased membrane fragility with resultant hemolysis. Inhibition of $\text{Na}^+\text{-K}^+\text{-ATPase}$ and pyrimidine-5'-nucleotidase may impair erythrocyte membrane stability by altering energy metabolism. The inhibition of pyrimidine-5'-nucleotidase is also thought to underlie the appearance of basophilic stippling in erythrocytes, representing clumping of degraded RNA, which is normally eliminated by this enzyme¹²¹ (Fig. 96–2).

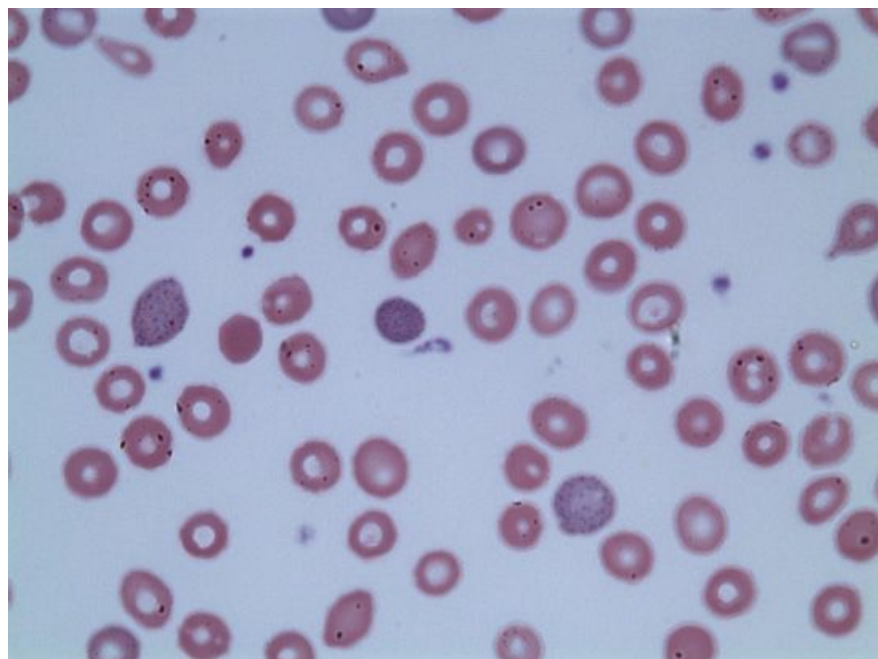


FIGURE 96–2. This peripheral smear of blood examined under high-power microscopy demonstrates the classic basophilic stippling associated with lead poisoning. The patient’s blood lead concentration was over 100 µg/dL. (Used with permission of The New York City Poison Center Toxicology Fellowship Program).

Nephrotoxicity

Functional changes associated with acute lead nephropathy include decreased energy-dependent transport, resulting in a Fanconilike syndrome of aminoaciduria, glycosuria, and phosphaturia. These changes are related to disturbed mitochondrial respiration and phosphorylation and are reversible with discontinuation of exposure or treatment.⁶¹ A pathologic finding is characteristic nuclear inclusion bodies in renal tubular cells composed of lead–protein complex. Chronic high-dose lead poisoning is associated with progressive interstitial fibrosis.⁸⁶ Lead is a renal carcinogen in rodent models, but its status in humans is uncertain.^{45,59}

The association of plumbism with gout (“saturnine gout”) was noted more than 100 years ago. Lead competitively decreases uric acid excretion in the distal tubule, resulting in elevated blood urate concentrations and urate crystal deposition in joints. Kidney function is virtually always impaired in patients with saturnine gout.

Cardiotoxicity

The most important manifestation of lead toxicity on the cardiovascular system is hypertension. This is likely caused by altered calcium-activated changes in contractility of vascular smooth muscle cells secondary to decreased Na^+ - K^+ -ATPase activity and stimulation of the Na^+ - Ca^{2+} exchange pump. Lead may also affect blood vessels by altering neuroendocrine input or sensitivity to such stimuli or by increasing reactive oxygen species that enhance nitric oxide inactivation.⁹³ Elevated serum renin activity is found with moderate toxicity but may be normal or decreased in chronic severe plumbism.¹⁷³ Rarely, direct cardiotoxicity is reported.^{114,135,157} Animal models demonstrate increased sensitivity to norepinephrine-induced dysrhythmias and decreased myocardial contractility, protein phosphorylation, and high-energy phosphate generation.⁸³ Lead-induced impairment of intracellular calcium metabolism may impact cardiac electrophysiology.

Reproductive Toxicity

Impairment of both male and female reproductive function is associated with overt plumbism. Gametotoxic effects in animals of both sexes and chromosomal abnormalities in workers with BLLs above 60 µg/dL are reported.⁵⁹ Testicular endocrine hypofunction occurs in smelter workers with BLLs in the 60 µg/dL range.¹³⁷

Endocrine Toxicity

Reduced thyroid and adrenopituitary function are found in adult lead workers.^{53,142} Children with elevated BLLs have a depressed secretion of human growth hormone and insulinlike growth factor.⁷⁰

Skeletal Toxicity

In addition to the importance of the skeletal system as the largest repository of lead body burden, studies suggest that bone metabolism also is adversely affected by lead.⁵⁹ Hormonal response is altered by reduced 1,25-dihydroxyvitamin D₃ concentrations and by inhibition of osteocalcin. Both new bone formation and coupling of normal osteoblast and osteoclast function may thus be impaired.⁵⁹ Bands of increased metaphyseal density on radiographs of long bones (“lead lines”) in young children with heavy lead exposure represent increased calcium deposition (not primarily lead) in the zones of provisional calcification (**Fig. 96–3**). Impaired bone growth and shortened stature are associated with childhood lead poisoning. Impaired calcium or cyclic adenosine monophosphate (cAMP) messenger systems may underlie these cellular effects.

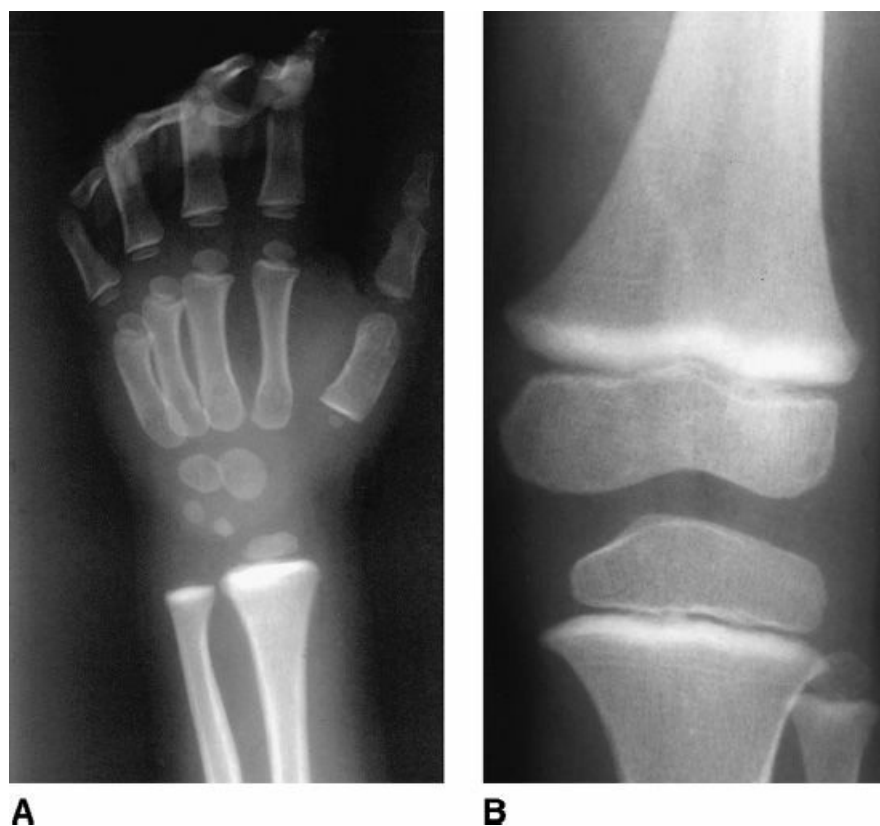


FIGURE 96–3. (A) Radiograph of the wrist reveals increased bands of calcification (“lead lines”) in the same patient as in **Fig. 96–1**. (B) Similar radiographic findings in another patient at the knee. (Part A used with permission of Department of Radiology, St. Christopher’s Hospital for Children, Philadelphia, PA. Part B used with permission of Richard Markowitz, MD, Department of Radiology, Children’s Hospital of Philadelphia, Philadelphia, PA.)

Gastrointestinal Toxicity

Lead toxicity causes constipation, anorexia, and colicky abdominal pain. Although the mechanisms are not fully elucidated, theories include impaired intestinal motility, alterations in luminal ion transport, and spasmodic contraction of intestinal wall smooth muscle.^{39,144}

CLINICAL MANIFESTATIONS

Inorganic Lead

The numerous observed lead-induced pathophysiologic effects accurately predict that the clinical manifestations of lead poisoning are diverse. These manifestations of lead toxicity are characterized into distinct acute and chronic syndromes (**Tables 96–3 and 96–4**). In most cases, these distinctions really describe a continuum of dose-and time-related severity. Rarely, patients with massive acute poisoning present with clinical findings that are somewhat unique but overlap considerably with cases of severe chronic plumbism. However, it should be first reemphasized that the occurrence of overt clinical effects in lead poisoning is, in most cases, the culmination of a long-term lead exposure. As the total dose increases, these effects are almost always preceded first by measurable biochemical and physiologic impairment followed, in turn, by subtle prodromal clinical effects that may only become apparent in hindsight. In general, children are considered to be more susceptible than adults to toxicity for a given measured BLL; however, the data for this primarily concern effects on the CNS.

TABLE 96–3. Clinical Manifestations of Lead Poisoning in Children

<i>Clinical Severity</i>	<i>Typical Blood Lead Concentrations (µg/dL)</i>
Severe CNS: Encephalopathy (coma, altered sensorium, seizures, bizarre behavior, ataxia, apathy, incoordination, loss of developmental skills, papilledema, cranial nerve palsies, signs of increased ICP) GI: Persistent vomiting Hematologic: Pallor (anemia)	>70–100
Mild to moderate CNS: Hyperirritable behavior, intermittent lethargy, decreased interest in play, “difficult” child GI: Intermittent vomiting, abdominal pain, anorexia	50–70
Asymptomatic CNS: Impaired cognition, behavior, balance, fine-motor coordination Miscellaneous: Impaired hearing, impaired growth	>49

CNS = central nervous system; GI = gastrointestinal; ICP = intracranial pressure.

TABLE 96–4. Clinical Manifestations of Lead Poisoning in Adults

<i>Clinical Severity</i>	<i>Typical Blood Lead Concentrations (µg/dL)</i>
Severe CNS: Encephalopathy (coma, seizures, obtundation, delirium, focal motor disturbances, headaches, papilledema, optic neuritis, signs of increased ICP) PNS: Foot drop, wrist drop GI: Abdominal colic Hematologic: Pallor (anemia) Renal: Nephropathy	>100
Moderate CNS: Headache, memory loss, decreased libido, insomnia PNS: peripheral neuropathy GI: Metallic taste, abdominal pain, anorexia, constipation Kidney: Arthritis due to saturnine gout (impaired urate excretion) Miscellaneous: Mild anemia, myalgias, muscle weakness, arthralgias	70–100
Mild CNS: Fatigue, somnolence, moodiness, lessened interest in leisure activities Miscellaneous: Adverse effects on cognition, reproduction, kidney function, or bone density; hypertension and cardiovascular disease; possible increased risk of cancer	20–69 ^a

^aChronic lead exposure at lower blood lead concentrations may lead to cumulative body burdens of lead associated with these clinical findings.

CNS = central nervous system; GI = gastrointestinal; ICP = intracranial pressure; PNS = peripheral nervous system.

Asymptomatic Children. Children with elevated body lead burdens but without overt symptoms represent the largest group of persons believed to be at risk for chronic lead toxicity. The subclinical toxicity of lead in this population centers around subtle effects on growth, hearing, and neurocognitive development. This last effect, in particular, is the subject of intense research interest and scrutiny. An effort to rigorously evaluate several modern (since 1979), carefully performed studies of the association of low lead and reduced intelligence (cross-sectional studies with blood or tooth lead and prospective studies) and combine their results with a statistical meta-analysis technique is reported.¹²⁷ The overall finding was that even though the majority of individual studies failed to achieve statistical significance, in pooled analysis there was a significant inverse association between lead exposure and IQ. The magnitude was on the order of 1 to 2 IQ points for chronic BLL increases from 10 to 20 µg/dL. Since that publication, another study evaluated IQ in children from 6 months to 5 years of age and found that BLLs were inversely correlated with IQ at 3 and 5 years of age and that the magnitude of effect for all subjects was an average 4.6 point decrement in IQ for each 10 µg/dL increase in BLL. Of particular concern, this effect was even greater, with an estimated 7.4 point loss, for the subset of children in the 1 to 10 µg/dL BLL range.¹⁶ The CDC recently compiled a number of studies confirming this steeper dose response at BLLs below 10 µg/dL²⁰ and revised screening guidelines to remove the term “threshold” and lower the action BLL to 5 µg/dL, a reference value to be evaluated every 4 years based on the 97.5 percentile in most recent NHANES data.^{27,88}

Symptomatic Children. Subencephalopathic symptomatic plumbism usually occurs in children 1 to 5 years of age and is associated with BLLs above 70 µg/dL but may occur with concentrations as low as 50 µg/dL. Unfortunately, common complaints in well children of this age (eg, the “terrible twos,” with functional constipation and who do not eat as much as parents expect) often overlap with the milder range of reported symptoms of lead poisoning. Frequently, parents of children diagnosed by routine blood screening recognize milder symptoms only in hindsight after chelation treatment results in

clinical improvement (“it seemed as if the child was going through a phase”)⁵⁴ This is especially true currently, when symptomatic plumbism is rarely reported.^{19,22} Other uncommon clinical presentations are described, including isolated seizures without encephalopathy (indistinguishable from idiopathic epilepsy), chronic hyperactive behavior disorder, isolated developmental delay, progressive loss of cortical function simulating degenerative cerebral disease, peripheral neuropathy (reported particularly in children with sickle cell hemoglobinopathy), and the occurrence of GI effects (colicky abdominal pain, vomiting, constipation) with myalgias of the trunk and proximal girdle muscles.^{34,46}

Acute lead encephalopathy is the most severe presentation of pediatric plumbism (Table 96–3). It may be associated with cerebral edema and increased ICP (Fig. 96–1). Encephalopathy is characterized by pernicious vomiting and apathy, bizarre behavior, loss of recently acquired developmental skills, ataxia, incoordination, seizures, altered sensorium, or coma. Physical examination may reveal papilledema, oculomotor or facial nerve palsy, diminished deep tendon reflexes, or other evidence of increased ICP.^{19,178} Encephalopathy usually occurs in children ages 15 to 30 months; is associated with BLLs above 100 µg/dL, although it is reported with BLLs as low as 70 µg/dL; and tends to occur more commonly in summer months, when BLLs peak.¹²⁵ Milder but ominous findings that may portend incipient encephalopathy include anorexia, constipation, intermittent abdominal pain, sporadic vomiting, hyperirritable or aggressive behavior, periods of lethargy interspersed with lucid intervals, and decreased interest in play activities. Many such patients seek medical advice for vomiting and lethargy during the 2 to 7 days before onset of frank encephalopathy.^{34,125} Physical examination of such children usually reveals no specific abnormalities.

Mortality caused by encephalopathy was 65% in the prechelation era, decreasing to below 5% with the advent of effective chelation. The incidence of permanent neurologic sequelae, including mental retardation, seizure disorder, blindness, and hemiparesis, is 25% to 30% in patients who develop encephalopathic symptoms before the onset of chelation (Fig. 96–4).³⁴

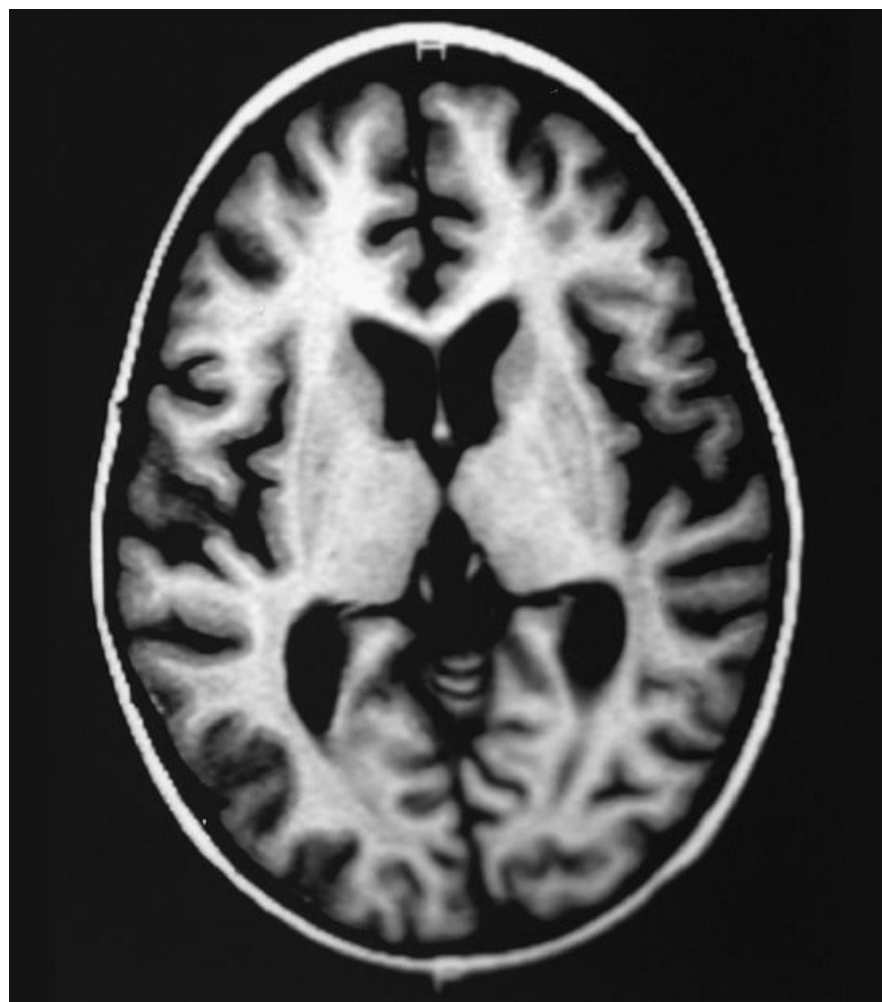


FIGURE 96–4. Magnetic resonance image of the brain reveals cortical atrophy and multiple areas of cerebral infarction in the same patient as in Fig. 96–1, done on hospital day 22. At this time, the child’s clinical status was notable for choreoathetoid movements and generalized hypotonia, inability to localize visual or auditory stimuli, and nonpurposeful movements of the extremities. (Used with permission of Eric Faerber, MD, Department of Radiology, St. Christopher’s Hospital for Children, Philadelphia, PA.)

Adults. Adults with occupational lead exposure may manifest numerous signs and symptoms representing disorders of several organ systems. Severity of symptoms correlates roughly with BLLs, although many conditions thought to be

associated with low-dose chronic lead exposure are better correlated with markers of cumulative dose, such as bone lead or the cumulative blood lead index (area under the curve of BLLs versus time).^{69,86} (Table 96–4). True acute poisoning occurs rarely, after very high inhalational,⁸² large oral,¹¹⁶ or intravenous (IV) exposures.¹¹⁷ Such patients may present with colicky abdominal pain, hepatitis, pancreatitis, hemolytic anemia, and encephalopathy over days or weeks. Most adult plumbism is related to chronic respiratory exposure, although some authors have used the term “acute poisoning” to include patients with such exposure whose symptoms are severe and of relatively recent onset (within 6 weeks of presentation) and whose exposure is relatively brief (average, one year or less).³⁸

In severe plumbism, the hallmark of toxicity is acute encephalopathy, which has been rarely reported in adults since the 1920s.³⁸ The majority of modern cases are actually not associated with occupational exposures but rather with more exotic exposures, such as ingestion of lead-contaminated illicit “moonshine” whiskey and ethnic alternative medications.^{81,161} Encephalopathy in adults is usually associated with very high BLLs (typically >150 µg/dL) and is manifested by seizures (75% of cases), obtundation, confusion, focal motor disturbances, papilledema, headaches, and optic neuritis.^{104,177} In addition, adult patients with severe plumbism often manifest attacks of abdominal colic, are virtually always anemic, and are at significant risk for severe peripheral neuropathy that manifests as wristdrop and footdrop. Nephrotoxic effects may include a Fanconilike syndrome, impaired kidney function, and progressive interstitial fibrosis. Rarely, ventricular dysrhythmias are reported, and long-standing lead toxicity is associated with prolonged QT and QRS intervals.^{49,135}

Moderate plumbism in adults typically involves CNS, peripheral nerves, hematologic, kidney, GI, rheumatologic, endocrine or reproductive, and cardiovascular findings.^{82,140,144} At BLLs above 70 µg/dL, such symptoms may include headache, memory loss, decreased libido, and insomnia. GI symptoms may include metallic taste, abdominal pain, decreased appetite, weight loss, and constipation. Abdominal guarding and tenderness are occasionally observed. Musculoskeletal and rheumatologic complaints at this stage include muscle pain and joint tenderness. Patients with saturnine gout may have typical joint findings of acute arthritis. Peripheral neuropathy may occur, primarily motor, manifesting as dominant hand or wrist weakness, numbness of the legs, paresthesias, and tremor. Many patients at this stage have mild anemia, and those with chronic exposure are at risk for neuropathy as described above.

Mild plumbism may manifest as minor CNS findings, such as changes in mood and cognition. Subtle abnormalities detectable by careful neuropsychiatric testing are found in both adults and children with modest elevations in BLLs and include impaired memory span, rapid motor tapping, visual motor coordination, and grip strength.³⁸ Studies document abnormal psychometrics and nerve conduction in workers recently exposed to lead as BLLs increased to above 30 µg/dL.⁹⁸ Early psychiatric effects, manifesting at BLLs of 40 to 70 µg/dL, include increased tiredness at the end of the day, disinterest in leisure time pursuits, falling asleep easily, moodiness, and irritability. The physical examination is usually normal,⁴¹ or hypertension may be present. A bluish-purple gingival lead line (Burton line), representing lead sulfide precipitation in patients with poor dentition, is described rarely. One author described grayish stippling of the retina circumferential to the optic disk,¹⁶⁰ but other authors dispute this finding.¹²²

Effects on reproductive function may also be apparent in this range of exposure. Historically, infertility and stillbirths were common among heavily exposed women lead workers. More recent studies found reduced sperm counts, impaired motility, and abnormal morphology in men who work in the battery industry with BLLs above 40 µg/dL⁵ and increased incidence of menstrual irregularity and spontaneous abortion in lead-exposed women who worked in China⁷⁵ and Mexico.¹⁰ Prematurity is more common in children of pregnancies associated with elevated maternal BLLs.¹¹³

Increased blood pressure is probably the most prevalent adverse health effect observed from lead toxicity in adults. Epidemiologic studies document significant associations between hypertension and body lead burdens. The association is particularly strong for adult men ages 40 to 59 years, with an approximate 1.5 to 3.0 mm Hg increase in systolic pressure for every doubling of BLL beginning at 7 µg/dL.^{126,167} Additional studies correlate body lead burden with several other disorders of aging, including a decline in cognitive ability,^{147,154} essential tremor,⁴³ cardiovascular and cerebrovascular events,^{73,86,108} electrocardiographic abnormalities,³⁰ chronic renal dysfunction,^{86,93} osteoporosis,¹⁵ and cataract prevalence.¹⁴⁵

Organic Lead

Clinical symptoms of TEL toxicity are usually nonspecific initially and include insomnia and emotional instability.^{9,144} Nausea, vomiting, and anorexia may occur. The patient may exhibit tremor and increased deep tendon reflexes. In more severe cases, these symptoms progress to encephalopathy with delusions, hallucinations, and hyperactivity, which may resolve or deteriorate to coma and, occasionally, death. Severely ill patients may also develop liver and kidney injury. Because many reported patients were exposed via intentional abuse of leaded gasoline, much of the literature reporting this syndrome may be confounded by accompanying volatile hydrocarbon toxicity.¹⁶⁴ Of note, in contrast to inorganic lead poisoning, patients with significant TEL toxicity do not consistently manifest hematologic abnormalities or elevations of heme synthesis pathway biomarkers. In addition, significant neurotoxicity may occur at BLLs considerably lower than those typically associated with inorganic lead poisoning.⁶⁷ A case report details the clinical course of a 13 year-old boy who

unintentionally ingested a mouthful of fuel stabilizer containing 80% to 90% TEL. He developed progressive tremor, weakness, hallucinations, myoclonus, and hyperreflexia and required mechanical ventilation for 2 days and prolonged hospitalization for management of persistent hallucinations, weakness, dysphagia, and urinary and fecal incontinence. His BLL peaked on the third day after ingestion at only 62 µg/dL.¹⁸⁰

DIAGNOSTIC TESTING

Clinical Diagnosis in Symptomatic Patients

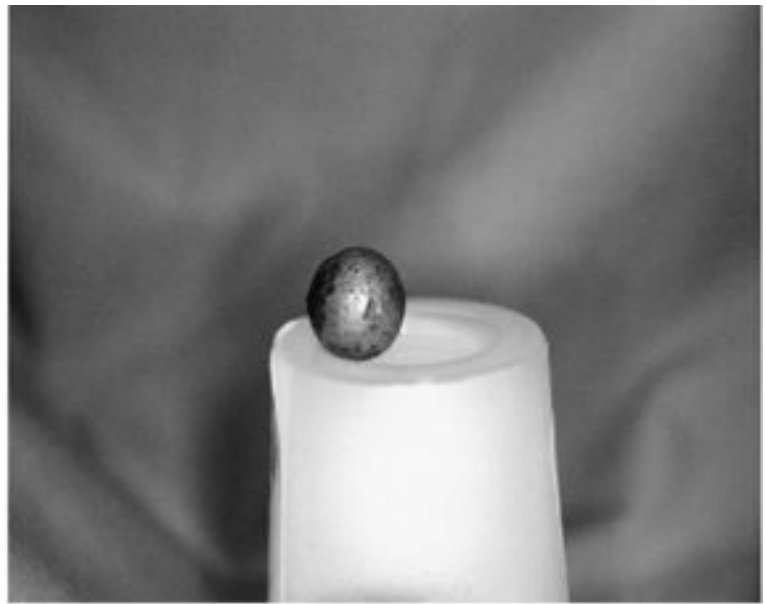
For all patients in whom plumbism is considered based on clinical manifestations, the medical evaluation should first include a comprehensive medical history. Further inquiry should elicit environmental, occupational, or recreational sources of exposure as detailed earlier (Tables 96–1 and 96–2). Plumbism is more likely in a child between the ages of 1 and 5 years with prior plumbism or noted elevated BLLs; history of pica or acute unintentional ingestions;⁶⁵ aural, nasal, or esophageal foreign bodies;¹⁷⁹ history of iron-deficiency anemia; residence in a pre-1960s–built home, especially with deteriorated paint, or one that has undergone recent remodeling; family history of lead poisoning; or foreign-born status.^{3,32,181} Affected children may manifest persistent vomiting, lethargy, irritability, clumsiness, or loss of recently acquired developmental skills; afebrile seizures; or evidence of child abuse or neglect.^{52,149} In adults, the history should focus on occupational and recreational activities that might involve lead exposure (Table 96–2), a history of plumbism, and gunshot wounds with retained bullets.

The differential diagnosis of plumbism is broad. Adult patients may be misdiagnosed as having carpal tunnel syndrome, Guillain-Barré syndrome, sickle cell crisis, acute appendicitis, renal colic, or infectious encephalitis. Children are often initially considered to have viral gastroenteritis or even to have insidious symptoms passed off as a difficult developmental phase.

A patient who presents to the emergency department with potential lead encephalopathy presents the physician with a dilemma: severe lead toxicity requires urgent diagnosis, but confirmatory blood lead assays are not usually rapidly available.¹²⁰ For adults, a history of occupational exposure is often available from medical records or family members, and lead encephalopathy can be strongly considered with positive supportive laboratory findings such as anemia, basophilic stippling, elevated erythrocyte protoporphyrin (especially >250 µg/dL, sometimes available on an urgent basis), and abnormal urinalysis. In this context, it might be appropriate to institute presumptive chelation therapy while awaiting a BLL. In children, a similar indication for presumptive treatment would be suggested by a constellation of clinical features and ancillary studies, such as age 1 to 5 years, a prodromal illness of several days to weeks duration (suggestive of milder lead-related symptoms), history of pica and source of lead exposure, the laboratory features noted above (which are equally helpful in young children), radiologic findings of dense metaphyseal “lead lines” at wrists or knees (Fig. 96–3), or evidence of recent pica for ingested foreign bodies or lead paint particles on abdominal radiographs (Figs. 96–5 and 96–6). Radiographic confirmation of retained bullets or shrapnel may be relevant in patients of any age (Fig. 96–7).^{50,94,148,153} In both adults and children, the decision to institute empiric chelation treatment should not deter additional emergent diagnostic efforts to exclude or to confirm other important entities while BLLs are pending. An important consideration in this context may be the suspicion of an acute, potentially treatable CNS infection (eg, bacterial meningitis or herpetic encephalitis). Lumbar puncture may be dangerous in patients with severe lead encephalopathy because of the risk of cerebral herniation.³⁵ If immediate lumbar puncture is thought to be essential, a computed tomography scan should be first obtained to determine cerebral edema, midline shift, or other evidence of high risk for herniation. If a lumbar puncture is performed, the minimal amount of fluid necessary for diagnosis (<1 mL) should be removed using a small-gauge needle.



A



B

FIGURE 96–5. An unusual source of lead poisoning. **(A)** Radiograph of the abdomen reveals ingested metallic foreign body. **(B)** The ingested foreign body was a Civil War era musketball from the collection of the patient’s father. (Used with permission of Evaline Alessandrini, MD, Division of Emergency Medicine, Children’s Hospital of Philadelphia, Philadelphia, PA.)



A



B

FIGURE 96–6. **(A)** Abdominal radiograph of a child who had massive paint chip ingestion. The dispersed radiodense (white) fragments are noted to follow the outline of the large intestine. **(B)** No remaining lead is seen on follow-up radiograph after whole-bowel irrigation. (Used with permission of Department of Radiology, St. Christopher’s Hospital for Children, Philadelphia, PA.)



FIGURE 96–7. Abdominal radiograph of an 8 year-old child who sustained a shotgun wound to the right paraspinal area, with resultant paraplegia and multiple visceral injuries. The blood lead concentration was found to be 60 $\mu\text{g}/\text{dL}$ at 11 weeks after injury, and chelation therapy was commenced. (Used with permission of Children’s Hospital of Philadelphia, Department of Radiology, Philadelphia, PA.)

Laboratory Evaluation

In patients suspected of having plumbism, laboratory testing is used to augment the evaluation of both lead exposure and lead toxicity. The whole BLL is the principal measure of lead exposure available in clinical practice, reflecting both recent and remote exposure. In any patient suspected of symptomatic plumbism, whole blood should be collected by venipuncture into special lead-free evacuated tubes. The BLL is typically determined by atomic absorption spectrophotometry. For asymptomatic children, BLL screening is often performed by capillary blood testing for convenience; however, venous confirmation of elevated capillary lead concentrations, unless extremely high (eg, $\geq 70 \mu\text{g}/\text{dL}$) or unless the patient is clearly symptomatic, is still considered mandatory before chelation or other significant interventions. Hair and urine lead concentrations have no clinical utility. The erythrocyte protoporphyrin concentration reflects inhibition of the heme synthesis pathway (Chap. 22) and was used as a screening tool in the past, but it is no longer considered sufficiently sensitive. The erythrocyte protoporphyrin concentration test may still be useful for tracking response to therapy and in distinguishing acute from chronic lead poisoning; as an adjunct to the emergency diagnosis of symptomatic plumbism if emergent BLL determination is not available; and, rarely, in the evaluation of suspected factitious plumbism. Routine serum chemistries, kidney function tests, liver function tests, urinalysis, and complete blood count are indicated in patients who are symptomatic or about to undergo chelation therapy. Radiographic studies may reveal retained bullets (Fig. 96–7) or recent lead ingestion. Abdominal radiographs may reveal lead paint chips or other ingested lead foreign material (Figs. 96–5 and 96–6). The finding of “lead lines,” metaphyseal densities at the ends of long bones in young children, may substantiate a clinical diagnosis of plumbism before BLLs are available (Fig. 96–3), although dense metaphyseal bands are rarely caused by other causes, including other metals (arsenic, bismuth, and mercury), healing rickets, and recovery from scurvy.^{130,180}

Finally, two measures of cumulative lead exposure are available. X-ray fluorescence technology measures bone lead, and thus indirectly estimates total body lead burden. The cumulative blood lead index, derived from several BLLs measured over the presumed course of lifetime lead exposure, calculated as an area under the concentration curve, is also described.⁶⁹ Both techniques are used in research studies of issues concerning past chronic lead exposure and a variety of current health outcomes.^{68,85,175}

SCREENING

Although outside the scope of this discussion, screening is an essential public health practice for the prevention of severe plumbism in both children and adults from high-risk settings. Table 96–5 outlines the current CDC^{20,26,27} pediatric recommendations, which also are endorsed by the American Academy of Pediatrics.³ Likewise, the Occupational Safety and Health Administration (OSHA) maintains a lead standard for US workers formulated to reduce workplace exposure to lead, decrease symptomatic lead poisoning, and provide quality medical care to workers with elevated BLLs.^{168–171} Table 96–6A summarizes the OSHA-mandated action BLL values for worker notification, removal, and reinstatement. An expert panel convened by the Association of Occupational and Environmental Clinics published an alternative set of health-based management recommendations for lead exposed workers. The authors propose that their recommendations are more reflective of recent research linking adverse health outcomes to chronic, low-dose lead exposure.⁸⁶ These guidelines are summarized in Table 96–6B.

TABLE 96–5. Pediatric Screening and Follow-up Guidelines^{3,20,24,27}

Screening

1. The AAP and CDC recommend screening all children who are Medicaid eligible at age 1 and 2 years (and those ages 3–6 years who have not been screened previously). Children who may not be Medicaid eligible but whose families participate in any poverty assistance program should also be screened.
2. Certain local health departments (eg, New York, Chicago, and Philadelphia) recommend screening at younger ages or more frequently. Such recommendations include starting at age 6–9 months, testing every 6 months for children younger than 2 years, and provision of additional education and more rapid follow-up testing for children younger than 12 months old whose BLLs are 6–9 µg/dL.
3. In addition, children who are not Medicaid eligible but are designated high-risk by their state or local health departments should be screened as per these local policies.^a
4. For children who are neither Medicaid eligible nor live in areas with locale-specific health department guidelines, recommendations are less clear. The AAP supports universal screening of such children as well.^b
5. Recent immigrants, refugees, or international adoptee children should be screened on arrival to the United States.

Follow-Up

B Pb (µg/dL)	Recommended Action
≤9 ^c	Retest in one year
10–14	Retest in 3 months; education ²⁹
15–19	Retest in 2 months; education; if the BLL is 15–19 µg/dL twice, refer for case management
20–44	Clinical evaluation; education; environmental investigation and lead hazard control
45–69	Clinical evaluation and case management within 48 hours; education; environmental investigation and lead hazard control; chelation therapy ^{1,22}
≥70	Hospitalize child; immediate chelation therapy; education; environmental investigation and lead hazard control

^aMany relevant state and city health department contacts may be located at: <http://www.cdc.gov/nceh/lead/about/program.htm>. ^bThe 1997 CDC guidance²⁸ allowed for targeted screening of some children of low-risk geographic and demographic background based on a personal risk questionnaire. Subsequent studies have found that such survey-based targeted screening is not well validated.¹ Nevertheless, a listing of potential risk factors may be instructive and is summarized here. Screening was recommended if a child had any of the following high-risk factors:

Housing: Lives in or regularly visits a home built before 1950; lives in or regularly visits a home built before 1978 undergoing remodeling or renovation (or renovated within 6 months).

Medical history: Pica for paint chips or dirt; iron deficiency.

Personal, family, and social history: Personal, family, or playmate history of lead poisoning; parental occupational, industrial, hobby exposures; live in proximity to major roadway; use of hot tap water for consumption; use of complementary remedies, cosmetics, ceramic food containers; trips or residence outside United States; parents are migrant farm workers, receive poverty assistance.

¹In 2012, the Advisory Committee for Childhood Lead Poisoning Prevention through the CDC reevaluated the use of the 10 µg/dL threshold concern and made two important changes: (1) replacing the term “threshold” with the 97.5 percentile reference values from NHANES data, to reflect no safe level of lead exposure for the young child, and (2) changing the action number to 5 µg/dL from 10 µg/dL. The formal screening recommendations have not yet been changed, but this is expected shortly.

Educational interventions as per Table 96–7.

Chelation therapy as per Table 96–8.

AAP = American Academy of Pediatrics; BLL = blood lead concentration; BPb = venous blood lead; CDC = Centers for Disease Control and Prevention.

TABLE 96–6A. Occupational Safety and Health Administration General Industry^a Standards for Various Blood Lead Concentrations (BLLs)

<i>Number of Tests</i>	<i>BLL (µg/dL)</i>	<i>Action Required</i>
1	≥40	Notification of worker in writing; medical examination of worker and consultation
3 (average)	≥50	Removal of worker from job with potential lead exposure
1	≥60	Removal of worker from job with potential lead exposure
2	<40	Reinstatement of worker in job with potential lead exposure

^aThe construction industry standard is similar for worker notification (at 40 µg/dL) and reinstatement (<40 µg/dL twice) but requires worker removal for a single value ≥50 µg/dL.

Data from US Department of Labor, Occupational Safety and Health Administration: *Medical Surveillance Guidelines—1910.1025 App C*.

http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10033. Retrieved July 1, 2013; and US Department of Labor, Occupational Safety and Health Administration: *Medical Surveillance Guidelines. Lead—1926.62*.

http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10642. Retrieved December 29, 2005. See also US Department of Labor.¹⁶⁸⁻¹⁷¹

TABLE 96–6B. Health-Based Occupational Surveillance Recommendations^a

<i>BLL (µg/dL)</i>	<i>Recommendation</i>
<10	BLL every month for 3 months and then every 6 months (unless exposure increases); if BLL increases >4 µg/dL, exposure evaluation or reduction effort; exposure evaluation or reduction if BLL 5–9 µg/dL for women who are or may become pregnant
10–19	As for BLL <10 µg/dL and BLL every 3 months; exposure evaluation and reduction effort; consider removal if no improvement with exposure reduction or complicating medical condition ^b ; resume BLL q 6 months if 3 BLLs <10 µg/dL
≥19	Remove from exposure if BLL >30 µg/dL or repeat BLL in 4 weeks; BLL every month; consider return to work after BLL <15 µg/dL twice

^aAll potentially lead-exposed workers warrant preemployment clinical evaluation, baseline blood lead concentration (BLL), and serum creatinine concentration. ^bSuch conditions include chronic kidney disease, hypertension, neurologic disorders, and cognitive dysfunction.

Data from Kosnett MJ, Wedeen RP, Rothenberg SJ, et al: Recommendations for medical management of adult lead exposure. *Environ Health Perspect.* 2007;115:463–471.

MANAGEMENT

There are several caveats about the management of patients with lead poisoning. First, the most important aspect of treatment is removal from further exposure to lead. Unfortunately, effective implementation of this therapy is often beyond the control of the clinician but rather depends on a complex interplay of public health, social, and political actions. Currently, the ability to control exposure is generally more applicable to adults with occupational exposures than to children exposed to residential hazards. Second, in children for whom some residual lead exposure potentially continues, optimization of nutritional status is vital in order to minimize absorption. Finally, pharmacologic therapy with chelators, although a mainstay of therapy for symptomatic patients, is an inexact science, with numerous unanswered questions despite almost 50 years of clinical use.^{2,4,85} The rationale for chelation therapy of lead poisoned patients is that chelators complex with lead, forming a chelate that is excreted in urine, feces, or both. Chelation therapy increases lead excretion, reduces blood concentrations, and reverses hematologic markers of toxicity during therapy. Reports from the 1950s found symptomatic improvement in adults chelated for lead colic.¹⁷⁴ The institution of effective combination chelation treatment of childhood lead encephalopathy in the 1960s contributed to the dramatic decline in mortality and morbidity of that

devastating degree of plumbism.³⁴ However, the same era saw major advances in pediatric critical care in general and medical management of increased ICP in particular. The situation of chelation therapy for asymptomatic patients with mildly to moderately increased body burdens of lead is even less clear, and many questions regarding efficacy and safety remain.^{32,60,85,124} To date, long-term reduction of target tissue lead content or reversal of toxicity is not demonstrated in human trials.^{42,102,138}

Decreasing Exposure

All patients with significantly elevated BLLs warrant identification of the lead exposure source, and specific environmental and medical interventions, or both (Table 96–7). In adults, this usually involves worksite changes.^{41,86,144} The risk of occupational lead exposure correlates with several factors that contribute to the occurrence of respirable lead fumes or dust particles in the worksite atmosphere.¹⁴⁴ First, there are hazards inherent in the work process itself, including high temperatures; significant aerosol, dust, or fume production; and a less mechanized workplace (with resulting greater “hands-on” employee exposure). Second, the adequacy of dust elimination, such as local and general ventilation, is critical. The third category is that of worksite and personal hygiene, including proper use of protective clothes and equipment, and thorough housekeeping. Remedial actions might include improvements in ventilation, modification of personal hygiene habits, and optimal use of respiratory apparatus. It is vital to prohibit smoking, eating, and drinking in a lead exposed work area. Work clothes should be changed after each shift and should not be lockered together with street clothes.

TABLE 96–7. Evaluation and Management of Patients with Lead Exposure

Workplace Efforts

Adults

- Implement careful lead exposure monitoring (Table 96–6B)
- Improve ventilation
- Use a respiratory protective apparatus
- Wear protective clothing; change from work clothes before leaving worksite
- Modify personal hygiene habits
- Prohibit eating, drinking, and smoking at the worksite
- Evaluate possible sources beyond occupational setting (Tables 96–1 and 96–2)

Children

- Notify the local health department to initiate home inspection and abatement as needed
- Home lead paint abatement (professional contractors if possible; use plastic sheeting, low dust-generating paint removal; replacement of lead-painted windows, floor treatment; final cleanup with high-efficiency particle air vacuum, wet mopping)
- Avoid most hazardous areas of the home and yard
- Dust control: Wet mopping, sponging with high-phosphate detergent; frequent hand, toy, and pacifier washing
- Soil lead exposure reduction by planting grass and shrubs around the house
- Use only cold, flushed tap water for consumption
- Optimize nutrition to reduce lead absorption: avoid fasting; give an iron, calcium, vitamin C sufficient diet; supplement iron and calcium as necessary
- Avoid food storage in open cans
- Avoid imported ceramic containers for food and beverage use

Evaluate parental occupations and hobbies and eliminate high-risk activity

Consider possible sources beyond lead paint exposure (Tables 96–1 and 96–2)

In patients with plumbism caused by retained bullets, surgical removal of this lead source should be considered.^{28,94,107} Table 96–7 also summarizes several specific educational guidelines that may be offered to parents of lead-exposed children.^{3,14,22} Overarching principles include home lead paint abatement (done preferably by professionals, with the family out of the home), home dust reduction techniques, decreasing soil lead exposure, and nutritional evaluation and counseling. Patients manifesting iron deficiency should be treated, and for others, a diet sufficient in trace nutrients, particularly iron and calcium (which may decrease lead absorption) and vitamin C (which may enhance renal lead excretion) is likely of value.³ Clinicians who have primary responsibility for children with elevated BLLs should refer to the exhaustive monograph developed by the CDC, which details such pediatric case management.²²

Occasionally, children may require urgent GI decontamination to reduce ongoing acute lead exposure. Patients with large burdens of lead paint chips may benefit from prompt institution of whole-bowel irrigation (WBI) (Fig. 96–6) (Antidotes in Depth: A2). The presence of ingested lead foreign bodies is a unique situation that requires careful individualization of management. Several case reports document rapid absorption, with significantly elevated BLLs measured within 24 hours of ingestion in some cases. Such patients warrant baseline BLL determination and frequent repeat BLLs, with consideration for prompt endoscopic removal, particularly with gastric location and increasing BLLs.^{106,112,172} Proton pump inhibitor and prokinetic therapy are recommended for gastric foreign bodies in an effort to decrease gastric acidity, retention time, and resultant lead dissolution.⁵¹ WBI may be an adjunct for more distally located foreign bodies but has not been uniformly successful. Endoscopic or surgical removal may be indicated with delayed passage of foreign bodies, inability to tolerate WBI due to intestinal obstruction, or rapid elevations in BLL soon after foreign body ingestion.^{51,112,172} The issue of concomitant chelation therapy in patients with significant GI lead burdens is addressed in the following section.

Chelation Therapy

The indications for and specifics of chelation therapy are determined by the age of the patient, the BLL, and clinical symptomatology (Table 96–8). Three chelators are currently recommended as drugs of choice for the treatment of lead poisoning: BAL (Antidotes in Depth: A25) and CaNa₂EDTA (Antidotes in Depth: A27) are used parenterally for more severe cases, and succimer (Antidotes in Depth: A26) is available for oral therapy. A fourth drug, D-penicillamine, has been used orally for patients with mild to moderate excess lead burdens. Unfortunately, D-penicillamine has a toxicity profile that includes life-threatening hematologic disorders and reversible, but serious, dermatologic and kidney effects; consequently, since 1991, its role in lead poisoning treatment at most centers has been largely replaced by succimer. Currently, the American Academy of Pediatrics recommends D-penicillamine use only when unacceptable adverse reactions to both succimer and CaNa₂EDTA occur, and it remains important to continue chelation.^{2,3}

TABLE 96–8. Chelation Therapy Guidelines^{2,3,22,82,125,128} for Initial Course of Treatment^a

Condition, BLL (µg/dL)	Dose	Regimen/Comments
Adults		
Encephalopathy	BAL 450 mg/m ² /d ^a and CaNa ₂ EDTA 1000–1500 mg/m ² /d ^a	75 mg/m ² IM every 4 hours for 5 days Continuous infusion or two to four divided IV doses for 5 days (start 4 hours after BAL)
Symptoms suggestive of encephalopathy or >100	BAL 300–450 mg/m ² /d ^a and CaNa ₂ EDTA 1500 mg/m ² /d ^a	50–75 mg/m ² IM every 4 hours for 3–5 days (base dose, duration on BLL, severity of symptoms; see text) Continuous infusion or two to four divided IV doses for 5 days (start 4 hours after BAL) Lab: Baseline CT scan; CBC, Ca ²⁺ , BLL, BUN, Cr, LFTs, U/A; repeat CBC, Ca ²⁺ , BUN, Cr, LFTs, U/A daily; BLL on days 3 and 5
Mild symptoms or 70–100	Succimer 700–1050 mg/m ² /d	350 mg/m ² tid for 5 days, then bid for 14 days. Remove from exposure (Table 96–7) Lab: CBC, BLL, BUN, Cr, LFTs, U/A; repeat CBC, LFTs, BLL on days 7 and 21
Asymptomatic and <70	Usually not indicated	—
Children		
Encephalopathy	BAL 450 mg/m ² /d ^a and CaNa ₂ EDTA 1500 mg/m ² /d ^a	75 mg/m ² IM every 4 hours for 5 days Continuous infusion or two to four divided IV doses for 5 days (start 4 hours after BAL) Lab: Baseline AXR, CT scan, CBC, Ca ²⁺ , Na ⁺ , BEL, BUN, Cr, LFTs, U/A; repeat CBC, Ca ²⁺ , Na ⁺ , BUN, Cr, LFTs, U/A daily; BLL on days 3 and 5
Symptomatic (without encephalopathy) or >49	BAL 300–450 mg/m ² /d ^a and CaNa ₂ EDTA 1000–1500 mg/m ² /d ^a	50–75 mg/m ² IM every 4 hours for 3–5 days (base dose, duration on BLL, severity of symptoms; see text) Continuous infusion or two to four divided IV doses for 5 days (start 4 hours after BAL) Lab: Baseline AXR, CBC, Ca ²⁺ , BLL, BUN, Cr, LFTs, U/A; repeat CBC, Ca ²⁺ , BUN, Cr, LFTs, U/A on days 3 and 5 and BLL day 5
Asymptomatic: 45–49	Succimer 700–1050 mg/m ² /d ^a or CaNa ₂ EDTA, 1000 mg/m ² /d ^a	350 mg/m ² tid for 5 days and then bid for 14 days Lab: Baseline AXR, CBC, BLL, LFTs; repeat CBC, LFTs, BLL days 7 and 21 Continuous infusion or two to four divided IV doses for 5 days (see text) Lab: Baseline AXR, CBC, Ca ²⁺ , BLL, BUN, Cr, LFTs, U/A; repeat Ca, BUN, Cr, LFTs, U/A on days 3 and 5 and BLL on day 5
20–44	Routine chelation not indicated (see text) Attempt exposure reduction	If succimer used, same regimen as per above group (Table 96–7)
<20	Chelation not indicated Attempt exposure reduction	(Table 96–7)

Subsequent treatment regimens should be based on postchelation BPs and clinical symptoms (see text).

Approximate equivalent doses are expressed in mg/kg: BAL 450 mg/m²/d (–24 mg/kg/d); 300 mg/m²/d (–16 mg/kg/d).

CaNa₂EDTA 1000 mg/m²/d (–25–50 mg/kg/d); 1500 mg/m²/d (–30–75 mg/kg/d); adult maximum dose 3–3 g/d; succimer 150 mg/m² (–10 mg/kg).

^aSome clinicians recommend CaNa₂EDTA alone in these contexts (see text).

AXR = abdominal radiography; BEL = blood lead concentration; BPs = venous blood lead; BUN = blood urea nitrogen; Ca = calcium; CaNa₂EDTA = edetate calcium disodium; CBC = complete blood count; Cr = creatinine; CT scan = computed tomography scan of the brain; IM = intramuscular; IV = intravenous; Lab = supported laboratory and radiologic evaluation; LFTs = hepatic aminotransferases; U/A = urinalysis with microscopy (frequent monitoring of urine depicts analysis for hematuria and proteinuria also advised during CaNa₂EDTA therapy).

Chelation is not a panacea for lead poisoning. It is a relatively inefficient process, with a typical course of therapy decreasing body content of metal by only 1% to 2%.^{85,111} Furthermore, there is little evidence that chelators have significant access to critical sites in target organs, particularly in the brain.³⁷ Assumptions that reducing BLL will improve subtle neurocognitive dysfunction or other subclinical organ toxicity are appealing theoretically but unproven.^{42,138}

Children

Lead encephalopathy is an acute life-threatening emergency and should be treated under the guidance of a multidisciplinary team in the intensive care unit of a hospital experienced in the management of critically ill children. Encephalopathy requires treatment by combination parenteral chelation therapy with maximum-dose BAL and CaNa₂EDTA along with meticulous supportive care.^{2,22,34} Such combination therapy has a dramatic effect on decreasing BLL—to 50% or less of baseline within 15 hours and to 75% to 80% of baseline by 48 to 72 hours. It is far superior to monotherapy with CaNa₂EDTA in this regard.³⁴

Chelation is instituted with 450 mg/m²/d (or 25 mg/kg/d) of intramuscular (IM) BAL in six divided doses.^{2,22} The second dose of BAL is given 4 hours later followed immediately by IV CaNa₂EDTA, in maximum concentration of 0.5%

solution, at 1500 mg/m²/d (or 50 mg/kg/d) as a continuous infusion or in divided-dose infusions over several hours.^{2,22,125} The delay in initiating CaNa₂EDTA infusion is based on past observations of clinical deterioration in encephalopathic patients treated with CaNa₂EDTA alone.^{2,34} Therapy is typically continued with both agents for 5 days, although in milder cases with prompt resolution of encephalopathy and decrease of BLL to below 50 µg/dL, BAL may be discontinued after 3 days, with continuation of CaNa₂EDTA alone for 2 more days.

The presence of radiopaque material in the GI tract on radiography has raised concern that parenteral chelation might enhance absorption of residual gut lead. This issue is not settled fully,^{32,78} but most experts advocate initiation of parenteral chelation without delay in seriously symptomatic patients. It seems reasonable to simultaneously attempt whole bowel irrigation with a polyethylene glycol preparation.² One case report described the successful use of chelation therapy begun with parenteral BAL and CaNa₂EDTA and then enteral succimer (initiated after 3 days of WBI) for a child with lead encephalopathy and an extraordinarily high BLL of 550 µg/dL.⁵⁷ This issue applies as well to ingested lead foreign bodies, as noted above.^{106,112,172} Generally, oral fluids, feedings, and medications are withheld for at least the first several days. Careful provision of adequate IV fluids optimizes kidney function while avoiding overhydration and the risk of exacerbating cerebral edema. The occurrence of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may be associated with lead encephalopathy,^{34,163} so urine volume, specific gravity, and serum electrolytes should be closely monitored, especially as fluids are gradually liberalized with clinical improvement (Chap. 19). In the context of lead encephalopathy, this approach would need to be tempered by the requirement for maintaining good urine output to optimize chelation efficacy.

Seizure control is usually accomplished with benzodiazepines. Ongoing anticonvulsant therapy is typically continued with phenytoin or phenobarbital. Rarely, continuous infusions of midazolam or high-dose pentobarbital therapy may be necessary.¹⁷⁸

Modern approaches to the management of cerebral edema and increased ICP have not been critically evaluated in the context of lead encephalopathy. Lumbar puncture should probably be avoided if lead encephalopathy is highly suspected and acute infectious processes are not. Of note, repeated lumbar puncture was used as an adjunct to the treatment of lead encephalopathy associated with increased ICP in the 1950s but was complicated by proximate death when signs of impending herniation were present.³⁵ It seems reasonable that measures such as prevention of hypoxia and hypercarbia with tracheal intubation and controlled ventilation, seizure treatment and prophylaxis, maintenance of adequate cerebral perfusion pressure, mild hyperventilation with PCO₂ of 30 to 35 mm Hg, and neutral head positioning with elevation of the head of the bed to 30 degrees might have a salutary effect at minimal risk of increased iatrogenic morbidity.^{2,162} Mannitol administration may prove beneficial in deteriorating patients and has been particularly suggested as an adjunctive therapy when cerebral edema is complicated by SIADH or impaired kidney function.³⁴ Whether more aggressive measures, such as acute hyperventilation for impending herniation, ICP monitoring, drainage of ventricular cerebrospinal fluid, decompressive craniectomy, induced hypothermia, or barbiturate coma would decrease mortality or morbidity further is unknown.

For children with milder effects or who are asymptomatic with BLL greater than 70 µg/dL, chelation with a two-drug regimen similar to that used for encephalopathy is recommended. It is likely that this group of patients will require only 2 to 3 days of BAL in addition to 5 days of CaNa₂ EDTA. Some authors have suggested that asymptomatic patients in this group, particularly those with BLLs below 100 µg/dL, might also be adequately treated with CaNa₂ EDTA alone,¹⁸¹ succimer plus CaNa₂ EDTA, or even succimer alone, most recently a large cohort of 1193 Nigerian children with moderate to severe lead poisoning were managed with succimer alone. Although data concerning long term efficacy is still emerging, this appears to be a safe alternative if circumstances preclude standard two drug chelation.^{164a} Intensive care monitoring may be prudent for such patients as well, at least during the initiation of chelation therapy.¹¹¹

Chelation therapy is widely recommended for asymptomatic children with BLLs between 45 and 70 µg/dL.^{2,4,22,111} Children without overt symptoms may be treated with succimer alone, which has documented efficacy in lowering BLLs and short-term safety since its approval by the Food and Drug Administration in 1991.^{63,91} Succimer is initiated at 30 mg/kg/d (or 1050 mg/m²/d) orally in three divided doses; this is continued for 5 days and then decreased to 20 mg/kg/d (or 700 mg/m²/d) in two divided doses for 14 additional days.^{2,62} The original data establishing this empiric dosing regimen were based on body surface area rather than weight.⁶² For younger children, the alternative dosing by body weight results in suboptimal dosing.¹³⁶ Although the ability to chelate children orally with succimer makes it tempting to prescribe routinely for outpatient therapy and some animal evidence suggests succimer does not enhance enteral lead absorption,⁸⁰ clinical reports suggest that children must be protected from continued lead exposure during succimer chelation.^{31,33} Home abatement and reinspection should be accomplished before initiation of ambulatory succimer therapy; if this is not feasible, hospitalization is still warranted. Alternative regimens (for rare patients with succimer intolerance or allergy or because of parental noncompliance) include parenteral chelation with CaNa₂EDTA at 25 mg/kg/d for 5 days.²

After initial chelation therapy, decisions to repeat treatment are based on clinical symptoms and follow-up BLLs. Patients with encephalopathy or any severe symptoms or with an initial BLL above 100 µg/dL often require repeated courses of treatment. It is suggested that at least 2 days elapse before restarting chelation. The precise regimen and dosing of chelating agents are determined by ongoing symptomatology and the repeat BLLs (Table 96–8). A third course of chelation should rarely be necessary sooner than 5 to 7 days after the second course ends.¹²⁵ For patients with milder degrees of plumbism (eg, asymptomatic, initial BLL <70 µg/dL), it is reasonable to allow 10 to 14 days of reequilibration before restarting treatment.²

The management of asymptomatic children with BLLs of 20 to 44 µg/dL is controversial.^{31,100,110,166} The National Institutes of Health–sponsored Treatment of Lead-exposed Children (TLC) trial found only modest efficacy of succimer in reducing BLL. Furthermore, at 3 years postenrollment, no benefit was noted in treated patients on measures of cognition, neuropsychiatric function, or behavior.¹³⁸ This large study enrolled 780 children in a multicenter, randomized, placebo-controlled, double-blind trial, but it still has been criticized, particularly for using a single chelator and having failed to lower BLL significantly over time between treated and control groups.¹⁵¹ Of note, small but statistically significant decrements in growth velocity were noted in the treatment group, which might reflect trace mineral depletion.¹²⁴ Since its initial publication, the primary findings of the TLC trial on lack of cognitive improvement were confirmed in a 7 year follow-up study.⁴² In addition, a reanalysis of the original data found that decreasing blood concentrations did correlate with improved cognitive scores over the initial 36 month trial period (~4 IQ points for each 10 µg/dL decrease in BLL), but only in the placebo group.⁹⁶ Nevertheless, there may still be potential indications for occasional chelation treatment in this group, including BLLs at the higher end of the range (eg, 35–44 µg/dL), especially if BLLs remain the same or increase over several months after rigorous environmental controls are instituted, in younger children (eg, younger than 2 years), in children with evidence of biochemical toxicity (an elevated erythrocyte protoporphyrin concentration, after iron supplementation, if necessary), or any hint of subtle symptoms. Currently, the CDC¹⁹ and the American Academy of Pediatrics^{2,3} recommend aggressive environmental and nutritional interventions with close monitoring of blood lead concentrations, without routine chelation therapy, for such children.

BLLs of 5 to 19 µg/dL are defined by the CDC as representing excessive exposure to lead but not requiring chelation therapy. Close monitoring (for the 5–14 µg/dL range) and careful environmental investigation and interventions as necessary (particularly for the 15–19 µg/dL range) are appropriate and sufficient.^{2,3,22} The educational approaches outlined earlier should be included in the case management of all children with even modestly elevated lead levels (Table 96–7).

Adults

General Considerations. The first principle in the treatment of adults with lead poisoning is that chelation therapy may not substitute for adherence to OSHA lead standards at the worksite and should never be given prophylactically.^{41,82} In addition to the guidelines for decreasing lead exposure noted earlier, chelation therapy is indicated for adults with significant symptoms (encephalopathy, abdominal colic, severe arthralgias, or myalgias), evidence of target organ damage (neuropathy or nephropathy), and possibly in asymptomatic workers with markedly elevated BLLs or evidence of biochemical toxicity.^{86,134,144,150} Table 96–8 outlines suggested chelation therapy regimens for adults. For encephalopathic adult patients, our practice is to recommend combined BAL and CaNa₂EDTA therapy, just as for children, although some clinicians suggest that adults with severe lead poisoning may be successfully treated with CaNa₂EDTA alone in doses of 2 to 4 g/d by continuous IV infusion.⁸⁴ Recent reports support the use of succimer in adult patients with mild to moderate plumbism after environmental and occupational remedies have been instituted.^{92,128} Chelation therapy should also be considered in the perioperative period for patients undergoing surgical removal of retained bullets or débridement of adjacent lead-contaminated tissue.^{94,107,148} Treatment of patients with acute TEL toxicity is largely supportive, with sedation as necessary. For patients seen soon after a large-volume ingestion, nasogastric suction, with airway protection as needed, may be warranted. In general, chelation therapy for TEL toxicity is associated with enhanced lead excretion¹² but has not been found to be clinically efficacious.^{144,164,180} However, for symptomatic, especially encephalopathic patients with very elevated BLLs (in whom there may be a significant component of metabolically derived inorganic lead toxicity), we recommend chelation therapy.

Pregnancy, Neonatal, and Lactation Issues. An area of particular concern in the management of adult plumbism involves decisions regarding therapy during pregnancy. As noted previously, lead freely passes the placental barrier and accumulates in the fetus throughout gestation. Chelation therapy during early pregnancy poses theoretical problems of teratogenicity, particularly that caused by enhanced excretion of potentially vital trace elements, or translocation of lead from mother to fetus (Antidotes in Depth: A25, A26, and A27). Symptomatic pregnant women with elevated BLLs certainly warrant chelation therapy, regardless of these concerns. Additionally, of some reassurance regarding fetal health, a case series and 25 year literature review of lead poisoning during pregnancy found no reports of chelation-associated birth defects in the handful of published cases.¹⁵² It should be noted that despite decreases in maternal BLL with chelation therapy, newborn BLLs may be considerably higher and, in some cases, may approximate the pretreatment maternal BLL,

implying limited efficacy for in utero fetal chelation. However, in these cases, the hemoglobin concentration of the newborn was generally much higher than that of the mother, and thus some of the maternal–neonatal difference in BLL may simply reflect this difference in hemoglobin concentration and hence total blood lead content. In general, there currently seems little support for routine chelation therapy in pregnant women who would not otherwise warrant treatment based on their own symptoms or degree of elevated BLL. Calcium carbonate supplementation may be considered because its use is associated with decreased bone resorption during pregnancy and thus possibly lessened fetal lead exposure.⁷⁴

Postnatally, infant BLLs may decline over time without chelation, but this occurs very slowly.¹⁴¹ In two reported neonates exposed to prenatal maternal chelation who were then monitored for 2 weeks postpartum, the BLL remained stable or increased until chelation therapy was instituted.^{123,165} In two additional cases of neonates whose mothers were not treated prepartum, BLLs also remained stable or increased for 17 days to 3 weeks.^{55,159} Thus, postpartum chelation therapy is warranted for neonates, depending on BLLs, as per the guidelines described above for older children. Exchange transfusion might be considered for neonates with extremely elevated BLLs.¹³ Succimer chelation therapy was used for one neonate with presumed organic lead exposure via maternal gasoline sniffing.¹²⁹

Lastly, the issue of allowing mothers with elevated BLLs to breastfeed their infants may arise. Breast milk from heavily exposed mothers may be a potential source of lead exposure and may require lead concentration analysis before breastfeeding can be safely recommended.^{7,48} One small case series found that breast milk from two women with BLLs of 34 and 29 µg/dL, respectively, had clinically insignificant lead content (<0.01 µg/mL).⁷ Breast milk analysis may be warranted in some cases, particularly with BLLs of 35 µg/dL or greater, before safely advising continued nursing. Despite these considerations, the majority of women without excessive lead exposure should still be encouraged to breastfeed. Of note, one study has found that a relatively simple intervention, calcium supplementation (1200 mg/d of elemental calcium as calcium carbonate), reduces breast milk lead content by 5% to 10%.⁴⁷

SUMMARY

- Lead is a widely distributed element that has long been used by humans for a variety of purposes, including waterproofing; electrical and radiation shielding; and the production of ammunitions, paints, plastics, ceramics, glass, and explosives.
- Lead poisoning, or plumbism, has an equally long history, but today it is primarily manifest in young children exposed to deteriorated lead paint and as an occupational toxic exposure for adult workers.
- Lead causes multiorgan toxicity, affecting especially the hematologic and neurologic systems in patients of all ages and causing hypertension in adults. This may result in a broad spectrum of clinical effects ranging from subtle neurocognitive effects to vague constitutional symptoms to acute encephalopathy, intracranial hypertension, cerebral edema, and death.
- The mainstays of treatment are removal from exposure. Chelation therapy is reserved for patients with symptoms or significantly elevated body lead burdens. Defining a group of asymptomatic patients that will benefit from chelation therapy has been difficult and controversial.
- Parenteral chelation with CaNa₂EDTA and BAL is efficacious in lowering BLLs and reducing mortality and morbidity from severe lead poisoning. Succimer, an oral chelator, also has efficacy in reducing BLLs in asymptomatic children, although the neurocognitive benefit of doing so is unproven.

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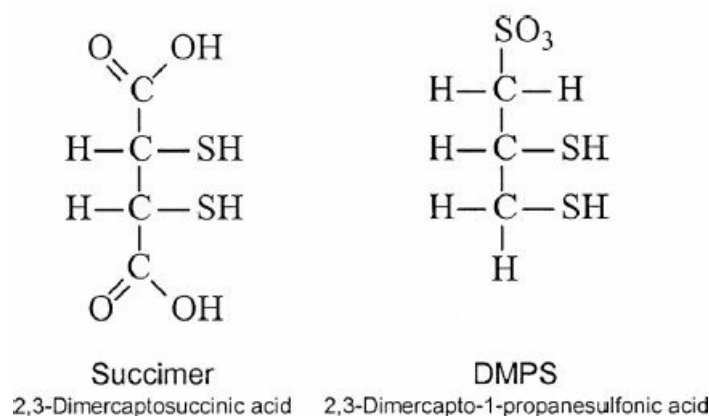
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A26 ANTIDOTES IN DEPTH

Succimer (2,3-Dimercaptosuccinic Acid)

Mary Ann Howland



INTRODUCTION

Succimer (meso-2,3-dimercaptosuccinic acid, DMSA) is an orally active metal chelator that is approved by the US Food and Drug Administration (FDA) for the treatment of lead poisoning in children with blood lead concentrations higher than 45 $\mu\text{g/dL}$. Succimer is also used to treat patients poisoned with arsenic and organic and inorganic mercury. Succimer has a wider therapeutic index and exhibits many advantages over dimercaprol and edetate calcium disodium (CaNa_2EDTA), the two other chelators used for the same clinical problems. Animal studies suggest that succimer does not redistribute lead or arsenic to the central nervous system. The role of succimer alone and in conjunction with other chelators to treat lead encephalopathy continues to be defined.^{60,73}

HISTORY

Succimer was initially synthesized in 1949 in England.⁷¹ In 1954, antimony-a,a'-dimercaptopotassium succinate (TWSb) was developed to treat schistosomiasis.⁴² TWSb is antimony bound to the potassium salt of succimer in a 2:3 ratio, forming a water-soluble xenobiotic with 50 times less toxicity than the previously used antimony compound, tartar emetic. Several years later, a group from Shanghai demonstrated the ability of the sodium salt of succimer to increase the LD_{50} of tartar emetic 16-fold in mice.¹⁰⁹ An early review of the Chinese experience with intravenous (IV) succimer in the treatment of occupational lead and mercury poisoning suggested efficacy similar to IV CaNa_2EDTA in increasing urinary lead and to intramuscular (IM) DMPS (racemic-2,3-dimercapto-1-propanesulfonic acid, unithiol) for mercury, with little observed toxicity.¹⁰⁵ This experience, the subsequent widespread use in Asia^{75,78,90,105,106,112} and Europe,^{17,34,40,43,63,99} and the realization that succimer could be used orally,^{7,49} led to US-based animal experiments, human trials, and FDA approval in 1991 for the treatment of lead-poisoned children.

PHARMACOLOGY

Chemistry

Succimer is a white crystalline powder with a molecular weight of 182 Da and a characteristic sulfur odor and taste.⁶ Succimer is the meso form of 2,3-dimercaptosuccinic acid. It is highly polar and water soluble.

Related Agents

DMPS (racemic-2,3-dimercapto-1-propanesulfonic acid, Na salt) is a chelator that, like succimer, is a water-soluble analog of British anti-Lewisite (BAL).^{7,9,23} A dose of 15 mg/kg of DMPS is equimolar to 12 mg/kg of succimer. DMPS has been used in the Soviet Union since the late 1950s and continues to be used in Russia and other former Soviet countries. DMPS, which is an investigational drug in the United States, is marketed in both oral and parenteral forms in Germany as Dimaval. DMPS seems promising in mercury and arsenic poisoning.^{3,5,7,9,11,14,23,45} DMPS is associated with an increase in the urinary excretion of copper and the development of Stevens-Johnson syndrome.^{26,104} Like succimer, DMPS does not appear to redistribute mercury or lead to the brain. Additional research is needed to determine whether DMPS is more advantageous than succimer, given its lower LD₅₀ in mice (5.22 mmol/kg versus 13.58 mmol/kg for succimer) when administered intraperitoneally.

Mechanisms of Action

Succimer contains four ionizable hydrogen ions, giving it four different pK_as—2.31, 3.69, 9.68, and 11.14—with the dissociation of the two lower values representing the carboxyl groups and the two higher values the sulfur groups.⁴ Lead and cadmium bind to the adjoining sulfur and oxygen atoms, whereas arsenic and mercury bind to the two sulfur moieties, forming pH-dependent water-soluble complexes (Fig. A26–1).⁸⁵

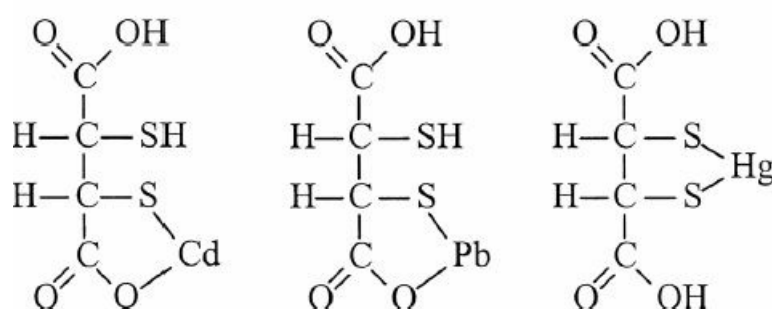


FIGURE A26–1. The chelation of cadmium, lead, and mercury with succimer.

Pharmacokinetics and Pharmacodynamics

Succimer is highly protein bound to albumin through a disulfide bond. Subhuman primate studies of IV and oral ²²C succimer indicate that following an IV dose, radiolabelled succimer is eliminated almost exclusively via the kidney, with only trace amounts (< 1%) excreted via feces or expired air.⁷¹ Following the administration of a single oral dose of 10 mg/kg, succimer is rapidly and extensively metabolized.⁶⁸ Approximately 20% of the administered oral dose is recovered in the urine, presumably reflecting the low bioavailability of the drug.¹⁰ Of the total drug eliminated in the urine (20%), 89% is altered and in the form of disulfides of L-cysteine. The majority of the altered succimer is in the form of a mixed disulfide with two molecules of L-cysteine to one molecule of succimer.⁸ The remaining 11% is excreted as unaltered free succimer.⁶⁸ Maximal excretion of succimer occurs in urine specimens collected between 2 and 4 hours after administration. Surprisingly, the blood only contains albumin-bound succimer and no evidence of the altered disulfide moieties, which suggests that the kidney may be involved in the biotransformation of succimer. It is likely that succimer gains entry to the kidney via an active organic anion transporter.^{21,111}

The pharmacokinetics of a single oral dose of succimer were determined in three children and three adults with lead poisoning and in five healthy adult volunteers.³³ Children received 350 mg/m² of succimer and adults received 10 mg/kg of succimer. The peak concentration and the time to peak blood concentration of total succimer (parent vs. altered oxidized metabolites) were similar for all three groups. The half-life of total succimer was 1.5 times longer in the children than in either adult group. The renal clearance of total succimer was greater in healthy adults (CrCl 77 mL/min) than in lead-poisoned adults (CrCl 25 mL/min) and children (CrCl 17 mL/min) with reduced creatinine clearances. Distribution of succimer (parent and/or oxidized metabolites) into erythrocytes appeared greater in poisoned patients than in the healthy adults.³³

The metabolism of succimer was studied in lead-poisoned children and in normal adults.¹⁵ The results indicate that succimer undergoes an enterohepatic circulation facilitated by gastrointestinal (GI) microflora. Similar to the previous pharmacokinetic study, moderate lead exposure impaired the renal elimination of succimer.

ROLE FOR LEAD EXPOSURE

In addition to precise analysis of metal elimination kinetics, measures of clinical outcome are essential for an understanding of the utility of this chelator. The Treatment of Lead-Exposed Children (TLC) trial was a step in that direction.¹⁰² The TLC

trial was a randomized, multicenter, double-blind, placebo-controlled study to examine the effects of succimer on cognitive development, behavior, stature, and blood pressure in children 1 to 3 years of age with blood lead concentrations between 20 and 44 $\mu\text{g/dL}$ and 780 children were enrolled.⁸⁶ The children received up to three courses of 26 days each of succimer compared to placebo. For the first 7 days the children received 350 mg/m^2 three times a day and for the remaining 19 days they received 350 mg/m^2 twice a day. The largest drop in blood lead occurred within the first week of therapy with succimer and then rebounded somewhat. This pattern was repeated with repeated courses. However, at the end of one year, no difference was seen in the blood lead concentrations between the succimer and the placebo groups. There was also no difference in test scores on cognition, behavior, or neuropsychological function.⁸⁶ A follow-up study conducted on those children at age 7 confirmed the lack of benefit in chelating children with succimer whose blood lead concentrations were 20 to 44 $\mu\text{g/dL}$, at ages 1 to 3 years.³⁵ A case study showed similar results. Similarly, succimer showed no benefit on growth in children aged 12 to 33 months with blood lead concentrations of 20 to 44 $\mu\text{g/dL}$.⁸²

Several groups are studying the efficacy of succimer in reducing blood, brain, and tissue lead by using rat and nonhuman primate models of childhood and adult lead poisoning.^{91,92,94} Although monkeys most closely resemble humans in their lead-associated toxicity, using them in studies is costly⁷⁷; the rat model is economical but limited because of species differences in lead and succimer metabolism and efficacy.

The validity of using blood lead concentrations as a marker of brain lead was studied in the adult rhesus monkey. Lead was administered orally for 5 weeks to achieve a target blood lead concentration of 35 to 40 $\mu\text{g/dL}$.³² Five days after the cessation of lead exposure, succimer chelation was initiated in the currently approved dosage regimen. Two IV doses of radioactive lead tracer were administered prior to succimer chelation to study the kinetics of recent versus chronic lead uptake and distribution. Four areas of the brain, as well as blood and bone, were assayed for lead. Merely stopping further lead exposure significantly reduced blood lead concentrations by 63% and brain lead concentrations by 34% compared with pretreatment concentrations, a finding that was not statistically different from succimer administration after halting exposure. However, when an integrated area under the serum lead concentration versus time curve (AUC) blood analysis was used over the 19-day succimer treatment course, instead of a single blood lead concentration, the differences between succimer and control were statistically significant. The clinical significance of these differences is unclear. Succimer-treated animals showed the greatest drop in blood lead concentrations over the first 5 days, while a similar end point was gradually achieved in the control. The lead from both the recent exposure (radioactive tracer lead) and chronic exposure declined to the same extent, independent of treatment with succimer. A better correlation was found between brain prefrontal cortex lead concentrations and an integrated blood lead analysis than with a single blood lead measurement.

Similarly, a study in neonatal rats demonstrated that increasing the duration of succimer chelation from 7 to 21 days decreased brain lead concentrations without a corresponding decrease in blood lead concentrations.⁹¹ The authors proposed that a slow rate of egress of brain lead to the blood was responsible for the demonstrable benefit of prolonging therapy to 21 days. In this study, succimer decreased blood lead concentration by approximately 50% when compared with the vehicle as the control, and this difference persisted for the 21 days of treatment. With succimer treatment, brain lead concentration decreased by 38% at 7 days and by 68% at 21 days. This same group also demonstrated that rats exposed to lead from postnatal days 1 to 30, then treated with succimer, demonstrated reductions in blood and brain lead concentrations and an improvement in cognitive deficits.⁹⁵ Previous animal studies demonstrated the ability of succimer to enhance urinary lead elimination^{41,49,94} and to reduce blood,^{16,30,38,39,54,80,92,94,96,98} brain,^{16,30,80,97,98} liver,⁹⁴ and kidney lead concentrations,^{16,30,38,54,80,98} while either reducing^{16,54,80,98} or demonstrating no effect on bone lead concentrations.^{30,94} These studies differ in the amounts and duration of lead administration prior to chelation, as well as in route, dose, and duration of chelation; however, several months after a course of succimer chelation, tissue lead concentrations had returned to concentrations found in the pretreatment stage.³⁰ Given the limited absolute amount of lead that is actually eliminated by chelation in comparison to the total body burden, particularly bone, these transient effects are not surprising.

Under a variety of experimental conditions in animals, succimer prevents the deleterious effect of lead on heme synthesis,^{16,49,80} blood pressure,⁵⁸ and behavior.⁹⁶

The use of succimer in both children and adults with chronic lead poisoning demonstrated consistent findings.^{18,27,50-52,64,76} During the first 5 days of succimer chelation (1050 $\text{mg/m}^2/\text{d}$ in children, 30 mg/kg/d in adults both in three divided doses), the blood lead concentration dropped precipitously by approximately 60% to 70%. This blood lead concentration remained unchanged during the next 14 to 23 days of continued therapy. Increases in urinary lead excretion are concurrent with the drop in blood lead concentration, with maximal excretion occurring on day 1.^{27,51} Urinary lead excretion exceeds estimated blood content which suggests that some lead is being removed from soft tissues as a concentration gradient is established from tissue to blood to urine.^{27,52} Typically, 2 weeks after the completion of succimer, blood lead concentration rebounds to values 20% to 40% lower than pretreatment values. In the one randomized, double-blind, placebo-controlled trial of succimer use in children with pretreatment blood lead concentrations of 30 to 45 $\mu\text{g/dL}$, follow-up at 1 month and at 6 months showed no differences between succimer-treated children and controls.⁷⁶ Succimer restores red blood cell D-aminolevulinic acid dehydratase activity, decreases erythrocyte protoporphyrin, and decreases

urinary excretion of D-aminolevulinic acid and coproporphyrin.^{18,27,51,52,76}

There is a large body of evidence reporting on the usage and safety profile of succimer in adults with chronic lead poisoning.^{13,17,27,40,43,44,47,48,59,61,69,83,100,103} The published experience outside the United States with the use of oral succimer for metal poisoning includes nearly 100 adult cases and contributes considerably to the supporting evidence. At least 74 additional individuals have been successfully treated parenterally (IM or IV) with the sodium salt of succimer.^{13,17,40,43}

ROLE FOR LEAD ENCEPHALOPATHY

The experience with the use of succimer in severely lead-poisoned patients, including those with encephalopathy, is limited.^{40,43,51} Three children with mean blood lead concentrations higher than 70 µg/dL who were treated with 5 days of succimer achieved comparable declines in blood lead concentration to two similar children who had been treated previously with a combination of BAL for 3 days and CaNa₂EDTA for 5 days.⁵¹ Three adult patients with encephalopathy achieved significant improvement following succimer chelation.⁴⁰ A 3 year-old child with a massive lead exposure superimposed on chronic lead poisoning and a blood lead concentration of 550 µg/dL was given BAL and CaNa₂EDTA for 5 days, with whole-bowel irrigation (WBI) performed on the first 3 days and succimer following WBI beginning on day 3 and continuing for 19 days. The blood lead concentration dropped from 550 to 70 µg/dL on day 5, but it rebounded to 99 µg/dL 2 days after BAL and CaNa₂EDTA—but not the succimer—were discontinued.⁴⁶

ROLE FOR ARSENIC EXPOSURE

Succimer has been used for arsenic toxicity in China and the Soviet Union since 1965.^{7,13} Animal studies with sodium arsenite and lewisite demonstrate the ability of succimer to improve the LD₅₀ with a good therapeutic index, lack of redistribution of arsenic to the brain as compared to BAL or control, and reduced kidney and liver arsenic concentrations.^{7,13,62,81,87} A few case reports attest to the ability of succimer to enhance the urinary excretion of arsenic^{31,88} and after 2 to 7 weeks of chelation urinary arsenic returned to normal concentrations following ingestion of arsenic trioxide ant bait by toddlers.¹⁰⁷ A randomized, placebo-controlled trial of succimer to treat 21 patients with chronic arsenic poisoning in India who had stopped ingesting arsenic contaminated water 5 months previously demonstrated improved clinical results and enhanced urinary excretion of arsenic in both the treatment and placebo groups, but no statistical differences could be demonstrated.⁷⁰ A comparison of BAL, succimer, and DMPS as arsenic antidotes demonstrated higher therapeutic indices for succimer and DMPS over BAL in chronic arsenic poisoning.⁷⁴

ROLE FOR MERCURY EXPOSURE

Succimer enhances the elimination of mercury and has been used to treat patients poisoned with inorganic, elemental, and methylmercury. It improves survival, decreases kidney damage, and enhances the elimination of mercury in animals following exposure to inorganic mercury^{4,22,54,57,65,84,110} and methylmercury.^{1,2,9,66} However, one study in mice subjected to intra-peritoneal mercuric chloride demonstrated an enhanced deposition of mercury in motor neurons following chelation with succimer or DMPS.³⁷ Of 53 construction workers who were exposed to mercury vapor, 11 received succimer and N-acetyl-dl-penicillamine in a crossover study.²⁰ Mercury elimination was increased during the period of succimer administration compared with the period of N-acetyl-d,l-penicillamine administration. Because the chelators were administered for only 2 weeks and late in the clinical course, therapeutic benefit could not be evaluated. When succimer was given to victims of an extensive Iraqi methylmercury exposure, blood methylmercury half-life decreased from 63 days to 10 days.⁷

ADVERSE EVENTS AND SAFETY ISSUES

Succimer is generally well tolerated with few serious adverse events reported.^{27,28,86,101} Common adverse events are typically GI in nature, including nausea, vomiting, flatus, diarrhea, and a metallic taste in 10% to 20% of patients. Rashes have been reported in about 4% of patients.²⁴ Some of these required discontinuation of the succimer. Mild elevations in aspartate aminotransferase and alanine aminotransferase are reported.^{21,26,28,52,64,79,111} Rarely, chills, fever, urticaria, reversible neutropenia, and eosinophilia are reported.^{18,27,28,47} Because neutropenia has been observed in some patients taking succimer and because bone marrow effects have been reported with other drugs in the same chemical class, the manufacturer's package insert recommends a complete blood count with a differential and a platelet count before and weekly during treatment.²⁴ During the latest open-label prospective study in children, apparently unrelated adverse events included an elevation in bone-derived alkaline phosphatase, eosinophils, and elevated serum aminotransferases.²⁷ One

patient developed severe hyperthermia and hypotension reportedly related to succimer administration.⁷⁹

The Chinese have reported a high incidence of more serious adverse effects (including dizziness and weakness) in response to IV or IM succimer.^{106,112} This discrepancy is undoubtedly related to the substantially greater dose of succimer delivered from parenteral administration compared with the relatively low (approximately 20%)⁷¹ oral bioavailability of succimer as a result of first-pass metabolism.

Incidental chelation of essential elements is always a concern with the use of chelators. A number of studies using succimer demonstrate no rise in urinary zinc, copper, iron, or calcium.^{27,40,43,50-52} Urinary excretion of essential elements was the focus of a study in a primate model of childhood lead exposure.⁹² Infant rhesus monkeys were exposed to lead for the first year of life to achieve blood lead concentrations of 40 to 50 µg/dL. Succimer was administered in the standard dosage regimen and complete urine collections over the first 5 days were analyzed for calcium, cobalt, copper, iron, magnesium, manganese, nickel, and zinc. Only when the data were analyzed collectively for all eight elements on all 5 days was there a statistically significant increased urinary elimination. These results raise concern that children subjected to repeated succimer chelation may also be at risk for enhanced elimination of essential elements.^{27,92,94} Therefore, children should be monitored and repleted as necessary. There is still relatively limited clinical experience with the xenobiotic, particularly with regard to long-term administration.

One concern with administering succimer orally is that outpatient management might permit continued unintentional lead exposure and the possibility for succimer-facilitated lead absorption. Studies with α-penicillamine, dimercaprol,⁵⁵ and CaNa₂EDTA demonstrate enhanced lead absorption and elevated blood lead concentrations.

Most blood lead concentrations are measured by graphite furnace atomic absorption spectrophotometry, in which case succimer does not interfere with the measurement. However, if blood lead concentrations were to be measured by anodic stripping voltammetry, succimer would affect the results by chelating the mercury in the electrode.²⁴ Succimer may cause a false-positive result for urinary ketones when tests using nitroprusside reagents (eg, Ketostix) are used, and a falsely decreased serum uric acid and creatine phosphokinase concentrations may be seen.²⁴

Animal studies suggest that succimer does not promote lead retention in the setting of continued exposure unless lead exposure is over-whelming.^{49,56,80} A radiolabeled lead tracer administered to adult volunteers suggested that succimer increased the net absorption of lead from the GI tract and may have distributed it to other tissues, as well as having enhanced urinary elimination.⁹³ Absorption is bimodal and consistent with an initial phase, followed by a delayed increase attributable to an enterohepatic effect. It may be that succimer-enhanced urinary lead elimination often exceeds enhanced lead absorption.⁸¹ One study reported two children with environmental exposure and dramatic rises in blood lead concentration while receiving succimer.²⁷ In the event of exposure to a new lead source, decontamination of the GI tract should complement oral succimer.⁷²

Although iron supplementation cannot be given concomitantly with BAL, because the BAL-iron complex may be a potent emetic, iron has been given concomitantly to patients receiving oral succimer without any adverse events.⁵³ The prevalence of both iron deficiency and elevated blood lead concentrations is highest among poor, inner-city children.⁶⁷ Because heme is a constituent of all cells, including those of the brain, it appears clinically indicated to provide iron supplementation during chelation therapy, when the heme pathway is freed of the inhibitory effects of lead. The timing of administration of the iron should be separate from administration of the succimer.²⁷

A case report describes a 3 year-old child who reportedly ingested 185 mg/kg of succimer and was asymptomatic.⁸⁹

PREGNANCY AND LACTATION

Succimer is FDA pregnancy category C. There are no adequate studies in pregnant women. The use of succimer in pregnancy is restricted to women who warrant therapy based on their symptoms.²⁷ There was a dose-dependent effect of succimer on early and late fetal resorption and on fetal body weight and length when succimer was administered to pregnant mice during organogenesis. No observed teratogenic effects were noted when 410 mg/kg, or approximately 5% of the acute LD₅₀, of succimer was administered subcutaneously.³⁶ However, doses of 410 to 1640 mg/kg/d of succimer administered subcutaneously to pregnant mice during organogenesis are teratogenic and fetotoxic, and doses of more than 510 mg/kg/d to pregnant rats also showed problems with reflexes in the offspring.²⁴ Succimer 30 to 60 mg/kg/d was administered by gavage to lead-poisoned rats from days 6 to 21 of gestation.²⁵ These doses of succimer decreased embryonic and fetal blood lead concentrations and normalized offspring body weight at 13 weeks. Although succimer was able to reverse some lead-induced immunotoxic effects, succimer itself caused problems with the immune system that persisted into adulthood.²⁵ Female mice exposed to lead in utero and then administered succimer from the fourth day of gestation to parturition demonstrated decreased blood lead concentrations; however, fetal liver and bone concentrations increased and worsened neural development in the offspring.¹⁰⁸ The use of succimer during pregnancy should only be undertaken if the potential benefit justifies the potential risk to the fetus.²⁴

COMBINED CHELATION THERAPY

Succimer can be combined with CaNa_2EDTA to take advantage of the ability of succimer to remove lead from soft tissues, including the brain, while capitalizing on the ability of CaNa_2EDTA to mobilize lead from bone.³⁰ A number of rodent models have examined this combination and found it to be superior in enhancing the elimination of lead, in reducing tissue concentrations of lead, and in restoring some lead-induced biochemical abnormalities.^{38,39,97} Although the addition of succimer to CaNa_2EDTA prevented the redistribution of lead to the brain caused by CaNa_2EDTA alone, the combination also increased urinary excretion of zinc, calcium, and iron.^{97,98} A retrospective review comparing dimercaprol plus CaNa_2EDTA to succimer plus CaNa_2EDTA in children with blood lead concentrations greater than 45 $\mu\text{g/mL}$, demonstrated a similar reduction in blood lead concentrations at the end of treatment and at 14 and 33 days following the termination of treatment.¹⁹ Blood lead concentration reductions were approximately 75%, 40%, and 37% at the end of therapy and at 14 and 33 days posttreatment, respectively. The succimer plus CaNa_2EDTA combination was better tolerated.

DOSING AND ADMINISTRATION

The dosage is 350 mg/m^2 in children, three times a day for 5 days, followed by 350 mg/m^2 twice a day for 14 days. In adults, the dosage is 10 mg/kg three times a day for 5 days followed by 10 mg/kg twice a day for 14 days. At approximately 5 years of age, dosing based on body surface area approximates the 10 mg/kg dose, while for children younger than 5 years of age dosing by body surface area, as was done during the premarketing trials, gives higher doses and is recommended.^{29,73} Repeated courses may be needed depending on the blood lead concentration. However a minimum of 2 weeks between courses is recommended unless blood lead concentrations mandate otherwise.²⁴ For patients who cannot swallow the capsule whole, it can be separated immediately prior to use and the contents sprinkled into a small amount of juice or on apple sauce, ice cream, or any soft food, or placed on a spoon and followed by a fruit drink (Table A26–1).

TABLE A26-1 A and B. Examples of Dosing Calculations

A. Succimer (available as 100-mg bead-filled capsules)					
	Avg. Height (in.)	Avg. Weight (lbs.)	m^2	350 mg/m^2 ^a	10 mg/kg ^a
<i>Child</i>					
2 year-old boy	36	30.5	0.593	189 mg	
2 year-old girl	35	29	0.57	200 mg	
4 year-old boy	42	39.75	0.73	255 mg	
4 year-old girl	41.75	38.75	0.72	250 mg	
<i>Adult</i>					
50 kg					500 mg
70 kg					700 mg
90 kg					900 mg
B. Chemet (Succimer) Pediatric Dosing Chart					
Pounds	Kilograms	Dose (mg) ^a	Number of Capsules ^a		
18–35	8–15	100	1		
36–55	16–23	200	2		
56–75	24–34	300	3		
76–100	35–44	400	4		
100	>45	500	5		

^aTo be administered every 8 hours for 5 days, followed by dosing every 12 hours for 14 days.

FORMULATION

Succimer (Chemet) is available as 100-mg bead-filled capsules.

SUMMARY

- Succimer (meso-2,3-dimercaptosuccinic acid) is an orally active metal chelator that is FDA approved for the treatment of lead poisoning in children with blood lead concentrations higher than 45 µg/dL.
- There is no evidence at this time that succimer improves cognitive performance in patients with blood lead concentrations lower than 45 µg/dL.
- Succimer is also used to treat patients poisoned with arsenic and organic and inorganic mercury.
- The advantages of succimer use include oral administration, limited effects on trace metals such as zinc, enhanced patient tolerance, limited toxicity, and the ability to coadminister iron (if needed). It is not contraindicated in glucose-6-phosphate dehydrogenase-deficient individuals.
- By contrast to CaNa_2EDTA , succimer does not redistribute lead to the brain of poisoned animals.^{11,30}

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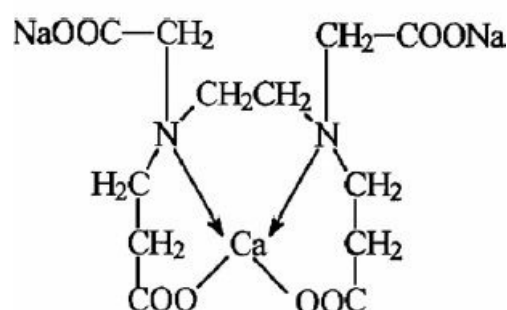
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A27 ANTIDOTES IN DEPTH

Edetate Calcium Disodium (CaNa_2EDTA)

Mary Ann Howland



INTRODUCTION

Edetate calcium disodium (CaNa_2EDTA) is a chelator that is primarily used for the management of severe lead poisoning (blood lead concentrations >70 mg/dL) in conjunction with dimercaprol (British anti-Lewisite {BAL}). Edetate calcium disodium has been replaced by succimer (2,3-dimercaptosuccinic acid) for the treatment of patients with lead concentrations between 45 and 70 $\mu\text{g/dL}$. Recently, in a clinical trial with much criticism, disodium EDTA (Na_2EDTA) (not approved by the US Food and Drug Administration {FDA} and extemporaneously compounded) was demonstrated to produce some reduction in adverse cardiovascular outcomes in patients with a history of myocardial infarction.^{3,21,32,38} This preparation is not to be used for lead chelation due to the potential for life-threatening hypocalcemia.

HISTORY

Ethylenediaminetetraacetic acid (EDTA) was first discovered and synthesized in the 1930s. In the late 1940s, it was approved by the FDA as a food additive. Work on using CaNa_2EDTA for lead toxicity began in the 1950s. At the same time, investigation into the uses of EDTA for the reversal of cardiovascular disease began. The CaNa_2EDTA mobilization test was once widely recommended as a diagnostic aid for assessing the potential benefits of chelation therapy.^{35,36} Currently, it can only be considered obsolete.^{14,18,21} Criticisms of the test include difficulties with administration of the antidote, unreliability as a predictor of total-body lead burden, expense, and the risk of worsening toxicity through redistribution of lead to either the kidney or the brain.¹⁸

PHARMACOLOGY

Chemistry

Edetate calcium disodium is an ionic, water-soluble compound with a molecular weight of 374.27 (anhydrous) and a formula of $\text{C}_{10}\text{H}_{12}\text{CaNa}_2\text{O}_8$.

Mechanism of Action

Edetate calcium disodium belongs to the family of polyaminocarboxylic acids. Although it is capable of chelating many metals, its current use is almost exclusively in the management of lead poisoning. The term chelate has its origin in the Greek word chele, which means 'claw,' implying an ability to tightly grasp the metal.⁴⁸ Implicit in chelation is the formation of a ring-structured complex. When CaNa_2EDTA chelates lead, the calcium is displaced and the lead takes its

place, forming a stable ring compound.³⁰ Bone is the primary source of lead chelated by CaNa_2EDTA . Blood lead concentration drops due to urinary elimination; however, once chelation is stopped, redistribution to soft tissues, including the brain, and then, ultimately, the return of lead to bone occurs.¹¹ Zinc is also capable of displacing calcium and forming a stable chelate, whereas copper and mercury are not.¹¹

PHARMACOKINETICS AND PHARMACODYNAMICS

Edetate calcium disodium is a highly polar drug with a small volume of distribution (V_d) due to its polar nature and approximates that of the extracellular fluid compartment in normal individuals,^{25,30} but the V_d is less in patients with renal dysfunction.³⁹ Edetate calcium disodium appears to penetrate erythrocytes poorly,^{2,25} and less than 5% of CaNa_2EDTA gains access to the spinal fluid.^{25,30} Oral administration of CaNa_2EDTA is not practical because of an oral bioavailability of less than 5%. The half-life is about 20 to 60 minutes.^{6,25,30} Renal elimination approximates the glomerular filtration rate,³⁷ which correlates with creatinine clearance,⁹ resulting in the excretion of 50% of CaNa_2EDTA in the urine within 1 hour, and more than 95% within 24 hours.^{25,30} Elimination is all kidney with no appreciable metabolism. When CaNa_2EDTA combines with lead, it forms a stable, soluble, nonionized compound subsequently excreted in the urine. Following CaNa_2EDTA administration, urinary lead excretion is increased 20-to 50-fold.^{13,40}

ROLE IN LEAD EXPOSURE

Animals

Animal studies demonstrate a decrease in tissue lead stores, including brain concentrations, when measurements are performed following CaNa_2EDTA therapy.²⁸ A rat study examining the effect of a single dose of CaNa_2EDTA on brain lead concentrations demonstrated a significant increase in brain lead concentrations,²¹ suggesting that CaNa_2EDTA may initially mobilize lead and facilitate redistribution to the brain. Additional doses enhance lead elimination, reduce blood lead concentrations, and subsequently reduce brain lead concentrations. The initial increase in brain lead may explain why some human case reports demonstrate worsening lead encephalopathy when CaNa_2EDTA is used without concomitant dimercaprol (BAL) chelation therapy.

Humans

Edetate calcium disodium is capable of reducing blood lead concentrations, enhancing renal excretion of lead, and reversing the effects of lead on hemoglobin synthesis.¹⁸ With chronic lead exposure, blood lead concentrations rebound considerably in the days to weeks following cessation of CaNa_2EDTA .^{1,2,27} Although CaNa_2EDTA has been used clinically since the 1970s, no rigorous clinical studies have ever been performed to evaluate whether CaNa_2EDTA is capable of reversing the neurobehavioral effects of lead.^{19,20} Chelators are incapable of dramatically decreasing the body burden of lead, because only several milligrams of lead are eliminated during chelation.^{13,15,41} Children evaluated with blood lead concentrations of 25 to 50 $\mu\text{g}/\text{dL}$ who were given CaNa_2EDTA for 5 days revealed very little difference in blood lead, bone lead, or erythrocyte protoporphyrin concentrations, when compared with pretreatment values.³³ A study in children demonstrated no additional benefits of CaNa_2EDTA on cognitive performance beyond that which was achieved by limiting further lead exposure and correcting an iron deficiency anemia.^{40,42} A follow-up study in children with initial blood lead concentrations between 25 and 55 $\mu\text{g}/\text{dL}$ also suggested an interaction between initial iron status, blood lead concentration, and an improvement in perceptual motor performance over a 6-month period. Both the correction of iron deficiency and a reduction in blood lead concentration (accomplished with limiting further exposure and or CaNa_2EDTA chelation) contributed to the improvement, emphasizing a critical need to correct iron-deficiency anemia as well as limit lead exposure.⁴³

ADVERSE EVENTS AND SAFETY ISSUES

The principal toxicity of CaNa_2EDTA is related to the metal chelates it forms. In mice, the intraperitoneal (IP) LD_{50} values of various CaNa_2EDTA metal chelates are CaNa_2EDTA , 14.3 mmol/kg; lead EDTA, 3.1 mmol/kg; and mercury EDTA, 0.01 mmol/kg.

When CaNa_2EDTA is given to patients with lead poisoning, the resultant sites of major renal toxicity are the proximal convoluted tubule, the distal convoluted tubule, and the glomeruli, possibly caused by the release of lead in the kidneys

during excretion.³⁰ Of the 130 children who received both dimercaprol and CaNa₂EDTA, 13% had biochemical evidence of nephrotoxicity, and 3% developed acute oliguric renal failure, which resolved over time; none needed hemodialysis.³⁶ Other studies failed to demonstrate any cases of renal failure in more than 1000 patient courses of therapy when CaNa₂EDTA was given in divided daily doses of 1000 mg/m² intravenously (IV) over 1 hour every 6 hours.³⁴ Because lead toxicity causes renal damage independent of chelation, it is important to monitor renal function closely during CaNa₂EDTA administration and to adjust the dose and schedule appropriately.^{37,38} Nephrotoxicity may be minimized by limiting the total daily dose of CaNa₂EDTA to 1 g in children or to 2 g in adults, although higher doses may be needed to treat lead encephalopathy. Continuous infusion while maintaining good hydration increases efficacy and decreases toxicity.³⁷ Because the administration of disodium EDTA can lead to life-threatening hypocalcemia and death, CaNa₂EDTA is the preparation of choice for lead toxicity and hypocalcemia is no longer a clinical concern.^{4,9} Other adverse clinical effects of CaNa₂EDTA, most of which are uncommon, include malaise, fatigue, thirst, chills, fever, myalgias, headache, anorexia, urinary frequency and urgency, sneezing, nasal congestion, lacrimation, glycosuria, anemia, transient hypotension, increased prothrombin time, and inverted T waves.^{11,30} Various mucocutaneous lesions in two patients included cheilosis and sore throat, magenta tongue, and papular lesions over the face, trunk and extremities, attributed to zinc deficiency.⁷ Mild increases in alanine aminotransferase and aspartate aminotransferase, which are usually reversible, and decreases in alkaline phosphatase are frequently reported. Extravasation may result in the development of painful calcinosis at the injection site.^{40,44} Depletion of endogenous metals, particularly zinc, and perhaps iron, and manganese, can result from chronic therapy.^{12,47} An animal study suggests that gastrointestinal lead absorption may be enhanced by either IP or oral administration of CaNa₂EDTA²⁹; consequently, removal of lead from the environment should always remain the first strategy in the management of lead toxicity. In the event of exposure to a new lead source, decontamination of the gastrointestinal tract must complement chelation.³⁵

PREGNANCY AND LACTATION

Although CaNa₂EDTA is FDA pregnancy category B, there are no adequate and well-controlled studies in pregnant women and a risk-to-benefit analysis must be made if its use is considered. It is not known whether CaNa₂EDTA is excreted in human milk, but Briggs considers breast-feeding a contraindication.⁸

In a model of lead poisoning in pregnant rats, fetal resorption decreased and the number of live fetuses increased when CaNa₂EDTA was used, although the placental concentrations of lead were increased.²³ Zinc concentrations were not affected. However, another study found that when CaNa₂EDTA was given to pregnant rats not poisoned with lead, increases in submucous clefts, cleft palate, adactyly/syndactyly, curly tail, and abnormal ribs and vertebrae resulted.¹⁰ These teratogenic effects occurred with doses of CaNa₂EDTA comparable to human doses and without causing noticeable changes in the mother except for weight gain. Use of zinc calcium EDTA and zinc EDTA preparations in pregnant rats caused no teratogenic effects at low doses, but resulted in the development of submucous cleft palates in 30% of the offspring receiving the higher dose of zinc calcium EDTA.¹⁰ Another study in rats with doses 25 to 40 times that used in humans revealed fetal malformations that were prevented by simultaneous zinc supplementation.¹¹

DOSING AND ADMINISTRATION

There has never been a clinical trial to identify the best dose of CaNa₂EDTA or how best to administer the dose. The most commonly recommended dose is determined by the patient's body surface area or weight (up to a maximum dose), the severity of the poisoning, and renal function (Chap. 96; [Tables 96-8 and A27-1](#)).^{18,33,40} For patients with lead encephalopathy, the dose of CaNa₂EDTA is 1500 mg/m²/d, approximately 50 to 75 mg/kg/d, by continuous IV infusion, starting 4 hours after the first dose of dimercaprol and after an adequate urine flow is established.¹⁷ The dose in obese patients has not been studied. A maximum dose of 3 g is suggested. Simultaneous dimercaprol and CaNa₂EDTA therapy is administered for 5 days, followed by a rest period of at least 2 to 4 days, which permits lead redistribution. For adults with lead nephropathy, the following dosage regimen is recommended: 500 mg/m² every 24 hours for 5 days for patients with a serum creatinine of 2 to 3 mg/dL; every 48 hours for three doses for a serum creatinine of 3 to 4 mg/dL; and one dose for a serum creatinine concentration higher than 4 mg/dL.¹¹ Previous recommendations were to limit the daily dose to 50 mg/kg when CaNa₂EDTA is used in patients with renal dysfunction.^{25,37,39} There is limited evidence to suggest that folic acid, pyridoxine, and thiamine increase the efficacy of CaNa₂EDTA⁴⁵; therefore, data are inadequate to recommend their routine administration. A blood lead concentration should be measured one hour after the CaNa₂EDTA infusion is discontinued in order to avoid falsely elevated blood lead concentration determinations.

TABLE A27-1. Calculations for IV Edetate Calcium Disodium Infusion Over 24 hours

	Avg. Height (in.)	Avg. Weight (lbs.)	m ³	1000 mg/m ² Over 24 hours IV	Dilute in D ₅ W or NS and Infuse Over 24 Hours ^a	1500 mg/m ² Over 24 Hours IV	Dilute in D ₅ W or NS and Infuse Over 24 Hours ^a
Child^b							
2 year-old boy	36	30.5	0.593	593 mg	200 mL	890 mg	300 mL
2 year-old girl	35	29	0.57	570 mg	200 mL	855 mg	300
4 year-old boy	42	39.75	0.73	730 mg	250	1095 mg	400
4 year-old girl	41.75	38.75	0.72	720 mg	250	1080 mg	400
Adult^{c,d}							
50 kg			1.5	1500 mg	500 mL	2250 mg	750 mL
70 kg			1.8	1800 mg	600 mL	2700 mg	1000 mL
90 kg			2.1	2100 mg	700 mL	3000 mg	1000 mL

Edetate calcium disodium comes in 5-mL ampules of 200 mg/mL.

^aDilute in D₅W or 0.9% NaCl to concentrations of less than 0.5% to avoid thrombophlebitis with IV administration. Be mindful of total fluid requirements if encephalopathic to avoid cerebral edema. If fluid is an issue consider intramuscular injection, otherwise infuse IV over 24 hours. ^bDo not exceed the adult dose. ^cFor adults with lead nephropathy, the following dosing regimen has been suggested: 500 mg/m² every 24 hours for 5 days for patients with serum creatinine concentrations of 2–3 mg/dL, every 48 hours for three doses for patients with creatinine concentrations of 3–4 mg/dL, and once weekly for patients with creatinine concentrations above 4 mg/dL. ^dThe dose in obese patients has not been studied. A maximum dose of 3 g seems reasonable.

D₅W = 5% dextrose in water; IV = intravenous; NS = 0.9% sodium chloride solution.

In symptomatic children without manifestations of lead encephalopathy, the dose of CaNa₂EDTA is 1000 mg/m²/d, approximately 25 to 50 mg/kg/d, in addition to dimercaprol at 50 mg/m² every 4 hours. However, with the FDA approval of succimer, and the demonstrated ability to reduce brain lead concentrations in animals, succimer has essentially replaced CaNa₂EDTA as the chelator of choice in lead-poisoned children without encephalopathy and lead concentration less than 70 µg/dL.^{15,27}

Due to the pain associated with intramuscular (IM) administration, it is recommended that CaNa₂EDTA be administered at concentrations of approximately 0.5% by continuous IV infusion over 24 hours in 5% dextrose or 0.9% NaCl.¹⁸ The package insert recommends infusing the dose over 8 to 12 hours.¹¹ Higher concentrations may lead to thrombophlebitis. Edetate calcium disodium is incompatible with other solutions. Careful attention to total fluid requirements in children and patients who have or who are at risk for, lead encephalopathy is paramount.^{30,40} Rapid IV infusions in patients with lead encephalopathy may increase intracranial pressure and cerebral edema. In children with acute lead encephalopathy, starting BAL 4 hours prior to CaNa₂EDTA appears to be more effective than starting CaNa₂EDTA prior to and simultaneously with BAL.^{16,19} In addition, treating with two chelators also reduces the blood lead concentration significantly faster than CaNa₂EDTA alone, while maintaining a better molar ratio of chelator to lead.¹⁶

If CaNa₂EDTA is to be administered IM to avoid the use of an IV and fluid overload, then either procaine or lidocaine is added to the CaNa₂EDTA in a dose sufficient to produce a final concentration of 0.5% (5 mg/mL). This can be accomplished by mixing 1 mL of a 1% procaine or 1% lidocaine solution with each mL of chelator.^{11,30} The procaine or lidocaine minimizes pain at the injection site.

COMBINATION THERAPY WITH SUCCIMER OR DMPS

The possible benefit of combining CaNa₂EDTA with succimer or 2,3-dimercapto-1-propane-sulfonic acid (DMPS) is under investigation in animals.^{22,24,46} The combination of CaNa₂EDTA with succimer appears more potent than either individual chelator in promoting urine and fecal lead excretion, and decreasing blood and liver lead concentrations. However, this approach may increase zinc depletion.⁴⁶

A retrospective analysis compared the combination of BAL and CaNa₂EDTA with succimer and CaNa₂EDTA in children with blood lead concentrations of about 35 to 70 µg/dL (up to 90 µg/dL for the BAL group).⁵ Equivalent reductions in blood lead concentrations were demonstrated with fewer adverse events in the succimer group. One case report of a child with lead encephalopathy and an extremely high blood concentration of 550 µg/dL employed initially a combination of BAL and CaNa₂EDTA followed by succimer, but a rebound increase in the lead concentration resulted in the addition of CaNa₂EDTA.²⁶ More data are needed to confirm this approach.

FORMULATION

Edetate calcium disodium is available as calcium disodium versenate in 5-mL ampules containing 200 mg of CaNa_2EDTA per mL (1 g per ampule).³⁰ Disodium edetate (sodium EDTA) should not be considered an alternative to CaNa_2EDTA because of the risk of life-threatening hypocalcemia associated with sodium EDTA use.

SUMMARY

- Edetate calcium disodium reduces blood lead concentrations, enhances urinary lead excretion, and reverses lead-induced hemato-logic effects.
- Edetate calcium disodium remains the standard of care for patients with lead encephalopathy when used in conjunction with dimercaprol.
- The first dose of dimercaprol should precede the first dose of CaNa_2EDTA by 4 hours.
- Recommended doses and schedules should not be exceeded and should be reduced when the creatinine clearance is reduced.
- Patients should be well hydrated to achieve an adequate urine flow prior to and during CaNa_2EDTA therapy.

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97 MANGANESE

Sari Soghoian

Manganese (Mn)

Atomic number	=	25
Atomic weight	=	54.94 Da
Normal concentrations		
Whole blood	=	4–15 µg/L
Serum	=	0.9–2.9 µg/L
Urine	<	10 µg/L

HISTORY AND EPIDEMIOLOGY

Manganese is the 12th most abundant element in the Earth's crust (0.106%). The name manganese derives from Magnesia, a prefecture of Thessaly in ancient Greece. Ores from this region are particularly abundant in manganese oxides and carbonates. Manganese salts are brightly pigmented and the earliest known uses were artisanal. Manganese dioxide was found in prehistoric paints and was used as a decolorant in glassmaking during the Roman Empire.

Adding manganese to iron produces a stronger metal alloy, and manganese-iron alloys are found in weapons from ancient Sparta. By the early 19th century, manganese became an important component in the manufacture of steel, which remains the largest industrial use of manganese today. Currently, more than 85% of manganese is used in the production of ferromanganese alloys. Manganese chloride is used in dry-cell battery manufacture and the metal is a catalyst for chlorination of organic compounds, manganese dioxide is used in batteries and glass production, and manganese sulfate is used to make ceramics, fungicides, and pesticides.

Most reported cases of manganese toxicity, or manganism, are associated with occupational exposure. Manganism was first described in 1837, when the development of a characteristic neuropsychiatric syndrome in French pyrolusite mill workers was linked with exposure to high concentrations of manganese oxide dusts.²⁰ Manganese, primarily in the form of oxides, is released during mining, and inhalation exposure to dusts from grinding manganese ore has historically been the most important source of manganese toxicity. Inhalation of inorganic manganese compounds may also occur during smelting, welding, or burning of coal, oil, or fuel containing manganese compounds. A neuropsychiatric syndrome in welders has been attributed to the inhalation of manganese oxide fumes.^{12,14,37,46,68}

Manganism has also been described in several nonoccupational settings. Manganese chloride and manganese sulfate are employed as nutritional supplements,⁹ and manganese toxicity is well documented in patients receiving excessive doses in total parenteral nutrition.^{24,52,58} Infants, young children, and patients with impaired clearance from chronic liver disease are particularly at risk. More recently, epidemic manganese toxicity has been reported from the use of intravenous psychostimulant drugs such as methcathinone and a “Russian cocktail” prepared using potassium permanganate as an oxidizing agent.^{41,79}

Environmental exposure to excessive manganese in drinking water has been linked to neurodevelopmental deficiencies in children, including effects on cognition, behavior, memory, and motor function.^{11,18,39} Concerns have also been raised about the potential environmental health risks of methylcyclopentadienyl manganese tricarbonyl (MMT), an antiknock agent added to gasoline as an alternative to lead.^{22,31} MMT has been allowed in Canada since 1976 and in the United States since 1995; however, more research is needed to understand its contribution to the environmental burden of manganese and to human health.⁷⁶

Potassium permanganate was first discovered to be a strong oxidizer in the 18th century. Weak solutions of potassium permanganate 0.01% are still used in medicine as topical drying and antiseptic skin preparations. Potassium, sodium, and barium permanganate also have uses in the pharmaceutical, chemical, and photographic industries. The toxicity of permanganates is mostly related to their oxidizing effects and is not discussed here.

CHEMISTRY

Manganese is a transition metal with atomic number 25, located between chromium and iron in the periodic table. It is dark-grey, brittle paramagnetic, and occurs in several mineral forms. Most manganese in the environment is found complexed to oxygen, carbon, or chloride. The most economically important ore is pyrolusite, or manganese dioxide (MnO_2), from which metallic manganese was first isolated in 1774.

Manganese can exist in oxidation states from -3 to $+7$. Divalent manganese (Mn^{2+}) is the most common, the most bioavailable, and the most physiologically important form. Mn^{3+} is also biologically important and is, for example, the form of manganese in superoxide dismutase.

PHARMACOLOGY AND PHYSIOLOGY

Manganese is an essential dietary element found in nuts, grains, legumes, fruits, and vegetables. Most people consume 2 to 9 mg of manganese compounds per day, but vegetarians may consume more. Manganese salts in well water also contribute to dietary intake.⁷³ Manganese is present in human breast milk in its trivalent form bound to lactoferrin, which is readily absorbed via receptors in the small intestine. Manganese salts—usually manganese sulfate or manganese chloride—are typically added to infant formulas, processed foods, and dietary supplements, although these are less well absorbed.

Manganese is a cofactor in many human enzyme systems, including superoxide dismutase, hexokinase, xanthine oxidase, and glutamine synthase. It is also present in several metalloproteins.⁹ Although deficiency in humans is not reported, experimental manganese restriction produced a scaling, erythematous, pruritic rash, alterations in calcium homeostasis (eg, hypercalcemia, hyperphosphatemia), and increased alkaline phosphatase in healthy volunteers.²⁷

Normally, less than 5% of dietary manganese is absorbed throughout the length of the small intestine. However, enteral manganese absorption may be altered depending on the dietary needs of the host and the presence of similarly charged compounds in the diet. For example, divalent manganese ion (Mn^{2+}) forms complexes with a variety of ligands in the body and can substitute for Mg^{2+} , Ca^{2+} , and Fe^{2+} in complexes with proteins and enzymes.⁵⁴ Because manganese can compete with iron for binding sites on transferrin, the percentage of absorbed manganese is increased in the presence of iron-deficiency anemia. Radioisotope studies demonstrate that absorption of dietary manganese is doubled in individuals with anemia.^{9,26} Manganese absorption from the gastrointestinal tract is also inversely proportional to the amount of calcium in the diet, most likely because of competition between divalent cations for transport.⁹

About 85% of manganese in the blood is bound to hemoglobin in erythrocytes, and normal measured whole blood concentrations may be as much as five times higher than those measured in serum.⁶³ The remaining manganese in plasma is mostly bound to transferrin, β_1 -globulin, and albumin.⁵ Manganese is widely distributed to all tissues, and crosses both the placental⁹ and the blood–brain barriers.⁶ Transport in the body is facilitated by transport proteins and for Mn^{2+} by the divalent metal transporter.⁹

Manganese is primarily eliminated via the bile in feces. It accumulates in bile against a concentration gradient, which suggests an active transport mechanism.⁴⁰ Renal excretion is negligible, whereas 67% of a radio-labeled manganese dose injected intravenously is recovered in feces within 48 hours, and less than 0.1% appears in the urine within 5 days of administration.⁴⁰

The elimination half-life of manganese from the body is approximately 40 days,⁵⁰ but this value is highly variable among individuals. Elimination of manganese may be prolonged in young women with high ferritin stores²⁶ or after the initiation of oral iron therapy for anemia.⁵⁰ This effect is most likely due to increased hepatic sequestration from increased production of iron transport and storage proteins. High concentrations of manganese are found in patients with hemochromatosis, supporting the idea that increased or abnormal iron storage proteins will also lead to increased hepatic manganese stores.¹

PATHOPHYSIOLOGY

Manganese toxicity may be due to overexposure or impaired elimination. Because of its low enteral absorption, excessive dietary ingestion of manganese is unlikely to cause toxicity in adults with normal elimination. Parenteral administration of either nutritional supplements or xenobiotics containing manganese presents a greater toxicologic risk. The major occupational route of exposure is inhalation of manganese dusts or fumes. Inhalation may acutely elevate blood concentrations, and possibly create pulmonary manganese deposits that prolong exposure and absorption even following patient removal from the environmental source.⁵⁹ Whereas normal liver function may protect against accumulation of manganese in soft tissue, patients with hepatic disease are at risk for manganese bioaccumulation and toxicity from normal dietary intake.^{64,70,74}

Although manganese is widely distributed in the body, major clinical features of manganese toxicity are primarily related to its accumulation in brain. Manganese is deposited throughout cerebral tissue but concentrates in the basal ganglia structures and, to a lesser extent, in the caudate and putamen. The exact mechanisms of manganese uptake into neurons and its transport within the brain are still being elucidated.³ Manganese influx into the central nervous system appears to involve several transport mechanisms. Transferrin-receptor mediated endocytosis of transferrin-bound manganese is thought to be the major route of entry under normal conditions.⁶ However, for unclear reasons nonprotein-bound manganese appears to cross the blood brain barrier more quickly than protein-bound manganese.^{57,67} Therefore, exposure to manganese in excess of blood ligand-binding capacity may promote its distribution to the brain. Transferrin may also play an important part in manganese accumulation in the basal ganglia, specifically, because these are areas of high transferrin-receptor density.^{5,23} The divalent-metal transporter is most likely also important, but more research is needed to understand its role.

The specific mechanisms of manganese neurotoxicity are also not well established, although oxidative stress, mitochondrial dysfunction, neuroinflammation, and alterations in neurotransmitter metabolism are all likely implicated. Mn^{2+} concentrates in mitochondria and inhibits both mitochondrial F1-ATPase and complex I in the electron transport chain, thereby disrupting oxidative phosphorylation and contributing to energy failure and cytotoxicity.^{16,28,29,87,88} Like other transition metals, manganese causes local damage by generating reactive oxygen species during redox cycling between the divalent and trivalent forms. The participation of manganese in Fenton reactions also occurs and results in oxidative tissue damage (Chap. 12). Manganese may also promote inflammatory neuronal injury by potentiating the release of nitric oxide, prostaglandin E1, TNF- α , and other inflammatory mediators from activated glial cells.^{25,47,56}

The clinical features of manganism share many similarities with idiopathic Parkinson disease (PD). Degeneration of nigrostriatal dopaminergic neurons is clearly implicated in PD, and the above mechanisms would suggest that this is also the case in manganese-induced neurotoxicity. However, newer evidence indicates that dopamine synthesis and dopamine transporters may be normal in patients with manganese related motor dysfunction.³⁰ By contrast, single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies in patients with PD show decreased presynaptic dopamine terminal markers in the striatum and reduced dopa decarboxylase activity. Although neuroimaging and neurochemical studies in patients with manganism are quite limited, the hypothesis that manganese does not cause neurodegeneration but rather an inability to release available dopamine bears further exploration.

CLINICAL MANIFESTATIONS

Early reports of manganism in German manganese workers⁹ and Chilean miners⁷⁵ described an acute phase characterized by psychiatric symptoms known as “manganese madness” and included visual hallucinations, behavioral changes, anxiety, impotence, and decreased libido.⁹ Currently accumulated evidence indicates that psychiatric and/or cognitive abnormalities such as attentional and memory deficits are common. However, classic manganism is best typified by a late-presenting syndrome of extrapyramidal movement abnormalities, including marked bradykinesia, rigidity, postural instability, loss of facial expression, impaired speech, and pronounced gait disturbance.⁸ Signs and symptoms vary with duration and level of exposure, may be insidious in onset, and may not become apparent for several years (Table 97–1). More work is needed to describe how these evolve, as well as to understand the relevance of subtle preclinical neuropsychological signs for predicting sequelae.

TABLE 97–1. Typical Features of Chronic Manganism

<i>System</i>	<i>Early Manifestations</i>	<i>Late Manifestations</i>
Constitutional	Asthenia, lethargy	—
Gastrointestinal	Anorexia	—
Neurologic	Fine intention tremor Headaches	Coarse intention tremor Visual hallucinations Cognitive impairment Loss of facial expression Dysphagia Micrographia Gait instability ^a Low-volume speech
Psychiatric	Apathy Irritability Emotional lability	Decreased libido or impotence Anxiety Additional behavioral changes
Musculoskeletal	Arthralgias	Muscle rigidity

^aDecreased arm swing, toe walking, and inability to turn or walk backward without falling.

Although the movement disorder that typically occurs in patients with manganism is similar to that seen in cases of idiopathic PD, including a typical “cock walk” on the balls of the feet, there are several distinguishing clinical features, including a lack of or atypical tremor, a particular tendency to fall backward, and an absence of severe progressive dementia.^{30,38} Cognitive impairment or vestibular–auditory dysfunction is typically mild, if present at all. In addition, an absent or unsustained clinical response to levodopa therapy may be considered a criterion for establishing a diagnosis of clinically probable manganism.⁶² Although symptomatic improvement with levodopa therapy has been reported in some patients,^{19,53,68} most evidence indicates that dopamine supplementation does not improve signs and symptoms of parkinsonian in patients with manganese associated neurotoxicity.^{30,42,49,79}

Acute inhalational exposure to high concentrations of manganese oxides can cause metal fume fever (Chaps. 91 and 124), with characteristic fever, chills, nausea, headache, myalgias, and arthralgias.⁹ Chronic occupational exposure to manganese oxide fumes is also associated with chemical pneumonitis and increased rates of bronchitis and pneumonia, but it does not appear to cause pulmonary fibrosis.^{48,69} Manganese exposure is also associated with neurodevelopmental deficits^{11,18,39} and hypertension.⁴⁵

DIAGNOSTIC TESTING

Manganism may be difficult to differentiate from other neurodegenerative disorders. Several tests may contribute to establishing the diagnosis, but each has important limitations. Careful consideration of plausible sources of exposure, findings on neurologic and neuropsychologic examinations, and determining hepatic function and iron reserve status are important. If movement abnormalities are present, then failure of sustained response to levodopa therapy is highly suggestive of manganism. Genetic mutations in the manganese transporter SLC30A10 have recently been linked to a neurodegenerative syndrome, and family history should also be explored.^{66,83}

Normal reference values for manganese in blood and urine are published (see above) and measurements may be helpful, but concentrations are poorly correlated with total body manganese burden. Whole blood manganese concentrations are the most reliable values for biomonitoring purposes, although they only correlate with group and not with individual exposures.^{7,9} Manganese concentrations in blood are most commonly determined by flame or furnace atomic absorption spectrophotometry. Whole blood manganese concentrations should be elevated after acute overexposure, but abnormal concentrations are neither sensitive nor specific for chronic manganese toxicity because manganese is rapidly cleared from the blood.⁸⁶ Signs and symptoms of manganism are insidious and may occur long after concentrations in urine or blood have normalized.

Urine manganese concentrations are not well correlated with either symptoms or extent of exposure.⁷ Increased urinary elimination of manganese after chelation challenge with calcium disodium ethylenediaminetetraacetic acid (CaNa₂EDTA) occurs but cannot be interpreted. In most situations, it is unclear whether the increased excretion signifies mobilization of physiologic manganese, an increased body burden of manganese, or toxicity. The utility of hair, nail clippings, and saliva as

biomarkers of chronic manganese exposure is not clearly established.^{7,44,78,84}

Patients with manganese associated movement disorders often have a characteristic pattern of abnormalities on magnetic resonance imaging (MRI) that includes a bilateral, symmetric, hyperintense signal in the basal ganglia, particularly in the globus pallidus, on T1-weighted images.^{4,37,38,61,79} This pattern is also reported in patients with iatrogenic manganism from long-term parenteral nutrition,^{10,24,36,55,81} and is sometimes seen in cirrhotic patients with impaired dietary manganese elimination.^{32,65,77} MRI studies in patients receiving total parenteral nutrition (TPN) have shown a positive correlation between the concentration of manganese in TPN mixtures and the intensity of increased basal ganglia signal on T1-weighted MRI images.^{10,81} An increased T1-weighted MRI signal throughout the basal ganglia has been demonstrated in welders and correlates with the length of welding exposure.²¹ These changes on MRI are reversible with TPN discontinuation in patients without neurologic symptoms.^{55,80} While highly suggestive of manganism in the correct clinical context, an increased T1-weighted signal in the basal ganglia is a nonspecific finding that may also reflect iron, copper or lipid deposition, hemorrhage, or neurofibromatosis.⁹

By contrast to these radiographic abnormalities, MRI findings in PD typically demonstrate a hypointense signal in the substantia nigra on T2-weighted images.^{43,82} Some evidence suggests that SPECT and PET may also help differentiate these two clinical entities. For example, molecular imaging studies of patients with chronic manganese exposure and extrapyramidal symptoms have largely failed to demonstrate abnormal nigrostriatal dopaminergic activity and projections, although these are clearly abnormal in patients with PD.^{30,61,85}

TREATMENT

Treatment for manganese toxicity is primarily supportive. Discovery and removal from the source of exposure is paramount, although clinical manifestations may still progress as manganese body stores fall.³⁵ Antiparkinsonian therapy is generally ineffective or has limited benefit in relieving motor symptoms. Antioxidant therapy has been proposed, based on the hypothesis that oxidant stress and mitochondrial dysfunction contribute to manganese induced cellular damage, but human data are lacking.^{15,17,33}

The clinical utility of chelation therapy in patients with manganese toxicity has not been well studied and remains controversial. Treatment with CaNa_2EDTA was reportedly useful in some cases (Antidotes in Depth: A27).³⁴ More often, chelation improves urinary excretion of manganese without affecting neurologic manifestations of toxicity.^{13,79} Chelation with dimercaptosuccinic acid had no effect on either manganese concentrations in blood and urine or on clinical signs of manganism in two patients.²

Treatment with the iron chelator deferoxamine would theoretically be counterproductive since iron and manganese tend to compete for ligands, and iron sequestration might leave more ion transporters available for manganese uptake. In vitro studies demonstrate increased rates of cellular apoptosis after coincubation with manganese and deferoxamine compared to incubation with manganese alone.⁷²

SUMMARY

- Accumulation of manganese in the brain produces a characteristic neurologic disorder, manganism, with cognitive, psychiatric, and movement abnormalities.
- The movement disorder has many parkinsonian features, including bradykinesia, rigidity, postural instability, gait abnormalities, and hypophonia, but it does not typically respond to levodopa therapy.
- An increased signal in the globus pallidus on T1-weighted MRI is typically but not invariably seen.
- Elevated whole blood manganese concentrations may also help differentiate the cause, but rapid clearance of manganese from the blood makes this a less sensitive test in cases where exposure is remote from the onset of symptoms.
- Treatment is primarily supportive because no chelation regimen has been shown to alter the clinical course.

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98 MERCURY

Young-Jin Sue

Mercury (Hg)		
Atomic number	=	80
Atomic weight	=	200.59 Da
Normal concentrations		
Whole blood	<	10 µg/L (50 nmol/L)
Urine	<	20 µg/L (100 nmol/L)

HISTORY AND EPIDEMIOLOGY

Mercury is a metal that is widely toxic to multiple organ systems. Its toxicologic manifestations are well known as a result of thousands of years of medicinal applications, industrial use, and environmental disasters.^{57,91} Mercury occurs naturally in small amounts as the elemental silver-colored liquid (quicksilver); as inorganic compounds such as mercuric sulfide (cinnabar), mercurous chloride (calomel), mercuric chloride (corrosive sublimate), and mercuric oxide; and as organic compounds (methylmercury and dimethylmercury). In recent centuries, mercury-containing preparations were widely used to treat both syphilis and constipation. The musician Paganini was one of several famous persons whose gingivitis, dental decay, ptyalism (excessive salivation), and erethism (pathologic shyness) were attributed to mercury therapy.⁶⁵ In the 1800s, the United States witnessed an epidemic of “hatters’ shakes” or “Danbury shakes” and “mercurial salivation” in hat industry workers.⁹⁹ Danbury, CT, was a US center of felt hat manufacturing in which mercuric nitrate was used to mat animal furs to make felt.^{91,99}

In the early 1900s, acrodynia, or “pink disease,” was described in children who received calomel for ascariasis or teething discomfort.¹² Vividly described in a series of 41 children, the development of acrodynia was more common in younger children, did not seem to correlate with mercury dose, and was not necessarily related to urine concentrations of mercury.⁹⁸

One of the most devastating epidemics of mercury poisoning occurred as the result of a decade of contamination of Minamata Bay in Japan by a nearby vinyl chloride plant during the 1940s. Methylmercury accumulated in the bay’s marine life and poisoned the inhabitants of the local fishing community. Although officially only 121 victims were reported, thousands more are believed to have been affected by what has subsequently been named Minamata disease.^{71,92} The largest outbreak of methylmercury poisoning to date occurred in Iraq in late 1971. Approximately 95,000 tons of seed grain intended for planting and treated with methylmercury as a fungicide were baked into bread for direct consumption, resulting in widespread neurologic symptoms, 6530 hospital admissions, and more than 400 deaths.^{5,18,77}

In 1990, the US Environmental Protection Agency (EPA) banned mercury-containing compounds from interior paints.³ However, mercury-containing paints manufactured before that ruling may still be on interior walls, and mercury-containing paint can still be sold for outdoor use. In 1997, a scientist succumbed to delayed, progressive neurologic deterioration after a minute dermal exposure to dimethylmercury.⁶³

Contemporary exposures occur in the form of mercury-tainted seafood and mercury-based preservatives (thimerosal). However, a once widely feared source of potential poisoning, mercury-containing dental amalgam, does not result in clinically important poisoning. Occasionally, exposure to mercury from broken thermometers leads to poisoning in the home.

The recent movement to replace incandescent light bulbs with compact fluorescent bulbs has once again raised the concern of exposure to mercury in the home and environment. Promoted to reduce greenhouse gas emissions, each bulb contains about 4 mg of elemental mercury.²

Table 98–1 lists some potential sources of mercury exposure.

TABLE 98–1. Exposures to Mercury

	<i>Elemental</i>	<i>Inorganic</i>	<i>Organic</i>
Manufacturing/ Industrial	Barometers	Batteries	Agriculture
	Bronzing	Chemistry sets	Embalming
	Ceramics	Dyes	Fungicides
	Chlorine manufacture	Explosives	Laboratory reagents
	Electroplating	Fireworks	Pesticides
	Jewelry	Laboratory reagents	Wood preservatives
	Paints	Tanneries	
	Paper pulp	Taxidermy	
	Photography	Vinyl chloride manufacture	
	Metal refineries		
	Amalgam	Antiseptics	Bactericidals
	Sphygmomanometry	Calomel	Preservatives
Medical/Medicinal	Tissue fixatives	Disinfectants	Pharmaceuticals
	Thermometers	Laxatives	
	Weighted nasogas- tric tubes		
	Patent		
	Ritualistic use		Seafood
Food/Other	Esthetic?		Grains
	Ayurvedic		(contaminated)

FORMS OF MERCURY AND TOXICOKINETICS

The three clinically important forms of mercury—elemental, inorganic, and organic—differ with respect to their toxicodynamics and toxicokinetics (Table 98–2). Each produces distinct clinical patterns of poisoning stemming in part from their unique kinetic features (Table 98–3). For each form, the specific manifestations are determined by the route of exposure, rate of exposure, distribution, biotransformation of mercury within the body, and relative accumulation or elimination of mercury by the target organ systems. Whereas elemental mercury produces pulmonary toxicity, inorganic mercury initially causes gastrointestinal (GI) symptoms followed by nephrotoxicity. A nearly pure neurologic toxicity results from organic (methylmercury) exposure.

TABLE 98–2. Classes of Mercury Compounds

	<i>Chemical Formula</i>	<i>Example</i>
Elemental	Hg ⁰	Quicksilver
Inorganic	Hg ⁺	Mercurous ion
	HgCl	Calomel, mercurous chloride
	Hg ²⁺	Mercuric ion
	HgCl ₂	Mercuric chloride
Organic	Short-chain alkyl–mercury compounds	Methylmercury Ethylmercury Dimethylmercury
	Long-chain mercury compounds	Methoxyethylmercury
	Aryl mercury compounds	Phenylmercury

TABLE 98–3. Differential Characteristics of Mercury Exposure

	<i>Elemental</i>	<i>Inorganic</i>	<i>Organic</i>
Primary route of exposure	Inhalation	Oral	Oral
Primary tissue distribution	CNS, kidney	Blood (transient, acute) Kidney CNS (delayed)	CNS, kidney, liver, blood, hair
Clearance	Renal, GI	Renal, GI	Methyl: GI Aryl: renal, GI
<i>Clinical effects</i>			
CNS	Tremor	Tremor, erethism	Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary	+++	–	–
Gastrointestinal	+	+++ (caustic)	+
Renal	+	+++ (ATN)	+
Acrodynia	+	++	–
Therapy	BAL, DMSA	BAL, DMSA	DMSA (early)

ATN = acute tubular necrosis; BAL = British anti-Lewisite; CNS = central nervous system; DMSA = dimercaptosuccinic acid; GI = gastrointestinal.

ABSORPTION

Elemental Mercury

Elemental mercury (Hg^0) is absorbed primarily via inhalation of vapor, although slow absorption after aspiration, subcutaneous deposition, and direct intravenous (IV) embolization occurs.^{48,60,97} Volatility, moderate at room temperature, increases significantly with heating or aerosolization, both of which occur with vacuuming.^{34,83} When inhaled by human volunteers, 75% to 80% of mercury vapor is absorbed.³⁴ However, elemental mercury is negligibly absorbed from an anatomically and functionally normal GI tract, and it is usually considered nontoxic when ingested. Abnormal GI motility prolongs mucosal exposure to elemental mercury and massive ingestion increases subsequent ionization to more readily absorbed forms. Similarly, anatomic GI abnormalities such as fistulae or perforation may be associated with extravasation of mercury into the peritoneal space where elemental mercury is oxidized to more readily absorbed inorganic forms.

Inorganic Mercury

The principal route of absorption for inorganic mercury is the GI tract. Approximately 10% of soluble divalent mercuric salts such as mercuric chloride (HgCl_2) are absorbed following ingestion and dissociation.⁵⁴ Absorption of a relatively insoluble monovalent mercurous compound, such as mercurous chloride (calomel; HgCl), is dependent on its oxidation to the divalent form.⁶⁴ Inorganic mercury is also absorbed across the skin and mucous membranes, as evidenced by urinary excretion of mercury after dermal application of mercurial ointments and powders containing HgCl .⁹⁸ The degree of dermal absorption varies by the concentration of mercury, skin integrity, and lipid solubility of the vehicle. With substantial dermal exposures to mercury salts, skin absorption may be difficult to distinguish from concomitant absorption via other routes, such as ingestion.

Organic Mercury

As in the case of inorganic mercury, organic mercury is primarily absorbed from the GI tract. Methylmercury, considered the prototype of the short-chain alkyl compounds, is approximately 90% absorbed from the gut. Aryl and long-chain alkyl compounds have more than 50% GI absorption.⁶⁴ Although both dermal and inhalational absorption of organic mercury is reported, precise quantitation and exclusion of concomitant absorption by ingestion are difficult to determine.

DISTRIBUTION AND BIOTRANSFORMATION

After absorption, mercury distributes widely to all tissues, predominantly the kidneys, liver, spleen, and central nervous

system (CNS). The initial distributive pattern into nervous tissue of elemental and organic mercury differs from that of the inorganic compounds because of their greater lipid solubility.

Elemental Mercury

Although peak concentrations of elemental mercury are delayed in the CNS as compared with other organs (2–3 days vs. 1 day),³⁴ significant accumulation in the CNS may occur after an acute, intense exposure to elemental mercury vapor. Conversion of elemental mercury to the charged mercuric (Hg^{2+}) cation within the CNS favors retention and local accumulation. Because elemental mercury does not covalently bind to other compounds, its toxicity depends on its oxidation initially to the mercurous ion (Hg^+) and then to the mercuric ion (Hg^{2+}) by the enzyme catalase.⁵⁴ Because this oxidation–reduction reaction favors the mercuric cation at steady state, the distribution and late manifestations of metallic mercury toxicity eventually resemble those of inorganic mercury poisoning. Conversely, and to a lesser extent, inorganic mercuric ions are reduced to the elemental state (Hg^0), although the site and mechanism of this reaction are not well understood.⁶⁴

Inorganic Mercury

The greatest concentration of mercuric ions is found in the kidneys, particularly within the renal tubules. At least in animal studies, administration of mercury induces the renal synthesis of metallothionein, a compound that binds to and detoxifies mercuric ions.⁹ Very little mercury is found as free mercuric ions. In blood, mercuric ions are found both within the red blood cells (RBCs) and bound to plasma proteins in approximately equal proportions. Blood concentrations are greatest immediately after inorganic mercury exposure, with rapid waning as distribution to other tissues occurs. Although penetration of the blood–brain barrier is poor because of low lipid solubility, slow elimination and prolonged exposure contribute to consequential CNS accumulation of mercuric ions. Within the CNS, mercuric ions are concentrated in the cerebral and cerebellar cortices. Although inorganic mercurials undergo organification in marine life, as in the Minamata Bay disaster, the importance of this conversion in humans is unknown. Animal studies demonstrate that the placenta functions as an effective barrier to mercuric ions.⁶⁴

Organic Mercury

Once absorbed, aryl (phenyl mercury) and long-chain alkyl mercury compounds differ from the short-chain organic mercury compounds (ie, methylmercury) in an important way—the former possess a labile carbon–mercury bond, which is subsequently cleaved, releasing the inorganic mercuric ion. Thus, the distribution pattern and toxicologic manifestations produced by the aryl and long-chain alkyl compounds beyond the immediate postabsorptive phase are comparable to those of inorganic mercury, but organification has facilitated absorption and reduced the local caustic effects.⁶⁴ By contrast, short-chain alkyl mercury compounds possess relatively stable carbon–mercury bonds that survive the absorptive phase, although conversion to the inorganic mercuric cation at a rate of less than 1% per day may occur after absorption.¹⁰⁰ Because it is lipophilic, methylmercury readily distributes across all tissues, including the blood–brain barrier and placenta.³⁶ An important consequence of this property is the devastating neurologic degeneration that develops in prenatally exposed infants with Minamata disease.

After methylmercury is distributed to brain tissue, its fate is uncertain. Animal evidence indicates that methylmercury is converted to inorganic mercury in brain tissue.⁵¹ Primates fed oral methylmercury daily for periods exceeding one year and then killed within days of the last exposure demonstrated an average brain inorganic mercury fraction of only 19%. By contrast, when the postexposure period was extended to between 150 and 650 days, the inorganic mercury fraction increased to 88%. Similarly, long-term survivors of methylmercury poisoning had a higher ratio of inorganic mercury to total mercury in their brains.²⁴ In one patient who survived 22 years after methylmercury ingestion, autopsy revealed that the level of brain mercury was nearly completely in the inorganic form.

Methylmercury concentrates in RBCs to a much greater degree than do mercuric ions, with an RBC-to-plasma ratio of about 10:1 (in contrast to 1:1 RBC-to-plasma ratio for inorganic mercury).¹⁰⁰ However, despite this apparent affinity for nervous tissue and RBCs, the greatest methylmercury concentrations are found in the kidneys and liver. In addition, because of the extensive sulfhydryl bonds in hair, methylmercury deposits in hair at concentrations approximately 250 times that found in whole blood.⁴⁵

ELIMINATION

Elemental Mercury and Inorganic Mercury

Mercuric ions are excreted through the kidney by both glomerular filtration and tubular secretion and in the GI tract by transfer across gut mesenteric vessels into feces. Small amounts are reduced to elemental mercury vapor and volatilized

from skin and lungs. The total-body half-life of elemental mercury and inorganic mercury is estimated at approximately 30 to 60 days.^{17,54}

Organic Mercury

By contrast to elemental mercury and inorganic mercury, the elimination of short-chain alkyl mercury compounds (such as methyl mercury) is predominantly fecal. Enterohepatic recirculation contributes to its somewhat longer half-life of about 70 days. Less than 10% of methylmercury is excreted in urine and feces as the mercuric cation.¹⁰⁰

PATHOPHYSIOLOGY

The pervasive disruption of normal cell physiology by mercury arises from its avid covalent binding to sulfur, replacing the hydrogen ion in the body's ubiquitous sulfhydryl groups. Mercury also reacts with phosphoryl, carboxyl, and amide groups, resulting in widespread dysfunction of enzymes, transport mechanisms, membranes, and structural proteins.

Because mercury deposits in all tissues, the clinical manifestations of mercury toxicity involve multiple organ systems with variable features and intensity. Necrosis of the GI mucosa and proximal renal tubules, which occurs shortly after mercury salt poisoning, is thought to result from direct oxidative effect of mercuric ions. An immune mechanism is attributed to the membranous glomerulonephritis and acrodynia associated with the use of mercurial ointments.¹⁰

Neurologic manifestations of methylmercury poisoning correlate with pathologic findings in the brains of both adults and children who were prenatally exposed.^{56,92} Grossly, atrophy of the brain is more severe in children who had prenatally or postnatally acquired methylmercury compared with the brains of those exposed as adults. In the adult brain, neuronal necrosis and glial proliferation are most prominent in the calcarine cortex of the cerebrum and in the cerebellar cortex. In fetal Minamata disease, similar lesions are present but in a more diffuse and severe form. Atrophy of the cerebellar hemispheres, postcentral gyri, and calcarine area of the brain demonstrated on magnetic resonance images in organic mercury-poisoned patients correlates with clinical findings of ataxia, sensory neuropathy, and visual field constriction, respectively.⁴⁷ Neuropathologic examination of the brain of a scientist who died after unintentional dermal exposure to dimethylmercury revealed lesions in the cerebellum, temporal lobe, and visual cortex.⁸⁶

In rats, neuronal cytotoxicity of methylmercury may result partly from muscarinic receptor-mediated calcium release from smooth endoplasmic reticulum of cerebellar granule cells.⁵⁰ There is animal evidence that methylmercury may trigger reactive oxygen species production. In addition, methylmercury inhibits astrocyte uptake of cysteine, the rate-limiting step in the production of glutathione, a major antioxidant in mammalian cell systems.⁸⁵ Cultured astrocytes accumulated methylmercury and exhibited increased mitochondrial permeability and oxidative injury.¹⁰¹

CLINICAL MANIFESTATIONS

Elemental Mercury

Symptoms of acute elemental mercury inhalation occur within hours of exposure and consist of cough, chills, fever, and shortness of breath. GI complaints include nausea, vomiting, and diarrhea accompanied by a metallic taste, dysphagia, salivation, weakness, headaches, and visual disturbances. Chest radiography during the acute phase may reveal interstitial pneumonitis and both patchy atelectasis and emphysema. Symptoms may resolve or progress to acute respiratory distress syndrome with respiratory failure and death. Survivors of severe pulmonary toxicity may develop interstitial fibrosis and residual restrictive pulmonary disease. The acute respiratory symptoms may occur concomitantly with or lead to the development of subacute inorganic mercury poisoning manifested by tremor, renal dysfunction, and gingivostomatitis.^{13,44,75} Thrombocytopenia may also occur during the acute phase.³⁰

Although acute exposure to elemental mercury vapor occurs most commonly in the occupational setting, poisonings caused by mishandling of the metal in the home are well reported.^{15,16,40,58,88} In fact, attempts at home metallurgy using metallic mercury have resulted in fatalities with ambient air concentrations of mercury as high as 0.9 mg/m³. The current US Occupational Safety and Health Administration permissible exposure limit for mercury vapor is 0.1 mg/m³ of air as a ceiling limit.⁶⁶

As with other inhaled toxins, children may be more sensitive to the pulmonary toxicity of mercury vapor because of their ratio of minute ventilation to body size.⁵⁸ Although pulmonary toxicity from elemental mercury usually results from inhalation of vapor, massive endobronchial hemorrhage followed by death has occurred secondary to direct aspiration of metallic mercury into the tracheobronchial tree.¹⁰³ Gradual volatilization of elemental mercury results in chronic toxicity from improper handling, such as vacuuming spilled mercury.⁸³

The clinical importance of volatilized metallic mercury from dental amalgams for both the dentist and patient is controversial. The preponderance of evidence refutes the idea that dental amalgam causes mercury poisoning. Several

comprehensive reviews of the subject conclude that (1) occupational exposure to mercury from dental amalgam is acceptably low, provided that recommended preventive measures such as adequate ventilation are adhered to, (2) the quantity of mercury vaporized from dental amalgam by mechanical forces, such as chewing, is clinically insignificant, and (3) only in exceedingly rare cases will immunologic hypersensitivity to mercury amalgam (manifested as cutaneous signs and symptoms and confirmed by patch testing) necessitate removal of the amalgam.^{27–29,49,87}

Unusual cases of chronic toxicity have resulted from intentional subcutaneous or IV injection of elemental mercury (Fig. 5–6 and Fig. 98–1).^{39,60} Aside from management of systemic mercury toxicity, local wound care and excision of deposits of mercury are additional therapeutic challenges presented by these cases. Serial or repeat radiographs are useful in guiding the removal of the radiopaque deposits.

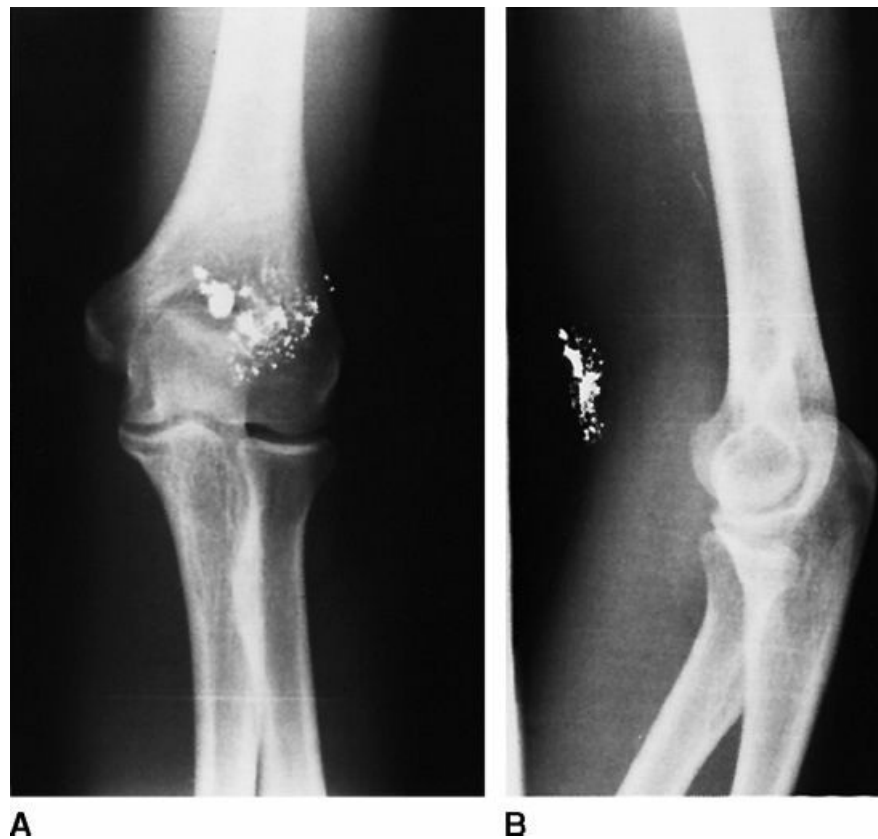


FIGURE 98–1. Anteroposterior (A) and lateral (B) views of the elbow after an unsuccessful suicidal gesture involving an attempted intravenous injection of mercury in the antecubital fossa. Note the extensive subcutaneous mercury deposition, which was partially removed by surgical intervention. (Used with permission of Diane Sauter, MD.)

Inorganic Mercury

Acute ingestion of mercuric salts produces a characteristic spectrum from severe irritant to caustic gastroenteritis. Immediately after the ingestion, a grayish discoloration of mucous membranes and metallic taste may accompany local oropharyngeal pain, nausea, vomiting, and diarrhea followed by abdominal pain, hematemesis, and hematochezia. The lethal dose of mercuric chloride is estimated to be 30 to 50 mg/kg.⁹⁴ The life-threatening manifestations of severe acute mercuric salt ingestion are hemorrhagic gastroenteritis, massive fluid loss resulting in shock, and kidney failure.⁸¹

Oropharyngeal injury, nausea, hematemesis, hematochezia, and abdominal pain were the most prominent symptoms in a series of 54 patients who presented after ingesting up to 4 g of mercuric chloride.⁹⁴ In this series, fatality was associated with the early development of oliguria (within 3 days) likely due in large part to lack of routinely available hemodialysis. The development of anuria appeared to be related to the dose of mercuric chloride ingested. The histopathologic finding of proximal tubular necrosis after mercuric salt poisoning results both from direct toxicity to renal tubules and from renal hypoperfusion caused by shock. Consequently, aggressive fluid therapy to maintain perfusion is useful.⁸²

Acute ingestion of mercuric salts is usually intentional, but unintentional ingestion occurs sporadically in both children and adults.⁴¹ Although ingestion of button batteries containing mercuric oxide is associated with a greater incidence of fragmentation than with other batteries, clinically significant systemic mercury toxicity by this route has not been reported.^{52,55} Mercuric chloride-containing stool preservatives are another potential source of unintentional inorganic mercury poisoning. Ingestion of 10 to 20 mL of a polyvinyl alcohol preservative that contained 4.5% mercuric chloride resulted in bloody gastroenteritis and proteinuria.⁸⁴ Patent³⁹ and Ayurvedic⁸⁰ medicines are also associated with unintentional inorganic mercury poisoning.⁴³ These xenobiotics are not subject to US Food and Drug Administration (FDA) regulation, available without prescription, of variable composition, and are often inadequately labeled (Chap. 45).

Subacute or chronic mercury poisoning occurs after inhalation, aspiration, or injection of elemental mercury; ingestion or application of mercury salts; or ingestion of aryl or long-chain alkyl mercury compounds. Slow in vivo oxidation of elemental mercury and dissociation of the carbon–mercury bond of aryl or long-chain alkyl mercury compounds result in the production of the inorganic mercurous and mercuric ions.

The predominant manifestations of subacute or chronic mercury toxicity include GI symptoms, neurologic abnormalities, and renal dysfunction. GI symptoms consist of a metallic taste and burning sensation in the mouth, loose teeth and gingivostomatitis, hypersalivation (ptyalism), and nausea.⁹⁸ The neurologic manifestations of chronic inorganic mercurialism include tremor, as well as the syndromes of neurasthenia and erethism. Neurasthenia is a symptom complex that includes fatigue, depression, headaches, hypersensitivity to stimuli, psychosomatic complaints, weakness, and loss of concentrating ability. Erethism, derived from the Greek word *erethē*, describes the easy blushing and extreme shyness of affected individuals. Other symptoms of erethism include anxiety, emotional lability, irritability, insomnia, anorexia, weight loss, and delirium. Mercury produces a characteristic central intention tremor (Chap. 24) that is abolished during sleep. In the most severe forms of mercury-associated tremor, choreoathetosis and spasmodic ballismus may be present. Other neurologic manifestations of inorganic mercurialism include a mixed sensorimotor neuropathy, ataxia, concentric constriction of visual fields (“tunnel vision”), and anosmia.

Chronic poisoning with mercuric ions is associated with renal dysfunction, which ranges from asymptomatic, reversible proteinuria to nephrotic syndrome with edema and hypoproteinemia. An idiosyncratic hypersensitivity to mercury ions is thought to be responsible for acrodynia, or “pink disease,” which is an erythematous, edematous, and hyperkeratotic induration of the palms, soles, and face, and a pink papular rash that was first described in a subset of children exposed to mercurous chloride powders.⁹⁸ The rash is described as morbilliform, urticarial, vesicular, and hemorrhagic. This symptom complex also includes excessive sweating, tachycardia, irritability, anorexia, photophobia, insomnia, tremors, paresthesias, decreased deep-tendon reflexes, and weakness. The acral rash may progress to desquamation and ulceration. The prognosis is favorable after withdrawal from mercury exposure. Childhood acrodynia has become uncommon since the abandonment of mercurial teething powders and diaper rinses. Occasional case reports are still noted, however, with fluorescent light bulbs and phenylmercuric acetate–containing paint implicated.^{3,95}

Thimerosal is an example of an aryl mercury compound that results in chronic inorganic mercury toxicity. It is a compound that was widely used as a preservative in the pharmaceutical industry (Chap. 55). Although initial kinetics have suggested a stable ethyl–mercury bond, the later elimination phase more closely resembles that of the inorganic mercury compounds. Thimerosal is approximately 50% mercury by weight. Generally considered safe, toxicity and death can nevertheless occur after both intentional overdose and excessive therapeutic application of merthiolate (0.1% thimerosal or 600 µg/mL mercury).^{70,76}

Concern that the cumulative dose of thimerosal in childhood immunizations may exceed federally recommended maximum mercury doses (EPA, 0.1 µg/kg/d; Agency for Toxic Substances and Disease Registry, 0.3 µg/kg/d; FDA, 0.4 µg/kg/d) led to a call by the American Academy of Pediatrics to reduce or eliminate thimerosal from vaccines.⁴ In particular, controversy exists whether thimerosal causes autism. Although sensitization after use in vaccinations has been reported in atopic children,⁶⁹ clinical mercury toxicity has not been reported in appropriately immunized children. Moreover, many studies suggest that the incidence of autism is unrelated to the use of thimerosal-containing vaccines.^{7,53,68,89} Similarly, no causal association with early thimerosal exposure and adverse neuropsychological outcomes was shown in children tested at 7 to 10 years of age.⁹³ At the present time, there is clearly more evidence for risk to child health from the diseases targeted for prevention by the vaccines than from thimerosal. In 2010, US courts rejected a causal relationship between thimerosal and autism.²⁶

Thimerosal continues to be used in medically underserved nations as a preservative in multidose vials in areas with inadequate refrigeration.³¹ Nevertheless, since 2001, routinely administered childhood vaccines in the United States no longer contain thimerosal.^{4,37}

Organic Mercury Compounds

By contrast to the inorganic mercurials, methylmercury produces an almost purely neurologic disease that is usually permanent except in the mildest of cases. Although the predominant syndrome associated with methylmercury is that of a delayed neurotoxicity, acute GI symptoms, tremor, respiratory distress, and dermatitis may occur.¹⁰⁰ In addition, abnormalities on electrocardiography (ECG; ST segment changes) and renal tubular dysfunction are associated with this poisoning.³⁵

The lipophilic property and slower elimination of methylmercury may contribute to its profound neurologic effects. Characteristically, clinical manifestations occur after the initial poisoning by a latent period of weeks to months. Consequently, the lethal dose of methylmercury is difficult to determine. As noted previously, infants exposed prenatally to methylmercury were the most severely affected individuals in Minamata. Often born to mothers with little or no manifestation of methylmercury toxicity themselves, exposed infants exhibited decreased birth weight and muscle tone, profound developmental delay, seizure disorders, deafness, blindness, and severe spasticity.

The development of neurologic symptoms in infants exclusively breastfed by women exposed to methylmercury after delivery and the detection of mercury in the milk of lactating women implies a risk for mercury poisoning via breast milk.⁴⁶ In one series of lactating women, mercury concentrations in milk were approximately 30% of the concentrations found in blood.⁶⁷ Seven year-old children from the Faroe Islands, who have a diet traditionally high in mercury-containing sea mammals, breast-fed as infants exhibited a diminished benefit (but not deficit) on neuropsychological testing when compared with their counterparts fed formula.³⁸

The rapid decline of blood mercury concentrations in both suckling rats and breastfeeding human infants is attributed to rapid growth of body volume combined with limited transport of mercury by milk.^{62,78,79} Several weeks after methylmercury-contaminated grain was ingested in Iraq, patients began to appear with paresthesias involving the lips, nose, and distal extremities. Symptomatic patients also noted headaches, fatigue, and tremor. More serious cases progressed to ataxia, dysarthria, visual field constriction, and blindness. Other neurologic deficits included hyperreflexia, hearing disturbances, movement disorders, salivation, and dementia. The most severely affected patients lay in a mute, rigid posture punctuated only by spontaneous crying, primitive reflexive movements, or feeding efforts.⁷⁷

Although the outlook for methylmercury neurotoxicity is generally considered dismal, observations over the subsequent 2 years in 49 Iraqi children poisoned during the 1971 outbreak revealed complete resolution or partial improvement in all but the most severely affected.⁵ Of the 40 symptomatic children, 33 mildly to severely affected children showed partial to complete resolution of symptoms, but the seven children classified as “very severely poisoned” remained physically and mentally incapacitated.

An important route of organic mercury exposure is through seafood consumption. The safe level of methylmercury in seafood remains controversial. The FDA action concentration of 1 ppm for methylmercury in fish was set to limit consumption of methylmercury to less than one-tenth of levels found in cases of symptomatic poisoning. The EPA established a reference dose for methylmercury of 0.1 $\mu\text{g}/\text{kg}/\text{d}$.^{72,96} Although elevated blood concentrations (19–53 $\mu\text{g}/\text{L}$) of mercury were found in one group of self-reported high consumers of seafood, increased incidence of cognitive and GI complaints were not.⁴² Even so, concentrations at which fetuses experience adverse effects are unknown. Longitudinal studies of fish-eating populations are conflicting. No effect of a high prenatal fish diet was found on developmental markers in children followed to 17 years of age in the Seychelles Islands.^{22,23}

However, in the studies done in the Faroe Islands and New Zealand, a subtle but significant effect on neuropsychological development was seen.^{20,32,90} In the Faroe Islands, this effect persisted when children were retested at 14 years of age.²⁵ One reason for the discrepancy that occurs between the two populations may be the different patterns of seafood consumption and concentrations of methylmercury in the seafood consumed by each. The Faroese consume low-level mercury containing fish one to three times a week with episodic feasts of highly contaminated pilot whale, whereas the Seychellois consume a more steady diet of low-level contaminated fish on average 12 times per week. The pilot whales consumed in the Faroe Islands were also contaminated with neurotoxic polychlorinated biphenyls, although these compounds were measured and controlled for as a potential confounding variable. The mean concentration of methylmercury in the whale meat consumed in the Faroe Islands was 1.6 $\mu\text{g}/\text{g}$, and the mean concentration of mercury found in New Zealand shark was 2.2 $\mu\text{g}/\text{g}$. By contrast, the mean methylmercury content of Seychellois fish was 0.3 $\mu\text{g}/\text{g}$.⁶¹ The threshold concentration for neuropsychological effects may lie between these concentrations.

No increase in cardiovascular disease risk was seen with mercury exposure in a large cohort of US adults.⁵⁹

The FDA recommends that at-risk populations (ie, pregnant women and women who may become pregnant, nursing mothers, and young children) avoid large predator fish (eg, shark, swordfish, tilefish, and king mackerel) that contain concentrations of methylmercury approaching 1 ppm (1 $\mu\text{g}/\text{g}$). The 2004 FDA/EPA consumer advisory emphasizes the health benefits of eating fish and allow for up to 12 ounces per week of fish and shellfish lower in mercury such as shrimp, canned light tuna, salmon, pollock and catfish and up to 6 ounces of albacore tuna per week. Given the beneficial effects of seafood, efforts should be aimed at decreasing anthropogenic release of mercury rather than elimination of dietary exposure.⁷³

Although methylmercury has greater importance worldwide, the extreme toxicity of another organic mercurial, dimethylmercury, was tragically demonstrated by the delayed fatal neurotoxicity that developed in a chemist who inadvertently spilled dimethylmercury on a break in the gloves on her hands.⁶³ Over a period of several days, she developed progressive difficulty with speech, vision, and gait. Despite chelation and exchange transfusion, she died of mercury neurotoxicity within several months of the exposure.

DIAGNOSTIC TESTING

The dual findings of unexplained neuropsychiatric and renal abnormalities in an individual should alert the clinician to the possibility of mercurialism, as should an at-risk occupation or access by the patient to a mercurial product (Table 98–1). Occupational or environmental exposure and a consistent clinical scenario may be suggestive of mercury poisoning, but

demonstration of mercury in blood, urine, or tissues is necessary for confirmation of exposure. Of the many methods available to measure mercury, cold atomic absorption spectrometry is rapid, sensitive, and accurate but cannot distinguish the various forms of mercury. Thin-layer and gas chromatographic techniques can be used to distinguish organic from inorganic mercury. Whole blood should be collected into a trace element collection tube obtained from the laboratory performing the assay. Urine should be collected for 24 hours into an acid-washed container obtained from a laboratory. Spot collections must be adjusted for creatinine concentration. Attempts to measure or otherwise handle the specimen should be avoided to prevent external contamination (Table 98–4).

TABLE 98–4. Diagnostic Testing for Mercury

	<i>Whole Blood</i>	<i>24-hour Urine</i>	<i>Hair</i>	<i>Clinical</i>
Elemental/ Inorganic	(+) Acute, transient	(++) Confirm exposure Monitor chelation Poor correlation to TBB	(+) Reflects past exposure and external adsorption	(+) Poor correlation to TBB Early detection
Organic	(++) Best reflects TBB	(–) Fecal elimination	(+) Reflects past exposure and external adsorption	(+) Poor correlation to TBB Reflects irreversible CNS toxicity Early detection

CNS = central nervous system; TBB = total body burden.

There is considerable overlap among concentrations of mercury found in the normal population, asymptomatic exposed individuals, and patients with clinical evidence of poisoning. There is no definitive correlation between either whole blood or urine mercury concentration and mercury toxicity. However, mercury serves no useful role in human physiology, and concentrations of 1.0 µg/L or less for whole blood and 0.5 µg/L for urine are generally considered to reflect background exposure in nonpoisoned individuals.¹⁶

For inorganic mercury poisoning, urine mercury concentrations may correlate roughly with exposure severity and neuropsychiatric symptoms,⁷⁴ but the relationship to total-body burden is probably poor. Urine mercury determinations have their greatest usefulness in confirming exposure and monitoring the efficacy of chelation therapy. Whole-blood mercury concentrations may reflect intense, acute inorganic mercury exposure but become less reliable as redistribution to tissues takes place.

Because organic mercury is eliminated via the fecal route, urine mercury concentrations are not useful in methylmercury poisoning. Because methylmercury concentrates in RBCs, the total-body methylmercury burden is best reflected acutely by whole blood concentrations. As methylmercury distributes to and accumulates in brain, the severity of clinical manifestations probably more closely reflects the degree of the irreversible neuronal destruction that has taken place rather than the current body burden of mercury. Correlation of increasing whole-blood mercury concentrations with prevalence of paresthesias was suggested in a population of Iraqis studied early in the course of methylmercury poisoning.¹⁹ However, in another group of patients, whole-blood concentrations did not correlate with severity of methylmercury poisoning.⁷⁷ This apparent discrepancy may have resulted from the finding that paresthesias are among the earliest reported symptoms of methylmercury poisoning.

Because mercury accumulates in the hair, hair analysis has been used as a tool for measuring mercury burden. However, because metal incorporation reflects past exposure and hair avidly binds to noningested environmental mercury, the reliability of this method is questionable and is not recommended. In addition to mercury assays, neuropsychiatric testing, nerve conduction studies, and urine assays for N-acetyl-β-D-glucosaminidase and β₂-microglobulin are advocated for early detection of subclinical inorganic and organic mercury toxicity.^{28,35,74}

GENERAL MANAGEMENT

After the initial assessment and stabilization, the early toxicologic management of a patient with mercury poisoning includes termination of exposure by removal from vapors, washing exposed skin, GI decontamination, supportive measures (eg, hydration, humidified oxygen), baseline diagnostic studies (eg, complete blood count, serum chemistries, venous blood gas, radiography, ECG), specific analysis of whole blood and urine for mercury, consideration of possible cointoxicants, and meticulous monitoring.

Elemental Mercury

Inhalation of mercury vapors or aspiration of metallic mercury may result in life-threatening respiratory failure; in this situation, stabilization of cardiorespiratory function is the initial priority. Postural drainage and endotracheal suction may be effective in removing aspirated metallic mercury. Parenteral deposition of subcutaneous or intramuscular (IM) mercury may be amenable to surgical excision, if well localized (Fig. 98–1).

An adjunct to the initial management of patients with mercury poisoning is consideration for environmental decontamination. Elemental mercury that spills onto solid surfaces should be adsorbed to sand and the resulting mixture then swept into tightly sealed containers. Ideally, a mercury decontamination kit should be used. The kit consists of calcium polysulfide, which contains excess sulfur to convert mercury to water-insoluble mercuric sulfide. Absorbent surfaces, such as carpets, should be removed. Spilled mercury compounds should not be vacuumed because vacuuming could volatilize the mercury.¹⁴ Broken CFL bulbs should be handled and disposed of according to EPA guidelines and local requirements.²

Recommendations for decontamination after breakage include opening windows to release vapor, using adhesive tape to pick up visible fragments, and discarding contaminated material in double-wrapped bags. Guidance for decontamination of major spills and disposal of materials can be provided by local and federal hazardous materials agencies.

Inorganic Mercury

Ingestion of inorganic mercuric may lead to cardiovascular collapse caused by severe gastroenteritis and third-space fluid loss. Fluid resuscitation is a priority. GI decontamination of ingested inorganic mercury is particularly problematic because of its causticity and risk for perforating injury. Nevertheless, one series of patients with mercuric chloride ingestion of up to 4 g reported recovery without long-term GI sequelae in patients who did not succumb to kidney failure.⁹⁴ Therefore, unless there is high suspicion for penetrating GI mucosal injury, removal of mercury from absorptive surfaces should take priority over endoscopic evaluation. The prominence of vomiting makes gastric lavage unnecessary for most patients with inorganic mercury poisoning.

Metals are among the substances that are often considered to be poorly adsorbed to activated charcoal. Nevertheless, the serious nature of late sequelae after mercury absorption, the typically small quantities of mercury ingested, and evidence that inorganic mercuric salts actually have substantial adsorption to activated charcoal (800 mg mercuric chloride can be adsorbed to 1 g activated charcoal) justify the routine administration of activated charcoal.⁶ Whole-bowel irrigation with polyethylene glycol solution may also be useful in removing residual mercury and should be considered, with its progress followed with serial radiographs.

Organic Mercury

Organic mercury exposures do not typically present as single acute ingestions but rather as chronic or subacute ingestion of contaminated food. Therefore, GI decontamination is generally moot with respect to organic mercury poisoning. Nevertheless, its irreversible toxicity coupled with unsatisfactory treatments calls for aggressive decontamination when acute ingestions or dermal exposures occur.

CHELATION

After initial stabilization and decontamination, early institution of chelators may minimize or prevent the widespread effects of poisoning. A high degree of protein binding and distribution to the brain are responsible for the lack of efficacy of other measures to increase mercury clearance, such as peritoneal dialysis and hemodialysis.⁸¹ In one report of the use of continuous venovenous hemodiafiltration in combination with a chelator in a patient with severe inorganic mercury poisoning, 12.7% of the ingested dose was recovered in the ultrafiltrate.²¹ Hemodialysis may nevertheless ultimately be necessary because of the acute kidney failure that often occurs after mercuric chloride poisoning.

Chelators have thiol groups that compete with endogenous sulfhydryl groups for the binding of mercury, thereby preventing inactivation of sulfhydryl-containing enzymes and other essential proteins (Antidotes in Depth: A25 and A26). A history of significant mercury exposure combined with the presence of typical symptoms of mercury poisoning is an appropriate indication for the institution of chelation therapy. Elevated whole-blood and urine mercury concentrations may help support the decision to begin chelation therapy in unclear cases and may also be used to guide the duration of therapy.

Provocative chelation, in which urinary mercury excretion before and after a chelating dose is compared to determine the degree of mercury poisoning, is of no value.⁴² Chelation tends to increase urinary elimination of mercury, regardless of exposure history and baseline excretion.

Elemental Mercury and Inorganic Mercury Salts

For symptomatic acute inorganic mercury poisoning, dimercaprol (BAL) should be administered for 10 days in decreasing dosages of 5 mg/kg/dose every 4 hours IM for 48 hours, then 2.5 mg/kg every 6 hours for 48 hours, followed by 2.5 mg/kg every 12 hours for 7 days. This dosing regimen of BAL, derived from the use of BAL in lead poisoning, may be adjusted according to clinical response and the occurrence of adverse reactions.

When a patient can take oral medications, BAL therapy may be replaced with succimer (2,3-dimercaptosuccinic acid) at 10 mg/kg orally three times a day for 5 days, then twice a day for 14 days if the GI tract is clear. Because headache, nausea, vomiting, abdominal pain, and diaphoresis may result from BAL chelation therapy, oral succimer is recommended in patients who are not acutely ill or who have been chronically poisoned.

Either BAL or succimer is considered the treatment of choice for inorganic mercury poisoning in the United States, but a few other chelators deserve mention. 2,3-Dimercapto-1-propanesulphonate (DMPS) is a water-soluble dimercaprol derivative that is used in Europe. It may be administered both IV and orally. D-Penicillamine is an orally administered monothiol. Its adverse events—GI distress, rashes, leukopenia, thrombocytopenia, and proteinuria—although uncommon in therapeutic doses, seriously limit the usefulness of the drug. N-acetyl-D,L-penicillamine (NAP), an investigational analog of D-penicillamine, is thought to be a more effective chelator of mercury than is D-penicillamine, perhaps because of its greater stability.^{8,33}

Organic Mercury Compounds

The neurotoxicity of methylmercury and other organic mercury compounds is resistant to treatment, and therapeutic options are less than satisfactory. In rats, both BAL and D-penicillamine effectively reduced tissue mercury and prevented neurologic toxicity if administered within the first day of a methylmercury injection.¹⁰² Neither treatment reversed neurologic toxicity when administered 12 days after methylmercury injection. DMPS, D-penicillamine, NAP, and a thiolated resin all led to a marked reduction of blood half-life of mercury (ie, 10, 24, 23, and 19 days, respectively, vs. 60 days) during the outbreak of methylmercury poisoning in Iraq in 1971.¹⁹ Clinical improvement was not observed in any treatment group, but it is reasonable to postulate that reducing the total-body burden of methylmercury may prevent or limit the progression of disease. When studied in mice poisoned with methylmercury,¹ succimer was superior to NAP, DMPS, and a thiolated resin in decreasing brain mercury and increasing urinary excretion. Brain mercury was decreased to 35% of control, and the total-body burden fell to 19%. Some animal evidence suggests that BAL may increase mercury mobilization into the brain.¹¹ For this reason and the lack of serious GI symptoms necessitating parenteral chelation, BAL should not be used for the treatment of patients with organic mercury poisoning.

Because the neurologic impairment associated with methylmercury is both profound and essentially irreversible, early recognition of poisoning and prevention of neurotoxicity are essential to a successful outcome. Although further investigation is necessary, succimer may prove to be the treatment of choice for methylmercury poisoning because of its apparently low toxicity and reported efficacy in animal trials.

SUMMARY

- Mercury poisoning by any of the three major forms—elemental, inorganic, and organic—presents a complex toxicologic problem associated with a large variety of clinical presentations.
- An ever-present awareness of the problems coupled with the knowledge of the differing clinical forms is essential for both early recognition and effective treatment.
- Although some chelators do show promise in the treatment of mercury poisoning, neurologic sequelae, particularly those resulting from organic mercury exposures, remain largely irreversible.
- Promotion of public education regarding the dangers of mercury, its avoidance, and proper disposal may aid in the prevention of mercury poisoning.

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99 NICKEL

John A. Curtis and David A. Haggerty

Nickel (Ni)	
Atomic number	= 28
Atomic weight	= 58.7 Da
Normal concentrations	
Serum	< 1 µg/L (17 nmol/L)
Urine	< 6 µg/L (100 nmol/L)

HISTORY AND EPIDEMIOLOGY

Nickel is a ubiquitous metal commonly found in both home and industry. It exists in a variety of chemical forms, from naturally occurring ores to synthetically produced nickel carbonyl. Elemental nickel is a white, lustrous metal whose name is derived from the German word “kupfernickel” or “devil’s copper.” Swedish chemist Baron Axel Fredrik first identified nickel in 1751 in a mineral known as niccolite. Nickel comprises 0.008% of the Earth’s crust and is found in diverse locations, ranging from meteorites and soil to bodies of fresh and saltwater.

First produced by the Chinese, nickel has been used as a component in a variety of metal alloys for more than 1700 years. The first malleable nickel was produced by Joseph Wharton following the American Civil War. Wharton went on to sell bulk quantities of nickel to the US government for the minting of 3-cent coins, and later donated the equivalent of 3.3 million of these coins to help fund what is today known as the Wharton School of Business.⁶⁵ The modern US 5-cent piece, the “nickel,” is actually only approximately 25% nickel by weight, and all US coins except the penny are made of nickel-containing alloys.¹⁰

Nickel ores typically consist of accumulations of nickel sulfide minerals of relatively low nickel content. Although a variety of technical methods for extracting nickel from ore have been developed, one method of special note was developed in 1890 by Ludwig Mond, who is credited with the discovery of nickel carbonyl. The Mond process for the extraction of nickel involves passing carbon monoxide over smelted ore. This creates nickel carbonyl, which then decomposes at high temperatures to produce purified nickel and carbon monoxide.⁶⁵ Nickel mining ceased 30 years ago in the United States, and despite an increasing worldwide demand, as of 2011 there were still no active domestic nickel mines.¹⁰ Nickel is imported into the United States from other nickel-rich countries, such as Canada, Russia, and Australia, while domestic production of nickel in the United States is essentially limited to the recycling of nickel-containing metals.

Nickel is a siderophoric material that forms naturally occurring alloys with iron, a property that has made it useful for many centuries in the production of coins, tools, and weapons. Today, most nickel is used in the production of stainless steel, a highly corrosion-resistant alloy containing 8% to 15% nickel by weight.

Occupational exposure to nickel and nickel containing compounds occurs in a variety of industries, including nickel mining, refining, reclaiming, and smelting. Chemists, magnet makers, jewelry makers, oil hydrogenator workers, battery manufacturers, petroleum refinery workers, electroplaters, stainless steel and alloy workers, and welders are at increased risk for exposure to nickel and nickel-containing compounds. Most nonindustrial human exposures to nickel are usually from dietary and environmental sources, although cigarette smoking is an important nickel exposure and elevates urinary nickel concentrations.⁶³ In the occupational setting, nickel carbonyl is responsible for the great majority of acute nickel toxicity, while in clinical practice, the most common health issue related to nickel is the development of allergic dermatitis from jewelry and clothing, as well as cosmetics and complementary and alternative medicines.^{9,19} Nickel and Toxicodendron species exposures are the most common causes of allergic contact dermatitis, with a large proportion of the population—particularly women—demonstrating nickel sensitivity.

TOXICOKINETICS

Exposure

Nickel occurs naturally in soil, volcanic dust, and fresh and saltwater, but it also enters the environment from the combustion of fuel oil, municipal incineration, nickel refining processes, and the production of steel and other nickel alloys that may allow aerosolized nickel to be disseminated into the environment.

The specific form of nickel emitted to the atmosphere depends on the source. Complex nickel oxides, nickel sulfate, and metallic nickel are associated with combustion and incineration, as well as smelting and refining processes. Consequently, ambient air concentrations of these forms of nickel tend to be higher in urban areas, and concentrations of nickel in urban household dust may be elevated under certain circumstances and thus may pose some variable exposure risk for young children who crawl or sit on floors.

Nickel carbonyl, $\text{Ni}(\text{CO})_4$, deserves special mention. This highly volatile and potentially dangerous liquid nickel compound is a product of the reaction of nickel and carbon monoxide and is commonly used in nickel refining and petroleum processing, and as a chemical reagent. Its high vapor pressure and high lipid solubility lead to rapid systemic absorption through the lungs. In the air and in the body, it decomposes into metallic nickel and carbon monoxide and its toxicity has been compared with hydrogen cyanide.³⁵ Workers exposed to nickel carbonyl are commonly screened for low level exposure, but disasters such as the Gulf Oil Company refinery incident in 1953, and the Toa Gosei Chemical company incident in 1969, resulted in hundreds of inhalational exposures.⁶⁵

However, non-occupational exposures to nickel are typically environmental and dietary. Ambient air nickel concentrations are typically around 10 ng/m^3 , while soil usually has nickel concentrations of 4 to 80 ppm, with some areas much higher. Concentrations of metallic nickel in drinking water in the United States are generally below $20 \text{ }\mu\text{g/L}$, but elevated concentrations of nickel in household and other potable and nonpotable water sources may result from corrosion and leaching of nickel alloys present in various plumbing fixtures, including valves and faucets.²² Although many water suppliers in the United States monitor nickel concentrations in their water, there is currently no US Environmental Protection Agency (EPA) regulation regarding how much nickel is permissible in drinking water.

Dietary intake is a recognized source of nickel exposure for humans. Foods high in nickel include nuts, legumes, cereals, licorice, and chocolate. In addition, certain homeopathic medications, ginseng products, Indian herbal teas, Nigerian herbal remedies, and Chinese herbal plants are high in nickel content, with some Nigerian herbal remedies reportedly containing up to $78 \text{ mg nickel/g substance}$.¹⁹ Nickel is not considered an essential element for human health and dietary recommendations for nickel have not been established. Normal consumption is between 0.3 to 0.6 mg per day, with the majority of this being unabsorbed by the gastrointestinal tract. A Danish meta analysis of 17 studies suggested that up to 1% of individuals may develop allergic contact dermatitis at the low level of oral nickel exposure represented by dietary and drinking water sources.³⁰ Although estimates vary widely, the total body burden for a 70-kg reference human is about 10 mg of nickel, giving an average body concentration of 0.1 ppm.²² No clear biologic function has been determined for nickel in humans, but it may serve as a cofactor for various enzymes.

Absorption

Nickel may enter the body through the skin, lungs, and gastrointestinal tract. The amount and rate of absorption is dependent on the water solubility of the nickel compound. Once in the body, nickel exists primarily as the divalent cation (Ni^{2+}). Independent of the particular nickel compound involved in the exposure, it is nickel ion (Ni^{2+}) that is typically measured in the serum or urine.

Following inhalational exposure, nickel accumulates in the lungs, but only 20% to 35% of nickel deposited in the human lung is systemically absorbed.²² The remainder of the inhaled material is swallowed, expectorated, or deposited in the upper respiratory tract. Subsequent systemic absorption from the respiratory tract is dependent on the solubility of the specific nickel compound in question. Soluble nickel salts (nickel sulfate and nickel chloride) are more easily absorbed, whereas the less-soluble oxides and sulfides of nickel are absorbed to a lesser extent.

Because water-soluble nickel compounds tend to be more readily absorbed from the respiratory tract when compared with poorly soluble nickel compounds, exposure to the soluble nickel chloride or nickel sulfate results in higher urinary nickel concentrations than does exposure to less-soluble nickel oxide or nickel subsulfide, while the less soluble compounds may have a longer apparent half-life. This likely at least partially represents a longer absorption phase.

The gastrointestinal absorption of nickel compounds varies with the particular nickel compound as well as coingestants. For example, approximately 27% of the total nickel in nickel sulfate given to humans in drinking water is absorbed, whereas only approximately 1% is absorbed when given in food. Serum nickel concentrations peak between 1.5 and 3 hours following ingestion.⁶⁸ The presence of food in the gastrointestinal tract appears to reduce the absorption of nickel, and most ingested nickel remains in the gut and is excreted in the feces.

While systemic absorption of nickel can occur through skin contact, much of the applied nickel remains in the keratinized skin, with limited absorption by keratinocytes.³⁷

Distribution

In human serum, the exchangeable pool of primarily divalent nickel is bound to albumin, L-histidine, and α 2-macroglobulin.⁴⁷ A nonexchangeable pool of nickel that is tightly bound to a transport protein known as nickeloplasmin also exists in the serum. Nickel crosses the placenta and is present in breast milk.

Nickel is also concentrated in various solid organs. An autopsy study of individuals not occupationally exposed to nickel reported the highest concentrations of nickel in the lungs, followed by the thyroid, adrenals, kidneys, heart, liver, brain, spleen, and pancreas.⁵¹ Nickel concentrations in the nasal mucosa are higher in workers exposed to less-soluble nickel compounds relative to soluble nickel compounds,⁷⁵ indicating that, following inhalation exposure, less-soluble nickel compounds remain deposited on the nasal mucosa.

Elimination

In humans, most ingested nickel is excreted in the feces; however, because more than 90% of ingested nickel does not leave the gut,⁶⁶ most of the nickel found in feces represents the unabsorbed fraction rather than the elimination of body nickel.⁶⁸ Absorbed nickel is primarily excreted in the urine and, to a lesser degree, other bodily fluids.

Regardless of the route of exposure, workers occupationally exposed to nickel have increased urinary concentrations of nickel.^{4,26} Animal studies indicate that nickel oxide, an insoluble compound, is slowly eliminated from the lungs via macrophages and excreted in feces, while more soluble compounds, such as nickel subsulfide, were excreted primarily in the urine.⁷

In nickel workers, urinary excretion increased from the beginning to the end of the shift, indicating that a fraction of absorbed nickel is rapidly eliminated.^{23,75} Similarly, urinary excretion increased as the work week progressed, indicating the presence of a fraction that is excreted more slowly. In fact, after a massive inhalational welding exposure, the half-life of nickel in urine and blood followed a biphasic exponential decay pattern of excretion, and was 25 and 610 days in urine, and 30 and 240 days in blood, indicating potential saturation of elimination pathways and delayed absorption and/or redistribution of nickel.⁵⁵

Studies of workers who unintentionally ingested water contaminated with nickel sulfate and nickel chloride reported a mean serum half-life of nickel was 60 hours, but was reportedly decreased substantially (≤ 27 hours) when the workers were treated with intravenous fluids.⁶⁷

The available literature supports the view that systemically absorbed nickel is excreted through the kidneys, with some excretion of insoluble compounds in the feces. Due to the previously mentioned factors affecting absorption, the apparent half-life following exposure may reflect continuing absorption and will therefore depend on the route of exposure and the particular nickel species involved.

CLINICAL MANIFESTATIONS

Acute

The clinical manifestations associated with acute exposure to nickel depend on the particular compound and route of exposure. Inhalation of nickel-containing aerosolized particles tends to affect the lungs and upper airways directly, whereas ingestion and intravenous administration may result in systemic toxicity, usually involving the nervous system (Table 99–1).

TABLE 99–1. Sequelae Associated with Nickel Carbonyl Poisoning

Acute respiratory distress syndrome/interstitial pneumonitis
Myocarditis
Altered mental status
Seizures
Profound weakness (sometimes requiring ventilatory support)
Prolonged neurasthenic syndrome (up to 6 months postexposure)
Death (secondary to interstitial pneumonitis or cerebral edema)

The most common disorder associated with exposure to nickel, by far, is an allergic dermatitis. Although acute toxicity

has been reported following various routes of exposure, the most important source of acute nickel toxicity is inhalational exposure to nickel carbonyl, which is associated with pulmonary, neurologic, and hepatic dysfunction.⁶⁵

Nickel Allergy and Dermatitis. Nickel dermatitis was first reported in the late 1800s in nickel-plating workers and was recognized as an allergic reaction in 1925. Since then, nickel has been recognized as a common cause of allergic contact dermatitis. Ni²⁺ is not itself antigenic but acts as a hapten, binding larger proteins and inducing conformational changes such that these become recognized as non-self-antigens.²⁸

The allergic reaction caused by contact with nickel is a type IV delayed hypersensitivity immune response that typically occurs in two phases. In the first phase, sensitization occurs when nickel enters the body. The second phase occurs when the body is re-exposed to nickel, at which time allergy manifests. The diagnosis of nickel allergy is suggested by specific historical findings listed in [Table 99–2](#).

TABLE 99–2. Findings Suggestive of Nickel Dermatitis

Previous history of allergic response to jewelry

Multiple body piercings

Eruptions at the site of metal contact, or flexor areas, if generalized

Eruptions following placement of orthodontic appliances containing high concentrations of nickel (unusual)

Seasonal dermatitis in warm months (increased metal–skin contact and increased sweating)

Facial dermatitis in mobile phone users

One population survey reported that 3% of men and 15% of women demonstrated evidence of allergy to nickel.⁴² More recent studies report even higher prevalences, ranging between 15% and 25%.³⁸ The fivefold greater prevalence of nickel allergy in women is presumably a consequence of their higher rates of body piercing and more frequent wearing of jewelry, both of which are risk factors for nickel sensitization. It is unclear if European nickel regulations have succeeded in reducing rates of nickel sensitivity although this has been suggested by several studies.⁷⁴

Nickel dermatitis is classified into two types: primary and secondary. The more common primary dermatitis presents as a typical eczematous reaction in the area of skin that is in contact with nickel. It is characterized initially by erythematous papules that may proceed to lichenification due to pruritus and scratching. These eruptions may mimic basal cell carcinoma.²⁵ Areas typically involved are the wrists, as a result of wearing watches and bracelets, the ears from earrings, and the periumbilical area at the site of contact with jewelry, nickel-containing buttons on jeans or nickel-containing belt buckles ([Fig. 99–1](#)). Approximately 50% of all belt buckles and 10% of buttons on blue jeans contain nickel.¹³ The most common cause for nickel dermatitis in women is direct contact from jewelry, garments, wristwatches, cosmetics, and occupational contact in the metal, hairdressing, tailoring, hotel, and restaurant industries. In men, nickel dermatitis is often occupational but may also, in some individuals, be related to jewelry, body piercing, garments, or even metal guitar strings.



Figure 99–1. Nickel dermatitis from jewelry. (Used with permission of Brian Wexler.)

The secondary form involves a more widespread dermatitis as a result of other exposures, such as ingestion or inhalation of nickel compounds, and implantation of metal medical devices, and may be regarded as a systemic contact dermatitis elicited by nickel. Secondary eruptions are typically symmetrically distributed and may localize in the elbow flexure, on the eyelids, on the sides of the neck and face, and can become widespread.

Nickel in foods, excessive skin contact, and certain orthodontic appliances with high nickel content are all linked to this eczematous eruption. Nonetheless, orthodontic exposure to nickel-containing alloys is unlikely to induce hypersensitivity reactions in patients without prior sensitization, and such reactions are still infrequent even in those sensitized.⁴⁹

Other types of medical devices containing nickel have the potential to induce either primary or local nickel dermatitis. Occlusion of a biliary stent attributed to nickel allergy has been reported.³² Much debate has arisen over the past decade regarding metallic coronary stents and the potential for nickel allergy-induced restenosis. Several studies have reported increased restenosis in nickel-allergic patients with bare-metal stainless steel³⁴ and cobalt-chromium² stents, although others have failed to find such a correlation.⁷³ Drug-eluting stents may mitigate any effect of metal allergy on rates of restenosis.⁴⁴

It is reported that the bimetallic core structure of the 1 Euro and 2 Euro coins creates an electrical potential that results in the release of nickel when in contact with sweat. While no general rise in the rate of nickel sensitivity has been confirmed, cases of dermatitis in certain high-risk patients are reported.⁵⁴

Recently, reports have emerged involving cases of contact dermatitis in users of certain types of cellular phones, with testing confirming nickel release in such phones.³⁹ Therefore, nickel should be considered a potential cause in cases of facial contact dermatitis of unknown etiology.

One study showed that following skin application nickel salts are retained in the skin for an extended period of time,³⁶ which could lead to prolonged antigen processing and consequent immune responses in dermal tissue. There may also be a genetic basis for nickel sensitization. Filaggrin gene mutations are reportedly associated with nickel contact dermatitis as a result of breakdown in nickel chelation in the stratum corneum, allowing for greater epidermal absorption of nickel.⁷² Development of an allergy, like most of toxicology, is probably dose and time related, and this is the basis of the recent EU regulations to limit consumer exposure to nickel.

INHALATIONAL EXPOSURE

Nickel Carbonyl

Nickel carbonyl is the most harmful form of nickel and the majority of acute occupational nickel exposures involve nickel carbonyl. Nickel carbonyl is described as having a “musty” or “sooty” odor, although thresholds for detection vary considerably and potentially harmful exposures cannot be excluded simply by a reported lack of odor. Exposure to concentrations less than 100 mg/m³ is fatal in rats after 20 minutes.^{33,69} Once dissociated, nickel carbonyl can be oxidized in tissues to Ni²⁺.

Nickel carbonyl exposure may cause symptoms rapidly or symptoms may be delayed. In a series of 179 exposures, approximately 40% of patients reported symptoms within 1 hour of exposure; however, it is important to note that symptoms were delayed for approximately 1 week in 20% of patients, and even patients with mild initial symptoms could develop severe delayed symptoms, although usually, within the next 2 days.⁵⁸ In patients who developed symptoms shortly following exposure, the initial manifestations involved nonspecific complaints, including respiratory tract irritation, chest pain, cough, dyspnea, frontal headache, dizziness, weakness, and nausea. Cases manifesting only these initial signs are categorized as mildly toxic.⁵⁸

Symptoms of severe acute nickel carbonyl poisoning generally develop over the course of several hours to days and may be associated with acute respiratory distress syndrome (ARDS) and interstitial pneumonitis. Myocarditis, marked by prolonged changes on electrocardiography, including ST- and T-wave changes, as well as QT prolongation, has been reported.⁵⁸ Neurologic symptoms associated with severe poisoning include altered mental status, seizures, and extreme weakness that sometimes necessitate mechanical ventilation. A moderate leukocytosis (10,000–15,000 white blood cells/mm³), nonspecific opacities on chest radiography, and elevation of aminotransferases may also occur, but these tend to resolve over the course of several weeks. Deaths from nickel carbonyl are typically caused by interstitial pneumonitis and cerebral edema occurring within 2 weeks of initial exposure.⁶⁹ Autopsy studies of those dying after nickel carbonyl exposure have shown diffuse pulmonary consolidation, organizing fibrosis, cerebral edema or hemorrhage, and cardiac dilation.⁵⁶ Survivors usually recover completely, although the development of a prolonged neurasthenic syndrome can occur and may last months in some cases.⁵⁸ Clinical features of nickel carbonyl poisoning are found in [Table 99–2](#).

Noncarbonyl Nickel

There are few human cases of inhalational nickel poisoning. However, from the available data, the primary concerns

appear to be pulmonary, neurologic and, perhaps, renal.

A case report described seizure activity in two patients following occupational inhalational exposure to non-carbonyl nickel. Both patients exhibited elevated urinary nickel concentrations, with no recurrence of seizure activity upon removal from exposure.²⁰ This complication was documented previously in rats with nickel sulfate toxicity.¹⁶ Although the mechanism for this is not quite clear, animal studies indicate that inhibition of the glutamate transporter may be involved.⁴⁰ Interstitial pneumonia is also associated with inhalational exposure while spray painting high-temperature nickel-chromium alloys.²⁷ As previously mentioned, inhalational exposure to metallic nickel particles/nanoparticles can induce ARDS, as well as acute tubular necrosis.^{48,50}

Parenteral Administration. Acute parenteral toxicity from nickel-containing compounds occurred following the use of water for hemodialysis that had been heated in a nickel-plated tank.⁷⁹ The concentration of nickel in the delivered water was 0.25 mg/L, and serum concentrations exceeded 3 mg/L. Through back extrapolation, serum concentrations were estimated to have been as high as 9 mg/L. These patients developed nonspecific symptoms, including headache, nausea, and vomiting, similar to nickel carbonyl poisoning, although no respiratory complaints were reported. The effects resolved after several hours, and the patients recovered without sequelae.

Ingestion. Acute ingestions of contaminated water containing 1.63 g Ni²⁺/L caused nausea, vomiting, diarrhea, weakness, and headache, as well as pulmonary symptoms, including cough and dyspnea, lasting up to 48 hours.⁶⁷ Estimated ingested doses of nickel (as Ni²⁺) were 0.5 to 2.5 g and serum concentrations as high as 13.4 µg/L were reported. The death of a 2 year-old girl followed ingestion of 2.2 to 3.3 g Ni²⁺ in the form of nickel sulfate crystals. Following ingestion, this child reportedly developed depressed level of consciousness, nuchal rigidity, mydriasis, erythema, tachycardia, and ARDS.¹⁸

Dermal Absorption. Although transdermal absorption is typically of minor clinical significance, disruption of the normal integument may allow for more efficient systemic absorption. A metal refinery worker suffered a 40% body surface area partial-thickness chemical injury resulting from exposure to a chemical mixture that included nickel carbonate and nickel sulfate.⁴⁵ Prior to the incident, this individual's measured serum nickel concentration was 0.023 µmol/L (1.33 µg/L). On the sixth day following the injury the serum concentration was 0.490 µmol/L (28 µg/L). Two five-day courses of chelation with CaNa₂EDTA were begun for concomitant cobalt poisoning, and the patient's serum and urine nickel concentrations were within normal limits by 21 days postexposure. He subsequently recovered without manifesting signs of nickel toxicity.

Chronic Nickel Exposure

Chronic inhalational exposure to nickel is associated with injury characterized by specific histologic changes in the nasopharynx and upper respiratory tract, including atrophy of the olfactory epithelium, rhinitis, sinusitis, nasal polyps, and septal damage.¹¹ Pulmonary effects may include asthma⁴¹ and pulmonary fibrosis.^{8,24}

The International Agency for Research on Cancer classifies nickel compounds as a group 1 carcinogen (carcinogenic to humans).²⁹ The potential for and mechanisms of carcinogenesis of nickel depend heavily on the specific compounds studied. Although nickel-induced carcinogenesis is fairly well established for nickel compounds, the role of metallic nickel is less clear.⁵⁹

An increased incidence of oral cancer has been associated with geographic areas containing higher concentrations of nickel in farming soil.⁶⁴ Although earlier studies of occupationally exposed workers, primarily electroplaters and refinery workers, also showed increased rates of nasal and pulmonary tumors, more recent studies of nickel-exposed workers in more modern environments with lower permissible limits of nickel exposure do not show a significantly increased risk of cancer or any cause of mortality.^{60,61}

Although the exact mechanism of any possible carcinogenesis remains to be firmly elucidated, studies indicate several potential mechanisms. Animal studies show a threshold dose–response curve for inflammation with soluble compounds (nickel sulfate), and similar curves describe the risks of pulmonary cancers with the less-soluble nickel oxides and nickel subsulfide.⁵⁷ Reactive oxygen species (ROS) formation occurs secondary to depletion of both glutathione and protein-bound sulfhydryl groups by nickel. Accumulation of ROS leads to lipid peroxidation and DNA damage.^{62,77} Formation of ROS consequently causes depletion of ascorbic acid (vitamin C) as a free radical scavenger in conjunction with vitamin E. In vitro studies of human airway epithelial cells have shown that depletion of intracellular ascorbate due to nickel causes the induction of hypoxic stress. Such nickel-induced stress leads to the activation of hypoxia-inducible factor (HIF-1) and upregulation of hypoxia-inducible genes.⁵² Hypoxia is encountered in tumors as they outgrow their blood supply, thus selecting for cells with altered energy metabolism, changes in growth regulation, resistance to apoptosis, or both. Therefore, HIF-1 activation and the upregulation of hypoxia-inducible genes mimics intracellular permanent hypoxia and may be related to nickel-induced carcinogenesis.⁵³

Soluble compounds such as nickel sulfate cause a threshold-dependent inflammatory response and may act as promoters

of malignancies without a directly genotoxic effect. Insoluble nickel oxides and nickel sulfide bind to chromatin and nucleic acids¹⁵ and also affect expression of various mRNAs.⁷⁸ Thus, under some conditions, these compounds may be carcinogenic through genetic mechanisms, epigenetic mechanisms, or both. The more potent carcinogenic effects of insoluble nickel compounds may be a consequence of their increased cellular uptake.¹⁷

Based on concerns about long-term health effects, exposure limits for various nickel compounds have been proposed (Table 99–3).

TABLE 99–3. US Nickel Exposure Limits

ACGIH TLV-TWA	Amount (mg/m ³)	Parts per million
Elemental	1.5	
Soluble inorganic	0.1	
Insoluble inorganic	0.2	
Nickel subsulfide	0.1	
Nickel carbonyl	0.35	0.05
OSHA PEL-TWA		
Noncarbonyl nickel	1	
Nickel carbonyl	0.007	0.001
NIOSH REL-TWA		
Noncarbonyl nickel	0.015	
Nickel carbonyl	0.007	0.001

DIAGNOSTIC TESTING

Although nickel is widely distributed to many body fluids and tissues, urine and blood are the most commonly analyzed samples. Urine collection should ideally use acid-washed, metal-free containers. Some authors recommend correcting urinary nickel concentration per gram of urine creatinine, but it is not clear that this offers any particular advantage in clinical decision making. The average nickel concentration in serum is 0.3 µg/L, whereas the value in urine ranges from 1 to 3 µg/L,⁷¹ although substantially higher values are reported even in non-occupationally exposed populations.^{31,43} Concentrations among workers occupationally exposed to nickel may be substantially higher and serum concentrations of more than 8 µg/L have been proposed as being indicative of excessive exposure.⁴³

Nickel concentrations rise in urine, serum, and whole blood following oral administration. In these studies, serum concentrations were slightly higher than, but correlated well with whole blood. Urine and blood concentrations primarily reflect exposure occurring within the previous 48 hours,¹⁴ which is roughly the biologic half-life calculated from various field studies.⁷⁶

Urine nickel concentrations are used more commonly than blood for monitoring of workplace exposures and for prognostic and therapeutic decision making in nickel carbonyl exposures. An 8-hour collection is typically performed, and the average urinary excretion of nickel (in these nickel workers) is 2 µg/L, with an upper limit of normal of 5 µg/L. In cases of nickel carbonyl poisoning, concentrations of less than 100 µg/L in the initial 8-hour specimen may imply mild toxicity. Concentrations of 100 to 500 µg/L are classified as moderate, while concentrations higher than 500 µg/L are categorized as severe poisonings.⁶⁹ These classifications have been used in guiding treatment decisions. Urine nickel concentrations rise prior to the onset of symptoms in nickel carbonyl poisoning, making this determination a potentially useful screening tool for both workforce surveillance and the management of acute exposures.

Testing for allergic contact dermatitis due to nickel is performed using patch testing, as for other types of contact dermatitis. Strip patch testing is more sensitive than standard patch testing by 16%.²¹ Testing metal surfaces for free nickel is possible and sometimes necessary in the evaluation and treatment of nickel dermatitis. Patients with clinically important sensitivity or suspect medical histories can order an inexpensive, commercially packaged dimethylglyoxime spot test, allowing them to test metal objects for the presence of free nickel.¹³

TREATMENT

The first step in treatment of nickel-related medical problems is eliminating the exposure, which includes detection and removal of the source. In the case of acute exposures to nickel carbonyl, removal of clothing to prevent continued exposure and thorough skin decontamination may be necessary.

Symptomatic treatment for pulmonary symptoms associated with hypoxia includes the administration of supplemental oxygen. The use of bronchodilators and corticosteroids may also be necessary for the treatment of concomitant bronchospasm. Mechanical ventilation may be required in the most severe cases.

The administration of intravenous fluids to promote diuresis reduces the half-life of orally ingested nickel chloride by approximately 50%.⁶⁷ Due to high levels of protein binding, hemodialysis does not effectively remove nickel from the serum.⁷⁹

Chelation

Because there are no controlled human trials, specific recommendations for the use of chelation to treat nickel toxicity are not currently supported by the literature. As a result, extrapolation from animal studies and case reports form the basis for most treatment regimens. Most studies and reports involving treatment have focused on workers exposed to nickel carbonyl.

Several drugs are proposed as potential treatments for nickel carbonyl exposures. Studies in rats with various chelators show some protection by administration of British anti-Lewisite (BAL) and D-penicillamine,⁸¹ whereas calcium disodium EDTA had no protective effect.⁸⁰ Although BAL was being used in the past,⁶⁹ the most recent literature has focused on the use of diethyldithiocarbamate (DDC; Chaps. 79 and 102).

DDC is a chelator formerly used as the color reagent for urine nickel measurements. Rats exposed to several times the LD₅₀ (median lethal dose for 50% of volunteers) for nickel carbonyl had dramatically reduced mortality when pretreated with DDC; however, the antidotal efficacy decreased with increasing delay to treatment.⁶ A proposed treatment regimen for exposed workers focused on analysis both of the exposure and of the initial 8-hour urine collection.⁶⁹ Patients with suspected severe poisonings are typically given the first gram of DDC in divided oral doses. When less-severe exposures are suspected, treatment decisions are based on the urinary nickel concentration. At concentrations below 100 µg/L, no initial therapy is recommended as delayed symptoms are unlikely to develop. At concentrations between 100 and 500 µg/L, an oral regimen consisting of 1 g DDC initially, 0.8 g at 4 hours, 0.6 g at 8 hours, and 0.4 g at 16 hours is used. DDC is continued at a dose of 0.4 g every 8 hours until there is symptomatic improvement and urine nickel concentration is normal. Severe exposures with urinary nickel concentrations more than 500 µg/L can be treated using the same regimen, although these patients frequently require closer monitoring. Critically ill patients are given parenteral DDC starting at a dose of 12.5 mg/kg. However, given the animal data that the route and timing of administration are important to survival, some authors recommend that parenteral DDC be given as soon as possible following nickel carbonyl poisoning.¹² Although typically well-tolerated, DDC is capable of inducing a disulfiram reaction (Chap. 79) if taken with alcohol, and there are concerns about using DDC when there is concurrent cadmium exposure, at least by the oral route.³ As with many chelators, there is also debate about whether the redistribution of nickel by chelating agents may be detrimental by increasing brain and organ concentrations.⁴⁶

Disulfiram is metabolized into two molecules of DDC. Given that DDC is not pharmaceutically available in the United States, there is some interest in the use of disulfiram as an antidote for nickel carbonyl. Although case reports describe successful treatment of nickel carbonyl toxicity with disulfiram,³⁵ concern exists because animal studies show that disulfiram increased nickel concentration in brain tissue.⁵ Disulfiram cannot be considered a standard of care, due to lack of convincing evidence, but would be recommended due to its theoretical efficacy. One treatment regimen was 750 mg given orally every 8 hours for 24 hours, followed by 250 mg every 8 hours.³⁵

Considering most of the literature and almost all human case reports of nickel carbonyl refer to the use of DDC, it is considered the treatment of choice for nickel toxicity. Although commonly available as a reagent, pharmaceutical-grade DDC is not produced commercially. While based on less robust evidence, given the fact that disulfiram is essentially a prodrug for the unavailable DDC, treatment of nickel carbonyl poisonings with disulfiram is recommended.

Treatments evaluated for divalent nickel exposure are D-penicillamine and N-benzyl-D-glucamine dithiocarbamate, which, while not commonly available, more effectively lowers brain nickel concentrations than does DDC, perhaps because of its lower lipid solubility.⁷⁰

Contact dermatitis from nickel is treated using standard measures, including avoidance, topical steroids, and oral antihistamines. Some patients have benefited from dietary alteration to reduce nickel intake. Although sometimes advised, there does not appear to be a role for avoiding stainless steel cookware to reduce the nickel content of food.¹

SUMMARY

- Nickel is a ubiquitous metal today.
- Allergic dermatitis due to hypersensitivity is the most common type of nickel-related disease.
- Nickel toxicity is rare and most often related to nickel carbonyl.
- There is inadequate evidence to consider chelation for toxicity.

- Chronic, excessive exposures to nickel compounds may increase the risk of aerorespiratory cancers.

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100 SELENIUM

Diane P. Calello

Selenium (Se)	
Atomic number	= 34
Atomic weight	= 78.96 Da
Normal concentrations	
Whole blood	= 0.1–0.34 mg/L (1.27–4.32 μ mol/L)
Serum	= 0.04–0.6 mg/L (0.51–7.6 μ mol/L)
Urine	< 0.03 mg/L (0.38 μ mol/L)
Hair	= 0.4–1.4 μ g/g (0.01 μ mol/g)

HISTORY AND EPIDEMIOLOGY

Selenium was discovered by Jöns Berzelius in 1817 as a contaminant in sulfuric acid vats that caused illness in Swedish factory workers. He originally believed it to be the element tellurium (from the Latin tellus, meaning “earth”); however, on finding it to be an entirely new, yet similar, element, he named it from the Greek selene, meaning “moon.” Selenium has unusual light-sensitive electrical conductive properties, leading to its widespread use in industry. The long-term health benefits and risks of selenium are the subject of much recent investigation. It is both an essential component of the human diet and a poison.

In the 1970s, the role of selenium as an essential cofactor of the enzyme glutathione peroxidase was discovered. Keshan disease, an endemic cardiomyopathy, was described in 1979 in Chinese women and children who chronically consumed a selenium-poor diet.¹¹ Kashin-Beck disease, a disease causing shortened stature from chondrocyte necrosis, is described in young children in Russia, China, and Korea; although other etiologies are also likely responsible, partial improvement results from selenium supplementation.^{3,18} Selenium is currently being investigated for the prevention and treatment of a myriad of conditions, including autoimmune thyroiditis, cancer, Alzheimer disease, depression, and tropical leishmaniasis.³⁸ However, it is becoming more evident that “the moon” has two faces, as reports emerge that selenium supplementation may increase the risk of diabetes, amyotrophic lateral sclerosis, and some forms of malignancy.^{20,46}

The recommended daily allowance (RDA) in the United States of selenium for adults was established in 1980 at 55 μ g/d. This was determined based on the degree of supplementation required to achieve optimal glutathione peroxidase activity in selenium-deficient study populations, and the amounts required to cause overt toxicity. Deficiency occurs when daily intake falls below 20 μ g/d.¹¹

Chronic selenium toxicity, or selenosis, was first described in animals. It manifested as the acute syndrome of “blind staggers,” and the more chronic “alkali disease” affected livestock eating plants grown in highly seleniferous soil. Findings included blindness, walking in circles, anorexia, weight loss, ataxia, and dystrophic hooves. Humans in seleniferous areas of China and Venezuela develop similar integumentary symptoms (dermatitis, hair loss, and nail changes) at an intake of approximately 6000 μ g/d.^{5,41} In recent years, there have been several outbreaks of chronic selenium toxicity related to improperly formulated dietary supplements.^{7,14,47}

Selenium is widely distributed throughout the Earth’s crust, usually substituting for sulfur in sulfide ores such as marcasite (FeS₂), arsenopyrite (FeAsS), and chalcopyrite (CuFeS₂). It is found in the soil where it has leached from bedrock, in groundwater, and in volcanic gas. The highest soil concentrations of selenium in the United States are in the Midwest and the West, specifically areas of the Dakotas, Wyoming, Nebraska, Kansas, Utah, Colorado, Arizona, and New Mexico.³ Dietary selenium is easily obtained through meats, grains, and cereals. Brazil nuts, grown in the foothills of the highly seleniferous Andes Mountains, contain the highest concentration measured in food, but chronic selenium toxicity from Brazil nuts has not been reported.^{3,22}

In industry, selenium is generated primarily as a byproduct of electrolytic copper refining and in the combustion of rubber, paper, municipal waste, and fossil fuels. Selenium compounds are used in glass manufacture and coloring, photography, xerography, rubber vulcanization, and as insecticides and fungicides. Selenium sulfide is the active ingredient

in many antidandruff shampoos. Gun bluing solution, used in the care of firearms to restore the natural color to the gun barrel, is composed of selenious acid in combination with cupric sulfate in hydrochloric acid, nitric acid, copper nitrate, or methanol. [Tables 100–1 and 100–2](#) list features and regulatory standards of common selenium compounds.

TABLE 100–1. Selenium Compounds

<i>Name</i>	<i>Chemical Formula</i>	<i>Oxidation State</i>	<i>Uses</i>
Selenium (elemental)	Se	0	Photography, catalyst, dietary supplement, xerography
Selenium sulfide	SeS ₂	2 [−]	Antidandruff shampoo, fungicide
Hydrogen selenide	H ₂ Se	2 [−]	—
Dimethylselenide	CH ₃ SeCH ₃	2 [−]	Metabolite, garlic odor
Selenium dioxide	SeO ₂	4 ⁺	Catalyst, photography, glass decolorizer, vulcanization of rubber, xerography
Selenium oxychloride	SeOCl ₂	4 ⁺	Solvent, plasticizer
Selenious acid	H ₂ SeO ₃	4 ⁺	Gun bluing solution
Sodium selenite	Na ₂ SeO ₃	4 ⁺	Glass and porcelain manufacture
Selenium hexafluoride	SeF ₆	6 ⁺	Gaseous electrical insulator
Sodium selenate	Na ₂ SeO ₄	6 ⁺	Glass manufacture, insecticide

TABLE 100–2. Selenium Regulations and Advisories

Oral—Recommended Intake and Exposure Limits			
RDA (2000)		55 µg/d ^a	(0.8 µg/kg/d)
NAS-TUL		400 µg/d	(5.7 µg/kg/d)
ATSDR-chronic oral MRL ^b		5 µg/kg/d	
Water—Limits			
WHO	Drinking water	0.01 mg/L	
FDA	Bottled water	0.05 mg/L	
EPA	MCL, drinking	0.05 mg/L	
Air—Limits^c			
NIOSH			
	REL (TWA)	0.2 mg/m ³	
	IDLH	1.0 mg/m ³	
OSHA			
	PEL (TWA)	0.2 mg/m ³	

^aValues differ for pregnant and lactating women, children, and neonates. ^bNo acute or intermediate MRL has been established. Chronic ≥ 365 days. ^cAmbient background air concentrations are usually in the ng/m³ range. AHTSDR = American Toxic Surveillance and Disease Registry; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IDLH = immediately dangerous to life or health; MCL = maximum contaminant level; MRL = minimal risk level; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RDA = recommended daily allowance; REL = recommended exposure limit; TUL = tolerable upper limit; TWA = time-weighted average; WHO = World Health Organization.

CHEMICAL PRINCIPLES

Selenium is a nonmetal element of group VIA of the periodic table along with oxygen, sulfur, tellurium, and polonium. Selenium exists in elemental, organic, and inorganic forms, with four important oxidation states: selenide (Se^{2-}), elemental (Se^0), selenite (Se^{+4}), and selenate (Se^{+6}). Water solubility generally increases with oxidation state. Selenium behaves similarly to sulfur in its tendency to form compounds and in biologic systems³ and is both photovoltaic (able to convert light to electricity) and photoconductive (conducts electricity faster in bright light), which has led to its use in photography, xerography, and solar cells.

At least three solid allotropes of elemental selenium are described, including “grey selenium,” which predominates at room temperature, red crystalline selenium, and a red amorphous powder.³ In general, toxicity from elemental selenium is rare and only occurs from long-term exposure. Hydrogen selenide (H_2Se) is formed from the reaction of water or acids with metal selenides or from the reaction of hydrogen with soluble selenium compounds; at room temperature, it exists in gaseous form and results in industrial inhalation exposures. The organic alkyl selenides (dimethylselenide, trimethylselenide) are the least toxic and are byproducts of endogenous selenium detoxification (methylation). Inorganic salts and acids are responsible for all cases of acute toxicity. Selenious acid (H_2SeO_3), generated from the reaction of selenium dioxide with water, is the most toxic form of selenium; ingestion of selenious acid is often fatal.

PHARMACOLOGY AND PATHOPHYSIOLOGY

Selenium exists in one of three forms in the body. First, selenoproteins contain selenocysteine residues and play specific selenium-dependent roles primarily in oxidation–reduction reactions. Second, nonspecific plasma proteins bind and may aid in transport of selenium; they may directly bind selenium (albumin, globulins) or contain it as selenocysteine or selenomethionine in place of cysteine and methionine, respectively. Third, there are several inorganic forms of selenium in transit throughout the body, such as selenate, alkyl selenides, and elemental selenium (Se^0).

There are at least 25 selenoproteins—which include glutathione peroxidases, iodothyronine 5-deiodinases, and thioredoxin reductase—each of which contain a selenocysteine or selenomethionine residue at the active site.³⁸ The most studied of these is glutathione peroxidase I, which is responsible for detoxification of reactive oxygen species. Using reduced glutathione (GSH) as a substrate, glutathione peroxidase catalyses the reduction of hydrogen peroxide to water and oxidized glutathione (GSSG, or glutathione disulfide); the reaction occurs by concomitant oxidation of the selenocysteine unit on the enzyme.^{4,37} Other selenocysteine-containing proteins, such as thioredoxin reductase, have antioxidant properties. The selenocysteine-containing thyroid hormone deiodinases are responsible for the conversion of thyroxine (T_4) to the active triiodothyronine (T_3) form (Chap. 56).

In selenium deficiency, glutathione peroxidase activity is decreased, and GSH and glutathione S-transferases are increased.³⁷ Consequently, selenium-deficient rats are more resistant to substances detoxified by glutathione S-transferase, such as acetaminophen and aflatoxin B,⁶ and less resistant to other prooxidants, such as nitrofurantoin, diquat, and paraquat.⁶ In animal studies of metal toxicity, selenium also appears to modify the effects of silver, cadmium, arsenic, copper, zinc, mercury, and fluoride; conversely, vanadium, tellurium, and arsenic modify the effects of selenium deficiency or excess.^{16,19,33,41} Although it is proposed that this is accomplished through the formation of insoluble selenium–metal complexes, these relationships are not entirely understood.¹³

Less is known about the biochemical mechanism of selenium toxicity, and what is known is generally from in vitro data. Paradoxically, excess selenium causes oxidative stress, presumably as a result of prooxidant selenide (R-Se^-) anions. In addition, the replacement of selenium for sulfur in enzymes of cellular respiration may cause mitochondrial disruption, and the substitution of selenomethionine in place of methionine may interfere with protein synthesis. Integumentary effects are also most likely a result of selenium interpolation into disulfide bridges of structural proteins such as keratin.⁴⁵

PHARMACOKINETICS AND TOXICOKINETICS

Gastrointestinal (GI) absorption varies with the type of selenium, and human data are limited. Elemental selenium is the least bioavailable ($\leq 50\%$), followed by inorganic selenite and selenate salts (75%)²⁸; selenious acid is well absorbed from the lungs and GI tract ($\sim 85\%$ in animal studies⁹). Organic selenium compounds are the best absorbed ($\sim 90\%$) as determined by isotope tracers in human studies.^{3,24} A breastfed infant developed selenosis exclusively from maternal overexposure, suggesting transmission through breastmilk.⁴⁸

Inhalational absorption was reported in a group of workers exposed to selenium dioxide and hydrogen selenide gas,^{3,15} but quantitative inhalation studies in humans are not available. Dermal absorption is limited. Selenium disulfide shampoos are not systemically absorbed as measured by urinary selenium concentrations⁹ except in cases of repeated use on

excoriated skin.³⁶

The toxic dose of selenium varies widely between selenium compounds, as demonstrated by LD₅₀ (median lethal dose for test subjects: 50%) animal studies,⁴¹ making milligram per kilogram exposure estimates difficult to interpret. Elemental selenium has no reported adverse effects in acute overdose, although long-term overexposure is harmful. The selenium salts, particularly selenite, are more acutely toxic, as is selenium oxide (SeO₂) through its conversion to selenious acid in the presence of water. Selenious acid may be lethal in children following ingestion of as little as a tablespoon of 4% solution in children.

Metabolic conversion of all forms of selenium to the selenide anion occurs through various means (Fig. 100–1), after which the selenide ion undergoes one of three fates: (1) incorporation into selenoproteins such as glutathione peroxidase and triiodothyronine, (2) binding by nonspecific plasma proteins such as albumin or globulins, or (3) hepatic methylation into nontoxic, excretable metabolites. Trimethylselenide is the primary metabolite and is excreted by the kidneys, the major elimination pathway for selenium. Fecal elimination also occurs. Dimethylselenide production is usually minor but increases with exposure; this compound is volatilized through exhalation and sweat and is responsible for the garlic odor of patients exposed to excess selenium. The remaining selenium in the body is greater than 95% protein bound within 24 hours.^{1,41} Toxicokinetic data are limited and vary by compound.

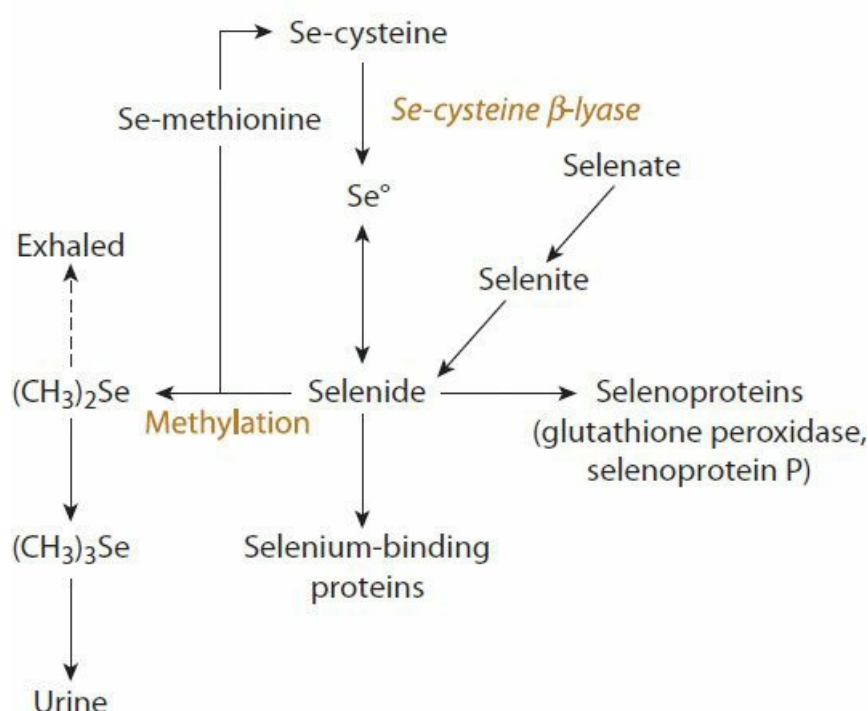


FIGURE 100–1. Metabolism of selenium. The selenide anion is central in selenium metabolism. Organic selenocysteine is converted via the β-lyase enzyme to elemental selenium and then to selenide. Selenomethionine may either undergo transsulfuration to selenocysteine or methylation to excretable metabolites. The selenate and selenite salts are reduced to selenide. Selenide then undergoes one of three processes: methylation, incorporation into selenoproteins, or binding by nonspecific plasma proteins.¹

CLINICAL MANIFESTATIONS

Acute

Dermal and Ophthalmic Exposure. Dermal exposure to selenious acid or to selenium dioxide (which is converted to selenious acid) and to selenium oxychloride (a vesicant hydrolyzed to hydrochloric acid) causes painful caustic burns.¹² Excruciating pain may result from accumulation under fingernails. Corneal injury with severe pain, lacrimation, and conjunctival edema is reported after exposure to selenium dioxide sprayed unintentionally into the face.²⁹ In chronic exposures, “rose eye,” a red discoloration of eyelids with palpebral conjunctivitis, is also described.

Inhalational Exposure. When inhaled, all selenium compounds have the potential to be respiratory irritants, although inhaled elemental selenium dusts are less injurious than those compounds that can be converted to selenious acid. Toxicity from hydrogen selenide inhalation is reported throughout the industrial literature.⁸ Hydrogen selenide is oxidized to elemental selenium, so acute toxic exposures are limited to confined spaces where the hazardous gas may accumulate; however, similar to hydrogen sulfide (H₂S), its ability to cause olfactory fatigue, rendering the exposed persons anosmic to the toxic fumes, may pose significant hazard (Chap. 26⁸ Acute exposure to high concentrations of hydrogen selenide gas

produces respiratory and mucosal irritation which may persist for years as residual restrictive and obstructive disease.³⁹

By contrast, selenium dioxide and selenium oxide fumes cause more injury through conversion to selenious acid in the presence of water in the respiratory tract. Twenty-eight workers in a selenium rectifier plant who were inadvertently exposed to smoke and high concentrations of selenium oxide in an enclosed area developed upper respiratory irritation, bronchospasm, and transient hemodynamic instability.⁴⁹ Some developed chemical pneumonitis, fever, chills, headache, vomiting, and diarrhea. Five patients required hospitalization for respiratory support, with fever, leukocytosis, and bilateral infiltrates. All patients recovered without sequelae.

Selenium hexafluoride is a caustic gas used in industrial settings as an electrical insulator. Its caustic properties are derived from its conversion to elemental selenium and hydrofluoric acid in the presence of water. Severe pain and burning of the eyes, skin, and respiratory tract similar to that seen with hydrofluoric acid exposure can occur after inhalation of selenium hexafluoride (Chap. 107).

Oral Exposure. Acute fulminant selenium toxicity occurs after ingestion of inorganic selenium compounds, the most toxic of which is selenious acid in the form of gun bluing solution. Similar toxicity may result from selenium oxide and dioxide, which are converted to selenious acid as well as sodium selenite and selenate. The underlying mechanism for this often fatal syndrome is not well understood but may stem from a multifocal disruption of cellular oxidative processes and antioxidant defense mechanisms. Elemental selenium and organic selenium compounds do not cause acute toxicity.

Some authors have proposed a “triphasic” course of acute inorganic selenium toxicity, with GI, myopathic, and circulatory symptoms as the toxic effects progress.⁴⁴ In reality, acute inorganic selenium poisoning is often rapid and fulminant, with onset of symptoms within minutes and, in some cases, death within one hour of ingestion. GI symptoms are the most commonly described and the first to occur and include abdominal pain, diarrhea, nausea, and vomiting. This may be partly caused by caustic esophageal and gastric burns but does not occur in all cases. Patients may have a garlic odor. The myopathic phase is characterized by weakness, hyporeflexia, myoclonus, fasciculations, and elevated creatine phosphokinase concentrations with normal myocardial band (MB) fraction. Acute kidney injury is also reported and presumably results from myoglobinuria and hemolysis. More severely poisoned patients may exhibit lethargy, delirium, and coma.

Circulatory failure is the hallmark of serious inorganic selenium toxicity. Patients present with dyspnea, chest pain, tachycardia, and hypotension. Initial electrocardiography (ECG) may demonstrate ST elevation, a prolonged QT interval, and T-wave inversions. Refractory hypotension occurs as a combined product of decreased contractility from toxic cardiomyopathy and decreased peripheral vascular resistance. Pulmonary edema, ventricular dysrhythmias, myocardial and mesenteric infarction, and metabolic acidosis all contribute to poor outcome in these patients.^{30,34,49} Death results from circulatory collapse in the setting of pump failure, hypotension, and ventricular dysrhythmias, often within 4 hours of ingestion.^{17,21,35,43} Other less frequent abnormalities include hypokalemia, hyperkalemia, coagulopathy, leukocytosis, hemolysis, thrombocytopenia, and metabolic acidosis with elevated lactate.^{40,44}

Chronic

Chronic elemental selenium toxicity, or selenosis, has received recent attention because of reports of improperly formulated selenium-containing dietary supplements. In 2008, at least 200 people developed painful skin lesions, diarrhea, alopecia, fever, fatigue, memory loss, and nail deformities after use of the errant supplement.^{2,27,47} The manufacturer voluntarily recalled the product, and a US Food and Drug Administration investigation revealed that the liquid supplement contained approximately 200 times the concentration stated on the packaging.¹⁰ The patients consumed approximately 40,000 µg/d while taking the supplement, or 1000 times the US RDA.² A similar outbreak occurred from a super-potent supplement in 1983, affecting at least 13 patients, all of whom recovered after discontinuation of the supplement.^{7,14}

Selenosis is similar to arsenic toxicity, with the most consistent manifestations being nail and hair abnormalities. As with arsenic toxicity, nail or hair findings alone are unlikely to be the sole evidence of selenosis, but their absence makes the diagnosis unlikely. The hair becomes very brittle, breaking off easily at the scalp, with regrowth of discolored hair and the development of an exfoliative pruritic scalp eruption with acneiform papules.²⁶ The nails also break easily, with white or red ridges that can be either transverse or longitudinal; the thumb is usually involved first, and paronychia and nail loss may develop.^{26,32} The skin becomes erythematous, swollen, and blistered, as well as slow to heal and has a persistent red discoloration. Increased dental caries may occur.²⁶ Neurologic manifestations include hyperreflexia, peripheral paresthesia, anesthesia, and hemiplegia. Although cardiotoxicity is described with both selenium deficiency and acute poisoning, no such cases are reported with human selenosis. Aside from one case described in endemically exposed patients in China⁵⁰ in which there were insufficient postmortem data, there have been no reported deaths from intermediate or chronic exposure.

Selenosis is implicated in a number of long-term environmental exposures. Many descriptions come from inhabitants of the Hubei province of China from 1961 to 1964, the majority of whom developed clinical signs after an estimated average consumption of 5000 µg/d of selenium (but as little as 910 µg/d) derived from local crops and vegetation.⁵⁰ Inhabitants of a

seleniferous area of Venezuela, consuming approximately 300 to 400 µg/d of selenium, also develop symptoms of selenium excess; however, the low socioeconomic and poor dietary status of the subjects may also contribute to their symptoms. By contrast, US residents in a seleniferous area with a high selenium intake (724 µg/d) over 2 years who were compared with a control population and monitored for symptoms and laboratory abnormalities remained asymptomatic, with only a clinically insignificant elevation of hepatic aminotransferases in the high-selenium group.^{22,25} Average selenium concentrations were serum, 0.215 mg/L; whole blood, 0.322 mg/L; and urine, 0.17 mg/L. A similar cohort with comparable blood concentrations was also reported in the Brazilian Amazon.²²

Selenosis is also reported in the industrial setting. Copper refinery workers develop garlic odor and GI and respiratory symptoms coincident with exposure to selenium dust and fumes.¹⁵ Long before workplace biologic monitoring took place, intense garlic odor of the breath and secretions was recognized as a reason to remove a worker from selenium exposure until the odor subsided. Neuropsychiatric findings such as fatigue, irritability, and depression are reported throughout the industrial literature and are difficult to quantify. Early reports describe the selenium factory worker who “could not stand his children about him” at the end of the day.¹²

Although carcinogenicity is suggested by a number of animal studies, in humans, the data available suggest, if anything, an inverse correlation between selenium intake and cancer risk. The International Agency for Research on Cancer does not list selenium as a known or suspected carcinogen.³ Animal studies also suggest that selenium has embryotoxic and teratogenic properties.¹³ A recent large randomized controlled trial of selenium supplementation reported an increased risk of diabetes mellitus with the ingestion of 200 µg/d of elemental selenium-fed baker’s yeast compared with placebo.^{20,46}

DIAGNOSTIC TESTING

Over time, selenium is incorporated into blood and erythrocyte proteins, making serum the best measure of acute toxicity and whole blood preferable for the assessment of patients with chronic exposure. Patients with acute poisoning generally have an initial serum concentration greater than 2 mg/L, which falls below 1 mg/L within 24 hours, reflecting redistribution.³² Patients with long-term elemental exposures are reported to have serum concentrations of 0.5 to 1.0 mg/L. However, there is no predictable relationship between selenium concentrations and exposure, toxicity, or time course. Population-based studies suggest an average serum concentration of 0.126 mg/L in the United States.³¹

Urine concentrations reflect very recent exposure because urinary excretion of selenium is maximal within the first 4 hours. In addition, urine concentrations are an imperfect measure because they can be affected by the most recent meal and hydration status. However, in general, a normal urinary concentration is less than 0.03 mg/L. Freezing of urine specimens after collection is recommended to retard the enzymatic formation of difficult-to-detect volatile metabolites.³²

Hair concentrations of selenium were measured in the Hubei Chinese populations of interest and during the contaminated supplement outbreak in 2008 and may be a useful qualitative measure of chronic exposure.^{26,42,50} However, the usefulness of hair selenium is limited in countries such as the United States where the use of selenium sulfide shampoos is widespread.

Other ancillary tests to assess selenium toxicity include ECG, thyroid function, platelet counts, hepatic aminotransferases, creatinine, and serum creatine phosphokinase concentrations. These are abnormal in some patients (eg, patients with selenious acid poisoning) and are not indicated in patients not expected to develop systemic toxicity.

MANAGEMENT

Pain

Aside from standard pain management strategies, a number of topical remedies for selenium burns have been suggested historically with little evidence supporting their use. For example, a 10% sodium thiosulfate solution or ointment to reduce selenium dioxide to elemental selenium is mentioned as a potential therapy for painful skin, nail bed, or ocular burns.¹² In one series, workers exposed to selenium dioxide fumes reported similar relief from inhalation of vapor from ammonium hydroxide-soaked sponges; the mechanism of this is unclear, and further study is required before this practice can be recommended.⁴⁹

Workers exposed to selenium hexafluoride gas may be treated with calcium gluconate gel to the affected areas. This is the same treatment as in hydrofluoric acid exposures, which is discussed in [Chap. 107](#).

Decontamination

As with any toxic exposure, prompt removal from the source is required if possible. Patients with dermal exposure should have their skin irrigated immediately. There are limited data to support the use of aggressive GI decontamination after the ingestion of most elemental selenium-containing xenobiotics because little expected acute toxicity is present. However, in

xenobiotics with the potential for producing systemic toxicity, such as the selenite salts, decontamination with gastric lavage or activated charcoal may be warranted. Although no activated charcoal adsorption data are available to guide this therapy, it should be considered in light of potential benefit until further information is available.

Special mention should be made of the ingestion of selenious acid. Given its toxicity, the judicious use of small nasogastric lavage may be indicated based on the time since ingestion, the amount and concentration ingested, the presence or absence of spontaneous emesis, the likelihood of caustic esophageal injury, and the clinical condition of the patient.

Chelation and Antidotal Therapy

There are no proven antidotes for selenium toxicity. Animal studies and scant human data suggest that chelation with dimercaprol (BAL),²⁴ edetate calcium disodium (CaNa₂EDTA), or succimer is not advised due to the formation of nephrotoxic complexes with selenium, do not speed clinical recovery and may, in fact, worsen toxicity.^{23,24} Arsenical compounds appear to ameliorate selenium toxicity through enhanced biliary excretion,^{8,13,15,23} but there are no studies to guide this inherently toxic therapy. Vitamin C is hypothesized to limit oxidative damage but has not been studied. Bromobenzene may accelerate urinary excretion of selenium,⁸ but its inherent toxicity limits its use, regardless of efficacy.

Extracorporeal removal techniques such as hemodialysis or hemofiltration decrease selenium concentrations in patients undergoing the procedure regularly for chronic kidney disease, so theoretically, this could be of use in lowering toxic serum selenium concentrations. However, because of extensive protein binding, this benefit may be only minor and only relevant to patients undergoing frequent dialysis. Although there are reports of using hemodialysis in patients with acute selenium poisoning, further study must occur before this can be recommended.^{19,21}

Supportive Care

This is the mainstay of therapy in selenium poisoning. In particular, patients with selenious acid toxicity require intensive monitoring and multisystem support to survive.

SUMMARY

- Selenium is an essential trace element and is required in the diet of both animals and humans.
- Ingestion of selenious acid is often fatal.
- Other selenium compounds cause variable toxicity, usually following setting of occupational exposure. Topical and inhalational exposure causes burns and pulmonary irritation, respectively. Acute systemic exposure results in gastrointestinal, myopathic, and circulatory signs and symptoms.
- Long-term exposure to elemental selenium may cause selenosis, of which alopecia is the most consistent finding.
- Although it is possible to obtain blood, urine, and hair selenium concentrations to confirm exposure, no clear relationship exists between concentration and clinical outcome.
- Supportive therapy remains the standard of care.

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101 SILVER

Melisa W. Lai Becker and Michele M. Burns

Silver (Ag)		
Atomic number	=	47
Atomic weight	=	107.9 Da
Normal concentrations		
Serum	<	1 µg/L
Urine (24 hour)	<	2 µg/L

HISTORY

Although the symbol of silver, Ag, is derived from the Latin and Greek words for silver—argentum and argyros—the word used in English is derived from Slavic and Germanic Silubr and Sirebro, as well as Old English Seolfor. The alchemy symbol of silver (a crescent moon) and dalton symbol (a coinlike circumscribed letter S) convey the impression of silver as a valued and precious element.

In Asia Minor and on islands in the Aegean Sea, dumps of slag (scum formed by molten metal surface oxidation) demonstrate that silver was likely separated from lead as early as 4000 b.c. The use of silver as a precious metal with trade value appears to have begun around 600 b.c, when weighed pieces of silver were exchanged for goods. Silver coinage debuted circa 550 b.c in the Mediterranean, and was adopted by various empires, dynasties, and nation-states thereafter. Today, only Mexico uses silver in circulating coinage.

The Phoenicians and early Greeks knew to store water, wine, and vinegar in silver-lined vessels during long sea voyages, just as later American pioneers added silver coins to water barrels and jugs of milk to keep them fresh.⁴¹ The phrase “born with a silver spoon in his mouth” referred originally to health and not wealth, as silver pacifiers and baby spoons were used to help ward off childhood illnesses.

A traded commodity on the world’s markets, silver had been used as an abstract financial standard for various economies throughout modern banking history until the late 19th century. While the United States incorporates silver purely in commemorative and proof coins, the state of Utah passed the “Legal Tender Act of 2011” to allow its residents to use silver and gold coins produced by the US Mint as cash with value based on weight rather than minted face value.^{50,60}

Beyond the economic role of silver, the electrical and thermal conductive properties of the element make it an invaluable material for scientific instrument manufacture and engineering. Because silver contacts neither corrode nor overheat, silver is commonly used in electronic devices and appliances. Silver was a key component of early telecommunications—it was the choice for Morse’s first telegraph contacts in 1844—and made the jet age possible, as only silver-plated bearings have the adequate dry lubricity necessary for safe engine shutdown without volatile oil lubricants. Today, washing machines, cars, smartphones, and many types of consumer electronics, from televisions to toaster ovens, all use small amounts of silver in their functional parts.

Silver is also used to “make rain”: silver iodide crystals, whose lattice structure is similar to ice, are released into “supercooled” (between 7 and 25°F) clouds, causing water droplets in clouds to attach and form ice crystals that become large and heavy enough to drop from the cloud and melt into raindrops en route to Earth.

The medicinal value of silver has been greatly exaggerated, with the element being touted by some as a “cure-all.” In the late 19th and early 20th century, claims were made that oral administration of colloidal silver proteins (CSPs; gelatinous suspensions of finely divided elemental silver) would successfully treat diverse diseases, most without evidence.^{16,57} However, in 1960, the US Dispensary declared that “there is no justification for this internal use, either theoretically or practically,” and silver was banned in all nonprescription drugs.¹⁴ In 1999, the US Food and Drug Administration issued a Final Rule declaring that all nonprescription drug products containing colloidal silver or silver salts were “not recognized as safe and effective and are misbranded.”¹⁵ However, CSPs and other silver-containing “natural” products were reintroduced for use as health and dietary supplements and, as such, are not subject to FDA regulation under the Dietary Supplement Health and Education Act of 1994 so long as they make no claim to treat or

prevent any disease.¹⁶ After the anthrax terrorist acts of 2001, the mayor of Tampa, Florida, called for CSPs to be mixed into the town’s water supply as a protective “elixir” without scientific justification.² As silver-containing products continue to be marketed and sold online as “natural” health supplements with few warnings as to the possible development of argyria—a permanent bluish-gray discoloration of the skin from chronic silver overexposure—there has been a small resurgence of case reports of argyria since the turn of the 21st century.¹⁹

EPIDEMIOLOGY

Humans are exposed to minute amounts of silver upon occupation: Silver is released into the environment during silver nitrate manufacture for use in photography (diminishing), mirrors, plating, inks and dyes, and porcelain; as well as for germicides, antiseptics, caustics, and analytic reagents. Silver-salt catalysts, used for oxidation-reduction and polymerization reactions, are another source of silver exposure, as are silver powder pigments and paints.³¹ Workplace exposure is often via transdermal, transmucosal, or inhalational routes as silver particles are liberated during various mining, refining, and manufacturing processes.

Additionally, industrial exposure of workers involved in silver mining and manufacturing increases the workplace risk of generalized argyria, although development of signs of argyria from uninterrupted occupational exposure reportedly takes up to 24 years.¹¹ Employees are susceptible to localized argyria following repeated topical exposure and corneal argyrosis (permanent ashen-grey discoloration of the conjunctiva) from working with smaller amounts of silver in specific applications, as in the coating of metallic films on glass and china, manufacture of electroplating solutions and photographic processing, preparation of artificial pearls, and simple cutting and polishing of silver.

Both the National Institute for Occupational Safety and Health and the Occupational and Safety Health Administration of the United States have established the safe occupational exposure limit to silver metal and soluble compounds as 10 µg/m³ air per 8-hour work shift. The estimated oral intake of silver from average environmental exposure for humans not working in silver-related industries ranges from 10 to 88 µg/d.¹³

Pharmacology

Following absorption, silver is transported by globulins in blood and stored mainly in skin and liver, with average daily intake excreted in the bile and eliminated in the feces (up to 30–80 µg/d) and urine (up to 10 µg/d).¹⁴ Silver elimination through the feces occurs in two phases: phase one has a relatively short $t_{1/2}$ ranging from 1 to 2.4 days, varying with route of administration (apparent $t_{1/2}$ is: oral, 1 day; inhalational, 1.7 days; intravenous, 2.4 days),^{14,17,39} and phase two elimination has a $t_{1/2}$ of 48 to 52 days, thought to represent liver deposition and clearance.^{34,40}

Although study of a single human showed 18% of an orally administered silver acetate salt was retained after 30 weeks, animal studies show little silver absorption along the GI tract, with 90% of ingested silver excreted within 2 days of ingestion.¹³

Humans retain up to 10% of their daily silver exposure of 10 to 88 µg/d.⁵⁹ Minute amounts of silver can accumulate in humans throughout life, with a possible estimated lifetime accumulation of 230 to 480 mg by 50 years of age.¹³

Silver has a 1⁺(Ag⁺) valence when bonding with other elements and compounds to form complex ions and salts. Because of the microcidal effects of silver cations at low concentrations,⁴⁹ silver is used for potential medicinal and bactericidal effects.

The antibacterial activity of silver is related to both direct binding to biotic molecules and to disruption of hydrogen ions and thus, pH balance. Silver ions bind to electron donor groups of proteins (sulfhydryl, amine, carboxyl, phosphate, and imidazole) to inhibit enzymatic activities and provoke protein denaturation and precipitation.¹⁶ Silver also intercalates with DNA without destroying the double helix, thereby inhibiting fungal DNase.¹⁴ Silver ions induce proton leakage through a bacterial (*Vibrio cholerae*) membrane, leading to loss of the proton motive force in oxidative phosphorylation, with subsequent energy loss and cell death.¹⁰ Bacterial resistance to silver was not reported until the mid 1970s, followed shortly thereafter by the identification of the genes for silver resistance in bacteria.⁴⁹

Although banned from routine administration via intravenous, intramuscular, and oral routes in the United States, silver salts are approved for use in topical medications, either as a caustic styptic (hemostatic) or as a key component of burn care. Approved medicinal uses for silver in the United States apply only to silver salts and compounds and specifically preclude use of elemental silver (Table 101–1).

TABLE 101–1. Medicinal Silver Containing Products

<i>Product Name/Device</i>	<i>Route of Administration/ Exposure</i>	<i>Applications</i>
Silver nitrate (1% AgNO ₃)	Ophthalmic	Prevention of gonorrheal ophthalmia neonatorum
Silver nitrate (10% AgNO ₃)	Cutaneous	Chemical cautery of mucosa and exuberant granulations (eg, in podiatry for corns, calluses, impetigo vulgaris, plantar warts, and papillomatous growths)
Silver sulfadiazine (0.2% or 1% micronized silver sulfadiazine)	Cutaneous	Antimicrobial adjunct for prevention and treatment of wound infection for patients with second- and third-degree burns
Silver-impregnated catheters and tubes	Nanoparticle coating	Antimicrobial adjunct for use in catheters (foley catheters, central venous catheters, extra ventricular drains, and endotracheal tubes)
Silver acetate	Mucocutaneous	Used in gum, sprays and lozenges as smoking cessation adjunct. Silver combined with smoke creates an unpleasant metallic taste in the user's mouth. ²⁸

Today silver is used in water filtration cartridges and supermarket products for washing vegetables; it was used to sterilize recycled drinking water on the Russian MIR space station and NASA space shuttle.⁴⁹ Silver sulfadiazine added to burn dressings kills bacteria and increases the rate of reepithelialization across partial-thickness wounds.⁹ However, concerns associated with long-term toxicity may limit use.^{8,55}

Central venous catheters impregnated with silver sulfadiazine and silver-impregnated Foley catheters have been used to lower rates of infection.³⁵ For example, extraventricular drains impregnated with silver have had one-half of the CSF infection risk as plain catheters.²⁷ In addition, silver-lined endotracheal tubes have been shown to reduce the risk of ventilator-assisted pneumonia by up to 51%, including specifically drug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.⁴⁸

PATHOPHYSIOLOGY

In great enough quantities, silver manifests cardiovascular, hepatic, and hematopoietic toxicity. Acutely, administration of 50 mg or more of particulate metallic (colloidal) silver intravenously in humans is fatal, leading to pulmonary edema, hemorrhage, and necrosis of bone marrow, liver, and kidneys.¹⁴ The mechanism for this acute toxicity was studied only in the water flea (*Daphnia magna*) where silver blocks Na⁺, K⁺-adenosine triphosphate activity.⁴ Toxicity in animals is listed by system (Table 101–2).

TABLE 101–2. Silver Toxicity: Systemic Manifestations

Cardiovascular	Rats given 0.1% silver nitrate in drinking water for 218 days developed ventricular hypertrophy that was not attributable to silver deposition in the heart despite advanced pigmentation in other body organs. ³⁸
Hepatic	Vitamin E and selenium-deficient rats developed hepatic necrosis with ultrastructural changes after administration of silver salts. ^{7,10,54} Silver can induce selenium deficiency that consequently inhibits synthesis of the selenoenzyme glutathione peroxidase.
Hematologic	Topical application of silver correlated with bone marrow depression with subsequent leukopenia or aplastic anemia. ⁷
Renal	Tubular lesions are demonstrated in animals, and acute tubular necrosis is rarely identified in humans. ³²
Neurologic	Silver deposits in peripheral nerves, basal membranes, macrophages, and elastic fibers were found in one reported case of a 55 year-old woman with progressive vertigo, cutaneous hypoesthesia, and weakness after self-administration of silver salts to treat oral mycosis for 9 years. ⁵⁶ Seizures were reported in a schizophrenic patient who ingested > 20 mg silver daily for 40 years. Serum silver concentrations were elevated (12 µg/L). Seizures resolved concurrently with discontinuation of silver ingestion and a subsequent decrease in silver serum concentration (12 µg/L). Seizures resolved concurrently with discontinuation of silver ingestion and a subsequent decrease in silver serum concentration. ³⁷
Dermatologic	Generalized argyria, localized argyria, and argyrosis (silver deposition in the eyes) developed after chronic administration of silver.

Silver is not classified as to human carcinogenicity and has not been found to be mutagenic; and no data link therapeutic use of silver to human cancer.¹³ Although studies in animals show that silver implanted subcutaneously can lead to local sarcoma formation, the EPA has deemed this reaction questionable with regard to human carcinogenicity, as implantation of other insoluble solids, such as plastic and smooth ivory, in animals produce similar results.¹³ Colloidal silver injected into rats induces growths at injection sites, but intramuscular injections of silver powder have not induced cancer.¹⁸ Local inflammatory responses notwithstanding, silver is considered an inert substance and not a human carcinogen.

Argyria

The most significant effect of silver overexposure in humans is argyria, a permanent bluish-gray discoloration of skin resulting from silver throughout the integument (Figs. 101–1 and 101–2).



FIGURE 101-1. Argyria, the slate or silver discoloration of the skin that results from silver overexposure is demonstrated in this image of herself. (Used with permission of Rosemary Jacobs.)



FIGURE 101-2. Long-term exposure to AgNO_3 in the workplace led to this patient's characteristic pigment changes of argyria. A normally pigmented arm is across the patient's chest. (Used with permission of New York University Department of Dermatology.)

Generalized argyria develops in stages, beginning with an initial gray-brown staining of gingiva, progressing to hyperpigmentation and bluish-gray discoloration in sun-exposed areas. Later, nail beds, sclerae, and mucous membranes become hyperpigmented; on autopsy, viscera are noted to be blue.

Cases of argyria have been reported in the medical literature since at least the early 19th century. One of the most famous cases of argyria is that of the Barnum and Bailey Circus' "Blue Man" who died at New York's Bellevue hospital in 1923 and was described on autopsy as follows²¹: "The color of the skin was of an unusually deep blue and from a distance appeared almost black. This deep color was almost uniform throughout the entire body, although it was more intense over the exposed skin areas." An American woman who developed argyria as a teenager during the 1950s from use of a nasal CSP for allergies has described her story on the Internet to warn others of the effects of prolonged contact with, or ingestion of, silver salts.²⁴ Her appearance was documented as an Image in Clinical Medicine in the New England Journal of Medicine.⁶ In 2002, libertarian party Montana legislator Stan Jones became known as the "blue" lawmaker who promoted the use of colloidal silver health supplements and developed argyria after manufacturing his own colloidal silver at home out of fears that the Y2K (year 2000) problem might cause a shortage of antibiotics.^{3,43}

Generalized argyria can result from either simple mechanical impregnation of skin by silver particles or inhalational and oral absorption of particulate silver. Local routes of silver absorption may be through the conjunctiva or oral mucous membranes after long-term topical treatment with silver salts.

Argyria occurs at exposure doses much lower than those associated with acutely toxic effects of silver; the degree of discoloration is directly proportional to the amount of silver absorbed or ingested.²⁰ The threshold dose for silver accumulation and retention resulting in generalized argyria varies considerably. Discoloration is reported from as little as a cumulative 1 g of metallic silver administered intravenously (from 4 g of silver arsphenamine used to treat syphilis over a 2-year period in the early 1900s), whereas others tolerated infusions containing up to 5 g of elemental silver over 9 months before clinical change was noted.²⁰

In 2002, a 42 year-old European man developed argyria after just 4 years of weekly application of a topical nasal vasoconstrictor (Coldargan, Siegfried, Sweden) available in Austria. The patient used this product to treat his rhinitis medicamentosa (rebound nasal congestion brought on by extended use of topical decongestants); each drop of medication contained 0.85 mg silver protein, which was considerably more than expected in chronic occupational exposure.⁵² More directly, colloidal silver protein ingestion for "health supplementation" leads to body burdens of silver that can produce argyria. In 1933, argyria was reported in a 33 year-old woman who had ingested 48 mg/d of elemental silver (from silver nitrate capsules) during alternating 2-week periods over 1 year to treat chronic gastrointestinal symptoms.⁵ Her serum silver concentrations remained at 500 µg/L for 3 months after discontinuation of the capsules, indicating significant silver deposition in tissues.

Mechanical impregnation of silver produces localized argyria following repeated contact with metallic silver or silver salts.²⁶ Localized argyria is reported from both implanted acupuncture needles and short-contact acupuncture, when particle deposition may occur from silver needles used repeatedly during brief therapeutic sessions.²⁹ Silver sulfadiazine use produces localized argyria in and around wound scars.^{17,55} Localized argyria of the tongue and gingiva is described in patients with silver dental amalgams.^{25,44} These patients may also have elevated tissue concentrations of silver, but there are no known cases of significant absorption resulting in generalized argyria.¹² Even the longstanding wearing of silver earrings has resulted in local contact argyria.^{33,51,53} Corneal argyrosis was frequently reported from prolonged use of colloidal silver disinfectant eyedrops; however, because these drops are no longer used, the condition has become an occupational disease caused by both inadequate eye protection and workers rubbing eyes with hands contaminated by silver particles.^{45,47,61}

Histopathology of Argyria

There are no pathologic changes or inflammatory reactions visible at a histologic level from silver deposition or impregnation. Rather, the skin discoloration of argyria comes from the silver itself and from the induction of increased melanin production. Silver granules are initially found within fibroblasts and macrophages, then extracellularly along the basement membrane of blood vessels, sweat glands, dermoepidermal junction, and beside erector pili muscles (Chap. 18). Patients with argyria commonly manifest increased pigmentation over sun-exposed skin. While the mechanism for this process is not yet fully understood, it has been proposed that silver-complexed proteins are reduced to their elemental form via photoactivation from sunlight, similar to photographic image development. Silver plus light then further stimulate melanogenesis, increasing melanin in light-exposed areas and enhancing this cycle.

Recent evidence demonstrates how silver comes to deposit in the skin: ingested silver nanoparticles dissolve in the acidic environment of the stomach, forming silver ions that are transported by glutathione and other biomolecules after absorption. These ions are reduced in the skin by sunlight and sulfur. Subsequently selenium ions align or collocate alongside silver atoms creating blue discoloration.³⁰

Skin biopsy can confirm the diagnosis of argyria, showing brown-black clusters of silver granules.

Diagnostic Testing

Urine and serum concentrations of silver can be measured as indices of silver exposure. Hair is also tested for silver, but airborne silver particles may bind to hair and contaminate samples.

In individuals without a history of medicinal silver ingestion or occupational exposure, the normal serum silver concentration is no more than 0.005 µg/mL, normal urinary silver concentration is no more than 0.005 µg/g, and normal fecal silver concentration is 1.5 µg/g.¹¹ In contrast, workers who smelt and refine silver or who prepare silver salts for use in the photographic industry, have had mean serum concentrations measured of 11 µg/L, urine silver concentrations of less than 0.005 µg/L, and fecal silver concentrations of 15 µg/g.¹¹

Treatment of Argyria

Chelators are ineffective in treating both silver toxicity and argyria.¹⁴ Dermatologic conventional wisdom has suggested that topical hydroquinone 5% may reduce the number of silver granules in the upper dermis and around sweat glands, as well as diminish the number of melanocytes.⁷ Sunscreens and opaque cosmetics can prevent further pigmentation darkening from sun exposure.

Successful treatment of argyria using laser technology has only recently been reported but appears promising with one case report of a full cure.^{22,42}

As oxidant deficiencies may enhance silver toxicity, antioxidants, such as selenium and vitamin E, may also play a role in reversing effects of silver exposure. Selenium-dependent glutathione peroxidase synthesis is diminished when silver binds to, and thus reduces, intracellular selenium.^{7,54} Supplemental vitamin E and selenium increase tolerance for silver in rats and chickens.⁸ Selenium and sulfur have been considered as possible treatments for argyria. Although the collocation of selenium with silver nanoparticles promotes argyria, selenium may act to precipitate or chelate silver by forming silver selenide complexes; in addition, silver selenide is insoluble in vivo and should reduce the availability of monovalent silver to interfere with normal enzymatic activities.^{1,36,46} Hence, increased selenium intake is theorized to bind silver for excretion rather than skin deposition. Silver–sulfur complexes may be investigated for similar effect, although the silver–sulfur complex is not as stable.⁴⁶

EMERGENCY MANAGEMENT

Although systemic toxicity of silver is predominantly a result of chronic exposure, clinicians may rarely encounter a patient who has ingested a colloidal silver product, a silver-containing medicinal product, or a silver salt. Emergency management should take into consideration the type of silver ingested.

Burns from silver-salt cautery should be managed as burns; ingested cautery should be treated as a caustic agent. Patients who ingest elemental silver should be managed supportively, as elemental silver should pass through the GI tract unchanged. Silver-salt ingestion (such as silver nitrate) should be treated as a caustic ingestion (**Chap. 106**). There is no support for gastric lavage or administration of activated charcoal as a decontamination method.

SUMMARY

- Silver toxicity—primarily argyria and burns—is still occasionally encountered^{23,52,57,58}; the workplace environment and health supplementation products are the main sources of exposure.
- Despite frequent therapeutic use of silver and silver compounds, there is no evidence of silver acting as a mutagen or carcinogen in humans.
- Significant toxicity is very rare, although argyria from chronic silver use is invariably a permanent manifestation.
- There are no proven effective means for removing accumulated silver and reversing argyria, although as of this publication there is one case report of “complete cure” through the use of lasers.

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102 THALLIUM

Maria Mercurio-Zappala and Robert S. Hoffman

Thallium (Tl)		
Atomic number	=	81
Atomic weight	=	204.37 Da
Normal concentrations		
Whole blood	<	2 µg/L (9.78 nmol/L)
Urine (24 hour)	<	5 µg/L (24.5 nmol/L)

HISTORY AND EPIDEMIOLOGY

Thallium (Tl^0), a metal with atomic number 81, is located between mercury and lead on the periodic table. Thallium is a soft, pliable metal that melts at 572°F (300°C), boils at 2699.6°F (1482°C), and is essentially nontoxic. Thallium forms univalent thallos (Tl^{+1}) and trivalent thallic (Tl^{+3}) salts, which are highly toxic. Thallium is a commonly found constituent of granite, shale, volcanic rock, and pyrites used to make sulfuric acid and is also recovered as flue dust from iron, lead, cadmium, and copper smelters.²⁵

In the early 1900s, thallium salts were used medicinally to treat syphilis, gonorrhea, tuberculosis, and as a depilatory for ringworm of the scalp.^{8,68} Although the usual oral dose given for ringworm was 7 to 8 mg/kg, fatal doses ranged from 6 to 40 mg/kg.^{15,57} Many cases of severe thallium poisoning (thallotoxicosis) resulted from this treatment for ringworm, with one author summarizing nearly 700 cases and 46 deaths.⁷¹

Because thallium sulfate is odorless and tasteless, it was also successfully used as a rodenticide. Commercially available as Thalgrain, Echol's Roach Powder, Mo-Go, Martin's Rat Stop liquid, and Senco Corn Mix, thallium sulfate was a very efficient rodenticide. As a consequence of numerous case reports of unintentional poisonings,^{71,72,83} the use of thallium salts as a household rodenticide was restricted in the United States in 1965. Ultimately, even the commercial use of thallium salts as a rodenticide was banned in the United States in 1972 because of continued reports of human toxicity.

Life-threatening unintentional poisoning continues to occur in other countries, especially where thallium salts are still commonly used as rodenticides.^{2,14,81,89,97,106} Additional cases of thallium poisoning are reported in the United States and other countries as a result of the use of thallium for homicide^{21,62,67,75,77,86,94} and through contamination of herbal products⁹¹ and illicit drugs such as heroin^{1,80} and cocaine.⁴⁴ Although occupational exposures to consequential amounts of thallium salts are uncommon, occupational toxicity is well described.³⁸

The following discussion of thallium toxicity refers to toxicity resulting from exposure to inorganic thallium salts, which represents virtually the entire literature on thallium poisoning. Although exceedingly rare, cases of poisoning with organic thallium compounds are reported⁴ and should be assessed and managed in a fashion similar to that used for patients with inorganic exposures. Although small amounts of thallium salts are used as radioactive contrast to image tumors and to permit the visualization of cardiac function, the doses used are insignificant without potential for thallium toxicity.⁶⁸

TOXICOKINETICS

Exposures usually occur via one of three routes: inhalation of dust, ingestion, and absorption through intact skin. Thallium is rapidly absorbed following all routes of exposure. Bioavailability is greatest after ingestion and exceeds 90%.⁴⁰ Distribution follows three-compartment toxicokinetics⁸² (Chap. 9) into a final volume of distribution that is estimated to be about 3.6 L/kg.¹⁹ Thallium can be found in all organs, but it is distributed unevenly, with the highest concentrations found in the large and small intestine, liver, kidney, heart, brain, and muscles.^{8,52} In animals, the highest concentrations of thallium are found in the kidneys.^{3,52}

The toxicokinetics of thallium can be described in the following three-phase model. The first phase occurs within the first 4 hours after oral exposure during which thallium is distributed to a central compartment and to well-perfused

peripheral organs such as the kidney, liver, and muscle. In the second phase, which may last between 4 and 48 hours, thallium is distributed into the central nervous system (CNS).⁸² Whereas some literature suggests that this distribution phase is generally completed within 24 hours of ingestion,⁸² one human case suggests slower distribution into the CNS as evidenced by increasing cerebrospinal fluid (CSF) concentrations in the days after exposure when blood concentrations were declining, which thereby excludes ongoing absorption.⁹⁴ The third or elimination phase usually begins within 24 hours after ingestion. The primary mechanism of thallium elimination is secretion into the intestine, but enteral reabsorption of thallium that is present in the bile subsequently reduces the fecal elimination.^{19,67} Thallium is excreted primarily via the feces (51.4%) and the urine (26.4%).⁵⁶ It is filtered by the glomerulus, with approximately 50% being reabsorbed in the tubules. Thallium is also secreted into the tubular lumen in a manner similar to potassium.⁷ The duration of the elimination phase depends on the route of exposure, dose, and treatment. Unlike many other metals, thallium does not have a major anatomic reservoir. For this reason, reported elimination half-lives are as short as 1.7 days in humans with thallium poisoning.⁴²

PATHOPHYSIOLOGY

The mechanism of thallium toxicity is not well established. Thallium behaves biologically in a manner similar to potassium because both have similar ionic radii (1.47 Å for thallium and 1.33 Å for potassium). Because cell membranes cannot differentiate between thallous (Tl^{+1}) and potassium (K^{+}) ions, thallous ions accumulate in areas with high potassium concentrations, such as the central and peripheral nervous system and hepatic and muscle tissue.^{63,106} This accumulation is the fundamental principle that governs the use of radioactive thallium in cardiac imaging studies. Thallium replaces potassium in the activation of potassium-dependent enzymes.⁶³ In low concentrations, thallium stimulates these enzyme systems, but in high concentrations, it inhibits them.^{9,65} Pyruvate kinase, a magnesium-dependent glycolytic enzyme that requires potassium to achieve maximum activity, has 50 times greater affinity for thallous ions than potassium ions.⁴⁸ Succinate dehydrogenase, an essential enzyme in the Krebs cycle, is inhibited by small doses of thallium in rats.³⁷ Sodium-potassium adenosine triphosphatase (ATPase), which is responsible for active transport of monovalent ions across cell membranes, can use thallous ions at extremely low concentrations because of an affinity that is 10-fold greater than that of potassium ions^{10,30} but is inhibited by thallium at higher concentrations.⁴⁵

Thallium also impairs depolarization of muscle fibers.⁶⁸ Mitochondrial energy is decreased as a result of the inhibition of pyruvate kinase and succinate dehydrogenase, resulting in a decrease of adenosine triphosphate (ATP) generation via oxidative phosphorylation. Enzymatic destruction results in swelling and vacuolization of the mitochondria after exposure to thallium.⁹⁵ At low concentrations, thallium can activate other potassium-dependent enzymes such as phosphatase, homoserine dehydrogenase, vitamin B₁₂-dependent diol dehydrogenase, L-threonine dehydrogenase, and adenosine monophosphate (AMP) deaminase.⁶⁸ The net result of these processes is a failure of energy production.

Thallous ions have been used to isolate riboflavin from milk in the form of a reversible precipitate. Thallous ions may also form insoluble complexes and cause intracellular sequestration of riboflavin in vivo.¹³ Riboflavin is the vitamin precursor of the flavin coenzyme flavin adenine dinucleotide (FAD). Because of a decrease in riboflavin, metabolic reactions dependent on flavoproteins decrease, causing disruption of the electron transport chain and a subsequent further decrease or impairment in the generation of cellular energy.¹³ This decrease in cellular energy may lead to a decrease in mitotic activity and cessation of hair follicle formation, resulting in the clinical sign of alopecia. Subsequent hair loss is the result of combined arrested formation and local destruction of hair shaft cells in the hair bulb^{13,83} (Chap. 18). Unfortunately, riboflavin supplementation was not beneficial in one animal model of thallium poisoning.⁶ Data also demonstrate that the dermatologic, neurologic, and cardiovascular effects of thallium toxicity mirror the manifestations of thiamine deficiency (beriberi), highlighting the inhibitory effect of thallium on glycolytic enzymes.^{13,68} It is unclear whether thiamine administration has any beneficial effect in patients with thallium poisoning.

Thallium has a high affinity for the sulfhydryl groups present in many other enzymes and proteins. Keratin, a structural protein, consists of many cysteine residues that cross-link and form disulfide bonds. These disulfide bonds add strength to keratin. Thallium interferes with the formation of disulfide bonds, which may lead to the development of alopecia and defects in nail growth, resulting in Mees lines.^{33,68,75,88,89} Additionally, the complexation of sulfhydryl groups with thallium results in a decrease in both the production of glutathione and the reduction of oxidized glutathione.^{35,107} This results in oxidative damage²⁸ and the accumulation of lipid peroxides in the brain (which is most prominent in the cerebellum) and appears as dark, pigmented, lipofuscinlike areas.³⁶ The complexity and presumable multifactorial nature of thallium poisoning are again highlighted by the inability of N-acetylcysteine (NAC)-induced augmentation of glutathione stores to protect against toxicity in an animal model.⁶

Thallium also adversely affects protein synthesis in animals by damaging ribosomes, particularly the 60S subunit.⁴³ Although ribosomes are primarily dependent on potassium and magnesium, thallium will be used if present. In an

experimental model, low concentrations of thallium are protective against hypokalemia-induced ribosomal inactivation. As thallium concentrations increase, the protective effects diminish, resulting in progressive destabilization and destruction of the ribosomes. Ribosomal destruction can also be produced by exposure to high potassium concentrations, but usually on the order of 4.5 to 20 times higher than the thallium concentrations necessary to achieve the same effect.⁴³

Pathologic studies of the CNS in patients with thallium poisoning reveal localized areas of edema in the cerebral hemispheres and brainstem. Chromatolytic changes are prominent in neurons of the motor cortex, third nerve nuclei, substantia nigra, and pyramidal cells of the globus pallidus. In chronic exposures, there are signs of edema of the pial and arachnoidal membranes and chromatolysis, swelling, and fatty degeneration in the ganglion cells of the ventral and dorsal horns of the spinal cord.^{8,83}

The peripheral nervous system, which is usually clinically affected before the CNS, develops a diffuse axonopathy in a classic dying back or Wallerian degeneration pattern^{7,8,17,23,64} (Chap. 24). Fragmentation and degeneration of associated myelin sheaths are accompanied by activation of Schwann cells.^{8,12,13} Because thallium affects the longer peripheral fibers—first sensory, then motor, and finally the shorter fibers—toxic effects occur initially in the lower extremities.^{55,74,111}

CLINICAL MANIFESTATIONS

Many of the effects of thallium poisoning are nonspecific and occur over a variable time course.⁵³ When combined, however, a clear toxic syndrome can be defined (Table 102–1). Alopecia and a painful ascending peripheral neuropathy are the most characteristic findings.^{7,27,67,74} Because of the delayed development of alopecia, the diagnosis of thallotoxicosis is often delayed. In fact, with acute exposures, a dose-dependent latent period of hours to days may precede initial symptoms.^{53,68} When death occurs, it is usually the result of coma with loss of airway protective reflexes, respiratory paralysis, and cardiac arrest.

TABLE 102–1. Clinical Manifestations of Thallium Poisoning

Organ System	Onset of Effects			Residual Effects
	Immediate (<6 hours)	Intermediate (Rarely in the first few days; within 2 weeks)	Late (>2 weeks)	
Gastrointestinal				
Nausea	†			
Vomiting	†			
Diarrhea	†			
Constipation	†	†		
Cardiovascular				
Nonspecific ECG changes	†	†		
Hypertension		†		
Tachycardia		†		
Respiratory				
Pleuritic chest pain	†	†		
Respiratory depression		†	†	
Renal				
Albuminuria		†		
Acute kidney injury		†		†
Dermatologic				
Dry skin		†		
Alopecia		†		†
Mees lines			†	†
Neurologic				
Painful ascending sensory neuropathy		†	†	†
Motor neuropathy		†	†	†
Cranial nerve abnormalities		†		
Delirium, psychosis, coma		†		†
Memory and cognitive deficits			†	†
Optic neuritis	†	†		†

† = Typical onset of symptoms. The time course outlined above may be accelerated with extremely large doses. When † appears in two adjacent columns, the time course is highly variable and may be dose dependent. With small ingestions, many of the effects listed above may not be evident. ‡ = Effects that may persist long after exposure, possibly permanently.

Unlike most other metal salt poisonings, diarrhea is often modest or even absent in thallium toxicity.¹⁵ The most common symptom is abdominal pain, which may be accompanied by vomiting and either diarrhea or constipation.^{21,50,53,65,88,108,109} Constipation may be a result of decreased intestinal motility and peristalsis caused by direct involvement of the vagus nerve.^{15,68} Rarely, severe symptoms occur, such as hematemesis, bloody diarrhea, or ulceration of the mucosal lining.

Pleuritic chest pain was described in a small series of poisoned patients.⁶² Another patient was reported to have developed “chest tightness” shortly after drinking thallium-poisoned tea.⁶⁷ The etiology for this finding is uncertain, although it may also relate to involvement of the vagus nerve.

Tachycardia and hypertension frequently occur in patients with thallotoxicosis and usually develop during the first or second week after acute ingestion. A poor prognosis may be associated with a persistent and pronounced tachycardia. No exact mechanism has been determined for these cardiovascular effects of thallium toxicity. Some authors theorize that they result from autonomic neuropathic dysfunction directly related to involvement of the vagus nerve,⁷⁴ but others have noted early electrocardiographic (ECG) changes, such as prolongation of the QT interval, T wave flattening or inversion, and nonspecific ST segment abnormalities, which might suggest direct myocardial injury.^{8,12,65,68,85} Another theory suggests that the direct stimulation of ATPase in the chromaffin cells by thallium may lead to increased output of catecholamines, resulting in sinus tachycardia.^{5,67}

Neurologic symptoms usually appear 2 to 5 days after exposure. Patients may develop severely painful, rapidly

progressive, ascending peripheral neuropathies.^{7,8,23,62} Pain and paresthesias are present in the lower extremities (especially the soles of the feet), and although numbness is present in the fingers and toes, there is also decreased sensation to pinprick, touch, temperature, vibration, and proprioception.^{7,91} The weight of bedsheets on the lower extremities may be sufficient to cause excruciating pain.^{62,64} Motor weakness is always distal in distribution, with the lower limbs more affected than the upper limbs.^{12,68}

Symptoms of confusion, delirium, psychosis, hallucinations, seizures, headache, insomnia, anxiety, tremor, ataxia, and choreoathetosis are common. The onset of these symptoms is variable and most likely dependent on dose. Ataxia may develop within 48 hours after ingestion. Insomnia occurs in most patients and may progress to total reversal of sleep rhythms. Coma may occur, especially with larger exposures.^{12,53,68,88} All cranial nerves can probably be affected by thallium, although abnormalities of cranial nerves I, V, and VIII have not been reported. Cranial nerve III involvement, as evidenced by ptosis, is common and may be asymmetric.¹² Nystagmus, another common finding, demonstrates involvement of cranial nerves IV and VI.¹² Cognitive abnormalities may persist for months after exposure.⁵⁹

Thallium is toxic to both the retinal fibers and the neural retina.⁹² In cases of a large, single ingestion of thallium, approximately 25% of patients may develop severe lesions of the optic nerve.^{68,88} Optic neuropathy may lead to optic atrophy and a permanent decrease in visual acuity. In the early stages, the optic disk shows signs of neuritis, which is red and poorly defined, and later develops pallor from resultant optic nerve atrophy. In patients exposed to multiple small doses, nearly 100% suffer optic nerve injury.⁶⁵ Visual complaints may be delayed in comparison to other neurologic findings⁹² and may include decreased acuity and central scotomata. Other described ophthalmic effects are noninflammatory keratitis, cataracts, and the color vision defect of tritanomaly (blue color defect).^{99,100}

Kidney function may remain normal in mild cases of thallium poisoning, even though the kidney has greater bioaccumulation than any other organ. Changes in kidney function in patients with severe thallotoxicosis include oliguria, diminished creatinine clearance, elevated blood urea nitrogen, and albuminuria.^{5,62,65,68} These findings correlate with morphologic studies in thallium poisoned rats, demonstrating abnormalities in the renal medulla, mainly in the thick ascending limb of the loop of Henle, that occur by the second day after exposure and resolve by the tenth day.⁵

Alopecia is the most common and classic manifestation of thallium toxicity.^{67,103} Typically occurring as the presenting symptom in patients with chronic exposures after an acute exposure, hair loss begins in approximately 10 days and is maximal within 1 month.^{27,67,71} Facial and axillary hair, especially the inner third of the eyebrows, may be spared, but in some cases, full beards, as well as all scalp hair, are lost.⁸³ Microscopic inspection of the hair reveals a diagnostic pattern of black pigmentation of the hair roots of the scalp in approximately 95% of poisoned patients,^{11,67,88,103} which can be found within 3 to 5 days of initial exposure^{11,65} (Fig. 102–1). In patients with recurrent exposures, several bands may be noted on the hair shaft, demonstrating multiple exposures. Initial hair regrowth is very fine and unpigmented but usually returns to normal after mild exposure.⁶⁵ In patients with severe exposures, alopecia may be permanent. Other dermatologic effects that are observed include acne, palmar erythema, and dry scaly skin that results from sebaceous gland damage.¹⁰³ Mees lines appear within 2 to 4 weeks after exposure^{67,75,88} (Fig. 89–4).



FIGURE 102–1. Hair from a patient with severe thallium poisoning (top) compared to a normal (bottom). Note the dark pigmented granules around the root of the poisoned patient. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Other less common findings include hepatotoxicity,⁴⁴ hypochloremic metabolic acidosis,⁸⁸ anemia, and thrombocytopenia.^{54,88}

Teratogenicity

In animal models, thallium is teratogenic.^{32,34} In humans, one study evaluated 297 children born in a region in which the population's urine thallium concentrations were higher than normal because of industrial contamination of their environment.²² Urine thallium concentrations in the exposed children were as high as 76.5 µg/L. Although these children had a slightly higher than expected incidence of congenital abnormalities, no causal relationship could be established with regard to thallium exposure.²²

There are few human reports of acute thallium poisoning during pregnancy. A comprehensive literature review demonstrated 25 cases, which included acute and chronic exposures that occurred during all trimesters.³⁹ Thallium slowly traverses the placenta and is able to cause characteristic fetal toxicity,^{24,73} which manifests initially as decreased fetal movement, possibly as a consequence of fetal paralysis. The classic clinical signs and symptoms of thallium poisoning are described both in the fetus after abortion and in neonate after viable delivery.^{24,65,73,81} However, the outcome of the pregnancy may be normal despite significant maternal toxicity.^{24,46} The only consistent finding is a trend toward prematurity and low birth weight, especially in children exposed during the first trimester.³⁹ One author recommends continuing the pregnancy as long as the mother is clinically improving.²⁴ It is reasonable to conclude that a fetus exposed to thallium during organogenesis has the potential for permanent injury. Those exposed later in pregnancy may recover without deficit if their exposures are limited and the mother recovers. If the exposure occurs closer to term, the child may be born with overt toxicity such as alopecia, dermatitis, nail growth disturbances, and permanent CNS injury.⁶⁵

These few case reports and animal studies provide confusing and sometimes contradictory results. It seems that fetal outcome is determined by both the trimester of pregnancy and the extent of maternal toxicity. However, because there are insufficient data to predict the outcome of pregnancy complicated by maternal thallium poisoning, no specific course of action can be recommended other than extensive fetal monitoring and aggressive treatment for the mother. When a viable child is delivered, it is important to note that thallium is eliminated in breast milk, and that ongoing evaluation of maternal toxicity is essential because nursing may result in continued exposure for the child.³⁷

ASSESSMENT

Most patients with acute thallium toxicity seek health care soon after exposure because of either alterations in their GI, cardiovascular, and neurologic function. Establishing the correct diagnosis at this early stage is essential to assure a satisfactory outcome. Unfortunately, many patients with either smaller acute exposures or chronic thallium poisoning first present days to weeks after their initial exposure and diagnosis is often further delayed. In these instances, many valuable epidemiologic aspects of the exposure history may be difficult to obtain. GI symptoms may not have occurred or their consequence or etiology may have gone unrecognized because of their nonspecific, mild, and transient nature. Many patients with small acute or chronic exposures usually seek care because of alopecia or neuropathy.

The differential diagnosis of the neuropathy includes poisoning by arsenic, colchicine, vinca alkaloids, and disorders such as botulism, thiamine deficiency, and Guillain-Barré syndrome. Both the sensory neuropathy and the preservation of reflexes help differentiate thallium-induced neuropathy from Guillain-Barré syndrome and most other causes of acute neuropathy.¹² When GI symptoms are present in addition to a neuropathy and other end-organ effects, poisoning with metal salts such as arsenic and mercury should be considered (**Chaps. 89 and 98**). The differential diagnosis of rapid onset alopecia is more restricted and includes arsenic, selenium, colchicine, and vinca alkaloid poisoning (**Chap. 18**). When present, Mees lines indicate past exposure to metals, mitotic inhibitors, or antimetabolites and as such are nonspecific for thallium poisoning (**Chaps. 18, 89, and 98**).

Diagnostic Testing

Radiographs of tampered food products⁶² or of the abdomen³³ can document the presence of a metal such as thallium, which is radiopaque. Although abdominal radiography may be useful shortly after a suspected exposure, the sensitivity and specificity of this test is unknown. Similarly, the yield from other routine studies, such as the complete blood count, electrolytes, urinalysis, and ECG, is limited in that these other studies are often normal or at most, merely demonstrate nonspecific abnormalities. Although microscopic inspection of the hair is intriguing, this test is unlikely to be conclusive for inexperienced observers.

The definitive clinical diagnosis of thallium poisoning can only be established by demonstrating elevated thallium concentrations in various body fluids or organs. Thallium can be recovered in the hair, nails, feces, saliva, CSF, blood, and urine, and standard assays and normal concentrations for most of these sources can be found.⁶⁸ Qualitative point of care urine spot tests notoriously give false negative results and require the use of dangerous chemicals that are not routinely

available (20% nitric acid) and therefore should be avoided.⁸⁸ The standard toxicologic testing method is to assay a 24 hour urine sample for thallium by atomic absorption spectroscopy.^{16,110} Normal urine concentrations are below 5 µg/L. Some authors suggest a potassium mobilization test to enhance urinary elimination, similar to the ethylenediaminetetraacetic acid (EDTA) mobilization test, to assist in the diagnosis of thallium exposure.^{11,44,88} We advise against this practice because of its lack of proven usefulness and its potential to exacerbate neurologic toxicity (see Potassium below).

MANAGEMENT

The treatment goals for a patient with thallium poisoning are initial stabilization, prevention of absorption, and enhanced elimination. After the initial assessment and stabilization of the patient's airway, breathing, and circulatory status, GI decontamination should be instituted in all patients with suspected thallium ingestions because of the morbidity and mortality associated with a significant exposure.

Decontamination

Patients who present within 1 to 2 hours after ingestion should be considered candidates for orogastric lavage ([Chap. 8](#)). If the patient presents more than 2 hours after ingestion or has had considerable spontaneous emesis, gastric emptying is unnecessary.

Thallium salts are substantially adsorbed to activated charcoal (AC) in vitro.^{41,50} Additionally, because thallium undergoes enterohepatic recirculation, AC may be useful both to prevent absorption after a recent ingestion and to enhance elimination of thallium in patients who present in the post-absorptive phase.¹⁰¹ In fact, a rat model of thallium poisoning demonstrated that multiple-dose AC (given as 0.5 g/kg twice daily for 5 days) increased the fecal elimination of thallium by 82% and substantially improved survival.⁵⁶ Other data demonstrate that AC alone is superior to either forced diuresis or potassium chloride therapy.⁵¹

In patients with severe thallium toxicity, constipation is common, so the addition of oral mannitol^{58,96,108} or another cathartic to the first dose of AC is appropriate. Although no studies address the efficacy of whole-bowel irrigation with polyethylene glycol electrolyte lavage solution, this technique may prove useful, especially when radiopaque material is demonstrated in the GI tract ([Antidotes in Depth: A2](#)).

Potassium

The similarities between the cellular handling of potassium ions and thallium ions led to the investigation of a possible role for potassium in the treatment of thallium poisoning. In humans, potassium administration is associated with an increase in urinary thallium elimination.^{15,29,76} The magnitude of this increase is reported to be on the order of two-to threefold.⁷⁶ This is supported by animal models that demonstrate some benefit in terms of either enhanced thallium elimination or animal survival.^{30,51,56} Potassium administration is believed to both block tubular reabsorption of thallium and mobilize thallium from tissue stores, thereby increasing thallium concentrations available for glomerular filtration.^{70,88} However, the mobilization of the thallium is of concern. Many authors report either the development of acute neurologic toxicity or the significant exacerbation of neurologic symptoms during potassium administration.^{7,29,62,76,85,104} Others cite data demonstrating that the augmentation of thallium elimination by potassium administration in humans is quite limited.⁴⁹ Additionally, animal models demonstrate that potassium loading enhances lethality⁶¹ and permits thallium redistribution into the CNS.³⁶ For these reasons, the routine use of potassium should be considered potentially dangerous. Some authors recommend forced diuresis, especially in conjunction with potassium chloride.^{20,101} However, no convincing experimental or clinical evidence can support the use of forced diuresis with or without potassium at this time.

Likewise, the similarities between thallium and potassium might suggest a role for administration of sodium polystyrene sulfonate (SPS) as a sodium–thallium exchange resin. Although in vitro binding between thallium and SPS is excellent, it is unlikely to be clinically useful because of preferential binding between potassium and SPS.⁴¹ Consequently, neither the use of potassium nor of SPS is recommended.

Prussian Blue

Prussian blue is approved by the Food and Drug Administration for thallium toxicity ([Antidotes in Depth: A28](#)).¹⁰² When given orally, Prussian blue acts as an ion exchanger for univalent cations, with its affinity increasing as the ionic radius of the cation increases. As such, Prussian blue interferes with the enterohepatic circulation of thallium by exchanging potassium ions from its lattice for thallium ions in the GI tract. This results in the formation of a concentration gradient, causing an increased movement of thallium into the GI tract.

Humans with thallium poisoning are routinely given Prussian blue, which appears to result in clinical benefits,

enhanced fecal elimination, and decreasing thallium concentrations.^{16,18,62,79,96,104,105,108,109} One series of 11 thallium poisoned patients demonstrated both the safety of Prussian blue and its ability to substantially increase fecal thallium elimination.⁹⁶ Unfortunately, because there have been no controlled trials in humans that compare Prussian blue with other drugs and because many of the patients reported above received multiple therapies, the actual efficacy of Prussian blue is unknown.

The dose of Prussian blue is 250 mg/kg/d orally via a nasogastric tube in two to four divided doses.⁹⁶ For patients who are constipated, the Prussian blue may have greater benefit if dissolved in 50 mL of 15% mannitol.¹⁰¹ Although any cathartic may be useful, most authors have used mannitol, possibly because of concerns regarding repeated use of magnesium containing cathartics in patients with neurologic findings and the use of sorbitol in patients with poor GI mobility. (Other dosing regimens are discussed in Antidotes in Depth: A28.)

Extracorporeal Drug Removal

Extracorporeal drug removal may have a limited beneficial role in patients with thallium toxicity, especially if it is begun shortly after the initial exposure while serum concentrations remain high before effective tissue distribution. Because a frequently quoted review attests to the benefits of hemodialysis,⁶⁵ many patients still receive this therapy.⁶⁴ The actual data, however, show that hemodialysis, at various stages of poisoning, is no better than forced diuresis.^{18,78} Reported thallium removal rates by hemodialysis are trivial: 143 mg of thallium was removed by 120 hours,⁷⁹ 222.8 mg was removed by 121 hours,¹⁸ and 128 mg was removed by 54 hours of hemodialysis.¹⁸ These quantities can be placed in perspective knowing that the minimum lethal adult dose of thallium is estimated to be on the order of 1 g,⁶⁸ and that many reported cases exceed that by a factor of 10. Data from a more recent hemodialysis experience suggest that by using high blood flow rates (300 mL/min), clearances as high as 90 to 150 mL/min could be obtained.⁵⁸ Although these clearances seem encouraging, they should be interpreted with an appreciation of the large volume of distribution that thallium achieves in the post absorptive phase. With lower blood flow rates, charcoal hemoperfusion may be two to three times more efficient than hemodialysis, providing clearance rates as high as 139 mL/min.¹⁸ Combined hemoperfusion and hemodialysis were used in several cases^{4,18,19} and were reported to remove as much as 93 mg of thallium within 3 hours of therapy.⁴ Although extracorporeal therapy alone is probably insufficient for patients with significant poisoning and unnecessary in those with small exposures, it may have some benefit when used in combination with other therapies, especially in patients with either underlying chronic kidney disease or acute kidney injury from thallium poisoning, and those with early massive, and presumed lethal, exposures. As is the case with other xenobiotics, thallium is probably not effectively removed by peritoneal dialysis.⁴⁹ A multidisciplinary consensus work group recently supported extracorporeal therapy in patients with acute poisoning when blood thallium concentrations are greater than 400 µg/L (if rapidly available), or, if in the absence of laboratory support severe signs and symptoms are present and treatment can be initiated within 24 to 48 hours of ingestion.³¹ Table 102–2 summarizes the suggested therapy for thallium poisoned patients.

TABLE 102–2. Treatment for Thallium Poisoning

Early (patients who present in the first 1–2 hours postexposure)

- Stabilize airway, breathing, and circulation if necessary.
- Consider orogastric lavage if the patient has not vomited.
- Consider whole-bowel irrigation with polyethylene glycol electrolyte lavage solution for patients with large ingestions or the presence of radiopaque material on abdominal radiographs.
- Begin multiple-dose activated charcoal therapy (MDAC); add a cathartic (preferably oral mannitol) to the first dose if the patient is constipated. Discontinue MDAC when Prussian blue becomes available.
- Give 250 mg/kg/d of Prussian blue in two or four divided doses dissolved in water or 50 mL of 15% mannitol if the patient is constipated.
- Consider simultaneous charcoal hemoperfusion and hemodialysis, especially if the patient has chronic kidney disease or acute kidney injury.

Late (patients who present more than 24 hours after exposure or with chronic toxicity)

- Stabilize airway, breathing, and circulation if necessary.
- Begin multiple-dose activated charcoal therapy; add a cathartic (preferably oral mannitol) to the first dose if the patient is constipated. Discontinue MDAC when Prussian blue becomes available.
- Give 250 mg/kg/d of Prussian blue in two or four divided doses dissolved in water or 50 mL of 15% mannitol if the

patient is constipated.

Chelation

Patients with thallium toxicity do not respond to traditional chelation therapy. Studies demonstrate that the use of EDTA and diethylenetriamine pentaacetic acid are without benefit.^{68,88} Dimercaprol (British anti-Lewisite {BAL}) and D-penicillamine also fail to enhance thallium excretion in experimental models.^{68,88} In one model in which D-penicillamine was able to enhance thallium elimination, the resultant substantial thallium redistribution into vital organs was a significant disadvantage.⁸⁴ More recently, a rodent model of combined use of Prussian blue with DL-penicillamine not only suggested a survival advantage for combined therapy but demonstrated reduced thallium concentrations in vital organs, including the brain.⁶⁶ Sulfur-containing compounds such as cysteine and NAC are not beneficial.^{56,60} Another chelator, diphenylthiocarbazone (dithizone), forms a minimally toxic complex with thallium, resulting in a 33% increase in fecal elimination of thallium in rats.⁹³ Unfortunately, dithizone is goitrogenic and diabetogenic in animal studies.^{56,69,101} Dithiocarb (sodium diethyldithiocarbamate), an intermediate metabolite of tetraethylthiuram disulfide (disulfiram, or Antabuse) (Chap. 79), also increases the urinary excretion of thallium.^{93,98} Before thallium elimination, however, the formation of a lipophilic thallium–diethyldithiocarbamate complex may result in the redistribution of thallium into the CNS.^{47,98} After decomposition of the chelate complex, thallium may remain in the CNS, potentially exacerbating neurologic symptoms.^{47,86} Because of the significant adverse effects of dithizone and the redistribution of thallium after Dithiocarb use, neither chelator is recommended in the treatment of patients with thallium poisoning.

Currently, there is renewed interest in the water-soluble analogs of BAL (DMPS and succimer). However, in an animal model, DMPS failed to decrease tissue concentrations of thallium.⁶⁹ Similarly, in another animal model, although succimer improved survival over control subjects, the benefit was less than that achieved for Prussian blue and was at the cost of an increase in brain thallium concentrations.⁸⁷ Preliminary animal investigations demonstrate reduction in serum thallium concentrations after administration of the iron chelators deferoxamine and deferasirox.^{26,90} Although worthy of additional study, these results are too preliminary to recommend either antidote in thallium-poisoned patients.

SUMMARY

- Thallium is a multisystem toxin whose effects result from cellular mimicry for potassium and avid binding to sulfhydryl groups.
- The elimination of thallium salts from depilatories and rodenticides has substantially reduced the incidence of both intentional and unintentional thallium toxicity in the United States.
- Cases of significant poisoning still occur in countries where thallium-containing rodenticides remain in use, as well as in this country, from attempted homicide and by personal injury from contamination of foods and illicit xenobiotics.
- Early recognition of the characteristic signs and symptoms of thallium poisoning, such as a painful ascending neuropathy and alopecia, followed by prompt initiation of safe and appropriate therapy will substantially improve the prognosis.
- Patients with acute oral poisonings should receive at least one dose of oral AC followed by either multiple dose activated charcoal (MDAC) or Prussian blue, if available. Oral mannitol can be added to either MDAC or Prussian blue when constipation is present.
- In severe acute poisoning, the addition of hemodialysis or combined hemodialysis and hemoperfusion in series may be beneficial.

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A28 ANTIDOTES IN DEPTH

Prussian Blue

Robert S. Hoffman

INTRODUCTION

Poisoning with salts of thallium or cesium are uncommon causes of life-threatening toxicity where supportive care may be insufficient to alter outcome. Radioactive cesium can be released as part of a nuclear incident or dispersed as a “dirty bomb,” producing radiation poisoning with sub-toxic cesium doses. Prussian blue is an orally available cation exchange resin that definitively enhances elimination of thallium and cesium in humans and animals and improves survivability in animals.

HISTORY

Prussian blue, the first artificially synthesized pigment, was discovered unintentionally by Diesbach in 1704 while attempting to make another pigment, cochineal red lake. Although immediately popular in art and later in printing, it took approximately 250 years to recognize that Prussian blue could attract monovalent alkali metals into its crystal lattice. Subsequently, in 1963, Nigrovic demonstrated that Prussian blue enhanced cesium elimination from the gastrointestinal tract of rats given either oral or intraperitoneal cesium.³⁷ In 2003, the US Food and Drug Administration (FDA) approved Prussian blue (Radiogardase) for the treatment of thallium and radioactive cesium poisoning.

The Prussian blue literature is complicated by many confusing chemical and physical terms. The product synthesized by Diesbach, $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$, commonly known as insoluble Prussian blue, is assigned the Chemical Abstracts Service (CAS) number 14038-43-8 and is the FDA-approved product Radiogardase (Fig. A28–1). Synonyms for Prussian blue include Berlin blue, Hamburg blue, mineral blue, Paris blue, and Pigment blue 27, among others.⁵⁶ These names are often used interchangeably to refer to both insoluble Prussian blue and a soluble (colloidal) Prussian blue that either has the molecular formula $\text{KFe}[\text{Fe}(\text{CN})_6]_3$ or $\text{K}_3\text{Fe}[\text{Fe}(\text{CN})_6]_3$. Thus “Prussian blue” also carries two additional CAS numbers: 25869-98-1 and 12240-15-2.³⁸ Compounds containing the same basic core structure, such as $\text{NH}_4\text{Fe}[\text{Fe}(\text{CN})_6]_3$ (ammonium ferric ferrocyanide or Chinese blue) and sodium ferric ferrocyanide, may have similar efficacy in binding monovalent cations and are also sometimes incorrectly called Prussian blue. For the purpose of clarity, general statements that follow use the term “Prussian blue.” In many instances the terms “insoluble” and “soluble” are chosen to highlight differences between the compounds. Unfortunately, because many studies do not specify which Prussian blue is used, some inherent ambiguity persists in the literature. Radiogardase, the currently available pharmaceutical preparation, is the insoluble form of Prussian blue, possibly selected preferentially for its efficacy in cesium poisoning.

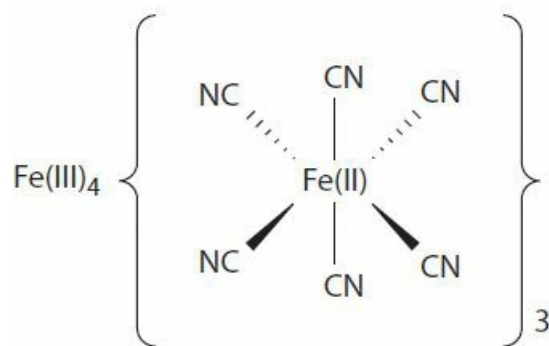


FIGURE A28–1. The chemical structure of insoluble Prussian blue. The Roman numerals II and III denote the valence state of iron. Although in most current nomenclature this would be expressed as Fe^{2+} and Fe^{3+} , the figure is drawn this way for consistency with most available references, which employ the older nomenclature.

PHARMACOLOGY

The crystal lattice of Prussian blue typically binds cationic potassium ions from the surrounding environment. However, because its affinity increases as the ionic radius of the monovalent cation increases, Prussian blue preferentially binds cesium (ionic radius: 1.69 Å) and thallium (ionic radius: 1.47 Å) over potassium (ionic radius: 1.33 Å).^{8,18} Additionally, strong binding for rubidium (ionic radius: 1.48 Å) is demonstrated.⁴⁸ Thus, when given orally, Prussian blue binds unabsorbed thallium or cesium in the gastrointestinal tract, preventing absorption and reversing the concentration gradient to enhance elimination through gastrointestinal dialysis. Prussian blue can also interfere with enterohepatic circulation, causing a further reduction in tissue stores.

Insoluble Prussian blue remains almost exclusively in the gastrointestinal tract and is eliminated nearly entirely in feces at a rate determined by gastrointestinal transit time. In a radiolabeled study of healthy pigs, 99% of a single ingested dose was recovered unchanged in the stool.³³ In contrast, soluble Prussian blue is slightly absorbed based on the clinical finding of a blue discoloration that develops in the sweat and tears of patients undergoing prolonged therapy.¹⁴ This discoloration appears to be without clinical significance and resolves within days when therapy ceases. No significant food or drug interactions are known to exist.

THALLIUM

In Vitro Adsorption

The chemical formulation of Prussian blue influences the in vitro and, presumably, the in vivo adsorption of thallium ions. An early investigation demonstrated that the soluble form more effectively adsorbs thallium than the insoluble form.¹⁰ In a more rigorous study, the in vitro adsorptions of both forms were similar when thallium concentrations remained low.¹⁷ However, as thallium concentrations increased, the colloidal (soluble) form demonstrated far greater adsorptive capacity. Although not proven, this difference may occur because the soluble form contains more potassium and can therefore exchange proportionally more cation. Furthermore, the actual size of the crystal lattice alters its efficacy. Laboratory synthesized Prussian blue (with a crystal size of 176.8 Å) was compared with a commercial preparation (with a crystal size of 311.9 Å). The laboratory synthesized product adsorbed more thallium in vitro because its smaller size increased its surface area.¹⁸ In vitro analysis of the FDA-approved antidote demonstrated that pH and hydration state greatly influenced adsorption, with the maximal adsorptive capacity (MAC) predicted to be as high as 1400 mg of thallium/g at pH 7.5.⁶⁷

In Vitro Comparison of Prussian Blue and Activated Charcoal

In one in vitro study, thallium was well adsorbed to Norit brand activated charcoal.¹⁷ Although numerical data are not supplied in the body of the paper, the 10% to 20% adsorption to activated charcoal demonstrated in a figure was far less than the results achieved with several different forms of Prussian blue tested simultaneously.¹⁷ Two other binding studies showed different results from the Norit activated charcoal study. An early investigation determined that the MAC of activated charcoal was 124 mg of thallium/g, whereas the MAC for Prussian blue was only 72 mg of thallium/g.¹⁹ More recently, a MAC of only 59.7 mg of thallium/g was calculated for CharcoAid activated charcoal, compared with a higher MAC for insoluble Prussian blue of 72.7 mg of thallium/g.¹⁵ Although the MACs for Prussian blue in these two studies are nearly identical, they differ significantly from the MAC reported above for the FDA approved formulation, possibly as a result of different experimental conditions.⁶⁷ Similarly, the variable results for activated charcoal may also be a function of the study pH or the different types of activated charcoal used.

Animal Data: Kinetics, Tissue Concentrations, and Survival

Thallium. Sublethal doses of thallium were used to evaluate the effects of various antidotes in rats over an 8 day period.¹⁹ Although the control group only eliminated 53% of the administered dose of thallium, 93% of the dose was eliminated in the activated charcoal, and 82% was eliminated in the insoluble Prussian blue groups. In contrast, other investigators demonstrated only a modest increase in thallium elimination in rats treated with oral activated charcoal while demonstrating a consistent benefit of Prussian blue.²⁰

Multiple studies demonstrate that Prussian blue not only decreases the half-life of thallium in animals but also lowers thallium content in critical organs such as the brain and the heart.^{13,30,31,47,49} Half-lives are typically reduced by approximately 50% when Prussian blue is given with or without a cathartic. The rationale for the cathartic is that constipation is invariably present in humans and animals with severe thallium poisoning.

Only a few studies evaluate the effects of Prussian blue on survival. In these studies, a statistically significant survival advantage is shown in thallium poisoned rats^{18,49} and mice²⁴ treated with Prussian blue. The experimental benefit is on the order of a 31% increase in the LD₅₀ (median lethal dose for 50% of poisoned animals).⁵⁰ Although most chelators have a

limited or detrimental effect in thallium poisoning (Chap. 102) and DL-penicillamine has no demonstrable benefit as a single antidote, in an animal model the combined use of Prussian blue and DL-penicillamine not only decreased thallium concentration in critical tissues such as the brain but also enhanced survival.²⁸ While interesting, these data are too premature to recommend the routine use of combined DL-penicillamine and Prussian blue in poisoned humans.

Radioactive Thallium. There is no published experience describing human poisoning with radioactive thallium. Prussian blue has demonstrable efficacy in an animal model of radioactive thallium poisoning, as would be expected because the ionic radii of isotopes are generally similar. In one small study, insoluble Prussian blue decreased the biologic half-life of radioactive thallium in rats by approximately 40%.³ Many humans receive radioactive thallium (²⁰¹Tl) chloride as part of myocardial scintigraphy, with a typical adult dose of 110 megabecquerels (MBq). Recent concerns about excess radiation exposure following the termination of diagnostic testing have led to the evaluation of Prussian blue to enhance post-imaging elimination. In vitro evidence suggests a MAC of 5000 MBq/g.² In a controlled trial, where Prussian blue was given to a patient post myocardial scintigraphy, radioactivity was reduced 18% and 30% after 24 and 48 hours, respectively.²

Thallium Poisoning in Humans

A thorough analysis of the efficacy of Prussian blue in thallium poisoning is severely hampered by many factors. First, and most importantly, there are no controlled human trials. Second, although multiple patients have received Prussian blue in the setting of thallium poisoning, many were simultaneously treated with a variety of therapies, including forced potassium diuresis, single-or multiple-dose activated charcoal, and either hemodialysis or hemoperfusion. Thus, it is impossible to determine the specific effects of Prussian blue on morbidity or mortality, and even toxicokinetic data must be interpreted with caution. Third, many reports fail to specify the exact type of Prussian blue used. Those investigations that do specify the type of Prussian blue typically employed the soluble form, which is presently unavailable as a pharmaceutical preparation in the United States. Discussions of the available data in the following sections are limited by these considerations.

Three patients, in 1971, were the first to receive Prussian blue as a treatment for thallium poisoning.¹⁷ Although daily fecal thallium concentrations were not determined in two of the three patients because of severe constipation, an approximately sevenfold increase in fecal thallium elimination over baseline was attributed to Prussian blue therapy in the third patient. Subsequently, many humans with thallium poisoning have received Prussian blue, with or without a cathartic, as part of their therapy.^{1,5,7,8,12,17,41,44,45,53,59,60,64} Unfortunately, other components of therapy that may have confounded the effects of Prussian blue in these cases include single-or multiple-dose activated charcoal and the use of D-penicillamine, dimercaprol, ethylenediaminetetraacetic acid (EDTA), succimer, 2,3-dimercaptopropane-1-sulphate (DMPS), forced potassium diuresis, and either hemodialysis or hemoperfusion. There are no controlled human trials of any of these modalities alone or in combination, and most of the data presented are based on single case reports or small case series.

One of the largest series was comprised of 11 thallium poisoned patients who were treated with soluble Prussian blue.⁵³ This report not only demonstrated the tolerability of Prussian blue, but also was the first to systematically evaluate its fecal elimination. In all individuals studied, fecal elimination remained high, even when urinary elimination fell, suggesting selective redistribution of thallium into the gut.⁵³ Although the authors commented on clinical improvement in these patients, the lack of controlled data makes these subjective observations difficult to interpret. Similarly, a substantial reduction in thallium half-life was demonstrated when Prussian blue was compared with no therapy at all in patients with thallium poisoning.⁸ More recently, a series of 14 patients with delayed presentation (9–19 days) were reported. These patients were treated with DMPS, followed by Prussian blue and hemodialysis, and 13 survived. Data are insufficient to make inferences about the effects of Prussian blue alone or as part of this treatment regimen.⁵⁴

Dosage and Administration

The dosage of Prussian blue has never been investigated systematically in either humans or animals. In most of the case reports and series mentioned above, a total dose of 150 to 250 mg/kg/d was administered orally or via a nasogastric tube in two to four divided doses.⁵³ Because constipation or obstipation is often present or expected, Prussian blue is generally administered dissolved in 50 mL of 15% mannitol.⁵⁵ Although any cathartic may be appropriate, mannitol is used most frequently, possibly because of concerns over the risks associated with repeated doses of magnesium or sorbitol (Antidotes in Depth: A2). The manufacturer of Radiogardase recommends that adults and adolescents with thallium poisoning receive a total dose of 9 g divided daily (3 g every 8 hours) and that children receive a total dose of 3 g divided daily (1 g every 8 hours). Although the manufacturer does not recommend using a cathartic, a high fiber diet is advocated when constipation is present. Because Prussian blue is well tolerated, the editors of this text continue to favor the 150 to 250 mg/kg/d dosing because it provides more antidote with limited adverse consequence, as most of the published experience has used this dose with essentially no adverse effects. In addition, because many severely poisoned patients cannot eat, the use of a cathartic should be considered when constipation is consequential.

The end point of therapy is similarly poorly defined. By convention, Prussian blue is usually continued until urinary thallium concentrations fall below 0.5 mg/d. Although this end point may not be a perfect measurement of thallium burden, as small amounts of fecal elimination continue, even when urinary elimination has diminished,⁵³ most laboratories are not equipped to measure fecal thallium concentrations. In patients who remain significantly symptomatic, Prussian blue therapy could be continued for a short period past the 0.5 mg/d endpoint on an individual basis.

CESIUM

The radioactive isotope of cesium (¹³⁷Cs), a common byproduct of nuclear fission reactions, is a strong β and γ emitter with a physical half-life of more than 30 years and a biologic half-life of about 110 days. Another isotope (¹³⁴Cs) is only produced by neutron activation of the stable isotope (¹³³Cs) and has a physical half-life of about 2 years and a biologic half-life comparable to ¹³⁷Cs. Cesium is absorbed in the small bowel, distributes like potassium, and undergoes enteric recirculation in a manner comparable to thallium.²⁹ Approximately 80% of a given dose of cesium is eliminated in the urine, with 20% cleared in the feces.

The isotope ¹³⁷Cs is used clinically as a radiotherapy source in nuclear medicine and to irradiate banked blood. Although uncommon, radiologic disasters such as Fukushima, Chernobyl, and Goiânia (see Human data below) have resulted in lethal incorporation exposures. Additionally, concerns over the use of ¹³⁷Cs in “dirty bombs” have increased the potential need to treat patients with radioactive cesium poisoning. Toxicity from nonradioactive cesium is also reported. Many cases of QT interval prolongation and torsade de pointes are reported in patients taking cesium chloride either as a dietary supplement or for its alleged antineoplastic effects.^{4,6,22,40,46,51,57}

In Vitro Adsorption

Standard binding studies compared the ability of activated charcoal, sodium polystyrene sulfonate (SPS), and both soluble and insoluble Prussian blue to adsorb ¹³⁷Cs over a range of gastrointestinal pHs.⁶² Unlike thallium, the adsorption of cesium to activated charcoal was negligible. Comparable to thallium, SPS offered no benefit, likely because of preferential effects on potassium. Although both forms of Prussian blue adsorbed cesium, the insoluble form was consistently superior. A pH of 7.5 was selected to represent the pH of the small bowel lumen, the location where most adsorption would occur. At this pH, a MAC of 238 mg of ¹³⁷Cs/g of insoluble Prussian blue was determined. In an interesting extension, when the same authors bound insoluble Prussian blue to a hemoperfusion column, they demonstrated a clearance of approximately 100 mL/min of ¹³⁷Cs from plasma and projected that a 4 hour treatment would adsorb about 0.3 terabecquerel (TBq) of radioactive cesium.⁶³ When the FDA approved antidote was analyzed, like thallium, pH and hydration introduced significant variations in binding, with a MAC of 715 mg of cesium/g noted at pH 7.5.¹¹

Animal Data: Kinetics, Tissue Concentrations, and Survival

Small animal investigations with either ¹³⁴Cs or ¹³⁷Cs consistently demonstrate that Prussian blue therapy reverses the urine-to-stool elimination ratio from 8:1 to 0.3:1 and reduces the biologic half-life and the total body area under the curve by as much as 60%.^{32,36,37,48,52} For example, rats given oral ¹³⁴Cs retained 84.7% of the ingested dose at 7 days. Treatment with insoluble and soluble Prussian blue, as well as Chinese blue, produced significant reductions in retained cesium (only 6.36%, 2.63%, and 2.43% of the dose was retained at 7 days, respectively).⁹

In addition to human toxicity, concern over radioactive cesium incorporation into cattle milk and meat has resulted in a number of large animal model investigations. Daily Prussian blue therapy reduced radioactive cesium concentrations in sheep by as much as 42%.^{16,43} Likewise, radioactive cesium transfer to milk was reduced by 85% in cows.⁵⁸ When dogs were contaminated with ¹³⁷Cs, Prussian blue reduced total body burden by as much as 51%.²⁶ Similar efficacy in reducing the amount of cesium was demonstrated in meat from pigs fed ¹³⁴Cs contaminated whey, with insoluble Prussian blue reducing activity from 359 Bq/kg to 11 Bq/kg over 27 days.⁹

Human Volunteer Studies

Two human volunteers ingested meals contaminated with ¹³⁴Cs to compare the efficacy of both the soluble and insoluble forms of Prussian blue with controls.⁹ At 14 days after exposure and without therapy, the volunteers retained 94.7% of the ingested dose, compared with retention of only 5.1% following therapy with insoluble Prussian blue and 4.9% following soluble Prussian blue. In another study, two volunteers demonstrated that Prussian blue decreased the biologic half-life of ingested radioactive cesium by approximately 33%.²³ Finally, in two volunteers, the effects of pretreatment were compared with simultaneous post-treatment Prussian blue. When a single dose of Prussian blue was administered 10 minutes before ¹³⁴Cs, absorption decreased from 100% (without therapy) to 3% to 10%. However, simultaneous administration of 0.5 or 1

g of Prussian blue with ^{134}Cs resulted in 38% to 63% absorption. Finally, when Prussian blue was given daily at a dose of 0.5 g every 8 hours in the post-absorptive phase, the biologic half-life of ^{134}Cs was reduced from 106 to 44 days.³⁵

Radioactive Cesium Poisoning in Humans

There are no controlled trials of Prussian blue in radioactive cesium poisoning. Experience is derived exclusively from treating disaster victims. In 1987, a number of people in Goiânia, Brazil, were incorporated with radioactive cesium from a discarded radiotherapy unit.³⁹ Although the reported total number of individuals treated is uncertain because of multiple reports that probably include the same patient several times, one group describes 37 patients who were given insoluble Prussian blue in doses ranging from 3 g/d in children up to 10 g/d in adults. Untreated, elimination kinetics were first order, and half-lives varied extensively from 39 to 106 days in adults (mean: 65.5 days in women and 83 days in men). Half-lives were shorter in children. Therapy with insoluble Prussian blue reduced half-lives by a mean of 32%,²¹ and reduced the retained cesium dose from between 51% and 84% of the total dose.²⁵

The nuclear disaster at Chernobyl, Ukraine, resulted in many cases of acute radiation exposure as well as incorporation into the population of radioactive iodine, cesium, and strontium. In one trial, insoluble Prussian blue was given to three victims of radioactive cesium incorporation many weeks after their exposure. The reported reduction in biologic half-life ranged from 12% to 52%.²⁷ The authors of this paper include data from the Chinese literature describing another six patients who demonstrated a similar reduction in the biologic half-life of cesium following Prussian blue therapy.

Non-Radioactive Cesium Poisoning in Humans

Two cases describe the use of Prussian blue for patients with non-radioactive cesium poisoning. A 58 year-old woman presented with syncope, polymorphic ventricular tachycardia, hypokalemia, and a QT interval of 590 msec after taking cesium chloride as an alternative therapy for cancer. The apparent half-life of cesium was reported as 7.9 days during Prussian blue therapy in comparison to 86.6 days after therapy. The authors state that there were no adverse effects of therapy.⁵⁷ Similarly, a 65 year-old woman presented with syncope and was found to have multiple episodes of torsade de pointes, hypokalemia, and a QT interval of 620 msec after taking cesium chloride for 6 weeks. Therapy with insoluble Prussian blue (3 g/d) was associated with a reduction in the apparent half-life for cesium from 61.7 to 29.4 days.⁴

Dosage and Administration

The manufacturer of Radiogardase recommends that for radioactive cesium poisoning, adults and adolescents 13 years or older receive a total daily dose of 9 g divided into 3 g, three times per day. Children aged two through twelve years should receive a total daily dose of 3 g divided into 1 g, three times per day. While the manufacturer offers no recommendation in children under the age of two years, administering 150 to 250 mg/kg/d in divided doses would be appropriate. Although these are the same doses used for thallium poisoning, therapy for cesium poisoning should be continued for at least 30 days. Even though there are no recommendations of other criteria to determine the end point of therapy, quantitative and radiologic evaluations of cesium elimination should be performed. Capsules can be opened and mixed in liquids and given via nasogastric tube for patients unable to swallow. Since constipation does not commonly occur with either radioactive or non-radioactive cesium poisoning, neither routine cathartic administration nor the use of a high fiber diet is recommended.

ADVERSE EFFECTS AND SAFETY ISSUES

Animal studies show no adverse effects of therapeutic doses.⁴² Oral lethal doses are not known or projected for humans, but are likely to be astronomic given that there is no or minimal absorption of Prussian blue and the absence of local toxicity in the GI tract. The only significant adverse effects reported in humans receiving therapeutic doses are constipation and hypokalemia,⁵⁵ and the constipation may be related more to the thallium toxicity than to Prussian blue.

Although there is some concern regarding the potential for cyanide liberation from Prussian blue, this release appears to be quantitatively minimal. Cyanide release from soluble Prussian blue was less than 3 mg/24 h in simulated gastric fluid.⁶¹ When three human volunteers were given 500 mg of soluble Prussian blue (radiolabeled with ^{59}Fe , either in the ferric or ferrous position and with ^{14}C on the CN), only 2 mg of cyanide were absorbed.³⁴ Over the physiological range of potential gastrointestinal pH, the maximal cyanide release from insoluble Prussian blue is only 135 $\mu\text{g/g}$ at pH 1.^{65,66} When extrapolated even for repeated therapeutic doses, only a trivial amount of cyanide would be liberated.

PREGNANCY AND LACTATION

Insoluble Prussian blue is listed as pregnancy category C. Because of the severe consequences of poisoning from radioactive cesium and thallium, and the lack of systemic absorption of insoluble Prussian blue, a risk-to-benefit analysis

would favor the use of the antidote in all poisoned pregnant patients.

FORMULATION AND ACQUISITION

Insoluble Prussian blue (Radiogardase) is available as a 0.5 g blue powder in gelatin capsules for oral administration manufactured from Haupt Pharma Berlin GmbH for distribution by HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG, Berlin (281-395-7040; fax 281-395-2320; see information at www.heytext.com). Prussian blue is part of the US Strategic National Stockpile, which can be accessed at CDC emergency response hotline: 770-488-7100; and is also stored at REAC/TS, Oak Ridge: emergency number 865-576-1005. Thirty capsules retail for about \$100 and have a 5 year shelf life.

SUMMARY

- Prussian blue is a crystalline lattice that adsorbs radioactive and non-radioactive isotopes of thallium and cesium.
- Animal data demonstrate the ability of Prussian blue to prevent absorption, enhance elimination, and improve survival following thallium or cesium administration.
- Although human data are limited, the use of Prussian blue appears beneficial in case reports and small case series.
- Since Prussian blue is essentially non-toxic, it should be used whenever severe thallium or cesium poisoning is suspected.
- If Prussian blue is unavailable, activated charcoal can be substituted for thallium poisoning, but not for cesium poisoning.

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Nima Majlesi

Zinc (Zn)	
Atomic number	= 30
Atomic weight	= 65.37 Da
Normal concentrations	
Blood	= $800 \pm 200 \mu\text{g/dL}$ ($122 \pm 31 \mu\text{mol/L}$)
Serum	= $109\text{--}130 \mu\text{g/dL}$ ($17\text{--}20 \mu\text{mol/L}$)
Urine (24 hour)	= $<500 \mu\text{g/d}$ ($76.5 \mu\text{mol}$)

HISTORY AND EPIDEMIOLOGY

The Babylonians used zinc alloys more than 5000 years ago,² and references to zinc oxide as a lotion to heal lesions around the eye can be found in the Ebers papyrus, written in 1500 b.c.¹⁸ Zinc oxide and zinc sulfate were used in Western Europe during the late 1700s and early 1800s for gleet (urethral discharge), vaginal exudates, and convulsions. In the late 1800s, brass workers who inhaled zinc oxide fumes were noted to develop “zinc fever,” “brass founders’ ague,” and “smelter shakes,” all of which are now identified as metal fume fever (Chap. 124).⁷⁰

Throughout history, humans have contaminated the environment with zinc. For example, release of zinc from mines elevates concentrations in the local water supply and vegetation, which may lead to elevated tissue zinc concentrations and clinical effects in the nearby population.^{54,64}

The antiinflammatory effects of zinc sulfate were studied in the late 1970s for acne vulgaris with mixed results. However, a double-blinded controlled study found no difference between zinc and placebo.⁷⁵ The more recent use of zinc supplementation as an alternative preventive and treatment strategy for upper respiratory infections is exposing large numbers of patients to undefined risks for unclear benefits.

In more recent history, an epidemic of hematologic and, more importantly, neurologic impairment due to large unintentional exposures to zinc via denture cream was reported. This syndrome sometimes referred to as “Zinc swayback” is further described below.^{3,11,42,58}

CHEMISTRY

Zinc, a transition metal, has two common oxidation states, Zn^0 (elemental or metallic) and Zn^{2+} . The pure element exists as a blue to white shiny metal, but it also combines with other elements to form many compounds: zinc chloride (ZnCl_2), zinc oxide (ZnO), zinc sulfate (ZnSO_4), and zinc sulfide (ZnS). Once the metal is exposed to moisture, it becomes coated with zinc oxide or carbonate (ZnCO_3).⁸⁵

Like the other transition metals iron (Chap. 46) and copper (Chap. 95), zinc ions participate in reactions that result in the generation of reactive oxygen species such as superoxide radicals or hydroxyl radicals which can damage both local and remote tissues (Chap. 12).

PHARMACOLOGY AND PHYSIOLOGY

Zinc is an essential nutrient and found in more than 200 metalloenzymes, including acid phosphatase, alkaline phosphatase, alcohol dehydrogenase, carbonic anhydrase, superoxide dismutase, and DNA and RNA polymerases.⁸⁵ The average daily intake of zinc in the United States is 5.2 to 16.2 mg; foods that contain zinc include leafy vegetables (2 ppm), meats, fish, and poultry (29 ppm).⁸⁵ The recommended daily allowance is 11 mg/d for men and 8 mg/d for women. Pregnant and nursing women require 12 mg/d. Zinc accumulates in erythrocytes resulting in whole blood concentrations six to sevenfold higher than those in the serum.⁷² Zinc and copper concentrations generally have an inverse relationship in the serum with

elevated zinc concentrations resulting in decreased copper concentrations ([Chap. 95](#)).

Zinc contributes to gene expression and chelates with either cysteine or histidine in a tetrahedral configuration, forming looped structures known as “zinc fingers”, which bind to specific DNA regions.^{12,105} Other functions of zinc include membrane stabilization, vitamin A metabolism, and the development and maintenance of the nervous system. Zinc is considered important for fetal growth. When 29 pregnant mothers who were at risk for small for gestational age babies were given zinc citrate, zinc sulfate, or zinc aspartate, no intrauterine growth retardation was observed.⁹¹ Subsequent studies demonstrate that zinc supplementation in women with low serum zinc concentrations in early pregnancy is associated with greater infant birth weights and head circumferences.³⁷ No adverse reproductive effects were observed in a rodent model exposed to inhalational zinc oxide.⁶⁷

Zinc is important in maintaining olfactory and gustatory function ([Chap. 26](#)). Serum, urine, and salivary zinc concentrations are lower in patients with dysfunctional senses of smell or taste. This is thought to be related to an abnormality in a salivary growth factor known as gustin/carbonic anhydrase VI.⁴³ Because this enzyme is zinc dependent, oral zinc may produce subjective improvement in taste and smell in patients with a known decrease in parotid gustin/carbonic anhydrase VI complex.⁴⁴ Oral zinc sulfate also improved subjective findings in a group of 25 patients with post-traumatic olfactory disorders.⁶

Zinc gluconate supplementation when added to corticosteroid therapy was beneficial in patients with sudden sensorineural hearing loss when compared to corticosteroid treatment alone. The antioxidant and antiinflammatory affect on the cochlea is thought to be the mechanism for this benefit.¹⁰⁷

The role of zinc in the immune system is undefined. Zinc as a treatment for non-specific infectious diarrhea remains controversial.⁸⁰ However, it appears to be beneficial specifically in the management of *Shigella* spp by improving the shigellacidal antibody response and increasing circulating B lymphocyte and plasma cells.^{82,83}

Zinc gluconate and zinc acetate containing lozenges are sold as dietary supplements with conflicting evidence that they can shorten the duration of the “common cold.”^{50,66} One placebo-controlled study found that zinc nasal gel shortened the duration of viral syndromes when applied within 24 hours of the onset of symptoms.⁴⁵ A recent systematic review of the current literature concluded that zinc administration within 24 hours of onset of symptoms reduces the duration and severity of the common cold in healthy people. In addition, when supplemented for at least 5 months, it reduces cold incidence, school absenteeism, and prescription of antibiotics in children.⁹²

Zinc deficiency, or hypozincemia, is a well described clinical entity. It can be either inherited as an autosomal recessive pattern known as acrodermatitis enteropathica, or developed due to a defect in zinc absorption in the GI tract.⁷⁷ Those patients at risk for acquiring the disorder include patients who receive total parenteral nutrition without adequate zinc supplementation, patients who have undergone intestinal bypass procedures, those with Crohn disease, and premature infants with low zinc storage. A nationwide shortage of injectable zinc resulted in the development of dermatitis in the diaper region, perioral erosions, and bullae on the dorsal surfaces of the hands and feet in premature infants requiring parenteral nutrition due to severe cholestasis.¹ Excessive ingestion of phytates found in whole grains, legumes, nuts, and seeds may decrease zinc absorption.⁴⁰ Physical findings that suggest the diagnosis of zinc deficiency, regardless of etiology, include the triad of dermatitis (acral and perioral), diarrhea, and alopecia. Zinc salts in initial doses of 5 to 10 mg/kg/d of elemental zinc followed by maintenance doses of 1 to 2 mg/kg/d are highly effective. In fact, skin lesions typically heal within 2 to 4 weeks, and hair growth also restarts during this time frame.

The FDA approved zinc acetate in 1997 for maintenance therapy of Wilson disease, a disorder associated with copper overload.^{13,63} Its use in this disorder is related to the ability of zinc to induce the formation of metallothionein, which assists in the elimination of copper from the blood and body tissues ([Chap. 95](#)).⁷

TOXICOKINETICS AND PATHOPHYSIOLOGY

When ingested, the main site of zinc absorption is the jejunum, although absorption is reported to occur throughout the intestine by binding to metallothionein which is a zinc protein complex in the luminal cells.¹⁰⁴ Metallothionein is a family of specific metal binding proteins with diverse and complex functions considered essential to metal homeostasis. Metallothioneins are of low molecular weight (3500–14,000 Da) and are rich in thiol ligands; it is these ligands that allow high affinity binding to metals such as zinc, copper, cadmium, mercury, and silver. Metallothioneins essentially regulate the peripheral utilization of zinc and copper once they have been bound.³³ Excess zinc absorption leads to upregulation of metallothioneins as a counter regulatory mechanism to prevent excess plasma absorption. However, the affinity of other metals, especially copper, is higher for metallothionein, resulting in excessive copper elimination and hence decreased absorption. The primary route of excretion of the copper and zinc metallothionein complexes is fecal. In addition, sequestration of copper in the absorptive cells of the enterocytes may also play a role in the decreased peripheral utilization of copper.²⁴ Very little metallothionein is bound to zinc or copper in the blood as it is primarily an intracellular

cytosolic molecule.⁸ Albumin binds about two thirds of zinc in the plasma, and the remainder is bound to α_2 -globulins.⁸⁵ Zinc concentrations in the body show a great variability by organ, with the prostate having the highest amount due to its high concentration of the zinc-containing enzyme acid phosphatase.⁹

Zinc salts are used to enhance the solubility of pharmaceuticals such as insulin. Certain salts, such as zinc oxide, are used in baby powder, sun blocks, and topical burn preparations, and may be used on both latex and latex-free gloves. However, the use of oral zinc salts within 3 hours of cephalexin administration decreased peak serum concentrations, which is suggested to result from its inhibitory effects on intestinal transport peptides. The absorption of all β -lactam antibiotics may be altered as they are all dependent on these intestinal transport peptides.²⁶

CLINICAL MANIFESTATIONS

The toxicity of zinc is dependent on the route of exposure. Each zinc compound has similar toxic manifestations following oral and dermal exposure. However, they have unique inhalational toxicities. The metallic form of zinc is not toxic per se, and only the salt forms are considered here unless otherwise specifically mentioned.

Acute

The hallmark of acute oral zinc (Zn^{2+}) toxicity is gastrointestinal (GI) distress, including nausea, vomiting, abdominal pain, and gastrointestinal hemorrhage.⁹ In initial studies that evaluated the oral use of zinc sulfate (ZnSO_4) as an acne therapy, epigastric distress was noted in 33% of patients.^{28,36} Zinc chloride solutions in concentrations greater than 20% are particularly corrosive when ingested. Partial- and full-thickness burns to the oral mucosa, pharynx, esophagus, and stomach, as well as to the laryngotracheal tree, can occur even following small unintentional ingestions of zinc chloride by children.^{22,56,71} Delayed gastric stricture may occur after acute⁷¹ or chronic zinc chloride consumption.^{20,98} Pancreatitis was noted in a piglet model³⁴ and also in a 24 year-old man who inadvertently ingested liquid zinc chloride.²²

Hyperamylasemia, acute respiratory distress syndrome (ARDS), hypotension, vomiting, diarrhea, jaundice, anemia, thrombocytopenia, and subsequent death occurred following an unintentional intravenous infusion of 7.4 g of zinc sulfate (via total parenteral nutrition) over 60 hours. The patient's serum zinc concentration was 4184 $\mu\text{g/dL}$.¹³ A 14 week premature neonate received a 1000 fold increased concentration of zinc in her total parenteral nutrition. Rather than 330 $\mu\text{g/dL}$, she received 330 mg/dL, which resulted in hypotension, respiratory failure, and death despite the administration of CaNa_2EDTA .³⁸

Inhalational toxicity will often depend on the type of zinc compound involved in the exposure. The water solubility of the various zinc salts plays an important role in the extent and time to onset of pulmonary toxicity. The solubility of zinc chloride in water at 77°F (25°C) is 432 g/100 mL, whereas that of zinc oxide at 84°F (29°C) is 0.00016 g/100 mL.⁸⁵ Acute inhalation of zinc chloride from smoke bombs produces lacrimation, rhinitis, dyspnea, stridor, and retrosternal chest pain. Upper respiratory tract inflammation, and ARDS may occur, generally without renal or hepatic manifestations of systemic absorption.^{35,47,48,68} Morbidity and mortality increase when the exposure to a zinc chloride smoke bomb occurs in an enclosed space.⁸⁸ Of 70 individuals exposed to a zinc chloride smoke bomb in a tunnel during World War II, 10 died within 4 days. Ambient zinc concentrations in the tunnel were measured at 33,000 mg/m.^{3,30} Inhalation of zinc oxide, a far less water soluble zinc salt, is associated with metal fume fever ([Chap. 124](#)) and not pneumonitis or ARDS despite similar ambient zinc concentrations.⁹ See below for further discussion on metal fume fever.

Despite the importance of zinc in gustatory function, there appears to be an association of intranasal zinc use and anosmia.⁹³ Animal research suggests that intranasal zinc sulfate use can cause transient or persistent anosmia as a consequence of disruption of functional connections between the olfactory bulb and the olfactory epithelium.⁶⁹ Topical zinc sulfate is used experimentally in both rat and mouse models to induce anosmia.¹⁰² Multiple patients, ages 31 to 55 years, who developed a burning sensation after intranasal zinc gluconate application to the olfactory epithelium later developed either a long lasting or permanent anosmia and olfactory dysfunction.⁵³ The mechanism of zinc-induced hyposmia and anosmia is thought to be a direct result of proteolytic destruction of the olfactory receptor cells.²⁵

US pennies (91.5% Zn and 2.5% Cu) lodged in the distal esophagus release zinc ions following exposure to gastric acids and can damage the local esophageal tissue.¹⁷ The phenomenon of acid dissolution is demonstrated in animal⁴ and in vitro models.⁷⁴

Rare reports of renal complications exist. Hematuria was observed in a 24 year-old man who ingested liquid zinc chloride but whose kidney function remained otherwise normal.²² Intravenous zinc sulfate administration can result in acute tubular necrosis and acute kidney injury.¹³

Certain zinc salts, such as zinc oxide, found in baby powders and calamine lotion, are usually nonirritating for intact skin.⁵ Although older studies suggested the possibility of pruritic, pustular rashes in workers who are exposed to zinc

oxide, other causative factors, including personal hygiene, were not considered.¹⁰⁰ One case report describes urticaria and angioedema in a 34 year-old welder following contact with zinc oxides fumes at a smelting plant.³¹ The patient was asymptomatic once he was removed from the environment and had no further difficulty during the welding process when personal protective equipment was employed.

Chronic

Several individual cases report the significant implication of chronic zinc exposure. Chronic zinc toxicity following nutritional supplements and the ingestion of coins can produce a reversible sideroblastic anemia manifested by anemia and granulocytopenia associated with bone marrow-demonstrated vacuolated precursors and ringed sideroblasts.¹⁴ The mechanism for this reversible myelodysplastic syndrome appears to be a zinc-induced copper deficiency.³²

A 55 year-old schizophrenic patient with a 15 year history of pica typically of metal objects and frequently zinc containing pennies, presented with pancytopenia, including a hemoglobin of 3 g/dL and a white blood cell count of $1300/\text{mm}^3$. He had a serum zinc concentration of 280 $\mu\text{g/mL}$ and low serum copper concentration of $<0.05 \mu\text{g/mL}$.⁵⁷ The patient refused surgery to remove the coins, which formed a massive bezoar in his GI tract. The patient continued to ingest coins and ultimately died of sepsis and multiorgan failure. An autopsy revealed a coin mass weighing 1870 g in his stomach and another bezoar at the site of a sigmoid volvulus.

Over a 6 to 7 month period, a 17 year-old boy used significant doses of oral vitamins and mineral supplements containing zinc to treat acne and developed copper deficiency and anemia, leukopenia, and neutropenia.⁸⁷ A 28 month-old boy developed anemia, neutropenia, and developmental delay after 11 months of parental administration of 314 mg/d of oral zinc gluconate (3.6 mg/kg/d of elemental zinc).⁹⁶ Hyperzincemia and hypocupremia were present and improved after discontinuation of zinc without copper supplementation.

It is suggested that zinc and other transition metals may be important in the pathogenesis of demyelinating diseases.^{59,81} Clusters of cases of multiple sclerosis (MS) were described in northern New York in a factory where zinc was the primary occupational exposure. One hypothesis is that the allele frequency for transferrin (an iron-and zinc-binding protein) may differ in these MS subjects.^{89,95} Another cluster was found in Canada where excess metals, including zinc, were found in the soil and water.^{39,51,52} A conclusive link to MS, however, has not been established.

Since the prostate contains the highest concentration of zinc in the human body, the role of zinc in the development of prostate cancer has been investigated. Specifically, American men participating in the Health Professionals Follow-Up Study were followed for 14 years, from 1986 to 2000. Of the 46,974 in the cohort, 2901 new cases of prostatic cancer were diagnosed, with 434 of them considered to be in an advanced stage.⁶³ Men who used zinc supplementation at a dose $>100 \text{ mg/d}$ had a relative risk of 2.29 for advanced prostate cancer, and those using zinc for longer than 10 years had a relative risk of 2.37. Neither the International Agency for Research on Cancer (IARC) nor the Environmental Protection Agency (EPA) currently classify zinc as a carcinogen.

The Third National Health and Nutrition Examination Survey examined the association of higher dietary zinc intake on the risk of kidney stone disease. Dietary zinc intake of greater than 15 mg/d was associated with a significantly increased risk of kidney stones compared to those with a dietary zinc intake less than 7 mg/d. More rigorous studies are required to determine causality and a potential underlying mechanism for this association.⁹⁷

A neurologic syndrome of progressive myeloneuropathy called “swayback” is defined by a spastic gait, usually a prominent sensory ataxia, and hematologic manifestations.^{58,59,61,62} These cases involve patients with copper deficiency and typically elevated serum zinc concentrations. A history of excess zinc exposure is obtained in some but not all patients. The potential of an inherited zinc overload syndrome has been considered.⁴¹ A 46 year-old man presented with evidence of bone marrow suppression followed by sensory ataxia and a progressive myelopathy. His neuroimaging evaluation was normal. His only remarkable laboratory studies included an elevated serum zinc concentration of 184 $\mu\text{g/dL}$ (28.2 $\mu\text{mol/L}$) and a low copper concentration of $<10 \mu\text{g/dL}$ ($<1.57 \mu\text{mol/L}$). There was no known occupational exposure or supplementation of zinc by history. Although his copper deficit improved with copper therapy, hyperzincemia persisted for more than the 3 years that he was followed. More recently, an unusual source of high zinc concentrations was related to denture creams, which may contain as much as 34 g of zinc per gram of cream. Four patients with chronic exposure to excess denture cream developed neurological abnormalities in the setting of hyperzincemia with associated hypocupremia.⁷³ Multiple other reports have confirmed the relationship between denture cream, hyperzincemia, hypocupremia, and the development of this progressive myeloneuropathy. The history in these patients often reveals poor fitting dentures as well as use of dentures during sleep.^{3,11,42,94}

Patients with underlying Wilson disease are also at risk for chronic zinc overload syndromes due to treatment. Recent reports have raised increased concerns for the use of zinc in the treatment of Wilson disease with recommendations for more frequent monitoring of zinc and copper blood concentrations.^{49,84,106}

Chronic inhalation of zinc oxide can lower blood copper and serum calcium concentrations. However, no long term effect on ventilatory function or chest radiography is reported.²⁹

Occupational Exposures

Since 1983, the US penny is composed of 97.5% zinc and 2.5% copper.¹⁰¹ Zinc is widely used in industry because it enhances the durability of iron and steel alloys; it also is commonly used in construction. Galvanization involves coating an iron product with metallic zinc to prevent it from oxidizing (rusting). Electroplaters, smelters, jewelers, artists working on stained glass or sculpting metal, as well as aircraft manufacturing workers, are routinely exposed to zinc. Zinc chloride is an essential component of flux, which can be used for soldering of galvanized iron.

Zinc is present in drinking water and beverages stored in metal containers or that flow through pipes coated with zinc. Zinc concentrations in air are typically low; average zinc concentrations in the United States are $<1 \mu\text{g}/\text{m}^3$. Air concentrations near industrial zones can be higher, and may be substantially greater in certain occupational settings. The currently accepted occupational threshold limit value (TLV)-time-weighted average (TWA) is $1 \text{ mg zinc}/\text{m}^3$.⁸⁵

Metal Fume Fever

Metal fume fever typically occurs within 12 hours after an exposure to metal oxide fumes. Patients can develop fever, chills, cough, myalgias, muscle cramping, chest pain, dyspnea, dry throat, and a metallic taste in the mouth. Although exposure to zinc oxide fumes is the commonest zinc etiology, other zinc compounds may be implicated. The chest radiograph is often normal, but may show an infiltrate. Hypoxia and tachycardia are rare, but may occur. Overall, however, the syndrome is relatively benign, with tolerance developing within days.²⁹ An immune mechanism is suggested, and chronic exposure may lead to sensitization (Chap. 124).²³

DIAGNOSTIC TESTING

Because zinc is ubiquitous in the environment and laboratory, great care must be taken to avoid contamination of any samples intended for investigation.⁸⁵ Because elevated zinc concentrations cause copper deficiency, a serum copper and ceruloplasmin concentration should be obtained in patients with suspected zinc poisoning.

Urine zinc concentrations are not well defined. In a cohort of non-occupationally exposed patients, the mean urine concentrations were $450 \mu\text{g}/\text{L}$, with a maximum concentration up to $1300 \mu\text{g}/\text{L}$.⁷² In the United States, normal urine values are generally accepted as $<500 \mu\text{g}/\text{d}$. The National Institute for Occupational Safety and Health established detection limits in urine and blood or tissue as low as $0.1 \mu\text{g}$ per sample and $1 \mu\text{g}/100 \text{ g}$, respectively. Testing requires extraction of the metals from urine with polydithiocarbamate resin prior to digestion with concentrated acids and analysis.⁸⁵

Errors can be caused by incorrect sample collection, equipment malfunction or miscalibration, inadequate reagent purity, and atmospheric deposition. Zinc oxide powder in some gloves can contaminate specimens, as can the rubber stoppers in certain blood collection tubes. Specific tubes are recommended with negligibly low concentrations of trace elements.¹⁹ During sample analysis, laminar flow is recommended to prevent airborne particles from interfering.

Abdominal radiographs may play a role in determining the gastrointestinal burden of zinc, especially following ingestions of pennies. This may guide the decision to continue gastrointestinal decontamination in certain circumstances.¹⁶ (See Management below.)

Neuroimaging in patients with chronic zinc exposure and secondary copper deficiency may reveal characteristic findings. The MRI typically reveals increased T2 signal in the dorsal columns of the cervical spinal cord similar to that found in B_{12} deficiency.⁶⁰ These lesions are thought to represent Wallerian degeneration and demyelination of white matter. One case showed evidence of bilateral subcortical hyperintense T2 abnormalities on an MRI of the brain.⁷³ These findings are the result of copper deficiency and not necessarily zinc toxicity.

MANAGEMENT

Treatment for acute oral zinc (Zn^{2+}) toxicity is primarily supportive. Efforts should focus on hydration and antiemetic therapy. H_2 receptor antagonists or proton pump inhibitors may relieve abdominal discomfort when given for several days following the zinc salt ingestion.⁹

Gastrointestinal decontamination after zinc salt ingestion may include whole-bowel irrigation (WBI). A radiograph in a 16 year-old boy who ingested 50 (500 mg) zinc sulfate tablets noted no change in tablet position 4 hours after gastric emptying with induced emesis followed by orogastric lavage. Within one hour of institution of WBI therapy, zinc tablets were present in the rectal effluent.¹⁶ Zinc containing penny ingestion may provide a unique challenge. A schizophrenic patient required laparotomy and gastrotomy to remove a total of 275 coins.⁷⁶

The data regarding the efficacy of chelation therapy for zinc is limited in humans. Edetate calcium disodium

(CaNa₂EDTA) was used successfully in several cases, including a child⁷⁹ and a 24 year-old man who were exposed to zinc chloride as a component of soldering flux.²² The combination of CaNa₂EDTA and BAL (British anti-Lewisite) was used successfully in a 16 month-old 74 hours after ingestion.⁷¹

Both DTPA (diethylenetriaminepentaacetic acid) and EDTA (ethylenediaminetetraacetic acid) were effective in enhancing the urinary excretion of zinc in a rodent model of zinc acetate poisoning.²⁷ DTPA had its greatest antidotal efficacy when given within 30 minutes of the intraperitoneal injection of zinc acetate.⁶⁵ The urinary excretion of zinc increased 1.6-to 44-fold following a 3 mg/kg intravenous dose of DMPS (sodium 2,3-dimercaptopropane-1-sulfonate) in one human study where metal toxicity in patients with dental amalgams was the focus.⁹⁹ Two potential zinc-selective chelators, DPESA (4- {[2-(bis-pyridin-2-ylmethylamino) ethylamino]-methyl} phenylmethanesulfonic acid) sodium salt, as well as TPESA (4- {[2-bis-pyridin-2-ylmethylamino)ethyl]pyridine-2-ylmethylamino}-methyl)phenyl]methanesulfonic acid) sodium salt, rapidly chelate zinc in vitro, but further detailed in vivo studies are needed before their clinical use can be considered.⁵⁵ Finally, an iron chelator, deferiprone, was incidentally noted to cause decreased serum zinc concentrations when it was used to lower iron concentrations in patients with transfusion overload (Antidotes in Depth: A7).¹⁰³ A subsequent prospective trial showed enhanced urinary excretion of zinc in children with thalassemia major who had received multiple blood transfusions.¹⁰

Many of the clinical manifestations and metabolic effects of zinc toxicity are due to its ability to cause copper deficiency. In patients with zinc overload related copper deficiency, the supplementation of oral copper alone improved the hematopoietic effects and prevent further neurological deterioration without chelation therapy.⁸⁶

Though treatment with copper sulfate alone may be adequate for patients with neurological sequelae and mild hematopoietic effects, chelation may be required for patients with hemodynamic compromise or other consequential systemic manifestations. Limited experience exists with regard to treatment of these patients; however, 1000 mg/m²/d IV CaNa₂EDTA divided every 6 hours seems to be a reasonable choice based on case reports of successful use. The potential of BAL to increase copper elimination should limit its clinical use.

Intravenous N-acetylcysteine (NAC) increased the urinary zinc excretion in a patient who had inhaled zinc chloride fumes.⁷⁸ Two individuals with inhalational zinc chloride induced ARDS had simultaneous transient decreases in serum zinc concentrations and increases in urinary zinc excretion when treated with intravenous and nebulized NAC.⁴⁷ However, these individuals succumbed at days 25 and 32 after inhalation. Although an increase in urinary zinc excretion was noted in one rat model, 10 healthy volunteers who were treated with oral NAC for 2 weeks had no significant change in either their serum or urine zinc concentrations.⁴⁶ This therapy requires further study and cannot be recommended at this time.

Supportive care is used for patients with inhalational zinc exposures, including oxygen therapy and bronchodilators as clinically indicated, but these patients may necessitate ventilatory support in severe cases. Exposure to zinc oxide fumes by rescuers is minimal, although respiratory protective equipment should be worn.⁹⁰ In a case series of five soldiers exposed to zinc chloride smoke bombs during military training, the two individuals not wearing gas masks developed ARDS;⁴⁷ the others remained clinically well. A 23 year-old man developed severe ARDS after inhalation of zinc chloride from a smoke bomb during a military drill. After extensive ventilatory supportive efforts, tube thoracostomy, intravenous antibiotics, and intravenous corticosteroids, the patient continued to deteriorate. The patient was placed on extracorporeal life support (ECLS), weaned off the ventilator by day 30, and survived. If ECLS is available, it may be beneficial. More prospective studies are required to determine the extent of the benefit of ECMO.²¹

Metal fume fever is typically self limited. Nonsteroidal antiinflammatory drugs should be sufficient to relieve the transient discomfort. Personal protective equipment and or adequate engineering design and strategies may allow the individual to continue to work in the particular occupational site.

Dermal decontamination is paramount to prevent direct epidermal effects or systemic absorption of zinc salts.¹⁵ However, water should not be used to perform dermal decontamination of patients exposed to metallic zinc because zinc metal may ignite when wet. Treatment in these situations includes mechanical removal of any metallic particles with forceps and the application of mineral oil to the affected skin to protect the metal from ambient moisture.

SUMMARY

- Zinc exposures in humans occur as part of the diet, medicinal uses, nutritional supplements, and in occupational settings.
- The clinical manifestations of zinc toxicity include acute, life-threatening gastrointestinal and pulmonary effects, which are generally treated with supportive care.
- Chronic zinc toxicity manifests primarily as copper deficiency.
- Copper supplementation alone often corrects systemic manifestations.
- Chelation therapy may be considered in acutely life threatening circumstances.

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J. HOUSEHOLD PRODUCTS

CASE STUDY 8

History A 38 year-old woman was brought to the hospital directly from the airport because she complained of shortness of breath immediately after exiting the airplane. She had a history of depression and took amitriptyline and zolpidem and admitted to daily alcohol use. She also had a history of hypertension but did not recall the name of her medication. She reported that she was well prior to getting on the flight and only drank two beers about 6 hours apart. During the flight, she noted some abdominal and back pain, followed by difficulty breathing. She denied ingestions or suicidal ideations.

Physical Examination On arrival to the hospital she was noted to be severely short of breath with the following vital signs: blood pressure, 156/92 mm Hg; pulse, 140 beats/min; respiratory rate, 42 breaths/min; temperature, 98.2°F (36.8°C); oxygen saturation, 100% on a 100% non-rebreather mask. Her head was without signs of trauma, and her pupils were equally round and sluggishly reactive to light. Her neck was supple and her chest was clear. Her heart was tachycardic but regular, and without murmurs, rubs, thrills, or gallops. Her abdomen was soft with normal bowel sounds and no organomegally. She was slightly tender in all four quadrants, but without guarding or rebound. Her extremities were without clubbing, cyanosis, or edema, and a brief neurological examination was without deficit or focality.

Immediate Management The patient was immediately intubated, sedated with midazolam, and attached to a mechanical ventilator. A rapid bedside glucose was reported as 50 mg/dL, and she was given 25 g of D₅₀W and 100 mg of thiamine intravenously. An arterial blood gas revealed a pH of 6.80, a PCO₂ of 24 mm Hg, and a PO₂ of 106 mm Hg on room air. A CT scan of the chest was negative for pulmonary embolus. Standard laboratories are shown in [Table CS8–1](#).

Table CS8–1. Laboratory Analyses

Sodium mEq/L	Potassium mEq/L	Chloride mEq/L	Bicarbonate mEq/L	BUN mg/dL	Creatinine mg/dL	Glucose* mg/dL	Calcium mg/dL
149	3.4	104	5	14	1.4	124	8.9

* = These studies were obtained after D₅₀W was given.

What Is the Differential Diagnosis? The laboratory analysis shows a severe metabolic acidosis with elevated anion gap (40 mEq/L). Of the many mnemonics used to help recall the differential diagnosis, one of the most popular is MUDPILES (Methanol; Uremia; Diabetic and other ketoacidoses; Phenformin and metformin; Iron and isoniazid; Lactate; Ethylene glycol; Salicylates) (Chap. 19). It should be remembered that this is an imperfect mnemonic in that it is easy to forget cyanide, theophylline, and a number of other xenobiotics that are not directly noted.

What Clinical and Laboratory Analyses Can Help Identify the Etiology? A rapid clinical assessment will help to narrow the differential diagnosis. For example, iron poisoning is almost always associated with vomiting ([Chap. 46](#)), and isoniazid rapidly produces seizures ([Chap. 58](#)). Uremia can be excluded based on the BUN and creatinine. Likewise, the presentation glucose concentration helps diminish the probability of diabetic ketoacidosis.

At this point, additional rapid tests are useful. A urinalysis showing ketones would be helpful in cases of alcoholic ketoacidosis ([Chap. 80](#)) or salicylates ([Chap. 39](#)) and might show oxalate crystals or fluorescence following ethylene glycol poisoning ([Chap. 109](#)). A lactate concentration would be elevated in patients with metformin toxicity ([Chap. 53](#)) and might be falsely elevated from glycolate accumulation following ethylene glycol poisoning ([Chap. 109](#)). Additionally, most laboratories can determine salicylate concentrations rapidly. An ethanol concentration is exceedingly helpful in that it might be low in those with alcoholic ketoacidosis and if elevated essentially excludes methanol or ethylene glycol poisoning because it would be protective. Finally, if ethanol and methanol concentrations are not available, an osmol gap can be calculated, although caution is advised when interpreting the results ([Chap. 19](#)).

Further Diagnosis and Treatment Additional studies revealed the following: urine was negative for ketones and crystals; a serum lactate was 6 mmol/L; ethanol and salicylate concentrations were negative. Despite receiving fluids, thiamine, and glucose (empiric treatment for alcoholic ketoacidosis), the patient's metabolic acidosis persisted. Because of the severity of the anion gap acidosis and the lack of alternative diagnoses, a loading dose of fomepizole was administered (Antidotes in Depth: A30) for presumed toxic alcohol (methanol or ethylene glycol) ingestion. Intravenous hypertonic sodium bicarbonate was infused for presumed methanol poisoning (Antidotes in Depth: A5) as a repeat creatinine concentration was slightly improved prior to fomepizole administration making ethylene glycol

poisoning less likely ([Chap. 109](#)).

Nephrology was consulted for hemodialysis, and two 4 hour hemodialysis treatments were performed 8 hours apart. A second dose of fomepizole was given in between the hemodialysis treatments. After the second treatment, her anion gap was 8 mEq/L, and sedation was weaned. The patient was extubated easily a few hours later, and her mental status and neurologic examination were normal. The next day her presentation methanol concentration was reported from the reference laboratory as 45 mg/dL. A formal ophthalmology evaluation was unremarkable, and the patient was transferred to psychiatry.

104 ANTISEPTICS, DISINFECTANTS, AND STERILANTS

Paul M. Wax

INTRODUCTION

Joseph Lister, often considered the father of modern surgery, revolutionized surgical treatment and dramatically reduced surgical mortality by introducing the concept of antisepsis to the surgical theatre.⁴⁸ It was Lister’s understanding that microorganisms contributed to infection and sepsis from even the most trivial wounds that led to his search for chemicals that would prevent such infection. Lister demonstrated that phenol (carbolic acid), a chemical that was used to treat foul-smelling sewage, could be used to clean out dirty wounds of patients with compound fractures and dramatically increase survival rates. Soon thereafter, the use of phenol was expanded to surgical instrument cleaning and as a surgical hand scrub wash, ushering in the modern surgical era.

Antiseptics, disinfectants, and sterilants are a diverse group of germicides used to prevent the transmission of microorganisms to patients (Table 104–1). Although these terms are sometimes used interchangeably and some of these xenobiotics are used for both antisepsis and disinfection, the distinguishing characteristics between the groups are important to emphasize. An antiseptic is a chemical that is applied to living tissue to kill or inhibit microorganisms. Iodophors, chlorhexidine, and the alcohols (ethanol and isopropanol) are commonly used antiseptics. A disinfectant is a chemical that is applied to inanimate objects to kill microorganisms. Bleach (sodium hypochlorite), phenolic compounds, formaldehyde, hydrogen peroxide liquid, ortho-phthalaldehyde, and quaternary ammonium compounds are examples of currently used disinfectants. Neither antiseptics nor disinfectants have complete sporicidal activity. A sterilant is a chemical that is applied to inanimate objects to kill all microorganisms as well as spores. Ethylene oxide, glutaraldehyde, hydrogen peroxide gas, and peracetic acid are examples of sterilants. Not unexpectedly many of the xenobiotics used to kill microorganisms also demonstrate considerable human toxicity.^{5,18,68}

TABLE 104–1. Antiseptics, Disinfectants, Sterilants, and Related Xenobiotics

<i>Xenobiotic</i>	<i>Commercial Product</i>	<i>Use</i>	<i>Toxic Effects</i>	<i>Therapeutics and Evaluation</i>
Acids				
Boric acid	Borax Sodium perborate Dobell solution	Antiseptic Mouthwash Eyewash Roach powder	Blue-green emesis and diarrhea Boiled lobster appearance of skin CNS depression; kidney failure	GI decontamination Hemodialysis (rare)
Alcohols (Chaps. 80 and 109)				
Ethanol	Rubbing alcohol (70% ethanol)	Antiseptic Disinfectant	CNS depression Respiratory depression Dermal irritant	Supportive
Isopropanol	Rubbing alcohol (70% isopropanol)	Antiseptic Disinfectant	CNS depression Respiratory depression Ketonemia, ketonuria GI irritation/bleeding Hemorrhagic tracheobronchitis	Supportive Hemodialysis (rare)
Aldehydes				
Formaldehyde	Formalin (37% formaldehyde, 12%–15% methanol)	Disinfectant Fixative Urea insulation	Caustic CNS depression Carcinogen	Gastric lavage Hemodialysis Sodium bicarbonate Endoscopy Folinic acid Supportive
Glutaraldehyde	Cidex (2% glutaraldehyde)	Sterilant	Mucosal and dermal irritant	Supportive
Chlorinated Compounds				
Chlorhexidine	Hibiclens	Antiseptic	GI irritation	Supportive
Chlorates	Sodium chlorate Potassium chlorate	Antiseptic Matches Herbicide	Hemolytic anemia Methemoglobinemia Kidney failure	Exchange transfusion Hemodialysis
Chlorine		Disinfectant	Irritant	Supportive
Chlorophors (sodium hypochlorite)	Household bleach (5% NaOCl) Dakin solution (1 part 5% NaOCl, 10 parts H ₂ O)	Disinfectant Decontaminating solution	Mild GI irritation	Endoscopy (rare)
Ethylene Oxide		Sterilant Plasticizer	Irritant CNS depression Peripheral neuropathy Carcinogen?	Supportive
Mercurials (Chaps. 55 and 98)				
	Merbromin 2% (Mercurochrome)	Antiseptic (obsolete)	CNS	Gastric lavage, activated charcoal dimercaprol, succimer
	Thimerosal (Merthiolate)		Renal	
Iodinated Compounds				
Iodine	Tincture of iodine (2% iodine, 2% sodium iodide, and 50% ethanol) Lugol solution (5% iodine)	Antiseptic	Caustic	Milk, starch, sodium thiosulfate Endoscopy
Iodophors	Povidone-iodine (Betadine) (0.01% iodine)	Antiseptic	Limited	Same as iodine
Oxidants				
Hydrogen peroxide	H ₂ O ₂ , 3%—household H ₂ O ₂ , 30%—industrial	Disinfectant	Oxygen emboli GI caustic	Gastric lavage Radiographic evaluation Endoscopy
Potassium permanganate	Crystals, solution	Antiseptic	Oxidizer, caustic; increased serum manganese	Decontamination Endoscopy as needed

Phenols				
Nonsubstituted	Phenol (carbolic acid)	Disinfectant	Caustic Dermal burns Cutaneous absorption CNS effects	Decontamination: polyethylene glycol or water Endoscopy as needed
Substituted	Hexachlorophene	Disinfectant	CNS effects	Supportive
Quaternary Ammonium Compounds				
Benzalkonium chloride	Zephiran	Disinfectant	GI caustic	Consider endoscopy

The choice of disinfectant or sterilant depends on the degree of risk for infection involved in use of medical and surgical instruments and patient care items. Surgical instruments and cardiac and urinary catheters that enter the vascular system or other sterile tissues (so called critical items) must be cleaned with a sterilant while instruments that contact mucous membranes or nonintact skin such as GI endoscopes and laryngoscope blades (semicritical items) can be cleaned with a high level disinfectant (ortho-phthalaldehyde, 7.5% hydrogen peroxide). Noncritical items such as bedpans, blood pressure cuffs, crutches, and computers are those that come in contact with intact skin but not mucous membranes and can be cleaned with intermediate level and low level disinfectants (bleach or phenol). Whether a chemical is classified as a sterilant or disinfectant may depend on how it is used. Device sterilization with glutaraldehyde 3% requires a 10-hour cleaning cycle while high-level disinfection using the same chemical requires a 25 minute cleaning cycle.

The use of these xenobiotics evolved during the 20th century as their toxicity and the principles of microbiology became better understood. Two of the more toxic antiseptics—iodine and phenol—were gradually replaced by the less toxic iodophors and substituted phenols. The use of mercuric chloride was superseded by the organic mercurials (eg, merbromin, thimerosal), which also proved toxic. In recent years, newer xenobiotics, such as quaternary ammonium compounds, ethylene oxide, glutaraldehyde, and a peracetic acid-hydrogen peroxide mixture, are more extensively used.

ANTISEPTICS

Chlorhexidine

This cationic biguanide has been in use as an antiseptic since the early 1950s. It is found in a variety of skin cleansers, usually as a 4% emulsion (Hibiclens), and may also be found in mouthwash. Chlorhexidine is reported to have low toxicity.

Clinical Effects. Few cases of deliberate ingestion of chlorhexidine are reported. Symptoms are usually mild, and gastrointestinal irritation is the most likely effect after ingestion.²⁶ Chlorhexidine has poor enteral absorption. In one case, ingestion of 150 mL of a 20% chlorhexidine gluconate solution resulted in oral cavity edema and significant irritant injury of the esophagus.¹²³ In the same case, liver enzymes concentrations rose to 30 times normal on the fifth day after ingestion. Liver biopsy showed lobular necrosis and fatty degeneration. In another case, the ingestion of 30 mL of a 4% solution by an 89 year-old woman did not result in any GI injury.⁵⁰ An 80 year-old woman with dementia ingested 200 mL of a 5% chlorhexidine solution and subsequently aspirated.⁷⁸ She rapidly developed hypotension, respiratory distress, coma, and died 12 hours following ingestion.

Intravenous administration of chlorhexidine is associated with acute respiratory distress syndrome (ARDS),⁸⁷ and hemolysis, although the latter may be caused by the hypotonicity of the injected solution.²⁷ Inhalation of vaporized chlorhexidine causes methemoglobinemia, likely as a consequence of the conversion of chlorhexidine to p-chloraniline.¹⁹⁹ In one patient, the rectal administration of 4% chlorhexidine resulted in acute colitis with ulcerations.⁶⁷

Topical absorption of chlorhexidine is negligible. Contact dermatitis is reported in up to 8% of patients who received repetitive topical applications of chlorhexidine.⁶⁸ More ominously, anaphylactic reactions, including shock, are associated with dermal application.^{7,141} Some of these cases of chlorhexidine-related anaphylaxis occurred during surgery, appearing 15 to 45 minutes after application of the antiseptic.¹³ Eye exposure may result in corneal damage.¹⁹³

Management. Treatment guidelines for chlorhexidine exposure are similar to those for other potential caustics (Chap. 106). Patients with significant symptoms may require endoscopy, but the need for such extensive evaluation is quite uncommon.

Hydrogen Peroxide

Hydrogen peroxide, an oxidizer with weak antiseptic properties, has been used for many years as an antiseptic and a disinfectant.²⁰² This oxidizer is generally available in two strengths: dilute, with a concentration of 3% to 9% by weight (usually 3%), sold for home use, and concentrated, with a concentration greater than 10%, used primarily for industrial purposes. Commercial strength hydrogen peroxide is commonly found in solutions varying from 27.5% to 70%. Home uses

for dilute hydrogen peroxide include cerumen removal, mouth gargle, vaginal douche, enema, and hair bleaching. Dilute hydrogen peroxide is also sometimes used as a veterinary emetic. Commercial uses of the more concentrated solutions include bleaching and cleansing textiles and wool, and producing foam rubber and rocket fuel. A 35% hydrogen peroxide solution is also available to the general public in health food stores and is sold as “hyperoxygenation therapy” and as a health food additive to aerate health food drinks.⁸⁴ This potentially dangerous therapy is touted as a treatment for a variety of conditions, including AIDS and cancer.

Toxicity from hydrogen peroxide may occur after ingestion, inhalation, injection, wound irrigation, rectal administration, dermal exposure and ocular exposure.²⁰² Hydrogen peroxide has two main mechanisms of toxicity: local tissue injury and gas formation. The extent of local tissue injury and amount of gas formation are determined by the concentration of the hydrogen peroxide. Dilute hydrogen peroxide is an irritant, and concentrated hydrogen peroxide is a caustic. Gas formation results when hydrogen peroxide interacts with tissue catalase, liberating molecular oxygen, and water. At standard temperature and pressure, 1 mL of 3% hydrogen peroxide liberates 10 mL of oxygen, whereas 1 mL of the more concentrated 35% hydrogen peroxide liberates more than 100 mL of oxygen. Gas formation can result in life-threatening embolization. The ingestion of two sips of 33% hydrogen peroxide resulted in cerebral gas embolization and hemiplegia.¹⁶⁴ Gas embolization may be a result of dissection of gas under pressure into the tissues or of liberation of gas in the tissue or blood following absorption. The use of hydrogen peroxide in partially closed spaces, such as operative wounds, or its use under pressure during wound irrigation increases the likelihood of embolization.

Clinical Effects. Airway compromise manifested by stridor, drooling, apnea, and radiographic evidence of subepiglottic narrowing may occur.⁴³ The combination of local tissue injury and gas formation from the ingestion of concentrated hydrogen peroxide may cause abdominal bloating, abdominal pain, vomiting, and hematemesis.^{53,116} Endoscopy may show esophageal edema and erythema and significant gastric mucosal erosions.^{154,171}

Symptoms consistent with sudden oxygen embolization include rapid deterioration in mental status, cyanosis, respiratory failure, seizures, ischemic ECG changes, and acute paraplegia.^{55,112} A 2 year-old boy died after ingesting 120 to 180 mL of 35% hydrogen peroxide.²⁹ Antemortem chest radiography showed gas in the right ventricle, mediastinum, and portal venous system. Portal vein gas is also a prominent feature in other cases.^{53,84,147} Arterialization of oxygen gas embolization may result in cerebral infarction.¹⁷⁷ Encephalopathy with cortical visual impairment²³ and bilateral hemispheric infarctions detected by MRI imaging may occur after ingestion of concentrated hydrogen peroxide.⁸⁶ In a case of acute paraplegia after the ingestion of 50% hydrogen peroxide, MRI revealed discrete segmental embolic infarctions of the cervical and thoracic spinal cord as well as both cerebral hemispheres and left cerebellar hemisphere.¹¹²

Death from intravenous injection of 35% hydrogen peroxide is also reported.¹⁰⁵ The use of a concentrated hydrogen peroxide solution as part of a hair highlighting procedure resulted in a severe scalp injury including necrosis of the galea aponeurotica.¹⁷²

Clinical sequelae from the ingestion of dilute hydrogen peroxide are usually much more benign.^{43,75} Nausea and vomiting are the most common symptoms.⁴³ A whitish discoloration may be noted in the oral cavity. Gastrointestinal injury is usually limited to superficial mucosal irritation, but multiple gastric and duodenal ulcers, accompanied by hematemesis, and diffuse hemorrhagic gastritis are reported.^{75,129} Portal venous gas embolization may occur as a result of the ingestion of 3% hydrogen peroxide.^{30,129,158}

The use of 3% hydrogen peroxide for wound irrigation may result in significant complications. Extensive subcutaneous emphysema occurred after a dog bite to a human's face was irrigated under pressure with 60 mL of 3% hydrogen peroxide.¹⁶² Systemic oxygen embolism, causing hypotension, cardiac ischemia, and coma, resulted from the intraoperative irrigation of an infected herniorrhaphy wound.¹² Gas embolism, resulting in intestinal gangrene, was reported to occur following colonic lavage with 1% hydrogen peroxide during surgical treatment of meconium ileus.¹⁷⁵ Multiple cases of acute colitis are reported as a complication of administering 3% hydrogen peroxide enemas.¹²⁵ The use of 3% hydrogen peroxide as a mouth rinse is associated with the development of oral ulcerations.¹⁶¹ Ophthalmic exposures may result in conjunctival injection, burning pain, and blurry vision.^{43,124} Optic neuropathy including transient blindness (ability to visualize shadows only) and subsequent optic atrophy from possible inhalational of hydrogen peroxide is described.⁴⁴ Cough, wheezing, and shortness of breath is associated with occupational exposure to peracetic acid-hydrogen peroxide mixtures used to clean endoscopic equipment.³⁵

Diagnosis. A careful examination should be performed to detect any evidence of gas formation. A chest radiograph might reveal gas in the cardiac chambers, mediastinum, or pleural space. An abdominal radiograph might show gas in the GI tract or portal system and define the extent of bowel distension. MRI and CT scan might be useful for detecting brain and spinal cord lesions secondary to gas embolism.^{6,86,112} Endoscopic evaluation can help determine the extent of mucosal injury.¹⁵⁴

Management. The treatment of patients with hydrogen peroxide ingestions depends, to a large degree, on whether the patient has ingested a diluted or concentrated solution. Those with ingestions of concentrated solutions require expeditious

evaluation. Dilution with milk or water, although unstudied, is unlikely to be helpful. Nasogastric aspiration of hydrogen peroxide might be helpful if the patient presents immediately after ingestion. Induced emesis is contraindicated and activated charcoal offers no antidotal benefit. Patients with abdominal distension from gas formation should be treated with nasogastric suctioning. Those with clinical or radiographic evidence of gas in the heart should be placed in the Trendelenburg position to prevent gas from blocking the right ventricular outflow tract. Careful aspiration of intracardiac air through a central venous line may be attempted in patients in extremis.²⁹ Case reports suggest that hyperbaric therapy may be useful in cases of life-threatening gas embolization after hydrogen peroxide ingestion.^{53,84,112,131,147,199} Asymptomatic patients who unintentionally ingest small amounts of 3% hydrogen peroxide can be safely observed at home.

Iodine and Iodophors

Iodine is one of the oldest topical antiseptics.¹⁷³ Iodine usually refers to molecular iodine, also known as I₂, free iodine, and elemental iodine, which is the active ingredient of iodine-based antiseptics. The use of ethanol as the solvent, such as tincture of iodine, allows substantially more concentrated forms of I₂ to be available. I₂ and tincture of iodine ingestions are much less common than in the past as a result of the change in antiseptic use from iodine to iodophor antiseptics.⁴⁵

Iodophors have molecular iodine compounded to a high-molecular-weight carrier or to a solubilizing agent. Povidone-iodine (Betadine), a commonly used iodophor, consists of iodine linked to polyvinylpyrrolidone (povidone). Iodophors, which limit the release of molecular iodine and are generally less toxic, are the current standard iodine-based antiseptic preparations. Iodophor preparations are formulated as solutions, ointments, foams, surgical scrubs, wound-packing gauze, and vaginal preparations. The most common preparation is a 10% povidone-iodine solution that contains 1% “available” iodine (referring to all oxidizing iodine species), but only 0.001% free iodine (referring only to molecular iodine).^{18,68}

Iodine is used to disinfect medical equipment and drinking water. Iodine is effective against bacteria, viruses, protozoa, and fungi, and is used both prophylactically and therapeutically.³⁶ Iodine is cytotoxic and an oxidant. It is thought to work by binding amino and heterocyclic nitrogen groups, oxidizing sulfhydryl groups, and saturating double bonds. Iodine also iodinates tyrosine groups.⁶⁸

There may be significant systemic absorption of iodine from topical iodine or iodophor preparations.¹⁴⁹ Markedly elevated iodine concentrations occur in patients who receive topical iodophor treatments to areas of dermal breakdown, such as burn injuries.¹⁰² Significant absorption occurs when iodophors are applied to the vagina, perianal fistulas, umbilical cords, and the skin of low-birth-weight neonates.¹⁸⁴ The mucosal application of povidone-iodine during a hysteroscopy procedure resulted in acute kidney injury (AKI) that transiently required hemodialysis.¹⁷ A fatality following intraoperative irrigation of a hip wound with povidone-iodine is also reported.³⁷ In this latter case, the postmortem serum iodine concentration was 7000 µg/dL (normal: 5–8 µg/dL).

Clinical Effects. Problems associated with the use of iodine include unpleasant odor, skin irritation, allergic reactions, and clothes staining. Ingestion of iodine may cause abdominal pain, vomiting, diarrhea, GI bleeding, delirium, hypovolemia, anuria, and circulatory collapse. Severe caustic injury of the GI tract may occur. The ingestion of approximately 45 mL of a 10% iodine solution resulted in death from multisystem failure 67 hours after ingestion.⁴⁶ In another case, the ingestion of 200 mL of tincture of iodine containing 60 mg/mL iodine and 40 mg/mL potassium iodide in 70% v/v ethanol resulted in AKI and severe hemolysis.¹¹⁹

Reports of adverse consequences from iodophor ingestions are rare. In one case report, a 9 week-old infant died within 3 hours of receiving povidone-iodine by mouth.¹⁰⁰ In this unusual case, the child was administered 15 mL of povidone-iodine mixed with 135 mL of polyethylene glycol by nasogastric tube over a 3-hour period for the treatment of infantile colic. Postmortem examination showed an ulcerated and necrotic intestinal tract. A blood iodine concentration of 14,600 µg/dL was recorded. Significant toxicity from intentional ingestions of iodophors in adults is not documented.

Acid–base disturbances are among the most significant abnormalities associated with iodine and iodophors. Metabolic acidosis occurred in several burn patients after receiving multiple applications of povidone-iodine ointment.^{102,150} These patients had elevated serum iodine concentrations and normal lactate concentrations. The exact etiology of the acidosis remains unclear. Postulated mechanisms for the acidosis include the povidone-iodine itself (pH 2.43), bicarbonate consumption from the conversions of I₂ to NaI, and decreased renal elimination of H⁺ as a consequence of iodine toxicity.¹⁵⁰ Metabolic acidosis associated with a high lactate concentration after iodine ingestion likely reflects tissue destruction.³⁶

Electrolyte abnormalities also may occur following the absorption of iodine. A patient with decubitus ulcers who received prolonged wound care with povidone-iodine-soaked gauze developed hypernatremia, hyperchloremia, metabolic acidosis, and AKI.³⁷ The hyperchloremia was thought to be caused by a spurious elevation of measured chloride ions as a consequence of iodine’s interference with the chloride assay. This interference occurs on the Technicon STAT/ION autoanalyzer, but does not occur when the silver halide precipitation assay is used.³⁶ Spurious hyperchloremia from iodine (or iodide) may result in the calculation of a low or negative anion gap (Chap. 19).^{24,52}

Other problems associated with topical absorption of iodine-containing preparations are hypothyroidism (particularly in neonates),^{24,180} hyperthyroidism,^{160,165} elevated liver enzyme concentrations, neutropenia anaphylaxis,¹ and hypoxemia.³⁶ Because of the lack of consistency between iodine concentrations and symptomatology, and because many of these patients had significant secondary medical problems that may have accounted for their symptoms, the exact relationship between iodine absorption and the development of a specific clinical syndrome remains speculative. However, a clinical controlled trial that compared preterm infants exposed to either topical iodinated antiseptics or to chlorhexidine-containing antiseptics showed that the infants exposed to topical iodine-containing antiseptics were more likely to have higher TSH concentrations and elevated urine iodine concentrations than was the chlorhexidine group.¹⁰⁹

Contact dermatitis can result from repetitive applications of iodophors.¹²⁰ A dermal burn may result from the trapping of an iodophor solution under the body of a patient in a pooled dependent position or under a tourniquet.^{111,135}

Management. The patient who ingests iodine (I_2) requires expeditious evaluation, stabilization, and decontamination. Careful nasogastric aspiration and lavage may be performed to limit the caustic effect of the iodine if signs of perforation are absent. Irrigation with a starch solution will convert iodine to the much less toxic iodide and, in the process, turn the gastric effluent dark blue-purple. This change in color may serve as a useful guide in determining when lavage can be terminated. If starch is not available, milk may be a useful alternative. Instillation of 100 mL of a solution of 1% to 3% sodium thiosulfate can also be used to convert any remaining iodine to iodide. Early endoscopy may help assess the extent of the gastrointestinal injury.

Most patients with iodophor ingestion require only supportive management. The use of starch or sodium thiosulfate may be considered in symptomatic patients. Hemodialysis and continuous venovenous hemodiafiltration were used successfully to enhance elimination of iodine in a patient with CKD who had become iodine toxic and developed renal deterioration after undergoing continuous mediastinal irrigation with povidone-iodine.⁹⁵ The benefit of hemodialysis or continuous venovenous hemodiafiltration is unknown in patients with normal renal function and therefore not recommended.

Potassium Permanganate

Potassium permanganate ($KMnO_4$) is a violet water-soluble xenobiotic that is usually sold as crystals or tablets or as a 0.01% dilute solution.⁹² Historically, it was used as an abortifacient, urethral irrigant, lavage fluid for alkaloid poisoning, and snakebite remedy. Currently, potassium permanganate is most often used in baths and wet bandages as a dermal antiseptic, particularly for patients with eczema.

Potassium permanganate is a strong oxidizer, and poisoning may result in local and systemic toxicity.¹⁸² Upon contact with mucous membranes, potassium permanganate reacts with water to form manganese dioxide, potassium hydroxide, and molecular oxygen. Local tissue injury is the result of contact with the nascent oxygen, as well as the caustic effect of potassium hydroxide. A brown-black staining of the tissues occurs from the manganese dioxide. Systemic toxicity may occur from free radicals generated by absorbed permanganate ions.²⁰⁸

Clinical Effects. Following ingestion, initial symptoms include nausea and vomiting. Laryngeal edema and ulceration of the mouth, esophagus, and, to a lesser extent, the stomach, may result from the caustic effects. Airway obstruction and fatal gastrointestinal perforation and hemorrhage may occur.^{42,126,143} Esophageal strictures and pyloric stenosis are potential late complications.⁹⁸

Although potassium permanganate is not well absorbed from the GI tract, systemic absorption may occur, resulting in life-threatening toxicity. Systemic effects include hepatotoxicity, AKI, methemoglobinemia, hemolysis, hemorrhagic pancreatitis, airway obstruction, ARDS, disseminated intravascular coagulation, and cardiovascular collapse.^{107,118,126,143} Elevation in blood or serum manganese concentration may also occur, confirming systemic absorption (normal concentrations blood manganese 3.9–15.0 $\mu g/L$; serum manganese 0.9–2.9 $\mu g/L$).

Chronic ingestion of potassium permanganate may result in classic manganese poisoning (manganism) characterized by behavioral changes, hallucinations, and delayed onset of parkinsonianlike symptoms. A 66-year-old man who mistakenly ingested 10 g of potassium permanganate instead of potassium iodate over a 4-week period (because of medication mislabeling) developed impaired concentration and autonomic and visual symptoms. He also developed abdominal pain, gastric ulceration, and alopecia. Serum manganese concentration was elevated. Nine months later, the patient's neurologic examination displayed extrapyramidal signs consistent with parkinsonism (**Chap. 97**).⁸²

Management. Because the consequential effects of potassium permanganate ingestion are a result of its liberation of strong alkalis, the initial treatment of such a patient should include assessment for evidence of airway compromise. Dilution with milk or water may be useful. Patients with symptoms consistent with caustic injury should undergo early upper GI endoscopy.⁹² Corticosteroids along with antibiotics may be warranted if laryngeal edema is present. Analysis of liver enzymes, BUN, creatinine, lipase, serum manganese, and methemoglobin concentrations should be performed when systemic toxicity is suspected. Methemoglobinemia, if clinically significant, should be treated with methylene blue (**Antidotes in Depth: A42**). Dermal irrigation with dilute oxalic acid may be successful in removing cutaneous staining.¹⁸² The administration of N-acetylcysteine (**Antidotes in Depth: A3**) to increase reduced glutathione production, thereby

limiting free radical–mediated oxidative injury in cases of systemic potassium permanganate poisoning, has been suggested, but clinical trials have not been performed.²⁰⁸

OTHER ANTISEPTICS

Alcohols

Isopropanol and ethanol (Chaps. 80 and 109) are commonly used as skin antiseptics. When sold as rubbing alcohol, the standard concentration for these solutions is usually 70%. In recent years, alcohol-based hand sanitizers containing 60% to 95% ethyl or isopropyl alcohol have become ubiquitous throughout patient care units, jails, and some public buildings as a primary infection control measure. Their antiseptic action is thought to be a result of their ability to coagulate proteins.

Isopropanol is slightly more germicidal than ethanol.⁶⁸ The alcohols have limited efficacy against viruses or spores.

Isopropanol tends to be more irritating than ethanol and may cause more pronounced central nervous system depression.²⁰⁰

Unfortunately readily available alcohol-based sanitizer may be a tempting source for patients admitted with alcohol abuse disorders.^{49,204} In a recent report a patient was admitted to the hospital with chest pain. While in the hospital the patient became hypotensive and delirious. He was later found in the bathroom drinking an alcohol-based hand wash that contained 63% isopropanol.⁴⁹ The clinical effects and treatment for alcohol poisoning are discussed in Chaps. 80 and 109.

Chlorine and Chlorophors

Chlorine, one of the first antiseptics, is still used in the treatment of the community water supply and in swimming pools. Chlorine is a potent pulmonary irritant that can cause severe bronchospasm and acute lung injury. Chapter 124 contains a further discussion of chlorine.

Sodium hypochlorite (NaClO), found in household bleaches and in Dakin solution, remains a commonly used disinfectant. First used in the late 1700s to bleach clothes, its usefulness arises from its oxidizing capability, measured as “available chlorine,” and its ability to release hypochlorous acid (HClO) slowly. It is used to clean blood spills and to sterilize certain medical instruments. A 0.5% hypochlorite solution is sometimes recommended for dermal and soft-tissue wound decontamination after exposure to biologic and chemical warfare agents (Chaps. 132 and 133).⁸⁵ Toxicity from hypochlorite is mainly a result of its irritant effects. The ingestion of large amounts of household liquid bleach (5% sodium hypochlorite) on rare occasions can result in esophageal burns with subsequent stricture formation.⁵⁴ In a cat model of bleach ingestion, a high incidence of mucosal injury and stricture formation was noted.²⁰³ However, the vast majority of household bleach ingestions in humans do not cause significant GI injuries.¹⁵¹ Accordingly, endoscopic evaluation is usually not warranted when assessing most patients with household liquid bleach ingestions. The ingestion of a more concentrated “industrial strength” bleach preparation (eg, 35% sodium hypochlorite) increases the likelihood of local tissue injury and should be managed accordingly (Chap. 106).

Mercurials

Both inorganic mercurials, such as mercuric bichloride (HgCl_2), and organic mercurials, such as merbromin ($\text{C}_{20}\text{H}_8\text{Br}_2\text{HgNa}_2\text{O}_6$) (mercurochrome) and thimerosal ($\text{C}_9\text{H}_9\text{HgNaO}_2\text{S}$) (merthiolate), which both contain 49% mercury, were used in the past as topical antiseptic agents. The usefulness of mercurials is significantly limited because of their relatively weak bacteriostatic properties and the many problems associated with mercury toxicity (Chap. 98). Repeated application of topical mercurials may result in significant absorption and systemic toxicity.^{132,166} The use of high-dose hepatitis B immunoglobulin (HBIG) may cause mercury toxicity because of the use of thimerosal as a preservative in the HBIG preparation.¹¹⁴ In one case, a 44 year-old man received 250 mL of HBIG (containing about 30 mg of thimerosal) over 9 days following liver transplantation.¹¹⁴ He developed speech difficulties, tremor, and chorea. His whole blood mercury concentration was 104 $\mu\text{g/L}$ (normal $<10 \mu\text{g/L}$). Increased mercury concentrations in both preterm and term infants, following immunizations with thimerosal-containing hepatitis B vaccine, have also generated much concern and led to the call to reduce or eliminate the mercury content of vaccines.^{64,184}

DISINFECTANTS

Formaldehyde

Formaldehyde is a water-soluble, highly reactive gas at room temperature. Formalin consists of an aqueous solution of formaldehyde, usually containing approximately 37% formaldehyde and 12% to 15% methanol. Formaldehyde is irritating to the upper airways, and its odor is readily detectable at low concentrations. Lethality in adults may follow ingestion of as little as 30 to 60 mL of formalin.⁴⁷

Formerly used as a disinfectant and fumigant, its role as a disinfectant is now largely confined to the disinfection of hemodialysis machines. Nonetheless, formaldehyde has many other applications. Formaldehyde is widely used in construction including the wood processing and the manufacturing of furniture, textiles, and carpeting.⁹⁶ Health care workers are probably most familiar with the use of formaldehyde as a tissue fixative and embalming agent. Medical students are routinely exposed to formalin in the anatomy laboratory.¹⁵⁹

Exposure to formaldehyde, a potent caustic, may result in both local and systemic symptoms, causing coagulation necrosis, protein precipitation, and tissue fixation. Ingestions of formalin may result in significant gastric injury, including hemorrhage, diffuse necrosis, perforation, and stricture.^{3,11} The most extensive damage appears in the stomach, with only occasional involvement of the small intestine and colon.²⁰⁷ Chemical fixation of the stomach may occur. Esophageal involvement is not very prominent, and, if present, is usually limited to its distal segment.

The most striking and rapid systemic manifestation of formaldehyde poisoning is metabolic acidosis, resulting both from tissue injury and from the conversion of formaldehyde to formic acid. The patient may present with profound acidemia, accompanied by a large anion gap. Although the methanol component of the formalin solution is readily absorbed and has resulted in methanol concentrations as high as 40 mg/dL,^{22,47} the rapid metabolism of formaldehyde to formic acid appears to be responsible for much of the acidosis (Chap. 109).

Clinical Effects. Patients presenting after formalin ingestions complain of the rapid onset of severe abdominal pain, which may be accompanied by vomiting and diarrhea. Altered mental status and coma usually follow rapidly. Physical examination may demonstrate epigastric tenderness, hematemesis, cyanosis, hypotension, and tachypnea. Hypotension may be profound with decreased myocardial contractility, as well as hypovolemic shock, contributing to the cardiovascular instability.^{77,191} Early endoscopic findings include ulceration, necrosis, perforation, and hemorrhage of the stomach, with infrequent esophageal involvement. Chemical pneumonitis occurs after significant inhalational exposure.¹⁵³ Intravascular hemolysis is described in hemodialysis patients whose dialysis equipment contained residual formaldehyde after undergoing routine cleaning.^{145,157}

Occupational and environmental exposure to formaldehyde receives considerable attention. In particular, there is concern over the potential off-gassing of formaldehyde from the widely used urea formaldehyde building insulation and particle boards.¹⁴² Headache, nausea, skin rash, sore throat, nasal congestion, and eye irritation are associated with the use of these polymers.³⁹ Formaldehyde, at concentrations as low as 1 ppm, may cause significant irritation to mucous membranes of the upper respiratory tract and conjunctivae.^{81,113} Formaldehyde is also a potential sensitizer for immune-mediated reversible bronchospasm.⁷⁴ The exact immunologic mechanism is not yet elucidated, although it is likely that formaldehyde acts as a hapten. In addition, formaldehyde is thought to be a dermal sensitizer.¹⁸¹

Concerns about the health effects from the off-gassing of formaldehyde in trailers used by the Federal Emergency Management Agency (FEMA) after Hurricane Katrina illustrates the potential public health issues related to low-level formaldehyde exposure.¹¹⁷ A Center for Disease Control (CDC) investigation revealed that air formaldehyde concentrations in closed, unventilated trailers are, in fact, high enough to cause acute symptoms in some people.⁴ Long term effects after these exposures remain undefined.

Both animal and human data suggest that formaldehyde exposure is associated with an increased incidence of nasopharyngeal carcinoma.^{2,70,148,167} Although its role in the pathogenesis of cancer in humans has been the subject of much debate,^{32,121} the International Agency for Research on Cancer (IARC) classifies formaldehyde as a Group 1, known, carcinogen.

Management. The immediate management of a patient who has ingested formalin includes dilution with water. Although such an approach may be useful in reducing the caustic effect, strong evidence for a beneficial result is lacking. Gastric aspiration with a small-bore nasogastric tube may limit systemic absorption. The role of activated charcoal is not studied, and it probably should not be used if endoscopy is considered likely. Significant acidemia should be treated with sodium bicarbonate and folinic acid (Chap. 109). Immediate hemodialysis may remove the accumulating formic acid as well as the parent molecules, formaldehyde, and methanol.⁴⁷ Independent treatment for methanol toxicity may be indicated (Antidotes in Depth: A30 and A31). Early endoscopy is recommended for all patients with significant GI symptoms to assess the degree of burn injury. Surgical intervention may be required for those with suspected severe burns and/or perforation.²⁰⁷ Emergent gastrectomy, as well as late surgical intervention to relieve formaldehyde induced gastric outlet obstruction, is infrequently required.^{71,99}

Phenol

Phenol, also known as carbolic acid, is one of the oldest antiseptics. It is rarely used as an antiseptic today, secondary to its toxicity, and has been replaced by the many phenolic derivatives. Currently, phenol is used as a disinfectant, chemical intermediary, and nail cauterizer. The last application uses a highly concentrated 89% solution. Phenol is also a component (0.1%–4.5%) of various lotions, ointments, gels, gargles, lozenges, and throat sprays.⁶⁸ Campho-Phenique and Chloraseptic

contain 4.7% and 1.4% phenol, respectively. Although many cases of phenol poisoning were reported in the past, acute oral overdoses of phenol containing solutions are uncommon today.⁶⁰

Phenol acts as a caustic causing cell wall disruption, protein denaturation, and coagulation necrosis. It also acts as a central nervous system (CNS) stimulant. Intentional ingestion of concentrated phenol, ingestion of phenol-containing water, occupational exposure to aerosolized phenol, dermal contact, and parenteral administration may all result in symptomatic phenol poisoning. Phenol demonstrates excellent skin penetrance.¹⁵ Severe dermal burns from phenol have resulted in systemic toxicity, even death within minutes to hours.^{15,106} Parenteral administration of phenol has also resulted in death. The lethal oral dose may be as little as 1 g.⁸³

Clinical Effects. Clinical manifestations can be divided into local and systemic symptoms. Systemic symptoms from gastrointestinal (GI) or dermal absorption of phenol are usually more dangerous than the local effects. Manifestations of systemic toxicity include CNS and cardiac symptoms. CNS effects include central stimulation, seizures, lethargy, and coma.⁶³ In a study of patients who had ingested Creolin (26% phenol), CNS symptoms predominated.¹⁸³ Of the 52 patients who were evaluated at the hospital, 9 developed lethargy and 2 developed coma. Seizures were not reported. Cardiac symptoms from phenol include tachycardia, bradycardia, and hypotension.⁶³ Parenteral absorption of 10 mL concentrated 89% phenol resulted in hypoxemia, ARDS, pulmonary nodular opacities, and AKI requiring intubation and hemodialysis.⁶² This last case was associated with a phenol concentration of 87 mg/dL (normal <2 mg/dL).

Other systemic symptoms that may develop include hypothermia, metabolic acidosis, methemoglobinemia, and rabbit syndrome.^{83,93} Rabbit syndrome is most commonly observed as a distinctive extrapyramidal effect from antipsychotic drugs and is characterized by fine rapid repetitive movements of the perioral musculature resembling a rabbit's chewing movements. Increased acetylcholine release and a relative dopaminergic hypofunction may explain the development of rabbit syndrome after phenol exposure.⁹³

Local toxicity to the GI tract from the ingestion of phenol may result in nausea, painful oral lesions, vomiting, bloody diarrhea, dark urine, and severe abdominal pain.^{8,91} Serious GI burns are uncommon, and strictures are rare. White patches in the oral cavity may be detected. In the Creolin study cited above, only 1 of 17 patients who underwent endoscopy had a significant esophageal burn.¹⁸³ Dermal exposures to phenol usually result in a light-brown staining of the skin. Excessive dermal absorption of phenol during chemical peeling procedures is associated with dysrhythmias and many of the other symptoms.^{196,201}

Markedly elevated blood and urine concentrations of phenol may be detected after ingestion, or dermal absorption, of phenol and phenol-containing compounds (eg, Campho-Phenique).^{15,83}

Management. When phenol is mixed with water, a bilayer with unique properties is created that makes it difficult to remove from tissues. A variety of treatments have been suggested for dermal and gastric decontamination of phenol. A study using a rat model showed that cutaneous decontamination with a low-molecular-weight polyethylene glycol solution decreased mortality, systemic effects, and dermal burns.²¹ Although this study suggested that polyethylene glycol (PEG) was superior to water as a decontamination agent, a subsequent study using a swine model could not demonstrate a difference between these two therapies.¹⁵⁶ In another swine model, PEG 400 and 70% isopropanol were both superior to water washes and equally effective in decreasing dermal burn.¹²⁸ Given the lack of definitive efficacy data, either low-molecular-weight PEG, for example, PEG 300 or 400 (not to be confused with high-molecular-weight PEG that is used for whole-bowel irrigation), or high flow water is currently recommended for dermal irrigation and careful gastric decontamination. Isopropanol could also be considered as another treatment for dermal decontamination. Endoscopic evaluation, as needed to determine the extent of GI injury, and good supportive care are also recommended.

Substituted Phenols and Other Related Compounds

Hexachlorophene (pHisoHex), a trichlorinated bis-phenol, is considered generally less tissue-toxic than phenol. During the 1970s, an association was observed between repetitive whole-body washing of premature infants with 3% hexachlorophene and the development of vacuolar encephalopathy and cerebral edema.¹²² There were also multiple reports of significant neurologic toxicity and death in children who became toxic after ingesting hexachlorophene.⁷⁶ In addition, fatalities also occurred after patients absorbed substantial amounts of hexachlorophene during the treatment of burn injuries.²⁸ The use of hexachlorophene has declined significantly.

Clinical Effects. pHisoDerm contains sodium octylphenoxyethoxyethyl ether sulfonate and lanolin, and is a safe antiseptic. Irritative effects (nausea, vomiting, diarrhea) would be the main adverse effects with ingestions.

In a study of poisoning admissions to Hong Kong hospitals, the ingestion of Dettol liquid, a household disinfectant that contains 4.8% chloroxylenol, 9% pine oil, and 12% isopropanol, accounted for 10% of admissions.²⁵ Aspiration (perhaps, in part, because of the pine oil) occurred in 8% of these patients, resulting in upper airway obstruction, pneumonia, and acute respiratory distress syndrome. More common symptoms included nausea, vomiting, sore mouth, sore throat, drowsiness, abdominal pain, and fever. Dermal contact with Dettol may result in full-thickness chemical burns.⁴⁰

Cresol, a mixture of three isomers of methylphenol, has better germicidal activity than phenol and is a commonly used disinfectant. Exposure to concentrated cresol may result in significant local tissue injury, hemolysis, AKI, hepatic injury, and CNS and respiratory depression.^{40,69,94,206} Phenol concentrations, as well as cresol concentrations, serve as markers of exposure.²⁰⁶

Management. Treatment is mainly supportive.

Quaternary Ammonium Compounds

Quaternary ammonium compounds, positively charged compounds where four organic groups are linked to a nitrogen atom (NR^{4+}), are a type of cationic surfactant (surface-active agent) that are used as disinfectants, detergents, and sanitizers. Chemically, the quaternary ammonium compounds are synthetic derivatives of ammonium chloride, and structurally similar to other quaternary ammonium derivatives, such as carbamate cholinesterase inhibitors and neuromuscular blockers. Other cationic surfactants include the pyridinium compounds and the quinolinium compounds. Benzalkonium chloride (Zephiran) was one of the most commonly employed quaternary ammonium compounds in the past. Many newer quaternary ammonium compounds have supplanted its use. However, nebulized solutions used for the treatment of asthma, including albuterol and ipratropium bromide, may contain small amounts of benzalkonium chloride.

Clinical. Quaternary ammonium compounds are usually less toxic than phenol or formaldehyde. Most of the infrequent complications that are described result from ingestions of benzalkonium chloride. Complications of these ingestions include burns to the mouth and esophagus, CNS depression, elevated liver enzyme concentrations metabolic acidosis, and hypotension.^{79,140,198} Paralysis is also occasionally described as a complication of these ingestions and is presumably a result of cholinesterase inhibition at the neuromuscular junction.⁶⁰ Chronic inhalational exposure is associated with occupational asthma.¹⁶ Topical use of the quaternary ammonium compounds can cause contact dermatitis.¹⁷⁸ Ingestion of a 2.25% ammonium chloride solution marketed as a bacteriostatic algae and odor humidifier treatment resulted in serious gastrointestinal and pulmonary injury.⁶⁶

Ingestions of other cationic surfactants, such as the pyridinium agent cetrymonium bromide (Cetrimide), are associated with caustic burns to the mouth, lips, and tongue.¹³⁰ Peritoneal irrigation with cetrymonium bromide can produce metabolic abnormalities, hypotension, and methemoglobinemia.^{9,127} Intravenous administration of cetrimide produced cardiac arrest, hemolysis, and muscle paralysis.⁵⁶

Management. Treatment recommendations following the ingestion of the quaternary ammonium compounds and other cationic surface-active agents are similar to those for other potentially caustic ingestions. Emergency department evaluation should be considered for all patients who ingest more than a taste of a dilute (less than 1%) solution. Therapy is mainly supportive. Endoscopy may be warranted if symptoms suggest the possibility of a burn injury.

STERILANTS

Ethylene Oxide

Ethylene oxide ($\text{C}_2\text{H}_4\text{O}$) is a gas that is commonly used to sterilize heat-sensitive material in health care facilities. Unlike antiseptics and disinfectants, which generally do not exhibit full sporicidal activity, sterilants, such as ethylene oxide, inactivate all organisms. Ethylene oxide is also used in the synthesis of many chemicals, including ethylene glycol, surfactants, rocket propellants, and petroleum demulsifiers, and has been used as a fumigant. Ethylene oxide has a cyclic ester structure that acts as an alkylating agent, reacting with most cellular components, including DNA and RNA.

Medical attention regarding ethylene oxide toxicity has centered on its mutagenic and possible carcinogenic effects.¹⁰¹ Approximately 270,000 workers (including 96,000 hospital workers) in the United States are at risk for occupational exposure to ethylene oxide.¹⁸⁷ Retrospective studies suggest a possible excess incidence of leukemia and gastric cancer in ethylene oxide exposed workers.^{80,187} These studies are inconclusive, and the carcinogenicity of ethylene oxide remains subject to debate. It is also suggested that an increased incidence of spontaneous abortions may be associated with occupational exposure to ethylene oxide.⁷³

Clinical Effects. The acute toxicity of ethylene oxide is mainly the result of its irritant effects. Conjunctival, upper respiratory tract, GI, and dermal irritation may occur. Dermal burns from acute exposure to ethylene oxide are reported. Acute exposure to a broken ethylene oxide ampule by a 43 year-old recovery room nurse resulted in nausea, lightheadedness, malaise, syncope, and recurrent seizures.¹⁷⁰ There were no long-term complications. In another case of acute exposure, coma was followed by an irreversible parkinsonism.¹⁰

Chronic exposure to high concentrations of ethylene oxide may cause mild cognitive impairment and motor and sensory neuropathies.^{20,61,139} The risk of cancer with occupational exposure is low.^{31,186,192}

Management. Treatment for patients with ethylene oxide exposure is supportive.

Glutaraldehyde

Glutaraldehyde is a liquid solution used in the cold sterilization of nonautoclavable endoscopic, surgical, and dental equipment. It is also employed as a tissue fixative, embalming fluid, preservative, and tanning agent, in radiographic solutions, and in the treatment of warts.⁵⁸ Glutaraldehyde ($C_5H_8O_2$) is a dialdehyde with two active carbonyl groups that is less volatile than formaldehyde. It kills all microorganisms, including viruses and spores. The germicidal ability of glutaraldehyde results from the alkylation of sulfhydryl, hydroxyl, carboxyl, and amino groups, within microbes interfering with RNA, DNA, and protein synthesis.¹⁶⁹ It is prepared as a 2% alkaline solution in 70% isopropanol (Cidex). Health care workers may be exposed to glutaraldehyde vapors when equipment is processed in poorly ventilated areas, or in open immersion baths or after spills. Under these circumstances, the evaporation of glutaraldehyde may result in the increase in ambient air concentrations that may easily exceed recommended limits. Approximately 35,000 workers are occupationally exposed to glutaraldehyde.¹⁵² Patients may be exposed when diagnostic instruments are inadequately rinsed following cold sterilization with glutaraldehyde.

Clinical. Clinical signs and symptoms are thought to be comparable to those of formaldehyde exposure, although human toxicity data are limited. Animal studies show that the inhalational and dermal toxicity of glutaraldehyde are comparable to those of formaldehyde at equivalent doses.¹⁹⁰

Glutaraldehyde is a mucosal irritant. Coryza, epistaxis, headache, asthma, chest tightness, palpitations, tachycardia, and nausea are all associated with glutaraldehyde vapor exposure.^{14,33,136,146} Occupational asthma, contact dermatitis, and ocular inflammation may also occur.^{38,144,174} Colitis is reported following the use of endoscopes contaminated with residual glutaraldehyde solution.¹⁷⁶ Patients with glutaraldehyde induced colitis typically present with fever, chills, severe abdominal pain, bloody diarrhea, and an elevated white blood cell count blood within 48 hours after colonoscopy or sigmoidoscopy.

The IARC has not ranked the carcinogenic potential of glutaraldehyde.

Management. Treatment recommendations are similar to those for patients with formaldehyde exposure. Prompt removal from the exposure is essential. Copious irrigation with water provides adequate dermal decontamination. Severe inhalational exposures may require hospital admission for observation, supportive care, and treatment of bronchospasm.

In recent years, some hospitals have started using ortho-phthalaldehyde (OPA) or a mixture of hydrogen peroxide and peracetic acid as alternatives to glutaraldehyde for high-level disinfection.¹⁶³ These alternative disinfectants do not appear to have the pulmonary or dermal sensitizing properties associated with glutaraldehyde, although they may still cause some irritation to skin and mucus membranes.¹⁶³

OTHER PRODUCTS

Boric Acid

Boric acid is an odorless, transparent crystal, although it is most commonly available as a finely ground white powder. It is also available as a 2.5% to 5% aqueous solution. Boric acid (H_3BO_3), prepared from borax (sodium borate; $Na_2B_4O_7 \cdot 10 H_2O$), was first used as an antiseptic by Lister in the late 19th century. Although used extensively over the years for antiseptics and irrigation, boric acid is only weakly bacteriostatic. As a result of its germicidal limitations and its inherent toxicity, boric acid is nearly obsolete in modern antiseptic therapy. Nonetheless, it continues to be used as an antimicrobial to treat such conditions as vulvovaginal candidiasis.¹⁵⁵ Boric acid is also employed in the treatment of cockroach infestation and as a soap, contact lens solution, toothpaste, and food preservative.⁶⁵

Boric acid is readily absorbed through the GI tract, wounds, abraded skin, and serous cavities. Absorption does not occur through intact skin. Boric acid is predominantly eliminated unchanged by the kidney. Small amounts are also excreted into sweat, saliva, and feces.⁵⁷ Boric acid is concentrated in the brain and liver.

The exact mechanism of action of toxicity remains unclear. Although it is an inorganic acid, it does not behave as a caustic. Local effects are limited to tissue irritation.

Over the years, boric acid has developed a reputation as an exceptionally potent toxin. This reputation was derived in great part from a series of reports involving neonatal exposures to boric acid resulting in high morbidity and mortality. Life threatening toxicity resulted from the repetitive topical application of boric acid for the treatment of diaper rash or the use of infant formulas unintentionally contaminated with boric acid.^{57,205} Fatality rates greater than 50% were reported in some series.²⁰⁵ Although infants appear to be the most sensitive to the toxic effects of boric acid, many cases of significant toxicity are also reported in adults. These cases date predominantly from the time when boric acid was widely used as an irrigant. Routes of exposure to boric acid, resulting in fatalities, include wound irrigation, pleural irrigation, rectal washing, bladder irrigation, and vaginal packing.¹⁹⁷

Clinical Effects. Classic boric acid poisoning usually involves multiple exposures over a period of days.

Gastrointestinal, dermal, CNS, and renal manifestations predominate. The initial symptoms—nausea, vomiting, diarrhea, and occasionally crampy abdominal pain—may be confused with an acute gastroenteritis. At times, the emesis and diarrhea are greenish blue.²⁰⁵ Following the onset of GI symptoms, the majority of patients develop a characteristic intense generalized erythroderma.²⁰⁵ This rash, described as producing a “boiled lobster” appearance, may appear indistinguishable from toxic epidermal necrolysis or staphylococcal scalded skin syndrome in the neonate.^{115,168} The rash may be especially noticeable on the palms, soles, and buttocks.⁵⁷ Typically, extensive desquamation takes place within 1 to 2 days. On occasion, prominent mucous membrane involvement of the oral cavity and conjunctivae is also apparent.²⁰⁵ At about the time of the development of the erythroderma, patients, particularly young infants, may develop prominent signs of CNS irritability, resembling meningeal irritation. Seizures, delirium, and coma can occur.⁵⁷ AKI is common, both a result of the renal elimination of this compound and prerenal azotemia from GI losses.⁵⁷ Other complications of boric acid poisoning include hepatic injury, hyperthermia, and cardiovascular collapse. The abandonment of boric acid as an irrigant and particularly its removal from the nursery setting have led to a marked decrease in the incidence of significant boric acid poisoning.

Two retrospective studies on boric acid ingestions suggest that a single acute ingestion of boric acid is generally quite benign.^{108,110} In these studies, 79% to 88% of patients remained asymptomatic. Symptoms, when present, primarily consist of GI irritative symptoms, such as nausea and vomiting. None of the 1184 patients in these two studies manifested the generalized erythroderma so commonly described in previous reports. Central nervous system manifestations of acute overdose were infrequent and limited to occasional lethargy and headache. Renal toxicity did not occur following single acute ingestions.

Fatalities from massive acute ingestion of boric acid have been reported in both unintentional ingestions in children and intentional ingestions in adults.^{65,162} Fatality resulted from a single ingestion of 2 cups (280 g) of boric acid crystals by a 45 year-old man. Signs and symptoms on presentation (2 days after ingestion) included nausea, vomiting, green diarrhea, lethargy, hypotension, AKI, and a prominent “boiled lobster” rash on his trunk and extremities. In another case, the ingestion of 30 g of boric acid by a 77 year-old man resulted in similar symptoms and death 63 hours postingestion, despite hemodialysis.⁸⁸ The diagnosis of boric acid poisoning can be confirmed with the measurement of blood or serum boric acid concentrations (normal = 1.4 nmol/mL), but this test is not routinely available.

Long-term chronic exposure to boric acid results in alopecia in adults and seizures in children.¹³⁸ A 32 year-old woman who chronically ingested mouthwash containing boric acid over a 7-month period developed progressive hair loss.¹⁸⁹ The chronic application of a borax and honey mixture to pacifiers resulted in the development of recurrent seizures in nine infants, which resolved after the mixture was withheld.^{59,138}

Management. Treatment of boric acid toxicity is mainly supportive. Activated charcoal is not recommended because of its relatively poor adsorptive capacity for boric acid.⁴¹ Since boric acid has a low molecular weight and relatively small volume of distribution, in cases of massive oral overdose or AKI, hemodialysis, or perhaps exchange transfusion in infants, may be helpful in shortening the half-life of boric acid.^{34,110,134,194} Although forced diuresis is suggested to enhance renal elimination, this is highly unlikely to be successful and the risks outweigh the benefits.¹⁹⁵

Chlorates

Sodium chlorate is a strong oxidizer. At one time, the chlorate salts, sodium chlorate and potassium chlorate, were used as medicinals to treat inflammatory and ulcerative lesions of the oral cavity and could be found in various mouthwash, toothpaste, and gargle preparations.¹⁸⁵ Although their use as local antiseptics is obsolete, chlorates are used as herbicides and in the manufacture of matches, explosives, and dyestuffs.⁸⁹ More recent cases of chlorate poisoning resulted from the ingestion of sodium chlorate containing weed killers, or dispensing errors that confused sodium chlorate with sodium sulfate or sodium chloride.⁸⁹ Sodium chlorate in the form of white crystals has also been mistaken for table sugar.⁷² A case of significant toxicity from the inhalation of atomized chlorates is also reported.⁸⁹

Sodium chlorate is rapidly absorbed from the GI tract and eliminated predominantly unchanged from the kidneys.⁹⁰ Its systemic effects are chiefly hematologic and renal. The major mechanism of toxicity of chlorate is its ability to oxidize hemoglobin and increase red blood cell membrane rigidity.¹⁷⁹ Consequently, significant methemoglobinemia and hemolysis may result. Chlorates may also be directly toxic to the proximal renal tubule.¹⁰³ The hemolysis and the resultant hemoglobinuria may secondarily cause disseminated intravascular coagulation and potentiate renal toxicity. The worsening renal function is especially problematic because of its adverse effect on chlorate elimination. The methemoglobinemia may be severe and cause significant hypoxic stress. Methemoglobinemia may occur prior to or after the development of hemolysis.^{137,188} Chlorates may also act locally as a GI irritant and cause mild CNS depression after absorption.⁶⁰

Clinical. Clinical signs and symptoms of chlorate poisoning usually begin 1 to 4 hours after ingestion.⁹⁷ The earliest symptoms are GI, including nausea, vomiting, diarrhea, and crampy abdominal pain. Subsequently, the patient may exhibit cyanosis from the methemoglobinemia and black-brown urine from the hemoglobinuria. Obtundation and anuria may ensue.

Laboratory studies may show methemoglobinemia, anemia, Heinz bodies, ghost cells, fragmented spherocytes, metabolic acidosis, decreased platelet count, and abnormal coagulation.⁵¹ Hyperkalemia may be particularly problematic if the patient ingests potassium chlorate preparations.¹³³ In a case of chlorate poisoning from the ingestion of 120 potassium chlorate–containing matchsticks, an MRI revealed symmetric abnormal signal intensity within the deep gray matter and medial temporal lobes.¹³³ This finding can be explained by the increased vulnerability to oxygen deprivation of the basal ganglia. Follow-up MRI two months later was normal.

Management. Treatment of a patient with a significant chlorate ingestion should include orogastric lavage and the use of activated charcoal.⁷² It has been suggested that administration of sodium thiosulfate may inactivate the chlorate ion by reducing it to the chloride ion,⁷² but an in vitro study did not confirm this hypothesis.¹⁸⁸ The utility of methylene blue in the treatment of symptomatic chlorate induced methemoglobinemia has been questioned as a consequence of the inactivation by chlorates of glucose–6-phosphate dehydrogenase, an enzyme that is required for methylene blue to effectively reduce methemoglobin.^{179,188} More recent experience suggests that early use of methylene blue prior to the onset of hemolysis may be useful in the treatment of chlorate induced methemoglobinemia.^{19,104} Exchange transfusion, peritoneal dialysis, and hemodialysis have also been advocated in the treatment of patients with severe chlorate poisoning.^{137,188} Because the chlorate ion is easily dialyzable, hemodialysis is capable of removing this xenobiotic as well as treating any concomitant AKI that may have developed.^{89,97,103}

SUMMARY

- A chemically diverse group of antiseptics, disinfectants, and sterilants exist.
- Many of the more toxic xenobiotics, such as iodine, phenol, and chlorates, are no longer commonly used as cleansers but may still be available in some settings.
- Formaldehyde exposures, although also uncommon, can also cause significant toxicity.
- Frequently employed antiseptics, such as chlorhexidine, pHisoDerm, and many of the currently used quaternary ammonium compounds, have a relatively limited toxicity.
- Ingestions of the iodophors do not usually cause significant toxicity, but absorption through other routes may produce significant adverse effects. Ingestion of hydrogen peroxide, particularly the more concentrated formulations, may result in life threatening injuries.

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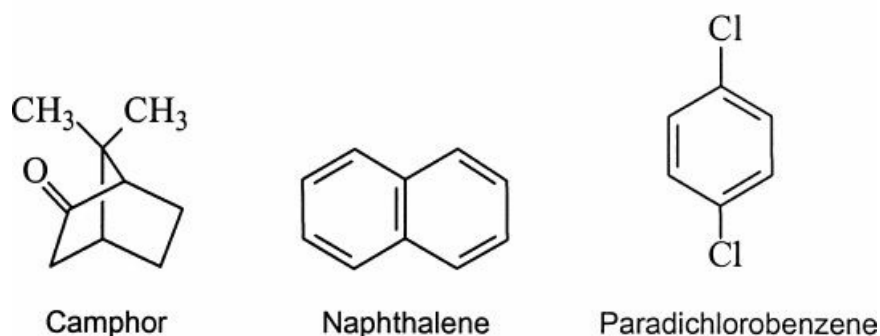
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105 CAMPHOR AND MOTH REPELLENTS

Hong K. Kim



Many different products have been used as moth repellents. In the United States, paradichlorobenzene has largely replaced both camphor and naphthalene as the most common active component of moth repellent and moth flakes because of its lower toxicity. However, life threatening camphor and naphthalene toxicity still occurs, especially in immigrant communities, from exposures to imported camphor or naphthalene-containing products.^{3,49,64,80} Therefore, toxicity of camphor, naphthalene, and paradichlorobenzene should be considered when evaluating possible exposure to moth repellents.

CAMPBOR

History and Epidemiology

Camphor (2-bormanone, 2-camphonone), a cyclic ketone of the terpene group, is an essential oil originally distilled from the bark of the camphor tree, *Cinnamomum camphora*. Today, camphor is synthesized from the hydrocarbon pinene, a derivative of turpentine oil. Camphor has been used for centuries as an aphrodisiac, contraceptive, abortifacient, suppressor of lactation, analeptic, cardiac stimulant and antiseptic.^{43,55,57,61,72,96,109} Camphor is a commonly used ingredient found in many nonprescription remedies for cold symptoms, cold sores, and in muscle liniments.^{2,75,77,93,97} Camphor is also rarely abused as a stimulant.⁶⁹

Camphorated oil and camphorated spirits contain varying concentrations of camphor. Historically, most camphorated oil was prepared as a 20% weight (of solute) per weight (of solvent) (w/w) solution of camphor with cottonseed oil, and most camphorated spirits contained 10% w/w camphor with isopropyl alcohol. Toxicity and death following ingestion of camphorated oil, which was frequently confused with castor oil and cod liver oil, prompted the FDA to ban the nonprescription sale of camphorated oil in the United States in 1980.^{11,61,76,120,125} The FDA ban of camphorated oil was followed by a restriction on camphor content in 1983, limiting the camphor concentration to less than 11% in nonprescription camphor containing products in the United States.¹²⁶ However, camphorated oil is still used as an herbal remedy and muscle liniment, and products containing greater than 11% camphor can still be purchased in local stores of various ethnic communities in the United States and in other countries.^{35,49,64,117}

Common camphor-containing products include ointments often used for herpes simplex on the lips (usually <1% camphor), muscle liniments, rubefacients (usually 4%–7% camphor), and camphor spirits (usually 10% camphor). Paregoric, camphorated tincture of opium, contains a combination of anhydrous morphine (0.4 mg/mL), ethanol (46%), and benzoic acid (4 mg/mL) but only a small amount of camphor.⁶⁸ For industrial uses, camphor can be purchased legally in the United States and contains up to 100% camphor. Occupational exposures to camphor occur during the manufacture of plastic, celluloid, lacquer, varnish, explosives, embalming fluids, and numerous pharmaceuticals and cosmetics.⁶⁸

Although products containing lower concentrations of camphor are implicitly safer, life threatening toxicity and death may still result from misuse or intentional overdose. Most reported cases of acute camphor poisoning are unintentional ingestions of camphor containing products mistaken for other medications or therapeutic misadventures from nonprescription products, including home remedies.^{3,11,35,49,61,64,100,118,121} According to data obtained by the American Association of Poison Control Centers (AAPCC), there are approximately 13,000 exposures to camphor containing

products each year with a majority of the exposure, approximately 80%, occurring in children under the age of 5 years (Chap. 136).

Prior to FDA ban of camphorated oil and restriction on camphor content in nonprescription products, high incidence of systemic symptoms and seizures, 46% and 20% respectively, were reported in children under 5 years of age.¹²⁹ A group of 530 camphor exposure cases showed that among all reported cases, 15% presented with systemic symptoms, and 4% had seizures.^{42,93} Unfortunately, limited data is available with regard to the true incidence of systemic toxicity and seizure since the FDA ruling in 1983. According to AAPCC data, seven reported deaths were attributable to camphor over the past 20 years, all in adults, and at least two of which occurred in the setting of an intentional suicidal ingestions. Although a majority of the patients with unintentional exposures remain asymptomatic and do not present to the health care facility, significant morbidity from unintentional camphor exposures still occurs in children.^{3,35,49,64,80,93,97,117} The public health implication of camphor exposure in children is of great concern because of its lack of therapeutic value and its potential life threatening toxicity.

Pharmacology

Camphor is a colorless glassy solid. Its pharmacologic activity is not well studied, and its mechanism of action remains unclear. It is unlikely that camphor has therapeutic benefit as an expectorant or an antiinfective. No therapeutic benefit of camphor has been proven in any well-controlled clinical trials. Camphor may provide some local analgesic and antipruritic effects, but much safer alternatives are available for these indications.

Pharmacokinetics and Toxicokinetics

There are limited data on the pharmacokinetics and toxicokinetics of camphor. Ingestion is the most common route of exposure, resulting in significant camphor toxicity.^{3,64,69,80,93,132} However, toxicity can be observed following inhalation, intranasal instillation, intraperitoneal administration, and from transplacental transfer, resulting in fetal death.^{29,102,107,111,115,132} Dermal exposures are also reported to cause systemic toxicity.^{35,49,64,98,121} Camphor is a highly lipophilic compound that is rapidly absorbed from the gastrointestinal tract and can be detected in the blood within 15 to 20 minutes following ingestion.^{93,102} The presence of food in the stomach may delay the absorption of camphor.¹ Due to lack of experimental data, the bioavailability from each route of exposure is unknown. In an animal experiment, a peak blood camphor concentration was achieved in 90 minutes when rats were administered an oral dose of 1 g/kg.³⁴ A significant amount of camphor can be absorbed through normal skin. Dermal absorption of camphor is slow but can produce systemic toxicity up to 72 hours following exposure.^{49,64} The volume of distribution is estimated at 2 to 4 L/kg with protein binding of approximately 61%.^{68,69}

Camphor is predominantly metabolized in the liver and eliminated by the kidneys. Up to 59% of the camphor is eliminated in urine as glucuronides but unchanged camphor (<1%) and other oxidative metabolites are eliminated without glucuronidation.^{69,104,109} Five inactive meta-bolites are produced by hydroxylation of a methylene group (the predominant pathway) and reduction of the oxo group.¹⁰⁴ Inactive metabolites, 3-hydroxycamphor, 5-hydroxycamphor (major metabolite), 8-hydroxycamphor, 9-hydroxycamphor, and borneol, are either conjugated with glucuronic acid or further oxidized and eliminated by the kidneys.^{69,104} The exact site of camphor metabolism is unknown, but CYP 2A6 and NADPH-P450 reductase are known to be involved in two in vitro experiments.^{50,84} Nine other CYP enzymes (1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2C6, 2E1, and 3A4) all failed to produce detectable metabolites of camphor.⁵⁰ CYP2A6 metabolized camphor to 5-hydroxycamphor, a major camphor metabolite.⁵⁰ In humans, a plasma elimination half-life of 93 minutes and 167 minutes was reported after 200 mg of camphor was ingested by a volunteer, with Tween 80 as a solvent (10 mL) or without the solvent, respectively.⁶⁸ A comparable elimination half-life of 144 minutes was found in an animal study after an oral ingestion.³⁴ Small amounts of camphor may be eliminated by exhalation, as noted by characteristic odor in breath, but no studies have assessed the significance of this route of elimination.^{69,75}

The reported toxic dose of camphor is highly variable.^{51,61,113} A potential lethal dose of 50 to 500 mg/kg of camphor is often cited for humans.^{35,42,80,93} Yet, as little as 1 g of camphor has reportedly resulted in death in a 19 month-old infant, while up to 42 g of camphor was ingested by an adult who recovered.^{2,113} There is insufficient data to suggest a clear toxic dose range of camphor. However, there is evidence to suggest that camphor can cause life threatening toxicity at low doses (estimated exposure of 700 to 1500 mg) based on a series of case reports in both adults and children.^{29,42,75,93,113,117} Currently, the AAPCC recommends that any patient who is exposed to 30 mg/kg or more of camphor should receive emergent medical attention.⁷⁷

Workplace standards determined by the Occupational Safety and Health Administration (OSHA) has set the permissible exposure limit (PEL) at 2 mg/m³.¹²³ The American Conference of Governmental Industrial Hygienists' (ACGIH) threshold limit value (TLV) is 12 mg/m³ (2 ppm), while the short-term exposure limit (STEL) is 19 mg/m³ (3 ppm). The National Institute for Occupational Safety and Health (NIOSH) Immediately Dangerous To Life or Health Concentration (IDLH) is

200 mg/m³.¹²²

Pathophysiology

The mechanism of toxicity of camphor is unknown. Camphor is an irritant. Pathologic changes following ingestion include cerebral edema, neuronal degeneration, fatty changes, centrilobular congestion of the liver, and hemorrhagic lesions in the skin, gastrointestinal tract, and kidneys.^{35,62,113,132}

Clinical Manifestations

Exposure to camphor can often be detected by its characteristic aromatic odor (Chap. 26). Ingestion of camphor typically produces oropharyngeal irritation, nausea, vomiting, and abdominal pain. Generalized tonic-clonic seizures may be the first sign of camphor toxicity, usually occurring within 1 to 2 hours of ingestion.^{13,18} The onset of systemic toxicity, particularly CNS toxicity, can occur as early as 5 minutes after ingestion.^{29,32,75,113} Most seizures are brief and self-limited, although some patients may have a more protracted course, including status epilepticus.^{13,45,49,67,111} Delayed seizures, occurring up to 9 hours following ingestion and up to 72 hours following dermal exposure, are reported.^{49,105} Central nervous system (CNS) depression is common, but camphor rarely compromises respiratory function.^{29,68} Other neurologic manifestations include headache, lightheadedness, transient visual changes, confusion, myoclonus, and hyperreflexia.^{65,102,107} Psychiatric manifestations include agitation, anxiety, and hallucinations.^{51,65,68} Dermal effects include flushing and petechial hemorrhages.^{29,55,115} Camphor does not typically cause life-threatening cardiovascular effects, although a case of myocarditis is reported.¹⁹ Deaths are reported secondary to status epilepticus.^{16,29,77,113} Case reports suggest that acute ingestion of camphor can cause transient elevations of the hepatic aminotransferases.^{11,62,102,107,111} Chronic administration of camphor to a child caused altered mental status and elevated hepatic aminotransferases concentrations suggestive of Reye syndrome.⁶² When hepatotoxicity occurs, however, camphor does not typically produce morphologic changes in the liver characteristic of Reye syndrome. Albuminuria can also occur.¹¹³

Camphor crosses the placenta. Both fetal demise and delivery of healthy neonates are reported in mothers who experienced acute camphor toxicity from both intentional and unintentional ingestion and delivered during the following 24 hours.^{20,102,132} Specific dose-related toxicity cannot be determined from these case reports.

Inhalational and dermal exposure from camphor usually produces only mucous membrane and dermal irritation, respectively.⁴⁸

Diagnostic Testing

No specific diagnostic test is available or indicated when managing patients with camphor toxicity. Camphor and its metabolites can be identified in blood and urine.^{69,104} But these tests are not clinically useful in most cases of acute toxicity as they are not readily available and have not been shown to correlate with clinical toxicity.^{55,69,104}

Management

Patients who should be evaluated in a health care facility after an acute ingestion include those who have signs or symptoms consistent with camphor toxicity, those who have ingested more than 30 mg/kg of camphor, suicidal patients, and any patient with a significant occupational exposure.⁷⁷

Gastric decontamination is not well studied in patients with acute camphor ingestion. Camphor is rapidly absorbed in the gastrointestinal tract due to its high lipophilic property. Thus, the benefit of gastrointestinal (GI) decontamination rapidly diminishes with time following acute ingestion. Gastric decontamination may be difficult to perform at times, as GI symptoms (eg, active vomiting) are frequently encountered. Gastric lavage has been performed in patients with acute camphor ingestions, but clinical benefit of such procedure in setting of camphor toxicity is unknown.^{42,93} If lavage is deemed necessary following recent ingestion of a camphor-containing solution, nasogastric suctioning and lavage are preferable to orogastric lavage. The utility of activated charcoal in acute camphor ingestion is unknown. One animal study showed that administration of activated charcoal (2 g/kg; 2:1 activated charcoal to toxin ratio) immediately following camphor ingestion did not alter the gastrointestinal absorption of camphor.³⁴ There are no human data in support for or against the use of activated charcoal in camphor ingestions. Given the lack of data, an AAPCC consensus panel has recommended against the use of activated charcoal in patients with isolated camphor ingestions.⁷⁷

There is no antidote for camphor. Most patients survive with supportive care. Although the management of camphor induced seizures is not well studied, the first line therapy for camphor induced seizures is a benzodiazepine. Repeat doses of benzodiazepines may be needed to control seizures. If benzodiazepines fail to control seizures, other sedative-hypnotics, including pentobarbital or propofol, should be administered. Case reports suggest that most patients who develop life-threatening camphor toxicity develop symptoms within a few hours postexposure. Based on this, an observation period of at

least 4 hours following a potentially toxic ingestion of camphor is reasonable. In case reports, hemodialysis with a lipid dialysate and either hemoperfusion using an Amberlite resin or charcoal hemoperfusion successfully removed camphor.^{11,44,67,68,78} However, neither isolated lipid hemodialysis nor lipid dialysis in combination with hemoperfusion is routinely recommended or widely available.

NAPHTHALENE

History and Epidemiology

Naphthalene ($C_{10}H_8$), an aromatic bicyclic hydrocarbon, is commonly found in products such as moth repellents, toilet-bowl and diaper-pail deodorizers, and soil fumigants.¹¹⁴ It is the single most abundant component of coal tar, approximately 11% by weight, and is used in the manufacture of numerous commercial and industrial products.^{24,114} Both crude oil and refined products such as gasoline and diesel fuels contain naphthalene.

Historically, naphthalene toxicity has mainly resulted from its use as an antihelminthic and an antiseptic.¹¹² In recent years, unintentional and intentional ingestions of mothballs containing naphthalene have become the major etiology of naphthalene toxicity.^{66,73,109,116,131} A single naphthalene mothball can contain between 0.5 and 5 g of naphthalene depending on its size.⁴ Toilet-bowl and diaper-pail deodorizers containing naphthalene have also caused toxicity.^{28,139} Chronic exposure to naphthalene occurs in occupational setting with variable levels of exposure depending on the industry. The most common use of naphthalene is in the production of phthalic anhydride, a compound used in chemical feedstock.⁴⁷ Other industrial uses of naphthalene include carbamate insecticides, dye intermediates, synthetic resins, bathroom (urinal) air fresheners, fuel additives, plasticizers, and the manufacture of other chemicals.^{47,114} Naphthalene is also generated as a by-product of combustion and is present in ambient air at low concentrations.⁴⁷

Most unintentional exposures to naphthalene-containing moth repellents occur in children and do not cause life-threatening toxicity. According to data from the AAPCC, each year there are between 1500 and 2000 exposures to naphthalene. Since 1998 there has not been a naphthalene-associated death reported to AAPCC, and reports of “major toxicity” are very unusual (Chap. 136). Mothball vapors are also intentionally inhaled as a form of inhalant abuse.^{70,131}

Pharmacology, Pharmacokinetics, and Toxicokinetics

Naphthalene is a white, flakey crystalline solid with a noxious odor. Synonyms include white tar and tar camphor. Naphthalene toxicity is reported following ingestion, dermal application, and inhalation.^{30,33,36,106,127} Although the absorption of naphthalene is not well studied, highly lipid-soluble compounds may increase both oral and dermal absorption. Naphthalene metabolism is complex and varies considerably among species and different anatomical regions.²² For instance, an in vitro study using human liver microsomes showed that multiple CYP450 enzymes are involved in naphthalene metabolism: 1A1, 1A2, 1B1, 2A6, 2B6, 2C19, 2D6, 2E1, and 3A4.²⁷ On the other hand, data from animal studies showed a different group of CYP450 isoenzymes are responsible for naphthalene metabolism.⁴ Metabolic pathways involve several intermediates and generate multiple reactive metabolites: 1,2-naphthalene oxide, 1,4-naphthoquinone, 1,2-naphthoquinone, and 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene^{4,22,23} (Fig. 105–1).

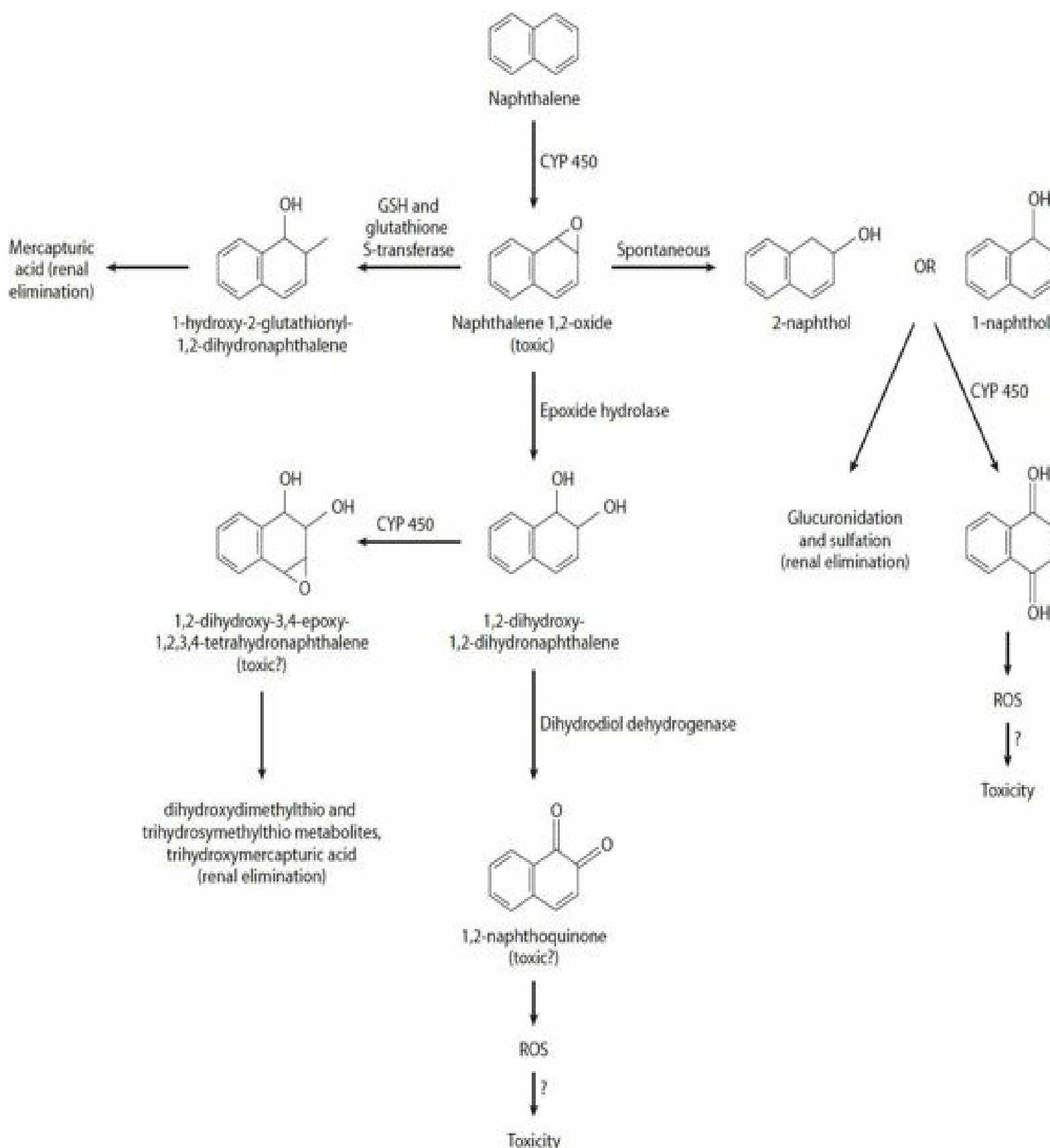


FIGURE 105–1. Hepatic metabolism of naphthalene and its respective metabolites. GSH = reduced glutathione; ROS = reactive oxygen species. (Adapted with permission from Buckpitt, et al 2002; Bogen, et al 2008; Agency for Toxic Substances and Disease Registry 2005.)

Naphthalene is initially metabolized to an unstable epoxide intermediate, 1,2-naphthalene oxide.^{4,23,114} Naphthalene 1,2-oxide can react with cellular components such as DNA and protein to form covalent adducts or can be spontaneously converted to 1-naphthol and 2-naphthol, which undergo glucuronidation or sulfation to form conjugates that are subsequently eliminated in urine.^{4,22,23} Glutathione-S-transferase and glutathione play an important role in detoxification of 1,2-naphthalene oxide by converting the reactive epoxide to nonreactive mercapturic acid metabolites.^{22,23,76} The depletion of glutathione prior to naphthalene exposure increases acute injury in lung Clara cells, one of the target organs of naphthalene toxicity in mice.^{94,95}

Reactive hepatic metabolites, 1-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone, are cytotoxins which deplete intracellular glutathione stores and generate reactive oxygen species.^{4,114,138} They are responsible for the oxidative stress leading to naphthalene-induced hemolysis and methemoglobinemia.

The toxic amount of naphthalene reported in the medical literature is highly variable. As little as one naphthalene mothball has resulted in toxicity, including hemolysis in an infant.^{41,139} Workplace standards include the OSHA PEL, which is 50 mg/m³ (10 ppm), ACGIH TLV, which is 52 mg/m³ (10 ppm), and the ACGIH STEL, which is 79 mg/m³ (15 ppm); NIOSH IDLH is 250 ppm (US Dept of Labor OSHA).¹²³

Pathophysiology

Naphthalene-induced (via oxidative metabolites: 1-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone) hemolysis and methemoglobinemia result when physiologic compensatory mechanisms to oxidative stress are overwhelmed. It is important to understand how oxidant stress affects erythrocytes and the normal mechanisms erythrocytes use to prevent and reverse the effects of oxidant stress.

Oxidant stressors can cause methemoglobinemia and/or hemolysis. When oxidant stress causes an iron atom from any of the four globin chains of hemoglobin to be oxidized from the ferrous state (Fe²⁺) to the ferric state (Fe³⁺), methemoglobin is formed ([Chap. 127](#)). When oxidant stress causes hemoglobin denaturation, the heme groups and the globin chains dissociate and precipitate in the erythrocyte, forming Heinz bodies. An erythrocyte with denatured hemoglobin is more susceptible to hemolysis and removal by the reticuloendothelial system ([Chap. 22](#)).

Hemolysis and methemoglobinemia can occur independently or simultaneously in patients with either normal or deficient glucose-6-phosphate dehydrogenase (G6PD) activity.^{43,58,127,139} Patients with G6PD deficiency are at increased risk for both hemolysis and methemoglobinemia following oxidant stress. Patients with G6PD deficiency are at much greater risk of hemolysis rather than methemoglobinemia due to their decreased glutathione stores.^{79,127,138} G6PD affects all races, but is most prevalent in patients of African, Mediterranean, and Asian descent. The gene that codes for G6PD is X-linked; consequently, men are affected more often than women.

Infants are also at increased risk of methemoglobinemia because fetal hemoglobin is more susceptible to the formation of methemoglobin and also because nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase activity is less well developed, impairing the reduction of methemoglobin to hemoglobin.⁶³

Injuries to other organs, eyes, lungs, and liver, have been reported in animal studies after exposure to naphthalene.^{40,89,99,114,128} However, there is a significant interspecies variation in the degree of toxicity. Human data on organ toxicity beyond hematologic effects of naphthalene are limited. A few case reports link the development of cataracts to occupational exposure; however, the causal relationship remains questionable.⁸⁹ The mechanism of cataract formation may involve oxidative destruction of lens proteins.¹¹⁴ Animal studies show that oxidative stress from naphthalene results in hepatic injury by lipid peroxidation and pulmonary epithelial necrosis.^{40,99,114} However, there is no evidence to suggest that hepatotoxicity or pulmonary toxicity occurs in humans from naphthalene exposure.

Clinical Manifestations

Both acute and chronic exposures to naphthalene result in similar toxicity.^{28,86,138} Ingestion and inhalational exposures to naphthalene commonly cause headache, nausea, vomiting, diarrhea, abdominal pain, fever, and altered mental status.^{28,74,91} Dermal exposure results in dermatitis.⁴⁶

Hemolysis and methemoglobinemia usually become clinically evident, as early as 24 to 48 hours postexposure, but more typically on the third day postexposure because of the time necessary for the hepatic metabolism of naphthalene.^{33,73} Anemia secondary to hemolysis often does not reach its nadir until 3 to 5 days postexposure.^{9,119}

Signs and symptoms of hemolysis and methemoglobinemia are nonspecific and include tachycardia, tachypnea, shortness of breath, generalized weakness, decreased exercise tolerance, and altered mental status. Methemoglobinemia may produce cyanosis, whereas hemolysis may produce pallor and jaundice ([Chap. 127](#)). Renal failure is reported as a complication of naphthalene-induced hemolysis and hemoglobinuria. Naphthalene or its metabolites cross the placenta.¹² Naphthalene pica during pregnancy causes both maternal and fetal toxicity. Children born to mothers who were experiencing naphthalene toxicity at the time of delivery have developed hemolytic anemia believed to be related to the maternal naphthalene exposure.¹³⁸ Although cataracts have been reported in animals following naphthalene exposure, human data are inconclusive.⁸²

Based upon animal data on carcinogenicity, naphthalene is classified by the International Agency for Cancer Research (IARC) as a Group 2B carcinogen (possibly carcinogenic to humans) and by the EPA as a Group C possible human carcinogen.^{47,60} The data supporting human carcinogenicity of naphthalene are limited. There are several case reports of the associated exposure with laryngeal cancer in East Germany and colorectal cancer in Nigeria but causal relationship cannot

be determined.^{7,47}

Diagnostic Testing

No specific diagnostic testing is indicated, although both naphthalene and its metabolites can be identified in blood and urine. Identification of 1-naphthol and 2-naphthol in the urine can confirm exposure to naphthalene. Qualitative or quantitative testing for naphthalene or its metabolites is not clinically indicated when managing a case of an acute overdose.⁹²

The presentation of naphthalene-induced hemolysis is similar to that of hemolysis from other causes. Reticulocytosis occurs as a response to restore a normal hemoglobin concentration. Hyperbilirubinemia from hemolysis is characterized by an elevation of the unconjugated bilirubin and a relatively normal conjugated fraction. Serum haptoglobin is usually low because the haptoglobin–hemoglobin complex is cleared by the kidneys. Both the direct and indirect Coombs tests are negative in naphthalene-induced hemolytic anemia. Lactate dehydrogenase is elevated due to its release from hemolyzed red blood cells. Hemoglobinuria is suggested by a urine dipstick that reacts strongly positive for hemoglobin with a paucity or absence of red blood cells on microscopic examination of the urine sediment. Hemoglobinemia should be differentiated from myoglobinuria, which has a comparable urine sediment, by measuring the serum creatine phosphokinase, which will be elevated in patients with rhabdomyolysis and myoglobinuria.

Examination of a peripheral blood smear can suggest hemolysis before a patient develops clinical or laboratory evidence of anemia. The peripheral smear may reveal red blood cell (RBC) fragmentation (schistocytes), anisocytosis, microspherocytosis, reticulocytosis, nucleated RBCs, Blister cells, and Heinz body formation ([Chap. 22](#)). Peripheral smear abnormalities and anemia may occur within the first 24 hours following ingestion.^{28,108,138,139} Testing for G6PD activity is not routinely recommended during an acute episode of hemolysis. Reticulocytes have higher G6PD activity than do older RBCs. If G6PD activity is measured during an episode of hemolysis when many of the older RBCs have already been destroyed, the G6PD activity may be falsely disproportionately elevated or normal. It is best to delay testing for G6PD activity for a few months following an episode of hemolysis. Family members of patients with life-threatening G6PD deficiency should also be tested.

Naphthalene-induced methemoglobinemia is similar in presentation to methemoglobinemia from other xenobiotics. The percentage of methemoglobin can rapidly be determined using a cooximeter ([Chap. 127](#)).

Management

Most patients with an unintentional exposure to no more than one naphthalene containing mothball do not require medical evaluation. Patients who should be evaluated in a health care facility following an acute ingestion include those who recently ingested more than one naphthalene-containing mothball equivalent, those with signs or symptoms of toxicity, especially hemolysis and/or methemoglobinemia, those with known or suspected G6PD deficiency, all intentional ingestions, and those patients with substantial inhalational exposures, particularly those occurring in an occupational setting.

Gastrointestinal decontamination is not well studied in patients who have ingested naphthalene. Most patients with unintentional exposures do not require gastrointestinal decontamination. Administration of activated charcoal, 1 g/kg, although not of proven efficacy, is reasonable because it is considered safe. Repeat doses of activated charcoal 0.5 g/kg and/or whole-bowel irrigation with polyethylene glycol electrolyte lavage solution would only be indicated for patients with large ingestions of naphthalene who are expected to have significant ongoing gastrointestinal absorption.

Diagnostic testing within the first 24 to 48 hours postexposure may detect the onset of methemoglobinemia and/or hemolysis before a patient becomes symptomatic. Most low-risk patients who are asymptomatic within the first 24 to 48 hours postexposure and who have no laboratory evidence of hemolysis or methemoglobinemia can be managed as outpatients if reevaluation within 24 to 48 hours can be arranged. Patients who are discharged should be instructed to return if they become symptomatic. High-risk patients, patients with laboratory evidence of hemolysis and/or methemoglobinemia, and patients who cannot be reliably managed as outpatients should be admitted.

Patients with life-threatening hemolysis and anemia should be transfused with packed red blood cells. However, most healthy patients will be able to compensate for the hemolysis and will not require a transfusion. Patients with symptomatic methemoglobinemia should receive methylene blue, 1 to 2 mg/kg (0.1–0.2 mL/kg of a 1% solution) intravenously. Repeat doses may be necessary ([Antidotes in Depth: A42](#)).

PARADICHLOROBENZENE

History and Epidemiology

Paradichlorobenzene (1,4-dichlorobenzene) is widely used as a deodorizer, disinfectant, repellent, fumigant, insecticide, fungicide, and industrial solvent. Today, paradichlorobenzene is the most common component of moth repellents in the

United States. Low level exposure to paradichlorobenzene in the United States is extremely common due to environmental contamination from release of paradichlorobenzene to air by industrial facilities.⁹⁰ The primary route of human exposure is inhalation in either an occupational setting or from indoor air where paradichlorobenzene is used as a deodorizer or moth repellent.⁹⁰ Paradichlorobenzene is also found in both water and numerous food items, including pork and fresh vegetables, from environmental contamination.^{90,103,130} In 1995, a study suggested that 2,5-dichlorophenol, a metabolite of paradichlorobenzene, was detectable in the urine in 98% of the US population.⁵⁸

Most unintentional exposures to paradichlorobenzene-containing moth repellents occur in children and do not cause toxicity. According to the AAPCC data, there were no deaths and no reports of major toxicity associated with paradichlorobenzene between 1998 and 2011.

Pharmacology, Pharmacokinetics, Toxicokinetics, and Pathophysiology

Paradichlorobenzene ($C_6H_4Cl_2$) is a colorless solid with a noxious odor. It is available as pure white crystals, as a solid in combination with other chemicals, or as a liquid dissolved in volatile solvents or oil.¹⁰ The mechanism of the toxicologic effect of paradichlorobenzene has not been studied. Although rare, paradichlorobenzene toxicity is reported following ingestion and inhalation.^{59,81} Inhalation toxicokinetics reveal that in humans there is rapid distribution and accumulation in tissues, specifically in adipose tissue.^{15,26,56,137} The major route of elimination is urinary excretion followed by hepatic metabolism, with none by exhalation.^{15,137} CYP2E1, CYP1A1, and CYP1A2 convert paradichlorobenzene to its primary metabolite, 2,5-dichlorophenol, which is eliminated as either sulfated or glucuronidated conjugates.^{21,54,56}

Workplace standards include the OSHA PEL, which is 450 mg/m³ (75 ppm) time-weighted average (TWA), ACGIH TLV, which is 60 mg/m³ (10 ppm) TWA, and the ACGIH STEL, which is 675 mg/m³ (110 ppm); NIOSH IDLH is 150 ppm.¹²⁴

Clinical Manifestations

Paradichlorobenzene is considered to have less toxicity than camphor and naphthalene. However, cases of clinical toxicity from paradichlorobenzene are reported ranging from hemolytic anemia to toxic leukoencephalopathy following acute and/or chronic exposure.^{14,25,26,37,39,52,53,56,71,81,83,101,109,110,131} Although paradichlorobenzene can be absorbed following inhalation, ingestion and cutaneous exposures are the routes of exposure that lead to toxicity.^{37,39,56,83,101,131} Acute unintentional exposure to paradichlorobenzene may cause limited transient clinical effects such as nausea and vomiting, headache, and mucous membrane irritation.^{31,59} However, significant neuropsychiatric dysfunction, specifically cerebellar dysfunction, motor weakness, and cognitive decline, is reported following chronic intentional and occupational exposure.^{37,39,56,71,81,83} In most cases, neurologic and cognitive deficits associated with paradichlorobenzene developed after several months of exposure and seldom resulted in complete resolution after cessation of paradichlorobenzene exposure.^{14,56,83} Other clinical signs and symptoms from chronic exposure include pulmonary granulomatosis, hepatotoxicity, an ichthyosislike dermatosis, aplastic anemia, and dyspnea.^{37–39,53,85,115,133}

Hemolytic and aplastic anemias are reported, as well as methemoglobinemia, following acute paradichlorobenzene ingestion.^{25,52,53,110}

Paradichlorobenzene is classified by IARC as a Group 2B, possibly carcinogenic to humans, based upon evidence of carcinogenicity from experimental animal studies. In mice and rats, chronic exposure was associated with the development of both hepatocellular carcinomas and adenomas in male and female mice, and renal tubular cell adenocarcinomas and mononuclear-cell leukemias developed in male mice.^{5,6,17,87,88,136} Evidence for carcinogenicity in humans from paradichlorobenzene exposure is limited. One case series reported five cases of leukemia that may have been associated with paradichlorobenzene exposure.^{88,135} No additional epidemiologic data on human carcinogenesis from paradichlorobenzene exposure is available.

Diagnostic Testing

Both paradichlorobenzene and its primary metabolite, 2,5-dichlorophenol, can be identified in blood and urine following exposure.¹⁵ Identification of 2,5-dichlorophenol can confirm exposure to paradichlorobenzene. Quantifying the amount of paradichlorobenzene in the urine of workers may be useful for monitoring occupational exposures.⁴¹ Qualitative or quantitative testing for paradichlorobenzene or its metabolites is not generally indicated when managing a patient with an acute overdose. Structural CNS abnormalities, including toxic leukoencephalopathy, may be noted on imaging studies such as MRI.¹⁴

Management

Most unintentional exposures to paradichlorobenzene do not cause life-threatening toxicity. Asymptomatic patients with unintentional exposures can be managed as outpatients. Patients who should be evaluated in a health care facility include those with clinical signs or symptoms, suicidal patients, and patients who have had a large exposure.

Gastrointestinal decontamination has not been studied in patients who ingest paradichlorobenzene. Most patients with unintentional exposures do not require gastrointestinal decontamination. However, administration of activated charcoal, 1 g/kg, although not studied, is reasonable for patients with large, intentional ingestions. If present, GI symptoms such as nausea and vomiting should be managed with supportive care, including hydration and antiemetics. Laboratory testing is generally not helpful in the acute setting unless there is clinical evidence for hemolysis or methemoglobinemia. Transfusion of packed red blood cells should be considered for hemolysis and anemia. Methylene blue should be considered for symptomatic methemoglobinemia.

Asymptomatic patients should be referred for follow-up evaluation in 24 to 48 hours postexposure as development of hemolysis or methemoglobinemia may be delayed. Careful discharge instruction should be provided to patients should they become symptomatic.

MOTH REPELLENT RECOGNITION

Health care providers occasionally must determine whether a mothball is made of naphthalene, paradichlorobenzene, or camphor since management and prognosis for each chemical is different. When the container is unavailable, as is often the case, mothballs are difficult to distinguish based on appearance, odor, texture, or size. Most mothballs are white, crystalline, and have a noxious odor.¹³⁴ Camphor moth repellents are more oily than both naphthalene and paradichlorobenzene mothballs. If controls are available, moth repellents can often be differentiated based on their odor and texture.⁸ Although most new paradichlorobenzene moth repellents are slightly larger than most new naphthalene moth repellents, all moth repellents shrink over time when exposed to air, making size an unreliable differentiating characteristic. Identifying a moth repellent as paradichlorobenzene can often permit outpatient management, saving both hospital resources and unnecessary concern. The tests described in [Table 105–1](#) and shown in [Fig. 105–2](#) might allow rapid identification of the component of an unknown moth repellent. When performing these tests, it is most helpful to have camphor, naphthalene, and paradichlorobenzene controls available for comparison.

TABLE 105–1. Moth Repellents: Laboratory Differentiation

Characteristic	Camphor	Naphthalene	Paradichlorobenzene
Water solubility (g/L)	1.2	0.03	0.08
Buoyancy in water	Floats	Sinks	Sinks
Buoyancy in water saturated with table salt	Floats	Floats	Sinks
Radiopacity	Radiolucent	Faintly radiopaque	Densely radiopaque
Melting point	350.6°F (177°C)	176°F (80°C)	127.4°F (53°C)
Placement in covered test tube in 140°F (60°C) water bath	Does not melt	Does not melt	Melts
Boiling point	399.2°F (204°C)	424.4°F (218°C)	345.2°F (174°C)
Addition of chloroform	Untested	Blue color	No reaction
Place on copper wire in a flame	Untested	Flame is yellow-orange	Initially flame is yellow-orange then bright green
Solubility in turpentine	Untested	Fast	Slow

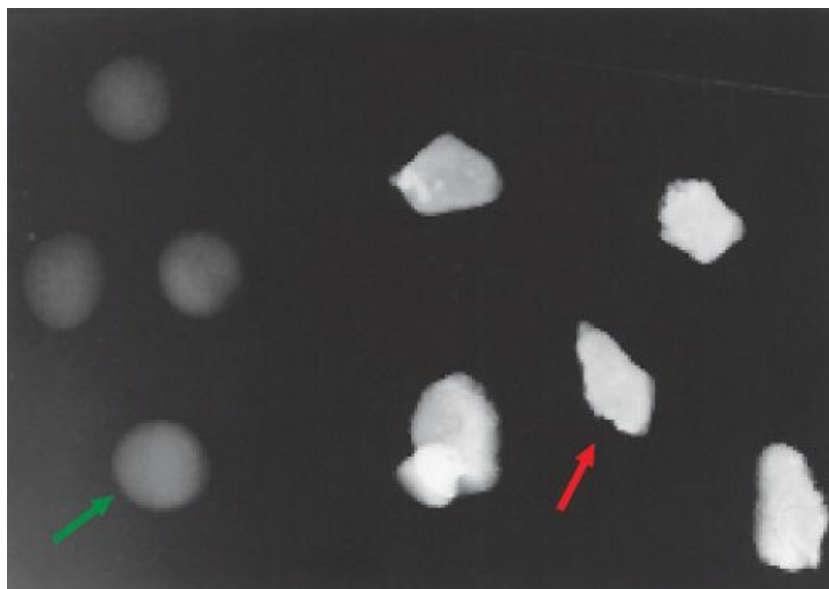


FIGURE 105–2. Radiograph of mothballs. Paradichlorobenzene (→) is densely radiopaque, whereas naphthalene (→) is faintly radiopaque.

SUMMARY

- Paradichlorobenzene has largely replaced both camphor and naphthalene in the United States, but exposures to all three compounds occur, especially in immigrant communities.
- It is reasonable to consider activated charcoal administration in patients with large ingestions if no contraindication is present, such as CNS depression, active vomiting, or seizures.
- Seizures are commonly observed after camphor ingestion, and deaths are reported due to status epilepticus. Camphor induced seizures are responsive to benzodiazepines, propofol, and barbiturates.
- Hemolytic anemia and methemoglobinemia can be observed after naphthalene and, less frequently, paradichlorobenzene exposures. Appropriate supportive care, packed red blood cell transfusions, and methylene blue administration should be considered for symptomatic patients.
- Simple tests such as radiography and buoyance tests may help identify the unknown mothball.

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HISTORY AND EPIDEMIOLOGY

As early as 1927, legislation in the United States governing the packaging of lye-and acid-containing products mandated that warning labels be placed on these products. In response to the recognition that caustic exposures were more frequent in children, the Federal Hazardous Substances Act and Poison Prevention Packaging Act were passed in 1970; these acts mandated that all caustics with a concentration greater than 10% be sold in child resistant containers. By 1973, the household concentration for child-resistant packaging was lowered to 2%. In addition, the subsequent development of poison prevention education dramatically decreased the incidence of unintentional caustic injuries in children in the United States. The positive impact of both regulatory legislation and public health intervention is evident when observing the decreasing number of significant exposures in the United States⁴⁹ compared to the number of exposures in developing nations that lack these policies.

In the United States, even though legislation limiting the concentration of caustics has existed since the early 20th century, exposures to both acids and alkalis continue to be significant. Data collected by the American Association of Poison Control Centers from 2007 through 2010 revealed 29,748 acid exposures and 13,800 alkali exposures. Of these, 4273 (14.4%) acid exposures and 2645 (19.2%) alkali exposures resulted in moderate to major outcomes and a total of 25 deaths occurred (Chap. 136).

In children, exposures usually consist of household products and occur in an unsupervised setting. In adults, exposures to household or industrial products may result from occupational exposure, suicide attempts, and assaults. Exposure to caustics may occur via the dermal, ocular, respiratory, and gastrointestinal routes.

Caustics cause diverse histologic and functional damage on contact with tissues depending on the tissue and caustic involved. Table 106–1 lists common caustics and the commercial products that contain them. Many are available for home use, in both solid and liquid forms, with variations in viscosity, concentration, and pH.

TABLE 106–1. Sources of Common Caustics

<i>Xenobiotic</i>	<i>Applications</i>
Acetic acid	Permanent wave neutralizers, photographic stop bath
Ammonia (ammonium hydroxide)	Toilet bowl cleaners, metal cleaners and polishes, hair dyes and tints, antirust products, jewelry cleaners, floor strippers, glass cleaners, wax removers
Benzalkonium chloride	Detergents
Boric acid	Roach powders, water softeners, germicide
Formaldehyde, formic acid	Deodorizing tablets, plastic menders, fumigant, embalming agent
Hydrochloric acid (muriatic acid)	Metal and toilet bowl cleaners
Hydrofluoric acid	Antirust products, glass etching, microchip etching
Iodine	Antiseptics
Mercuric chloride (HgCl ₂)	Preservative
Methylethyl ketone peroxide	Industrial synthetic agent
Oxalic acid	Disinfectants, household bleach, metal polish, antirust products, furniture refinisher
Phenol (creosol, creosote)	Antiseptics, preservatives
Phosphoric acid	Toilet bowl cleaners
Phosphorus	Matches, fireworks, rodenticides, methamphetamine synthesis
Potassium permanganate	Illicit abortifacient, antiseptic solution
Selenious acid	Gun bluing agent
Sodium hydroxide	Detergents, paint removers, drain cleaners and openers, oven cleaners
Sodium borates, carbonates, phosphates, and silicates	Detergents, electric dishwasher preparations, water softeners
Sodium hypochlorite	Bleaches, cleansers
Sulfuric acid	Automobile batteries, drain cleaners
Zinc chloride	Soldering flux

Morbidity and mortality from exposures to caustics is a worldwide problem. One study from India that described outcomes in patients with acid ingestions found that acute complications occurred in 39.1% of cases and death in 12.2%.¹⁰⁶

Although less frequent, intentional exposures by adults are invariably more significant. One study noted that while children comprised 39% of admissions for caustic ingestions, adults comprised 81% of patients requiring treatment.³⁶ The severity of a caustic injury may not be immediately evident in patients who present shortly after exposure. Predicting which patients will require immediate interventions to prevent morbidity and mortality requires the determination and evaluation of multiple clinical and laboratory parameters. This chapter reviews the pathophysiology and approach to patients with potentially serious exposures.

PATHOPHYSIOLOGY

A caustic is a xenobiotic that causes both functional and histologic damage on contact with tissue surfaces. Although there are many ways to categorize caustics, they are most typically classified as acids or alkalis. An acid is a proton donator and causes significant injury, generally at a pH below 3. An alkali is a proton acceptor and causes significant injury, generally at a pH above 11. [Chapter 12](#) contains a more detailed discussion of the chemistry of acids and bases. The extent of injury is modulated by duration of contact; ability of the caustic to penetrate tissues; volume, pH, and concentration; the presence or absence of food in the stomach; and a property known as titratable acid/alkaline reserve (TAR). TAR quantifies the amount of neutralization needed to bring the pH of a caustic to that of physiologic tissues. Neutralization of caustics takes place at the expense of the tissues, resulting in the release of thermal energy, producing burns. Generally, as the TAR of a caustic increases, so does the ability to produce tissue damage.^{5,40} Some xenobiotics, such as zinc chloride and phenol, have a high TAR and are capable of producing severe burns even though their pH is near physiologic.

Alkalis

Following exposure to an alkaline xenobiotic, dissociated hydroxide (OH^-) ions penetrate tissue surfaces, producing a histologic pattern of liquefactive necrosis ([Figs. 106–1 and 106–2](#)). This process includes protein dissolution, collagen destruction, fat saponification, cell membrane emulsification, transmural thrombosis, and cell death.⁵ Animal studies following alkali exposure to the eye³⁹ demonstrate rapid formation of corneal epithelial defects with eventual deep penetration that may lead to perforation. Similarly, animal studies of the esophagus demonstrate that erythema and edema of the mucosa occur within seconds followed by an inflammatory reaction extending to the submucosa and muscular layers. The alkali, such as sodium hydroxide (“liquid lye”), then continues to penetrate until the OH^- concentration is sufficiently neutralized by the tissues.^{5,53}



FIGURE 106–1. Photograph demonstrating burns to the lips and tongue of a 20 year-old man following ingestion of sodium hydroxide. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

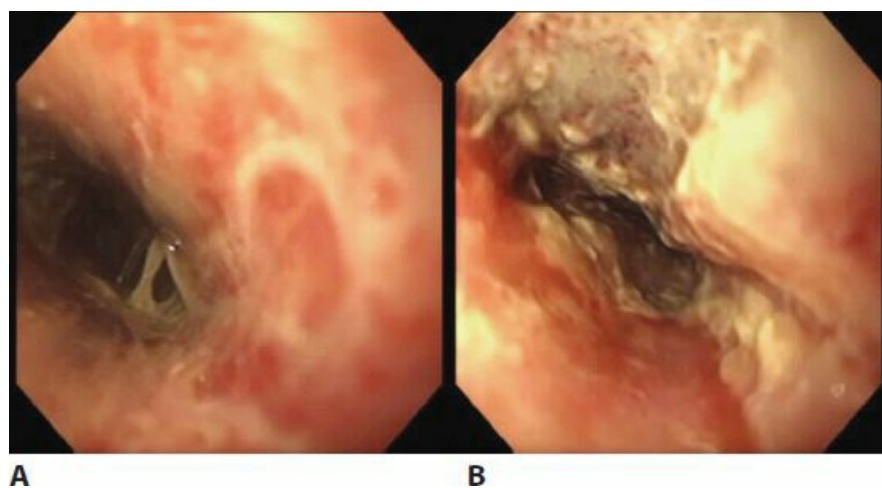


FIGURE 106–2. Endoscopy images of a 20 year-old man following ingestion of sodium hydroxide. (A) Grade IIa

noncircumferential burn of the midesophagus. **(B)** Grade IIb circumferential burn of the distal esophagus. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Although federal regulations have lowered the maximal available household concentration of many caustics, two industrial strength products seem to be readily available and therefore warrant special mention: ammonium hydroxide and sodium hypochlorite. Ammonia (ammonium hydroxide) products are weak bases—partially dissociated in water—that can cause significant esophageal burns, depending on the concentration and volume ingested.³⁶ Household ammonium hydroxide ranges in concentration from 3% to 10%. Strictures have formed in patients who ingested 28% solutions.⁷² Sodium hypochlorite is the major component in most industrial and household bleaches. Severe injuries typically only occur in patients with large-volume ingestions of concentrated products and most other patients do well with supportive care.^{13,36} A series of 393 patients with household bleach ingestions demonstrated no stricture formation.⁵² Likewise, a canine model found that although vomiting was commonly associated with bleach ingestion, no esophageal lesions were noted, and perforation occurred only following prolonged contact.⁵²

Ingestion of button batteries were once considered a unique caustic exposure. Composed of metal salts and a variety of alkaline xenobiotics, such as sodium and potassium hydroxide, leakage of battery contents was a legitimate concern. In recent years, however, new techniques used in the production of button batteries that effectively prevent leakage have shifted the concern following their ingestion from caustic to foreign body exposure with the potential for electrical injury. For a more in-depth review of the management of button battery ingestion, the reader is referred to the previous editions of this text and one recent study that describes the electrical injuries that follow ingestion of large-diameter lithium cells lodged in the esophagus for longer than 2 hours.⁵⁴

Household detergents, such as laundry powders, laundry pods,⁸⁹ and dishwasher detergents, contain silicates, carbonates, and phosphates, and have the potential to induce caustic burns and strictures, even when ingested unintentionally.¹⁴ Airway compromise also may occur,^{14,21,60} but the majority of exposures result in only minor toxicity.

Cationic detergents include quinolinium compounds, pyridinium compounds, and quaternary ammonium salts. These are frequently found in products for industrial use, as well as household fabric softeners. A concentration greater than 7.5% can cause severe burns.⁵⁸

Acids

In contrast to alkaline exposures, following exposure to an acid, hydrogen (H^+) ions desiccate epithelial cells, producing an eschar and resulting in a histologic pattern of coagulation necrosis. This process leads to edema, erythema, mucosal sloughing, ulceration, and necrosis of tissues. Dissociated anions of the acid (Cl^- , SO_4^{2-} , PO_4^{3-}) also act as reducing agents, further injuring tissue.

Ophthalmic exposure to acids results in coagulative necrosis that tends to prevent further penetration into deeper layers of the eye.

In most series, following an acid ingestion, both the gastric and esophageal mucosa are equally affected.^{19,106} On occasion, the esophagus may be spared damage while severe injury is noted in the stomach^{27,36} (Fig. 106–3). This result tends to be a rarer finding than concomitant injury to both stomach and esophagus and is probably related to the rapid transit time of liquid acids through the upper gastrointestinal tract. Skip lesions from acid ingestions may be a function of viscosity and contact time.³⁶ Additionally, acid-induced pylorospasm may lead to gastric outlet obstruction, antral pooling, and perforation.^{19,105} A cat model of the effects of sulfuric acid on the esophagus revealed a coagulative necrosis of the mucosa with whitish discoloration of the tissues and underlying smooth muscle spasm.⁵ Other animal models demonstrate esophageal motility dysfunction and shortening.^{92,93}



FIGURE 106–3. Postmortem specimen from a man with an intentional ingestion of a mixture of phosphoric and hydrochloric acid that was used as a brick cleaner. Note the relative sparing of the esophagus in contrast to full-thickness injury with perforation of the stomach. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Chapters 98 and 107 contain a more detailed discussion of mercury and hydrofluoric acid, respectively, each a unique caustic, and the management specific to their exposure.

Classification and Progression of Caustic Injury

Esophageal burns, secondary to both alkali and acid exposures, are classified based on endoscopic visualization that employs a grading system similar to that used with burns of the skin. Grade I burns are generally defined by hyperemia or edema of the mucosa without evidence of ulcer formation.^{17,105} Grade II burns include submucosal lesions, ulcerations, and exudates. Some authors further divide grade II lesions into grade IIa, noncircumferential lesions, and grade IIb, near-circumferential injuries.¹³ Grade III burns are defined as deep ulcers and necrosis into the periesophageal tissues (Table 106–2).^{26,30}

TABLE 106–2. Evaluation of Caustic Injuries and Management

<i>Grading of Caustic Injury by Endoscopic Visualization</i>	<i>Associated Tissue Findings</i>	<i>Likelihood of Stricture Formation</i>	<i>Suggested Nutritional Support</i>	<i>Indication for Antibiotics, Steroids</i>	<i>Indication for Stenting</i>
I	Hyperemia or edema of mucosa without ulcer formation	None	Resume diet as tolerated	None	None
IIa	Submucosal lesions, ulcers, exudates that are noncircumferential	Low	Soft diet as tolerated or tube feeds (following nasogastric tube placement under direct visualization)	No indication for steroids; antibiotics only with identified source of infection	None
IIb	Submucosal lesions, ulcers, exudates that are near-circumferential	High	Due to risk of perforation, feeding via gastrostomy, jejunostomy, or total parenteral nutrition should be instituted as rapidly as possible	No indication for steroids; antibiotics only with identified source of infection	Consider intraluminal stents, nasogastric tubes to prevent strictures
III	Deep ulcers and necrosis into periesophageal tissues	High	Due to risk of perforation, feeding via gastrostomy, jejunostomy, or total parenteral nutrition should be instituted as rapidly as possible	No indication for steroids; antibiotics only with identified source of infection	Consider intraluminal stents, nasogastric tubes to prevent strictures

Human case reports, postmortem studies, histologic inspection of surgical specimens, and experimental animal models

reveal a consistent pattern of injury and repair following caustic injury.⁸⁶ As wound healing of gastrointestinal tract tissue occurs, neovascularization and fibroblast proliferation take place, laying down new collagen and replacing the damaged tissue with granulation tissue. A similar pattern of repair occurs following caustic injuries of the eye.

Burns of the esophagus may persist for up to 8 weeks as remodeling takes place and may be followed by esophageal shortening. If the initial injury penetrates deeply enough, there is progressive narrowing of the esophageal lumen. The dense scar formation presents clinically as a stricture. Strictures can evolve over a period of weeks to months, leading to dysphagia and significant nutritional deficits. Grade I burns carry no risk of stricture formation.^{17,105} Grade II circumferential burns lead to stricture formation in approximately 75% of cases. Grade III burns invariably progress to stricture formation and are also at a high risk of perforation.^{3,36}

CLINICAL MANIFESTATIONS

The gastrointestinal tract, respiratory tract, eyes, and skin of a patient can be sites of caustic injury. Caustics may produce severe pain on contact with any of these tissues. By far, the majority of long-term morbidity and mortality from caustic exposure results from ingestion.

In general, patients who have ingested either alkalis or acids have similar initial presentations. Depending on the type, amount, and formulation (solid vs. liquid) as well as the percent of tissue exposed, ingestion may lead to the development of severe pain of the lips, mouth, throat, chest, or abdomen. Oropharyngeal edema and burns may lead to drooling and rapid airway compromise. Symptoms of esophageal involvement include dysphagia and odynophagia, whereas epigastric pain and hematemesis may be symptoms of gastric involvement.

Respiratory tract damage may occur through direct inhalation or aspiration of vomitus, leading to the clinical manifestations of hoarseness, stridor, and respiratory distress. Injury may result in epiglottitis, laryngeal edema and ulceration, pneumonitis, and impaired gas exchange. Patients may also be tachypneic or hyperpneic as a compensatory response to the metabolic acidosis, with elevated lactate concentrations from necrotic tissue or hemodynamic compromise.

Predictors of Injury

Many attempts have been made to define a method for clinical identification of patients with grade II or III esophageal injuries as these injuries typically progress to severe complications. Various studies, mostly involving alkaline xenobiotics, examine the predictive value of stridor, oropharyngeal burns, drooling, vomiting, and abdominal pain. A retrospective study of 378 children admitted for a caustic injury found that signs or symptoms could not be used to predict significant esophageal injury.²⁶ However, one prospective study of 79 children evaluated for vomiting, drooling, and stridor found that a combination of two or more of these signs were predictive of significant esophageal injury as visualized on endoscopy.¹⁷ Another study found that drooling, buccal mucosal burns, and white blood cell count were significant independent predictors of severe gastrointestinal tract injury following acid ingestions.³⁵ Studies evaluating the presence or absence of oropharyngeal burns as a predictor of distal esophagogastric injury have repeatedly found this finding to be poorly predictive.^{1,17,26,30,80,99} In one study esophageal injury was present 51.5% of the time in the absence of oropharyngeal lesions, and 22.2% of these were second- and third-degree burns.⁸⁰ A prospective study of alkali ingestions in both adults and children found that stridor was 100% specific for significant esophageal injury, but this was based on only three patients with this sign.³⁰

Based on these findings, endoscopy, a standard diagnostic tool used in the management of caustic ingestions, is recommended in all patients with intentional ingestions. Endoscopy should also be performed in any patient with an unintentional ingestion in the presence of stridor and in any patient with two or more of the following findings: pain, vomiting, and drooling.^{17,82} Children with unintentional caustic ingestions who remain completely asymptomatic and tolerate liquids after a few hours of observation probably require no further medical care.

The abdominal examination is likewise an unreliable indicator of the severity of injury. The presence of abdominal pain suggests tissue injury, but the absence of pain or findings on abdominal examination does not preclude life-threatening gastrointestinal damage.^{22,104} Esophageal perforations result in mediastinitis and are commonly associated with fever, dyspnea, chest pain, and subcutaneous emphysema of the neck and chest. Although indicative of viscus perforation, abdominal peritoneal signs are late findings.

In addition to the direct effects that occur with tissue contact, systemic absorption of acids may result in damage to the spleen, liver, biliary tract, pancreas, and kidneys. This may also produce a metabolic acidosis, hemolysis, and, ultimately, death.⁴²

Significant complications can occur at various stages of wound recovery. Most importantly, these include airway compromise, hemodynamic instability secondary to hemorrhage from vascular erosion or septic shock, perforations of the gastrointestinal tract with the development of mediastinitis or peritonitis, and other overwhelming infections from bacteria residing in the oropharynx. A patient who survives acute injury with an acid or an alkali may also subsequently develop

stricture formation, gastric atony, decreased acid secretion, pseudodiverticula, and gastric outlet obstruction.^{29,105}

Other complications include dysmotility of the pharynx and esophagus,¹⁸ formation of aorto-and trachea-esophageal fistulas, delayed massive hemorrhage from erosion into a great vessel, and pulmonary thrombosis.^{9,36,70,91} Those patients surviving a few weeks after a grade II or III injury may subsequently present with dysphagia and vomiting from stricture formation. Injury involving the entire length of the esophagus as well as hematemesis and increased serum lactic dehydrogenase were useful indicators for the development of strictures in one study.⁷³ Strictures may also present with esophageal motility disorders caused by impaired smooth muscle reactivity. The early assessment and long-term prognosis may be better defined by manometric studies of the esophagus, which provide precise information about the severity of the initial injury and aid in long-term prognosis.²⁸

Long-term survivors of moderate and severe injury of the esophagus have a risk of esophageal carcinoma that is estimated to be 1000 times higher than that of the general population and appears to present with a latency of up to 40 years.⁴

DIAGNOSTIC TESTING

Laboratory

All patients with presumed serious caustic ingestion should have an evaluation of serum pH, blood type and cross-match, complete blood count, coagulation parameters, electrolytes, and urinalysis. Elevated prothrombin time (PT) and elevated partial thromboplastin time (PTT),¹⁰⁴ as well as an arterial pH lower than 7.22,¹¹ are associated with severe caustic injury.

Absorption of nonionized acid from the stomach mucosa may result in acidemia. Following ingestion of hydrochloric acid, hydrogen and chloride ions (both of which are accounted for in the measurement of the anion gap) dissociate in the serum resulting in a hyperchloremic normal anion gap metabolic acidosis. Other acids, such as sulfuric acid, result in an elevated anion gap metabolic acidosis because the sulfate anion (SO_4^{2-}) is not measured in the calculation of the anion gap. Although alkalis are not absorbed systemically, necrosis of tissue may result in a metabolic acidosis with an elevated lactate concentration.

A gastric pH greater than 7.30 correlated retrospectively with severe alkaline injury. The prospective usefulness of this information is limited, as obtaining gastric secretions without direct visualization is dangerous. One prospective study in children also found an increase in uric acid and decreases in phosphate and alkaline phosphatase concentrations to be useful in predicting the presence of esophageal injuries.⁷⁵

Radiology

Chest and abdominal radiographs are useful in the initial stages of assessment to detect gross signs of esophageal or gastric perforation. Signs of alimentary tract perforation that may be present on plain radiographs include pneumomediastinum, pneumoperitoneum, and pleural effusion. However, these studies have a limited sensitivity, and an absence of findings does not preclude perforation.¹⁰⁴ Free intraperitoneal air is best visualized on an upright chest radiograph. Occasionally, free air may only be visible on the lateral view. In patients too ill to obtain an upright chest radiograph, an abdominal radiograph obtained with the patient in a left-side-down position may reveal free intraperitoneal air adjacent to the liver. Additionally, bedside ultrasound may be useful in the diagnosis of free air and is based entirely on the lack of visualization of the usual intraperitoneal structures.^{10,71} Computed tomography (CT) scanning is considerably more sensitive than both radiography and ultrasound for detecting viscus perforation and should be obtained in patients with potentially serious caustic ingestions as soon as is feasible.^{23,101}

A contrast esophagram is useful for defining the extent of esophageal injury (Fig. 106–4). Late after the ingestion, it can detect stricture formation. In patients for whom there is a high suspicion for esophageal perforation and in whom adequate visualization of the upper gastrointestinal tract by endoscopy is not possible (grade IIb circumferential burns or grade III burns), an enteric contrast study (esophagram and upper gastrointestinal series) can be obtained 24 hours after the ingestion.⁸¹ Extravasation of contrast outside of the gastrointestinal tract is diagnostic of perforation.¹⁰⁵ Water-soluble contrast should be used when perforation is suspected as it is less irritating than barium contrast agents to mediastinal and peritoneal tissues if extravasated. However, barium contrast agents are more radiopaque than water-soluble agents and offer greater radiographic detail. Consequently, some authors recommend barium swallow if the water-soluble contrast study is nondiagnostic but demonstrates no leak.^{32,57,94} In addition, if there is risk of aspiration, barium is preferred because water-soluble contrast material can cause a severe chemical pneumonitis. Significant necrosis with impending perforation may be suspected on enteric contrast studies when there is esophageal dilation, displacement of the pleural reflection, and widening of the pleuroesophageal line. Enteric contrast studies may fail to detect perforation and therefore must be interpreted within the context of the patient's clinical status.^{9,15,34}

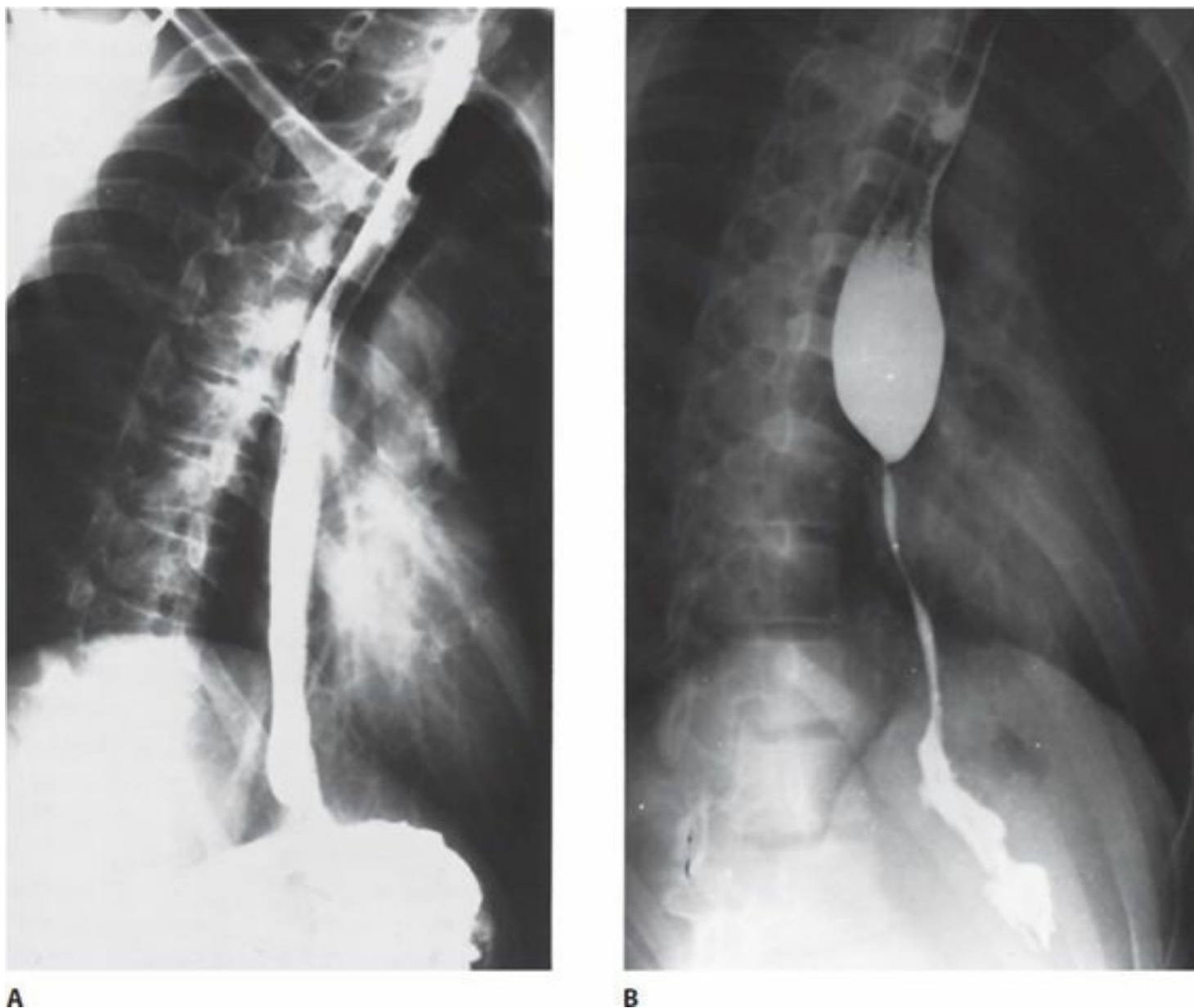


FIGURE 106-4. (A) Barium swallow several days after ingestion of liquid lye shows the esophagus to be atonic. There is poor coating of the esophagus, suggesting edema and intramural penetration. Note that the initial evaluation immediately following a caustic ingestion to assess the extent of injury is esophagoscopy, rather than a contrast esophagram. (B) Four months later, a repeat barium esophagram shows a severe stricture below the middle third of the esophagus. The barium barely passes the stricture, and the remainder of the esophagus is pencil thin. (Used with permission of Emil J. Balthazar, MD, Professor of Radiology, New York University.)

The role for CT scans in caustic ingestions has not been prospectively investigated. In the acute stage, CT has great sensitivity at detecting extraluminal air in the mediastinum or peritoneal cavity as a sign of perforation. In addition, CT can visualize the esophagus and stomach distal to severe caustic burns that cannot be safely seen using endoscopy or an esophagram. CT may therefore replace enteric contrast radiography for detection of perforation within 24 hours of a caustic ingestion. Additionally, one retrospective study suggests that CT grading of esophageal injuries may be superior to endoscopy for prediction of the degree of esophageal damage and the development of stricture formation. These results suggest a promising future role for this noninvasive study following caustic ingestions.⁸⁸ Other imaging modalities have been proposed for assessing esophageal injury after ingestion of caustic substances, including technetium 99m-labeled sucalfate swallow for the presence of injury⁶⁶ and esophageal ultrasonography for determining the depth of injury.⁶⁹

Another use of radiographic imaging is to noninvasively follow the patient after initial evaluation and stabilization. For example, contrast radiography is routinely used in the weeks or months following a caustic ingestion to detect esophageal narrowing representing stricture formation.⁹⁶ Chest CT may also be useful to determine the response of strictures to dilation procedures.

Endoscopy

Endoscopy should be performed within 12 hours and generally not later than 24 hours postingestion. Numerous case series demonstrate that the procedure is safe during this period. Early endoscopy serves multiple purposes in that it allows patients with minimal or no evidence of gastrointestinal injury to be discharged. It also offers a rapid means of obtaining

diagnostic and prognostic information while shortening the period of time that patients forego nutritional support, permitting more precise treatment regimens.^{13,22,36,56,65,82,90,100,105} The use of endoscopic assessment from the second or third day postingestion is discouraged and should be avoided between 5 days and 2 weeks postingestion; at this time, wound strength is least and the risk of perforation is greatest.

The choice of rigid versus flexible endoscopy is dependent on the comfort and experience of the endoscopist. The flexible endoscope has a smaller diameter but may require gentle insufflation of air to achieve or enhance visualization. A prospective evaluation of the role of fiberoptic endoscopy in the management of caustic ingestions recommended the following guidelines: (a) direct visualization of the esophagus prior to advancing the instrument, (b) minimal insufflation of air, (c) passage into the stomach unless there is a severe (particularly circumferential) esophageal burn, and (d) avoidance of retroversion or retroflexion of the instrument within the esophagus. Provided that the patient is hemodynamically stable and endoscopy is indicated, every attempt should be made to visualize the esophagus, stomach, and duodenum as soon as possible after a caustic ingestion.¹⁰⁵ The absence of burns in the esophagus does not imply that severe necrosis and ulcerations do not exist in the stomach^{65,99,105} and duodenum. In the case of termination of endoscopy because of grade IIb or grade III esophageal burns, barium studies,⁸² CT scan, or consideration of surgical exploration should be undertaken to visualize remaining structures.

Endoscopy permits limited evaluation of gastrointestinal injury. For example, the endoscopist is able to appreciate only the mucosal surface of tissues, not the serosal side. This is especially evident in stomach ulcerations, which may appear black and necrotic from a true burn through the layers of the stomach or from the effect of stomach acid on the blood exposed from a shallow lesion. As mentioned above, in these cases, endoscopic ultrasonography during endoscopy may improve assessment of injury depth.^{7,52} Often, however, only direct visualization of serosal and mucosal tissues with laparoscopy or laparotomy allows for definitive evaluation.

Most cases of perforation clearly linked to endoscopy have occurred when the endoscope was advanced through an esophagus with severe circumferential lesions—a violation of current endoscopic standards.¹⁰⁰ In addition, perforations are also more likely to occur when rigid instruments are used in children or in uncooperative patients. Thus the use of the flexible endoscope and adequate procedural sedation has decreased the complications from endoscopic evaluation.⁸² Some authors advocate the presence of a surgeon during endoscopy to assist in the assessment for potential surgical intervention.

MANAGEMENT

Acute Management

As in the case of any patient presenting with a toxicologic emergency, the health care provider must adhere to universal precautions utilizing early decontamination as described in the following section. Initial stabilization should include airway inspection and protection, basic resuscitation principles, and decontamination. Examination of the oropharynx for signs of injury, drooling, and vomitus, as well as careful auscultation of the neck and chest for stridor, may reveal signs of airway edema that should prompt immediate airway protection. Careful and constant attention to signs and symptoms of respiratory distress and airway edema, such as a change in voice, are essential and should prompt early intubation as airway edema may rapidly progress over minutes to hours.

If airway involvement is significant enough to warrant intubation, it is best to mobilize a team of the most skilled physicians early in case of unforeseen complications. A delay in prophylactic airway protection may make subsequent attempts at intubation or bag-valve-mask ventilation difficult or impossible. Direct visual inspection of the vocal cords with a fiberoptic laryngoscope may also reveal signs of impending airway compromise. Patients necessitating intubation are best served by direct visualization of the airway either via direct laryngoscopy or fiberoptic endoscopy, as perforation of edematous tissues of the pharynx and larynx is a grave complication that may occur during blind nasotracheal intubation attempts. Neuromuscular blockers should be avoided for induction of intubation as airway edema and bleeding may distort the anatomy limiting the ability to successfully ventilate via bag-valve-mask should intubation be unsuccessful.

Nonsurgical airway placement is recommended whenever possible as both cricothyrotomy and tracheostomy may interfere with the surgical field if esophageal repair is required.¹⁰⁴ Some patients with significant ingestions, however, may require emergent surgical airway intervention. The decision to perform a surgical airway is dependent on the status of the patient, the ability to orotracheally or nasotracheally intubate via a fiberoptic endoscope, and the comfort of the physician performing the procedure.

Following control of the airway, large-bore intravenous access should be secured and volume resuscitation initiated. Although not studied, most clinicians agree that patients with signs of caustic-induced airway edema benefit from dexamethasone 10 mg (intravenous) in adults and 0.6 mg/kg up to a total dose of 10 mg in children. Both acid and alkali ingestions cause “third spacing” of intravascular fluid to the interstitial space, which can result in hypotension. Empiric rehydration with clinical assessment of central venous pressures should be used to guide individual fluid requirements. Serial physical examinations and constant monitoring of the vital signs and urine output may provide information on the severity of the exposure and the progression in clinical status.

Decontamination, Dilution, and Neutralization

Decontamination should begin with careful, copious irrigation of the patient's skin and eyes when indicated to remove any residual caustic and to prevent contamination of other patients, staff, and equipment.

Gastrointestinal decontamination is usually limited in patients with a caustic ingestion. Induced emesis is contraindicated, as it may cause reintroduction of the caustic to the upper gastrointestinal tract and airway. Activated charcoal is also contraindicated, as it will interfere with tissue evaluation by endoscopy and preclude a subsequent management plan. Additionally, most caustics are not adsorbed to activated charcoal.

Exceptions, such as cationic detergents, that do bind well to activated charcoal⁵⁷ have not been evaluated with a large series. For this reason, therapy with activated charcoal following any caustic ingestion cannot be recommended. Gastric emptying via cautious placement of a narrow nasogastric tube with gentle suction may be attempted to remove the remaining acid in the stomach only in patients with large, life-threatening, intentional ingestions of acid who present within 30 minutes. Although this technique has never been studied and carries the risk of perforation, the outcome for this particular group of patients with massive exposure is often grave, and options for treatment are limited. Therefore, preventing absorption of some portion of the ingested acid may have potential benefit in reducing systemic toxicity. Although the procedure has the potential to induce injury, a risk-to-benefit analysis favors gastric emptying following a presumed lethal ingestion.

In contrast, gastric emptying should be avoided with alkaline and unknown caustic ingestions as blind passage of a nasogastric tube carries the risk of perforation of damaged tissues, a risk that outweighs the benefit.

Exceptions to the general rules of gastrointestinal decontamination of caustics exist in the management of zinc chloride (ZnCl_2) and mercuric chloride (HgCl_2).^{49,95} Both are caustics with severe systemic toxicity.^{12,62,63,79} Ingestion of these xenobiotics causes life-threatening illness from cationic metal exposure. The local caustic effects, though of great concern, are less consequential than the manifestations of systemic absorption. Therefore, prevention of systemic absorption should be addressed primarily, followed by the direct assessment and management of the local effects of these xenobiotics. Initial management to prevent systemic absorption includes aggressive decontamination with gentle nasogastric tube aspiration and administration of activated charcoal. In vitro data exist to suggest adequate activated charcoal adsorption of Hg^{2+} .²

The use of dilutional therapy has been examined using in vitro, ex vivo, and in vivo models in an attempt to assess its efficacy in caustic ingestions. An early in vitro model demonstrated a dramatic increase in temperature when either water or milk was added to a lye containing crystal drain opener (NaOH).⁸⁷ Another in vitro model found less consequential increases in temperature despite large volumes of diluent. Results of both studies suggested that dilutional therapy was of limited benefit.⁶¹ Dilutional therapy was also attended by an increase in temperature in an ex vivo study of harvested rat esophagi that examined the histopathologic effects of saline dilution after an alkali injury. Additionally, the usefulness of dilution appeared to be inversely related to the length of time from exposure, with minimal efficacy when delay to initiation was as short as 30 minutes.^{42,43} In contrast, an in vivo canine model of alkaline injury demonstrated that water dilution did not cause an increase in either temperature or intraluminal pressures.⁴⁵

The extrapolation of these variable results to humans with caustic ingestions is limited and suggests that histologic damage can only be attenuated by milk or water when administered within the first seconds to minutes following ingestion.^{5,42-45,53} For solid, as opposed to liquid, substances (eg, crystal lye), there may be some value for delayed dilutional therapy, as tissue contact time is increased with solids and their concentration is usually 100% over a small surface area. Milk may be the best diluent to attenuate the heat generated by a caustic.

Caution should be used in advising patients or family members about the use of diluents. A child who refuses to swallow or take oral liquids should never be forced to do so. In general, dilutional therapy should be limited to the first few minutes after ingestion in patients who have no airway compromise; are not complaining of significant pharyngeal, chest, or abdominal pain; are not vomiting; and are alert. Dilutional therapy should be avoided in patients with nausea, drooling, stridor, or abdominal distension as it may stimulate vomiting and result in reintroduction of the caustic into the upper gastrointestinal tract.⁸⁷

Attempts at neutralization of ingested caustics should likewise be avoided. This technique has the potential to worsen tissue damage by forming gas and generating an exothermic reaction. In vitro and ex vivo models demonstrate that neutralization of caustics generates heat, requires a large volume to attain physiologic pH, and may have limited usefulness in preventing histologic damage if delayed beyond the first several minutes following caustic exposure.^{41,87} In one in vivo canine model, orange juice was used to neutralize sodium hydroxide-induced gastric injury and demonstrated no change in temperature or intraluminal pressure.⁴⁵ Despite this study, neutralization is not recommended; there are no other data demonstrating that clinical outcome is improved.

Surgical Management

The decision to perform surgery in patients with caustic ingestions is obvious in the presence of either endoscopic or diagnostic imaging evidence of perforation,¹⁰⁴ severe abdominal rigidity, or persistent hypotension. Hypotension is a grave

finding and often indicates perforation or significant blood loss. Additionally, elevated PT and PTT,¹⁰⁴ as well as acidemia,¹¹ are correlated with severe caustic injury.

Many patients will not have an obvious indication for surgical intervention despite impending perforation, necrosis, sepsis, or delayed hemorrhage. Although more challenging to diagnose, all these sequelae are potentially avoidable if surgery is performed early⁷⁴ as morbidity and mortality increase in patients whose surgery is delayed.^{22,47,85} For this reason, some surgeons advocate surgery for all patients with grades II and III esophageal burns identified on endoscopy.^{22,65} This aggressive approach allows for direct inspection of serosal surfaces and an opportunity for early surgical repair.

Multiple studies have attempted to codify the signs and symptoms necessary or sufficient to rapidly identify patients who would benefit from surgery but who lack clear clinical indications. Several retrospective and prospective series of caustic ingestions found that patients with large ingestions (>150 mL), shock, acidemia, or coagulation disorders tended to have severe findings on surgical exploration. These studies also reinforce that the abdominal examination was frequently unreliable in predicting the need for surgery.^{104,106} It should be noted, again, that patients with severe acid injuries may lack abdominal pain, abdominal tenderness, and have positive findings on diagnostic imaging.^{19,106} One author used a stepwise approach of bronchoscopy, endoscopy, and abdominal ultrasonography to provide additional information regarding extent of injury prior to surgery. Respiratory distress, ascites, pleural fluid, and a serum pH less than 7.2 were used as indications for surgery.¹⁰⁴ A history of a large-volume caustic ingestion (between 40 and 200 mL) should also prompt consideration of early surgical intervention as delay is associated with increased mortality.^{19,104}

Surgical intervention may include laparotomy for tissue visualization, resection, and repair of perforations. Laparoscopy may also be used, although it may not allow inspection of the posterior aspect of the stomach.

Subacute Management

The extent of tissue injury dictates the subsequent management and disposition of patients with caustic ingestions.

Grade I Esophageal Injuries. Patients with isolated grade I injuries of the esophagus do not develop strictures and are not at increased risk of carcinoma. Their diet can be resumed as tolerated. No further therapy is required. These patients can be discharged from the emergency department as long as they are able to eat and drink and their psychiatric status is stable.

Grade IIa Esophageal Injuries. If endoscopy reveals grade IIa lesions of the esophagus and sparing of the stomach, a soft diet can be resumed as tolerated or a nasogastric tube can be passed under direct visualization. If oral intake is contraindicated because of the risk of perforation, feeding via gastrostomy, jejunostomy, or total parenteral nutrition should be instituted as rapidly as possible. Providing interim enteral support is imperative as metabolic demands are increased in any patient with a significant burn.

Grades IIb and III Esophageal Injuries. Patients with grades IIb and III lesions must be followed for the complications of perforation, infection, and stricture development. Strictures are a debilitating complication of both acid and alkali ingestions that can evolve over a period of weeks or months. Strictures form as a result of the natural process by which the body repairs injured tissue through the production of collagen with resultant scar formation. Although corticosteroid therapy is theorized to arrest the process of inflammatory repair and potentially prevent stricture formation, there is some evidence that grade III burns, in particular, will progress to stricture formation regardless of therapy.^{3,36,100} In addition to stricture formation, patients with grade III burns are also at high risk for other complications, including fistula formation, infection, and perforation with associated mediastinitis and peritonitis. The use of corticosteroids in the management of grade III burns may mask infection and make the friable, necrotic esophageal tissue more prone to perforation.⁷⁸ For these reasons, corticosteroid therapy is not a recommended therapy for grade III esophageal burns. When required in these patients for other indications such as caustic-induced airway inflammation, short-term corticosteroids should be administered.

Currently, some controversy exists regarding the use of corticosteroid therapy in the management of grade IIb circumferential esophageal burns. A meta-analysis of studies completed from 1956 to 1991, with a total of 361 patients, evaluated the efficacy of corticosteroid therapy and found that in patients with grades II and III esophageal burns, strictures formed in 19% of the corticosteroid-treated group and in 41% of the untreated group.⁴⁶ The usefulness of the results of this study, however, are limited as no distinction was made between grades II and III burns. Another meta-analysis of studies from 1991 to 2003, with a total of 211 patients, was unable to find a benefit in treating patients with corticosteroids with grades II and III esophageal burns.⁷⁸ However, no distinction was made between grades II and III burns. A systematic pooled analysis of studies from 1956 to 2006, with a total of 328 patients, attempted to reevaluate the usefulness of corticosteroid therapy in grade II esophageal burns. Although methodologically limited, this study found no benefit in treating patients with steroids with grade II esophageal burns. A major limitation to the clinical usefulness of this study is that no distinction was made between grades IIa and IIb burns.²⁴ In addition, a multitude of case series also failed to clearly differentiate between grades IIa, IIb, and III lesions, making clinical application of their results difficult.^{3,15,68,100}

Two prospective studies attempted to evaluate the efficacy of corticosteroid therapy for caustic injuries to the esophagus. Both these studies failed to show a benefit of corticosteroid therapy, and one even suggested harm.^{2,3,49} It is imperative that the clinician understands that neither study clearly differentiates between grades IIb and III lesions.

Adequate human data demonstrating the efficacy of corticosteroids with or without antibiotics in the treatment of grade IIb circumferential lesions have yet to be generated. Because of the inherent risks involved in this therapy and the paucity of data supporting their use, corticosteroid therapy in the management of grade IIb esophageal burns can no longer be routinely recommended.

No major outcome studies have investigated the use of antibiotics alone as prophylactic treatment for stricture prevention, but most clinicians would agree that it is probably best to reserve antibiotics for an identified source of infection.

A variety of other management strategies have been used in an attempt to prevent strictures and esophageal obstruction. In both animal models⁸⁴ and in human case series,^{38,67,83} intraluminal stents and nasogastric tubes⁶⁷ made of silicone rubber tubing can successfully maintain the patency of the esophageal lumen. For nutritional support, the stents are usually attached to a feeding tube secured in the nasopharynx through which the patient can receive feedings without interfering with esophageal repair. These tubes are left in place for 3 weeks^{83,84} and are often used with concomitant corticosteroid and antibiotic therapy. In animal models, the use of a stent for 3 weeks is superior in maintaining esophageal patency when compared to corticosteroids and antibiotics alone.⁸⁴

Potential disadvantages of esophageal stents include mechanical trauma at the site and increased reflux, both of which may inhibit healing.⁹³ A feline model of esophageal exposure to sodium hydroxide used stents but reported deaths from aspiration and mediastinitis.⁸⁴ One series of 251 humans exposed to caustics who were managed with silicone rubber stents found that the procedure was successful in preventing stricture formation.⁸

Additionally, a plethora of animal models have attempted to identify therapies that attenuate oxidative damage, inhibit synthesis, or stimulate breakdown of collagen and thereby prevent stricture formation. β -Amino propionitrile,⁵⁹ penicillamine,²⁷ N-acetylcysteine,⁵⁵ halofuginone,^{31,77} vitamin E, sphingosylphosphorylcholine, colchicine, erythropoietin,⁶ mitomycin C,⁹⁸ ozone,³³ fibroblast growth factor,⁷⁶ 5-fluorouracil,²⁰ ibuprofen,³⁷ and retinoic acid¹⁶ are some of these xenobiotics. As none of these treatments have been adequately studied in humans, they cannot currently be recommended in the routine management of caustic ingestions.

Chronic Treatment of Strictures

Commonly, the management of esophageal strictures includes early endoscopic dilation, for which a variety of types of dilators are available. Contrast CT can be used to determine maximal esophageal wall thickness, which can then be used to predict response, as well as the number of sessions required to achieve adequate dilation. Multiple dilations are often necessary. In one study, patients with a maximal esophageal wall thickness of 9 mm or greater required more than seven sessions to achieve adequate dilation. This was significantly higher than in patients with a lesser maximal wall thickness. Measurement of maximal wall thickness may be also be useful in determining long-term follow-up, type of nutritional support, and the potential need for surgical repair as an alternative to dilations. It may also provide an indication for those who should undergo dilation under fluoroscopy to limit the risk of perforation.

The risk of perforation from esophageal dilation is decreased if the initial procedure is delayed beyond 4 weeks postingestion, when healing, remodeling, and potential stricture formation in the esophagus have already taken place. Several series report perforation secondary to esophageal dilation.^{36,81,100} Following perforation, patients may complain of dyspnea or chest pain with associated subcutaneous emphysema or pneumomediastinum. Diagnostic imaging may identify the perforation and provide information for emergent surgical repair if the diagnosis is unclear.

Patients with stricture formation require long-term endoscopic follow-up for the presence of neoplastic changes of the esophagus that may occur with a delay of several decades.⁶

Management of Ophthalmic Exposures

Ophthalmic exposures frequently occur from splash injuries and malicious events as well as from the alkaline byproducts of sodium azide released in automobile air bag deployment and rupture.¹⁰² The mainstay of therapy for these patients is immediate irrigation of the eye for a minimum of 15 minutes with 0.9% sodium chloride, lactated Ringer solution, or tap water, if it is the only therapy immediately available. Several liters of irrigation fluid are recommended. The normal pH of ophthalmic secretions is approximately 6.5 to 7.6. This can be tested colorimetrically by using a urine dipstick, which can test a range of pH from 5 to 9.⁶⁴ Litmus paper can be used in the same fashion. Another useful option in acid exposures is Nitrazine paper, which changes color from yellow to dark blue at a pH above 6.5.²⁵ These different test strips can be applied to the ophthalmic secretions to test the baseline pH and followed with intermittent evaluations after 15 minutes of lavage to determine the adequacy of irrigation. If these xenobiotics are not readily available, irrigation should not be

delayed, as the depth of penetration of the caustic agent will determine outcome. Anterior chamber irrigation may be required and should be performed emergently by an ophthalmologist. A thorough eye examination should be completed, and follow-up should be arranged. [Chapter 25](#) contains a more detailed description of the evaluation and management of toxicologic emergencies of the eye.

SUMMARY

- Initial management of all patients with caustic exposures begins with universal precautions in an effort to prevent further contamination of staff, other patients, and equipment.
- In patients with caustic ingestions, airway assessment and stabilization are of primary importance. Airway edema is the only indication for initiation of corticosteroid therapy.
- There is no routine recommendation for induced emesis, lavage, activated charcoal, neutralization, or dilutional therapy.
- Significant caustic injury should be suspected in all patients with intentional ingestions and in patients with unintentional ingestions presenting with stridor; vomiting; drooling; and pain in the oropharynx, chest, or abdomen.
- All patients with suspected significant ingestions should undergo endoscopy or CT emergently so that effective treatment strategies may be initiated expeditiously.
- Surgeons should be involved in the initial assessment of all patients with suspected significant ingestions and those who have an acute abdomen or hypotension so that any surgical intervention deemed necessary may be performed promptly.

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107 HYDROFLUORIC ACID AND FLUORIDES

Mark Su

HISTORY AND EPIDEMIOLOGY

Hydrofluoric acid (HF) has been known for centuries for its ability to dissolve silica. The Nuremberg artist Schwanhard is given credit for the first attempt to use HF vapors to etch glass in 1670.⁴⁷ Today, HF has multiple applications and is widely used throughout industry. In addition to glass etching, HF is used in brick cleaning, etching microchips in the semiconductor industry, electroplating, leather tanning, rust removal, and the cleaning of porcelain.⁴⁷ From 2009 to 2011, the American Association of Poison Control Centers reported more than 1000 exposures to HF and at least 3 deaths (Chap. 136). The hands are the commonest part of the body injured. Exposures to HF often occur as an unintentional occupational hazard. The actual number of work-related poisonings from HF appears difficult to quantitate because of limitations in International Classification of Diseases (ICD) medical coding and the lack of notification of regional poison centers by worksites.¹⁰

HF is also the commonest cause of fluoride poisoning, although other forms of fluoride, including sodium fluoride (NaF), ammonium bifluoride (NH_4HF_2), and sodium or zinc fluorosilicate, may also produce significant toxicity. Historically, NaF has been used as an insecticide, rodenticide, an antihelminthic for swine, and a delousing powder for poultry and cattle. NH_4HF_2 is mainly used in industrial inorganic chemistry, especially in the processing of alloys and in glass etching. Other fluoride salts are widely used in the steel industry, drinking water, toothpaste additives, electroplating, lumber treatment, and the glass and enamel industries.

The widespread use of HF and fluoride containing compounds has resulted in significant toxicity. In 1988, an oil refinery in Texas released a cloud of hydrogen fluoride gas that resulted in 36 people requiring hospital treatment.³⁸ The petroleum industry has since been plagued by similar HF incidents.⁹⁸ NaF was responsible for the poisoning of 263 people and 47 fatalities when it was mistaken for powdered milk and unintentionally combined with scrambled eggs.⁵⁵ Following ingestion, fluoride salts can be converted to HF in vivo, resulting in significant fluoride toxicity.

CHEMISTRY

HF is synthesized as the product of gaseous sulfuric acid and calcium fluoride, which is subsequently cooled to a liquid.⁵⁷ Aqueous HF is a weak acid, with a pK_a of approximately 3.2; as such, it is approximately 1000 times less dissociated than an equimolar strong acid such as hydrochloric acid. HF is generally available in concentrations from 3% to 40%, for use in both industry and the home. Anhydrous HF is highly concentrated (>70%) and used almost exclusively for industrial purposes. HF has unique properties that can cause life-threatening complications following seemingly trivial exposure.

Sodium fluoride is commonly synthesized by the reaction of sodium hydroxide (NaOH) with HF, with subsequent purification by recrystallization. NaF is highly soluble in water and readily dissociates.⁴

To synthesize NH_4HF_2 , ammonium fluoride (NH_4F) is first formed by the reaction of ammonium hydroxide (NH_4OH) and HF. Ammonium fluoride is then converted to bifluoride by dehydrating the aqueous solution.

Fluorine is the most electronegative element in the Periodic Table due to the relatively large number of protons in the nucleus compared to molecular size and the minimal amount of screening or shielding by inner electrons. Other halides possess lesser electronegative properties. Consequently, the corresponding anion of fluorine, the fluoride ion (F^-), is a weak base because it possesses a limited ability to donate its electrons. Liberation of the fluoride ion from the previously mentioned compounds is believed to be the major determinant of toxicity.

PATHOPHYSIOLOGY

Exposures to HF occur via dermal, ocular, inhalation, oral and rectal routes.¹⁸ A permeability coefficient of 1.4×10^{-4} cm/sec allows HF to penetrate deeply into tissues prior to dissociating into hydrogen ions and highly electronegative fluoride ions.³⁴ These fluoride ions avidly bind to extracellular and intracellular stores of calcium and magnesium,

depleting them, and ultimately leading to cellular dysfunction and cell death.^{11,54,63} The alteration in local calcium homeostasis causes neuroexcitation and accounts for the development of neuropathic pain. Furthermore, ischemia related to calcium dysregulation mediated localized vasospasm is likely an additional contributory factor to the development of pain.^{42,89}

Formation of insoluble calcium fluoride (CaF_2) is proposed as the etiology for both the precipitous fall in serum calcium concentration and the severe pain associated with tissue toxicity. There are several theories regarding the actual fate of calcium and fluoride ions in tissues. In vitro evidence suggests that fluorapatite is formed in the presence of phosphate and hydroxyapatite. This may be a more likely pathway for disposition of the fluoride ion.¹¹ Fluorapatite, like calcium fluoride, is insoluble and its formation may contribute to the clinical findings recognized following HF toxicity.

Fluoride also binds magnesium and manganese and there is in vitro evidence that this interferes with many enzyme systems. In the anhydrous form, the high concentration of hydrogen ions in HF also produces a caustic burn similar to that caused by strong acids (**Chap. 106**). The minimal lethal oral dose in humans is approximately 5 to 10 g of sodium fluoride.⁵

CLINICAL MANIFESTATIONS

Local Effects

Skin. The extent of tissue injury following dermal exposure is determined by the volume, concentration, and contact time with the tissues. Following dermal exposure, the concentration of HF is directly related to the onset of pain at the contact site.^{31,56,88} High concentrations (greater than 50%) cause immediate pain with visible tissue damage.⁸² Exposure to household rust-removal products (6% and 12% HF) is often associated with a delay of several hours before pain develops.^{31,83,93,94} The initial site of injury may also appear relatively benign despite significant subjective complaints of pain. Over time, the tissue may become hyperemic, with subsequent blanching and coagulative necrosis. As calcium complexes precipitate, a white discoloration of the affected area may appear.⁷³ (**Fig. 107–1**) The development of ulceration is dependent on the concentration and duration of contact.^{27,48,56} If more than 2% of the body surface area is burned with highly concentrated HF, life-threatening systemic toxicity should be expected.^{20,70,72,82,88} Small body surface area exposures to low concentrations typically do not result in life-threatening systemic toxicity, although fatalities have resulted with dermal exposures to concentrated HF covering less than 5% body surface area.⁸⁷



FIGURE 107–1. Severe injury to the fingers resulted from exposure to hydrofluoric acid. Note the arterial line in place for administration of calcium. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Pulmonary. Patients with inhalational exposures can present with a variety of signs and symptoms depending on the HF concentration and exposure time. Thirteen oil refinery workers exposed to a low-concentration HF mist experienced minor upper respiratory tract irritation.⁵² In contrast, in a mass inhalational exposure to HF, throat burning, and shortness of breath were among the more common chief complaints.⁹⁸ Some of these patients developed hypoxemia and hypocalcemia, and they had altered pulmonary function tests. Stridor, wheezing, rhonchi, and erythema and ulcers of the upper respiratory tract were described. Eye pain was also noted, reinforcing the fact that ocular injury typically accompanies inhalational or dermal exposures.^{52,61,77,98}

Gastrointestinal. Intentional ingestion of concentrated HF (or other fluoride salts) causes significant gastritis yet often

spares the remainder of the gastrointestinal tract. Patients promptly develop vomiting and abdominal pain. Although systemic absorption is rapid and almost invariably fatal, there is at least one report of a patient who ingested a low concentration (8%) of HF and suffered multiple episodes of ventricular fibrillation but was successfully resuscitated⁸⁵ Following HF ingestion, patients may present with an altered mental status, airway compromise, and dysrhythmias^{13,55,58,85}

Ocular. HF results in more extensive injury to the eye than most other acids⁶⁴ Ocular exposures from liquid splashes or hydrogen fluoride gas can rapidly denude the corneal and conjunctival epithelium, leading to stromal corneal edema, conjunctival ischemia, sloughing, and chemosis⁴⁷ Fluoride ions can penetrate deeply to affect the anterior chamber structures⁴⁷ The effects are usually noted within one day⁴⁷ Other possible findings include corneal revascularization, recurrent epithelial erosions, and, sometimes, keratoconjunctivitis sicca (dry eye) developing as a long-term complication with subsequent corneal ulcers^{7,64,78}

Systemic Effects

Significant systemic toxicity can occur via any route of exposure because of the ability of HF to penetrate tissues. The potential for systemic toxicity is an important consideration in management as patients should be rapidly decontaminated and treated.^{12,16,33,81,82,90,91} Fatal exposures to HF by any route share the similar features of hypocalcemia, hypomagnesemia, and, in many cases, hyperkalemia as preterminal events.^{4,13,19,23,33,56,58,65,66,88} In some circumstances, the hypocalcemia severely disrupts the coagulation cascade, resulting in the inability of blood clotting, even on postmortem examination.^{58,68,69}

Fatalities from HF may occur as a result of either sudden onset myocardial conduction failure or ventricular fibrillation. Although the evidence regarding the mechanism of myocardial irritability is inconclusive, electrolyte disturbances that lead to ventricular dysrhythmias, including ventricular fibrillation, are thought to be the primary cause of death in patients with severe systemic fluoride poisoning.^{20,71,82,88,102} Although one postmortem human case reveals significant structural myocardial injury,⁶² interestingly, histologic abnormalities of the myocardium do not occur in canine models.^{25,68}

Systemic fluoride toxicity results in hypocalcemia, by mechanisms not fully elucidated. In addition, fluoride may cause calcium ions to accumulate intracellularly, leading to an efflux of potassium ions into the extracellular space.^{25,54,68} One in vitro study performed with human erythrocytes suggests that fluoride inhibition of $\text{Na}^+\text{-K}^+\text{-ATPase}$ and $\text{Na}^+\text{-Ca}^{2+}$ exchange lead to intracellular hypercalcemia.⁶⁷ The subsequent hyperkalemia may alter the automaticity and resting potential of the heart, leading to fatal dysrhythmias⁶⁵ (Chap. 64). Dogs treated with quinidine, a potassium efflux blocker, are protected from lethal doses of intravenous sodium fluoride.²⁵ Likewise, amiodarone, which also blocks potassium efflux, has demonstrable efficacy in both in vitro and in vivo models of fluoride toxicity.⁸⁶ However, efficacy in humans has not been studied or documented. Furthermore, the mechanism of toxicity may be much more complicated.¹⁰⁴ A child with systemic fluoride toxicity, who was appropriately repleted with calcium, and had normal electrolytes still experienced nonfatal ventricular fibrillation.^{12,104} Perhaps this is because serum potassium, calcium, and magnesium concentrations only partly represent tissue concentrations.^{11,12,25,65,66} Furthermore, HF may directly impair myocardial function. Rabbits exposed to topical HF over 2% of their total body surface area developed focal necrosis of myocardial fibers, as well as significant elevations in cardiac enzymes that persisted for almost 5 days after injury.¹⁰³

Assessing Severity of Clinical Exposures

Historical and clinical features of an exposure will determine which HF exposures are life threatening. All oral and inhalational exposures should be considered potentially fatal, as should burns of the face and neck, regardless of HF concentration. Inhalational exposure should be assumed for all patients with skin burns of greater than 5% body surface area, any exposure to HF concentrations greater than 50%, and head and neck burns.⁴⁶ Patients presenting with altered mental status directly related to HF are critically ill and necessitate rapid therapy.

HF concentrations of greater than 20% have the potential for significant toxicity in any patient, even if only a small surface area is exposed.⁶⁰ As a general rule, patients who experience severe pain within minutes of contact are most likely exposed to a very high concentration of HF, and their condition can rapidly deteriorate. An otherwise well appearing patient may have a precipitous demise without any clinical manifestations of hypocalcemia. Furthermore, it is possible that systemic toxicity may occur following a seemingly trivial exposure. A 36 year-old man was exposed to 20% HF over 3% of his body surface area and subsequently developed hypocalcemia, hypomagnesemia, and cardiac arrest 16 hours later.¹⁰⁰

DIAGNOSTIC TESTING

Diagnostic testing for systemic fluoride poisoning is currently based on monitoring of serum electrolytes. Ionized calcium, magnesium, and potassium should be serially monitored.³³ Additional information may be obtained from a venous or

arterial blood gas analysis. As systemic toxicity progresses, a metabolic acidosis will likely develop.¹¹ Serum fluoride concentrations may be assessed but the results will not return in a clinically relevant timeframe. Although a serum fluoride concentration of 0.3 mg/dL has been reported as fatal, one patient survived with a serum fluoride concentration of 1.4 mg/dL.^{88,104}

Electrocardiographic (ECG) findings of both hypocalcemia (prolonged QT interval) and hyperkalemia (peaked T waves) may be reliable indicators of toxicity (Chap. 16).^{4,16,33,36,41,69,88} In fact, ECG findings of peaked T waves from hyperkalemia have preceded the onset of ventricular dysrhythmias in reported cases, thus potentially serving as a marker of severe fluoride toxicity.^{12,66} It should be noted that in some cases of HF poisoning, hypokalemia is reported^{26,32,100} and for unclear reasons, may be specifically related to sodium fluoride toxicity.⁹⁵

MANAGEMENT

General

For patients with more than localized exposure to low concentration HF or any exposure to high concentration HF, the mainstay of management is to prevent or limit systemic absorption, assess for systemic toxicity, and rapidly correct any electrolyte imbalances. Intravenous access should be secured. An ECG should be obtained and examined for dysrhythmias and signs of hypocalcemia, hypomagnesemia, and hyperkalemia. The patient should be attached to continuous cardiac monitoring and have a rapid assessment of serum electrolyte concentrations. A Foley catheter should be placed as indicated to follow urine output if the patient cannot void.

Rapid airway assessment and protection should occur early in patients with inhalation or ingestion, respiratory distress, vomiting, or burns significant enough to cause a change in mental status or voice.

For patients with less significant dermal exposures, recent studies have focused on alternatives to irrigation with water or saline as topical decontamination techniques. The compound “hexafluorine” is promoted for dermal and ocular decontamination of HF splashes.^{59,84} Hexafluorine is a proprietary name whose chemical formula is not disclosed, and papers that report success have strong ties to the manufacturer. In a controlled and blinded experimental study, hexafluorine treatment was less effective than irrigation with water followed by the application of topical calcium.⁴⁰ In a follow-up animal study, water irrigation was as effective as hexafluorine in preventing systemic toxicity from HF.⁴³ At this time, until further objective data are available, the use of hexafluorine for initial decontamination of HF exposures is not indicated.

An iodine containing preparation was evaluated in a guinea pig model of HF-induced burns and found to be associated with significant reductions in ulceration area.⁹⁹ Iodine is hypothesized to inhibit apoptosis and has demonstrated protective effects against burns from various alkylating agents, including mustard gas.⁹⁹ Unfortunately, because experience with iodine treatment of human HF burns is lacking, it cannot be recommended at this time.

The most important therapy for skin exposures is rapid removal of clothing and irrigation of the affected area with copious amounts of water or saline, whichever is more readily available.^{2,51,53,57}

One report describes a woman who was dying from severe HF toxicity who was treated by amputation of the affected limb and survived. Although rarely considered, this may be an alternative measure for patients who are critically ill and demonstrate an inadequate response to all other therapeutic modalities.^{15,49}

Dermal Toxicity

Several therapeutic options are studied and described in animal models for treatment of topical HF burns. Unfortunately, many study designs use histologic or subjective wound inspection as outcome parameters,^{17,74} some with unblinded inspection.^{14,29,49,51,71} These animal models do not address the clinically important parameters of pain reduction, cosmesis, and functionality.

Topical calcium gel should be applied to the affected area (Antidotes in Depth: A29). A commercial gel is available in the United States, but an acceptable substitute may be created, if necessary. This is accomplished by mixing 3.5 g of calcium gluconate powder in 150 mL of sterile water-soluble lubricant, or 25 mL of 10% calcium gluconate in 75 mL of sterile water-soluble lubricant.^{2,17,46} If calcium gluconate is unavailable, calcium chloride or calcium carbonate can be used in a similar formulation.²¹ This topical therapy for severe and non-life-threatening exposures scavenges fluoride ions. An animal study examining the efficacy and mechanism of topical calcium gel therapy found that the fluoride ion concentration in the calcium gel was significantly higher than non calcium-containing gel controls. Although this was a limited study, these animals also had a decrease in urinary fluoride ion concentration as compared to controls, suggesting less overall tissue absorption of the HF.⁵¹ Delivery of calcium transcutaneously may be enhanced by various means. In a rodent study of HF burns, iontophoretic (facilitated transport using an electromotive force) delivery of calcium ions appeared to increase calcium concentrations in vitro and improve pathologic changes in vivo.¹⁰¹ Significant limitations to this study are timing to administration of therapy and feasibility in patients with complex burns.⁷⁹ Human data are lacking.

Dimethyl sulfoxide (DMSO) mixed with topical calcium salts may also facilitate the transport of calcium ions through the skin to penetrate deeply into the tissues. DMSO also is able to act as a scavenger of free radicals, thus limiting inflammation and ongoing injury.³⁶ Although one group of authors recently advocated the combined use of DMSO and calcium,³⁶ concerns remain over reported adverse effects of DMSO.⁴⁷ There are currently inadequate data to support the use of DMSO in the treatment of HF burns.

Four therapies have had variable success in human exposures; the application of calcium via topical, intradermal, intravenous, and intraarterial routes. After irrigation, a gel solution of calcium carbonate or gluconate can be applied directly to the affected area or mixed directly into a sterile surgical glove and then placed on the burned hand for 30 minutes. Two case series report limited success with this therapy.^{2,21} Some patients describe prompt and dramatic relief of pain. Alternatively or simultaneously, analgesics can be administered orally or parenterally as needed but preferably not to the point of sedation, because local pain response will guide therapy. Digital nerve blocks with subcutaneous lidocaine or bupivacaine can be used for patients presenting 12 to 24 hours after the injury from a low concentration of HF and with no systemic signs of toxicity, at which time topical calcium salts are unlikely to be effective.²⁸

If topical gel therapy fails within the first few minutes of application, consideration should be given to intradermal therapy with dilute calcium gluconate, because the benefit of topical gel in pain control often occurs immediately. This treatment may have limited usefulness, however, in nondistensible spaces such as fingertips. Histologic studies in animal models demonstrate that 10% calcium chloride solution can be damaging to the tissues and is contraindicated.^{28,35} The preferred method is to approach the wound from a distal point of injury and inject intradermally no more than 0.5 mL/cm² of 5% calcium gluconate. Although one author recommends a palmar fasciotomy whenever this method of treatment is used in the hand,² this practice is not currently recommended unless a compartment syndrome is present. The potential for iatrogenic injury exceeds the potential benefit of injections in the hand. The limits of intradermal injection include the potential to increase soft tissue damage without adequate relief, infection, and inadequate space to safely inject without causing a compartment syndrome.

Effective pain relief is especially problematic for nail bed involvement, leading some authors to suggest removal of the nail. This approach has some advantages in accessing the affected area. However, it is a painful procedure that is often cosmetically undesirable and the outcome is not always significantly improved.

If the wound is large or on a section of the fingerpad or an area that is not amenable to intradermal injections, consideration should be given to the use of intraarterial calcium gluconate. This procedure delivers calcium directly to the affected tissue from a proximal artery. Placement should be ipsilateral and proximal to the affected area, usually in the radial or brachial artery. The method of obtaining access is somewhat debated. Because of the potential to damage the endothelial lining of the artery and because extravasation can have potentially devastating consequences, angiographic confirmation or direct visualization of the vessel was formerly recommended. This practice is still prudent if cannulation of the artery is expected to be difficult because of prior surgery or if an anatomic deformity is suspected. If the arterial line is carefully placed in a single attempt, and a good confirmatory arterial wave form is obtained, the infusion can be started. The recommended protocol consists of 10 mL of 10% calcium gluconate added to either 40 mL of D₅W (dextrose 5% in water) or 0.9% sodium chloride solution infused continuously over 4 hours.^{1,2,75,83,92,93} This results in a 2% calcium gluconate solution. An animal model examined the effect of undiluted 10% calcium gluconate intraaortically. Although the model did not involve exposure to HF, there was significant tissue injury in the vessel wall as compared to a 2% calcium gluconate solution.²⁸ Calcium chloride has also been used successfully, although the potential for vessel injury and extravasation are significant and there is no defined benefit over calcium gluconate.^{92,105} The complications associated with the use of intraarterial calcium infusion in several case series were relatively benign and included radial artery spasm, hematoma, inflammation at the puncture site, and a fall in serum magnesium.^{80,93} After the infusion is initiated, patients typically experience significant pain relief. Patients requiring an arterial line for treatment should be admitted to the hospital, as the majority will require more than one treatment, and some patients may require as many as five separate infusions of calcium gluconate. Although wounds may require Debridement,² some suggest that following intraarterial calcium infusion, tissue can be salvaged that initially would not have been considered viable.⁹⁴ There are no reported cases of clinically significant hypercalcemia following infusion as the total dose infused is quite low, although serum calcium concentrations were not always routinely recorded.

Magnesium salts are an alternative or adjunctive therapy to the administration of calcium salts for patients with dermal HF burns. Magnesium hydroxide and magnesium gluconate gel show histologic evidence of efficacy in rabbit models of dermal HF burns.¹⁷ Two other animal models of intravenous magnesium for dermal HF burns also suggest wound healing efficacy.^{24,97} Magnesium is suggested to be an antidote for fluoride poisoning because magnesium fluoride is more soluble than calcium fluoride and magnesium is readily excreted by the kidneys.⁹⁸ However, these magnesium models inadequately address the disadvantage of magnesium salt solubility, and both topical and intravenous magnesium therapy remain incompletely evaluated in humans and therefore not routinely recommended.

Another reported therapy for localized HF poisoning is an intravenous Bier block technique that uses 25 mL of 2.5%

calcium gluconate. In one case, the effects lasted 5 hours and there were no adverse events.³⁹ In two other cases of patients exposed to HF, a 6% calcium gluconate solution administered using this procedure resulted in rapid and complete analgesia with minimal tissue necrosis.⁸⁰ Although the intravenous Bier block technique is not reported as being used in a substantial number of patients, it may be particularly useful when intraarterial infusion is problematic.⁸⁰ Further data are required before this therapy is routinely recommended.

All patients with digital exposures to HF should be observed over 4 to 6 hours, as the pain is likely to recur and reapplication of the gel or an alternative therapy may be necessary. Even if successful pain control is achieved, the patient will require specialized follow-up and wound care.

Inhalational Toxicity

Patients with symptomatic inhalational injuries can be treated with nebulized calcium gluconate. A report of patients exposed to a low concentration of HF and treated with 4 mL of a 2.5% nebulized calcium gluconate solution demonstrated a subjective decrease in irritation with no adverse effects.⁵² Another report demonstrated a good outcome following nebulization of a 5% calcium gluconate solution in a patient with an inhalational exposure.⁵⁰ Because nebulized calcium gluconate appears to be a relatively benign therapy, a dilute solution should be given to all patients with symptomatic inhalational exposures to any concentration of HF.³⁰

Ingestions

In patients with intentional ingestions of HF, gastrointestinal decontamination poses a dilemma. Induction of emesis is potentially harmful and not recommended. Although placement of a nasogastric tube to perform gastric lavage is clearly associated with risks to the patient, insertion of a nasogastric tube may be beneficial if done safely and in a timely manner. Consequently, gastric emptying via a nasogastric tube should be considered because these exposures are almost universally fatal.^{4,13,58,69} Health care providers should exercise extreme caution during this procedure because secondary dermal or inhalational exposures to the provider can occur in the absence of appropriate personal protection. If there is a possibility of inhalation by the provider, the area should be well ventilated. Acceptable forms of hand protection include gloves made of nitrile, butyl rubber, polyvinyl chloride, or neoprene. Latex gloves should not be used. Because aqueous HF is a weak acid, the risk of perforation by passage of a small nasogastric tube may be lower than the risk of death from systemic absorption.^{4,58} In the acidic environment of the stomach, more of the weak acid solution remains unionized, thus penetrating the gastric mucosa and causing rapid systemic poisoning. Moreover, activated charcoal is unlikely to adsorb the relatively small fluoride ions.

If an oral exposure occurs, a solution of calcium or magnesium salt should be delivered to the stomach as soon as possible to prevent HF penetration and to provide an alternative source of cations for the damaging electronegative fluoride ions.

When comparing the efficacy of calcium to magnesium salts, calcium may be better than magnesium in reducing the bioavailability of fluoride as described in a murine model.³⁸ Magnesium citrate in a standard cathartic dose, magnesium sulfate, or any of the calcium solutions can be administered orally to prevent absorption (Antidotes in Depth: A29). Although intuitive, evidence for the benefit of oral calcium or magnesium salts is limited. In a mouse model of oral HF toxicity, administration of calcium or magnesium containing solutions did not change average survival time.³⁷ The study results, however, were limited because the calcium and magnesium salts were premixed together with the HF during administration, thus being an inadequate model for the study of HF ingestion. In a more recent study, the survival rate of mice poisoned with NaF was significantly greater when treated with high doses of oral CaCl₂ or MgSO₄.⁴⁵

Ocular Toxicity

Patients with ocular exposures should have each eye irrigated with 1 L of 0.9% sodium chloride solution, lactated Ringer solution, or water.⁶⁴ Although there are limited data, repetitive or prolonged irrigation appears to worsen outcome.⁶⁴ A complete ophthalmic examination should be performed after the patient is deemed stable, and an ophthalmology consultation should be obtained (Chap. 25). One case report demonstrated a good outcome following ocular HF exposure with the use of 1% calcium gluconate eyedrops.⁷ Although two reviews also recommend the use of 1% calcium gluconate for this purpose,^{30,36} calcium salts tend to be irritating to the eye, and this therapy has not been adequately studied; consequently, use is not indicated at this time. There is no role for gel therapy or intraocular injection in these patients, because most calcium and magnesium salts are potentially toxic to ocular tissues and may actually worsen outcome.^{6,64}

Systemic Toxicity

If there is a clinical suspicion of severe toxicity, the immediate intravenous administration of both calcium and magnesium salts is recommended. In general, calcium gluconate is preferred over calcium chloride because of the risks associated with

extravasation (Antidotes in Depth: A29). Patients may require several grams of calcium to treat severe HF toxicity.³³ Intravenous magnesium can be administered to adults as 20 mL of a 20% solution (4 g) over 20 to 30 minutes. An approach that uses intravenous calcium or magnesium, and local calcium or magnesium gels, to limit absorption may protect against life threatening hypocalcemia and hyperkalemia. Due to the numerous adverse effects of systemic fluoride poisoning, administration of calcium and magnesium salts alone may be insufficient in improving survival from systemic fluoride poisoning.²² Furthermore, an animal model of hydrogen fluoride toxicity found that maintaining a normal acid–base balance was protective against HF toxicity.⁹⁶ Moreover, in a study of patients receiving enflurane anesthesia, urine alkalinization improved the excretion of fluoride.⁷⁶ Thus, it may be beneficial to correct any significant acidemia with hydration and intravenous sodium bicarbonate (calcium salts and sodium bicarbonate cannot be mixed). Since standard treatment for systemic fluoride toxicity includes administration of calcium salts and sodium bicarbonate, hyperkalemia is also addressed.

Treatment with large quantities of calcium and magnesium has not generally resulted in significant hypercalcemia or hypermagnesemia.³⁰ Several explanations are proposed. First, in systemically HF poisoned patients, total-body calcium and magnesium stores are severely decreased so that large doses are required for adequate repletion. Also, most patients who are exposed to HF are young and healthy, with normal kidney function.³⁰ Administration of calcium also results in antidiuretic hormone antagonism on renal tubular reabsorption resulting in polyuria, which facilitates the urinary excretion of calcium and magnesium.³⁰

Because most of the fluoride ions are eliminated renally,^{8,44,51,81} hemodialysis may be considered in patients with severe HF poisoning, particularly if kidney function is compromised. There are several reported cases of successful clearance of fluoride ions via hemodialysis with one case also using continuous venovenous hemodialysis.^{3,8,9} Furthermore, prolonged hemodialysis, beyond the standard 4-hour course, may be necessary in some cases.³ Because the reported clearance rate did not differ significantly from normally functioning kidneys, it is unclear whether hemodialysis alters outcome in patients with normal kidney function.

Although the use of quinidine, a potassium channel blocker, is protective in dogs,⁶⁸ it has not been studied or used in humans. At this time it cannot be routinely recommended but may be considered in the presence of life-threatening ventricular dysrhythmias.

SUMMARY

- Although HF has a pKa of approximately 3.2 and is considered a weak acid, it causes local and systemic toxicity because of fluoride binding to cations.
- Dermal exposure to HF causes severe pain, often before any physical manifestations are evident.
- Patients with greater than 2.5% body surface area HF burns should have serum calcium, magnesium, and potassium checked periodically. Admission may be required for prolonged electrolyte and cardiac monitoring.
- Therapy for local toxicity includes topical calcium salts and systemic analgesia. In some cases, intradermal or intraarterial administration of calcium may be required.
- Therapy for systemic toxicity includes all treatments for local toxicity plus intravenous calcium and magnesium salts, sodium bicarbonate, and potentially hemodialysis.

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A29 ANTIDOTES IN DEPTH

Calcium

Mary Ann Howland

INTRODUCTION

Calcium is essential to maintain the normal function of the heart, vascular smooth muscle, skeletal system, and the nervous system. It is vital in enzymatic reactions, in neurohormonal transmission, and in the maintenance of cellular integrity.²¹ The endocrine system maintains calcium homeostasis. Approximately half of the total serum calcium is ionized and active, and the remainder is primarily bound to albumin. Hypercalcemia raises the threshold for nerve and muscle excitation, resulting in muscle weakness, lethargy, cardiac conduction disturbances, and coma.²¹ Hypocalcemia can result in hyperreflexia, muscle spasms, tetany, seizures, and QT interval prolongation (Chaps. 16 and 19).²¹

PHARMACOLOGY

Early evidence suggested that in hypocalcemic children,¹⁰ intravenous (IV) infusions of calcium chloride produce slightly larger increases in ionic calcium than infusions of calcium gluconate, but this concept has been challenged.^{43,70} Administration of equivalent molar doses of calcium found in calcium chloride (1 g CaCl₂ 10%) and calcium gluconate (3 g Ca gluconate 10%) produce similar serum ionized calcium concentrations, with both peaks occurring within 30 seconds in a model utilizing the anhepatic stage of liver transplant.⁴³ These results support the concept that simple dissociation of calcium from gluconate is responsible for releasing calcium, rather than hepatic metabolism.

ROLE IN CALCIUM CHANNEL BLOCKER TOXICITY

Calcium enters cells in numerous ways. In cardiac and smooth muscles the voltage-dependent L-type channels are inhibited by the calcium channel blockers (CCBs) available in the United States.^{5,60} Patients with CCB overdose (Chap. 61) may develop nausea, vomiting, hypotension, bradycardia, myocardial depression, sinus arrest, atrioventricular (AV) block, and metabolic acidosis with hyperglycemia, shock, pulmonary edema, altered mental status, and seizures.⁵⁰ Because CCBs do not alter either receptor-operated channels or the release of calcium from intracellular stores,⁶⁵ the serum calcium concentration remains normal in overdose.

IV administration of calcium to dogs poisoned with verapamil or diltiazem improves cardiac output secondary to increased inotropy.²⁵ The heart rate and cardiac conduction are affected minimally, if at all.^{22,25,56} Case reports and reviews of the literature suggest similar findings in humans.^{2,3,11,17,20,26,31,34,41,53,54,62}

Calcium should be administered to symptomatic patients with CCB overdoses.^{30,37,40} Unfortunately, the most seriously ill patients respond inadequately, and other measures are often required. The dose of calcium needed to treat patients with CCB overdose is unknown. In animal experiments, there appears to be a dose-related improvement.^{11,25} Since calcium chloride is extremely irritating to small vessels, subcutaneous tissue, and muscle, and may cause necrosis following extravasation, it is usually only administered through a central venous line. The customary approach is to administer an initial IV dose of 3 g of calcium gluconate (30 mL of 10% calcium gluconate) or 1 g of calcium chloride (10 mL of 10% calcium chloride) to adults.⁵⁰ Based on case reports, this dose may need to be repeated as clinically indicated. The hypothesis is that sufficient calcium must be present to compete with the CCB for binding to the L-type calcium channel. One author used a total of 10 g of calcium gluconate as 1 g boluses over 12 minutes after diltiazem induced asystole and another 2.5 g of calcium gluconate minutes later for a second asystolic event, with a resultant serum calcium concentration of 13.44 mg/dL (normal: 8.4–10.2 mg/dL) approximately 1 hour after administration of the calcium gluconate.³² Several authors have successfully treated patients with a total of 18 to 30 g of calcium gluconate or 13 g of calcium chloride over 2 to 12 hours, either by intermittent bolus dose or infusion, without apparent adverse effects.^{11,30,31,37,40,41} However, following the use of large doses of calcium, hypercalcemia can occur and is associated with severe consequences including

myocardial depression and intense vasoconstriction leading to multiorgan ischemia.⁶⁰ Introduction of hyperinsulinemia euglycemia (Antidotes in Depth: A17) and intravenous fat emulsion (Antidotes in Depth: A20) in the treatment of CCB overdose has diminished the need for extensive calcium administration. The provision of massive calcium doses should be limited, and if used, meticulous monitoring of ionized calcium is advised to avoid hypercalcemia (Table A29–1).

TABLE A29–1. Calcium Salts for Intravenous Use

	<i>Calcium Gluconate^a</i>	<i>Calcium Chloride (CaCl₂)^{a,b}</i>
10% Solution	10 mL = 1 g of Ca ²⁺ gluconate 10 mL = 4.5 mEq elemental Ca ²⁺	10 mL = 1 g of CaCl ₂ 10 mL = 13.6 mEq elemental Ca ²⁺
Adult dose	3 g (30 mL of 10% solution) over 10 minutes (unless in extremis—deliver over 30–60 seconds) Repeat every 10–20 minutes up to 3–4 doses as necessary	1 g (10 mL of 10% solution) over 10 minutes (unless in extremis—deliver over 30–60 seconds) Repeat every 10–20 minutes up to 3–4 doses as necessary
Pediatric dose (not to exceed the adult dose)	60 mg/kg (0.6 mL/kg) of 10% solution infused over 5–10 minutes (unless in extremis—deliver over 30–60 seconds) Repeat every 10–20 minutes up to 3–4 doses as necessary	20 mg/kg (0.2 mL/kg) infused over 5–10 minutes (unless in extremis—deliver over 30–60 seconds) Repeat every 10–20 minutes up to 3–4 doses as necessary

^aMonitor calcium after several doses and every 30 minutes during administration. ^bUse of a central venous line is recommended to avoid extravasation.

The administration of calcium to a patient with toxicity from cardioactive steroids such as digoxin might prove harmful.^{24,69} In the event of concurrent overdose with both a cardioactive steroid and a CCB, the early use of digoxin-specific antibody fragments (Antidotes in Depth: A19) should enable the subsequent safe use of calcium (Chap. 65).

Therapy in children is based on more limited data. The American Heart Association pediatric guidelines suggest an initial dose of 20 mg/kg of 10% calcium chloride (0.2 mL/kg), not to exceed the adult dose.¹ This is infused over 5 to 10 minutes, preferably into a central venous line. If a beneficial effect is observed, an infusion of 20 to 50 mg/kg/h follows. These guidelines preferentially suggest calcium chloride based on the study mentioned above that compared the chloride to the gluconate salt in critically ill children with hypocalcemia.¹⁰ However, since CaCl₂ may be irritating, calcium gluconate may be preferable, especially if central venous access is unavailable. The starting dose in children should be 60 mg/kg of 10% calcium gluconate (0.6 mL/kg), not to exceed the adult dose.

ROLE IN β -ADRENERGIC ANTAGONISTS TOXICITY

In vitro studies suggest that the negative inotropic action of β -adrenergic antagonists are related to interference with both the forward and reverse transport of calcium in the sarcoplasmic reticulum and the inhibition of microsomal and mitochondrial calcium uptake (Chap. 62).^{18,38,48} In a canine model of propranolol poisoning, the administration of calcium chloride improved mean arterial pressure, the change in maximal left ventricular pressure over time, and peripheral vascular resistance, but it had no significant effect on bradycardia or QRS complex prolongation.³⁹ Several case reports attest to the beneficial effects of IV calcium in β -adrenergic antagonist overdose.^{9,33,52,57} Because distinguishing an overdose of a CCB from that of a β -adrenergic antagonist may be difficult and the two may be taken simultaneously, a trial of IV calcium is appropriate for a presumed β -adrenergic antagonist overdose if cardioactive steroid toxicity can be excluded.

ROLE IN HYPOCALCEMIA SECONDARY TO ETHYLENE GLYCOL

Following ethylene glycol poisoning (Chap. 109) metabolism of the parent molecule generates oxalic acid, which complexes with calcium and subsequently precipitates in the kidneys, brain, and elsewhere, resulting in hypocalcemia.^{2,31,49,60,63} After exposure to ethylene glycol, the ionized calcium concentration should always be monitored, along with repeated examinations for signs of hypocalcemia such as QT interval prolongation, hyperreflexia, muscle spasms, tetany, and seizures (Chap. 19). IV calcium should be administered in the customary recommended doses (as above) to patients with these findings.

ROLE IN HYPOCALCEMIA SECONDARY TO HYDROFLUORIC ACID AND FLUORIDE-RELEASING XENOBIOTICS

Deaths from dermal, gastrointestinal, and pulmonary hydrofluoric acid (HF) exposures are well documented in the literature.^{13,23,68} In these cases, hypocalcemia is invariably present. Any body contact with HF (Chap. 107) can result in severe burns and death, depending on concentration, area exposed, and duration of exposure. The toxicity results from (a) release of free hydrogen ions; (b) complexation of fluoride with calcium and magnesium to form insoluble salts, which cause cellular necrosis; (c) liberation of potassium ions; and (d) cellular dehydration.^{12,19,42,44} Soluble salts of fluoride and bifluoride (eg, sodium, potassium, and ammonium) have all the toxicity associated with HF and should be managed accordingly. Following HF exposure, the gluconate salt of calcium is used topically and subcutaneously to manage minor to moderate cutaneous burns, intravenously to treat systemic hypocalcemia, and intraarterially to manage significant burns.^{2,12–14,16,19,23,42,44,47,51,55,58,66,67,72} Experimental studies demonstrate that when concentrated HF burns are immediately flushed with water and then treated with topical calcium, burn size is significantly reduced.⁸ Management of HF burns with a topical dimethyl sulfoxide (DMSO)–calcium gluconate combination seems promising, but a randomized clinical trial has yet to be published.²⁷ Although a DMSO preparation is not commercially available, a 2.5% calcium gluconate topical gel is marketed. In the event that the commercial preparation is inaccessible, a topical calcium gel can be prepared from calcium carbonate tablets, calcium gluconate powder or solution, and a water-soluble jelly such as K-Y Jelly (mix 3.5 g calcium gluconate powder or 35 mL of a 10% calcium gluconate solution or 10 g of calcium carbonate tablets or seven 500 mg crushed calcium gluconate tablets with 5 ounces of K-Y Jelly). An experimental study in rats demonstrated that iontophoretic delivery of calcium chloride appeared to enhance the delivery of calcium and to significantly reduce the burn area if applied within 30 minutes, and this may be a promising modality in the future.^{56,71}

The chloride salt is also acceptable for topical therapy. However, calcium chloride should never be injected into tissues (subcutaneously, intramuscularly), since severe tissue necrosis can result.

In patients with severe topical HF exposures, aggressive administration of regional IV calcium using a Bier block technique (10 mL of 10% calcium gluconate in a total volume of 40 mL) or intraarterial calcium (10 mL of 10% calcium gluconate in 50 mL (total volume) of 5% dextrose solution over 4 hours) may be required, along with frequent serum calcium determinations to titrate the dose.^{27,64} One patient who was massively exposed to HF required a total of 267 mEq of calcium infused over a 24 hour period.²³

In patients with life-threatening poisoning and particularly HF inhalation, simultaneous administration of IV, oral, and nebulized 2.5% calcium gluconate can be given to facilitate the availability of the maximum amount of calcium. To prepare nebulized calcium gluconate, mix 1.5 mL of 10% calcium gluconate solution with 4.5 mL of sterile water or 0.9% sodium chloride to make a 2.5% solution. For moderate to severe burns (generally from HF concentrations >10%) of the fingers and hands, an intraarterial calcium infusion may be more effective than local or IV therapy, although it is more invasive^{51,58,64,66,67} and more hazardous.⁵⁸ A calcium gluconate solution (10 mL of 10%) mixed in 40 to 50 mL of 5% dextrose solution can be infused intraarterially over 4 hours followed by subsequent 40 to 50 mL intraarterial infusions after 4 hours when pain persists.⁶⁶ Serum calcium, potassium, and magnesium concentrations should be carefully monitored in all severely poisoned patients.

Hypocalcemia from the ingestion of household fluoride-containing dental products (eg, dental fluoride rinses, sodium fluoride tablets) rarely occurs and is dose dependent. Hypocalcemia and significant morbidity and mortality occur with ingestion of industrial strength fluoride cleaners or fluoride releasers (eg, ammonium bifluoride used for cleaning white wall tires). Patients with these exposures should be treated with calcium in a manner similar to the hypocalcemia from other causes.

ROLE IN HYPOCALCEMIA SECONDARY TO PHOSPHATES

Inappropriate use of oral and rectal phosphates, as a laxative can result in hypocalcemia, hyperphosphatemia, and hyperkalemia with resultant morbidity and mortality.⁴ IV calcium may be needed for life threatening hypocalcemia. However, since administration of calcium in the presence of hyperphosphatemia risks precipitation of calcium phosphate throughout the body, hemodialysis and other therapies should be considered in non-life-threatening cases.

ROLE IN HYPERMAGNESEMIA

Hypermagnesemia causes both direct and indirect depression of skeletal muscle, resulting in neuromuscular blockade, loss of reflexes, and profound muscular paralysis, with attendant ventilatory failure (Chap. 19).^{36,46} Excess magnesium also causes prolongation of the PR interval and QRS complex on electrocardiography (ECG) and depression of the sinoatrial node, leading to a bradycardic arrest. IV calcium serves as a physiologic antagonist to these adverse effects of magnesium (Table A29–1).

ROLE IN HYPERKALEMIA

Hyperkalemia causes significant myocardial depression. The resultant ECG changes are well defined. The height of the T wave increases and lengthening of the PR interval and QRS complex occur; ultimately, a sine wave pattern precipitating cardiac arrest may occur (Chaps. 16 and 19).²¹ Calcium makes the membrane threshold potential less negative, restoring the resting and threshold potential difference so that a larger stimulus is required to depolarize the cell from the resting potential. This stabilization antagonizes the hyperexcitability caused by modest hyperkalemia. However, when severe hyperkalemia exists, voltage-gated sodium channels are inactivated and cannot be depolarized, regardless of the strength of the impulse. Calcium may transform the voltage sensor of the sodium channel from inactive to closed, thus allowing the sodium channel to be opened with depolarization.²⁹ If hyperkalemia is secondary to the toxic effects of cardioactive steroids on the Na^+/K^+ -adenosine triphosphatase (ATPase) pump, IV calcium can potentially exacerbate an already excessive intracellular calcium concentration, making IV calcium potentially harmful (Chap. 65).²¹

ADVERSE EFFECTS AND SAFETY ISSUES

Severe hypercalcemia is defined by a serum calcium concentration greater than 14.0 mg/dL (3.5 mmol/L) in a patient with a normal albumin concentration. The adverse effects of hypercalcemia (independent of the rate of administration) include nausea, vomiting, constipation, ileus, hypertension if intravascular volume is adequate, polyuria, polydipsia, cognitive difficulties, hyporeflexia, coma, and enhanced sensitivity to cardioactive steroids.⁶ Significant hypercalcemia may lead to myocardial depression. The symptoms exhibited depend on the patient's age, rate of increase in the serum calcium concentration, and duration of the hypercalcemia.⁶

Neither calcium chloride nor calcium gluconate should be combined and administered intravenously with sodium bicarbonate because calcium carbonate, a precipitate, is formed. Calcium chloride is an acidifying salt and is extremely irritating to tissue. It should never be given intramuscularly, subcutaneously, or perivascularly.^{21,45} Calcium gluconate is less irritating, but care should also be taken to avoid extravasation. The best reason for choosing calcium gluconate in almost all clinical situations is that the tissue risk is far less. If extravasation should occur, subcutaneous injection of aliquots of hyaluronidase can be injected around the site (Special Considerations: SC4).

PREGNANCY AND LACTATION

Calcium injection is in Food and Drug Administration pregnancy category C. Animal reproduction studies have not been conducted. Benefit is expected to outweigh risk when indicated as life saving therapy for the mother. Calcium is excreted in breast milk but is likely safe.

DOSING AND ADMINISTRATION

IV calcium must be administered slowly, at a rate not exceeding 0.7 to 1.8 mEq/min or one 10 mL vial of calcium chloride or three 10 mL vials of calcium gluconate over 10 minutes in adults, unless the patient is in extremis. More rapid administration may lead to vasodilation, hypotension, bradycardia, dysrhythmias, syncope, and cardiac arrest.^{7,15,35,45,61} In cases of life threatening hypocalcemia or for a patient in extremis, a slow IV push may be required. Repeat doses may be administered as clinically indicated. Total and ionized calcium should be monitored.

Topical, nebulized, and intraarterial administration is specifically addressed in the section on the role of calcium in the management of HF.

FORMULATION AND ACQUISITION

A variety of calcium salts are available for parenteral administration. The two most commonly used are calcium chloride (10%) and calcium gluconate (10%) (Table A29-1).

A topical calcium gluconate gel (Calgonate) (2.5%) 25 g is available. Topical preparations can be extemporaneously made as described in the section on role in hypocalcemia secondary to HF. A commercially prepared calcium gluconate 1% solution (Calgonate emergency eyewash) is available in 120 mL squirt bottles.

SUMMARY

- IV calcium infusion is an effective antidote for the hypocalcemia induced by ethylene glycol, HF, and fluoride releasing xenobiotics.
- Equivalent molar calcium doses found in appropriate volumes of calcium gluconate and calcium chloride deliver

equal amounts of ionized calcium.

- Calcium serves as a physiologic antagonist to the cardiac and or neurologic effects of hypermagnesemia and hyperkalemia and counteracts some of the effects of CCB overdoses.
- Calcium may have some benefit in the treatment of β -adrenergic antagonist overdoses.
- Great care must be taken to avoid extravasation, as calcium chloride in particular can cause tissue necrosis.
- ECG monitoring and frequent ionized calcium concentration measurements are required to prevent iatrogenic toxicity.
- Although most clinical experience involves IV use, advances in intraarterial, topical, inhalational, and intraosseous calcium therapy may offer unique potential advantages.

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HISTORY AND EPIDEMIOLOGY

The modern world could not exist without hydrocarbons. Virtually everything we touch is either coated with or made up primarily of hydrocarbon products. Organic chemistry originated during the Industrial Revolution, evolving largely due to advances in coal tar technology. In the coking process, bituminous (soft) coal is heated to liberate coal gas. This gas contains volatile hydrocarbons that can be captured and separated into a variety of natural gases. The viscous residue left over from the coking process forms coal tar, which can, in turn, be distilled into kerosene and other hydrocarbon mixtures.

Over the years, petroleum has replaced coal tar as the principal source of commercial organic compounds. Crude oil processing involves heating to a set temperature within processors that separate (distill) hydrocarbon fractions by vapor (or boiling) point. Because of the relationship between boiling point and molecular weight, distillation roughly divides hydrocarbons into like sized molecules. The most volatile fractions come off early as gases, and these are used primarily as heating fuels. The least volatile fractions (larger than about 10 or 12 carbons) are used chiefly for lubricants or as paraffins, petroleum jelly, or asphalt. The remaining mid sized distillation fractions (5 to 10 carbons) are those most commonly used in combustion fuels and as solvents. Petroleum distillates are used as chemical feedstocks and as precursors or intermediates in feedstock production.

For decades in the United States, kerosene ingestion in children was a major public health concern.¹²¹ Only through public education, consumer product safety initiatives, and modernization of the use and distribution of cooking and heating fuels has this problem been largely eliminated. However, in the developing world, these same challenges have yet to be resolved, with large numbers of children ingesting kerosene from poorly labeled and poorly secured containers.^{1,18,19,46,63,93,109,125,137,159}

Recent public attention and debate surrounds the potential for hydrocarbon exposures following environmental spills. Even more controversial is the practice of “induced hydraulic fracturing” of rock or shale, commonly called “fracking.” Fracking is performed on up to 60% of oil and gas wells drilled today, to liberate pockets of trapped gas or oil from within the fractured rock.^{103,165} The intent is to capture and collect trapped hydrocarbons, but some escape into nearby aquifers, thereby entering water supplies or otherwise contaminating human environments. Critics are concerned about the composition of the hydraulic fluids used, as these may be comprised mainly of methanol, ethylene glycol, benzene, or other hydrocarbons. Components of these fluids are found in area groundwater, with resultant risk of human exposure^{62,175} and untoward health effects.⁹⁹

The true epidemiology of hydrocarbon exposure and illness is difficult to ascertain from available data sources. But three populations appear to be at particular risk for hydrocarbon related illness. These are children who suffer unintentional exposures, often ingestion with pulmonary aspiration; workers with occupational exposures, often inhalational and dermal; and adolescents or young adults who intentionally abuse solvents by inhalation. People in specific occupations who are at risk for exposure include petrochemical workers, plastics and rubber workers, printers, laboratory workers, painters, and hazardous waste workers. Most hydrocarbon exposures do not involve ingestion, and most do not result in illness. Exposures may range from self-pumping gasoline, to painting a spare bedroom, or to applying or removing fingernail polish. Because hydrocarbon solvents are often volatile, inhalation is extremely common. Lipid solubility results in dermal absorption when skin is exposed.⁶⁵ Data from US poison centers suggest that about 30% of reported exposures to hydrocarbons were in children younger than 6 years of age (Chap. 136). Largely not captured in these data is an alarming rate of intentional misuse of volatile solvents by young people, which is discussed in more depth in Chap. 84.

Most commonly encountered hydrocarbons are mixtures of compounds, often obtained from a common petroleum distillation fraction. The many applications for these in consumer and household products include paints and thinners, furniture polish, lamp oils, and lubricants. Table 108–1 lists frequently encountered hydrocarbon compounds and their properties. This chapter focuses principally on toxicity of hydrocarbons present in these commercially available mixtures. Individual hydrocarbons are discussed only when they are commonly available in purified form, or when specific xenobiotics result in unique toxicologic concerns.

TABLE 108–1. Classification and Viscosity of Common Hydrocarbons

Compound	Common Uses	Viscosity (SUS) ^a
Aliphatics		
Gasoline	Motor vehicle fuel	30
Naphtha	Charcoal lighter fluid	29
Kerosene	Heating fuel	35
Turpentine	Paint thinner	33
Mineral spirits	Paint and varnish thinner	30–35
Mineral seal oil	Furniture polish	30–35
Heavy fuel oil	Heating oil	>450
Aromatics		
Benzene	Solvent, reagent, gasoline additive	31
Toluene	Solvent, spray paint solvent	28
Xylene	Solvent, paint thinner, reagent	28
Halogenated		
Methylene chloride	Solvent, paint stripper, propellant	27
Carbon, tetrachloride	Solvent, propellant refrigerant	30
Trichloroethylene	Degreaser, spot remover	27
Tetrachloroethylene	Dry cleaning solvent, chemical intermediate	28

^aDirect values for kinematic viscosity in Saybolt universal seconds (SUS) were not available for the following compounds: naphtha, xylene, methylene chloride, carbon tetrachloride, trichloroethylene, perchloroethylene, and toluene. SUS was calculated by converting from available measurements in centipoise viscosity and/or centistokes viscosity using the following conversions: the value in centistokes is estimated by dividing centipoise by density at 68°F (20°C); SUS is approximated from centistokes using $y = 3.2533x + 26.08$ ($R^2 = 0.9998$). Centipoise viscosity for naphtha was estimated from the value for butylbenzene. Centipoise viscosity for xylene is the average of *o*-, *m*-, and *p*-xylene.

CHEMISTRY

A hydrocarbon is an organic compound made up primarily of carbon and hydrogen atoms, typically ranging from 1 to 60 carbon atoms in length. This definition includes products derived from plants (pine oil, vegetable oil), animal fats (cod liver oil), natural gas, petroleum, or coal tar. There are two basic types of hydrocarbon molecules, aliphatic (straight or branched chains) and cyclic (closed ring), each with its own subclasses. The aliphatic compounds include the paraffins (alkanes, with a generic formula C_nH_{2n+2}); the olefins (alkenes have one double bond and alkadienes have two double bonds); acetylenes (alkynes) with at least one triple bond; and the acyclic terpenes (polymers of isoprene, C_5H_8). Some aliphatic compounds have branches in which the subchain also contains carbon atoms; both the chain and branches are essentially straight.

The cyclic hydrocarbons include alicyclic (three or more carbon atoms in a ring structure, with properties similar to the aliphatics), and aromatic compounds, as well as the cyclic terpenes. The alicyclics are further divided into cycloparaffins (naphthenes) such as cyclohexane, and the cycloolefins (two or more double bonds) such as cyclopentadiene.

Saturated hydrocarbons contain carbon atoms that exist only in their most reduced state. This means that each carbon is bound to either hydrogen or to another carbon, with no double or triple bonds present. Conversely, unsaturated compounds are those with hydrogens removed, in which double or triple bonds exist.

Solvents are a heterogeneous class of xenobiotics used to dissolve and provide a vehicle for delivery of other xenobiotics. The most common industrial solvent is water. The common solvents most familiar to toxicologists are organic solvents (containing one or more carbon atoms), and most of these are comprised of hydrocarbons. Most are liquids in the conditions under which they are used. Specifically named solvents (Stoddard solvent, white naphtha, ligroin) represent mixtures of hydrocarbons emanating from a common petroleum distillation fraction.

Aromatic hydrocarbons are divided into the benzene group (one ring), naphthalene group (two rings), and the anthracene group (three rings). Polycyclic aromatic hydrocarbons (polynuclear aromatic hydrocarbons) have multiple, fused benzenelike rings. Aromatic organic compounds may also be heterocyclic (where oxygen or nitrogen substitutes for carbon in the ring). Structurally, all of these molecules are flat, with reactive electron clouds above and below the ring.

The cyclic terpenes are the principal components of the variety of plant-derived essential oils ([Chap. 43](#)), often

providing color, odor, and flavor. Limonene in lemon oil, menthol in mint oil, pinene in turpentine, and camphor are all terpenes.

Physical properties of hydrocarbons vary by the number of carbon atoms and by molecular structure. Unsubstituted, aliphatic hydrocarbons that contain up to 4 carbons are gaseous at room temperature, 5 to 19 carbon molecules are liquids, and longer-chain molecules tend to be tars or solids. Branching of chains tends to destabilize intermolecular forces, so that less energy is required to separate the molecules. The result is that, for a given molecular size, highly branched molecules have lower melting and boiling points and tend to be more volatile.

The various definitions of paraffin warrant discussion. In chemistry, paraffin is a general term for any alkane. In North American common use, paraffin describes either medicinal paraffin or paraffin wax. Medicinal paraffin is the same as mineral oil, a viscous mixture of longer-chained alkanes (typically 15–50 carbon atoms per molecule) derived from a petroleum source. The molecules in mineral oil exhibit considerable branching, making it a viscous liquid at room temperature and pressure. Molecules in paraffin wax are nearly identical to these in size, but less branching increases the number of intermolecular interactions, forming a waxy/solid at room temperature. Outside North America, the term paraffin often refers to kerosene—a mixture of medium-chain alkanes typically used for lighting and heating.

Gasoline is a mixture of alkanes, alkenes, naphthenes, and aromatic hydrocarbons, predominantly 5 to 10 carbon atoms in size. Gasoline is separated from crude oil in particular distillation fractions and then usually blended with several other fractions in refinery processors. More than 1500 individual molecular species may be present in commercial grades, but most analytical methods isolate only 150 to 180 constituent compounds in gasoline. Notably, n-hexane is present at up to 6%, and benzene is present between 1% and 6%, depending on the origin and processing technique. A number of additives may go into the final formulation: alkyl leads, ethylene dichloride, and ethylene dibromide in leaded gasoline, and oxygenates such as methyl t-butyl ether (MTBE), as well as methanol and ethanol.

Organic halides contain one or more halogen atoms (fluorine, chlorine, bromine, iodine) usually substituted for a hydrogen atom in the parent structure. Examples include chloroform, trichloroethylene, and the freons.

Oxygenated hydrocarbons demonstrate toxicity specific to the oxidation state of the carbon, as well as to the atoms adjacent to it (the “R” groups). The alcohols are widely used as solvents in industry and in household products. Their toxicity is discussed in Chaps. 80 and 109. Ethers contain an oxygen atom bound on either side by a carbon atom. Acute toxicity from ethers tends to mirror that of the corresponding alcohols. Aldehydes and ketones contain one carbon–oxygen double bond ($C=O$), the former at a terminal carbon, the latter somewhere in the middle. Organic acids, esters, amides, and acyl halides represent more oxidized states of carbon; human toxicity is agent specific.

Phenols consist of benzene rings with an attached hydroxyl (alcohol) group. The parent compound, phenol, has only one hydroxyl group attached to benzene. The toxicity of phenol can be dramatically altered by addition of other functional groups to the benzene ring (Chap. 104). Cresols, catechols, and salicylate are examples of substituted phenols.

A variety of amines, amides, nitroso and nitro compounds, as well as phosphates, sulfites, and sulfates are used commercially and industrially. The addition of these functional groups to hydrocarbons dramatically alters the characteristics, including the toxicity of the compound.

PHARMACOLOGY

The effects of hydrocarbons on humans are chiefly related to interactions with lipid bilayers in cellular membranes. Inhaled hydrocarbon vapor depresses consciousness. As such, acute central nervous system (CNS) toxicity from occupational overexposure or recreational abuse parallels the effect of administering an inhaled general anesthetic. The concentration of volatile anesthetic that produces loss of nociception in 50% of patients defines the minimum alveolar concentration (MAC) required to induce anesthesia. Similarly, inhaled solvent vapor produces unconsciousness in 50% of subjects, when the partial pressure in the lung reaches its median effective dose (ED_{50}). The ED_{50} in occupational terms is effectively the same as the MAC in anesthesiology terms (Chap. 68). Virtually all patients will be anesthetized when the partial pressure is raised 30% above the MAC ($MAC \times 1.3$). If ventilation is not supported, death typically occurs when the concentration reaches two to four times the MAC.⁸⁵ Dose–response curves suggest that essentially no individual will be rendered unconscious by an inhaled dose 30% below the MAC. Nonetheless, impaired cognitive and motor function may occur at much lower doses.²³

The physical property of an inhaled anesthetic that correlates most closely with its ability to extinguish nociception is its lipid solubility. Inhalational exposure to lipid-soluble solvents, such as aromatic, aliphatic, or chlorinated hydrocarbons, is more likely to cause acute and chronic CNS effects than exposure to water-soluble hydrocarbons such as alcohols, ketones, and esters. The Meyer-Overton hypothesis, proposed more than 100 years ago, implies that an anesthetic dissolves into some critical lipid compartment of the CNS, causing inhibition of neuronal transmission. According to this hypothesis, the target structure for general anesthetics is the neuronal lipid membrane itself.⁶⁶

Unfortunately, this hypothesis is likely too simplistic. Numerous protein receptor interactions also occur. Halothane, isoflurane, sevoflurane, enflurane, and desflurane inhibit fast sodium channels.¹¹⁷ Toluene, trichloroethylene,

perchloroethylene, and others inhibit neuronal calcium currents.^{114,135} The halogenated hydrocarbons increase the outward potassium rectifying current.¹³⁶ Specific ligand-receptor interactions occur,⁴³ such as the inhibition of receptor function at nicotinic,¹⁶⁷ and at glutamate receptors,⁴² as well as enhancement of type-A γ -aminobutyric acid (GABA_A) and glycine receptor currents.¹⁷ Independent of other mechanisms, halogenated hydrocarbons appear to decrease exocytosis of neuronal synaptic vesicles.⁶⁸

Pharmacodynamic properties of inhaled hydrocarbons and other volatile xenobiotics (Chap. 68) suggest some receptor–ligand interaction, and a growing body of evidence suggests that the Meyer-Overton hypothesis cannot explain the many neurochemical activities demonstrated by this broad class of xenobiotics.⁷⁰ Perhaps a more elegant approach to the lipid bilayer interaction has been termed the “modern lipid hypothesis.” The hypothesis is thermodynamically derived, purporting an increase in lateral pressure on protein receptors within the neuronal bilayer. Lateral pressure leads to conformational changes in membrane ion channels, modulating the capacity for activation.³² While this hypothesis is mechanistically plausible and thermodynamically defensible, no in vitro or in vivo work has yet substantiated it. Thus, to date, no single mechanism fully explains the pharmacologic and toxicologic activity of volatile hydrocarbons on neuronal tissues.

TOXICOKINETICS

Hydrocarbons are variably absorbed into human systems by ingestion, inhalation, or dermal routes. Human toxicokinetic data are lacking for most of these xenobiotics, so much of our understanding derives from in vitro studies and animal research. Partition coefficients, in particular, are useful predictors of the rate and extent of the absorption and distribution of hydrocarbons into tissues. A partition coefficient for a given chemical species is the ratio of concentrations achieved between two different media at equilibrium. The blood-to-air, tissue-to-air, and tissue-to-blood coefficients directly relate to the pulmonary uptake and distribution of hydrocarbons. The tissue-to-blood partition coefficient is commonly derived by dividing the tissue-to-air coefficient by the blood-to-air coefficient.^{55,120} The higher the value, the greater the potential for distribution into tissue. Table 108–2 lists partition coefficients for commonly encountered hydrocarbons. Where human data are limited, rat data is presented in the table, because human and rat data often correlate.¹²⁰

TABLE 108–2. Kinetic Parameters of Selected Hydrocarbons

	Partition Coefficients ^a			<i>t</i> _{1/2}		Elimination	Relevant Metabolites
	Blood/Air	Fat/Air	<i>a</i>		<i>β</i>		
Aliphatics							
<i>n</i> -Hexane	2.29	159	0.17 hours		1.7 hours	10%–20% exhaled; liver metabolism by CYP2E1	2-Hexanol, 2,5-hexanedione, γ -valerolactone
Paraffin/tar	Not absorbed or metabolized		—			—	—
Aromatics							
Benzene	8.19	499	8 hours		90 hours	12% exhaled; liver metabolism to phenol	Phenol, catechol, hydroquinone, and conjugates
Toluene	18.0	1021	4–5 hours		15–72 hours	Extensive liver extraction and metabolism	80% metabolized to benzyl alcohol; 70% renally excreted as hippuric acid
<i>o</i> -Xylene	34.9	1877	0.5–1 hour		20–30 hours	Liver CYP2E1 oxidation	Toluic acid, methyl hippuric acid
Halogenated							
Methylene chloride	8.94	120	Apparent <i>t</i> _{1/2} of COHb 13 hours		0.7 hours	92% exhaled unchanged. Low doses metabolized; high doses exhaled. Two liver metabolic pathways	(a) CYP2E1 to CO and CO ₂ (b) Glutathione transferase to CO ₂ , formaldehyde, formic acid
Carbon tetrachloride	2.73	359	~1.5 hours		1.5–8 hours	Liver CYP2E1, some lung exhalation (dose-dependent)	Trichloromethyl radical, trichloromethyl peroxy radical, phosgene
Trichloroethylene	8.11	554	3 hours		30 hours	Liver CYP2E1—epoxide intermediate; trichloroethanol is glucuronidated and excreted	Chloral hydrate, trichloroethanol, trichloroacetic acid
1,1,1-Trichloroethane	2.53	263	0.7 hours		53 hours	91% exhaled; liver CYP2E1	Trichloroacetic acid, trichloroethanol
Tetrachloroethylene	10.3	1638	2.7 hours		33 hours	80% exhaled; liver CYP2E1	Trichloroacetic acid, trichloroethanol

^afat/blood partition coefficient is obtained by dividing the fat/air coefficient by the blood/air coefficient, as determined in rat models. All coefficients are determined at 38.6°C (101°F).

Inhalation is a major route of exposure for most volatile hydrocarbons. Most cross the alveolar membrane by passive diffusion. The driving force is the difference in vapor concentration between the alveolus and the blood. The absorbed dose is determined by the air concentration, duration of exposure, minute ventilation, and the blood-to-air partition coefficient. Hydrocarbons that are highly soluble in blood and tissues are readily absorbed, and blood concentrations rise rapidly following inhalation exposure. While aromatic species are generally well absorbed, absorption of aliphatic hydrocarbons varies by molecular weight: aliphatic hydrocarbons with between 5 and 16 carbons are readily absorbed through inhalation, whereas those with more than 16 carbons are less extensively absorbed.

Absorption of aliphatic hydrocarbons through the digestive tract is inversely related to molecular weight, ranging from complete absorption at lower molecular weights, to approximately 60% for C-14 hydrocarbons, 5% for C-28 hydrocarbons, and essentially no absorption for aliphatic hydrocarbons with more than 32 carbons. Oral absorption of aromatic hydrocarbons with between 5 and 9 carbons ranges from 80% to 97%. Oral absorption of aromatics with more than 9 carbons is poorly characterized, as data are lacking.

While the skin is a common area of contact with solvents, the dose of dermally absorbed hydrocarbons is quite small relative to that through other routes such as inhalation. The skin is comprised of both hydrophilic (proteinaceous portion of cells) and lipophilic (cell membranes) regions (Chap. 18). While many hydrocarbons can remove lipids from the stratum corneum, permeability is not simply the result of lipid removal; permeability also increases with hydration of the skin. The rate of skin absorption is highest when xenobiotics have a water-to-lipid partition coefficient near one. Solvents that contain both hydrophobic and hydrophilic moieties (eg, glycol ethers, dimethylformamide, dimethylsulfoxide) are particularly well absorbed through skin. Other factors that determine penetration across the skin include the thickness of the skin layer, the difference in concentration of the solvent on either side of the epithelium, the diffusion constant, and skin integrity (ie, normal vs. cut or abraded).

The dose absorbed through skin is proportional to the exposed surface area and the duration of contact. Although highly volatile compounds may have a short duration of skin contact because of evaporation, skin absorption can also occur from contact with hydrocarbon vapor. In studies with human volunteers exposed to varying concentrations of hydrocarbon vapors, the dermal dose accounted for only 0.1% to 2% of the inhalation dose. With massive exposure (eg, whole-body immersion), dermal absorption may contribute significantly to toxicity. Significant dermal absorption with resultant toxicity is described with carbon tetrachloride,⁷⁴ tetrachloroethylene,⁶⁵ and phenol.⁹¹

Once absorbed into the central compartment, hydrocarbons are distributed to target and storage organs based on their

tissue-to-blood partition coefficients and on the rate of perfusion of the tissue with blood. During the onset of systemic exposure, hydrocarbons accumulate in tissues that have tissue/blood coefficients greater than 1 (eg, for toluene, the fat-to-blood partition coefficient is 60). [Table 108–2](#) lists the distribution half-lives of selected hydrocarbons.

Hydrocarbons can be eliminated from the body unchanged, for example, through expired air, or can be metabolized to more polar compounds, which are then excreted in urine or bile. [Table 108–2](#) lists the blood elimination half-lives (for first-order elimination processes) and metabolites of selected hydrocarbons. Some hydrocarbons are metabolized to toxic compounds (eg, methylene chloride, carbon tetrachloride, n-hexane, methyl-n-butyl ketone). The specific toxicities of these metabolites are discussed later in this chapter.

PATHOPHYSIOLOGY AND CLINICAL FINDINGS

Respiratory

Several factors are classically associated with pulmonary toxicity after hydrocarbon ingestion. These include specific physical properties of the xenobiotics ingested, the volume ingested, and the occurrence of vomiting. Physical properties of viscosity, surface tension, and volatility are primary determinants of aspiration potential.

Dynamic (or absolute) viscosity is the measurement of the ability of a fluid to resist flow. This property is measured with a rheometer and is typically given in units of pascal-seconds. More frequently, engineers work with kinematic viscosity, measured in square millimeters per second, or centistokes. Dynamic viscosity is converted to kinematic viscosity by dividing the dynamic viscosity by the density of the fluid. An older system for measuring viscosity was initially popularized by the petroleum industry and expresses kinematic viscosity in units of Saybolt Universal seconds (SUS). Unfortunately, many policy statements were developed in an era when SUS units were popular, and many still describe viscosity in SUS units. Various look-up tables and calculators are available to convert kinematic viscosity to SUS units. [Table 108–1](#) shows kinematic viscosity of common hydrocarbons, measured in SUS. A unit conversion approximation is given in the table's footnote.

Hydrocarbons with low viscosities (<60 SUS; eg, turpentine, gasoline, naphtha) have a higher tendency for aspiration in animal models. The US Consumer Products Safety Commission issued a rule in 2001, requiring child-resistant packaging for products that contain 10% or more hydrocarbon by weight and have a viscosity less than 100 SUS.

Surface tension is a cohesive force generated by attraction due to the Van der Waals forces between molecules. This influences adherence of a liquid along a surface (“its ability to creep”). The lower the surface tension, the more effectively the liquid will creep, producing a higher aspiration risk.⁵⁷

Volatility is the tendency for a liquid to become a gas. Hydrocarbons with high volatility tend to vaporize, displace oxygen, and potentially lead to transient hypoxia.

Early reports conflicted in their attempts to relate risk of pulmonary toxicity (1) to the amount of hydrocarbon ingested or (2) to the presence or absence of vomiting. One prospective study addressed both these variables. The cooperative kerosene poisoning (COKP) study was a multicenter study that enrolled 760 patients with hydrocarbon ingestion. Of these, 409 individuals could provide an estimate of the amount ingested. Patients who reportedly ingested more than 30 mL had a 52% chance of developing pulmonary complications, compared with 39% of those who ingested less than 10 mL. Risk of central nervous complications was 41%, compared with 24% using the same criterion. There was a 53% incidence of pulmonary toxicity when vomiting occurred, compared with 37% when there was no history of vomiting.¹²¹ While this knowledge may help modify the index of suspicion regarding possible pulmonary toxicity, none of these parameters is completely predictive. Severe hydrocarbon pneumonitis may occur after ingestion of “low-risk” hydrocarbons.¹³¹ Patients may develop severe lung injury after low-volume (<5 mL) ingestions, as well as after ingestions with no history of coughing, gagging, or vomiting.⁸

It is widely held that aspiration is the main route of injury from ingested simple hydrocarbons. The mechanism of pulmonary injury, however, is not fully understood. Intratracheal instillation of 0.2 mL/kg of kerosene causes physiologic abnormalities in lung mechanics (decreased compliance and total lung capacity) and pathologic changes such as interstitial inflammation, polymorphonuclear exudates, intraalveolar edema and hemorrhage, hyperemia, bronchial and bronchiolar necrosis, and vascular thrombosis.⁶¹ These changes most likely reflect both direct toxicity to pulmonary tissue and disruption of the lipid surfactant layer.¹⁷¹

Most patients who develop pulmonary toxicity following hydrocarbon ingestion will have an initial episode of coughing, gagging, or choking. This usually occurs within 30 minutes after ingestion and is presumptive evidence of aspiration. The majority of patients who have respiratory signs and symptoms in addition to the initial history of gagging, choking, and coughing develop radiographic pneumonitis. Pulmonary toxicity may manifest as crackles, rhonchi, bronchospasm, tachypnea, hypoxemia, hemoptysis, acute respiratory distress syndrome (hemorrhagic or nonhemorrhagic), or respiratory distress. Cyanosis develops in approximately 2% to 3% of patients. This may result from simple asphyxiant effects from volatilized hydrocarbons, from ventilation–perfusion mismatch, or, rarely, from methemoglobinemia (aniline, nitrobenzene, or nitrite-containing hydrocarbons). Clinical findings often worsen over the first several days but typically

resolve within a week. Death is distinctly uncommon and typically occurs after a severe, progressive respiratory insult marked by hypoxia, ventilation–perfusion mismatch, and barotrauma.^{75,92,179}

Intravenous (IV), subcutaneous, and even intrapleural injection of hydrocarbons are reported.^{45,129,163} Severe hydrocarbon pneumonitis may occur following IV exposure. Animal experiments show that intravascular hydrocarbons injure the first capillary bed encountered.^{127,173} The clinical course after IV hydrocarbon injection is comparable to that of aspiration injury.

Radiographic evidence of pneumonitis develops in 40% to 88% of patients admitted following aspiration.^{16,44,115} Findings can develop as early as 15 minutes or as late as 24 hours after exposure (Fig. 108–1).^{22,54,121,164} Chest radiographs performed immediately on initial presentation are not useful in predicting infiltrates in either symptomatic or asymptomatic patients.⁸ Ninety percent of patients who develop radiographic abnormalities do so by 4 hours postingestion.²² Clinical signs of pneumonia (eg, crackles, rhonchi) are evident in 40% to 50% of patients.⁴⁴ A small percentage (<5%) are completely asymptomatic after a period of observation, yet to have radiographic findings.⁸



A



B



C

FIGURE 108–1. Three sequential radiographs of a young girl with severe hydrocarbon aspiration. (A) Initial: Patchy densities appear in the basilar areas of both lung fields with increased interstitial markings and peribronchial thickening. (B) Day 2: More extensive diffuse alveolar infiltrates are apparent. (C) Day 6: Dense consolidation and atelectasis are evident in the right lower lobe. (Used with permission of Nancy Genieser, MD, Professor of Radiology, New York University.)

Specific radiologic findings include perihilar densities, bronchovascular markings, bibasilar infiltrates, and pneumonic consolidation.⁵⁸ Right-sided involvement occurs in 75% of cases and bilateral involvement in approximately 50%. Upper-lobe involvement is uncommon. Pleural effusions develop in 3% of cases, with one-third appearing within 24 hours.¹⁰⁰ Pneumothorax, pneumomediastinum, and pneumatoceles occur uncommonly.^{10,20,78} Initial radiographs after ingestion may reveal two liquid densities in the stomach, known as the “double-bubble” sign. This represents an air–fluid (hydrocarbon or water) and a hydrocarbon–water interface, as the hydrocarbon is not miscible with gastric (aqueous) fluid and may have

a specific gravity less than that of water.³⁸

Radiographic resolution does not correlate with clinical improvement but rather lags behind by several days to weeks. There are few reports of long-term follow-up on patients with hydrocarbon pneumonitis.^{64,154} Frequent respiratory tract infections are described after hydrocarbon pneumonitis, but these studies are not well controlled.^{54,157} Delayed formation of pneumatoceles may occur.^{20,78} Bronchiectasis and pulmonary fibrosis are reported but appear to be uncommon.^{60,124} In one study, 82% of patients examined 8 to 14 years after hydrocarbon-induced pneumonitis had asymptomatic minor pulmonary function abnormalities. The abnormalities were consistent with small-airway obstruction and loss of elastic recoil. The authors hypothesized that this group may be predisposed to chronic obstructive pulmonary disease.⁶⁴

Cardiac

The most concerning cardiac effect from hydrocarbon exposure is precipitation of dysrhythmias through myocardial sensitization.¹¹⁰ Malignant dysrhythmias may occur after exposure to high concentrations of volatile inhalants or inhaled anesthetics. Such events are described with all classes of hydrocarbons, but halogenated compounds are most frequently implicated, followed by aromatic compounds.^{13,126} Atrial fibrillation, ventricular tachycardias, junctional rhythms, ventricular fibrillation, and cardiac arrest are reported.^{29,105,111,126} This is termed the “sudden sniffing death syndrome.”¹⁴ Prolongation of the QT interval in some cases raises additional concern for the development of torsade de pointes.^{14,133}

Cardiac sensitization is incompletely understood.^{43,110,134} Halothane and isoflurane inactivate sodium channels,¹⁴² whereas chloroform and others attenuate potassium efflux through voltage-gated channels.¹³³ Sensitization may be mediated by slowed conduction velocity through membrane gap junctions. Dephosphorylation of connexin-43 results in a conformational change that increases gap junctional resistance. Halocarbons, in the presence of epinephrine, cause dephosphorylation of this gap junction protein, thereby increasing resistance and slowing conduction velocity in myocardial tissue.⁷⁶

Any route of exposure to hydrocarbons may result in cardiotoxicity. Classically, sudden death follows an episode of sudden exertion, presumably associated with an endogenous catecholamine surge.¹⁴ Tachydysrhythmias, cardiomegaly, and myocardial infarction are rarely reported after ingestion of hydrocarbons.^{72,144} A retrospective follow-up cohort of exposed methylene chloride workers did not find evidence of excess long-term cardiac disease.¹¹⁶

Central Nervous System

Transient CNS excitation may occur after acute hydrocarbon inhalation or ingestion, but more commonly, CNS depression or general anesthesia occurs.⁴⁴ In cases of aspiration, hypoxemia from pulmonary damage may contribute to CNS depression.^{95,174} Coma and seizures are reported in 1% to 3% of cases.^{115,124,178} Chronic occupational exposure or volatile substance use may lead to a chronic neurobehavioral syndrome, the painter’s syndrome, most notably described after toluene overexposure. Clinical features include ataxia, spasticity, dysarthria, and dementia, consistent with leukoencephalopathy.^{50–53} Autopsy studies of the brains of chronic toluene abusers show atrophy and mottling of the white matter, as though the lipid-based myelin were dissolved away. Microscopic examination shows a consistent pattern of myelin and oligodendrocyte loss with relative preservation of axons.⁸⁴ Animal models of toluene poisoning reveal norepinephrine and dopamine depletion. The severity and reversibility of this syndrome depends on the intensity and duration of toluene exposure.¹³² Infrequent exposure may produce no clinical neurologic signs, whereas severe (daily) use can lead to significant neurologic impairment after as little as 1 year, but more commonly after 2 to 4 years of continuous exposure. The specific cognitive and neuropsychological findings in toluene-induced dementia have been termed a white matter dementia.^{50–52}

Initial findings of white matter dementia include behavioral changes, impaired sense of smell, impaired capacity to concentrate, and mild unsteadiness of hand movements and gait. Further exposure leads to slurred speech, head tremor, poor vision, deafness, stiff-legged and staggering gait, and subsequent dementia. Physical findings may include nystagmus, ataxia, tremor, spasticity with hyperreflexia, plantar extension, deafness, impaired vision, and a broad-based, staggering gait. An abnormal brainstem auditory-evoked response appears to be a sensitive indicator of toluene-induced CNS damage. The electroencephalogram can show mild, diffuse slowing. Computed tomography in severe cases shows mild-to-moderate cerebellar and cortical atrophy. Magnetic resonance imaging (MRI) findings are consistent with white matter disease. Most cases show clinical improvement after 6 months of abstinence, although with moderate to severe abuse, improvement may be incomplete. While toluene abuse is addicting, withdrawal or abstinence syndrome is surprisingly uncommon and, when present, appears relatively benign.^{50–52}

Exposures in the occupational setting are rarely as extreme as those that occur with intentional volatile substance misuse. Given the significantly lesser exposures, the findings among workers overexposed to solvent concentrations above permissible exposure limits are often subclinical and detected primarily through neurobehavioral testing. In rare cases, however, a worker may be acutely overexposed to solvent concentrations that can produce acute CNS depression.

Repeated, symptomatic overexposures over a protracted period of time have the potential to lead to a chronic encephalopathy, as evident from the experience with solvent abusers.⁵¹

Peripheral Nervous System

Peripheral neuropathy is well described following occupational exposure to n-hexane or methyl-n-butyl ketone (MnBK).²⁵ This axonopathy results from a common metabolic intermediate, 2,5-hexanedione. The mechanism by which this intermediate causes peripheral neuropathy probably relates to decreased phosphorylation of neurofilament proteins, with disruption of the axonal cytoskeleton. Methyl ethyl ketone may exacerbate this neurotoxicity, probably by interfering with metabolic pathways of n-hexane and MnBK.^{7,130} Other organic solvents, such as carbon disulfide, acrylamide, and ethylene oxide, may cause a similar peripheral axonopathy.⁵⁹ Cranial and peripheral neuropathies are reported after acute and chronic exposure to trichloroethylene (TCE).^{77,90,151} Pathologically, TCE appears to induce a myelinopathy.^{48,59}

TCE exposure is associated with trigeminal neuralgia.^{34,47,90} Symptoms can develop within 12 hours of a single intense exposure and persist for many years.⁴⁸ Trigeminal nerve damage was documented by evoked potentials following 15 minutes of TCE inhalation.⁹⁰ Some evidence suggests that decomposition products or impurities in TCE may be responsible for cranial neuropathy.^{34,47,85}

Axonopathy from MnBK or n-hexane exposure typically begins in the distal extremities and progresses proximally (a classic, “dying-back” neuropathy) (Chap. 24). Exposure to one of these hydrocarbons should be considered in the differential diagnosis of the patient with Guillain-Barré syndrome (GBS), although sensory findings are present with MnBK and absent in GBS.¹⁴⁰ The longest axons appear to be affected initially, so that the patient manifests a “length-dependent polyneuropathy.” With discontinuation of exposure many of the effects reverse over weeks to months.^{69,80,122,177} Alternatively, the phenomenon of “coasting” may occur, in which neuropathy progresses for a time (weeks to months) after discontinuation of the toxic insult.¹⁴⁰ A reversible peripheral neuropathy occurred in 40% of chronic toluene abusers and was characterized by severe motor weakness without sensory deficits or areflexia.¹⁵⁰ It is unclear whether the toluene in this series might have been contaminated by n-hexane or MnBK.⁷

Gastrointestinal

Hydrocarbons irritate gastrointestinal mucous membranes. Nausea and vomiting are common after ingestion. As discussed earlier, vomiting may increase the risk of pulmonary toxicity.^{113,115} Hematemesis was reported in 5% of cases in one study,¹¹³ and gastrointestinal ulcerations are reported in animal studies⁸¹.

Hepatic

The chlorinated hydrocarbons (Table 108–1) and their metabolites are hepatotoxic. In most cases, activation occurs via a phase I reaction to form a reactive intermediate (Chap. 13). In the case of carbon tetrachloride, this intermediate is the trichloromethyl radical. This radical forms covalent bonds with hepatic macromolecules and may initiate lipid peroxidation.²⁷ Carbon tetrachloride causes centrilobular necrosis after inhalational, oral, or dermal exposure.¹⁰² Hepatotoxicity in animals has been ranked for common hydrocarbons as follows: carbon tetrachloride is greater than benzene, and trichloroethylene is greater than pentane.¹⁷² Vinyl chloride is a liver carcinogen, and trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane are considered less acutely hepatotoxic than vinyl chloride.¹⁰² Hepatotoxicity rarely follows ingestion of petroleum distillates.⁷³ Hepatic injury, manifested as aminotransferase elevation and hepatomegaly, is usually reversible except in massive exposures.

Renal

Halogenated hydrocarbons such as chloroform, carbon tetrachloride, ethylene dichloride, tetrachloroethane, 1,1,1-trichloroethane, and TCE are nephrotoxic. Acute kidney injury (AKI) and distal renal tubular acidosis occur in some painters and volatile-substance abusers.¹⁵ Toluene causes a renal tubular acidosislike syndrome (see Toluene later in the chapter).

Hematologic

Hemolysis has been sporadically reported to occur following hydrocarbon ingestion.^{2,6,148} One retrospective study of 12 patients showed hemolysis in three individuals and disseminated intravascular coagulation in another.⁶ Although one patient required transfusion, hemolysis is usually mild and typically does not require red blood cell transfusion (also see discussion of the effects of benzene on bone marrow, under Benzene later in the chapter).

Immunologic

Hydrocarbons disturb the integrity of membrane lipid bilayers, causing swelling and increased permeability to protons and other ions. This alters the structural and functional integrity of the membrane. Changes in the lipid composition of the membrane occur, and membrane lipopolysaccharides and proteins are disturbed.¹³⁸ Resultant toxicity may directly destroy capillary endothelium.²⁶ Additionally, there appears to be significant basement membrane dysfunction, and this is postulated to underlie both alveolar and glomerular toxicity of hydrocarbons.¹⁴⁵ Immune mechanisms may account for basement membrane dysfunction in chronic exposures. Hydrocarbon exposure is suggested as one possible cause of the Goodpasture syndrome (immune dysfunction causing both pulmonary damage and glomerulonephritis),²⁴ although the association is not widely accepted. Measurable changes in immune function occur after hydrocarbon exposure,¹² but our knowledge of any clinical relevance is incomplete.

Dermatologic

Most hydrocarbon solvents cause nonspecific irritation of skin and mucous membranes. Repeated, prolonged contact can dry and crack the skin. The mechanism of dermal injury appears to be defatting of the lipid layer of the stratum corneum. Up to 9% of workers may develop eczematous lesions from dermal contact.¹⁷⁶ Limonene and turpentine contain sensitizers that can rarely result in contact allergy (Chap. 18).

Contact dermatitis and blistering may progress to partial-and even full-thickness burns.⁶⁷ Severity is proportional to duration of exposure. Hydrocarbons are irritating to skin. Acute, prolonged exposure can cause dermatitis and even full-thickness dermal damage.⁶⁷ Chronic dermal exposure to kerosene or diesel fuel can cause oil folliculitis.^{39,162} A specific cutaneous lesion called chloracne is associated with exposure to chlorinated aromatic hydrocarbons with highly specific stereochemistry such as dioxins and polychlorobiphenyls.

Soft tissue injection of hydrocarbon is locally toxic, leading to necrosis.⁴⁵ Secondary cellulitis, abscess formation, and fasciitis can occur. Infectious complications are treated by meticulous wound care, with surgical débridement as necessary. A particularly destructive injury involves high-pressure injection gun injury. These injuries typically involve the extremities, with high-pressure injection of grease or paint into the fascial planes and tendon sheaths. Emergent surgical débridement is necessary in most of these cases.^{49,107}

HYDROCARBONS WITH SPECIFIC AND UNIQUE TOXICITY

n-Hexane

Hexane is a six-carbon simple aliphatic hydrocarbon. It is a constituent of some brake-cleaning fluids, rubber cement, glues, spray paints, coatings, and silicones. Outbreaks of n-hexane-related neurotoxicity have occurred in printing plants, sandal shops, furniture factories, and automotive repair shops.³⁵ Human exposure occurs primarily by inhalation. Both n-hexane and MnBK are well-known peripheral neurotoxins that cause a classic “dying-back” peripheral polyneuropathy, beginning in a “stocking-glove” distribution.³⁶ Neurotoxicity does not appear to be directly caused by the parent compounds but results from a common metabolic intermediate—2,5-hexanedione. Toxicity appears related to the ability of this intermediate to form a ringed pyrrole structure, which causes decreased phosphorylation of neurofilament proteins, disrupting the axonal cytoskeleton.⁵⁹ Similar five- and seven-carbon species do not induce similar neurotoxicity, except those that are direct precursor intermediates in the metabolic pathway producing 2,5-hexanedione^{59,152} (Fig. 108–2).

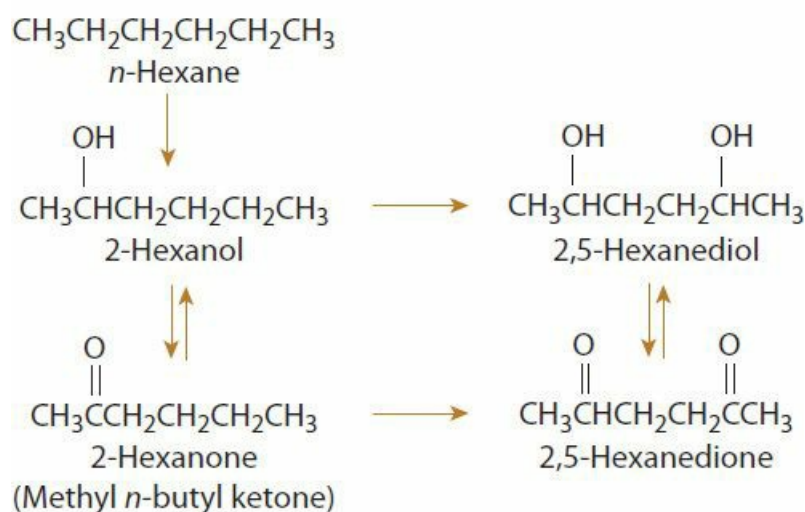


FIGURE 108–2. The metabolism of both organic solvents n-hexane and methyl n-butyl ketone produces the same common metabolite, 2,5-hexanedione.

Methylene Chloride

Methylene chloride is commonly found in paint removers, cleansers, degreasers, and aerosol propellants. Like other halogenated hydrocarbons, it can rapidly induce general anesthesia by inhalation or ingestion. Unlike other hydrocarbon agents, methylene chloride and similar one carbon halomethanes such as methylene dibromide are metabolized by liver P450 2E1 mixed-function oxidase to carbon monoxide. Significant, delayed, and prolonged carboxyhemoglobinemia can occur^{3,123} (Table 108–2 and Chap. 125).

Carbon Tetrachloride

Carbon tetrachloride (CCl₄), although not actually a hydrocarbon, has been used as an industrial solvent and reagent. Its use in the United States has declined dramatically since recognition of its toxicity caused the Environmental Protection Agency to restrict its commercial use. Absorption occurs by all routes, including dermal. CCl₄ is an irritant to skin and mucous membranes and gastric mucosa when ingested. As in the case of other halogenated hydrocarbons, aspiration can result in pneumonitis, and systemic absorption may result in ventricular dysrhythmias.

CCl₄ exposures are hepatotoxic and nephrotoxic. Both occur more commonly with repetitive occupational exposure.^{74,155} Toxicity follows phase-I dehalogenation of the parent compound, which produces free radicals and causes lipid peroxidation and the production of protein adducts.²⁷ Localization of specific phase I hepatic enzymes in the centrilobular area of the liver results in regionalized (zone 3) centrilobular injury after CCl₄ exposure (Chap. 23). Hepatotoxicity is typically manifested as reversible aminotransferase concentration elevations with or without hepatomegaly. Cirrhosis is reported in both animal models and in humans with prolonged excessive exposures. Nephrotoxicity is less studied but may result from a similar mechanism. CCl₄ is a suspected human carcinogen.¹⁰⁸

Trichloroethylene

TCE is a commonly used industrial solvent, cleanser, and degreaser. Systemically absorbed TCE, as might occur in the occupational setting, may competitively inhibit aldehyde dehydrogenase. Concomitant ethanol consumption may result in a disulfiramlike reaction that has been termed “degreaser’s flush”¹⁴⁷ (Chap. 79).

TCE was used for years as a general anesthetic, and hundreds of disposal sites in the United States remain sources of ongoing human exposure. The use of TCE as a general anesthetic was abandoned because of associated acute cardiotoxicity. TCE is also hepatotoxic, neurotoxic, and nephrotoxic in humans and animals. TCE exposure is linked to the development of neurodegenerative diseases, such as parkinsonism.⁵⁶ Evidence suggests that TCE is a human carcinogen.^{112,118,146}

Benzene

Benzene is hematotoxic and associated with acute hemolysis or with the delayed development of aplastic anemia and acute myelogenous leukemia.^{4,86,101,119} Other aromatic hydrocarbons that are reported to cause similar hematologic effects most likely are contaminated with benzene. An excess risk of hematologic toxicity has not been demonstrated in groups with long-term exposure to toluene, xylene, or other aromatic hydrocarbons.^{9,40,128,166,170} Other hematologic malignancies also may be linked to benzene, including chronic myelocytic leukemia, myelodysplastic syndromes, and lymphoma.¹⁵⁶ Chromosomal changes are believed to provide a marker for carcinogenicity.¹⁶¹ Because of the carcinogenic risk, most benzene-based solvents have been removed from the US market, and the Occupational Safety and Health Administration has limited the permissible worker exposure concentration to 1 ppm.

Toluene

Toluene has essentially replaced benzene as the primary organic solvent in many commercial products. Many oil paints and stains primarily contain toluene as solvent. As such, it is readily available and readily abused as an inhalant. The CNS sequelae of chronic solvent inhalation are most frequently related to chronic toluene exposure.

Chronic toluene abuse can also cause a syndrome that resembles transient distal renal tubular acidosis (RTA).^{153,168} Although the mechanism is incompletely understood, the acidosis results in great part from the urinary excretion of hippuric acid (Table 108–2).^{33,79} Renal potassium loss may be severe and can result in symptomatic hypokalemia.⁷⁹ Clinical findings are a hyperchloremic metabolic acidosis, hypokalemia, and aciduria. Typically an associated transient azotemia occurs, as well as proteinuria and an active urine sediment.^{150,168} Some also report a proximal RTA, or the Fanconi

syndrome.^{106,168} A metabolic acidosis resulting from the metabolism of toluene to benzyl alcohol through alcohol dehydrogenase to benzoic acid may be an adequate explanation for the serum and urine acid–base disturbances.

Pine Oil and Terpenes

Pine oil is an active ingredient in many household cleaning products. It is a mixture of unsaturated hydrocarbons composed of terpenes, camphenes, and pinenes. The major components are terpenes, which are found in plants and flowers. Wood distillates including pine oil and turpentine are derived from pine trees. Patients who ingest pine oil often emit a strong pine odor. Wood distillates are readily absorbed from the gastrointestinal tract, and ingestion may cause CNS and pulmonary toxicity without aspiration.

The clinical features of pine oil ingestion can include CNS depression, respiratory failure, and gastrointestinal dysfunction, which are rarely fatal.^{83,169} Aspiration pneumonitis remains the primary clinical concern. Acute toxicity and management are similar to that of petroleum distillate ingestion. Rare reported complications of wood distillate ingestion include turpentine-associated thrombocytopenic purpura, AKI, and hemorrhagic cystitis.^{87,169}

Lipoid Pneumonia

Ingestion of low-viscosity hydrocarbons poses risk of pulmonary aspiration with subsequent acute pneumonitis. Conversely, viscous hydrocarbons rarely lead to pulmonary aspiration. Alternatively, inhalation of aerosolized oil droplets can occur in various occupational settings, and exogenous lipoid pneumonia may result. The most common xenobiotics involved are mineral or vegetable oils.^{21,89,96}

Initially, inhaled oil droplets are emulsified in the alveoli by surfactant, and then they are engulfed by alveolar macrophages. Unfortunately, the macrophages are unable to readily process the internalized, exogenous oil. Microscopically, persistent cytoplasmic droplets give a “foamy” appearance to these “lipophages” that may persist for weeks to years. Not uncommonly, the initial manifestations are limited or even subclinical, but once symptoms arise, illness may be prolonged from months to years. Ultimately, irreversible proliferative fibrosis may develop.¹⁴¹

Silicone-based polymers share structural similarities and some physical properties with long-chain hydrocarbons. Silicone polymers such as dimethicone exist as oily, viscous liquids at room temperature and are widely used as lubricants, antifoaming agents, and even as medicine and food additives. Pulmonary aspiration or inhalation of aerosolized silicone droplets causes clinical pneumonitis that is indistinguishable from that caused by their viscous hydrocarbon counterparts. The time course of lung injury is similarly protracted, and complications may be expected.¹³⁹

Tar and Asphalt Injury

Tar and asphalt injuries are common occupational hazards among construction workers. Asphalt workers are at risk for toxic gas exposure of hydrogen sulfide, carbon monoxide, propane, methane, and volatilized hydrocarbons.⁷¹ In addition, cutaneous exposure to these hot hydrocarbon mixtures can cause severe burns. The material quickly hardens and is very difficult to remove. However, immediate cooling with cold water is important to limit further thermal injury. Complete removal is essential to ensure proper burn management and to limit infectious complications. Attempts to remove hardened tar or asphalt mechanically often cause further damage. Dissolving the material with mineral oil, petroleum jelly, or antibacterial ointments are met with variable success. Surface-active agents combined with an ointment (De-Solv-it, Tween-80, Polysorbate 80) are more effective.^{41,149,160}

DIAGNOSTIC TESTING

Laboratory and ancillary testing for hydrocarbon toxicity should be guided by available information regarding the specific xenobiotic, the route of exposure, and the best attempt at quantifying the exposure. Inhalation or ingestion of hydrocarbons associated with pulmonary aspiration is most likely to result in pulmonary toxicity. The use of pulse oximetry, end-tidal CO₂, and arterial blood gas testing in this group of patients is warranted when clinically indicated. Early radiography is indicated in patients who are severely symptomatic; however, radiographs performed immediately after hydrocarbon ingestion have a poor predictive value for the occurrence of aspiration pneumonitis. In the asymptomatic patient, early radiography is not cost effective. Patients observed for 6 hours after an ingestion, who have adequate oxygenation, are not tachypneic, demonstrate no abnormal pulmonary findings, and have a normal chest radiograph obtained after the 6-hour observation period have a good medical prognosis with very low risk of subsequent deterioration.⁸

The choice of specific diagnostic laboratory tests to assess organ system toxicity or function following exposure to a hydrocarbon depends on the type, dose, and route of exposure, and on the assessment of the patient's clinical condition. Useful clinical tests may include pulse oximetry, end-tidal CO₂, and an ECG. Laboratory tests may include serum or urine electrolytes, venous or arterial blood gas, complete blood counts, and creatine phosphokinase as clinically indicated. If a

hydrocarbon has specific target organ toxicities (eg, benzene/bone marrow, CCl₄/liver, or n-hexane/peripheral nervous system), evaluating and monitoring target organ system function is indicated.

Specific diagnostic testing for hydrocarbon poisoning can include (a) bioassays for the specific hydrocarbon or its metabolites in blood, breath, or urine, or (b) assessment of toxicity. Bioassays for a hydrocarbon are seldom necessary for diagnosis or management of hydrocarbon poisoning in the emergency setting and rarely clinically available. Exceptions might include testing to assist in differential diagnosis (eg, testing for CCl₄ in a comatose patient with unexplained hepatic and renal toxicity or a carboxyhemoglobin determination in a paint stripper with chest pain), testing for worker compensation purposes (eg, testing for urinary trichloroethanol and trichloroacetic acid in a worker exposed to TCE with unexplained bouts of dizziness), or for forensic purposes (eg, sudden death in a huffer).

Chronic overexposures to hydrocarbons, as occur with volatile substance use, can result in persistent damage to the CNS. Damage can be detected and quantified using neuroimaging methods such as MRI or positron emission tomography. Major MRI findings in patients with chronic toluene abuse include atrophy, white matter T2 hyperintensity, and T2 hypointensity involving the basal ganglia and thalamus.³¹ Neurobehavioral testing can be used to detect subtle central nervous system effects following chronic occupational overexposures.

MANAGEMENT

Identification of the specific type, route, and amount of hydrocarbon exposure is rarely essential to achieve effective management.

Decontamination is one of the cardinal principles of toxicology, with priority that is second only to stabilization of the cardiopulmonary status. Safe decontamination can avoid further absorption and also avoids secondary casualties in those attempting to provide care. Protection of rescuers with appropriate personal protective equipment and rescue protocols is paramount, especially in situations where the victim has lost consciousness. The principle of removing the patient from the exposure (eg, vapor or gaseous hydrocarbon) or the exposure from the patient (eg, hydrocarbon liquid on skin or clothing), while protecting the rescuer, implies that personal protective equipment be considered at each level of the health care delivery system.

Exposed clothing should be removed and safely discarded as further absorption or inhalation of hydrocarbons from grossly contaminated clothing can worsen systemic toxicity. Decontamination of the skin should have a high priority in massive hydrocarbon exposures, particularly those exposures involving highly toxic hydrocarbons. Water alone may be ineffective in decontaminating most hydrocarbons, but early decontamination with soap and water may be adequate. The caregiver should remain aware that certain hydrocarbons are highly flammable and pose a fire risk to hospital staff ([Chap. 131](#)).

Several studies have attempted to evaluate the role of gastric decontamination after hydrocarbon ingestion. Results were largely inconclusive and the level of evidence, poor. In the subset of patients who were randomized to receive gastric lavage, 44% had pulmonary complications, compared with 47% of those who were not lavaged.¹²¹ Although available studies do not offer a conclusive answer to the question of gastric emptying after hydrocarbon ingestion, the high incidence of spontaneous emesis and the risk of aspiration essentially eliminate any consideration of gastric emptying in all but the rarest of cases.

Activated charcoal (AC) has limited ability to decrease gastrointestinal absorption of hydrocarbons and may distend the stomach and predispose patients to vomiting and aspiration.^{87,104} The use of AC may be justified in patients with mixed overdoses, but its role in isolated hydrocarbon ingestions appears very limited.

Antibiotics were once frequently administered in the setting of hydrocarbon pneumonitis to treat possible bacterial superinfection,¹⁶⁴ and they are still occasionally used today as fever and infiltrates are common. Although animal models rapidly demonstrate superinfection, prophylactic antibiotics only appear to alter pulmonary flora.²⁸ Prophylactic antibiotics did not affect length of stay or otherwise impact the outcome of 48 pediatric patients admitted for respiratory distress from hydrocarbon poisoning.⁷⁵ Similarly, in a randomized controlled study of pediatric patients suffering from kerosene-induced pneumonitis, prophylactic amoxicillin did not affect signs or symptoms, the rate of clinical deterioration (treatment failure), or duration of hospitalization.¹¹ However, antibiotic administration may be justified in severely poisoned patients. Ideally, sputum Gram stain or culture results should direct antibiotic use.

Corticosteroids, like antibiotics, have been prophylactically administered in the setting of hydrocarbon pulmonary toxicity.^{60,154} The rationale for their use is prevention and limitation of the pulmonary inflammatory response after hydrocarbon injury. Animal models do not show any benefit of corticosteroid administration^{5,143} and may increase the risk of bacterial superinfection. Furthermore, a controlled human trial failed to show a benefit from corticosteroid administration.⁹⁷ It is clear that corticosteroid use does not improve the acute course of hydrocarbon pulmonary toxicity, although some authors suggest improved outcome with delayed corticosteroid therapy there is little supporting evidence.^{78,82} Coupled with the possible increased risk of bacterial superinfection, corticosteroid administration in this

setting is not recommended.

Patients with severe hydrocarbon toxicity pose unique problems for management. Respiratory distress requiring mechanical ventilation in this setting may be associated with a large ventilation–perfusion mismatch. The use of positive end-expiratory pressure (PEEP) in this setting is often beneficial. However, very high levels of PEEP may be required, with subsequent increased risk of barotrauma.^{131,179} High-frequency jet ventilation (HFJV), using very high respiratory rates (220–260) with small tidal volumes, has helped to decrease the need for PEEP.³⁰ Patients who continue to have severe ventilation–perfusion mismatch despite PEEP and HFJV have benefited from extracorporeal membrane oxygenation (ECMO).^{131,179} ECMO appears to be a useful option in severe pulmonary toxicity after other treatments have failed. Early administration of surfactant may reduce pulmonary toxicity, but experience under these circumstances is limited.⁹⁸

Cyanosis is uncommon after hydrocarbon toxicity. Although this is most often caused by severe hypoxia, methemoglobinemia associated with hydrocarbon exposure is reported.^{37,88} The potential for methemoglobinemia should be investigated in patients who remain cyanotic following normalization of arterial oxygen tension ([Chap. 127](#)).

Hypotension in severe hydrocarbon toxicity raises additional concerns. The etiology of hypotension in this setting is often compromise of cardiac output because of high levels of PEEP. Hydrocarbons do not have significant direct cardiovascular effects, and decreasing the PEEP may improve hemodynamics. The use of β -adrenergic agonists such as dopamine, epinephrine, isoproterenol, and norepinephrine should be avoided if possible, as certain hydrocarbons predispose to dysrhythmias.^{13,110,126}

Management of dysrhythmias associated with hydrocarbon toxicity should include consideration of electrolyte and acid–base abnormalities such as hypokalemia and acidosis result from toluene, hypoxemia, hypotension, and hypothermia. Ventricular fibrillation poses a specific concern, as common resuscitation algorithms recommend epinephrine administration to treat this rhythm. If it is ascertained that the dysrhythmia emanates from myocardial sensitization by a hydrocarbon solvent, catecholamines should be avoided. In this setting, lidocaine has been used successfully, as have β -adrenergic antagonists.¹⁰⁵

Hyperbaric oxygen (HBO) was studied in a rat model of severe kerosene-induced pneumonitis.¹³⁴ HBO at 4 ATA showed some benefit in 24-hour survival rates. No follow-up studies have been performed. Patients with CCl₄ poisoning, however, may benefit from hyperbaric oxygen.^{27,158} ([Antidotes in Depth: A37](#)).

In the past, hospital admission was routinely recommended for patients who ingested hydrocarbons, because of concern over possible delayed symptom onset and progression of toxicity. Several reports documented patients with relatively asymptomatic presentations who rapidly decompensated with respiratory compromise. However, progressive symptoms after hydrocarbon ingestion are rare,^{8,94} and these recommendations predate noninvasive assessments of gas exchange. In a retrospective study of 950 patients, only 14 (1.5%) had progression of pulmonary toxicity.⁸ Of these 14, seven had persistence of symptoms for less than 24 hours. Eight hundred patients were asymptomatic on initial evaluation with normal chest radiographs, remained asymptomatic after 6 to 8 hours of observation, and had a normal repeat radiograph. No patient in this group of 800 had progressive symptoms, and all were discharged without clinical deterioration. Seventy-one of the 950 patients had initial respiratory symptoms but were asymptomatic at initial medical evaluation. Of the 71 patients, 36 had radiographic evidence of pneumonitis. Of these 36 patients, two (6%) developed progression of pulmonary symptoms during the 6-hour observation period. Of the 35 who had a normal radiograph, two (6%) developed pulmonary symptoms and radiographic pneumonitis during the 6-hour observation period. The four patients who were hospitalized for progression of symptoms became asymptomatic over the next 24 hours and had no complications.

A separate poison center–based study evaluated 120 asymptomatic patients over an 18-hour telephone follow-up period.⁹⁴ Sixty-two patients had initial pulmonary symptoms that quickly resolved. One of the 62 patients (1.6%) developed progressive pulmonary toxicity. This patient was hospitalized and had resolution of symptoms within 24 hours without complications.

A number of investigators have suggested protocols for determining which patients can be safely discharged.^{8,81,94} None of these protocols has been prospectively validated. However, rational guidelines for hospitalization can be recommended. Those patients who have clinical evidence of toxicity, and most individuals with intentional ingestions, should be hospitalized. Patients who do not have any initial symptoms, have normal chest radiographs obtained at least 6 hours after ingestion, and who do not develop symptoms during the 6-hour observation period can be safely discharged. Care should be individualized for patients who are asymptomatic but who have radiographic evidence of hydrocarbon pneumonitis and for patients who have initial respiratory symptoms but quickly become asymptomatic during medical evaluation. Reliable patients may be considered for possible discharge with next-day follow-up.

SUMMARY

- Hydrocarbons are a diverse group of xenobiotics that can cause toxicity by inhalation, ingestion, or dermal absorption.
- Populations at particular risk for toxicity include children who ingest hydrocarbon compounds, workers who are

occupationally exposed by inhalation or dermal absorption, and youths who intentionally inhale volatile hydrocarbons.

- Aspiration pneumonitis is the primary concern after hydrocarbon ingestion, with the risk of aspiration dependent on many factors including viscosity, volatility, surface tension, amount ingested, and the presence of emesis.
- Many hydrocarbons are poorly absorbed from the gastrointestinal tract and unlikely to produce systemic poisoning. Acute systemic toxicity is unlikely to occur in the absence of CNS effects such as excitation or sedation.
- An exposed child who is asymptomatic after 6 hours of observation and who has a normal chest radiograph taken after 6 hours of observation is most likely safe for discharge.

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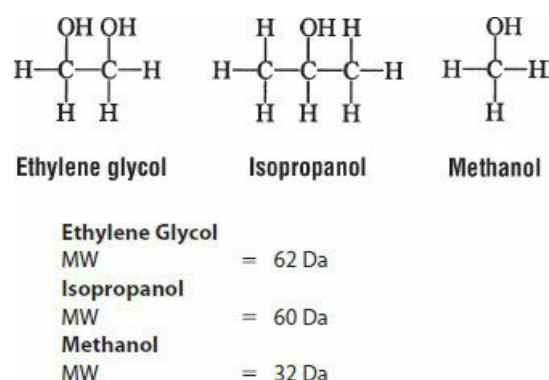
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109 TOXIC ALCOHOLS

Sage W. Wiener



HISTORY AND EPIDEMIOLOGY

Methanol was a component of the embalming fluid used in ancient Egypt. Robert Boyle first isolated the molecule in 1661 by distilling boxwood, calling it spirit of box.²⁹ The molecular composition was determined in 1834 by Dumas and Peligot, who coined the term “methylene” from the Greek roots for “wood wine.”²⁰² Industrial production began in 1923, and today most methanol is used for the synthesis of other chemicals. Methanol containing consumer products that are commonly encountered include model airplane and model car fuel, windshield washer fluid, solid cooking fuel for camping and chafing dishes, photocopying fluid, colognes and perfumes, and gas line antifreeze (“dry gas”). Methanol is also used as a solvent by itself or as an adulterant in “denatured” alcohol.¹³⁸ Most reported cases of methanol poisoning in the United States involve ingestions of one of the above products, with more than 60% involving windshield washer fluid,⁵⁸ although most inhalational exposures involve carburetor cleaner.⁸⁷ In a Tunisian series, ingested cologne was the most common etiology.³⁰ In a Turkish series, cologne was also most common, accounting for almost 75% of ingestions.¹²⁹ Perfume was one of several exposures in a patient with methanol poisoning in a report from Spain,¹⁷³ and methanol poisoning from cologne has also been reported in India.¹² There are sporadic epidemics of mass methanol poisoning, most commonly involving tainted fermented beverages.^{23,130} These epidemics are a continuing problem in many parts of the world.^{16,146,153,166,187,218,257}

Ethylene glycol was first synthesized in 1859 by Charles-Adolphe Wurtz and first widely produced as an engine coolant during World War II, when its precursor ethylene oxide became readily available.⁷⁰ Today its primary use remains as an engine coolant (antifreeze) in car radiators. Antifreeze used in gas tanks generally contains methanol. Because of its sweet taste, it is often consumed unintentionally by animals and children. Aversive bittering agents may be added to ethylene glycol containing antifreeze to try to prevent ingestions by making the antifreeze unpalatable, an approach required by law in two states. However, there is no evidence that this strategy is effective, and comparisons in poison center data between ethylene glycol ingestions where bittering agents were required and where they were not have revealed no significant differences in frequency or volume of ingestion, or any other outcome variable (Chap. 135).^{253,254}

Isopropanol is primarily available as rubbing alcohol. Typical household preparations contain 70% isopropanol. It is also a solvent used in many household, cosmetic, and topical pharmaceutical products. Perhaps because it is so ubiquitous, inexpensive, and with a common name that contains the word “alcohol”, isopropanol ingestions are the most common toxic alcohol exposure reported to poison centers in the United States,³⁶ typically in cases where it was used as an ethanol substitute (Chap. 136).

CHEMISTRY

Alcohols are hydrocarbons that contain a hydroxyl (-OH) group. The term “toxic alcohol” traditionally refers to alcohols other than ethanol that are not intended for ingestion. In a sense, this is arbitrary, since all alcohols are toxic, causing inebriation and end organ effects if taken in excess. The most common clinically relevant toxic alcohols are methanol and

ethylene glycol (1,2-ethanediol). Ethylene glycol contains two hydroxyl groups; molecules with this characteristic are termed diols or glycols because of their sweet taste. Other common toxic alcohols include isopropanol (isopropyl alcohol or 2-propanol), benzyl alcohol (phenylmethanol), and propylene glycol (1,3-propanediol). Primary alcohols, such as methanol and ethanol, contain a hydroxyl group on the end of the molecule (the terminal carbon), whereas secondary alcohols, such as isopropanol, contain hydroxyl groups bound to middle carbons. Glycol ethers are glycols with a hydrocarbon chain bound to one or more of the hydroxyl groups (forming the basic structure $R^1O-CH_2-CH_2-O-R^2$ or $R^1O-CH_2-CH_2-CH_2-OR^2$). Glycol ethers commonly encountered include ethylene glycol butyl ether (also known as 2-butoxyethanol, ethylene glycol monobutyl ether, or butyl cellosolve), ethylene glycol methyl ether (2-methoxyethanol), and diethylene glycol (2,2'-dihydroxydiethyl ether). Poisoning with these compounds may clinically resemble toxic alcohol poisoning, and diethylene glycol is discussed in detail in Special Considerations: SC7.

TOXICOKINETICS/TOXICODYNAMICS

Alcohols are rapidly absorbed after ingestion^{74,88} but are not completely bioavailable because of metabolism by gastric alcohol dehydrogenase (ADH), as well as by first-pass hepatic metabolism. Occasionally, delayed or prolonged absorption may occur.⁶⁸ Although methanol may also be absorbed in significant amounts by inhalation, poisoning by this route is uncommon. In workers exposed to methanol fumes from industrial processes for up to 6 hours at concentrations of 200 ppm (Occupational Health and Safety Administration {OSHA} permissible exposure limit {PEL}), there was no significant accumulation of methanol or its metabolite formate.¹⁴⁸ Another study showed that with methanol use in the semiconductor industry, ambient methanol concentrations generally do not approach this OSHA limit even in a room with poor ventilation due and with no local exhaust ventilation.⁸⁰ Surprisingly, concentrations far in excess of the OSHA PEL can be present within the passenger compartment of a car when using the windshield wipers with methanol-containing windshield washing fluid.²¹ No cases of human poisoning are reported from this type of exposure, probably because these concentrations are not sustained over a long time. Two patients with occupational inhalational exposure aboard a tanker carrying methanol developed consequential toxicity, including the death of one; both patients reportedly used appropriate personal protective equipment.¹³⁹ Additionally, cases of inhalational poisoning are reported with intentional inhalation of methanol as a drug of abuse, typically in the form of carburetor cleaning fluid (“huffing”) (Chap. 84), and with massive exposures of rescue workers responding to the scene of an overturned rail car filled with methanol.^{14,75,87,158,244,250} Two case series suggest that patients who present after chronic inhalation of methanol have good clinical outcomes with folate and ADH blockade alone and without need for hemodialysis,^{20,158} although in another series, patients with inhalational exposure were as likely to require dialysis as patients with methanol ingestion.⁸⁷ Transdermal methanol exposure can be consequential if exposure is prolonged.¹³¹ Ethylene glycol has low volatility and is not reported to cause poisoning by inhalation. In one study, human volunteers inhaled vaporized ethylene glycol at a concentration of 1340 to 1610 ppm for 4 hours to simulate an industrial exposure. Afterward, the volunteers had detectable but not clinically significant concentrations of ethylene glycol and its metabolites.²⁴² Most alcohols have some dermal absorption, although isopropanol and methanol are able to penetrate the skin much better than ethylene glycol.^{63,154,248} Most reported cases of toxic alcohol poisoning by this route involve infants⁵⁷ because of their greater body surface area-to-volume ratio, and likely this also involved simultaneous inhalation. One reported case of transdermal methanol poisoning involved a 51 year-old woman, but details of the exposure were not reported.²³⁰ Another case involved a 52 year-old woman who reportedly frequently massaged with methanol containing cologne and spirit over the course of 3 days. That patient suffered significant visual and neurologic sequelae despite aggressive treatment with ethanol and hemodialysis.² One methanol fatality was deemed to be caused by transdermal absorption (in addition to blunt trauma) when high tissue methanol concentrations were measured in the absence of detectable methanol in the gastrointestinal tract,¹⁵ but inhalational exposure could also conceivably have contributed. When human volunteers were exposed to 100% ethylene glycol applied to a 66 cm² area of skin under an occlusive dressing for 6 hours, detectable but not clinically significant amounts were absorbed.²⁴²

Once absorbed, alcohols are rapidly distributed to total body water. In human volunteers given an oral dose of methanol on an empty stomach, the measured volume of distribution was 0.77 L/kg, with a distribution half-life of about 8 minutes.⁸⁸ This is only slightly longer than the absorption half-life, so serum concentrations typically peak soon after ingestion and then begin to fall.

Without intervention, toxic alcohols are metabolized through successive oxidation by ADH and aldehyde dehydrogenase (ALDH), each of which is coupled to the reduction of NAD^+ to NADH. Methanol is metabolized to formaldehyde, then to formic acid (Fig. 109–1). Ethylene glycol has two hydroxyl groups that are serially oxidized by ADH and ALDH, producing, in turn, glycoaldehyde, glycolic acid, glyoxylic acid, and finally oxalic acid (Fig. 109–2). Like ethanol, this metabolism follows zero-order kinetics, with a rate that is reported to be about 10 mg/dL/h.^{50,118,169} Additionally, this rate is apparently unchanged in chronic ethanol users.^{97,98} Alternate minor metabolic pathways such as catalase exist for methanol and ethylene glycol.

FIGURE 109–2. Pathways of ethylene glycol metabolism. Thiamine and pyridoxine enhance formation of nontoxic metabolites.

After methanol ingestion, the formate metabolite is bound by tetrahydrofolate and then undergoes metabolism by 10-formyltetrahydrofolate dehydrogenase to carbon dioxide and water. Ethylene glycol is also metabolized to ketoadipate and glycine using thiamine and pyridoxine as cofactors.¹⁷⁸ Because of the low toxicity of these ethylene glycol metabolites, these normally minor metabolic pathways are attractive targets for potential therapy.

Methanol and ethylene glycol are eliminated from the body as unchanged parent compounds. When kidney function is normal, ethylene glycol is cleared with a half-life of approximately 11 to 18 hours.^{28,47,226} Methanol does not have significant renal elimination (about 1% of the ingested dose in patients with intact hepatic metabolism) and is cleared much more slowly than is ethylene glycol, presumably as a vapor in expired air (half-life, 30–54 hours).^{34,144,188}

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Acute Central Nervous System Effects

All alcohols may cause inebriation, depending on the dose. Based on limited animal data, it appears that higher molecular weight alcohols are more intoxicating than lower molecular weight alcohols on a molar basis (therefore, isopropanol \approx ethylene glycol $>$ ethanol $>$ methanol).²⁵¹ However, the absence of apparent inebriation does not exclude ingestion, particularly if the patient chronically drinks ethanol and is thereby tolerant to its central nervous system (CNS) effects.²³⁵ Additionally, serum methanol concentrations of 25 to 50 mg/dL may potentially be associated with toxicity, whereas in most states one may legally drive a car with a blood alcohol concentration of up to 80 mg/dL.

The CNS manifestations of toxic alcohol poisoning are incompletely understood. It is assumed by analogy that inebriation is similar to that of ethanol, where effects are mediated through increased γ -aminobutyric acid (GABA)–ergic tone both directly and through inhibition of presynaptic GABA, GABA_A receptors as well as inhibition of the N-methyl-D-aspartic acid glutamate receptors.^{10,42,90,105,172} Although the CNS effects of other alcohols are clinically similar, there is no direct evidence that they are mechanistically the same.

Metabolic Acidosis

Metabolic acidosis with an elevated anion gap is a hallmark of toxic alcohol poisoning. This is a consequence of the metabolism of the alcohols to toxic organic acids. The acids have no rapid natural metabolic pathway of elimination, and therefore they accumulate, unlike acetic acid resulting from ethanol metabolism, which can enter the Krebs cycle. In methanol poisoning, formic acid is responsible for the acidosis, whereas in ethylene glycol poisoning, glycolic acid is the primary acid responsible for the acidosis, with other metabolites making a minor contribution. An exception to the formation of an acid metabolite is isopropanol, which is metabolized to acetone. Acetone is a ketone, not an aldehyde, and therefore cannot be further metabolized by ALDH (Fig. 109–3). Thus isopropanol has no organic acid metabolite and does not cause metabolic acidosis. In fact, ketosis without acidosis is essentially diagnostic of isopropanol poisoning. Occasionally, a non-anion gap (hyperchloremic) metabolic acidosis may result from ethylene glycol poisoning (almost 18% in one series), often concurrently with anion gap acidosis.²²⁹ The mechanism for this is unclear, but a similar pattern has been observed in the setting of diabetic ketoacidosis, alcoholic ketoacidosis, and toluene poisoning.

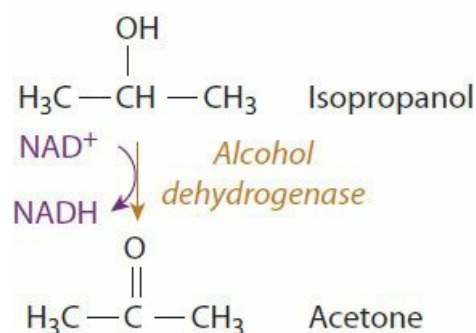


FIGURE 109–3. Isopropanol metabolism.

End-Organ Manifestations

Additional end-organ effects depend on which alcohol is involved. Methanol causes visual impairment, ranging from blurry or hazy vision or defects in color vision, to “snowfield vision” or total blindness in severe poisoning. Although it is counterintuitive, vision loss may not be symmetric.^{48,161} On physical examination, central scotoma may be present on visual

field testing, and both hyperemia and pallor of the optic disc, papilledema, and an afferent papillary defect are described as characteristic findings.^{23,183,260} Electroretinography may demonstrate a diminished b-wave,²⁴⁰ a marker of bipolar cell dysfunction, and optical coherence tomography (similar in principle to ultrasound, but using reflected light waves to image translucent tissues) may demonstrate peripapillary nerve fiber swelling and intraretinal fluid accumulation.⁷⁷ Formate is a mitochondrial toxin, inhibiting cytochrome oxidase and it thereby interferes with oxidative phosphorylation.^{69,179,180} Although it is unclear why this results in ocular toxicity while other tissues are relatively spared, retinal pigmented epithelial cells and optic nerve cells appear to be uniquely susceptible.^{66,165,239,240} Proteomic analysis of retinas in rats poisoned by methanol showed 24 proteins were different from baseline (14 increased, 10 decreased),⁴⁶ so the underlying pathophysiology of retinal toxicity from methanol may be more complex than is currently understood. Years after exposure, optic nerve atrophy, disc pallor and severe cupping may be still be present, even with normal intraocular pressure.²²¹

Interestingly, neurons in the basal ganglia appear to be similarly susceptible to this toxicity. Bilateral basal ganglia lesions, bilateral necrosis of the putamen (with or without hemorrhage), and less commonly, caudate nucleus are characteristically abnormal visualized on cerebral computed tomography (CT) or magnetic resonance imaging (MRI) after methanol poisoning.^{3,6,12,24,26,60,64,72,78,99,100,123,124,131,190,205,208,217,224,237,243} While lesions of this type are nonspecific, and may also occur in hypoxia, hypotension, and carbon monoxide poisoning, in methanol poisoning they occur in the absence of hypotension and hypoxia,¹⁶⁷ suggesting a direct toxic mechanism. Patients have developed parkinsonism after poisoning by methanol, a finding consistent with the lesions in the basal ganglia lesions.^{92,166,200} In one series, typical radiological lesions were present in six of nine cases.²¹⁷ Other CNS lesions reported include necrosis of the corpus callosum¹³⁴ and intracranial hemorrhage.^{13,216} Pathologic examination of the brain reveals lesions similar to those found radiologically.¹³² Increased glial fibrillary acidic protein and decreased CD34 expression are pathologic markers in affected tissues, although how these relate to the underlying pathophysiology is not yet clear.²⁴¹

Both retinal and neurological toxicity of methanol poisoning may be permanent. Among 86 survivors of a methanol poisoning outbreak in Estonia in 2001, 26 had died six years later (many from alcohol intoxication) and 33 could not be tracked down. Of the five patients who could be found out of 20 patients that had been discharged with retinal or neurologic sequelae, all had persistent effects. Interestingly, 8 out of the 22 patients found who were discharged without sequelae had newly identified neurological and visual sequelae 6 years later (among 66 initially discharged without sequelae). The newly identified visual sequelae may have actually been present initially but missed due to lack of ophthalmologic evaluation, or symptoms may have developed more gradually in these patients. New neurologic symptoms were probably due to continued drinking.¹⁸⁶ In another series from Iran, 37 of 50 survivors of methanol poisoning with retinal toxicity were followed 1 year later; 16 patients improved before discharge from the hospital. Seven patients had their visual disturbance resolve within 2 weeks; 5 were blind at discharge but partially recovered within 3 to 4 weeks; 5 were blind at discharge and had no improvement 1 year later; and 4 were blind at discharge, had partial recovery within 1 month, but then had worsening vision within the subsequent 9 months.²¹¹ This suggests that, long-term outcomes of retinal toxicity are difficult to predict.

Rarely, injury to other tissues may also occur. Both acute kidney injury (AKI) and pancreatitis are reported after methanol poisoning.^{102,140} For unclear reasons, one case series showed a much higher incidence of pancreatitis (50%)¹⁰² and in another, 11 of 15 patients had pancreatitis,²⁴⁷ but this is not typical. Some of the AKI that results from methanol poisoning may be due to myoglobinuria.⁹¹ In one series of methanol poisoned patients with AKI about half had associated myoglobinuria, presumably due to atraumatic rhabdomyolysis. One reported patient with methanol poisoning had rhabdomyolysis severe enough to cause compartment syndrome in both legs, requiring fasciotomy.⁵¹ Patients with AKI were also more likely than a control group of patients to have severe poisoning, as manifested by low initial serum pH, high initial osmolality, and high peak formate concentration.²⁴⁷ Pathologic abnormalities of the liver, esophagus, and gastric mucosa are also found in some fatal cases of methanol poisoning.^{4,44}

The most prominent end-organ effect of ethylene glycol is nephrotoxicity. The oxalic acid metabolite forms a complex with calcium to precipitate as calcium oxalate monohydrate crystals in the renal tubules, leading to AKI.^{73,93,95,168,196,234,238} The diagnosis of ethylene glycol poisoning has been established at autopsy by demonstrating this abnormality, including in one homicide case^{11,151}; in another case, the diagnosis was established by kidney biopsy.¹³⁴ Although the intermediate products of ethylene glycol metabolism, and possibly ethylene glycol itself, are directly toxic to the renal tubules in some studies,^{49,73,195,198} this appears not to occur at clinically relevant concentrations.⁹³ Currently no explanation exists for the presence of necrotic lesions to the glomerular basement membrane on some pathology specimens⁷³ as oxalic acid generally does not cause glomerular injury.¹²⁵

Ethylene glycol can occasionally affect other organ systems. In severe poisoning, the oxalic acid metabolite may be present in sufficient amounts to cause hypocalcemia following precipitation as calcium oxalate. This can result in prolongation of the QT interval on the electrocardiogram and ventricular dysrhythmias.²¹⁵ Cerebral edema was present on CT scan in two patients who died of ethylene glycol poisoning.^{76,238} Two reported patients had delayed neurological

manifestations. One patient developed increased intracranial pressure, with papilledema and an abducens (CN VI) palsy approximately 9 days after recovering from acute ethylene glycol poisoning and without another clear etiology.⁵⁹ Another patient developed the same cluster of delayed effects (increased intracranial pressure, papilledema and an abducens palsy) on day 13 of hospitalization, after fomepizole, thiamine, pyridoxine, and hemodialysis. He subsequently developed a facial (CN VII) palsy, sensory neuropathy, and autonomic neuropathy, including postural hypotension and gastroparesis.¹⁹⁹ Precipitation of calcium oxalate crystals in the brain was found on autopsy after severe ethylene glycol poisoning^{8,73,76} and may account for the multiple cranial nerve abnormalities that occasionally develop,^{59,231} although there is as yet no direct evidence of causation. Peripheral polyradiculoneuropathy can be diagnosed by electromyography and nerve conduction studies in cases of ethylene glycol poisoning,^{7,17} and intracranial hemorrhage involving the globus pallidus can occur.³⁹ A leukemoid reaction may also occur in the setting of severe ethylene glycol poisoning, but the mechanism remains unclear.^{160,176} One pediatric case of hemophagocytic syndrome and liver failure in the setting of ethylene glycol poisoning resulted in fatality.¹⁴⁵ Parkinsonism can also occur.²⁰⁰ Two severe cases of unintentional ethylene glycol ingestion in the United Kingdom resulted in blindness and deafness; one with associated cranial neuropathies and one with multiple peripheral neuropathies.^{41,62} One patient had a myocardial infarction with ST segment elevation while poisoned with ethylene glycol, but survived after cardiac catheterization and placement of five stents, as well as treatment with ethanol and hemodialysis.²³⁶ Finally, death can result from massive ethylene glycol ingestion with no elevation of its metabolites, suggesting direct toxicity of the alcohol, probably through respiratory depression.⁸¹

Hemorrhagic gastritis is associated with isopropyl alcohol intoxication. Although this is often assumed to be caused by a local irritant effect, one reported case of hemorrhagic gastritis after percutaneous isopropanol exposure suggests that this is not the only mechanism, and may in fact be a specific end-organ effect.⁶⁵ Hemorrhagic tracheobronchitis has occurred in fatal cases of isopropanol aspiration.⁵ The acetone metabolite of isopropyl alcohol may also interfere with some creatinine assays, causing a falsely elevated result,¹³⁷ but it does not actually cause AKI.

DIAGNOSTIC TESTING

Toxic Alcohol and Metabolite Concentrations

Serum methanol, formate, ethylene glycol, oxalate, and isopropanol concentrations (as appropriate) would be the ideal tests to perform when toxic alcohol poisoning is suspected shortly after exposure. However, these concentrations are most commonly measured by gas chromatography with or without mass spectrometry confirmation, methodologies that are not available in most hospital laboratories on a 24 hour basis, if at all. In fact, in many hospitals these are only available as “send out” tests, so results arrive too late for early clinical decision making.¹³³ Enzymatic assays for methanol, formic acid, ethylene glycol, and glycolic acid have been developed,^{27,232,249} and these may lead to more readily available clinical tests. However, the commercial product is currently approved for veterinary use only. This veterinary test is effective for confirming the qualitative presence of ethylene glycol in human poisoning, although false positives may occur with propylene glycol.¹⁵⁷ In a murine model, a commercially available ethanol in saliva point of care test can detect the presence of a low concentration of methanol but not ethylene glycol.⁹⁶ Unfortunately, it would not distinguish between methanol and ethanol, limiting the clinical utility of this test. A group in Finland described a point of care breath test for methanol, using a portable Fourier transform infrared (FT-IR) analyzer similar to the “breathalyzers” used by law enforcement agents.¹⁴⁷ Although analyzers like this are used to check for methanol as a combustion product in industry, they are not yet approved for medical use in the United States. Once approved, they would be useful for early clinical decision making because they are easy to use and provide a rapid result. They also can provide continuous monitoring of concentrations, a feature that would be very helpful during hemodialysis. Unfortunately, this methodology could not be used to detect ethylene glycol because of its low volatility.

Patients presenting late after ingestion may already have metabolized all parent compound to toxic metabolites and thus may have low or no measurable toxic alcohol concentrations. Fortunately, the enzymatic assay for ethylene glycol is also capable of detecting glycolic acid, although as mentioned, this assay is approved only for veterinary use. Some authors have actually advocated for routine testing for glycolic acid in addition to testing for the parent compound when ethylene glycol poisoning is suspected.¹⁹⁸ Serum and urine oxalate concentrations may also be determined,²³³ although their clinical utility is unclear. Similarly, a formate concentration may be valuable when a patient presents late after methanol ingestion.^{115,184} Formate was detected in blood samples from 97% of patients who died of methanol poisoning in one series; all of these patients also had detectable blood or vitreous methanol concentrations.¹²⁶ Clearly, a low or undetectable toxic alcohol concentration must be interpreted within the context of the history and other clinical data, such as the presence of acidosis and end-organ toxicity, with glycolate and formate concentrations as potentially valuable additions.

Samples must be handled correctly for accurate toxic alcohol results. Particularly with the more volatile alcohols methanol and isopropanol, concentrations may be falsely low if the sample tubes are not airtight. This commonly results in low concentrations if alcohol concentrations are done as “add on” tests to samples already opened for electrolyte or osmol

determinations.

Other alcohols such as benzyl alcohol and propylene glycol are not routinely assessed for by gas chromatography. Thus these xenobiotics present a much greater diagnostic challenge than methanol and ethylene glycol. Enzymatic assays for methanol or ethylene glycol would also fail to detect these, although false positive ethylene glycol tests may occur if propylene glycol is present. Thus a high index of suspicion is critical to establishing the diagnosis in these cases. If suspected on the basis of history, specific toxic alcohol testing should be performed.

Once alcohol concentrations are obtained, their interpretation represents a further point of controversy. Traditionally, a methanol or ethylene glycol concentration greater than 25 mg/dL has been considered toxic, but the evidence supporting this as a threshold is often questioned. In a case series of methanol poisoned patients from the 1950s, a methanol concentration of 52 mg/dL was the lowest associated with vision loss.²³ This may have been the origin of the 25 mg/dL threshold, incorporating a 50% reduction as a margin of safety. However, the patient with the 52 mg/dL concentration presented 24 hours after his initial ingestion, and therefore was much more severely poisoned than suggested by his serum concentration at that point. In fact, almost all reported cases of methanol poisoning involve patients with delayed presentations who already have a metabolic acidosis.¹⁴¹ The only reported patient who went untreated after presenting early with an elevated methanol concentration (45.6 mg/dL) never developed acidosis or end-organ toxicity.^{32,141} A systematic review found that 126 mg/dL was the lowest methanol concentration resulting in an acidosis in a patient who arrived early after ingestion and met the inclusion criteria. The authors concluded that the available data are currently insufficient to apply a 25 mg/dL treatment threshold in a patient presenting early after ingestion without acidosis.¹⁴¹ However, until better data are available demonstrating the safe application of a higher concentration, it seems prudent to use a conservative concentration such as 25 mg/dL as a threshold for treatment.

Because of the problems with obtaining and interpreting actual serum concentrations, many surrogate markers have been used to assess the patient with suspected toxic alcohol poisoning. The initial laboratory evaluation should include serum electrolytes, including calcium, blood urea nitrogen, serum creatinine concentrations, urinalysis, measured serum osmolality, and a serum ethanol concentration. Blood gas analysis with a lactate concentration is also helpful in the initial evaluation of ill appearing patients.

Anion Gap and Osmol Gap

For a full discussion of the anion gap concept, refer to [Chap. 19](#). As previously discussed, anion gap elevation is a hallmark of toxic alcohol poisoning. In fact, the possibility of methanol or ethylene glycol poisoning is often first considered when patients present with an anion gap acidosis of unknown etiology, frequently with no history of ingestion. Unless clinical information suggests otherwise, it is important to exclude metabolic acidosis with elevated lactate concentration and ketoacidosis, which are the most common causes of anion gap acidosis, before pursuing toxic alcohols in these patients. This is because of the extensive evaluation required and expensive, potentially invasive course of therapy to which they are otherwise committed. However, elevated lactate concentrations may be present in the setting of both methanol and ethylene glycol poisoning.^{163,170,219}

The unmeasured anions in toxic alcohol poisoning are the dissociated organic acid metabolites discussed above. The acidosis takes time to develop, sometimes up to 16 to 24 hours for methanol. Thus the absence of an anion gap elevation early after reported toxic alcohol ingestion does not exclude the diagnosis. If ethanol is present in the body, the development of acidosis will not begin to occur until enough ethanol has been metabolized that it can no longer effectively inhibit ADH (see Ethanol Concentration, below).

A potential early surrogate marker of toxic alcohol poisoning is an elevated osmol gap (the principles and the calculations are discussed in detail in [Chap. 19](#)). However, it is important to recognize that osmol gap elevation is neither sensitive nor specific for toxic alcohol poisoning. Since a baseline osmol gap is generally not available when evaluating a patient (with rare exceptions),¹¹³ and a normal osmol gap ranges from -14 to +10 osmols, so-called “normal” osmol gaps cannot exclude toxic alcohol poisoning.¹⁰⁸ For example, in a patient with a baseline osmol gap of -10, a current gap of +5 potentially represents a methanol concentration of 47 mg/dL or an ethylene glycol concentration of 93 mg/dL, values that might require hemodialysis. Inversely, a moderately elevated osmol gap (+10 to +20) is not necessarily diagnostic of toxic alcohol poisoning because other disorders such as alcoholic ketoacidosis and metabolic acidosis with elevated lactate concentration, may raise the osmol gap.²¹⁴ Furthermore, mean osmol gaps vary within populations over time, further limiting their utility.¹⁴² However, a markedly elevated osmol gap (>50) is difficult to explain by anything other than a toxic alcohol.

Further complicating matters, the anion gap and osmol gap have a reciprocal relationship over time. This is because soon after ingestion, the alcohols present in the serum raise the osmol gap but do not affect the anion gap because metabolism to the organic acid anion has not yet occurred. As the alcohols are metabolized to organic acid anions, the anion gap rises while the osmol gap falls, because the metabolites are negatively charged particles that have already been accounted for in the calculated osmolality by doubling of the sodium. Thus patients who present early after ingestion may have a high osmol gap and normal anion gap, while those who present later may have the reverse.^{111,117} [Figure 109–4](#)

depicts a more intuitive visual representation of this process.

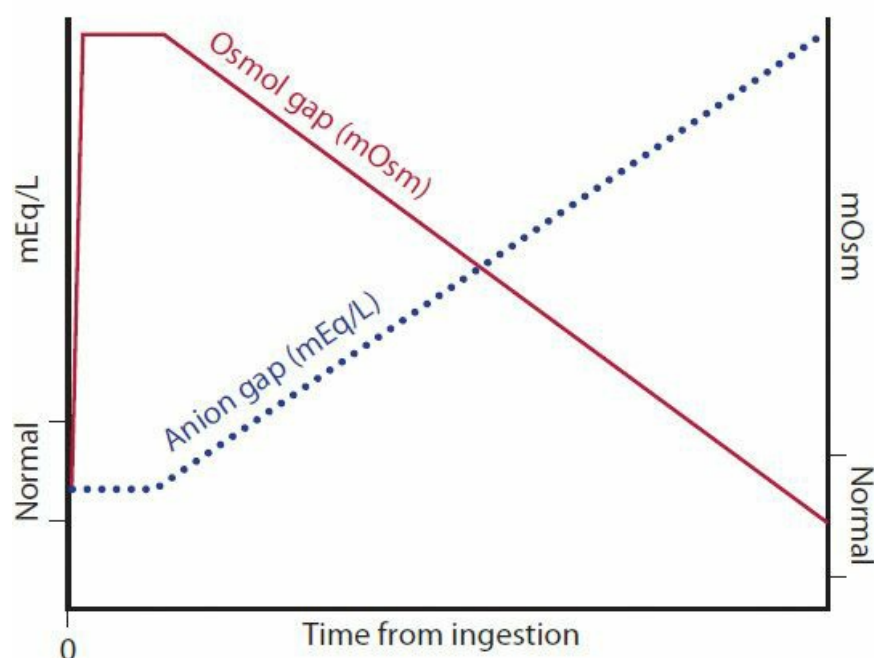


FIGURE 109-4. The reciprocal relationship of anion gap and osmol gap over time (hours). Note that patients presenting early may have a normal anion gap while patients who present late may have a normal osmol gap.

One retrospective and one prospective study have attempted to evaluate the performance characteristic of the osmol gap as a diagnostic test. Although in both cases, the osmol gap performed fairly well, the studies were small, 20 patients with toxic alcohol poisoning in the retrospective study and 28 patients with methanol poisoning in the prospective study, and the prospective study identified three patients with significant poisoning and acidosis but “normal” osmol gaps, defined in the study as less than 25.^{111,162} Therefore, these data do not eliminate the concern that a patient with significant poisoning could be missed by relying on the osmol gap alone to exclude poisoning.

Ethanol Concentration

A serum ethanol concentration is an important part of the assessment of the patient with suspected toxic alcohol poisoning. As discussed in [Chap. 19](#), the ethanol concentration is necessary to determine the calculated osmolality. In addition, because ethanol is the preferred substrate of ADH (4:1 over methanol and 8:1 over ethylene glycol), a significant concentration would be protective if coingested with a toxic alcohol. In fact, ethanol concentrations near 100 mg/dL virtually preclude toxic alcohols as the cause of an unknown anion gap metabolic acidosis because the presence of such a concentration should have prevented metabolism to the organic acid. A possible exception would be ingestion of ethanol several hours after ingestion of a toxic alcohol.¹⁰⁶ If a breath alcohol analyzer is used to determine ethanol concentration, a false positive ethanol value may be obtained if significant methanol concentrations are present, and the machine may not indicate that an interfering substance is present (as it does with acetone).⁴⁰ Therefore, even if a prehospital breath alcohol analyzer indicates a significant ethanol concentration, this should be confirmed by determining the serum ethanol concentration.

Lactate Concentration

Both methanol and ethylene glycol poisoning can result in elevated lactate concentrations, for different reasons. Formate, as an inhibitor of oxidative phosphorylation, can lead to anaerobic metabolism and resultant lactate elevation. Additionally, metabolism of all alcohols results in an increased NADH/NAD⁺ ratio, which favors the conversion of pyruvate to lactate. Furthermore, hypotension and organ failure in severely poisoned patients can also produce an elevated lactate concentrations. However, lactate production by these mechanisms tends to result in serum concentrations no greater than 5 mmol/L.

In ethylene glycol poisoning, the glycolate metabolite may also cause a false positive lactate elevation when measured by some analyzers, particularly with whole blood arterial blood gas analyzers. The Radiometer ABL series (625, 700, 725, 825, 835) is most widely reported to result in a false positive lactate; other specific models implicated to varying degrees include: Beckman LX 20, Bayer/Chiron Rapidlab series (860, 865), Roche Modular, Architect c8000, Vitros Fusion 5.1, Cobas Integra, GEM Premier 4000 and Hitachi 911 analyzers, but not the Vitros 950 or Vitros 250 or the Beckman Coulter DxC-800 chemistry analyzer.^{35,45,53,71,163,170,175,191,197,213,256} In such cases, the degree of lactate elevation directly correlates

with the concentration of glycolate present,^{163,170} and the artifact results from the lack of specificity of the lactate oxidase enzyme used in these machines,^{170,175,197,256} although direct oxidation of glycolate at the analyzer anode is also suggested as a possible mechanism.²²² Thus the presence of a “lactate gap” might also be used to diagnose ethylene glycol poisoning in hospitals where lactate assays are available with and without sensitivity to glycolate, or two lactate assays with different sensitivities to lactate.^{222,246} Ingestion of propylene glycol can also result in elevated lactate concentrations, but in this case, it is not a false positive lactate but rather an accurate measurement of a metabolite of propylene glycol.^{127,128}

Other Diagnostics

Serum glucose concentration is generally obtained as part of routine laboratory analysis. Hyperglycemia, defined as serum glucose greater than 140 mg/dL (7.77 mmol/L) in nondiabetic patients, portended a greater risk of death after methanol poisoning, with an odds ratio of 6.5 in one retrospective study.²¹⁰ This has not yet been prospectively validated.

The urine may provide information in the assessment of the patient with suspected ethylene glycol poisoning. Calcium oxalate monohydrate (spindle-shaped) and dihydrate (envelope-shaped) crystals may be seen when the urine sediment is examined by microscopy, although this finding is neither sensitive nor specific.^{79,118,174} In fact, calcium oxalate crystals were present in the urine of only 63% (12 of 19) of patients with proven ethylene glycol ingestion in one series.³³

Some brands of antifreeze contain fluorescein to facilitate the detection of radiator leaks. If one of these products is ingested and the urine is examined with a Woods lamp within the first 6 hours, there may be urinary fluorescence.²⁵⁵ Gastric aspirate may also demonstrate fluorescence.⁵⁶ False positive fluorescence may result from examining the urine in glass or plastic containers due to the inherent fluorescence of these materials, so if this test is performed, an aliquot of the urine should be poured onto a piece of white gauze or paper. Recent work has suggested a lack of utility of this test. Almost all children had urinary fluorescence, and there was poor interrater agreement in determining fluorescence of specimens.^{43,189}

The evaluation of patients with known or suspected ethylene glycol poisoning should also include serum calcium and creatinine concentrations. Patients with methanol poisoning and abdominal pain also warrant an assessment of liver function tests and serum lipase because of the possibility of associated hepatitis and pancreatitis.

Although characteristic brain CT and MRI abnormalities are frequently reported in the setting of methanol poisoning, it is unclear what role they have in the routine evaluation of these patients. The presence of putaminal hemorrhage or insular subcortex white matter necrosis was associated with a greater odds ratio of death (8 and 10, respectively) in one study of patients with methanol poisoning.²³⁷ However, in the absence of neurological abnormalities on physical examination, routine CT or MRI are probably not indicated.

Diagnostic Testing and Risk Assessment

Increases in both anion gap and osmolar gap may be useful for risk stratification in methanol poisoning, and a venous or arterial blood gas should be performed. A review of reported toxic alcohol cases attempted to identify risk factors for mortality in adults with methanol or ethylene glycol poisoning. For methanol poisoning, no patient with an anion gap less than 30 mEq/L or an osmolar gap less than 49 osmols died. A pH less than 7.22 was an even better predictor of mortality, as no patient with a pH greater than 7.22 died. For ethylene glycol, the tests were less useful. One patient with an osmolar gap of only 25 osmols died, no patient with an anion gap less than 20 mEq/L died, and pH did not predict mortality with statistical significance.⁵⁴ This study has been criticized for missing a substantial number of patients,²⁰⁷ and it still needs to be validated in another population. Another retrospective study of risk factors for poor outcomes in methanol poisoning only found that pH less than 7.00 (as well as coma or a >24-hour delay to presentation) was associated with death.¹⁰³ In a large series from several epidemics of methanol poisoning, a pH less than 7.00 and coma were again identified as risk factors associated with death. In patients with a pH less than 7.00, PCO₂ greater than or equal to 23.3 mm Hg (3.1 kPa) was also a risk factor.¹⁸⁵ In methanol poisoned patients unlikely to die, the pH may still be useful for predicting retinal toxicity. Another retrospective study examined markers for poor visual outcome after methanol poisoning and again found pH to be the best predictor, with a pH greater than 7.20 associated with a high likelihood of only transient visual sequelae.⁶¹

MANAGEMENT

As always, immediate resuscitation of critically ill patients starts with management of the airway, breathing, and circulation. Because alcohols may cause respiratory depression and coma, intubation and mechanical ventilation are commonly necessary for patients with severe poisoning. Alcohol-induced vasodilation combined with vomiting often lead to hypotension, and many patients will require fluid resuscitation with intravenous crystalloid. Gastrointestinal decontamination is rarely, if ever, indicated for toxic alcohols because of their rapid absorption and limited binding to activated charcoal. However, placement of a nasogastric tube and aspiration of any gastric contents is probably worthwhile

in intubated patients, as absorption may sometimes be delayed after a large dose.⁶⁸

Alcohol Dehydrogenase Inhibition

The most important part of the initial management of patients with known or suspected toxic alcohol poisoning (after initial resuscitation) is blockade of ADH. This allows for the establishment of a definitive diagnosis and arrangement for hemodialysis while preventing the formation of toxic metabolites. Additionally, in some cases ADH blockade may itself serve as definitive therapy.

Teleologically, ADH exists for the purpose of metabolizing ethanol, so it is not surprising that the enzyme has a higher affinity for ethanol than for other alcohols. ADH metabolizes ethanol with a K_m that is 15 to 20 times lower in vitro than its K_m for methanol metabolism and 67 times lower than its K_m for ethylene glycol metabolism.^{55,192,193} Thus significant concentrations of ethanol prevent metabolism of other alcohols to their toxic products. Ethanol is the traditional method of ADH inhibition and may still be the only option in some institutions. A 10% solution is administered through a central venous catheter and titrated to maintain a serum concentration of 100 mg/dL (Antidotes in Depth: A31). Complications of the infusion include hypotension, respiratory depression (with supratherapeutic concentrations), flushing, hypoglycemia, hyponatremia, pancreatitis, and gastritis, as well as inebriation, so patients receiving intravenous ethanol require admission to an intensive care unit. The true incidence of these adverse events is unclear. In one study, complications of ethanol infusion in children were uncommon.²⁰³ However, in another review of 49 adults treated with ethanol infusions for toxic alcohol poisoning, 92% of patients had at least one adverse event.²⁵² Orally administered ethanol is also effective and may be considered when intensive monitoring is unavailable, particularly in rural areas where there may be a significant delay in getting the patient to a hospital.

Fomepizole is a competitive antagonist of ADH that has many advantages over ethanol. It reliably inhibits ADH when administered as an intravenous bolus every 12 hours, and concentrations do not need to be monitored as with an ethanol infusion.^{33,34} It does not cause inebriation and is associated with fewer adverse effects, so it does not require intensive care unit monitoring.^{18,19,33,34,150} For these reasons, it has become the preferred method of ADH blockade, despite being significantly more expensive than ethanol.²²⁵ In theory, the savings in intensive care unit (ICU) monitoring and laboratory costs probably compensate for the higher drug cost of fomepizole, unless the patient requires intensive monitoring regardless based on the severity of illness.²⁸ However, one study showed that even after fomepizole was introduced to their hospital, 95% of patients received ICU admission and hemodialysis,⁸⁹ so this may not be a large area of savings. Additionally, the cost difference will vary depending on the setting of poisoning and the health care delivery system of the country involved. A series in Belgium found that treating with ethanol and dialysis was much less expensive than fomepizole without dialysis within their system.⁹

The dose of fomepizole is 15 mg/kg intravenously as an initial loading dose followed by 10 mg/kg every 12 hours. Bradycardia and hypotension may occur after fomepizole infusion, so vital signs should be monitored closely during and after each dose.¹⁴⁹ After 48 hours of therapy, fomepizole induces its own metabolism, so the dose must be increased to 15 mg/kg every 12 hours. Although one review advocates giving doses as high as 20 mg/kg every 12 hours with no adjustment for induced metabolism,²⁵ this dosing regimen is not supported by the manufacturer or any current clinical guideline. A review of reported cases in which fomepizole was used in children suggests that it is safe and effective with the same weight based dosing as adults.³² Pharmacokinetic data from a human volunteer study show that there is no significant difference in serum concentrations between oral and intravenous fomepizole.¹⁶⁴ However, there is currently no oral preparation of fomepizole on the market (Antidotes in Depth: A30).

Indications for fomepizole or ethanol therapy may be based on the history or on laboratory data. Any patient with a believable history of methanol or ethylene glycol ingestion should be treated until concentrations are available because, as previously discussed, early symptoms and laboratory markers other than serum concentrations may be absent. In addition, any patient with an anion gap acidosis without another explanation or a markedly elevated osmol gap should also be treated. Once concentrations are available, therapy should be continued until the serum toxic alcohol concentration is predicted or measured to be below 25 mg/dL, although as discussed previously, this value is based more on consensus opinion than on data.

The antiretroviral medication abacavir is a substrate for ADH and seemed to delay metabolism of methanol in one case.⁸⁴ It has been suggested that abacavir could have potential as an alternative to fomepizole in places where fomepizole is unavailable.²¹² Similarly, ranitidine is an inhibitor of gastric and hepatic ADH, and in a rat model, ranitidine improved pH, formate concentrations, and retinal histopathology.⁶⁷ Although these are intriguing possibilities, there are currently no data to support the use of either abacavir or ranitidine in human poisoning.

Hemodialysis

The definitive therapy for symptomatic patients poisoned by toxic alcohols is hemodialysis. Hemodialysis clears both the alcohols and their toxic metabolites from the blood and corrects the acid–base disorder. The indications for hemodialysis

have become more restricted with the advent of fomepizole because of its effectiveness combined with its low incidence of adverse effects. Particularly for ethylene glycol, which can generally be expected to be cleared within a few days once ADH is blocked as long as the glomerular filtration rate is normal,^{37,152,245} some have argued that the risks of an invasive and costly procedure such as hemodialysis are not warranted in minimally symptomatic patients with normal kidney function and without acidosis.^{38,82} Even a patient with a moderately elevated serum methanol concentration, 80 mg/dL (2.5 mmol/L), was successfully treated with fomepizole alone.²⁰⁴ Based on toxicokinetic data, some patients with methanol poisoning might be treated without dialysis or with delayed dialysis, particularly in epidemic scenarios, where the need for hemodialysis may exceed the availability.¹¹² However, patients with end-organ toxicity or severe acidosis have significant amounts of toxic metabolites, a problem not addressed by ADH blockade, and acidosis is associated with poor prognosis.¹⁵⁶ Additionally, although formate is normally cleared rapidly once ADH is blocked, the half-life increases with higher serum methanol concentrations and varies from 2.5 to 12.5 hours.^{101,110} In one patient with severe poisoning, formate was eliminated at an extremely slow rate with a half-life of 77 hours until hemodialysis was initiated,¹¹⁴ underscoring the importance of hemodialysis in patients with significant metabolic acidosis. In addition, patients with AKI will not eliminate the parent compound once ADH is blocked, except very slowly in expired air in the case of methanol. Therefore, the consensus is that metabolic acidosis, signs of end-organ toxicity, including coma and seizures, and AKI are indications for hemodialysis. A “toxic concentration” and possibly a very high osmol gap¹⁹⁴ are more relative indications for hemodialysis, and decisions must be based on the judgment of the clinician for the specific clinical scenario, considering the available resources. Some authors have advocated using toxic metabolite concentrations if available as additional criteria for hemodialysis. In data from one case series, an elevated formate concentration appears to be a better predictor of clinically important toxicity than methanol concentrations.¹⁸⁴ Similarly, glycolate concentrations are a better predictor of death and AKI than ethylene glycol concentrations.¹⁹⁸ However, although clearance of formate by hemodialysis is substantial,^{121,122,136} the overall clearance in one case series did not appear to increase significantly above endogenous clearance in patients also treated with folate and bicarbonate.¹³⁶ Some have questioned the data quality in this series, pointing out that (a) the predialysis clearance in two patients was calculated using only two data points and in the three others was calculated using three points, generally considered the minimum; (b) several patients actually had decreased clearance during dialysis, contradicting all previous data; and (c) two of the patients had variable blood flow during dialysis.^{112,258}

The American Academy of Clinical Toxicology (AACT) practice guidelines are ambiguous with respect to a threshold methanol concentration for hemodialysis in the absence of acidosis, AKI, end-organ effects, or worsening clinical status.¹⁸ However, until additional investigations are completed, a methanol concentration of 50 mg/dL remains a reasonable indication for consideration of hemodialysis in the absence of significant acidosis or end-organ effects. The AACT guidelines for ethylene glycol actually advise against hemodialysis for a concentration alone without any of these clinical indications.¹⁹ Still, ethylene glycol remains the second most common toxin to be removed by hemodialysis in the US.¹⁰⁹ Clearly, there are still insufficient data to establish threshold concentrations of alcohols or their metabolites where dialysis is absolutely indicated, and the decision is ultimately a subjective one based on the overall clinical scenario.¹⁰⁷

Although hemodialysis effectively clears isopropanol and acetone from the blood, it is rarely if ever indicated for this purpose. Because isopropanol does not cause a metabolic acidosis and very rarely results in significant end-organ effects, the risks of hemodialysis likely outweigh the benefits.

Many patients will require multiple courses of hemodialysis to clear the toxic alcohol. Nephrologists may estimate the dialysis time required using the formula:

$$t = -V \ln(5/A)/0.06k$$

where t is the dialysis time required to reach a 5 mmol/L toxin concentration, V is the Watson estimate of total body water (liters), A is the initial toxin concentration (mmol/L), and k is 80% of the manufacturer specified dialyzer urea clearance (mL/min) at the observed initial blood flow rate.^{104,259} Additionally, the normalization of the osmol gap may guide the required duration of dialysis, but this has not been validated.¹¹⁶ Regardless of how the duration of dialysis is determined, ADH blockade should be continued during and after hemodialysis until a subsequent concentration of the offending alcohol is confirmed to be nontoxic. Ethanol infusion rates must be increased during hemodialysis to maintain a therapeutic serum concentration as the ethanol is cleared (Antidotes in Depth: A31). Fomepizole should be redosed every 4 hours during hemodialysis to maintain therapeutic serum concentrations.^{18,19}

Continuous renal replacement therapy (CRRT) such as venovenous hemodiafiltration has occasionally been used in patients with toxic alcohol poisoning. Hemodialysis is much more efficient at clearing xenobiotics than CRRT and is virtually always the preferred modality if available. However, if there is a contraindication to hemodialysis, such as hemodynamic instability or severe cerebral edema,⁸⁶ or if hemodialysis is unavailable, CRRT may be considered as an intervention that may offer some advantage over no extracorporeal removal at all. In a pharmacokinetic model, the addition of CRRT can decrease the treatment time by 40%.⁵⁵

Adjunctive Therapy

There are several therapeutic adjuncts to ADH blockade with or (especially) without hemodialysis that should be considered for these patients. One of the differences that has been invoked to explain the absence of retinal toxicity from methanol in some species is the relative abundance of hepatic folate stores in these species such as the rat. Folate and leucovorin enhance the clearance of formate in animal models.^{181,182} Thiamine enhances the metabolism of ethylene glycol to ketoacid, and pyridoxine enhances its metabolism to glycine and ultimately hippuric acid (Fig. 109–2).¹⁷⁸ While all of these modalities offer theoretical advantages, they have yet to be proven to change outcome in humans. However, there is one human case report showing enhanced formate elimination with folinic acid therapy.¹²⁰ Additionally, some have suggested that the apparent lack of an increase in formate clearance by hemodialysis was because it was dwarfed by the effectiveness of folate supplementation in both the study group and the control group.¹³⁶ Because of the safety of vitamin supplementation, the potential benefit likely outweighs the risk of therapy (Antidotes in Depth: A10, A14, and A24).

Formate is much less toxic than undissociated formic acid, likely because formic acid has a much higher affinity for cytochrome oxidase in the mitochondria, the ultimate target site for toxicity.¹⁵⁵ In addition, the undissociated form is better able to diffuse into target tissues.¹²² Alkalinization with a bicarbonate infusion shifts the equilibrium to favor the less toxic, dissociated form, in accordance with the Henderson-Hasselbalch equation. This also enhances formate clearance in the urine by ion trapping.¹²² Data from uncontrolled case series demonstrate that patients treated with bicarbonate alone had better than expected outcomes after severe methanol poisoning,¹⁷⁷ but the results are equivocal in patients also treated with ADH blockade and hemodialysis.^{34,119,171} Additionally, the severity of the metabolic acidosis after methanol poisoning is a good predictor of severe neurological effects such as coma and seizures,¹⁵⁶ although it is not proven that alkalinization prevents these effects. However, in the absence of contraindications to a bicarbonate infusion (eg, hypokalemia, volume overload), alkalinization should be used in the patient with suspected methanol poisoning and a significant acidemia. A blood pH greater than 7.20 is a reasonable endpoint. Alkalinization should also be considered for patients with ethylene glycol poisoning and life-threatening metabolic acidosis.

Aluminum citrate has potential promise as an adjunctive therapy for ethylene glycol poisoning. It interacts with the surface of calcium oxalate monohydrate crystals and prevents their aggregation. This decreases tissue damage from calcium oxalate monohydrate crystals in an in vitro model of human proximal tubule cells.⁹⁴ However, there are not yet any in vivo human studies or even case reports, so it cannot be recommended for clinical use.

Some have suggested a possible benefit of corticosteroids for retinal injury following methanol poisoning. In an uncontrolled case series, 13 of 15 patients showed improvement in their vision after treatment with 1 g of methylprednisolone daily for 3 days, with one having worsening vision and one unchanged.²²³ A patient in another case report had permanent vision loss despite corticosteroid therapy using the same regimen.⁷⁷ Another uncontrolled case series used a slightly different dosing regimen, with 250 mg of intravenous methylprednisolone administered every 6 hours followed by oral prednisolone 1 mg/kg daily for 10 days. After treatment, the mean best corrected visual acuity improved, but methanol concentrations were not reported so exposure was not confirmed, and acuity data were not reported for individual patients, so it is unclear whether any worsened.^{1,209} Another series of four patients with mild methanol poisoning given the same treatment regimen showed some improvement in vision.²²⁸ An uncontrolled case series with delayed presentations, incomplete follow up, and an inconsistent corticosteroid regimen showed improvement in some patients.^{206,220} In a series of 63 patients with methanol poisoning from a 2009 epidemic in India, all patients with evidence of optic neuritis (at least 60% of 46 survivors), were treated with retrobulbar injections of triamcinolone (dose not reported); 75% had some improvement.²¹⁸ Currently, however, these data are insufficient to support the routine use of corticosteroids in methanol poisoning.²²⁷

SPECIAL POPULATIONS

Pregnant Women and Perinatal Exposure

There are very few reported cases of pregnant women with toxic alcohol poisoning, but some conclusions can be drawn from the available data. Toxic alcohols readily cross the placenta, and perinatal maternal methanol ingestion has resulted in death of a newborn.²² One woman was initially misdiagnosed with eclampsia after ingesting ethylene glycol and presenting with seizures and metabolic acidosis in her 26th week of pregnancy. An emergency cesarean section was performed, and she was later treated with hemodialysis and ethanol once the correct diagnosis was recognized. The child was severely ill, with an initial pH of 6.63 and an initial serum ethylene glycol concentration of 220 mg/dL. The baby was treated with exchange transfusion and ultimately survived without sequelae after a long hospital course.¹⁴³ In rat but not rabbit models of chronic high dose ethylene glycol exposure, fetal axial skeletal malformations occur and are thought to be caused by glycolate.⁵² No human case of chronic exposure has yet been reported.

OTHER ALCOHOLS

Propylene Glycol

Propylene glycol is commonly used as an alternative to ethylene glycol in “environmentally safe” antifreeze. It is also used as a diluent for many pharmaceuticals (such as phenytoin and lorazepam). This alcohol is successively metabolized by ADH and ALDH to lactate, so a metabolic acidosis results. This can result in extremely high lactate concentrations typically that would be incompatible with life if generated by any disease process. In other diseases associated with lactate accumulation and acidosis, the lactate is a reflection of underlying anaerobic metabolism, a marker of severe illness rather than part of the underlying pathophysiology. Lactic acidosis from propylene glycol is surprisingly well tolerated because it represents nothing more sinister than its own metabolism, and it is rapidly cleared by oxidation to pyruvate, which then undergoes normal carbohydrate metabolism ([Chap. 55](#)).

Benzyl Alcohol

Benzyl alcohol is used as a preservative for intravenous solutions. Although it is no longer used in neonatal medicine, it has been responsible for “neonatal gasping syndrome,” involving multiorgan system dysfunction, metabolic acidosis, and death because of its metabolism to benzoic acid and hippuric acid ([Chap. 55](#)).^{83,159}

SUMMARY

- Early symptoms of toxic alcohol poisoning may include inebriation, and subsequent toxicity results from metabolism to organic acid anions that cause metabolic acidosis and end organ effects.
- The time required for this metabolism results in a delay before toxicity is clinically manifest.
- Until serum concentrations are available, the serum anion gap and osmol gap may help with decision making but do not exclude toxicity if the history is concerning.
- Therapy consists of ADH antagonism with fomepizole or ethanol, as well as adjunctive therapy with bicarbonate, folate or folinic acid, pyridoxine, and thiamine.
- Hemodialysis is the definitive therapy for clinically ill patients as it removes the alcohol as well as toxic metabolites while correcting the metabolic acidosis and electrolyte abnormalities.

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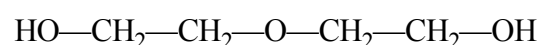
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SC7 SPECIAL CONSIDERATIONS

Diethylene Glycol

Joshua G. Schier



HISTORY AND EPIDEMIOLOGY

Diethylene glycol (DEG) is a solvent with physical and chemical properties similar to propylene glycol used throughout the chemical industry. Pharmaceutical-grade propylene glycol is a safe and commonly used solvent for water-insoluble pharmaceuticals (Chap. 55). However, unlike propylene glycol, DEG is a potent nephrotoxic and neurotoxic chemical. Substitution of DEG for propylene glycol and other diluents such as glycerin in oral pharmaceutical elixirs has repeatedly caused epidemics of mass poisoning (Chap. 2). This substitution has occurred early in the pharmaceutical manufacturing process due to the intentional mislabeling of DEG as a replacement for the intended pharmaceutical-grade glycerin,⁴² for financial gain⁴⁹ and other reasons, without regard to safety-grade glycerin.¹⁵ As medication-associated DEG mass poisonings have recurred, numerous quality assurance and control guidelines have been developed to identify DEG-contaminated materials. Failure to adhere to these guidelines throughout the pharmaceutical manufacturing and distribution process contributes to this public health problem.⁴⁹ In DEG poisoning, patients develop acute kidney injury (AKI) that can rapidly progress to renal failure and death. Those patients who do not die quickly after exposure, but who develop AKI, often become dialysis dependent and may go on to develop neurological signs and symptoms. These patients may deteriorate further after onset of neurotoxic signs and symptoms and subsequently die.

The metabolism of DEG and the pathophysiology of DEG-associated disease are incompletely understood and most of what is known comes from animal studies. Indeed, very little data are available in humans. Previously, DEG was thought to be metabolized to two ethylene glycol molecules which, when metabolized to glycolic acid and oxalic acid, caused AKI; this theory has been disproven.⁵⁷ Current evidence supports that the terminal DEG metabolite diglycolic acid (DGA) is nephrotoxic. Diglycolic acid appears to be neurotoxic as well based on a single, published case report of poisoning-grade glycerin.⁴⁴ This chapter will provide a brief history and epidemiology of DEG poisoning, describe existing pharmacokinetic and toxicokinetic data collected primarily from animal studies, and then discuss available information on the toxic dose, pathophysiology, clinical manifestations, testing and treatment for DEG poisoning. When specific doses of DEG in the literature were reported in mL/kg, they were converted to g/kg by taking into account the density of DEG (1.118 g/mL) and the concentration. If information on concentration was not provided, then a 100% concentration was assumed. For the reader's convenience, the original dose (if it was in mL/kg) and commensurate DEG concentration are provided following the converted dose in g/kg or mg/kg.

DEG is produced by the condensation of two ethylene glycol molecules forming an ether bond,¹ which yields a compound with a molecular weight of 106 g/mol.^{1,46} It was first identified in 1869 and has been used in industry and manufacturing since 1928.¹ It has found use as an antifreeze, as a finishing agent for wool, cotton, silk, and other fabrics, as well as in dye manufacturing. DEG is chemically inert and has a higher boiling point than ethylene glycol.^{20,58} Its other physical properties are quite similar to ethylene glycol, including a sweet taste.^{20,58} It is often used as an intermediate in the production of polymers, higher glycols, morpholine, and dioxane.³⁵ Its physical properties enable it to serve as an excellent solvent for delivery of water-insoluble substances. Unfortunately, its use as a solvent for various pharmaceuticals intended for human consumption has resulted in the vast majority of reported cases of poisoning.^{6,8,9,12,14,15,17,18,28,32,38,42,50,52,58} In these recurring events, DEG was substituted for a safe and appropriate diluent such as glycerin or propylene glycol. DEG poisoning has also resulted from the intentional addition of DEG to wine as a sweetener^{55,56} or when it was consumed as a substitute for ethanol.⁶⁰ Finally, there are numerous isolated case reports of DEG poisoning resulting from the consumption of DEG-containing products such as radiator fluid or antifreeze,³⁶ brake fluid,⁷ Sterno,⁴³ “fog solution,”¹⁹ cleaning solutions,¹ and wallpaper stripper.³⁴

PHARMACOKINETICS/TOXICOKINETICS

Absorption and Distribution

In rodents DEG is highly (>75%) and almost immediately absorbed after ingestion. It is distributed primarily based on blood flow, with the kidneys receiving the most DEG, followed by the brain, the spleen, liver, and muscles.²⁰ The degree of protein binding and the volume of distribution (Vd) in humans is unknown but the Vd in the rat is approximately 1 L/kg.²⁰ Maximal DEG plasma concentrations occur within 4 hours of ingestion: the ratio of DEG in plasma to red blood cells is 3:2 (approximately 60% of a dose is found in the plasma).^{3,20,58} DEG readily crosses the blood–brain barrier,^{20,58} and concentrations peak in brain tissue (CSF concentration was not reported) within 3 to 4 hours of exposure.²⁰

Metabolism. Existing animal data demonstrate that as much as 40% of an ingested dose may undergo hepatic metabolism with most of that eliminated in the urine.^{20,25,33} Diethylene glycol is metabolized by alcohol dehydrogenase (ADH) to 2-hydroxyethoxyacetaldehyde which is then further metabolized by aldehyde dehydrogenase (ALDH) to 2-hydroxyethoxyacetic acid (HEAA).^{4,57} HEAA is either renally excreted, oxidized to DGA (also known as 2,2-oxybisacetic acid) or converted to 1,4-dioxan-2-one under extremely acidic conditions.⁵⁶ The predominant pathway depends on numerous factors such as dose, degree of kidney function, and acid-base status of the patient.^{4,30,33,57} The DEG ether bond linking the two ethylene glycol molecules is stable and is not hydrolyzed. Ingestion of DEG and subsequent metabolism does not therefore result in ethylene glycol release.^{4,35,57} However, a small amount of ethylene glycol may be formed as an intermediate after formation of 2-hydroxyethoxyacetaldehyde (Fig. SC7–1).⁴ Serum HEAA concentrations peak approximately 4 hours following small DEG ingestions (2 g/kg), but a delayed peak at 8 to 24 hours occurs with larger exposures (10 g/kg) in rodents. Rats which ingest relatively small doses of DEG (2 g/kg) and rats given larger amounts of DEG with coadministration of an ADH blocker (10 g/kg + fomepizole) do not accumulate DGA in their serum over time. Blood DGA concentrations in rats dosed with 10 g/kg of DEG and fomepizole are not significantly different from control rat blood DGA concentrations. Furthermore, DEG elimination half-lives in the two groups dosed with 10 g/kg (one with fomepizole and without) were not significantly different, and almost the entire DEG dose given to the DEG plus fomepizole group was recovered in the urine. This suggests that elimination from the body is mainly controlled by urinary elimination of DEG, rather than by metabolism. Larger doses (10 g/kg) in rat studies, without simultaneous coadministration of an ADH inhibitor, are associated with clinically significant serum DGA concentrations that peak at 24 hours postingestion. If kidney function is impaired, concentrations of both HEAA and DGA continue to climb in a dose dependent manner.³

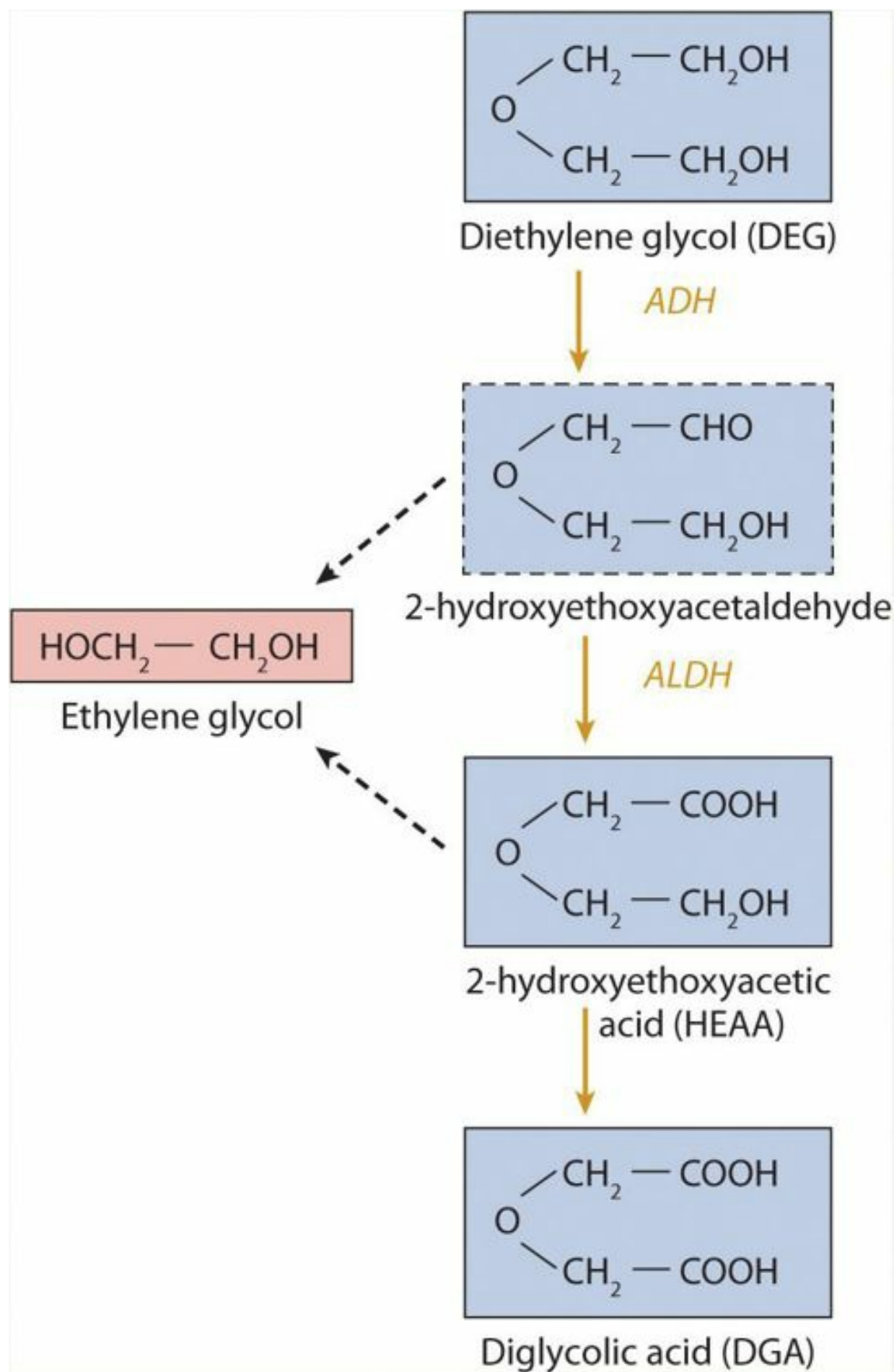


FIGURE SC7-1 Metabolic pathway for DeG based on previous animal studies and on the results presented in this report. Metabolites in solid boxes have been observed following administration of DeG to animals; those in dashed boxes are theoretical intermediates. Because fomepizole reduced the amount of eG in the urine, its origin is shown as coming from the aldehyde or acid intermediate, rather than from DeG itself. ALDH = aldehyde dehydrogenase. DGA is also known as oxybisacetic acid. (Reproduced with permission from Oxford University Press from Besenhofer LM, Adegboyega PA, Bartels M, et al. Inhibition of metabolism of diethylene glycol prevents target organ toxicity in rats. *toxicol Sci.* 2010;117(1):26.)

Elimination

Animal studies utilizing DEG with radiolabeled carbon report that most (> 60%) of a dose is eliminated within 24 hours of ingestion and almost all (> 90%) within 72 hours.^{33,35} The majority of a DEG dose is eliminated unchanged in the urine (> 60%).^{20,33} The proportion of DEG excreted in the urine increases when compared to metabolites as the dose increases due probably to saturation of hepatic metabolism.^{33,35} This effect persists for approximately 24 hours following exposure. This effect may not be demonstrable beyond 24 hours because either the dose was small enough such that it was rapidly eliminated or because the dose was large enough to induce AKI.³³ As the dose increases, the probability of developing AKI increases, which will result in a decreased elimination of both DEG and its metabolites. Up to 30% of a DEG dose may be eliminated via the kidneys as HEAA.^{3,13,33,57} Most initial work did not either look for or detect DGA, probably due to small exposures in the range of 1.1 g/kg, which did not result in substantial DGA generation.⁵⁷ For those reasons DGA metabolic data was not available until recently.^{3,4} Although both HEAA and DGA are taken up into the liver and the kidneys in a dose-dependent manner, the kidney tissue concentrations of HEAA are correlated directly with peak blood concentrations, but DGA concentrations are not. In fact, kidney tissue DGA concentrations are approximately 100 times greater than peak blood DGA concentrations suggesting much greater accumulation in the kidney.³ This accumulation explains the low concentrations of urinary DGA seen experimentally.⁴ In rodent studies of DGA ingestion limited to 48 hours, DGA is detected in the urine, but at concentrations 50 times lower than HEAA.⁴ However, biologic samples in DEG poisoned humans many days after exposure and in the presence of AKI demonstrated a predominance of urinary DGA concentrations and a relative absence of urinary HEAA.⁴⁸ These findings may be due to a number of different reasons such as the delayed blood peak of DGA when compared with HEAA, the greater time interval from exposure to sampling, which may have afforded a greater likelihood of HEAA metabolism to DGA (compared with experimental animal data), and saturation of kidney tubule cell uptake of DGA. Finally, small amounts of a given DEG dose are eliminated in a dose-dependent fashion via fecal excretion (< 3%) and exhalation (< 7%).^{20,33,35,46} Animal studies also demonstrate that small amounts of DEG radiolabeled carbon is not eliminated but distributed to and collected in certain tissues such as muscle, fat, and skin (< 4% each) and the intestines, liver, and kidneys (< 2% each).^{33,35}

Two studies have reported data on half-lives calculated from serial DEG concentrations. The first reported that oral doses of 6.7 and 13.4 g/kg (6 mL/kg and 12 mL/kg of assumed 100% DEG) result in half-lives of 8 and 12 hours, respectively.⁵⁸ The second report suggests that when animals are given DEG doses of 1.1, 5.5, and 10.9 g/kg (1, 5, and 10 mL/kg of 97.5% DEG), most (64%, 87%, and 91%, respectively) of the dose is eliminated in the first 16 hours after exposure with calculated half-lives of 3 to 4 hours.²⁰ The remainder is then eliminated much more slowly with half-lives ranging from 39 to 49 hours.²⁰

Several rodent studies have reported data on elimination half-lives collected from serial urinary DEG measurements in pharmacokinetic investigations. These same studies have demonstrated that a DEG dose-dependent osmotic diuresis occurs. As the ingested dose increases from 1.1 to 19.6 g/kg (–17.5 mL/kg of > 99% DEG), it induces a fourfold increase in urine production. This effect appears to plateau at approximately 19.6 g/kg (17.5 mL/kg of > 99% DEG).²⁰ DEG appears to undergo zero order kinetics for the first 9 to 18 hours following ingestion. This correlates temporally with the osmotic diuresis which may contribute to this phenomenon.^{20,33} During this time, elimination half-lives range from 6 hours at doses of 1.1 to 5.5 g/kg (1–5 mL/kg of 97.5% DEG) to 10 hours for doses of 10.9 g/kg (10 mL/kg of 97.5% DEG).²⁰ First order kinetics ensue thereafter with elimination half-lives that are dose-dependent and range from 3 to 13 hours.^{3,4,20,33} Based on some animal data, 12 hours may be sufficient to eliminate 94% of a dose assuming an elimination half-life of 3 hours at doses of 1.1 to 5.5 g/kg (1–5 mL/kg of 97.5% DEG).^{20,24} However, several other studies with similar exposures (2 g/kg) suggest that urinary elimination half-lives may be as high as 5 to 6 hours, which suggests that more than 12 hours is needed to eliminate the majority of an similar dose.^{4,20} Half-lives can be prolonged to at least 13 hours in more substantial poisonings (10 g/kg)³ and as kidney function becomes impaired DEG and its metabolites are unable to be excreted effectively, thereby prolonging elimination half-lives further. This information is of importance in determining the appropriate observation period for a suspected or known DEG exposure.

TOXIC DOSE

Rodent studies suggest that doses of up to 2 g/kg are minimally toxic and that doses of approximately 10 g/kg result in significant toxicity.⁴ However, rodents are relatively resistant to the clinical effects of DEG poisoning compared to humans. Human data are limited, established primarily from the history of affected patients from mass poisoning events, and usually represent an estimated cumulative exposure that occurred over a certain time period, rather than a single point of time. The median estimated toxic dose from the 1995 Haitian epidemic was approximately 1.5 g/kg (range, 0.25–4.94 g/kg) (1.34 mL/kg; range, 0.22–4.42 mL/kg of 100% DEG).³⁸ This estimation is similar to the doses reported for the elixir of sulfanilamide outbreak in the United States in the 1930s.⁸ The estimated toxic dose (0.35 g/kg) based on patient recall in the

2006 DEG mass poisoning in Panama was lower than previous events (personal communication, Nestor Sosa, MD). The lower toxic dose in this outbreak may be due in part to an older population with more chronic diseases when compared with other outbreaks that affected younger, presumably healthier persons (unpublished data from author). Postmortem DEG concentrations from an Argentinean outbreak reported a lethal dose ranging from 0.014 to 0.170 mg/kg,^{12,14} although these data were suggested to be inaccurate, possibly by a factor of 1000.⁴⁵ In addition, the analytical testing techniques used in this report may have been subject to error due to cross-reactivity with other metabolites formed as the result of normal postmortem processes.¹⁶ These data also are inconsistent with the fact that polyethylene glycol solutions with trace DEG concentrations yielding average total DEG exposures of 11 mg (range, 2–22 mg) administered for whole bowel irrigation in adults are without adverse effects.⁵⁹ The trace DEG concentrations found in these polyethylene glycol solutions may simply reflect a minor contamination or byproduct produced during the manufacturing process. This issue has not been studied. Quantities far in excess of the Argentinean analysis are estimated to occur in adults from nonprescription health products containing trace amounts of DEG (maximum value, 6.3 mg) currently sold in the United States.⁴⁸ There are no reports of DEG poisoning associated with these products.⁴⁸

In summary, the minimum toxic DEG dose in an acute, single dose exposure is unknown but limited data suggest that single, small total exposures of ≤ 22 mg in an adult are not associated with adverse health effects. Analysis of outbreaks of DEG poisoning suggests that cumulative exposures of as little as 250 mg/kg are associated with illness,³⁸ but the minimum toxic DEG dose may be lower.

The minimum toxic dose of DGA is unknown but ingestion of 100 g in an adult was fatal. The actual toxic dose is probably much less since the patient in this case report vomited immediately after ingestion but still died.⁴⁴

PATHOPHYSIOLOGY

Accumulation of HEAA and DGA in the blood causes a metabolic acidosis that can be prevented by early administration of an ADH inhibitor such as fomepizole.^{3,4} Although there are no published reports examining the efficacy of ethanol to block DEG metabolism, it would be expected to do this also. Inhibition of DEG metabolism with an ADH inhibitor prevents kidney and liver toxicity⁴ and decreases lethality in rodents.⁵⁷ The parent compound DEG does not appear to be toxic based on these same studies.^{4,30,57} Diglycolic acid is likely to be the major if not sole cause of nephrotoxicity in DEG poisoning. Studies with human proximal tubule cells demonstrate that DGA induced cell death is due to necrosis via uptake by a sodium-dicarboxylate-1 transporter, which probably occurs due to its structural similarities to citric acid cycle intermediates. This results in interruption of mitochondrial respiration, leading to energy depletion and ultimately cellular necrosis. This study also suggests that neither DEG nor HEAA cause cellular toxicity in kidney tissue (in vitro proximal tubule cell testing) and that acidemia may enhance DGA toxicity.^{30,31} Elevations in blood urea nitrogen and plasma creatinine concentrations correlate moderately well with elevations in tissue DGA concentrations.⁴ The histopathology of DEG associated nephrotoxicity primarily involves the proximal convoluted tubules as expected and affects the renal cortex where necrosis, hemorrhage and vacuolization can be seen.⁴⁶ Elevations in hepatic aminotransferases can also occur probably due to DEG, HEAA, and DGA accumulation in the liver.^{3,34,46} The spectrum of DEG associated neurotoxicity is complex. Some case reports document primarily demyelinating peripheral neuropathies,^{34,43} but data from the large numbers of patients who received nerve conduction testing from the Panama outbreak and other case reports^{19,50} demonstrate that axonal sensorimotor neuropathy with secondary demyelination is probably the typical clinical course. Only those DEG poisoned patients who develop some degree of AKI seem to be at risk for developing neurotoxicity.^{41,46} The mechanism of neurotoxicity of DEG is unknown but may also be related to DGA (unpublished data from author). The single reported human case of a pure DGA ingestion demonstrated clinical and pathologic findings very similar to DEG poisoning, supporting the notion that DEG poisoning is likely due in great part to DGA.⁴⁴

CLINICAL MANIFESTATIONS

The signs and symptoms of DEG poisoning are dependent on duration of exposure, dose, and other intrinsic host factors such as the presence of comorbidities. Following ingestion, symptoms typical of ethanol intoxication such as lethargy, confusion, “drunkenness,” and altered mental status may begin rapidly and last for several hours.^{5,46} This may be followed by clinical signs and symptoms of a metabolic acidosis including tachypnea and hypernea.^{3,46} Although nausea, vomiting, abdominal pain, diarrhea, headache, and confusion are reported with DEG poisoning,^{7,46} AKI remains the single consistent feature of all cases. This finding manifests over 1 to 3 days following ingestion^{6,9,12,14,18,28,38,42,46,50,52} as a progressive history of oliguria, anuria, or both develops.

In some of the reported DEG mass poisonings, patients have presented in AKI with profound acidosis and acidemia.³⁹ Many of these mass poisonings have occurred in children who received relatively high DEG doses in the form of a

pediatric pharmaceutical such as liquid acetaminophen.^{38,39} In the 2006 Panama mass poisoning, the overwhelming majority of patients were adults who probably ingested smaller doses per unit body weight when compared to child victims of past mass poisonings (although they were probably consumed for a longer period of time). Most of these patients presented to health care facilities with vague gastrointestinal or respiratory symptoms and were found to have AKI.^{42,51} Many subsequently developed bilateral cranial nerve VII paralysis and peripheral extremity weakness, often within several days. Finally, many also rapidly developed encephalopathy, coma, and death in the subsequent 24 to 48 hours.⁵¹ This pattern of AKI followed days later by the appearance of neurological signs and symptoms such as unilateral or bilateral cranial nerve VII (facial nerve) paresis or paralysis, peripheral neuropathy, frank encephalopathy, autonomic nervous system instability, and coma is reported in several case reports, a case series, and two previous mass poisonings.^{1,18,19,43,46,51}

Long-term outcomes among DEG poisoning survivors are not well characterized. Patients who develop AKI that does not improve quickly may become permanently hemodialysis dependent. Those who rapidly recover from their AKI appear to retain normal or at least adequate long-term kidney function. Patients with DEG-associated neurological findings tend to improve over time. In a study that followed DEG poisoning survivors for 2 years following their acute poisoning, delayed-onset renal and neurologic toxicity did not occur.¹¹

DIAGNOSTIC TESTING

The clinician will likely have to rely on a high index of suspicion, a good exposure history and more commonly encountered “routine” testing methodologies including serum electrolytes, blood gas measurements, and renal function studies. Use of the osmol gap calculation has limitations²² but may be helpful in patients with acute ingestions.²³ Although the osmol gap should never be used to exclude the possibility of a toxic alcohol ingestion, if it is very large (> 50) it is unlikely to be due to anything else, especially in the setting of a suspected poisoning. The reader is referred to [Chap. 109](#) for a complete discussion on this topic. Nerve conduction studies may prove helpful in establishing the pattern of neuropathy if present. Otherwise, routine laboratory and diagnostic tests should be used as needed to help evaluate end organ damage.

Although laboratory assays for DEG in whole blood, serum, plasma, and urine are commercially available at specialized toxicology testing laboratories, they are not available in most hospital laboratories. A study conducted during the 2006 Panama DEG mass poisoning demonstrated statistically significant differences ($P < .001$) in urinary DEG concentrations among cases (range, 50–4000 ng/mL) and controls (undetectable); unfortunately the assay used is not available.⁴² Biologic samples collected from the 2006 Panama investigation demonstrated that serum and urine DGA concentrations were significantly associated with case status ($OR > 999$; $P < .0001$).⁴⁸ Diglycolic acid holds promise as a potential biomarker for DEG poisoning, but further work validating the methodology is needed.⁴⁸

TREATMENT

Treatment options include observation, gastrointestinal decontamination, supportive care, administration of an ADH inhibitor therapy, and hemodialysis. There is no evidence of clinical benefit or even reduced bioavailability of DEG following gastric or nasogastric lavage or the administration of oral activated charcoal.²⁶ Nevertheless, given the limited data regarding the role of gastrointestinal decontamination techniques in DEG poisoning, the profound dose-related clinical effects, and the liquid state of the xenobiotic, nasogastric lavage for an individual who presents soon after ingestion for a significant amount may help remove unabsorbed DEG. Since absorption begins immediately after ingestion, the efficacy of lavage after one hour is probably minimal.

Animal evidence suggests that the osmotic diuretic effect of DEG can cause large urinary volume losses in the immediate postexposure period which may not be effectively corrected due to concurrent inebriation. Adequate volume repletion and resuscitation should be performed as soon as possible. The patient should be closely monitored for decreases in urine output, fluid input and output recorded, their function tests closely followed, and appropriate fluid adjustments made for any signs of AKI. There is currently no evidence for forced diuresis; however, all patients should be aggressively hydrated (after appropriate resuscitation if needed) to ensure maintenance of euvolemia and a steady urine output. This is for several reasons, including (1) DEG is primarily eliminated unchanged in the urine via the kidneys, (2) inadequate resuscitation and/or suboptimal hydration beyond the initial fluid resuscitation period may contribute to prerenal azotemia thereby decreasing elimination of unchanged DEG, (3) any impairment in kidney function will result in decreased elimination of unchanged DEG with a corresponding increase in available DEG for metabolism to toxic metabolites such as DGA, and (4) animal studies suggest that when doses associated with adverse health effects (10 g/kg) are given in addition to fomepizole, almost the entire dose is eliminated unchanged in the urine.^{3,30} Careful attention to acid-base status is advised since limited in vitro work with DGA and human proximal tubule cells suggest that acidemia may enhance DGA’s toxicity.^{30,31} Intravenous bicarbonate therapy may be of benefit in treating DEG-associated metabolic acidosis for this reason, but this is unstudied.

Available evidence supports the use of an ADH inhibitor such as fomepizole in suspected or known DEG poisoning to prevent nephrotoxicity, although most of this evidence is from animal studies. This same evidence suggests that the parent compound is not nephrotoxic.^{4,30,57} However, there is no evidence demonstrating that the parent compound is not neurotoxic (the mechanism of DEG associated neurotoxicity is still completely unstudied). Because neurotoxicity seems to only appear following DEG metabolite-associated AKI, the likelihood of the parent compound being neurotoxic seems low. Fomepizole monotherapy for DEG poisoning may be entirely appropriate (similar to other toxic alcohols); however, definitive evidence is lacking. Furthermore, data to guide dosing and duration of administration are also lacking. Considering the aforementioned factors and the current lack of human data confirming safety and efficacy of fomepizole in DEG poisoning, patients presenting soon after (within a few hours) a highly suspected or known moderate to large ingestion of DEG should be started on fomepizole therapy and then urgently hemodialyzed if available. If hemodialysis is not available the patient should be transferred to a facility with that capability. Although the minimal toxic dose is unknown, cumulative exposures at or above 250 mg/kg (the lower limit of the range reported in the Haiti mass poisoning) should be considered potentially life threatening. A single report documented higher prehemodialysis and lower posthemodialysis concentrations of DEG suggesting that it is cleared by hemodialysis, although the gradient was relatively small (0–1.6 mg/dL).⁷ Nevertheless, the volume of distribution and molecular weight of DEG suggest that hemodialysis should be effective.^{20,46} The endpoint of fomepizole therapy or need for additional rounds of dialysis is unclear, but the relatively new commercial availability of techniques for the determination of whole blood, plasma, serum and urine DEG concentrations with careful attention to acid-base status should be helpful in guiding therapy. Considering the lack of fomepizole data in DEG poisoning, dosing should be comparable with the treatment regimens for the other toxic alcohols (Antidotes in Depth: A30).

Exposures to amounts less than those known to be associated with poisoning present management dilemmas. The following sections consist of suggested guidelines which may need to be modified depending on the individual situation. In all exposures, a toxicologist should be consulted as the circumstances surrounding the exposure are invariably different and may affect management.

Outbreak-derived toxic doses of DEG are not reliable measures for excluding poisoning. Patients with a reliable history of a minimal ingestion, such as an unintentional sip of a low concentration DEG containing product, are unlikely to be at risk for toxicity. Those adult patients with slightly larger DEG ingestions with relatively low concentrations liquids (< 10%) such as exposures consisting of more than a sip but less than a “mouthful” can be considered for careful observation alone, as long as it is coupled with serial chemistries and blood gas measurements to rapidly identify onset of renal function and acid-base abnormalities. Although the true minimum toxic dose of DEG is unknown, an example of the aforementioned situation might involve an unintentional ingestion of 30 mL (mouthful) of a 5% DEG product by volume in an adult. This is approximately 1.5 mL of DEG which is equivalent to about 1.7 g, which in an 80-kg adult is about 21 mg/kg. The lower end of the estimated toxic dose range in Haiti was 250 mg/kg, which is more than 10 times higher (1090% increase). Therefore careful observation might be reasonable in this situation if you believed you had correct values for the dose and product concentration and there were no other potential risk factors for DEG-associated illness (eg, preexisting renal disease). Such an exposure in a 3 year-old child weighing 16 kg would yield a dose of 110 mg/kg, an exposure of greater concern that might warrant more aggressive treatment. Unfortunately, ascertainment of the true volume ingested and product concentration may be difficult, which contributes to the problem of estimating risk based on patient history.

Patients with signs or symptoms of alcohol intoxication, but who did not consume ethanol should be suspected of having a potentially life threatening DEG ingestion and treated as discussed in the previous section. Asymptomatic patients with ingestions beyond the “unintentional sip or taste” should probably be observed for at least 24 hours regardless of therapy offered. Serial laboratory determinations should be obtained and evaluated for at least 24 hours following exposure based on what is known of DEG toxicokinetics.

Fomepizole monotherapy (without hemodialysis) can be considered at the discretion of the attending physician and consulting toxicologist or poison center, as emerging evidence suggests that fomepizole can prevent nephrotoxicity. However, if the decision to use fomepizole monotherapy is made, the physician should remember that, albeit unlikely, the safety and efficacy of fomepizole monotherapy in DEG poisoning is not yet established, thereby necessitating that the risks be explained to the patient.

Unless laboratory testing documents a minimal or nonexposure, the patient’s clinical, acid-base, and kidney function status should probably be followed for at least 24 hours for evidence of DEG poisoning. For patients receiving fomepizole, this 24 hour period should begin 12 hours following the last dose of fomepizole. If signs and symptoms of nephrotoxicity begin to appear, then fomepizole should be given and the patient hemodialyzed.

For those patients presenting to health care facilities with a metabolic acidosis, oliguria or anuria within 24 to 36 hours of an DEG ingestion, fomepizole should be given and emergent hemodialysis should be performed, regardless of the patient’s acid-base and electrolyte status. This suggestion is based in part on animal studies showing that serum DGA concentrations peak at 24 hours following ingestion, DGA sequesters in kidney tissue, it is nephrotoxic,^{3,30} and half-lives increase with larger doses.³ Early presentation to health care facilities (< 10 hours from ingestion) and aggressive treatment (gastrointestinal decontamination, fomepizole, and hemodialysis) appeared to be associated with better outcomes in the

five reports in which fomepizole or ethanol was administered for DEG exposure.^{1,5,7,19,43} In one of these cases, a 15 year-old girl who was witnessed to ingest approximately 22.4 g of DEG (patient's weight was not reported) was managed with orogastric lavage and early (< 3 hours) fomepizole therapy alone; the patient had a good outcome with no renal or neurological dysfunction (other than inebriation).⁵ For those patients presenting later than 36 to 48 hours after a DEG ingestion with the aforementioned signs and symptoms, fomepizole and hemodialysis should be considered, but may be too late to be beneficial with regard to removal of DEG and toxic metabolites. However, it may be of value with regard to electrolyte imbalances and or AKI.

Although there are no published reports examining the efficacy of ethanol to block DEG metabolism, it is expected to act similarly to fomepizole. Hence, it may be an alternative therapy if fomepizole and hemodialysis are unavailable and a rapid transfer to another hospital is not possible.

SUMMARY

- Patients with suspected or known exposures to DEG present a diagnostic and therapeutic challenge.
- Emerging work shows that the DEG metabolite DGA, and not the parent compound, is nephrotoxic.
- Alcohol dehydrogenase inhibitor therapies such as fomepizole have a role in treating DEG poisoning, but urgent hemodialysis is still indicated for substantial ingestions.
- Diethylene glycol poisoned patients who develop AKI are at risk for severe neurotoxicity.
- The etiology of DEG associated neurotoxicity is unclear. Diethylene glycol ingestion should be suspected in patients presenting with AKI and neurological signs and symptoms such as cranial nerve VII paresis or paralysis, or extremity weakness consistent with a peripheral neuropathy.

Disclaimer

The findings and conclusions in this article are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.

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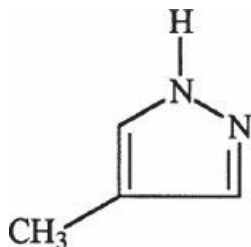
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A30 ANTIDOTES IN DEPTH

Fomepizole

Mary Ann Howland



INTRODUCTION

Fomepizole, a competitive inhibitor of alcohol dehydrogenase (ADH), prevents the formation of toxic metabolites from ethylene glycol and methanol. It may also have a role in halting the disulfiram–ethanol reaction and in limiting the toxicity from a variety of xenobiotics that rely on ADH for metabolism to toxic metabolites. In addition, as both an inducer and an inhibitor of certain cytochrome P450 CYP enzymes, the presence of fomepizole may lead to drug interactions.

HISTORY

In 1963, Theorell described the inhibiting effect of pyrazole on the horse ADH nicotinamide adenine dinucleotide (NAD⁺) enzyme–coenzyme system.^{70,89} Pyrazole blocked ADH by complexation, and the administration of pyrazole to animals poisoned with methanol and ethylene glycol improved survival.⁹⁰ However, pyrazole also inhibited other liver enzymes, including catalase and the microsomal ethanol oxidizing system.⁶² Additional adverse effects of pyrazole administration resulted in bone marrow, liver, and kidney toxicity, and these effects increased in the presence of ethanol and methanol.⁷⁴ These factors led to the search for less toxic compounds with comparable mechanisms of action.

In 1969, Li and Theorell found that both pyrazole and 4-methylpyrazole (fomepizole) inhibited ADH in human liver preparations,⁶¹ and studies in rodents found that fomepizole, unlike pyrazole, was relatively nontoxic regardless of the presence or absence of ethanol.¹³ Subsequent studies of fomepizole in monkeys and humans poisoned with methanol and ethylene glycol confirmed both the inhibitory effect and relative safety of fomepizole.^{19,20,74}

PHARMACOLOGY

Chemistry

Fomepizole has a molecular weight of 82 Da, and a pKa of 2.91 at low concentrations and a pKa of 3.0 at high concentrations. The free base is used in the United States, whereas the salts are used in Europe. The free base is chemically equivalent to the chloride and sulfate salts at physiologic pH.²⁴

Mechanism of Action

Fomepizole works by being a potent inhibitor of ADH thereby blocking the metabolism of methanol and ethylene glycol to their respective toxic metabolites.

Values for K_m have been estimated for the toxic alcohols and the K_i with fomepizole. The smaller the K_m , the higher the affinity of the substrate (alcohol) for the enzyme, and the lower the concentration of the substrate to achieve saturation of 50% of the enzyme. Studies in monkey and human liver tissue demonstrate that fomepizole is a competitive inhibitor of alcohol dehydrogenase.^{65,82} In monkey liver, fomepizole demonstrated very similar K_i s for both ethanol and methanol at 7.5

and 9.1 $\mu\text{mol/L}$, respectively.⁶⁵ The affinity was 10 times higher when human liver was used.⁸¹ Studies in monkeys demonstrate that a fomepizole concentration of 9 to 10 $\mu\text{mol/L}$ (0.74–0.8 $\mu\text{g/mL}$) is needed to inhibit the metabolism of methanol to formate.^{13,74} In human liver, the concentration needed to achieve inhibition is about 0.9 to 1 $\mu\text{mol/L}$.^{61,81} The most recent trial using intravenous (IV) fomepizole attempted to maintain a serum fomepizole concentration above 10 $\mu\text{mol/L}$. Current dosing calls for a serum fomepizole concentration of 100 to 300 $\mu\text{mol/L}$ to ensure a margin of safety.¹

CYP2E1 oxidizes ethanol and a number of other xenobiotics, including acetaminophen, carbon tetrachloride, nitrosamines, and benzene to toxic metabolites. Fomepizole, like ethanol and isoniazid, induces CYP2E1 in rat liver and kidney, but not in the lung, through a posttranscriptional mechanism via stabilization and not involving increased messenger RNA.⁷⁶ However, when fomepizole is present, CYP2E1 is inhibited. It is not until after fomepizole is eliminated that the consequences of induction are manifest.^{16,95,96} In hepatocyte culture, fomepizole stabilizes and maintains the induced metabolic activity of the isoenzyme for about one week.⁹⁷

Pharmacokinetics

The volume of distribution of fomepizole is about 0.6 to 1 L/kg; it is metabolized to 4-carboxypyrazole, an inactive metabolite that accounts for 80% to 85% of the administered dose.^{71,76} In healthy human volunteers, oral doses of fomepizole are rapidly absorbed and demonstrate saturation and nonlinear kinetics.^{44,67,76} The K_m was estimated to be 75 $\mu\text{mol/L}$ in two studies, and 0.94 $\mu\text{mol/L}$ at a dose of 15 mg/kg to 2.49 $\mu\text{mol/L}$ at a dose of 7 mg/kg in the two most recent analyses, although the reason for the discrepancy is not known.^{44,67,68,76} First-order kinetics were exhibited at concentrations below the K_m , whereas zero-order elimination occurred at concentrations 100% to 200% of the K_m .⁴⁴ Thus, elimination of fomepizole at doses of 10, 20, 50, and 100 mg/kg was 3.66, 5.05, 10.3, and 14.9 $\mu\text{mol/L/h}$, respectively.⁴⁴ Classical Michaelis-Menten kinetics would predict that the elimination rate should be comparable at the two higher doses. The authors speculate that the differences are attributable to the existence of other metabolic pathways with different affinities that predominate at different fomepizole concentrations. Following multiple doses, the elimination of fomepizole increases at 36 to 48 hours, most likely because of autoinduction.⁷⁶ After 96 hours fomepizole elimination apparently changed to first order elimination with a half-life of 1.5 to 2 hours, from zero order elimination. At a single dose of 20 mg/kg, the apparent half-life of fomepizole calculated from the linear portion of the curve was 5.2 hours and occurred when serum concentrations were less than 100 $\mu\text{mol/L}$. Peak concentrations after oral administration were achieved within 2 hours and were 132, 326, 759, and 1425 $\mu\text{mol/L}$ following 10, 20, 50, and 100 mg/kg doses, respectively. Every increase of 10 mg/kg in the oral dose of fomepizole raised the serum concentration 130 to 160 $\mu\text{mol/L}$.⁴⁴ The renal clearance was low (0.016 mL/min/kg), and only 3% of the administered dose was excreted unchanged in the urine.⁴⁴

In the two most recent pharmacokinetic studies in healthy volunteers, oral administration produced similar serum concentrations to IV fomepizole.^{67,76} The pharmacokinetics of IV fomepizole were studied in 14 patients being treated for ethylene glycol toxicity.⁵² A mean peak concentration of 342 $\mu\text{mol/L}$ (200–400 $\mu\text{mol/L}$) was achieved following a loading dose of 15 mg/kg (183 $\mu\text{mol/kg}$).^{71,86} A significant weakness of the study involving toxicokinetic data is that the effect of simultaneous serum ethanol concentrations was not analyzed. The lowest serum fomepizole concentration of 105 $\mu\text{mol/L}$ was present at 8 hours after the loading dose. The rate of elimination was determined to be zero order at 16 $\mu\text{mol/L/h}$ compared with a first-order elimination half-life of 3 hours during hemodialysis. Other authors have reported similar fomepizole clearances (12.99 $\mu\text{mol/L/h}$).²¹ A recent pharmacokinetic analysis in patients poisoned with methanol or ethylene glycol demonstrated a mean peak fomepizole concentration of 226 $\mu\text{mol/L}$ (19 $\mu\text{g/mL}$), an apparent half-life of 14.5 hours (in the presence of methanol or ethylene glycol), and an apparent half-life of 40 hours in the presence of ethanol, and methanol or ethylene glycol. In the sole death, hepatic tissue contained 12 $\mu\text{g/g}$ of fomepizole, even when the serum concentration was less than 1 $\mu\text{g/mL}$ (12 $\mu\text{mol/L}$).⁹³

The hemodialysis clearance of fomepizole ranges from 50 mL/min to 137 mL/min.^{30,51} An analysis using determinations of dialysis fluid revealed an extraction ratio of approximately 75% and a dialysance of 117 mL/min, which was very similar to a simultaneous ethylene glycol determination.³⁰ The dialysance was similar to urea in a pig model and suggests no significant protein binding of fomepizole.⁴⁵

The pharmacokinetic interactions between fomepizole and ethanol were studied in a double-blind crossover design in healthy human volunteers.⁴⁹ Fomepizole was given orally in doses of 10, 15, and 20 mg/kg 1 hour prior to oral ethanol at 0.5 to 0.7 g/kg as a 20% solution in orange juice. Fomepizole decreased the elimination rate of ethanol by approximately 40%, from 12 to 16 mg/dL/h to about 7 to 9.5 mg/dL/h. When IV fomepizole was administered at 5 mg/kg over 30 minutes and ethanol was administered orally at doses to achieve a concentration of 50 to 150 mg/dL for 6 hours beginning at the end of the fomepizole infusion, the elimination of fomepizole was decreased by approximately 50%.⁴⁹ This decrease occurred without a change in the amount or fraction of unchanged fomepizole appearing in the urine. The authors suggested that the ethanol probably inhibited the metabolism of fomepizole to 4-carboxypyrazole. A single low dose of fomepizole given to humans had a maximal effect on ethanol metabolism at 1.5 to 2 hours.¹² Thus, ethanol and fomepizole mutually inhibit the

elimination of the other, thereby maintaining higher serum concentrations than otherwise expected.^{66,72} Methanol also decreases the elimination of fomepizole by approximately 25% in the monkey.⁷⁴

ROLE IN METHANOL TOXICITY

In Vitro and Animal Studies

Studies using human livers demonstrate the inhibitory effect of fomepizole on alcohol dehydrogenase.⁸¹ Studies in monkeys, the animal species that most closely resembles humans in metabolizing methanol, also clearly demonstrate the inhibitory effect of fomepizole in preventing the accumulation of formate.^{11,74,75}

Human Experience

The two largest fomepizole case series to date involved 11 and 8 patients, respectively, who were given IV fomepizole in the approved US dosing regimen.^{18,20,39} Following administration, formate concentrations in all patients fell, and the arterial pH increased.²⁰ Case reports demonstrate similar findings.^{21,32,35}

Effect on Methanol and Formate Concentrations

Methanol exhibits dose-dependent kinetics.⁴⁸ At low doses (0.08 g/kg), which achieve serum concentrations of about 10 mg/dL, methanol elimination is first order, with a half-life of about 2.5 to 3 hours.^{52,55} In concentrations of approximately 100 to 200 mg/dL, methanol exhibits zero order kinetics and is eliminated at about 8.5 to 9 mg/dL/h in untreated humans⁵⁰ and 4.4 to 7 mg/dL/h in untreated monkeys.^{28,78} When monkeys were given 3 g/kg of methanol with resultant serum concentrations of about 500 mg/dL, the elimination of methanol exhibited apparent first-order kinetics. This alteration is likely caused by the greater contribution of other first-order pathways, such as pulmonary and urinary elimination, which may account for a greater fraction of the total body clearance under these circumstances.⁴⁸ Once fomepizole was administered, the elimination of methanol became first order in humans, and the half-life of methanol was about 54 hours.^{20,39} When the metabolism of methanol to formate is blocked, formate is eliminated with a half-life dependent on dose and with an uncertain effect of folate and bicarbonate therapies. When formate was administered to monkeys in the absence of methanol, formate half-life was 30 to 50 minutes.²⁵ In monkeys given methanol followed by fomepizole, the formate concentrations decreased by more than 80% in 2 hours.¹¹ An analysis of formate concentrations in six patients with methanol poisoning treated with fomepizole, folate, and sodium bicarbonate revealed a formate half-life of 235 ± 83 minutes.⁵³ A more recent analysis involving eight patients with methanol poisoning treated with fomepizole and sodium bicarbonate revealed a formate half-life of 156 minutes.³⁹

ROLE IN ETHYLENE GLYCOL TOXICITY

In Vitro and Animal Studies

Monkeys given 3 g/kg of ethylene glycol intraperitoneally recovered without treatment, whereas those given 4 g/kg died without therapy. All those given 4 g/kg of ethylene glycol with fomepizole survived.²⁵

Human Experience

The first three patients treated with oral fomepizole improved clinically and tolerated the therapy.⁴ Subsequent case reports and case series using fomepizole orally or IV, with or without hemodialysis, also demonstrated the effectiveness of fomepizole in preventing glycolate accumulation.^{5,14,19,33,36,38,51,77,80,86}

Effect on Ethylene Glycol and Glycolate Concentrations in Humans

Kidney function is essential in the elimination of ethylene glycol. With normal kidney function, the half-life of ethylene glycol is about 8.6 hours.⁸⁶ Based on pooled human data, the half-life of ethylene glycol after alcohol dehydrogenase is blocked by fomepizole is about 14 to 17 hours in patients with normal kidney function, and about 49 hours in patients with impaired kidney function.^{4,36,60,86} Based on a limited number of determinations, the renal clearance of ethylene glycol averaged 31.5 mL/min during the first 2 days; the corresponding creatinine clearance was 112 mL/min, and estimated total body clearance during fomepizole therapy was 57 mL/min.⁵ These calculations suggest that the renal clearance of ethylene glycol accounted for only 55% of estimated total body clearance. In a study where neither kidney function was defined nor the amount of glycolate excreted unchanged by the kidneys described, glycolate had a mean half-life of 10 ± 8 hours in patients treated with fomepizole before hemodialysis, and a mean half-life of less than 3 hours during hemodialysis.^{46,54,77}

ROLE IN TOXICITY FROM DISULFIRAM AND OTHER XENOBIOTICS

Fomepizole successfully terminated the adverse reactions resulting from the use of disulfiram administered to volunteers pretreated with a small dose of ethanol, the adverse reaction occurring in a chronic alcoholic surreptitiously given disulfiram by his wife, and in two patients who intentionally ingested ethanol along with an overdose of disulfiram.^{63,84} Pretreatment with oral fomepizole was also successful in preventing the facial flushing and tachycardia typically associated with ethanol administration in ethanol-sensitive Japanese volunteers.^{42,43}

Limited animal studies and a few case reports suggest that fomepizole may be effective in limiting the toxicity secondary to diethylene glycol, triethylene glycol, and 1,3-difluoro-2-propanol.^{9,14,31,85,91} The role of fomepizole in overdoses secondary to 2-butoxyethanol (ethylene glycol monobutyl ether, butyl Cellosolve) is unclear,⁴¹ but fomepizole may be useful if administered within several hours of ingestion and before rapid metabolism of butoxyethanol to butoxyacetic acid occurs.^{69,79} Isopropanol is probably metabolized at least in part by alcohol dehydrogenase, but fomepizole therapy is not indicated, as this intervention would prolong the metabolism of isopropanol to acetone.^{1,56}

COMPARISON TO ETHANOL

Ethanol has been used for many years to inhibit the metabolism of methanol and ethylene glycol to their respective toxic metabolites.^{34,92} Although very inexpensive, ethanol has many disadvantages, compared to fomepizole.^{7,58,94} Ethanol causes central nervous system depression that is at least additive to that of the methanol or ethylene glycol, and dosing difficulties occur as a result of the rapid and often unpredictable rate of ethanol metabolism (Antidotes in Depth: A31).^{7,8,94} Fomepizole has the advantage of being a very potent inhibitor of alcohol dehydrogenase without producing CNS depression. Fomepizole dosing is much easier and does not require therapeutic monitoring of its serum concentration. Limited adverse effects of fomepizole include local reactions at the site of infusion when concentrations exceeding 25 mg/mL are used, nausea, dizziness, anxiety, headache, rash, transiently elevated aminotransferases, and eosinophilia. Fomepizole is preferred to ethanol for all of the above reasons. Ethanol should be used only when fomepizole is not readily available.^{59,87}

ADVERSE EFFECTS AND SAFETY ISSUES

Retinol dehydrogenase, which is responsible for converting retinol to retinal in the eye, is an isoenzyme of ADH. As such, it was essential to study whether fomepizole would inhibit this enzyme and produce retinal damage.^{74,75} Studies in several animal species demonstrated that fomepizole has limited toxicity, with no ophthalmic toxicity.¹¹ Two of the largest case series and two recent case reports confirm the lack of retinal toxicity with fomepizole and demonstrate the reversibility of methanol-induced visual toxicity when patients are treated with fomepizole and hemodialysis before permanent ophthalmic damage developed.^{19,20,29,88}

The LD₅₀ (median lethal dose for 50% of test subjects) of fomepizole in mice and rats is 3.8 mmol/kg after IV administration, and 7.9 mmol/kg following oral administration.⁶⁴ An oral placebo-controlled, double-blind, single-dose, randomized, sequential, ascending-dose study was performed in healthy volunteers to determine fomepizole tolerance at 10 to 100 mg/kg.⁴⁸ There were no adverse effects in the 10 and 20 mg/kg groups, whereas at 50 mg/kg, three of four subjects experienced slight to moderate nausea and dizziness within 2.5 hours of fomepizole administration. All subjects reported comparable symptoms at 100 mg/kg, which lasted for 30 hours in one individual without vital sign or laboratory abnormalities. The most common adverse effects of the use of fomepizole reported by the manufacturer (in a total of 78 patients and 63 volunteers) were headache (14%), nausea (11%), and dizziness, increased drowsiness, and bad or metallic taste (6%).¹ Other less commonly observed adverse effects include phlebitis, rash, fever, and eosinophilia. A case report of a patient severely poisoned with ethylene glycol describes a temporal association between IV fomepizole administration during hemodialysis and the development of bradycardia and hypotension. However, this patient was severely acidemic, and when the patient received the fomepizole postdialysis no such adverse effects were noted.⁵⁷ Divided daily doses of fomepizole up to 20 mg/kg for 5 days have been administered without any demonstrable toxicity.⁷³ The most common laboratory abnormality after fomepizole administration is a transient elevation of aminotransferase concentrations, which was reported in 6 of 15 healthy volunteers.⁴⁷ In the two largest case series of patients treated with fomepizole for toxic alcohol poisoning, there were no adverse events classified as “definitely” or “probably” related to fomepizole.^{19,20} Fomepizole safety and effectiveness in pediatric patients have not been established, but it has been used successfully in children who have ingested ethylene glycol and methanol.^{6,15,17,22,26,27,37,93}

PREGNANCY AND LACTATION

Fomepizole is pregnancy category C and thus should be used when clearly indicated. It is not known whether fomepizole is excreted into breast milk.

DOSING AND ADMINISTRATION

The loading dose of fomepizole is 15 mg/kg IV, followed in 12 hours by 10 mg/kg every 12 hours for 4 doses. If therapy is necessary beyond 48 hours, the dose is then increased to 15 mg/kg every 12 hours, for as long as necessary. This increase is recommended because fomepizole stimulates its own metabolism.⁷⁶ Patients undergoing hemodialysis require additional doses of fomepizole to replace the amount removed during hemodialysis.

The manufacturer recommends dosing fomepizole every 4 hours during hemodialysis.¹ Fomepizole should be administered at the beginning of hemodialysis if the last dose was more than 6 hours earlier. At the completion of hemodialysis, administer the next scheduled dose if more than 3 hours have transpired, or one-half of the dose if 1 to 3 hours have passed. Then continue with every 12-hour dosing.

Fomepizole must be diluted in 100 mL of 0.9% sodium chloride solution or 5% dextrose in water (D₅W) prior to IV administration, and then infused over 30 minutes to avoid venous irritation and thrombophlebitis. Once diluted, fomepizole remains stable for 24 hours when stored in the refrigerator or at room temperature.¹

Fomepizole therapy should be continued until the methanol or ethylene glycol is no longer present in sufficient concentrations to produce toxicity. Although these concentrations are not precisely known, 25 to 50 mg/dL of either ethylene glycol or methanol is a conservative estimate that may need to be lowered in the presence of acid–base disturbances.^{1–3}

The threshold concentrations for hemodialysis of methanol or ethylene glycol can be based on measurements when analyses can be done in a timely fashion. The duration of fomepizole therapy in the absence of hemodialysis can be estimated based on the assumption of half-life of the toxic alcohol when blocked with fomepizole. The half-life of methanol is approximately 54 hours in the presence of fomepizole.¹⁴ The half-life of ethylene glycol in the presence of fomepizole is approximately 14 to 17 hours in patients with normal kidney function, and 49 hours in patients with impaired kidney function.^{4,38,86}

The need for hemodialysis is based on the presence of toxic metabolites inferred by the presence of metabolic acidosis and end-organ damage; the ability of the kidney to eliminate ethylene glycol and glycolic acid, and formate, the risk benefit of hemodialysis, and the length of time to remain hospitalized for elimination of the remaining methanol and ethylene glycol.^{40,83}

FORMULATION AND ACQUISITION

Fomepizole is marketed as Antizol injection by Paladin Labs (Dover, DE; originally by Orphan Medical) in 1.5 mL vials of 1 g/mL. It is now also available generically by various manufacturers. Temperatures of less than 77°F (25°C) cause the contents of the fomepizole vials to solidify. Warming reliquesfies the product without adversely affecting its potency.

SUMMARY

- Fomepizole is a potent competitive inhibitor of ADH that is useful in inhibiting the metabolism of methanol, ethylene glycol, and other xenobiotics that use ADH in the formation of toxic metabolites.
- Once ADH is blocked, the decision to use hemodialysis depends on how much damage has occurred to the organs of elimination, and how well the body can eliminate both the parent compound and the toxic metabolites formed prior to fomepizole administration.
- Fomepizole appears to be safe and, although it has been used successfully orally, only an IV dosing regimen is approved and available.
- Fomepizole is more costly than ethanol, but its many advantages over ethanol, including the ability to often deliver care outside an intensive care unit, make fomepizole the preferred antidote in most circumstances.
- Ethanol might be preferred in a mass casualty situation until sufficient supplies of fomepizole could be procured.

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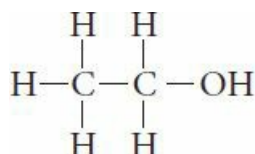
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A31 ANTIDOTES IN DEPTH

Ethanol

Mary Ann Howland



INTRODUCTION

Ethanol is used therapeutically as a competitive substrate for xenobiotics metabolized by alcohol dehydrogenase, thus limiting the bioactivation of those xenobiotics to toxic metabolites. Methanol and ethylene glycol are potentially lethal xenobiotics metabolized by this pathway.^{11,12} Ethanol may also inhibit the metabolism of short chain polyethylene glycols, such as di- and triethylene glycol,⁵³ and possibly compete with monofluoroacetate and fluoroacetamide for binding to the tricarboxylic acid cycle. Ethanol also affects the cytochrome P450 CYP enzyme system, especially CYP2E1, for which it has biphasic properties as an inducer and an inhibitor similar to fomepizole and isoniazid. The competitive relationship of ethanol with potentially toxic xenobiotics can be used to therapeutic advantage, but the effect of ethanol on the CYP system often leads to unwanted drug interactions and pharmacokinetic tolerance after several days of administration.

HISTORY

Ethanol has been used as an antidote for methanol poisoning since the 1940s and for ethylene glycol since the 1960s.²

PHARMACOLOGY

Mechanism of Action

Ethanol works as a competitive substrate for alcohol dehydrogenase, inhibiting the metabolism of xenobiotics like methanol and ethylene glycol that use this enzyme.

Affinity for Alcohol Dehydrogenase

The dose of ethanol necessary to achieve competitive inhibition depends on the relative concentrations of the toxic alcohols and their affinity for the enzyme. An affinity constant, K_m , is used to express the degree of affinity: the lower the K_m value, the stronger the affinity. The following equates mmol or mg for alcohols: 1 mmol ethanol equals 46 mg, 1 mmol methanol equals 32 mg, and 1 mmol ethylene glycol equals 64 mg. A millimolar concentration means mmol/L. A summary of in vitro experiments using human liver cells demonstrated a K_m of 30 mM for ethylene glycol, 7 mM for methanol, and 0.45 mM for ethanol.^{29,42,43} This means that the molar affinity of ethanol for alcohol dehydrogenase is 67 times that of ethylene glycol and 15.5 times that of methanol. Studies in methanol-poisoned monkeys revealed that when ethanol was administered at a molar ethanol-to-methanol ratio (E:M) of 1:4, the metabolism of methanol was reduced by 70%; at a 1:1 E:M ratio, metabolism was reduced by greater than 90%.³² In these experiments, the dose of methanol was kept constant at about 1 g/kg (31 mmol/kg), whereas the dose of ethanol was varied. Although the serum methanol concentration was not measured, a calculation using this dose and a volume of distribution (Vd) of 0.6 L/kg would predict a serum concentration of about 166 mg/dL. Even in molar ratios as high as 1:8, methanol did not inhibit ethanol metabolism. When ethylene glycol and methanol are administered together in a 0.5:1 molar ratio, ethylene glycol did not inhibit methanol metabolism.³² When compared with methanol smaller amounts of ethanol are required to block the metabolism of ethylene glycol, as the affinity of ethylene glycol for alcohol dehydrogenase is less than that of methanol.^{22,29,42,43,45,51} Most authors^{1,22,51} recommend either a serum ethanol concentration of 100 mg/dL, or at least a 1:4 molar ratio of ethanol to methanol or ethylene glycol,

whichever is greater. Using this ratio, 100 mg/dL (~ 22 mmol/L) of ethanol protects against 88 mmol/L (286 mg/dL) of methanol or 88 mmol/L (546 mg/dL) of ethylene glycol. Inhibiting the metabolism of methanol and ethylene glycol impedes the formation of toxic metabolites and prevents the development of metabolic acidosis.^{13,16,21,51} After this toxic metabolic pathway is blocked with ethanol, renal, pulmonary, and extracorporeal routes of toxic alcohol removal become the sole mechanisms for elimination.

PHARMACOKINETICS

Ethanol administered orally is rapidly absorbed and achieves peak concentrations in about 1 to 1.5 hours.^{8,15,30,52} The amount of ethanol absorbed after oral administration is highly variable and dependent on a number of factors, such as ethanol dose, fasting, nutritional status, accelerated gastric emptying, gender, genetics, chronic alcohol use, lean body mass, and increasing age, as well as the presence of certain H₂-receptor antagonists.^{6,9,15,25,27,37,54,57} Sufficient concentrations are generally achieved when 0.8 g/kg of ethanol is given orally over 20 minutes.^{6,8,9,15,27,52}

Given that the Vd for ethanol is approximately 0.6 L/kg,^{10,58} the loading dose of ethanol is obtained by the following formula:

$$\begin{aligned}\text{Loading dose} &= C_p \times V_d \\ &= 1 \text{ g/L (100 mg/dL)} \times 0.6 \text{ L/kg} \\ &= 0.6 \text{ g/kg} \\ C_p &= \text{plasma concentration which is comparable} \\ &\quad \text{to the serum concentration}\end{aligned}$$

For a 70 kg person, the loading dose would be 42 g (70 kg × 0.6 g/kg) of ethanol, or 420 mL of 10% V/V (volume-to-volume) ethanol. This calculation assumes that the specific gravity of ethanol is 1 g/mL. However, a 0.8 g/kg or 8 mL/kg loading dose of a 10% ethanol solution is recommended in order to provide a margin of safety because of the variabilities in Vd and the ongoing metabolism that occurs during administration.^{26,44} The intravenous (IV) loading dose should be administered over 20 to 60 minutes, as tolerated by the patient. The 10% ethanol concentration is preferable to the 5% concentration to limit the volume of fluid administered. It is also preferred over the more concentrated solutions to limit local venous irritation and avoid postinfusion phlebitis. Because of the free water content and significant hypertonicity of the 10% solution, the patient should be closely observed for the development of hyponatremia.

To maintain an ethanol concentration of 100 mg/dL, ethanol replacement must equal ongoing elimination (66–130 mg/kg/h). The average hourly dose for a 70 kg person is 4.6 g, but higher doses are required in ethanol tolerant patients (100–154 mg/kg/h) or others who may have induced enzymes, and in those undergoing hemodialysis (250–350 mg/kg/h; Chap. 10).^{12,22,33,40,41}

ROLE IN METHANOL AND ETHYLENE GLYCOL TOXICITY

When administered in a timely fashion after the toxic alcohol ingestion and before the accumulation of the toxic metabolites, case reports confirm the efficacy of ethanol in preventing the sequelae of methanol and ethylene glycol poisoning.^{7,9,24,50,55} In the presence of sufficient inhibitory concentrations of ethanol, the half-life of ethylene glycol in two patients with normal kidney function was 17.5 hours, which was comparable with 17 hours in a case series of patients receiving fomepizole alone with normal kidney function.^{7,49} A half-life of 46.5 hours for methanol was reported in a patient who had received a sufficient blocking quantity of ethanol⁴⁰ which is quite similar to the 54 hours reported in a case series of methanol-poisoned patients treated only with fomepizole.^{5,24}

ADVERSE EFFECTS AND SAFETY ISSUES

Problems encountered with the administration of ethanol include further risk of central nervous system (CNS) depression, behavioral disturbances, or ethanol related toxicity, such as hepatitis and pancreatitis, hypoglycemia, dehydration, fluctuating serum concentrations, and potential drug interactions resulting in disulfiramlike reactions.^{3,14,18,28,34,38,39,56,59}

PREGNANCY AND LACTATION

Ethanol (injection) is US Food and Drug Administration pregnancy category C. Ethanol crosses the placenta and reaches the fetus. Ethanol is teratogenic, and the American Academy of Pediatrics (AAP) recommends that pregnant women abstain

from all alcohol consumption. It is likely that the short duration of ethanol therapy, when used to compete with alcohol dehydrogenase, during the second or third trimester, has a minimal risk of inducing fetal alcohol syndrome. Ethanol should only be used following a risk benefit analysis, particularly in the first trimester. Ethanol crosses into breast milk and may cause CNS depression and ethanol toxicity in the breast-fed infant.

DOSING AND ADMINISTRATION

Ethanol can be given either orally or IV (Tables A31–1 and A31–2). Concentrations of 20% to 30% orally and 5% to 10% IV are well tolerated. Intravenous administration has the advantages of complete absorption²⁶ and avoidance of most gastrointestinal symptoms, and can be used in an unconscious or uncooperative patient. The disadvantages of IV ethanol include difficulty in obtaining and preparing an IV ethanol solution, the hyperosmolarity of a 10% ethanol solution (~ 1900 mOsm/L), and the possibilities of osmotic dehydration, hyponatremia, and venous irritation.

TABLE A31–1. Intravenous Administration of 10% Ethanol						
Loading Dose ^a	Volume (mL) ^b (given over 1 hour as tolerated)					
	10 kg	15 kg	30 kg	50 kg	70 kg	100 kg
0.8 g/kg of 10% ethanol (infused over 1 hour as tolerated)	80	120	240	400	560	800
Maintenance Dose ^c	Infusion Rate ^d (mL/h for various weights) ^e					
	10 kg	15 kg	30 kg	50 kg	70 kg	100 kg
Ethanol naïve						
80 mg/kg/h	8	12	24	40	56	80
110 mg/kg/h	11	16	33	55	77	110
130 mg/kg/h	13	19	39	65	91	130
Ethanol tolerant						
150 mg/kg/h	—	—	—	75	105	150
During hemodialysis						
250 mg/kg/h	25	38	75	125	175	250
300 mg/kg/h	30	45	90	150	210	300
350 mg/kg/h	35	53	105	175	245	350

^aA 10% V/V concentration yields approximately 100 mg/mL. ^bFor a 5% concentration, multiply the amount by 2. ^cInfusion to be started immediately following the loading dose. Concentrations above 10% are not recommended for intravenous administration. The dose schedule is based on the premise that the patient initially has a zero ethanol concentration. The aim of therapy is to maintain a serum ethanol concentration of 100 to 150 mg/dL, but constant monitoring of the ethanol concentration is required because of wide variations in endogenous metabolic capacity. Ethanol will be removed by hemodialysis, and the infusion rate of ethanol must be increased during hemodialysis. Prolonged ethanol administration may lead to hypoglycemia. ^dRounded to the nearest mL.

Adapted with permission from Roberts JR, Hedges J, eds. *Clinical Procedures in Emergency Medicine*. Philadelphia: WB Saunders; 1985:1073–1074.

TABLE A31–2. Oral Administration of 20% Ethanol

	Volume (mL)					
	10 kg	15 kg	30 kg	50 kg	70 kg	100 kg
Loading Dose^a						
0.8 g/kg of 20% ethanol, diluted in juice (may be administered orally or via nasogastric tube)	40	60	120	200	280	400
mL/h for various weights^{c,d}						
Maintenance Dose^b	10 kg	15 kg	30 kg	50 kg	70 kg	100 kg
Ethanol naïve						
80 mg/kg/h	4	6	12	20	28	40
110 mg/kg/h	6	8	17	27	39	55
130 mg/kg/h	7	10	20	33	46	66
Ethanol tolerant						
150 mg/kg/h	—	—	—	38	53	75
During hemodialysis						
250 mg/kg/h	13	19	38	63	88	125
300 mg/kg/h	15	23	46	75	105	150
350 mg/kg/h	18	26	53	88	123	175

^aA 20% V/V concentration yields approximately 200 mg/mL. ^bConcentrations above 30% (60 proof) are not recommended for oral administration. The dose schedule is based on the premise that the patient initially has a zero ethanol concentration. The aim of therapy is to maintain a serum ethanol concentration of 100 to 150 mg/dL, but constant monitoring of the ethanol concentration is required because of wide variations in endogenous metabolic capacity. Ethanol will be removed by hemodialysis, and the dose of ethanol must be increased during hemodialysis. Prolonged ethanol administration may lead to hypoglycemia. ^cRounded to the nearest mL. ^dFor a 30% concentration, multiply the amount by 0.66.

Adapted with permission from Roberts JR, Hedges J, eds. *Clinical Procedures in Emergency Medicine*. Philadelphia: WB Saunders; 1985:1073–1074.

Regardless of route, the objective is to rapidly achieve and maintain a serum ethanol concentration of at least 100 mg/dL, which is adequate for enzyme inhibition in most cases. Inhibition is best achieved by administering a loading dose of ethanol, followed by a maintenance dose.

Because ethanol elimination varies in each individual, frequent serum ethanol determinations should be obtained to ensure adequate dosing while also monitoring blood glucose and fluid and electrolyte status. In addition, any increase in the anion gap or decrease in bicarbonate concentration implies that the ethanol dose is inadequate to achieve blockade of alcohol dehydrogenase and the ethanol dosing should be increased.

FORMULATION AND ACQUISITION

A practical problem often involves preparing the ethanol to be given since commercial preparations of 5% ethanol in 5% dextrose are no longer available for IV administration.⁴ Not having a commercially available preparation increases the delay to administration of IV ethanol and the potential for a medication error in preparation. Sterile ethanol USP (absolute ethanol) can be added to 5% dextrose to make a solution of approximately 10% ethanol concentration; 55 mL of absolute ethanol is added to 500 mL of 5% dextrose to produce a total volume of 555 mL (10% = 10 mL in 100 mL; in this case, 55 mL in 555 mL or 55/555). If oral administration is chosen, then it is important to remember that in the United States the “proof” number on the label is double the concentration; that is, “100-proof” ethanol is 50% ethanol by volume (50 mL/100 mL). If there will be any delay in preparing ethanol for IV use and fomepizole is not available or used, then oral therapy with ethanol should be initiated immediately.

COMPARISON TO FOMEPIZOLE

Although ethanol has been used as an antidote for toxic alcohols for many years in both adults and children,⁴⁶ and has the advantages of easy accessibilities to oral ethanol and low acquisition cost, fomepizole is a very potent inhibitor of alcohol dehydrogenase with many important advantages.^{17,19,23,31,35,36} Fomepizole does not produce CNS depression, is easier to dose, and does not require serum concentration monitoring. Although fomepizole is more costly than ethanol, its many advantages over ethanol make fomepizole the preferable antidote (Antidotes in Depth: A30 and [Chap. 109](#)).^{28,48,56}

SUMMARY

- When administered appropriately, ethanol is an excellent first step in preventing further metabolism of methanol and ethylene glycol to their respective toxic metabolites.
- The disadvantages of ethanol compared with fomepizole (when available) make ethanol an outmoded antidote under most circumstances.
- Neither fomepizole nor ethanol affects the toxic metabolites already present in the body.
- Once alcohol dehydrogenase is blocked, the decision whether to use hemodialysis depends on the degree of end-organ damage that has occurred, how well the body can eliminate the parent compound without the benefit of hemodialysis, and the extent to which toxic metabolites are already present.
- With the use of either ethanol or fomepizole without subsequent hemodialysis, the increase in hospital length of stay in an intensive care unit or on a medical floor may be substantial for methanol poisoned patients.^{20,47}

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K. PESTICIDES

CASE STUDY 9

History A 2 year-old (12 kg) girl was brought to the hospital by ambulance after having a witnessed seizure at home. The child was healthy, born at term, and without any significant past medical history. Although her family had recently immigrated to the United States, she was followed in a primary care clinic and was fully vaccinated. She had one screening test for lead, which was “normal.” Her mother relates that their house had problems with roaches, mice, and rats and she thinks her husband applied a chemical to deal with the problem.

About 20 minutes before the girl became ill, her mother saw the child pick up something from the corner of the room and immediately thereafter removed some material that looked like food from the child’s mouth. She subsequently lost consciousness and began to shake. The mother called 9-1-1 and when EMS arrived the child was intermittently seizing. Lorazepam (1 mg IM) was administered and EMS gave the child supplemental oxygen for transport. The paramedics reported that the child stopped seizing during transport but started again upon arrival to the emergency department.

Physical Examination On arrival, the child was seizing with the following vital signs: blood pressure, 90/40 mm Hg; pulse, 160 beats/min; respiratory rate, 36 breaths/min; temperature, 100°F (37.7°C); oxygen saturation, 100% on a 100% nonrebreather mask. There were no signs of trauma. The skin was moist, pupils were 4 to 5 mm and fixed, the chest was clear, heart sounds were regular, and her abdomen was soft. Neurologic examination revealed repetitive symmetrical movements of the limbs, slight eye deviation to the left, and a lack of responsiveness to stimulation.

Initial Management Another 1 mg dose of lorazepam was given IM, while an IV was being inserted. A rapid bedside glucose was 160 mg/dL, and blood samples were obtained for complete blood count, electrolytes, liver function tests, and creatine phosphokinase. The child continued to seize and a 2 mg IV dose of lorazepam was administered that terminated the seizure. Repeat vital signs were notable for a pulse of 165 beats/min and a rectal temperature of 100.6°F (38.1°C). Blood cultures were sent and the child was given an empiric dose of ceftriaxone. An ECG was obtained and showed sinus tachycardia with normal axis and intervals.

What is the Differential Diagnosis? In addition to infectious, structural, and traumatic causes for repeated seizures, the history is suggestive of pesticide poisoning. Pesticides are defined by the US Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as “any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, and any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant.” Since 1947, the production, use, and distribution of pesticides in the United States have been regulated under FIFRA and its subsequent amendments in 1972, 1975, and 1978. In 1970, the US Environmental Protection Agency (EPA) was given the authority to administer and enforce FIFRA regulations. Under FIFRA, all pesticides and their manufacturers must be registered with the EPA, and the pesticide must be classified for either general use or restricted use by licensed or certified applicators. Additionally, according to FIFRA, rodenticides are classified by their toxicities and must be labelled by signal words as designated in [Table CS9–1](#). The WHO applies a similar classification scheme for all pesticides based on either oral or dermal LD₅₀ as shown in [Table 113–1](#).

Table CS9–1. US Environmental Protection Agency Toxicity Classification of Pesticides

Category and Signal Word	Oral LD ₅₀ (mg/kg)	Dermal LD ₅₀ (mg/kg)	Inhalation LC ₅₀ (mg/L)	Eye Irritation	Skin Irritation
I Danger	0–50	0–200	0–0.05	Corrosive: corneal opacity not reversible within 21 days	Corrosive
II Warning	50–500	200–2000	0.05–0.5	Corneal opacity reversible within 8–21 days; irritation persisting for 7 days	Severe irritation at 72 hours
III Caution	500–5000	2000–20,000	0.5–5.0	Corneal opacity; irritation reversible within 7 days	Moderate irritation at 72 hours
IV None	> 5000	> 20,000	> 5.0	Irritation cleared within 24 hours	Mild or slight irritation at 72 hours

Unfortunately, as is so commonly the case, not only was the mother unaware of the name or type of pesticide used, but also both the original container and label were missing. Furthermore, there was a possibility that the product used was brought from the parent’s home country and was either illegal or unlicensed in the United States. As a result, clinicians are often forced to provide empirical treatment based largely on clinical diagnosis. An understanding of the likely possibilities improves both diagnostic utility and treatment decisions.

What Clinical Factors Help Narrow the Differential Diagnosis? A review of [Table CS9–2](#), and chapters throughout this text, especially those that immediately follow this case will help identify those pesticides when ingested that are most

likely to result in seizures or status epilepticus. The possible xenobiotics include organic phosphorous compounds and carbamates, organic chlorines, monofluoroacetate and fluoroacetamide, strychnine, thallium, zinc and aluminum phosphide, and tetramine. The absence of associated clinical manifestations helps eliminate some of the choices: organic phosphorous compounds and carbamates (eg, salivation, lacrimation, urination, defecation, bradycardia, bronchorrhea, miosis), thallium (the onset was rapid and there was an absence of painful peripheral neuropathy), strychnine (not true seizures, consciousness should be preserved until hyperthermia, hypoxia, or hypercarbia becomes severe), and aluminum phosphide (absence of vomiting with characteristic odor of rotten fish). Although routine laboratory testing has little utility here, the absence of a profound metabolic acidosis might suggest that monofluoroacetate and fluoroacetamide are not responsible for this clinical presentation. Certain dangerous rodenticides imported for illicit use include tetramine (status epilepticus) and aldicarb (a carbamate found in tres pasitos). Unfortunately, since there are no rapidly available tests to help establish this diagnosis, treatment will have to be based entirely on the clinical assessment.

Table CS9–2. Management of Specific Rodenticide Ingestions

Anticoagulant Name	Physical Characteristics	Toxic Mechanism	Estimated Fatal Dose	Signs and Symptoms	Onset	Antidote and/or Treatment*
Highly Toxic Signal Word: DANGER (LD₅₀ < 50 mg/kg)						
Tallinon	White, crystalline, odorless, tasteless	Interferes with mitochondrial oxidative phosphorylation	14 mg/kg	Anorexia, abdominal pain, diarrhea, gastric emptying, infection, coma, ataxia, oliguria (adult), hemolysis	12 symptoms usually after ingestion 12–14 hours delay	Activated charcoal, Proton pump inhibitors
Sodium Fluoracetate (SFA, compound 100)	White, crystalline, odorless, tasteless, water soluble	Fluoracetate is fluorinated, interferes with mitochondrial and cycle	3–7 mg/kg	Seizures, coma, tachycardia, PRTs VT, VT, ST-T wave changes, leukoencephalopathy (hypoxic/hemorrhagic)	12–20 hours	Experimental regimens (Chap. 11.5)
Sodium Fluoracetamide (compound 101)	Same as SFA	Same as SFA, fluoride toxicity	15–20 mg/kg	Same as SFA	Same as SFA	Same as SFA
Strychnine	Bitter taste	Cystine receptor antagonist on spinal cord motor neurons	Children 11 mg Adults 1–2 mg/kg	Reflexes, anxiety, sweating, hyperextension alternating with relaxation, stridor, gasp, tremor or hand grasping ("rice water"), inability to swallow, apnoeic convulsions	15–20 minutes	Good control, IV benzodiazepines, succinylcholine blockade
Toxopnepton	Heavy grey, crystalline powder, water insoluble, "rotten fish" or "phosphorus" odor, normally used as 1% concentration	Releases phosphine in contact with water or acid or in GI tract	40 mg/kg in rat	"Rotten fish" breath odor, black vomitus, GI and cardiovascular toxicity, acute respiratory distress syndrome, apnoea, coma, seizures, hepatic and renal toxicity	Within hours; inhalation may have delayed onset	Decontam with sodium bicarbonate water or milk
Trinitrophenol (yellow or white phosphorus)	Yellow, waxy paste, fat soluble, water insoluble	Local irritation and burns on contact followed by GI, liver, and kidney damage, and interferes with clotting	1 mg/kg (lower toxic if dissolved in alcohol, fat, oil)	Skin and GI burns, "smoking" brown vomit contents and stools with garlic odor, jaundice, dysrhythmias, coma, delirium, seizures, cardiac arrest	1–2 hours	Supportive care
Veronal (barbiturate)	White, crystalline powder	Interferes with oxidative phosphorylation and interferes with a variety of respiratory reactions	1–4 mg/kg	Cerebral depression and vomiting, bloody diarrhea, cardiovascular collapse, VT, toxicologic pulmonary edema, altered mental status, life-threatening gastric emptying	Barbiturates: 1 hour Death: 1–24 hours	Decontam, decontaminated with water or milk, concentration < 50 mg/L, hemodialysis to remove (barbiturate removed if acute kidney injury develops)
Veronal (barbiturate) carbonate, chloride, hydroxide	White, white, slightly bitter, long	Hypokalemia, succinylcholine blockade	25–30 mg/kg	Bradycardia, parosmia, muscle weakness, paralysis, nausea, vomiting, diarrhea, abdominal pain, prolonged QT interval, dysrhythmias, cardiac and pulmonary failure	1–4 hours	Decontam (except with Na ₂ CO ₃ or another alkali salt) (succinylcholine, potassium replacement)

PCNA (c-prothionin) V- nitrophenyl urea, base	White, eventually colored or yellow green (pink in heat, also powder)	Interacts with nucleoside metabolism in general; destroys precursors (cells, central and peripheral nervous system, and heart)	1 mg/kg	Acute and chronic, abdominal pain, severe ulceration (gastric and duodenal ulcers), hyperemia with or without leukostasis, gastric- intestinal perforation, peritonitis, necropsis	4–48 hours	Acetaminophen (paracetamol) 500 mg IV or PO (intracutaneously used, but likely unavailable), strong diuretic (furosemide)
Tetracycline (tetracycline hydrochloride, TTS, TIO)	White powder	Non-competitive GABA antagonism by direct blockade of chloride receptors	5–20 mg/kg	Intoxication with epilepsy, laryngitis, acute urinary infection	15–30 hours	Acetaminophen, antibiotics, prokinetic, muscle relaxants
Moderately Toxic Signal Word: WARNING (LD ₅₀ 50–500 mg/kg)						
α-Naphthylthiourea (ANT)	Crystals, slightly bitter, fine, fine-grained powder, white- crystalline	Acute respiratory distress syndrome	> 4 g/kg	Hypothermia, dyspnea, cardiac, acute pulmonary edema, cyanosis	1	Supportive care
Cholecalciferol (vitamin D ₃)	0.025% yellow, 0.04% white/light (1 tablet = 2000 IU vitamin D)	Hypocalcemia	1	Neutropenia, leukopenia, anemia, thrombocytopenia, acute kidney injury and failure, hypotension, hypocalcemia	Hours to days	Fluids, if severe hypocalcemia, phosphate replacement, high phosphate hemodialysis
Low Toxicity Signal Word: CAUTION (LD ₅₀ 500–5000 mg/kg)						
Red spin	White taste	Cardiovascular arrest/poisoning	1	Hypocalcemia, hypotension, renal failure, hypocalcemia	30 minutes–4 hours	Supportive care, IV, atropine
Metformin (dimethylformamide)	White crystalline, fine, powder tablets, 1% concentration	Hypoglycemia and lactic acidosis in severe cases (specific to metformin injection in oral solution form)	Unknown, toxicity at ≥ 100 mg	Hypoglycemia and hypotension	1	Supportive care
Benzocaine	7.5% concentration, green pellets, with 80% alcohol solution (benzocaine)	Hypoxia, systemic hypoxia due to rapid onset of anesthesia	1	Block nerve, muscle, joint, block of major vessels, central nervous system, local anesthetic	Immediate	Supportive care
Anticoagulants: Short Acting						
Warfarin	Yellow crystalline, white, white (0.025%)	Anticoagulation via interference with clotting factors II, VII, IX, X	> 5–20 mg/kg for ≥ 5 days	Increased PT, bleeding death from hemorrhage	12–48 hours	Warfarin, fresh frozen plasma or blood products, vitamin K, prothrombin complex concentrate
Fenitoin	Warfarin (0.025%) plus vitamin K (0.025%)	Anticoagulant activity continues for 48 hours (central nervous system) 8 weeks long exposure	10	Increased PT, bleeding death from hemorrhage		
Anticoagulants: Long Acting						
Hydrocortisone A hydrocortisone	0.025% white, white, white	Anticoagulation via interference	1	Increased PT, bleeding	Increased several days	Warfarin, fresh frozen plasma or blood

Formulation (formulation)		with chelating factor A, B, C, D	death from acute renal failure		Permethrin complex concentrate
Barbiturate (concentration)	0.1% to 0.25% white powder, tablets, tablets				
Indication:					
Propofol	White, amorphous, fully yellow powder, concentration 0.001–2.5%	Intoxication via intravenous with chelating factor A, B, C, D	Chronic ingestion possibly profound cardiac and respiratory depression, elevated BUN, bleeding, death from acute renal failure	Delayed several days	Vitamin K, fresh frozen plasma or red blood cells, Permethrin 1 complex concentrate
Propofol	0.5%				
Diazepam	0.001–2.5%				
Chlorhexidine	0.001–2.5%				
Water	0.001–2.5%				

Environmental decontamination should be provided as appropriate (Chapter 8); only unique environmental agents are discussed in this table.

The LD₅₀ values listed in this table are derived from data on acute oral ingestion of the commercial product by rats. In some cases, the commercial product contains a very small percentage of the active ingredient. The signal words that appear on labels of registered products may differ from the signal word assigned to the acute oral LD₅₀, but because the label may also reflect another study (acute dermal or inhalational LD₅₀) requiring a more severe signal word. See [Table 11.1-1](#) for the Consumer Product Safety Commission definitions and use of signal words as indicators of potential hazard of toxicity. Permethrin 1, Permethrin 1 complex concentrate, Permethrin 1 complex concentrate, EPA, Washington, DC.

Treatment Shortly after the third dose of lorazepam the child began to seize again and endotracheal intubation was performed. Following intubation the child was placed on a continuous infusion of propofol. A nasogastric tube was inserted and 10 g of activated charcoal were instilled into the stomach. The child was transferred to the PICU and attached to a video EEG monitor where intermittent seizure activity was noted over the next 12 to 16 hours. A CT scan of the head was normal and a lumbar puncture was performed to exclude meningitis. The following day the father brought in the original package and the product was identified as tetramine.

Over the subsequent 24 hours the propofol infusion was titrated to a lower dose and then discontinued. The child was able to be extubated and appeared clinically normal. Since the package was brought from their home country and not imported, authorities were not notified. The parents were educated about safe use of pesticides and a social worker was able to help coordinate legal exterminating efforts by the landlord.

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110 BARIUM

Andrew Dawson

Barium (Ba)		
Atomic number	=	56
Atomic weight	=	137.3 Da
Normal concentration		
Serum	<	0.2 mg/L (1.46 μ mol/L)

HISTORY AND EPIDEMIOLOGY

Although barium is utilized in various forms in developed nations, exposure to barium salts is uncommon and clinically significant poisoning is rare. Acute, clinically relevant exposures occur most commonly following the intentional ingestion of the soluble salts found in rodenticides,⁹ insecticides, or depilatories.¹⁰ Barium carbonate has an appearance similar to flour and has been responsible for most unintentional barium poisonings.^{8,12}

Barium salts and barium hydroxide are extensively employed in industry particularly in thermoplastics and the manufacture of synthetic fibers, soap manufacture, and in lubricants (Table 110–1). Toxicity occurs following occupational exposure to barium salts through ingestion, inhalation,³² or explosion of the propellant barium styphnate.¹⁴ Despite the fact that barium sulfate is insoluble, rare cases of unintentional toxicity are reported during radiographic procedures and include complications associated with oral²² and rectal administration.^{13,18,20,25} Toxicity and death occurred when soluble barium salts were unintentionally permitted to contaminate contrast solutions.²⁷

TABLE 110–1. Barium Salts: Solubility and Common Usages

Barium Salt	Solubility (mg/L at 20°C)	Common Uses
Acetate	58.8	Textile dyes
Carbonate	0.02 increases in an acid pH; also, can be converted to barium chloride by gastric acid (HCl)	Rodenticide, welding fluxes, pigments, glass, ceramics, pyrotechnics, electronic devices, welding rods, ferrite magnet materials, optical glass, manufacture of caustic soda and other barium salts
Chloride	375	Textile dyes, pigments, boiler detergents, in purifying sugar, as mordant in dyeing and printing textiles, as water softener, in manufacture of caustic soda and chlorine, polymers, stabilizers
Fluoride	1.2	Welding fluxes
Nitrate	87	Optical glass, ceramic glazes, fireworks (green), explosives, antiseptic preparation
Oxide	34.8	In glass, ceramics, refining oils and sugar, as an additive in petroleum products and also as materials of plastics, pharmaceuticals, polymers, glass and enamel industries
Styphenate	—	Propellant used in manufacture of explosive detonators
Sulfate	0.002	Radiopaque contrast media, manufacture of white pigments, paper making
Sulfide	Slightly soluble in H ₂ O	Depilatories, manufacture of fluorescent tubes

CHEMISTRY

Barium is a soft metallic element that was first isolated by Sir Humphry Davey in 1808. With an atomic weight of 137.3 Da, barium is located at number 56 in the periodic table (between cesium and lanthanum). The metal oxidizes easily when exposed to water or alcohol, has a melting point of 1341°F (727°C) and a boiling point of 3398°F (1870°C). Elemental barium is not found in nature; it normally occurs as an oxide, dioxide, sulfate (barite), or carbonate (witherite). Chemically,

barium resembles calcium more than it resembles any other element. While some barium salts are naturally occurring, most used commercially are produced from the more commonly found carbonates or oxides. Barium salts are typically classified as either water soluble or insoluble, but the solubility of all barium salts increases as the milieu becomes more acidic. The soluble salts acetate, chloride, hydroxide, oxide, nitrate, and (poly) sulfide are the most commonly associated with toxicity (Table 110–1). Barium (poly) sulfide also produces toxicity through the formation of hydrogen sulfide when ingested and exposed to gastric hydrochloric acid.

The solubility of barium carbonate is low at physiological pH, but it increases significantly as the pH is lowered. In the presence of gastric acid conversion to the highly soluble barium chloride occurs. The other insoluble barium salts such as arsenate, chromate, fluoride, oxalate, and sulfate are rarely associated with toxicity. However, toxicity has occurred in the unusual situation of intravasation of barium sulfate (see Toxicokinetics).

TOXICOKINETICS

Toxicity can result from ingestion of as little as 200 mg of a barium salt. Oral lethal doses are reported to range from 1 to 30 g of a barium salt. Occupational exposure to barium fumes of greater than 0.02 mg/m³ are associated with health effects.³⁶ Exposure to inhaled particulate barium may cause pulmonary baritosis, which consists of very fine punctate and annular lesions and some slightly larger nodular lesions.³⁶

Following ingestion, 5% to 10% of soluble barium carbonate salts are absorbed,¹⁵ with the rate of absorption dependent on the degree of water solubility of the salt. The time to peak serum concentration is 2 hours.¹⁵

The toxicokinetics are characterized by a rapid redistribution phase, followed by a slow decrease of serum barium concentrations, with a reported half-life ranging between 18 and 85 hours.^{15,26} Renal elimination of the absorbed dose accounts for 10% to 28% of total barium excretion, with the predominant route of elimination through the gastrointestinal tract in the feces.

Serum barium concentrations range from 3.7 to 41.1 mg/L in published case reports of symptomatic patients.^{2,8,21,23,26,29,31} Death is uncommon following exposure but occurs most commonly following ingestion in clinical settings with limited health care resources.¹² Death from an ingestion of barium chloride was associated with the following barium concentrations at autopsy: blood, 9.9 mg/L; bile, 8.8 mg/L; urine, 6.3 mg/L; and gastric contents, 10 g/L.¹⁶

Intravasation is a rare but serious complication of radiologic studies in which barium sulfate is administered under pressure, such as a barium enema. Following a small perforation, barium sulfate leaks into the peritoneal cavity or portal venous system.²⁰ Although sudden cardiovascular collapse may occur, it is unclear whether this is the result of venous occlusion (pulmonary embolism), overwhelming sepsis, or barium toxicity.^{6,30,35} In at least one case report of intravasation, signs and symptoms were consistent with barium toxicity and elevated barium concentrations were confirmed.²² If hypokalemia is present, then barium toxicity should be assumed.

Additionally, intravenous administration of barium sulfate has occurred as the result of iatrogenic error. Rapid recognition followed by aspiration through a central venous catheter was associated with a good outcome.²⁸

PATHOPHYSIOLOGY

At a cellular level barium induces hypokalemia by two synergistic mechanisms. Barium is a competitive blocker of calcium activated potassium efflux channels. It may also directly increase cell membrane permeability to sodium. This causes a secondary increase Na⁺-K⁺ pump electrogenesis leading to a shift of extracellular potassium into the cell.

Intracellular trapping of potassium leads to depolarization and paralysis.¹⁷ Additionally, the inhibition of potassium channels increases vascular resistance and reduces blood flow^{3,5} and is the likely mechanism for hypertension and metabolic acidosis with an elevated lactate concentration.

While severe hypokalemia contributes significantly to paralysis, some authors have found that muscle weakness correlates better with barium concentrations than with potassium concentrations.^{23,31} This suggests a possible direct effect of barium on either skeletal muscle or neuromuscular transmission.

CLINICAL MANIFESTATIONS

Abdominal pain, nausea, vomiting, and diarrhea commonly occur within 2 hours of ingestion.¹² Esophageal injury and hemorrhagic gastritis are also reported.^{1,16}

Severe hypokalemia is the cardinal feature of barium toxicity and can occur within 2 hours following oral or parenteral exposure. Hypokalemia may be exacerbated by blood transfusions, suggesting that fresh red blood cells provide a new reservoir for K⁺ sequestration.¹⁴ Progressive hypokalemia is associated with severe ventricular dysrhythmias, hypotension,

profound flaccid muscle weakness, and respiratory failure (Chaps. 16, 16, and 3).

Other effects less commonly reported include metabolic acidosis with an elevated lactate concentration, hypophosphatemia, and rhabdomyolysis.¹⁵ Altered level of consciousness, seizures,⁷ and parkinsonism with findings on magnetic resonance imaging of bilateral hyperintensity of the basal ganglia are reported.¹¹ It is unclear whether these later findings are due to direct toxicity, deposition of barium, or secondary to tissue ischemia.

DIAGNOSTIC TESTING

Barium can be measured by a variety of techniques. Mass spectrometry and graphite furnace atomic absorption spectrometry can quantitate barium in blood and urine.¹⁷ Serum barium concentrations are not readily available, but values greater than 0.2 mg/L are considered abnormal.⁴

Following acute exposures, patients should have serum electrolytes (particularly potassium and phosphate) measured hourly while performing continuous electrocardiographic monitoring. Creatine phosphokinase (CPK), acid base status, and kidney function should also be measured. Plain abdominal radiography may show barium, but the sensitivity and specificity of radiography has never been determined for barium poisoning.¹⁷

MANAGEMENT

Toxicologic etiologies for flaccid paralysis such as hypermagnesemia, botulism, and the administration of neuromuscular blockers should also be considered while the serum potassium concentration is being evaluated. Once the hypokalemia is diagnosed, other causes of acute hypokalemia (Chap. 19) associated with paralysis such as periodic hypokalemic paralysis, toluene toxicity, and diuretic use should be considered if there is no history or laboratory confirmation of barium exposure.

Patients who are asymptomatic at 6 hours following ingestion with normal potassium concentrations can be discharged. Patients with signs or symptoms of toxicity should be admitted to an intensive care unit with expectant management of respiratory compromise and cardiovascular instability.

DECONTAMINATION

Activated charcoal is unlikely to be effective. Orogastric lavage should be considered in patients who present early after ingestion, but lavage is unlikely to provide substantial benefit in patients who are already symptomatic or who have had spontaneous emesis. Oral sodium sulfate administration may prevent absorption by precipitating unabsorbed barium ions as insoluble, nontoxic barium sulfate. Oral magnesium sulfate has had similar efficacy.¹⁹ The oral dose of magnesium sulfate is 250 mg/kg for children and 30 g for adults. Intravenous magnesium sulfate or sodium sulfate is not advised as it may lead to acute kidney injury due to precipitation of barium in the renal tubules.^{23,34}

Patients in respiratory failure should receive assisted ventilation. Expedient correction of hypokalemia is important to minimize the risk or to treat cardiac dysrhythmias. Large doses of potassium replacement (400 mEq in 24 hours) may be required to correct serum potassium although repletion may be inadequate to improve the resting membrane potential or muscle strength¹⁷ (Chap. 19). As hypokalemia is due to intracellular sequestration of potassium, potassium supplementation increases the total body potassium load. In this situation, rebound hyperkalemia may occur when barium is eliminated, especially in patients with acute or chronic kidney disease. Observation and serial evaluation for this clinical complication is essential.

Elimination Enhancement

If hypokalemia is unable to be corrected or if the correction of hypokalemia does not restore normal motor function and muscle strength, hemodialysis should be considered. Case reports suggest that hemodialysis for the management of severe barium toxicity is associated with rapid clinical improvement.^{2,26,29,33} Additionally, in a case report, continuous veno-veno hemodiafiltration provided a clinically significant increase in measured barium elimination, stabilized serum potassium concentrations, and was associated with rapidly improved motor strength.¹⁷ Either method of enhanced elimination should be considered in any severely symptomatic patient who does not respond to correction of hypokalemia.

Management of Intravasation

Following intravasation of oral barium sulfate patients should be admitted to an intensive care unit. Expectant management should include considerations of intraabdominal sepsis, hemorrhage and trauma, pulmonary embolus, and barium toxicity.²⁰ Prophylactic antibiotics seem reasonable and serial determinations of serum potassium concentrations are warranted. Computed tomography scanning of the chest and abdomen can demonstrate both the location and extent of the barium sulfate

administered.³⁰

SUMMARY

- Although poisoning by barium salts is rare, these salts are widely used in industry and therefore represent a substantial risk for human exposure.
- The hallmark of barium salt toxicity is rapidly developing and severe hypokalemia with attendant weakness progressing to paralysis.
- In addition to supportive care the mainstay of treatment is rapid correction of hypokalemia.
- Hypokalemia results from an intracellular shift of potassium. As toxicity resolves and potassium redistributes into the extracellular space, cautious evaluation for the development of hyperkalemia is essential.
- Extracorporeal therapies should be considered in cases of refractory hypokalemia.

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111 FUMIGANTS

Shahin Shadnia

Proper use of pesticides can have a beneficial role in human health by increasing the quality and quantity of crops. Alternatively, their improper use can lead to a variety of acute and chronic poisonings.⁵⁶ Pesticide poisoning is a global public health problem,⁵⁴ and each year approximately 300,000 deaths occur worldwide due to pesticides.⁵³

Fumigants are nonspecific pesticides applied to kill and control rodents, nematodes, insects, weed seeds, and fungi anywhere in soil, on structures, crops, grains, and commodities.⁴⁹ They represent a diverse group of xenobiotics that are dissimilar in their chemical structures, physical properties, and mechanisms of toxicity (Tables 111–1 and 111–2). Many fumigants, particularly the halogenated solvents, have been largely abandoned because of their toxicity. In the 1987 Montreal Protocol, an international agreement was adapted to phase out ozone-depleting chemicals, such as methyl bromide, which was scheduled to be discontinued in 2005. Unfortunately, many agricultural companies received exemptions, as satisfactory substitutes for some of its uses have not emerged.

TABLE 111–1. Physical Properties and Industrial Uses of Fumigants

	<i>Color</i>	<i>State</i>	<i>Flammability</i>	<i>Odor</i>	<i>Use</i>
Phosphine	Colorless	Gas	High	Rotten fish Garlic	Rodenticide
Methyl bromide	Colorless	Gas	No	None ^a	Soil Structural Crop
Dichloropropene	Yellow	Liquid	No	Garlic	Soil
Sulfuryl fluoride	Colorless	Gas	No	None	Structural

^aIt has a sweet chloroformlike smell at high concentrations.

TABLE 111–2. Comparison of Clinical Effects of Fumigants

	<i>Mucous Membrane Irritation</i>	<i>Dermatitis</i>	<i>Burns (Frostbite)</i>	<i>Gastrointestinal: Nausea, Vomiting, Abdominal Pain</i>	<i>Hepatic Dysfunction</i>	<i>Chest Pain</i>	<i>Adult Respiratory Distress Syndrome</i>	<i>Cardiovascular Hypotension</i>	<i>Dysrhythmias</i>	<i>Nephrotoxicity</i>	<i>Mental Status Changes</i>
Phosphine	++	–	–	+	+	+	+	+	++	+	+
Methyl bromide	± High concentration	+	+	+	+	+	+	+	+	+	+
Dichloropropene	+	+	–	+	+	+	+	+	+	+	+
Sulfuryl fluoride	± High concentration	+	+	+	–	–	+	+	++	–	+

– = Absence; + = Presence; ++ = Very substantial; ± = Variable.

Since fumigants exist as solids that can release toxic gases on reacting with water (zinc phosphide, aluminum phosphide) or with acids (sodium or calcium cyanide), as liquids (ethylene dibromide, dibromochloropropane, formaldehyde) that can vaporize at ambient temperature, or as gases (methyl bromide, hydrogen cyanide, ethylene oxide),

inhalation is the most common route of exposure (Table 111–1). In their gaseous forms fumigants are generally heavier than air and will stay concentrated just above the ground surface and lower floors of buildings.

Their exposure risk is enhanced by their general lack of good warning properties, non–species-selective effects, and high potency. Although chemicals from many different classes were used in the past as fumigants, only a few remain in use today in the United States. This chapter summarizes those remaining and also highlights important fumigants that are in use in developing countries.

PHOSPHIDES AND PHOSPHINE

Introduction

In addition to the organic phosphorus and organic chlorine compounds, metal phosphides (aluminum, zinc, magnesium, and calcium) have long been used as rodenticides and fumigants around the world. The metal phosphides are advantageous due to their low cost, high effectiveness in destroying harmful insects and rodents, freedom from toxic residue, and lack of adverse effect on seed viability. Phosphides are used to protect grain held in silos, in the holds of ships, and during transportation by rail. They are generally admixed with the grain at a predetermined rate at the initiation of storage.^{26,56} Upon exposure to ambient moisture, the metal phosphides release phosphine gas (PH₃). Exposure to water results in rapid release highlighting the concern for their use as chemical weapons.¹⁶

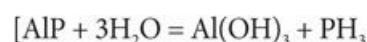
History and Epidemiology

From 1900 until 1958 only 59 cases of PH₃ and metal phosphides poisoning were reported in the literature, the majority of which were unintentional. Fatal outcomes were reported in 26 of these cases.^{95,105} Over the last 35 years, cases of poisoning have escalated, carrying a high mortality rate, likely related to the use of these chemicals for suicidal purposes.¹²⁰ Aluminum phosphide (AIP) poisoning is now one of the commonest causes of poisoning in agricultural societies, such as those found in India, Sri Lanka, Iran, Jordan, and Morocco.^{16,46,48,96,115,120} The incidence of phosphide poisoning is rare in Europe and North America.^{100,107}

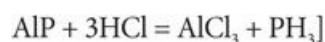
Physicochemical Properties

Commercially, AIP is most widely available as a greenish-gray tablet that has a garlic odor. The tablets usually contain 3 g of AIP (56%), ammonium carbamate, and urea. Zinc phosphide (Zn₃P₂; molecular weight of 258.1 Da) is available as a dark gray powder and or quadrilateral crystals that has odor of acetylene or rotten fish. Calcium phosphide (Ca₃P₂; molecular weight of 182.2 Da) is available as a reddish-brown crystal powder.⁹

In the presence of moisture, phosphide is converted to gaseous PH₃ (hydrogen phosphide, phosphorus trihydride), ammonia, and carbon dioxide:



OR



Each AIP tablet liberates up to 1 g of PH₃. The release of PH₃ is even more vigorous after contact with an aqueous acid, such as hydrochloric acid. The residue Al(OH)₃ is nontoxic.^{9,48,136} PH₃ may be flammable, and other byproducts of commercial tablets (aluminum oxide and diphosphine gas) are spontaneously flammable in air.^{38,69,117,146,147}

Although PH₃ is colorless and odorless in pure form up to toxic concentrations (200 parts per million {ppm}), the presence of substituted phosphines and diphosphines imparts a decaying fish or garlic odor that is detectable at concentrations of as little as 2 ppm.^{26,27,104}

Toxicokinetics

Following ingestion, the most common route of exposure, metal phosphides react with acidic fluid in the gastrointestinal (GI) tract to release PH₃, which is rapidly absorbed. Phosphides may be absorbed as microscopic particles of unhydrolyzed salt and subsequently converted to PH₃. PH₃ can be absorbed from respiratory tract mucosa if inhaled. Dermal and ocular absorption occurs.⁹

There are no data on the distribution of PH₃ to tissues, but one would expect this small soluble molecule to readily

reach all organs.^{9,89} PH₃ is detectable in the blood and liver of decedents following ingestion.^{6,32} Hypophosphite is the major degradation product in the urine, and smaller amounts of phosphate and phosphite may be identified, while PH₃ itself is exhaled.⁵⁷

Toxicodynamics

PH₃ is a protoplasmic toxin that interferes with enzymatic function and synthesis of proteins.¹²⁰ The mechanism of toxicity includes blocking the electron transport chain and oxidative phosphorylation through noncompetitive inhibition of cytochrome-c oxidase. This inhibits cellular respiration and leads to the formation of highly reactive hydroxyl radicals that cause additional damage.^{17,42,123} PH₃ also inhibits catalase, induces superoxide dismutase, and reduces the glutathione (GSH) concentration. All of these effects combine to result in lipid peroxidation and protein denaturation of cell membranes, leading to widespread cellular damage and ion channel dysfunction.^{30,31,34,65}

PH₃ directly injures the alveolar capillary membrane in addition to producing oxidative injury, leading to acute respiratory distress syndrome (ARDS).^{57,120} Although both AIP and PH₃ inhibit cholinesterase activity, this effect is unlikely to have substantial clinical relevance.^{3,84,85,94,108}

Toxic Dose

Ingestion of 1 g of ZnP can cause toxicity in humans and death has been reported after ingestion of 4 g. Ingestion of 500 mg of AIP can be fatal.¹⁰ The recommended exposure limit (REL) of PH₃ in workplace is less than 0.3 ppm as a time-weighted average (TWA) for up to 10 hours per day during a 40 hour work week, and 1 ppm as a 15-minute short-term exposure limit (STEL) that should not be exceeded at any time during a workday. The National Institute of Occupational Safety and Health has established 50 ppm as the concentration that is immediately dangerous to life or health (IDLH) for PH₃, and the concentration of 400 to 600 ppm could be lethal within 0.5 hours.^{98,132} Workplace standards are not available for AIP specifically.¹³²

Clinical Manifestations

The smell of garlic or decaying fish on the breath is a common finding and can be the result of oral or inhalational poisoning with phosphides and PH₃.¹⁰⁷ The clinical manifestations are dependent on the dose, route of entry, and time since exposure.⁵⁷ After ingestion, the onset of toxicity usually is slightly more rapid for AIP (10–15 minutes) than for ZnP (20–40 minutes).^{56,74} In patients with mild poisoning, nausea, repeated vomiting, diarrhea, abdominal discomfort or pain, especially epigastric pain, and tachycardia are common clinical manifestations. In those with moderate to severe effects, GI manifestations, refractory hypotension and shock, palpitations, cardiovascular collapse, dysrhythmias, tachypnea, and ARDS occur early.^{48,109}

Restlessness, anxiety, dizziness, ataxia, numbness, paresthesias, and tremor are universally observed, but central nervous system (CNS) manifestations are not prominent until a secondary event, such as hypoxia occurs. Late and severe neurologic findings include delirium, convulsions, and coma.

Following limited PH₃ inhalational exposure, patients commonly have airway irritation and breathlessness.²⁶ Other features may include dizziness, tightness in the chest, headache, nausea, vomiting, diarrhea, ataxia, numbness, paresthesias, tremor, muscle weakness, and diplopia.^{48,56,132} In patients with significant inhalations, ARDS, cardiac failure, dysrhythmias, convulsions, coma, and delayed manifestations of hepatotoxicity and nephrotoxicity may also occur.^{48,132}

Uncommon complications of phosphides and PH₃ poisoning include gastroduodenitis, hepatitis,³⁵ ascites,¹⁴ pancreatitis,¹⁴³ myocardial infarction,^{72,76} acute pericarditis,²⁷ pleural effusion,¹³³ skeletal muscle damage and rhabdomyolysis,¹⁰⁹ acute tubular necrosis, adrenocortical congestion, hemorrhage and/or necrosis,⁷ and delayed esophageal stricture or tracheoesophageal fistula.^{73,81,142} Hepatic and kidney failure, as well as disseminated intravascular coagulation (DIC), may occur following acute poisoning.^{14,48,109}

Diagnostic Testing

Initial investigations should include electrocardiography (ECG) and continuous cardiac monitoring, chest radiograph, blood glucose, blood gases, serum electrolytes, complete blood count, and liver and kidney function studies. Hypokalemia is common after oral poisoning and is probably due to vomiting, although this effect may be catecholamine related.¹⁰⁹ Magnesium concentrations may be normal,¹²⁴ increased, or decreased.^{23,25,28,29,121,122}

Hypoglycemia as a result of impaired gluconeogenesis, glycogenolysis, and possibly due to adrenal insufficiency is

common and may be severe and persistent.^{36,45} Hyperglycemia has also been reported.^{89,90} Metabolic acidosis or mixed metabolic acidosis and respiratory alkalosis are common.¹⁰⁹ Intravascular hemolysis, methemoglobinemia, and microangiopathic hemolysis are unusual complications of phosphide poisoning.^{77,118,127}

ECG abnormalities are very common, but highly variable, and include rhythm disturbances, ST segment and T wave changes, and conduction defects.^{25,71,128} During the first 3 to 6 hours after poisoning, sinus tachycardia is predominant, followed over the next 6 to 12 hours by ST segment and T wave changes, conduction disturbances, and dysrhythmias.^{45,126} Ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia, and atrial flutter/fibrillation are the most common consequential dysrhythmias.¹²⁵ Echocardiography may reveal dysfunction, dilation, and hypokinesia or akinesia of the left ventricle that typically resolves over several days.^{2,15,55}

Toxicological Analyses. Chemical analysis for PH₃ in blood or urine is not recommended and is not typically helpful as PH₃ is rapidly oxidized to phosphite and hypophosphite.¹⁴⁷ Gas chromatography with a nitrogen-phosphorous detector is the most specific and sensitive test.⁹⁷ The presence of PH₃ is suggested by a positive silver nitrate test on gastric content or exhaled breath. In this test which is not clinically available and is not validated paper impregnated with silver nitrate will turn black (silver phosphate) in the presence of PH₃.⁹³

Prognosis

The mortality rate following metal phosphide ingestion is 31% to 77%.^{23–25,116} Most of the deaths occur within 12 to 24 hours and are due to cardiovascular collapse.^{5,128} After 24 hours, most of the deaths are due to refractory shock, severe acidemia, and ARDS.¹⁴⁵ Fulminant hepatic failure may develop within 72 hours after poisoning and may be another cause of death.⁷

A high Acute Physiology and Chronic Health Evaluation Score, a high Simplified Acute Physiology Score, shock, decreased level of consciousness, lack of vomiting after ingestion, acidemia, hyperglycemia, uremia, hemoconcentration, leukocytosis, and ECG abnormalities are all poor prognostic factors.^{23–25,80,89,90,115,116,128}

Treatment

The victim of PH inhalation should immediately be removed to fresh air and supplemental oxygen should be provided as needed.^{57,109} Clinical staff and other health care professionals should use universal precautions, including gloves and masks,⁹³ with the understanding that a particulate mask will not protect against PH₃. As PH₃ may be absorbed by the cutaneous route, the patient's clothes should be removed and their skin and eyes decontaminated with water as early as possible.⁴⁸ GI decontamination may be useful if it is done within 1 to 2 hours of ingestion. The acidic content of stomach assists the conversion of phosphide to PH₃, and some have suggested the oral administration of sodium bicarbonate, but this is not supported by experimental evidence.^{57,82} Potassium permanganate (1:10,000) has also been suggested in case reports as an adjunct to gastric lavage to oxidize PH₃ to nontoxic phosphate.^{82,103}

There is limited evidence that activated charcoal (AC) 100 g may reduce GI absorption if the patient arrives within 1 hour after ingestion of a large amount of poison. Its routine use is not recommended as PH₃ is rapidly absorbed from the GI tract.⁸² In vitro studies suggest that lipid, mainly vegetable oils and liquid paraffin, inhibit PH₃ release from the ingested ALP.⁵¹ This approach was utilized in a single case report.¹¹⁴

Management should be rapidly initiated based on a history and clinical examination that support phosphides/PH₃ poisoning, and should not be delayed for the confirmatory diagnosis.⁵⁷ Standard supportive care to address ventilatory and vital sign abnormalities should be administered. If necessary, norepinephrine or phenylephrine should be employed. Vasopressors with greater β -receptor agonist action like dopamine and dobutamine should be used cautiously as they are prone to induce dysrhythmias.⁵⁷

As there is no known specific antidote, management remains primarily intensive monitoring and supportive treatment, to allow the toxin to be eliminated. ARDS, hypoglycemia, hypokalemia, and metabolic acidosis should be managed conventionally.^{57,109}

Dysrhythmias should be treated with standard antidysrhythmics. Recently, a few studies hypothesized that treatment with digoxin could have beneficial effects on myocardial contractility and blood pressure.^{91,112}

The benefit of hyperinsulinemia-euglycemia treatment is suggested by preliminary investigations in that insulin promotes energy production from carbohydrates, restores calcium flux, and improves myocardial contractility.⁵⁹ The use of an intraaortic balloon pump is reported,¹¹⁹ but the usefulness of extracorporeal life support in circulatory failure due to phosphides/PH₃ poisoning was not formally evaluated.¹³

N-acetylcysteine (NAC) has been shown in an experimental animal model⁸ and human study¹³⁵ to be beneficial. As the experimental and clinical evidence shows that both PH₃ and aluminum inhibit acetylcholinesterase,^{3,84,85,108} pralidoxime may have a role in the management. Further studies are recommended to confirm usefulness of oximes,⁹⁴ and they are not currently recommended.

Experimental data show that hyperbaric oxygenation may improve the survival time of poisoned rats, with no change in the mortality rate.¹¹¹ Magnesium sulfate acts as a cell membrane stabilization factor and, possibly by this mechanism, reduces the incidence of fatal dysrhythmias.^{28,29} Magnesium also has antioxidant effects and combats free radicals due to PH₃.^{33,34} Although likely of low risk, the use of magnesium sulfate in phosphides/PH₃ poisoning is controversial.^{57,109} Hemodialysis is not very effective in removing PH₃, although it may be useful in the setting of a patient with acute kidney failure, severe metabolic acidosis, or fluid overload.⁵⁷ As stated previously, the sole recognized approach remains intensive care monitoring and supportive treatment. All other approaches remain experimental.

METHYL BROMIDE

History and Epidemiology

Methyl bromide was used as an anesthetic in the early 1900s, but fatalities halted this practice. Today, methyl bromide is used widely as a fumigant for all types of dry food stuffs, in grain elevators, mills, ships, warehouses, greenhouses and food-processing facilities for the control of nematodes, fungi and weeds. It is termed a structural or commodity fumigant which is a class term for the Environmental Protection Agency.

Methyl bromide is also used as a methylating chemical in manufacturing and as a low-boiling solvent for extracting oils from nuts, seeds and flowers. Methyl bromide has also been used as a refrigerant and fire retardant. Historically, poisoning incidents involving the general public were mainly associated with the methyl bromide used in fire extinguishers. Other poisoning incidents have involved unauthorized entry into buildings being fumigated with methyl bromide.^{12,60}

Occupational and environmental exposures to methyl bromide as a fumigant are most common. Hazardous materials incidents are reported for methyl bromide, during manufacture or as a result of use and transport,^{20,106} but they are relatively uncommon in plant employees or residents living adjacent to agricultural fields where methyl bromide is applied.²⁰ Before 1955, the majority of methyl bromide poisonings resulted from chemical manufacture and filling operations. Since then, fumigation has become the major source of fatalities and fumigators, and greenhouse workers are the highest risk group. In many countries the use of methyl bromide is restricted to trained and licensed personnel.⁴⁴

Methyl bromide has a threshold limit value-time weighted average (TLV-TWA) of 5 ppm and IDLH concentration is 2000 ppm. The Occupational Safety and Health Administration (OSHA) permissible exposure limit is 20 ppm.

Methyl bromide is a colorless gas at room temperature and standard pressure. It is three times heavier than air. It is odorless except at high concentrations when it has a burning taste and a sweet chloroformlike smell. Commercially it is available as a liquefied gas. The formulations also may contain chloropicrin or amyl acetate as a warning agent.

Toxicokinetics

Inhalation is the primary route of exposure, although methyl bromide is rapidly absorbed through the dermal and oral routes. After absorption, methyl bromide or metabolites are rapidly distributed to many tissues, including the lungs, adrenals, kidneys, liver, brain, testis, and fat. The major organs of distribution observed immediately after exposure includes fat, lungs, liver, adrenals, and kidneys.

The metabolism of methyl bromide has not been completely elucidated. Methyl bromide is partially converted to inorganic bromide in man and bromide concentrations in blood and target organs increase after exposure to methyl bromide.^{12,64} It is metabolized to methyl glutathione by the enzyme glutathione S-transferase (GST) and is then converted into the neurotoxic metabolites of methanethiol and formaldehyde.⁷⁹

Depending on the route of exposure, 16% to 40% is eliminated as metabolized methyl bromide in the urine and only 4% to 20% is eliminated in the expired air as parent compound. Biliary excretion accounts for about 46% of the elimination, generally within 24 hours following oral exposure.^{4,87,88} Methyl bromide is hydrolyzed and produces methanol and hydrobromic acid in animal models.

Toxicodynamics

The mode of action of methyl bromide is still not understood. Several mechanisms of toxicity are postulated, including the direct cytotoxic effect of the intact methyl bromide molecule or toxicity due to one of its metabolites.

Methyl bromide is a potent alkylating agent with high affinity for sulfhydryl and amino groups. It reacts in vitro with a number of sulfhydryl-containing enzymes and causes irreversible inhibition of microsomal metabolism.^{12,50,129}

It binds to amine groups in amino acids, interfering with protein synthesis and function. Also it may methylate many other cellular components such as GSH, proteins, DNA, and RNA.¹³⁰ The methanethiol and formaldehyde metabolites may have a role in neurologic and visual changes. The bromide ion concentrations are insufficient to explain methyl bromide toxicity.

Clinical Manifestations

Inhalation of more than 10,000 ppm for more than a few minutes may cause death.⁶⁰ Severe poisoning may result in tremor, convulsion, rapid loss of consciousness, dysrhythmias, and death. Convulsions generally occur in fatal cases, but ARDS leading to respiratory failure or cardiovascular collapse is the leading cause of death. Pulmonary symptoms begin with cough or shortness of breath that may rapidly progress to bronchitis, pneumonitis, and ARDS.⁶³ By contrast, following low concentration exposure, a characteristic delay of up to 48 hours in the onset of symptoms is expected. Headache, dizziness, abdominal pain, nausea, vomiting, chest pain, and difficulty breathing are the manifestations of mild to moderate exposure. Some individuals may initially manifest irritant symptoms of the eye, nasopharynx, and oropharynx, which may be misdiagnosed as influenza or another viral illness. Visual disturbances such as blurred or double vision may also appear.^{22,49}

The neurologic effects of methyl bromide poisoning are the most consequential and may occur without antecedent irritant effects. Initial CNS signs and symptoms that may manifest in the first few hours after exposure include headache, dizziness, numbness, drowsiness, euphoria, confusion, diplopia, dysmetria, dysarthria, agitation and mood disorders, or inappropriate affect. Those that may progress rapidly in the first day or manifest over the next few days include ataxia, intention tremor, fasciculation, myoclonus, delirium, seizures, and coma.^{39,40}

Methyl bromide can also cause skin lesions, including severe irritation, erythema, corrosive skin injury, blisters, and vesicles predominantly in moist areas or pressure points such as groin, axilla and wrist.¹⁴⁸ Liver and kidney damage have also been described.^{12,60}

Most patients who develop seizures or coma will not survive, and in the few survivors recovery typically may take months. Permanent sequelae such as neuropsychiatric impairment, ataxia, muscular weakness, irritability, blurred vision, myoclonus, and electroencephalographic (EEG) disturbances are frequent.^{19,137}

Diagnostic Testing

The standard laboratory evaluations such as a complete blood count, serum electrolytes, blood urea nitrogen (BUN) creatinine, ammonia concentration, blood gases, urinalysis, hepatic enzymes, chest radiography, ECG, and EEG should be obtained after an acute exposure. Hemoglobin adducts are used as a biologic index for exposure to methyl bromide.⁷⁰ Hemoglobin adducts have a life span of about 2 months, so workers who have only intermittent exposure to methyl bromide may benefit from testing.

Although a serum bromide concentration may help confirm the diagnosis, it is not readily available in most laboratories. Furthermore, it does not always correlate with the severity of the exposure and does not facilitate clinical management. Serum bromide concentrations may also remain elevated for a week or more following an acute exposure.⁶⁶

The findings on magnetic resonance imaging following methyl bromide intoxication are symmetric T2 signal abnormalities in posterior putamen, subthalamic nuclei, restiform bodies, vestibular nuclei, inferior colliculi, and periaqueductal gray matter and also symmetric involvement of inferior colliculi and periaqueductal gray, as well as dentate nuclei, dorsal pons, and inferior olives.⁴⁷

Treatment

Rescue and decontamination should be performed only by personnel wearing personal protective equipment. In patients with respiratory and cardiac arrest, cardiopulmonary resuscitation should be initiated immediately if it is safe to perform. Following inhalation, the patient should be safely removed from the exposure site. The outer clothing should be removed carefully, as methyl bromide may adhere to clothing, including rubber and leather, and the affected skin should be washed with soap and water. Decontamination includes irrigation of the eyes with copious amounts of 0.9% NaCl solution or water. It is also reasonable to administer at least one dose of oral AC following ingestion, although there is no supporting documentation for any benefit. Medical management should proceed as it would for any hazardous materials event ([Chap. 131](#)).

Management is primarily general and supportive care, and may require intensive care unit management of coma, seizures, ARDS, hepatic and kidney failure. Administer supplemental oxygen and treat bronchospasm, ARDS, and seizures. Seizures are common and difficult to control with traditional anticonvulsants such as benzodiazepines and phenytoin. Pentobarbital, high-dose thiopental, and propofol have been required in many cases.⁶⁶ All exposed patients should be monitored for a minimum of 24 to 48 hours to detect delayed symptoms, especially ARDS.

Although British anti-Lewisite (dimercaprol) has been used for the treatment of methyl bromide poisoning, its effectiveness is only reported in less severely affected patients.⁶⁰ The usage of NAC is not studied in controlled prospective trials, but its effectiveness is reported in mild to moderate poisonings.⁶⁶

There are no data indicating the benefit of alkalinization or hemoperfusion. Hemodialysis can rapidly clear serum bromide, but tissue injury following exposure occurs as the bromide is released into the serum, suggesting that the methylation of neuronal proteins has already occurred and the neurologic injury occurs. Posthemodialysis neurologic improvement is reported, but severe disabilities may remain. There is little evidence to support routine hemodialysis. There is little evidence to support these experimental approaches.

DICHLOROPROPENE

History and Epidemiology

1,3-Dichloropropene is a volatile chlorinated aliphatic hydrocarbon that was introduced in 1945 and is primarily used as a soil fumigant for nematodes. Its use escalated after the restriction of ethylene dibromide, methyl bromide, and dibromochloropropane in 1956. The current formulation contains dichloropropene in soybean oil.¹³⁸

Exposures are reported during production, application, and ingestion, most commonly in occupational settings where formulations are manufactured or applied. Unintentional releases during transport resulted in several poisonings.⁸³ The OSHA standard TLV-TWA for dermal exposure is 1 ppm.⁷⁸

Toxicokinetics

Dichloropropene is rapidly absorbed by the oral, inhalational, and dermal routes. Oral exposure is theoretically possible through contaminated groundwater, but this has not been reported in humans.¹³² Inhalation is the primary route of human exposure and dichloropropene is rapidly absorbed from the lungs.^{18,140}

No human data describe systemic distribution, but animal studies show that tissue concentrations after dichloropropene ingestion were highest in the stomach, followed by the blood, bone, brain, heart, kidneys, liver, bladder, skin, skeletal muscle, spleen, ovaries, testes, and fat.⁴¹

The metabolism of dichloropropene is similar to that of other chlorinated hydrocarbon solvents such as carbon tetrachloride and chloroform (Chap. 108). In humans, dichloropropene is metabolized in liver via oxidation in a phase I biotransformation,^{86,92,131} which is catalyzed by cytochrome P450 (CYP2E1)⁵² and then glutathione dependent biotransformation.^{18,102,140,141} Toxicity may result from metabolism via an electrophilic epoxide intermediate.¹⁴⁴

Most of the glutathione-conjugated form of dichloropropene is eliminated by the kidneys and smaller amounts are eliminated in the feces.^{37,67,138}

Toxicodynamics

Human and animal health effects may include damage to the liver, kidney, lung, CNS, myocardium, GI tract, skin, and mucous membranes. The exact mechanisms of toxicity are not clear, but data suggest that there may be more than one mechanistic pathway in humans.

GSH depletion has been documented in the rat model.⁵⁸ The dose and route correlated with toxicity and outcome in rodent models of dichloropropene toxicity. At 100 mg/kg in mice, hepatotoxicity occurs by the intraperitoneal route, but not after oral gavage. At 700 mg/kg administered by the intraperitoneal route, hepatic failure and death result.¹¹ The higher dose correlated with a 130 fold increase in dichloropropene epoxide formation. Interestingly, in a rat hepatocyte model, pretreatment with the antioxidant, α -tocopherol, prevented cell death.¹³⁴

Clinical Manifestations

Signs and symptoms of acute oral or inhalational exposure include nausea, vomiting, bloody diarrhea, pancreatitis, hepatotoxicity, tachycardia and hypotension,⁶² dyspnea,⁶⁸ ARDS,⁶² CNS depression,⁸³ acute kidney injury (acute tubular necrosis),⁶² and muscle pain and weakness.⁸³ Coagulopathy and thrombocytopenia, hyperglycemia, severe metabolic acidosis,⁶² and intravascular fluid depletion secondary to hemorrhage are reported. Dermal manifestations include contact hypersensitivity,^{60,138,139} erythema,⁸³ and profuse sweating.⁶² Mucous membrane irritation including erythema, edema, and irritation of the eyes, ears, nose, and throat occurs.^{83,138} Concentrations above 1000 ppm cause lacrimation.¹ Hematologic malignancies including lymphoma and histiocytic lymphoma were reported after prolonged (6 years) dichloropropene exposure.⁸³

Radiographic abnormalities typically lag behind clinical signs. It may take up to 8 hours before abnormalities appear on

chest radiography, even in symptomatic patients.⁶²

Weight loss, hyperemia and superficial ulcerations of the nasal mucosa, inflammation of the pharynx, bleeding from swollen gums,⁸³ liver aminotransferase elevations, and renal function abnormalities¹⁸ are reported after chronic exposure to dichloropropene.

Diagnostic Testing

Liver and kidney function should be monitored following acute poisoning.⁶² No additional or specific tests are recommended beyond those needed for supportive care. Biomonitoring for exposure to dichloropropene is under development.¹⁸ Hepatic γ -glutamyl transpeptidase concentrations are increased in fumigators, but the increase is not statistically significant. However, this finding suggests hepatic enzyme induction. In fumigators, erythrocyte GST and GSH concentrations decreased with increased serum creatinine concentrations and increased urine concentrations of albumin and retinol-binding protein when compared with controls.¹⁸

Treatment

Because of the volatility of dichloropropene, caution should be used to avoid continued inhalational and dermal exposure for both the patient and the health care professional. Symptomatic and supportive care should be provided as for methyl bromide. Following ingestion, oral AC can be administered, but there is no proven value. Orogastric lavage may be appropriate in a patient presenting shortly following ingestion. Exposed eyes should be irrigated with copious amounts of water or 0.9% NaCl solution for at least 15 minutes, and exposed skin should be similarly washed with soap.

There are no data to support specific therapies beyond supportive care, although the use of antioxidant therapy and NAC warrants further study. The patients should be monitored for at least 24 hours after exposure.

SULFURYL FLUORIDE

History and Epidemiology

Sulfuryl fluoride has been used since 1957 as a structural fumigant insecticide to control wood boring insects such as termites in homes. Structure or tent fumigation is performed by completely enclosing a house or other structure in plastic or a tarpaulin, and then sulfuryl fluoride is pumped in as a compressed gas. Chloropicrin is typically added as a warning agent. Although sulfuryl fluoride is commonly used in Florida, California,¹⁰¹ and Washington, a 5-year review of fumigant illness did not contain any reports of sulfuryl fluoride toxicity.²⁰

Toxicokinetics and Toxicodynamics

Sulfuryl fluoride gas is colorless, odorless, and heavier than air. The TLV-TWA for sulfuryl fluoride is 5 ppm; TLV-STEL is 10 ppm; IDLH is 200 ppm.⁹⁹

Little is known about the toxicokinetics of sulfuryl fluoride in humans and the exact mechanism of toxicity is not understood. The respiratory, central nervous, and cardiovascular systems are the primary target organ systems.⁴³ The measurable fluoride concentrations in patients with sulfuryl fluoride poisoning and the development of fluorosis in models of chronic, low concentration exposures suggest that the release of fluoride may be of major pathophysiologic consequence.¹⁰¹ Fluoride complexes with calcium and magnesium, resulting in hypocalcemia and hypomagnesemia (Chap. 107).⁶¹

Clinical Manifestations

Case reports of sulfuryl fluoride exposure describe acute and subacute clinical courses that share many similarities to methyl bromide poisoning. Initial symptoms, especially in limited exposures, may include nausea, vomiting, diarrhea, abdominal pain, cough, and dyspnea. Irritation of mucosal surfaces may produce salivation and nasopharyngitis, lacrimation, and conjunctival injection. CNS manifestations include paresthesias, irritability, agitation, tetany, refractory seizures, and coma. Finally, fluoride toxicity may result in profound shock, cardiac dysrhythmias, wide QRS complexes, prolongation of the QT interval, torsade de pointes, hyperkalemia, and ARDS (Chap. 107).^{101,113}

Memory and dexterity testing were abnormal in structural fumigation workers exposed to both methyl bromide and sulfuryl fluoride.²¹

Diagnostic Testing

Patients with sulfuryl fluoride exposure require monitoring of serum calcium, magnesium, and potassium concentrations. Patients should have an ECG performed and be attached to continuous cardiac monitoring to observe for QRS widening,

QT interval prolongation, and dysrhythmias. Serum fluoride concentrations, although not helpful for acute management, may help as a confirmatory diagnostic test.

Treatment

In patients with inhalational exposure, after removal from the scene to fresh air, the patients should be partially disrobed to avoid further exposure to any liberated sulfuric fluoride gas.

In treating sulfuric fluoride poisoning, aggressive treatment of hypocalcemia with calcium gluconate or calcium chloride may be needed (Antidotes in Depth: A29). Similar to the management of methyl bromide, supportive care may be needed for the seizures, dysrhythmias, bronchospasm, and ARDS. As the fluoride ion is excreted in the urine, fluid resuscitation may be needed to maintain a steady urine output.¹¹⁰

METHYL IODIDE

Iodomethane or methyl iodide is currently under review by the US Environmental Protection Agency. It is proposed as a fumigant to replace methyl bromide. However, several reports from Europe suggest that the toxicity of methyl iodide may be similar to that of methyl bromide.^{39,67} A recent report describes dermal exposure with severe burns and delayed neuropsychiatric sequel, similar to that associated with methyl bromide exposures.²¹

SUMMARY

- Exposure to fumigants may be through ingestion or inhalation depending on the specific fumigant and the physical state.
- The fumigants are associated with multisystem organ failure and, following acute exposure, adversely affect both the cardiovascular and central nervous systems.
- Treatment involves removal from exposure and removal of outer clothing. Dermal decontamination is not generally needed given the volatile nature of most fumigants.
- Staff and patient protection from inhalation is important to prevent iatrogenic toxicity.

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112 HERBICIDES

Darren M. Roberts

HISTORY, CLASSIFICATION, AND EPIDEMIOLOGY

An herbicide, any chemical that regulates the growth of a plant, encompasses a large number of xenobiotics of varying characteristics. Herbicides are used around the world for the destruction of plants in the home environment and also in agriculture where weeds are particularly targeted. Poisoning may occur following acute (intentional or unintentional poisoning) or chronic (such as occupational) exposures. Depending on the herbicide and the characteristics of the exposure, this may lead to clinically significant poisoning, including death. This chapter focuses on the most widely used herbicides and also those associated with significant clinical toxicity. In particular, risk assessment and the management of patients with a history of acute herbicide poisoning are emphasized.

Prior to the 1940s, the main method of weed control and field clearance was manual labor, which was time consuming and expensive. A range of xenobiotics were tested, including metals and inorganic compounds; however, their efficacy was limited. The first herbicide marketed was 2,4-dichlorophenoxyacetic acid during the 1940s, followed by other phenoxy acid compounds. Paraquat was marketed in the early 1960s, followed by dicamba later that decade. The development of new herbicides is an active area of research and new herbicides and formulations are frequently released into the market. This includes a number of novel structural compounds for which clinical toxicology data are unavailable. Hundreds of xenobiotics are classified as herbicides and a much larger number of commercial preparations are marketed. Some commercial preparations contain more than one herbicide to potentiate plant destruction. From another perspective, crops are being developed that are resistant to particular herbicides to maximize the selective destruction of weeds without reducing crop production.

Herbicides are the most widely sold pesticides in the world, where in 2007 they accounted for approximately 40% of the total world pesticide market and 48% of the pesticide market in the United States. Home and garden domestic use accounts for 13% of the overall herbicide use in the United States, while the remainder is used in agriculture, government (eg, vegetation control on highways and railways), and industry. In each of the US market sectors, herbicides were four of the top five used pesticides in 2007, including glyphosate, atrazine, acetochlor, and 2,4-dichlorophenoxyacetic acid.³³

Not all herbicide exposures are clinically significant. In developed countries, most acute herbicide exposures are unintentional and the majority of patients do not require admission to hospital. The National Poisoning Database System (NPDS) of the American Association of Poison Control Centers (AAPCC) describes approximately 10,000 herbicide exposures each year. Over the last 12 years, there were approximately five deaths per year and 20 patients per year with clinical outcomes categorized as “major” that were attributed to herbicide poisoning (Chap. 136). Most deaths were due to paraquat and diquat, although recently glyphosate and phenoxy acid compounds are more commonly implicated. Cases of severe poisoning that required hospitalization usually followed intentional self-poisoning. Significant toxicity may also occur with unintentional (eg, storage of a herbicide in food or drink containers) or criminal exposures.

Classification

Hundreds of xenobiotics have herbicidal activity and they may be subclassified by a number of methods. Most commonly they are categorized in terms of their spectrum of activity (selective or nonselective), chemical structure, mechanism of action (contact herbicides or hormone dysregulators), use (preemergence or postemergence), or their toxicity to rats (LD₅₀). Certain xenobiotics are classified as plant growth regulators rather than herbicides, but in this chapter all are considered to be herbicides.

Table 112–1 lists the extensive range of herbicides in current use.⁴⁹ By convention, they are subclassified according to their chemical class and their World Health Organization (WHO) hazard classification. Unfortunately, the utility of these (or any other) methods of classification to predict the hazard to humans with self-poisoning is not proven.

TABLE 112–1. Characteristics of the Major Herbicides Categorized by Chemical Class and WHO Hazard Classification

Contraindications	Pregnancy, relative to paracetamol	II	Acetaminophen, propofol	Propofol induces mild renal toxicity in most cases, but gastrointestinal erosion, ulcers, and death due to respiratory failure are reported. Limited human data for the others.
	In 2017, rifabutin and propofol were among the top 10 antibiotics used in the United States overall, while rifabutin and propofol were among the top 10 used in the domestic sector (children) intravenous assembly	I	Rifabutin (Bimel), rifampin, dexamethasone, rifampicin, erythromycin, propofol, rifabutin	Adverse reactions are reported from rifabutin and erythromycin, which may induce neutropenia and hemolysis with prolonged exposure. In rats, rifabutin induces hepatotoxicity, tumor, and renal impairment to death. Apoptosis, necrosis, and large area of necrosis following intrathecal use of rifabutin. Many of these compounds are poorly absorbed and may be subject to enterohepatic recycling.
Epinephrine	Potentially (particularly local anesthetics)	II	Acetaminophen, Bupivacaine	Limited human data

	Contact herbicide, inhibits photosynthesis inhibits, and/or inhibits carotenoid biosynthesis Atrazine is also an insecticide	U	Atrazine, alachlor, chlorothalopach, oxyfluorfen	
Herbicide glyphosate	Inhibits lipid synthesis	U	Glyphosate, flupropyluron	Limited human data
Isoproturon	Inhibits carotenoid synthesis, interfering with branched amino acid synthesis	U	Isoproturon, metazachlor, metazachlor, metazachlor	Limited human data. In a small case series, isoproturon induced urticaria, respiratory distress, metabolic acidosis, hypotension, and hepatocellular dysfunction
Isoproturon	Nonselective	U	Isoproturon	Nausea, vomiting, diarrhea, metabolic acidosis, kidney failure, hemolysis, methemoglobinemia, rhabdomyolysis, and disseminated intravascular coagulation. In animal studies hemolysis and methemoglobinemia and plasma hemolysis. Methemoglobinemia is usually responsive to methylene blue (a single report suggested benefit when used within 1 hour of exposure ¹⁰) but when thrombocytopenia has been noted
Metolachlor	Phenylalanine, selective for glycine inhibits photosynthesis, a photosynthetic and/or inhibition of cell wall synthesis, synthesis Lampricide (chlorinated with phenylalanine and inorganic)	U U U	Aminocyclopropane Bromoxynil, isoproturon Dichlorodimethyl	Limited human data Limited human data. In animal, it inhibits carotenoid biosynthesis and urticaria (25 toxicity may be prevented by DOP)
Disinfectant Disinfectant	Disinfectant (broad-spectrum)	U	Disinfectant, DMC (4,4-dimethyl-2-oxo-1,3-dioxane)	Limited human data. methemoglobinemia is reported in animal. Disinfectant inhibits carotenoid biosynthesis
Organic phosphorus	Respiratory phosphorus, selective for glycine Glyphosate and glyphosate are nonselective post- emergence herbicides In 2007, glyphosate was the most used pesticide in the United States and the second most used in the domestic sector Glyphosate and glyphosate inhibit photosyn- thesis, biosynthesis, lipid synthesis, and glycine inhibits PEP synthase, which interferes with amino acid synthesis	U U U	Glyphosate, glyphosate (broad-spectrum), alachlor, isoproturon, glyphosate Glyphosate Isoproturon, glyphosate	Limited human data. Glyphosate is metabolized to glyphosate in plants, but in humans only the metabolite 3-amino-4-hydroxyphenyl phosphonic acid has been found. Clinical effects of poisoning include apnea, anemia, and metabolic acidosis. Inhibitors and biosynthesis are known to inhibit amino acid biosynthesis See text for glyphosate and Fig. 13-1 See text for glyphosate and Fig. 13-1. Limited human data for isoproturon

<p>Name</p> <p>Probenecid, sodium salt</p> <p>Commonly substituted with acetaminophen</p> <p>cytate, inhibits uric acid excretion, blocks renal tubular reabsorption</p>	<p>U</p>	<p>Active ingredient</p>	<p>Limited human data on single-agent exposures. Ingestion of 25 mg/kg in a human and > 400 mg/kg in an animal did not induce symptoms</p>
<p>Name</p> <p>inhibits uric acid excretion</p>	<p>U</p>	<p>Probenecid</p>	<p>Limited human data</p>
<p>Substitution</p> <p>inhibits uric acid excretion. New herbicide or other active compound</p>	<p>U</p>	<p>Debutolol, flunitrazepam, venlafaxine</p>	<p>Limited human data. A review is reported from occupational exposures to flunitrazepam</p>

attributed to the surfactant nonylphenol ethoxylate used in this product, which has an LD₅₀ of 75 mg/kg IP. In vitro studies with a number of formulations demonstrate increased cardiovascular toxicity compared with the technical herbicides.¹³ Similarly, coformulants increase the in vitro toxicity from phenoxyacetic acid derivatives and glufosinate.

Impurities may also be generated during manufacture or storage of the herbicide formulation, which can contribute to toxicity. For example, phenolic byproducts from the manufacture of phenoxyacetic acid herbicides may be found as impurities in commercial formulations. Some proprietary products contain a combination of herbicidal compounds that probably have additive effects, further complicating the risk assessment of an acute exposure.

Epidemiology

The incidence of poisoning with individual herbicides depends on their availability. Availability is associated with local marketing practices and is reflected in sales in the domestic sector. For example, paraquat poisonings are now rare in the United States, while the incidence of glyphosate poisoning has increased. Similarly, after paraquat was banned in Japan in the late 1980s there was an increase in the number of glufosinate poisonings.

Herbicide poisoning is a major issue in developing countries of the Asia-Pacific region where subsistence farming is common and herbicide use is relatively high. By contrast, the incidence of severe herbicide poisoning is less in developed countries because the population is concentrated in urban areas where access is limited to lower toxicity herbicides that are sold in smaller volumes as diluted formulations intended for household use (Chaps. 113 and 137).

Regulatory and Considerations

When properly used, most herbicide formulations have a low toxic potential for applicators because they are poorly absorbed across the skin and respiratory membranes. When inappropriately used, in particular when there is enteral (or rarely parenteral) exposure, toxicity is more pronounced.

The toxicity of herbicides varies among individual xenobiotics, but as a group, they appear to be intrinsically more toxic than medications when ingested with suicidal intent. Restrictions of the availability and formulation of toxic herbicides by regulatory authorities may improve outcomes from herbicide poisoning. For example, in the context of self-poisoning, the replacement of highly toxic pesticides with less toxic compounds can decrease the overall mortality⁹⁷ without altering agricultural outputs.⁷² Prospective cohort studies have been useful for estimating the case fatality of individual herbicides in the context of intentional self-poisoning, particularly when encountered in the same clinical environment. For example, in Sri Lanka the following herbicide case fatalities are reported: fenoxaprop-P-ethyl, 0%¹³²; bispyribac, 1.8%³⁰; glyphosate, 3.2%¹⁰⁰; 4-chloro-2-methylphenoxyacetic acid (MCPA), 4.4%⁹⁸; propanil, 10.7%⁹⁹; and paraquat, 50% to 70%.¹²⁸ This information is of interest to regulatory authorities in their control of the marketing, sales, and formulation of herbicides.

Regulatory bodies must also consider other factors, including the cost and efficacy of herbicides and their fate in the environment. An ideal herbicide is one that is selective for the target plant and does not migrate far from the site of application. Selective targeting can occur when the herbicide is rapidly inactivated or binds strongly to soil components. For example, paraquat and glyphosate are inactivated when they contact soil, which is favorable because they remain in the region of application. By contrast, atrazine is more mobile, allowing it to leach into groundwater and migrate great distances. While the concentration of atrazine at distant sites is low, there is concern that it has the potential to alter the growth and development of nontarget plants and animals.¹⁰⁴

GENERAL COMMENTS FOR THE MANAGEMENT OF ACUTE HERBICIDE POISONING

Diagnosis

Herbicide poisoning is diagnosed following a specific history or other evidence of exposure (such as an empty bottle) and associated clinical symptoms. A detailed history, including the type of herbicide, amount, time since poisoning, and symptoms, is essential. It is necessary to determine the actual brand in many cases due to variability in salts, concentrations, and coformulants. Further, in some cases it is also necessary to determine the specific type of a brand; for example, the product called Roundup contains glyphosate but it is sold in different formulations worldwide within market sectors.

Depending on local laboratory resources it may be possible to confirm the diagnosis with a specific assay, such as paraquat and glufosinate, but these are not usually available in a clinically meaningful timeframe.

The low incidence of herbicide poisoning in some regions may mean that it is not considered in the differential diagnosis when a history is not available. Therefore, a high index of suspicion is necessary and clinicians should be familiar with the features of herbicide poisoning.

The pathophysiology of acute herbicide poisoning, and therefore the clinical manifestations, varies between individual compounds. Some herbicides induce multisystem toxicity due to interactions with a number of physiologic systems. The mechanism of toxicity and pathophysiological changes in humans are discussed below for each herbicide individually.

Initial Management

An accurate risk assessment is necessary for the proper triage and subsequent management of patients with acute herbicide poisoning. Risk assessment involves consideration of the dose ingested, time since ingestion, clinical features, patient factors, and availability of medical facilities. All intentional exposures should be considered significant. If a patient presents to a facility that is unable to provide sufficient medical and nursing care or does not have ready access to necessary antidotes, then arrangements should be made to rapidly and safely transport the patient to a health care facility.

For many herbicides the initial management of an acute poisoning follows standard guidelines. All patients should receive prompt resuscitation emphasizing the airway, breathing, and circulation. Gastrointestinal toxicity, such as nausea, vomiting, and diarrhea, is common, leading to salt and water depletion that requires the administration of antiemetics and intravenous fluids.

Gastrointestinal decontamination may decrease absorption of the herbicide from the gut, reducing systemic exposure. Gastric lavage is generally not recommended in acute poisoning because patients usually present too late or have self-decontaminated from vomiting and diarrhea. Lavage has been used by some practitioners for patients presenting shortly after an ingestion of a liquid formulation for which treatment options are limited. Depending on the procedure used, this treatment may cause harm and should only be conducted by an experienced clinician when the airway is protected. Ingestion of a corrosive product is a relative contraindication. Oral activated charcoal may be given if the patient presents within 1 to 2 hours of ingestion of an herbicide known to cause significant poisoning. In the case of some herbicides there is prolonged absorption (eg, propanil, MCPA), so later administration of activated charcoal may be reasonable.

Specific antidotes are available for only a few herbicides, which reflect their ill defined mechanisms of toxicity.

Extracorporeal techniques, including hemoperfusion and hemodialysis, may decrease the systemic exposure by increasing the rate of elimination. The role of these treatments is discussed below for each pesticide.

Dermal decontamination is necessary if the patient has incurred cutaneous exposure. The patient should be washed with soap and water and contaminated clothes, shoes, and leather materials should be removed and safely discarded.

Laboratory investigations may be useful for determining the evolution of organ toxicity, including serial measurement of liver and kidney function, electrolytes, and acid–base status. Abnormalities should be corrected where possible. Respiratory distress and hypoxia with focal respiratory crackles soon after presentation are likely to result from aspiration pneumonitis, which can be confirmed on chest radiography.

Patients with a history of acute ingestion should be observed for a minimum of 6 hours. Patients with a history of intentional ingestion and gastrointestinal symptoms should be observed for at least 24 hours depending on the herbicide given that clinical toxicity may progress or be delayed in some cases.

Occupational and Secondary Exposures (Including Nosocomial Poisoning)

Concern has been expressed regarding the risk of nosocomial poisoning to staff and family members who are exposed to patients with acute herbicide poisoning. However, the risk to health care staff providing clinical care is low compared with other occupations, such as agricultural workers in whom toxicity is rarely observed. Universal precautions employing nitrile gloves are most likely to provide sufficient protection for staff members.

Few cases of secondary poisoning, if any, have been confirmed, and effects in these potentially exposed individuals were generally mild, such as nausea, dizziness, weakness, and headaches, probably relating to inhalation of the hydrocarbon solvent. These symptoms usually resolve after exposure to fresh air. Biomarkers for monitoring occupational exposures, as in the case of pesticide applicators, are outside the scope of this chapter.

Amide Compounds, Particularly Anilide Derivatives

Anilide compounds are the most widely used amide herbicides, of which propanil (3'4'-dichloropropionanilide {DCPA}), alachlor (2-chloro-2',6'-diethyl-N-methoxymethylacetanilide), and butachlor (N-butoxymethyl-2-chloro-2',6'-diethylacetanilide) are particularly common. Other amide herbicides and available toxicity data are listed in [Table 112–1](#). In 2007, acetochlor, propanil, metolachlor, and dimethenamid were among the top herbicides used in the United States.³³ Anilide compounds are selective herbicides used mostly in rice cultivation in many parts of the world. Acute self-poisoning is reported particularly in Asia where subsistence farming is common. Data are limited for most compounds, except for propanil, butachlor, metachlor, and alachlor. The case fatality of propanil exceeds 10% compared with a combined mortality of less than 3% for butachlor, metachlor, and alachlor. Poor outcomes may reflect the inadequacies of current treatment regimens.

Pharmacology

Most of the clinical manifestations of propanil poisoning are mediated by its metabolites. 3,4-Dichlorophenylhydroxylamine is the most toxic metabolite and it directly induces methemoglobinemia and hemolysis in a dose-related manner. 3,4-Dichlorophenylhydroxylamine is cooxidized with oxyhemoglobin (Fe^{2+}) in erythrocytes to produce methemoglobin (Fe^{3+} ; Chap. 127).

However, toxicity may not be solely attributed to methemoglobinemia. Isolated methemoglobin levels exceeding 50% are usually required for fatal outcomes, but fatal propanil poisoning is reported with methemoglobin levels as low as 40%.^{17,86,129,130} Therefore, other toxic mechanisms may contribute to clinical outcomes. Rats show signs of toxicity despite inhibition of the hydrolytic enzymes that metabolize propanil (Fig. 112–1) and in the absence of methemoglobinemia, supporting direct toxicity from propanil itself.¹¹⁵ Coformulants may also contribute.

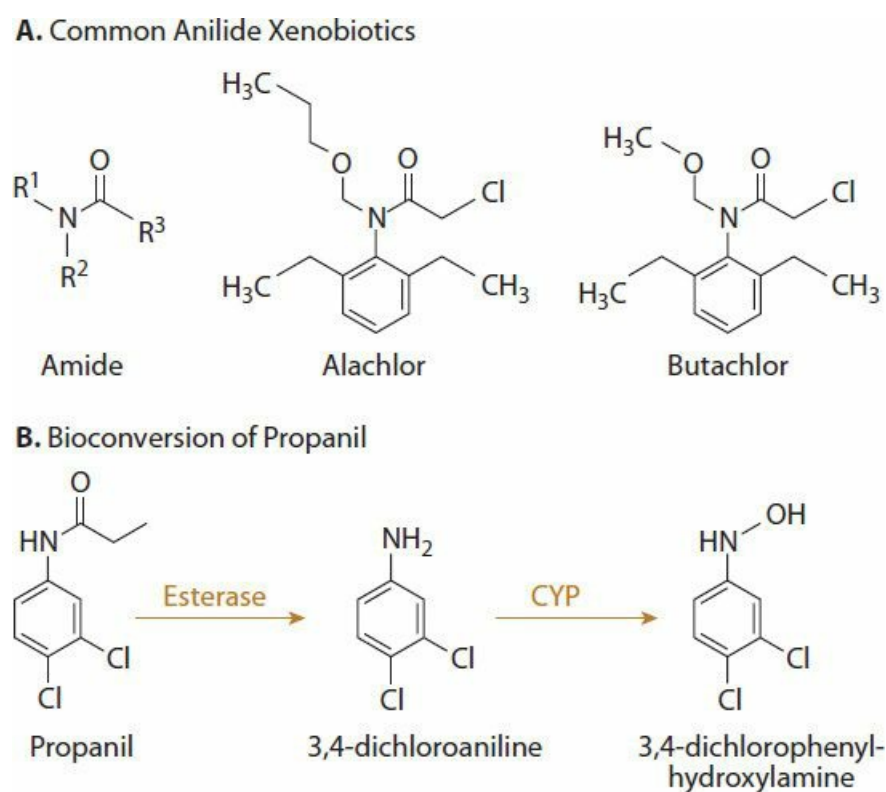


FIGURE 112–1 Structures of common anilide compounds and the bioconversion of propanil.

The hydroxylamine metabolite depletes glutathione, which may induce toxicity, although this is not consistently reported. Other possible toxicities from the metabolism of propanil include nephrotoxicity, lipoperoxidation, myelotoxicity, and immune dysfunction; the significance of these toxicities is poorly defined.

Para-hydroxylated aniline and other compounds are products of alachlor, butachlor, and acetochlor (2-chloro-N-ethoxymethyl-6'-ethylacet-o-toluidide) metabolism and may reduce glutathione and induce hepatotoxicity or cancer, particularly in rats.

Pharmacokinetics and Toxicokinetics

Absorption is rapid in animals, with a peak serum concentration expected one hour postingestion. The volume of distribution (V_d) of propanil has not been determined, but is expected to be large given that both propanil and 3,4-dichloroaniline are highly lipid soluble. This V_d is consistent with data in the channel catfish where uptake and distribution of propanil were noted to be extensive. Anilide compounds interact with adenosine triphosphate (ATP)-binding cassette transporters, which may also influence the kinetics.

Anilide compounds undergo sequential metabolic reactions that produce toxic xenobiotics (Fig. 112–1). The first reaction is hydrolysis of the anilide to an aniline compound. This reaction is catalyzed by an esterase known as arylamidase, which has a high capacity in humans compared to rats ($K_m = 473 \mu\text{M}$ and $271 \mu\text{M}$, respectively) and sometimes by the cytochrome P450 system. Examples include the bioconversion of propanil to 3,4-dichloroaniline and also conversion of alachlor and butachlor to 2,6-diethylaniline. These aniline intermediates are then oxidized by cytochrome P450, although the responsible isoenzyme has not been determined. N-hydroxylation of 3,4-dichloroaniline produces the hydroxylamine compound that induces hemolysis and methemoglobinemia, which are the most obvious manifestations of propanil poisoning.^{76,77,115}

These bioactivation reactions appear to be fairly rapid, whereas 3,4-dichloroaniline and methemoglobin are formed

within 2 to 3 hours of parenteral administration of propanil to animals. The hydroxylation of 3,4-dichloroaniline may be saturable ($K_m = 120 \mu\text{M}$ in rats) and slower than arylamidase, leading to a prolonged elimination of 3,4-dichloroaniline following large exposures. In the case of alachlor, butachlor, and acetochlor, parahydroxylated aniline compounds are produced, which appear to be carcinogens in rats.

These metabolic reactions are similar to those of dapsone, which are well characterized: the severity of methemoglobinemia relates to the amount of the dapsone hydroxylamine, which varies with dose, and cytochrome P450 activity ([Chap. 127](#)).

Propanil displays nonlinear toxicokinetics in humans with prolonged absorption continuing for approximately 10 hours following ingestion. Bioconversion to 3,4-dichloroaniline occurs largely within 6 hours, although it is particularly variable, which may reflect interindividual differences in esterase activity, dose, or coexposure to cholinesterase inhibitors.⁹⁹ The median apparent elimination half-life of propanil is 3.2 hours compared with 3,4-dichloroaniline, which has a highly variable elimination profile. In general, the concentration of 3,4-dichloroaniline exceeds that of propanil and remains elevated for a longer period.⁹⁹ In a case of coingestion of carbaryl, the peak 3,4-dichloroaniline concentration was observed at 24 hours,⁴² while in a fatal case the concentration of 3,4-dichloroaniline continued to increase until at least 30 hours postingestion.⁹⁹ By 36 hours postingestion the concentration of 3,4-dichloroaniline is low in survivors, so clinical toxicity is unlikely to increase beyond this time.⁹⁹

Pathophysiology

The predominant clinical manifestation in acute poisoning is methemoglobinemia. Methemoglobin is unable to bind and transport oxygen, inducing a relative hypoxia at the cellular level despite adequate arterial oxygenation. This leads to end-organ dysfunction, including central nervous system depression, hypotension, and acidemia. Because the plasma concentration of 3,4-dichloroaniline remains elevated, methemoglobinemia persists for a similar time.^{42,86,129} Sedation due to the direct effect of propanil or a hydrocarbon coformulant solvent may cause hypoventilation, which contributes to cellular hypoxia. Failure to correct these abnormalities may lead to irreversible injury and death.

Clinical Manifestations

Methemoglobinemia, hemolysis and anemia, coma, and death are reported following acute propanil poisoning. These occur in the clinical context of cyanosis, acidemia, and progressive end-organ dysfunction. A case fatality as high as 10.7% is reported and the median time to death was 36 hours. Patients who die tend to be older with a depressed Glasgow Coma Scale score and elevated concentration of propanil. Nausea, vomiting, diarrhea, tachycardia, dizziness, and confusion are also reported in patients who do not develop severe poisoning.⁹⁹

Alachlor, metachlor, and butachlor appear to be less toxic than propanil, with a case fatality less than 3% with self-poisoning.^{71,112} The manifestations of acute poisoning are usually mild, including gastrointestinal symptoms, agitation, dyspnea, and abnormal liver enzymes.^{71,112} Major symptoms include seizures, rhabdomyolysis, acidemia, kidney failure, and cardiac dysrhythmias; hypotension and coma preceded death.^{71,112} Methemoglobinemia was not reported in these studies. Hepatic dysfunction was reported following dermal occupational exposure to butachlor.

Cyanosis was reported following acute ingestion of mefenacet (2-benzothiazol-2-yloxy-N-methylacetanilide) and imazosulfuron (1-{2-chloroimidazo(1,2-a) pyridin-3-ylsulfonyl}-3-{4,6-dimethoxypyrimidin-2-yl}urea) in the context of normal cooximetry. This was attributed to formation of a green pigment (green-colored urine was also reported) and no other symptoms of toxicity were observed.¹¹⁴

Acute metolachlor (2-chloro-N-{6-ethyl-o-tolyl}-N-{(1RS)-2-methoxy-1-methylethyl}acetamide) poisoning in goats induced predominantly neuromuscular symptoms, including tremors, ataxia, and myoclonus, which progressed rapidly to death. Kidney and hepatocellular toxicity were also noted. Acute acetochlor exposures in rats induced methemoglobinemia and hepatocellular toxicity.

Diagnostic Testing

Patients with a history of propanil poisoning should be investigated for the presence of methemoglobinemia ([Chap. 127](#)).

While the concentrations of propanil and 3,4-dichloroaniline appear to reflect clinical outcomes, this relationship is less marked for 3,4-dichloroaniline during the first 6 hours, which probably relates to the time for bioconversion from propanil.⁹⁹ However, propanil and 3,4-dichloroaniline assays are not commercially available and this observation has not been validated. Further, the relationship between concentration and outcomes may depend on patient comorbidities.

Management

The minimum toxic dose has not been determined and the potential for severe poisoning and death is high, so all patients with herbicide ingestions should be treated as significant and monitored for a minimum of 12 hours. Patients with

symptomatic ingestions should be treated cautiously, including continuous monitoring for 24 to 48 hours, preferably in an intensive care unit.

Routine clinical observations are sufficient to detect signs of poisoning, in particular, sedation and clinical cyanosis. Until more data are available it seems reasonable to focus treatment on reversal of methemoglobinemia. There is sufficient time to initiate specific treatments in propanil poisoning given that clinical signs of poisoning are noted early postingestion, yet the time to death is usually greater than 24 hours. There are no controlled clinical or laboratory data available on the effect of any specific treatment in acute symptomatic propanil poisoning, so management is largely empirical.

Resuscitation and Supportive Care. Prompt resuscitation and close observation are required in all patients. Patients should be monitored clinically including pulse oximetry, and receive supportive care including supplemental oxygen, intravenous fluids, and ventilatory and hemodynamic support as required. In the absence of cooximetry analysis, significant methemoglobinemia should be suspected when cyanosis does not correct with high-flow oxygen and ventilatory support. Bedside visual assessment, using blood added to absorbent paper, is an accurate method to quantify the degree of methemoglobinemia¹¹³ Euglycemia should be ensured since adequate glucose concentrations are required for reversal of methemoglobin

Hemoglobin concentrations should be monitored to detect hemolysis, and folate supplementation may be necessary during the recovery phase if anemia is significant.

Gastrointestinal Decontamination. Toxicokinetic studies of propanil have demonstrated a prolonged absorption phase, so it is reasonable to administer activated charcoal to the patient a number of hours postingestion

Extracorporeal Removal. Treatment with combined hemodialysis and hemoperfusion was associated with a propanil elimination half-life of one hour, although clearance was not directly measured⁸⁶ However, half-lives as short as one hour have been reported in patients who have not received this treatment⁹⁹ so its efficacy remains unknown. Exchange transfusion has the potential to decrease the concentration of propanil and free hemoglobin, while replacing reduced hemoglobin and hemolyzed erythrocytes. However, the function of transfused erythrocytes is temporarily impaired posttransfusion because of depletion of 2,3-bisphosphoglycerate during storage. Further, transfusion reactions such as acute respiratory distress syndrome may occur, which is of concern when oxygenation is already impaired. In the absence of controlled studies, the role of such treatments in the routine management of acute propanil poisoning is poorly defined (Chap. 10).

Antidotes. Antidotes are largely used for the treatment of methemoglobinemia. Methylene blue (Antidotes in Depth: A41) is considered the first-line treatment for methemoglobinemia. Methylene blue has a half-life of 5 hours, which is commonly shorter than that of 3,4-dichloroaniline, so rebound poisoning (ie, an increase in methemoglobin following an initial recovery postadministration of methylene blue) is anticipated and has been observed with a bolus regimen. This may be prevented by administration of methylene blue as a constant infusion

Other potential treatments include toluidine blue, N-acetylcysteine, ascorbic acid, and cimetidine, but no clinical studies have assessed the role of these potential antidotes in the management of propanil poisoning.

BIPYRIDYL COMPOUNDS, PARAQUAT AND DIQUAT

Bipyridyl compounds are nonselective contact herbicides. The most widely used is paraquat (1,1'-dimethyl-4,4'-bipyridinium), but diquat (1,1'-ethylene-2,2'-bipyridylium) is also commonly used (Fig. 112-2). Paraquat is one of the most toxic pesticides available. Ingestion of as little as 10 to 20 mL of the 20% wt/vol solution is sufficient to cause death. Overall, the mortality rate varies between 50% and 90%; however, in cases of intentional self-poisoning with concentrated formulations, mortality approaches 100%. An increasing number of countries are banning the sale of paraquat in view of its high toxicity. Diquat is less toxic than paraquat, so it may be coformulated with paraquat (allowing a lower concentration of paraquat) or used as an alternative in countries where paraquat is severely restricted. Because more data are available on paraquat than diquat, much of the following discussion and information relates particularly to paraquat.

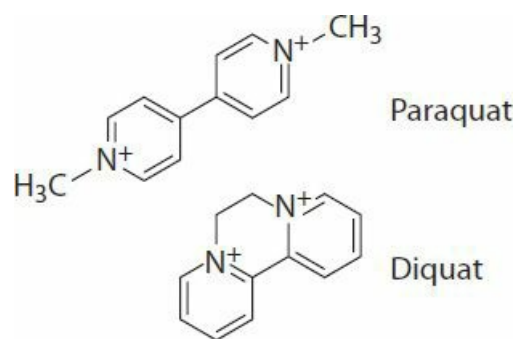


FIGURE 112-2 Structures of paraquat and diquat.

Pharmacology

Paraquat and diquat formulations are highly irritating and often corrosive, causing direct injury. Paraquat induces intracellular toxicity by the generation of reactive oxygen species that nonspecifically damage the lipid membrane of cells, inducing cellular injury and death. Once paraquat enters the intracellular space it is oxidized to the paraquat radical. This radical is subsequently reduced by diaphorase in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) to re-form the parent paraquat compound and superoxide radical, a reactive oxygen species. This process is known as redox cycling (Fig. 112–3). The superoxide radical is susceptible to further reactions by other intracellular processes, leading to formation of other reactive oxygen species, including hydroxyl radicals and peroxynitrite. Reactive oxygen species are potent cytotoxics. Paraquat redox cycling continues as long as NADPH and oxygen are available. Depletion of NADPH prevents recycling of glutathione and interferes with other intracellular processes, including energy production and active transporters, exacerbating toxicity. Intracellular protective mechanisms, such as glutathione, superoxide dismutase, and catalase, are overwhelmed or depleted following large exposures. Taken together, these cytotoxic reactions induce cellular necrosis, which is followed by an influx of neutrophils and macrophages. The reactions contribute to the inflammatory response and promote fibrosis and destruction of normal tissue architecture over a number of days.^{18,22}

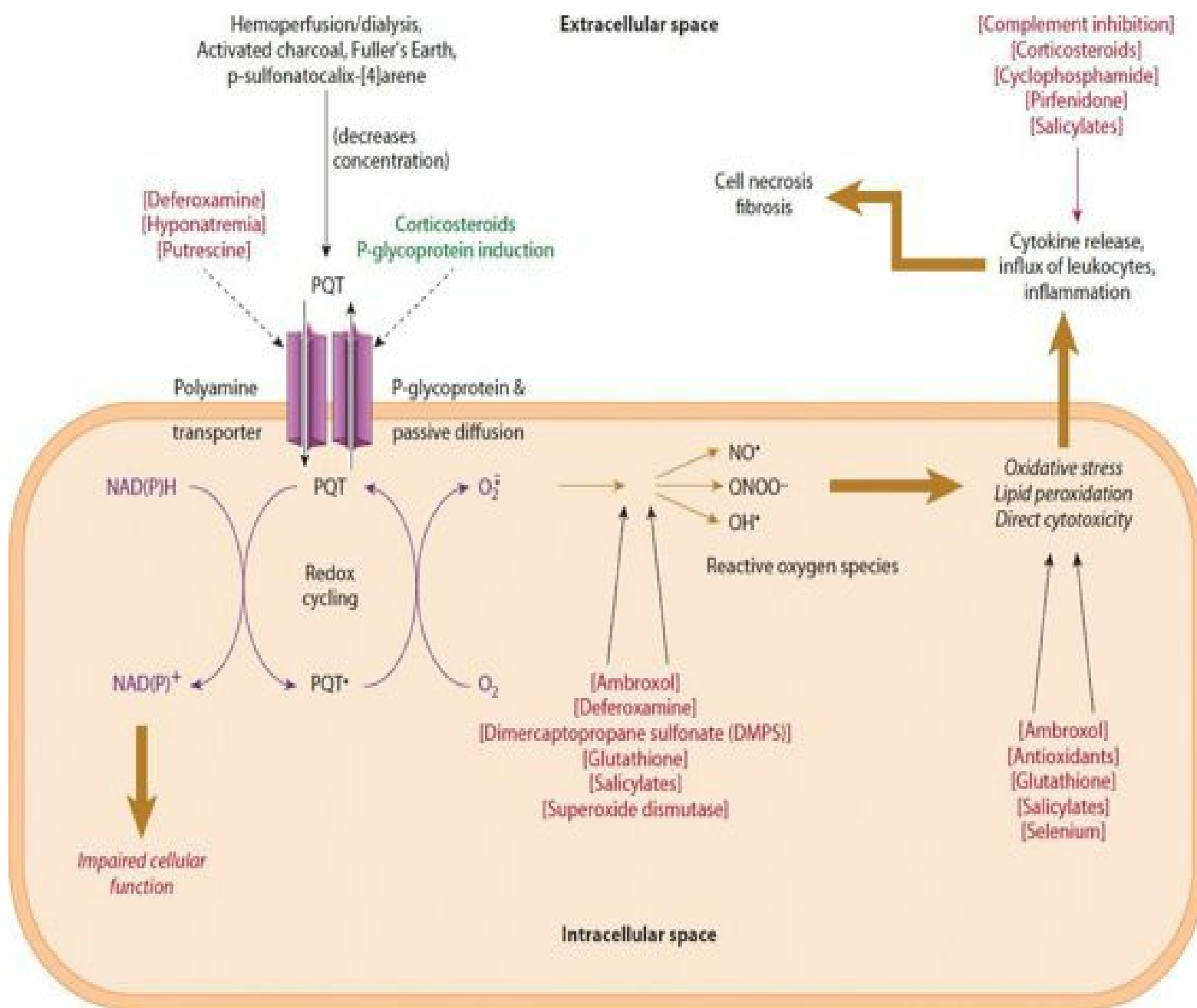


FIGURE 112–3 Toxicology of paraquat (PQT) and proposed mechanisms of action of potential treatments. Antioxidants include vitamins C and E and glutathione donors (particularly N-acetylcysteine, S-carboxymethylcysteine). PQT• = paraquat radical; NO• = nitric oxide; ONOO• = peroxynitrite; OH• = hydroxyl radical.

Supplemental oxygen probably increases the generation of reactive oxygen species.

Pharmacokinetics and Toxicokinetics

Absorption is limited following dermal exposures, although prolonged exposures (at least several hours) to concentrated formulations may degrade the epithelial barrier, allowing some systemic absorption. Absorption across the respiratory epithelium is limited.

The oral bioavailability of paraquat varies among animal species, but overall it is low (< 10%). The bioavailability of paraquat in humans is estimated to be less than 5%,¹⁶ yet an oral exposure of as little as 10 mL of the 20% wt/vol formulation allows sufficient paraquat to be absorbed for significant poisoning to occur. Absorption is rapid and the peak concentration occurs within one hour. Coingestion of food may decrease the absorption of paraquat. Recently, paraquat was reformulated with an increased emetic along with an alginate (Gramoxone Inteon) that formed a gelatinous mixture on contact with gastric acid, limiting release of the paraquat into the stomach. This formulation reduced paraquat absorption in animals³⁷ and initially appeared to improve outcomes from self-poisoning in humans (mortality of 64% compared with 74% with the standard preparation),¹²⁶ but it may not have been sustained.¹²⁸

Paraquat binds minimally to plasma proteins. Paraquat and diquat rapidly distribute to all tissues where they accumulate but may redistribute back to the central circulation.⁸⁴ In humans the distribution half-life is approximately 5 hours. Paraquat is taken up by alveolar cells through an active energy-dependent polyamine transporter. Paraquat accumulates in alveolar cells, peaking at around 6 hours postingestion in patients with normal kidney function; this may be delayed in the context of kidney impairment.⁵ Paraquat slowly redistributes from the lungs into the systemic circulation as the plasma concentration falls, which may reflect impaired pneumocyte function from acute respiratory distress syndrome. By contrast, diquat uptake occurs to a limited extent.

Paraquat and diquat are not metabolized and elimination is primarily renal with more than 90% of a dose being excreted within the first 24 hours of poisoning if kidney function is maintained.⁴⁵ Its clearance initially exceeds that of creatinine because of active secretion and also through increased renal blood flow.¹² Renal clearance may be reduced by exogenous compounds or an acidic urine pH.¹² Impaired kidney function is commonly reported with paraquat and diquat poisoning, which decreases excretion and potentiates poisoning. Elimination is prolonged in this setting with a terminal half-life of around 80 hours in humans.⁴⁵ Paraquat is detected in the urine of surviving patients beyond 30 days despite plasma concentrations being quite low 48 hours postingestion.³ In animals, the terminal elimination half-life of paraquat is more than 50 hours.⁸⁴

Pathophysiology

Paraquat induces nonspecific cellular necrosis. Lung and kidney injuries are prominent in acute paraquat poisoning because of the high concentrations found in these cells.

Acute pneumonitis and hemorrhage, followed by ongoing inflammation and progressive pulmonary fibrosis, reduces oxygen diffusion and induces dyspnea and hypoxia, which interferes with normal cellular function.²²

Paraquat induces acute tubular necrosis due to direct toxicity to the proximal tubule in particular, and to a lesser degree distal structures. Other factors contributing to the development of acute kidney injury include hypoperfusion from hypovolemia and/or hypotension and direct glomerular injury. Varying degrees of oliguria, proteinuria, hematuria, and glycosuria are reported.¹² Acute kidney impairment interferes with normal fluid and electrolyte homeostasis, as well as interfering with paraquat elimination, which promotes systemic toxicity.

Necrosis of the gastrointestinal tract limits intake and causes fluid shifts that contribute to hypotension induced by direct vascular toxicity. Hypotension impairs tissue perfusion and if uncorrected progresses to irreversible shock. Failure to correct these abnormalities may lead to irreversible organ injury and death.

Clinical Manifestations

Topical exposures may induce painful irritation to the eyes and skin, progressing to ulceration or desquamation depending on the concentration of the solution, duration of exposure, and adequacy of decontamination. Intravenous administration induces severe poisoning from small exposures.

Most ingestions of bipyridyl compounds induce poisoning, where ingestion of as little as 5 mL of paraquat 20% wt/vol can cause death in more than 50% of cases. Gastrointestinal toxicity occurs early, including nausea, vomiting, and abdominal and oral pain. Diarrhea, ileus, and pancreatitis are also reported. Necrosis of mucous membranes (occasionally referred to as pseudodiphtheria¹¹⁷) and ulceration are prominent symptoms that occur within 12 hours. Oromucosal injury has been observed following brief oral exposures without swallowing. Dysphagia and odynophagia follow larger exposures and may progress to esophageal rupture, mediastinitis, subcutaneous emphysema, and pneumothorax, which are preterminal events. Death is more likely in those patients who experience a peripheral burning sensation.²⁹

Respiratory symptoms are prominent in paraquat poisoning, including acute respiratory distress syndrome manifesting as dyspnea, hypoxia, and increased work of breathing. Ingestions of greater than 50 mL of 20% wt/vol formulation causes multiorgan dysfunction with rapid onset of death within days of ingestion in most patients. Features include hypotension,

acute kidney and liver injury, severe diarrhea, and hemolytic anemia.

By contrast, acute lung injury is less marked with diquat ingestion or following smaller exposures of paraquat (< 15–20 mL of 20% wt/vol formulations). In the case of paraquat the acute respiratory impairment may be followed by progressive pulmonary fibrosis and death weeks or months postingestion. Varying degrees of acute kidney injury and hepatic dysfunction can also occur.^{6,48} Acute kidney injury peaks around 5 days postingestion and resolves within 3 weeks in survivors.⁵⁴ Paraquat-induced pulmonary injury can resolve to near-normal function over months to years in survivors.⁶⁶

Diquat does not concentrate in the pneumocytes as readily as paraquat. Therefore, if the patient survives the multiorgan dysfunction, pulmonary fibrosis is less likely to occur.¹³¹ Seizures are reported with diquat poisoning and uncommonly with paraquat.

Ingestion of the adjuvant for Gramoxone Inteon can induce minor gastrointestinal symptoms, an elevated serum osmolar gap and metabolic acidosis with hyperlactatemia, but outcomes are favorable.⁸⁰

Diagnostic Testing

Paraquat poisoning is diagnosed when there is a history of exposure and the clinical symptoms, so a high index of clinical suspicion is required. Differential diagnoses include other corrosive exposures, sepsis, or other cellular poisons such as phosphine, colchicine, or iron.

The presence of a bipyridyl compound in blood confirms exposure but availability of these assays is increasingly limited. The urinary dithionite test is a simple and quick method for confirming (or excluding) paraquat and diquat poisoning. Various methods are reported, including the addition of 1 g of sodium bicarbonate and 1 g of sodium dithionite, or 1 to 2 mL of 1% sodium dithionite in 1 to 2 M sodium hydroxide, to 10 mL of urine. A color change (blue for paraquat and green for diquat) confirms ingestion—the darker the color, the higher the concentration.^{3,58,103} If the test is negative on urine beyond 6 hours after ingestion, a large exposure is unlikely, but repeat testing should be conducted over 24 hours. The dithionite test can also be conducted on plasma (eg, add 200 μ L of 1% sodium dithionite in 2 M sodium hydroxide to 2 mL plasma from the patient), whereas a positive result is specific for death, but a negative test does not exclude severe poisoning or death.⁵⁸

Given that outcomes from paraquat poisoning are generally poor, diagnostic tests may help differentiate patients who may survive from those in whom death is almost certain. The dose of paraquat is a well-established predictor of death, although this information may not be accurately known at the time of admission. Investigations in patients with acute paraquat poisoning have attempted to determine the severity of poisoning and better define prognosis. Unfortunately, few have been validated so their predictive ability is unconfirmed. A range of prognostic tests has been reviewed²⁴ and a selection of these are discussed below.

Quantitative analysis of the concentration of paraquat in plasma is useful for prognostication, and a number of similar nomograms have been developed to assist with this process (Fig. 112–4). The paraquat concentration must be interpreted relative to the time since ingestion and each method performs similarly.¹¹⁰ The Severity Index of Paraquat Poisoning (SIPP) can also be calculated with this information, by multiplying the plasma concentration (mg/L) by the time since ingestion (hours). Here, SIPP less than 10 predicts survival, SIPP 10 to 50 predicts death from lung fibrosis, and SIPP more than 50 predicts death from circulatory failure.¹⁰⁷ Determination of the concentration of paraquat in the urine of exposed patients also predicts outcomes. Barriers to the use of these methods include the limited availability of quantitative paraquat assays (leading to a long turnaround time) and the accuracy of the time of ingestion.

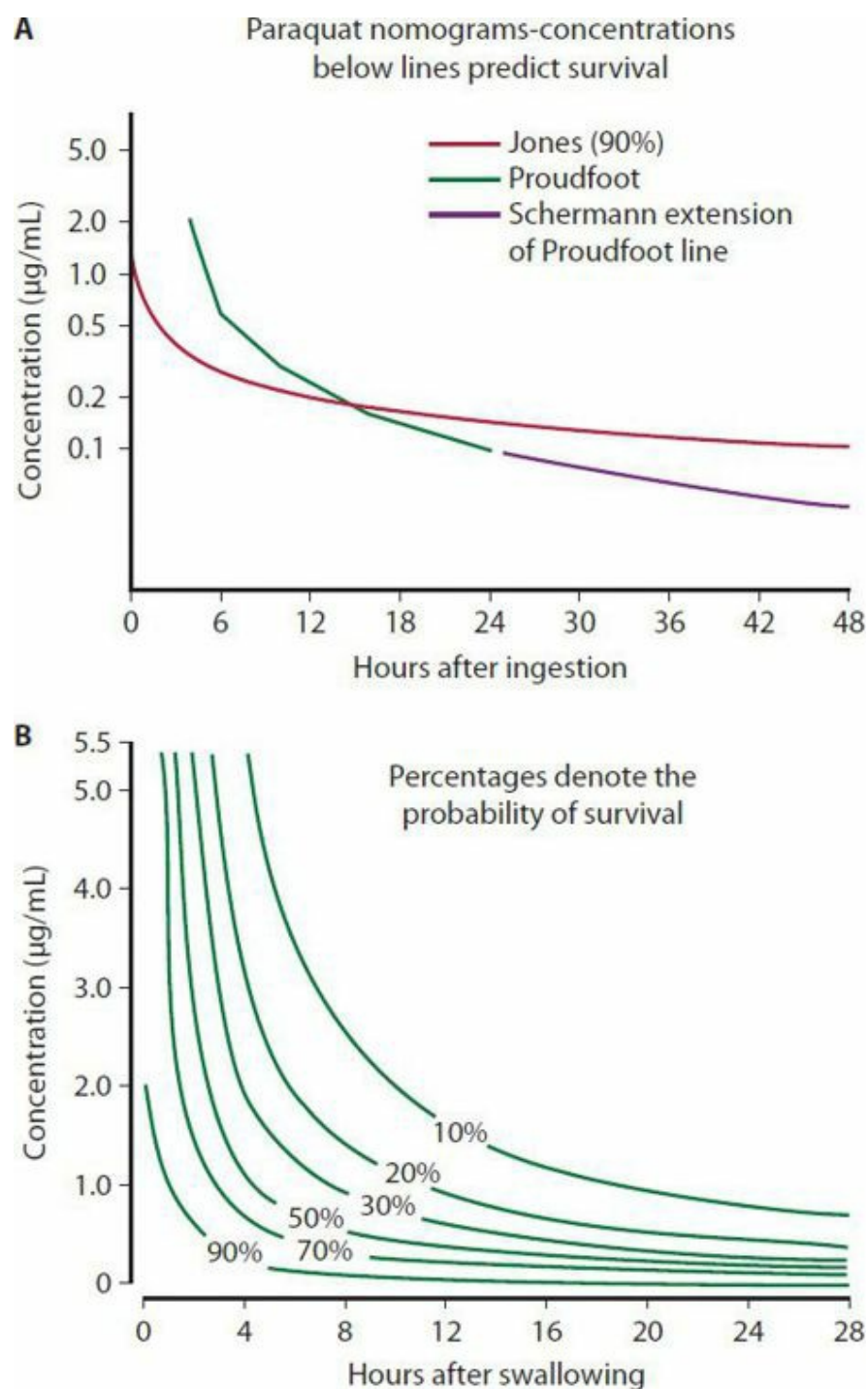


FIGURE 112-4 Nomograms for plasma paraquat concentrations. (A) Compilation of three nomograms proposed by Proudfoot et al,⁹⁴ Scherrmann et al,¹⁰⁸ and Jones et al.⁵² (B) Hart paraquat nomogram.³⁶ In A, concentrations below lines predict survival. In B, lines link concentrations of equal probability of survival. (Reproduced with permission from Eddleston M, Wilks MF, Buckley NA. Prospects for treatment of paraquat-induced lung fibrosis with immunosuppressive drugs and the need for better prediction of outcome: a systematic review, *QJM* 2003;96(11):809–824.)

Other methods for predicting outcomes from paraquat poisoning have used combinations of simple laboratory tests including blood gas analysis, complete blood count, electrolytes, kidney function, and liver function tests.²⁴ Various specific changes have been proposed to predict death (eg, metabolic acidosis with hyperlactatemia), but few have been validated. In general, any abnormal result raises the suspicion of a significant poisoning.

A raised admission creatinine concentration predicts death but is neither sensitive nor specific, although the higher the creatinine concentration, the higher the risk of death.^{31,54,58,102}

The rate of increase in creatinine concentration is a simple and practical test to predict prognosis. An increase less than 0.03 mg/dL/h (3 $\mu\text{mol/L/h}$) over 5 hours predicts survival,⁹⁵ or greater than 0.05 mg/dL/h (4.3 $\mu\text{mol/L/h}$) over 12 hours (sensitivity 100%, specificity 85%, likelihood ratio 7) predicts death.¹⁰² A similar relationship was noted for cystatin C, where a rate of increase in cystatin C greater than 0.009 mg/L/h over 6 hours (sensitivity 100%, specificity 91%, likelihood ratio 11) predicted death.¹⁰² This method of prognostication is advantageous because the rate of increase can be determined irrespective of the time of poisoning. Paraquat and diquat interfere with creatinine assays using the Jaffe method, but this is mostly an issue with concentrations exceeding 100 mg/L, which are rarely observed and likely to be associated with severe

clinical toxicity.⁹²

Other biomarkers of kidney function have been explored but their role in clinical management is not confirmed nor did they improve on existing methods.

Management

Because death can occur following ingestion of as little as 5 mL of the 20% wt/vol paraquat, all exposures should be treated as potentially life threatening. Patients suspected of ingesting paraquat should be observed in hospital for at least 6 hours postingestion or until a urinary dithionite test can be conducted.

Many medical interventions have been proposed for the treatment of patients with acute paraquat poisoning but data supporting their efficacy are lacking; dose–response studies for most of these interventions are also unavailable.

Given the high likelihood of death from acute paraquat poisoning, many publications report concurrent administration of a number of therapies in the hope of a benefit, including activated charcoal, acetylcysteine, vitamins C and E, immunosuppressants, and hemodialysis and/or hemoperfusion. The literature is complicated by case reports describing survival in patients who were administered one or a combination of therapies, despite apparently poor prognosis. Various other treatments have been studied in animals including pirfenidone, complement inhibition, p-sulfonatocalix-[4]arene, dimercaptopropane sulfonate, ambroxol, and selenium, but human data are lacking.

The choice of which interventions should be administered to a patient is best made on a case-by-case basis by the treating physician in consultation with relevant resources. Detailed discussion with the patient and relatives early in the presentation is recommended to determine their preference for treatment modalities in the context of the estimated prognosis (see above). In general, a comprehensive treatment regimen is reasonable in patients who present very early (within 2 hours of poisoning) or those with a faintly positive dithionite urinary test. Treatments that reduce the exposure to paraquat by either reducing absorption or increasing clearance must be initiated promptly. In contrast, active treatment seems unlikely to be of assistance to patients in whom this test is strongly positive, or those with evolving multiorgan dysfunction. Instead, palliation should be the priority, including oxygen for hypoxia and morphine for dyspnea and oropharyngeal and abdominal pain.

Serial pulse oximetry measurements and chest radiographs will demonstrate development and progression of lung injury. Lung transplantation has been tried in patients with delayed respiratory failure, but it was largely unsuccessful because of the prolonged elimination half-life of paraquat.⁶ Patients developing acute kidney injury should receive hemodialysis or hemofiltration per usual guidelines if active treatment is to be pursued, and these treatments may also enhance elimination of herbicide if commenced promptly (see below).

Resuscitation and Supportive Care. All patients should receive prompt routine resuscitation and close observation. Oxygen should be administered to patients for palliation only when there is confirmed hypoxia and/or prognosis is extremely poor. Although controlled hypoxia does not prevent the development of pulmonary injury, unnecessary supplemental oxygen can theoretically hasten the progression of injury. Intravenous fluids should be administered to patients who are volume depleted from poor intake, diarrhea, or third-space shifts, as this may reduce the extent of acute kidney injury and promote renal clearance of paraquat. Care is required with volume resuscitation in the context of acute kidney injury to prevent fluid overload. Electrolyte abnormalities may also occur and these should be corrected as required.

Ongoing management includes regular clinical observations including urine output quantification, daily routine laboratory tests (or more frequently if clinically indicated) in patients receiving active treatment and supportive care. Analgesia for oral and abdominal pain should be administered as required, including intravenous opioids, such as morphine, and possibly topical anesthetics, such as lidocaine. Plain radiographs or a CT of the chest can provide information on lung and esophageal injury.

Gastrointestinal Decontamination. Paraquat is coformulated with an emetic so self-decontamination may have occurred by the time of presentation to hospital. Fuller's Earth and activated charcoal have been advocated to decrease absorption of paraquat. Both adsorb paraquat to a similar extent but Fuller's Earth is of limited supply.⁴ However, paraquat is rapidly absorbed so decontamination should be commenced within a few hours of ingestion. Gastric lavage has not been shown to improve outcomes and may even be harmful if administered to patients ingesting less than 30 mL.¹²⁷

Extracorporeal Removal. Extracorporeal techniques, including charcoal hemoperfusion, plasmapheresis, and hemodialysis/filtration, have been studied to decrease the systemic exposure by increasing the rate of elimination. Paraquat clearance by hemoperfusion is similar to endogenous clearance but exceeds it when there is impaired kidney function.^{53,67} Hemoperfusion is more efficient than hemodialysis, and clearance is maximized when treatment is initiated within the first couple of hours because the plasma concentration is high.³⁹ Further, given that paraquat rapidly distributes from the circulation, prompt treatment is necessary to limit the uptake into pulmonary and other tissues.⁸⁹

Experimentally, hemoperfusion reduces mortality in dogs only when it is commenced within a few hours of poisoning, and repeated treatments did not increase clearance to a large extent.⁸⁹ Other animal studies have suggested benefits from hemoperfusion when performed within one hour, including a decrease in paraquat exposure, less end-organ damage and a

reduction in inflammatory cytokines, but no mortality benefit.

Past experience suggested that extracorporeal treatments do not sufficiently improve mortality in humans, particularly when the concentration is greater than 3 mg/L.³⁵ Hemoperfusion followed by continuous venovenous hemofiltration may prolong the time to death compared with hemoperfusion alone without changing the overall mortality in a randomized, controlled trial. All patients in this study also received high-dose dexamethasone and ascorbic acid.⁵⁷ However, increasing publications from eastern Asia suggest a clinical benefit from these therapies if commenced early but confirmatory data would be of interest.

Extracorporeal techniques may also induce harm because of the requirement for central venous access, metabolic disequilibrium, or increased clearance of antidotes. Therefore, their use requires careful consideration on a case-by-case basis.

Antidotes. A large number of potential antidotes have been studied in the treatment of acute paraquat poisoning. They attempt to counteract the effects of paraquat by targeting various steps in the pathogenesis of organ dysfunction or to alter cellular uptake (Fig. 112–3). Unfortunately, none of these antidotes are proven to reduce mortality. Some of the interventions that decrease paraquat exposure by decreasing absorption¹²⁶ or increasing elimination⁵⁷ were shown to prolong the time to death. Therefore, combining these treatments with effective antidotes in a multimodal approach to treatment may reduce mortality. The combination (if any) that will improve outcomes is not known, more research is required to determine the role of the various proposed antidotes in routine clinical care.

Immunosuppression with corticosteroids (dexamethasone or methylprednisolone) and cyclophosphamide are the most extensively studied antidotes in humans. Early randomized controlled trial data (three trials, n = 164 patients) suggested a benefit from these treatments but due to limitations in study design these results were not considered conclusive.⁶⁸ This was followed by a larger randomized controlled trial (n = 298) that reported no mortality benefit from high dose immunosuppression (cyclophosphamide, methylprednisolone, dexamethasone) in patients with acute paraquat poisoning.²⁸ Therefore, this immunosuppressive regimen is not currently recommended.

Generation of reactive oxygen species is an important step in the pathogenesis of paraquat poisoning (Fig. 112–3). This leads to cytotoxicity, the extent of which depends on the concentration of paraquat at the cellular level and the efficiency of endogenous protective mechanisms. Scavenger defense mechanisms against reactive oxygen species include antioxidants such as vitamin C (ascorbic acid), vitamin E (α -tocopherol), and glutathione. Administration of these vitamins and/or a glutathione donor (eg, N-acetylcysteine, S-carboxymethylcysteine, captopril) to patients did not improve outcomes in every human or animal study. Poor intracellular penetration to the site of redox cycling may limit the effect of some compounds. Potentially, vitamin C might increase oxidative toxicity.²² Typical doses that have also been used in patients with acute poisoning include: vitamin E 300 mg orally twice daily, vitamin C 25 mg/kg/day or 3 g/day for 7 days, and N-acetylcysteine 150 mg/kg over 3 hours as a loading dose followed by 500 mg/kg/day by continuous infusion. The scavenging agents superoxide dismutase and amifostine and the iron chelator deferoxamine have also been studied, but results were not encouraging.

Some treatments may influence the toxicokinetics of paraquat at the cellular level. Xenobiotics that decrease the uptake of paraquat into pneumocytes have been studied such as putrescine, spermidine, and deferoxamine, but their effect is limited and they do not alter efflux. Corticosteroids, particularly dexamethasone and methylprednisolone, have been shown in animal models to induce p-glycoprotein, which increases the cellular efflux and excretion of paraquat.

Salicylates are proposed to inhibit multiple steps in the pathogenesis of paraquat poisoning, including decreasing production of reactive oxygen species, inhibition of NF- κ B, antithrombotic effects, and chelation of paraquat.^{20,21} Sodium salicylate 200 mg/kg decreased reactive oxygen species production and inflammation and improved survival in rats.²⁰ Similarly, lysine acetylsalicylate 200 mg/kg improved survival in rats in a dose-finding study.^{23,46} A small pilot study in Sri Lanka noted a delayed time to death in patients receiving intravenous acetylsalicylic acid. Other antidotes and treatments have also been proposed, but less information regarding their effects is available.

Treatment Recommendations. Most clinical studies have not demonstrated favorable outcomes, in contrast to animal studies, which may reflect higher toxicity or delayed institution of therapy. Studies reporting a delayed time to death suggest a possible effect, prompting further research into dose-response and the effect of combination therapy. Active treatment, particularly with invasive modalities such as hemoperfusion/dialysis is anticipated to interfere with end-of-life care. Based on these principles, our recommendations favor intervention where there may be a hope of recovery, while limiting therapeutics desperation. The prognosis in patients presenting more than 12 hours after ingesting 50 mL or more of paraquat 20% wt/vol, those with a positive plasma dithionite test, or those with a SIPP greater than 50 is so poor that treatment should focus on symptom control and end-of-life support and palliation. The prognosis in patients presenting within 6 hours of ingesting less than 50 mL of paraquat, those with a faint-positive dithionite test, or those with a SIPP less than 50 is also poor but prompt multimodal treatment with volume resuscitation, oral activated charcoal (or Fuller's earth), hemoperfusion or hemodialysis, intravenous corticosteroids, acetylsalicylate, acetylcysteine, deferoxamine, and vitamin E can be commenced. It cannot be over-emphasized that any potential benefit of these treatments is time-critical so they must be commenced immediately. If any of these treatments are not available at the initial treatment center it is reasonable to

transfer the patient to a center that can provide them within the stated timeframe. Other exposures not yet mentioned are associated with poor prognosis and unlikely to respond to treatment. However, if resources are available and psychosocial factors support aggressive treatment then the previous-mentioned treatment regimen can be attempted (but a benefit is not anticipated). In particular, it is not recommended that such patients be transferred to another center to receive active treatment

GLUFOSINATE

Glufosinate ($\{2RS\}$ -2-amino-4-{hydroxy(methyl)phosphinoyl}butyric acid; **Fig. 112–5**) is a nonselective herbicide used predominantly in Japan, which is where most cases of acute poisoning are reported; however, use is increasing in other parts of Asia. Commercial preparations contain 14% to 30% glufosinate as the ammonium or sodium salt, with anionic surfactants. Case fatalities between 6.1% and 17.7% are reported from glufosinate poisoning and increasing age is a risk factor.⁷⁴

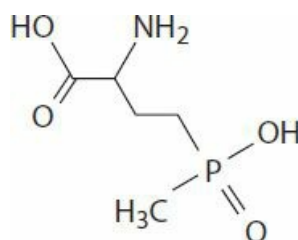


FIGURE 112–5 Structure of glufosinate.

Pharmacology

Glufosinate is neurotoxic, although the specific mechanism is incompletely described. Because it is structurally similar to glutamate, studies have explored whether it interferes with glutamate networks in the central nervous system. Studies in rats demonstrate both agonism and antagonism to glutamate receptors and no effect on other receptors in the brain.³⁴ Glufosinate also interferes with glutamine synthetase activity, which can induce hyperammonemia. Ammonia concentrations were not markedly altered in rats,³⁴ but hyperammonemia has been observed following self-poisoning.^{34,60,73,124}

Glufosinate was not found to inhibit cholinesterase enzymes in rat studies,³⁴ although this is reported in humans on occasion, including one case where it decreased to 40% of the lower limit of normal with subsequent recovery.¹²⁴

The extent to which the surfactant contributes to clinical toxicity has not been confirmed. Rat studies suggest that hemodynamic changes due to glufosinate ammonium formulations are entirely caused by the surfactant component rather than glufosinate itself.⁵⁹ Surfactants may also cause uncoupling of oxidative phosphorylation, although this was not observed in a single case report of glufosinate ammonium poisoning.⁷⁰

Pharmacokinetics and Toxicokinetics

Kinetic analysis of glufosinate is limited to animal studies and a few human case reports. Minor differences in kinetics of the D- and L-glufosinate enantiomers are observed between patients, the clinical implications of which are not known.

The peak concentration is observed 1 hour postingestion in mice administered the formulated product, and less than 15% of a dose is absorbed by rats.

Glufosinate does not appear to bind to plasma proteins to a significant extent. The V_d was calculated to be 1.44 L/kg in a case of acute poisoning by assuming that the renal excretion of glufosinate is similar to animals.³⁸ Glufosinate distributes to the central nervous system, and in a case of acute poisoning the cerebrospinal fluid concentration was one-third the serum concentration 27 hours postingestion. The rate of distribution to the cerebrospinal fluid has not been characterized, but it is theorized that glufosinate might distribute to the central nervous system slowly (perhaps due to active transporters) where it accumulates, which is why the onset of respiratory depression is delayed.⁴⁴ This theory was not supported in a case where glufosinate was not detected in the cerebrospinal fluid 6 hours after a seizure that occurred 30 hours postingestion.¹²¹ Indeed, seizures have occurred in some patients after glufosinate was no longer detectable in the blood.¹²⁴ Seizures occur 3 hours postadministration of intracerebral glufosinate in rats, which further challenges the theory that distribution kinetics influence the delayed onset of seizures in humans.³⁴

Glufosinate is subject to minimal metabolism and the majority of the bioavailable dose of glufosinate is excreted unchanged in urine.

The elimination half-life is 4 hours in rats, while in rabbits elimination is biphasic with a terminal elimination half-life of 1.9 hours, which is not dose dependent. Kinetic data in humans are limited to a small number of cases of acute

intentional poisoning where the elimination profile appeared biphasic with a distribution half-life of 2 to 4 hours and a terminal elimination of 10 to 18 hours.^{38,41,118}

Pathophysiology

It is not known whether the manifestations of glufosinate poisoning represent a primary (toxic) or secondary (downstream) effect. The most important manifestations are neurological, with respiratory impairment that reduces oxygen delivery and subsequently compromises cellular function. Hypotension also impairs tissue perfusion and if uncorrected progresses to shock. Failure to correct these abnormalities may lead to irreversible cellular injury and death.

Clinical Manifestations

Nausea and vomiting are early features of acute poisoning. An altered level of consciousness precedes severe neurotoxicity, which occurs between 4 and 50 hours postingestion, and includes seizures and central respiratory failure requiring ventilatory support.^{60,73,74} These symptoms may persist for a number of days. In rats, the onset of seizures is also delayed by a number of hours; however, the time to onset of the seizures decreased in a dose-dependent manner following the intraperitoneal administration of glufosinate.⁷⁵

Other manifestations include cardiac dysrhythmias, fever, amnesia (antegrade and retrograde), diabetes insipidus, and rhabdomyolysis. Refractory hypotension may be preterminal.^{60,73,74}

Diagnostic Testing

Glufosinate poisoning is diagnosed clinically in the context of a history of exposure. Glufosinate assays are available for clinical use in Japan and a nomogram was developed for predicting clinical outcomes (Fig. 112–6).⁴⁰ Clinical chemistry assays including kidney function, blood gases, electrolytes, creatine kinase, and ammonia concentrations may support clinical management. Metabolic acidosis is more common with severe poisoning.⁷⁴ The ammonia concentration is not often markedly elevated or does not consistently correlate with clinical outcomes. If serial measurements identify an increasing concentration this may suggest increased risk of neurotoxicity.^{34,60,73}

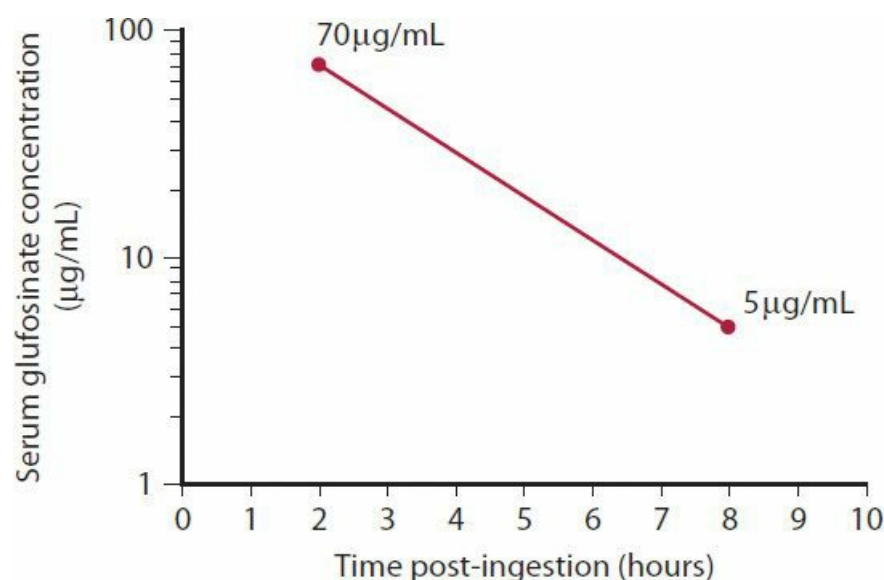


FIGURE 112–6 Glufosinate nomogram as described by Hori et al.⁴⁰ Concentrations above the line are associated with more severe poisoning.

Management

Although toxicity appears to be dose dependent, severe symptoms are reported following unintentional ingestion, so all patients with oral exposures should be carefully monitored. Patients with confirmed exposures should be monitored for a minimum of 48 hours because the onset of clinical toxicity can be delayed. Prior to discharge, each patient should be carefully screened to identify those with memory deficits.

Resuscitation and Supportive Care. Routine resuscitation, close observation, and supportive care are required. Careful monitoring for the onset of respiratory failure is necessary and early intubation and ventilation is recommended in symptomatic patients. Given that glufosinate and metabolites are primarily renally cleared, intravenous fluids to maintain a consistent urine output is suggested. Seizures should be treated in a standard manner initially with benzodiazepines as first-line therapy. This approach is suggested to be effective on the basis of animal studies. Biochemical and acid–base abnormalities should be corrected where possible.

Gastrointestinal Decontamination. In most reports of glufosinate poisoning, gastric lavage and activated charcoal were administered, but it is not possible to determine whether these interventions improved clinical outcomes. The high incidence of both seizures and respiratory failure from glufosinate poisoning are relative contraindications to the administration of activated charcoal to patients with an unprotected airway.

Extracorporeal Removal. Hemodialysis and hemoperfusion have been used in the management of acute glufosinate poisoning. Hemodialysis appears to be superior to hemoperfusion in terms of extraction of glufosinate from whole blood in vitro, with an extraction ratio of 80%. However, the clearance by hemodialysis is less than 60% of renal clearance in patients with normal kidney function. Prompt hemodialysis in patients decreases the concentration of glufosinate and probably ammonia but it is not known if this prevents the occurrence of neurotoxicity such as seizures, so its role in routine management is poorly defined. It is reasonable to consider these treatments in patients with severe poisoning and also in those with impaired kidney function.

Antidotes. Specific antidotes are not available. Rat studies did not demonstrate benefit with the use of atropine and pralidoxime. Ethanol coingestion appears to be protective. Benzodiazepines should be first-line therapy for seizures.

GLYPHOSATE

Glyphosate (N-{phosphonomethyl} glycine; Fig. 112–7) is a nonselective postemergence herbicide. It is used extensively worldwide, most commonly as the isopropylamine salt but also a potassium salt. Glyphosate-containing herbicides are available in various formulations: 1% to 5% glyphosate (ready to use) or 30% to 50% (concentrate requiring dilution before use). In 2007, glyphosate was the most frequently used herbicide in the United States and the second most commonly used herbicide in the domestic sector.³³ Products containing glyphosate trimesium are less widely used and may differ with respect to their toxicity profile.

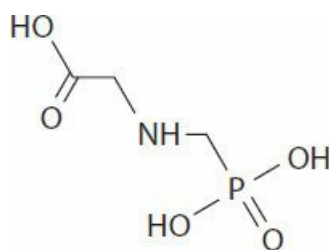


FIGURE 112–7 Structure of glyphosate.

Pharmacology

Glyphosate inhibits 5-enolpyruvylshikimate-3-phosphate synthase in plants, which interferes with their aromatic amino acid synthesis; this enzyme is not present in humans.

The mechanism of toxicity of glyphosate-containing herbicides to humans is not adequately described. The formulation is irritating and high concentrations are corrosive, causing direct injury to the gastrointestinal tract. Despite being an organic phosphorus compound, glyphosate does not inhibit acetylcholinesterase. Patients with severe poisoning manifest multisystem effects, suggesting that the formulation is either nonspecific in its action or that it interferes with a physiologic process common to a number of systems. Proposed mechanisms include disruption of cellular membranes and uncoupling of oxidative phosphorylation, which may be interrelated. Indeed, the mechanism of toxicity may vary between different glyphosate salts. In two cases of glyphosate trimesium poisoning, cardiopulmonary arrest occurred within minutes of ingestion.^{81,116} Since this is not reported from glyphosate isopropylamine, it is possible that these products differ in the mechanism of toxicity.

Experimentally, there is minimal (if any) mammalian toxicity from glyphosate itself. Glyphosate is categorized as WHO class “U” (unlikely to present acute hazard in normal use; LD₅₀ > 4000 mg/kg).⁴⁹ Surfactant coformulants are considered the more toxic component in glyphosate-containing herbicides. Polyoxyethyleneamine (tallow amine; LD₅₀ equal to 1200 mg/kg) is the most common surfactant formulated in these products, but others are also used. Systemic exposure to surfactants induces hypotension, which is primarily due to direct effects on the heart and blood vessels.¹³ Surfactants directly disrupt cellular and subcellular membranes, including those of mitochondria, which has the potential to lead to systemic symptoms.³² Coformulated potassium and isopropylamine may also contribute to toxicity. Isopropylamine has a rat LD₅₀ of 111 to 820 mg/kg, decreases vascular resistance, and may either increase or decrease cardiac contractility and rate.^{50,93}

Pharmacokinetics and Toxicokinetics

The kinetics of the surfactant has not been described. The relevance of the kinetics of glyphosate is questioned because its

contribution to clinical toxicology is minimal; however, it is summarized here for completeness. Glyphosate does not penetrate the skin to a significant extent. Up to 40% of an oral dose is absorbed in rats, although this could increase when ingested as a concentrated solution with injury to the gastrointestinal epithelium. The peak glyphosate plasma concentration occurs within 2 hours of ingestion and distribution appears to be limited (glyphosate does not readily cross the placenta according to an ex vivo model⁸²). Glyphosate has an elimination half-life that is less than 4 hours and is excreted unchanged in the urine.^{7,9,43,100,125}

Pathophysiology

It is not known whether the manifestations of glyphosate poisoning represent a primary (toxic) or secondary (downstream) effect. Disruptions of oxidative phosphorylation globally impair normal cellular function as a result of limited energy supply (discussed further with the pathophysiology of phenoxy herbicides). Similarly, direct toxicity to cell membranes (including those of the mitochondria) interferes with normal cellular processes such as ion channels. Both disruptions induce multiorgan toxicity. Hypotension and dysrhythmias impair tissue perfusion, and liver and kidney injuries induce metabolic disequilibria and acidosis, which impair normal physiologic processes. Pulmonary toxicity may lead to hypoxia, which further compromises normal cellular functioning. Failure to correct these abnormalities may lead to irreversible cellular toxicity and death.

Clinical Manifestations

Abdominal pain with nausea, vomiting, and/or diarrhea are the most common manifestations of acute poisoning. These may be mild and self-resolving, but in patients with severe poisoning there may be inflammation, ulceration, or infarction. Severe diarrhea and recurrent vomiting may induce dehydration. Gastrointestinal burns and necrosis occur with high doses of concentrated formulations and may be associated with hemorrhage. Extensive erosion of the upper gastrointestinal tract is associated with more severe systemic poisoning and a prolonged hospitalization.^{14,15,47,79,100}

Severe poisoning manifests as multiorgan failure, including hypotension, cardiac dysrhythmias, kidney and liver dysfunction, hyperkalemia, pancreatitis, pulmonary edema or pneumonitis, altered level of consciousness including encephalopathy, and metabolic acidosis. These effects may be transient or severe, progressing over 12 to 72 hours to resistant shock, respiratory failure, and death. The mechanism of hypotension may relate to both hypovolemia (fluids shifts and increased losses) and/or direct cardiotoxicity.^{7,15,65,69,79,100,111,120}

Intravenous self-administration of glyphosate-containing herbicide caused hemolysis in one patient, and intramuscular self-administration caused rhabdomyolysis in another.

A large prospective study reported a case fatality of 3.2% in patients presenting to rural hospitals in Asia where resources are limited,¹⁰⁰ but mortality reported in other studies varied from 2% to 30%.¹⁵ These differences in outcomes may reflect differences in timely access to health care services, available medical facilities, variability in glyphosate formulations, or selection bias related to case-referral. Proposed risk factors for death include a large exposure, delayed presentation to hospital, elevated glyphosate concentration, and increasing age.^{15,79,100,111}

Respiratory, ocular, and dermal symptoms may occur following occupational use of these preparations but are usually of minor severity. Significant skin reactions from topical exposure are also reported.

Diagnostic Testing

Acute poisoning with a glyphosate-containing herbicide is diagnosed on the basis of a history of exposure and clinical findings. The differential diagnoses are wide, including any xenobiotic or medical condition associated with gastrointestinal effects and progressive multisystem toxicity.

A number of clinical criteria for the classification of severity are suggested, but none have been validated.^{7,100,120,122} There are no readily available specific clinical investigations to guide management or estimate prognosis in acute poisoning. Higher glyphosate plasma concentrations are associated with more severe poisoning; for example concentrations greater than 734 mg/L predicted death in one study,¹⁰⁰ while a review noted that severe poisoning is associated with concentrations greater than 1000 mg/L.⁷ These concentrations probably reflect the amount of exposure, since glyphosate is minimally toxic. However, quantitative glyphosate assays are not routinely available for clinical use.

Targeted laboratory and radiological investigations should be conducted in patients demonstrating anything more than mild gastrointestinal symptoms. Pulse oximetry and blood gas measurements may be useful for detection of metabolic disequilibria and respiratory impairment. Electrolytes should be measured early because some formulations contain glyphosate as a potassium salt and severe hyperkalemia is reported.

Patients who develop marked nonspecific organ toxicity (eg, acute kidney injury, pulmonary edema, metabolic acidosis, sedation, dysrhythmias, hypotension) are more likely to die.^{15,62,64,79,100}

Endoscopy can diagnose erosions or ulceration following exposures to the concentrated formulation. However, this

procedure may be complicated by perforation and may not change management, so its use requires careful consideration.

Management

Retrospective studies suggest a correlation between ingestion, severity of poisoning, and death.^{64,100,106,122} All patients except for those with trivial exposures should be observed for a minimum of 6 hours. In particular, patients presenting with intentional self-poisoning or ingestion of a concentrated formulation must be carefully monitored. If gastrointestinal symptoms are noted then the patient should be observed for a minimum of 24 hours given that clinical toxicity may progress. Because the toxicity of individual surfactants has not been determined, treatment does not vary depending on specific coformulants.

Resuscitation and Supportive Care. All patients should receive prompt resuscitation, close observation, and routine supportive care; other treatments are largely empiric. The airway is usually maintained but respiratory failure and respiratory distress occur, which require supplemental oxygen and possibly mechanical ventilation. The optimal management of hypotension is complicated because its etiology is potentially related to hypovolemia, negative inotropy, and/or reduced vascular resistance. A detailed clinical review is required, followed by cautious administration of intravenous fluids to the patient. If the response to prompt administration of 20 to 30 mL/kg intravenous fluid to the patient is insufficient or there is increasing pulmonary congestion, then vasopressors should be used. Other investigations such as echocardiography, central venous pressure, or pulmonary artery catheter may also guide management, if available.

Biochemical and acid–base abnormalities, such as hyperkalemia, should be corrected where possible. The contribution of uncoupling of oxidative phosphorylation to clinical toxicity and death has been proposed, but no specific treatment is available if this develops. In the context of acute poisoning with glyphosate-containing herbicides, signs suggestive of uncoupling of oxidative phosphorylation, such as hyperthermia, metabolic acidosis with elevated lactate concentration, and hypoglycemia, may be a preterminal event. Hemodialysis or hemofiltration should be administered to patients developing acute kidney injury per usual guidelines if active treatment is to be pursued.

Gastrointestinal Decontamination. No data exist to support the role of gastrointestinal decontamination in acute poisoning with glyphosate-containing herbicides beyond the usual recommendations discussed above.

Extracorporeal Removal. Patients who received hemodialysis have survived severe poisoning; however, other patients have died despite this treatment. Plasmapheresis has also been studied but clearances were not determined. Early initiation of any of these treatments may be required for best results. The role of extracorporeal removal in routine care is not known given that there are limited quantitative data reporting direct clearances, and uncertainty regarding what compound to measure.

Antidotes. No specific antidote has been proposed or tested for the treatment of acute poisoning with glyphosate-containing herbicides, which relates in part to the unknown mechanism of toxicity.

PHENOXY HERBICIDES (PHENOXYACETIC DERIVATIVES), INCLUDING 2,4-D AND MCPA

Phenoxy compounds are selective herbicides that are widely used in both developing and developed countries. A large number of compounds are included in this category; however, the most widely used are the phenoxyacetic derivatives. This includes 2,4-dichlorophenoxyacetic acid (2,4-D), MCPA, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T; no longer available), and mecoprop (MCP; 2-(4-chloro-2-methylphenoxy)propionic acid; Fig. 112–8). Other phenoxy herbicides and available toxicity data are listed in Table 112–1. In 2007, 2,4-D was the fifth most commonly used herbicide in the United States but the most commonly used herbicide in the domestic sector (MCP was fourth most commonly used in the domestic sector).³³

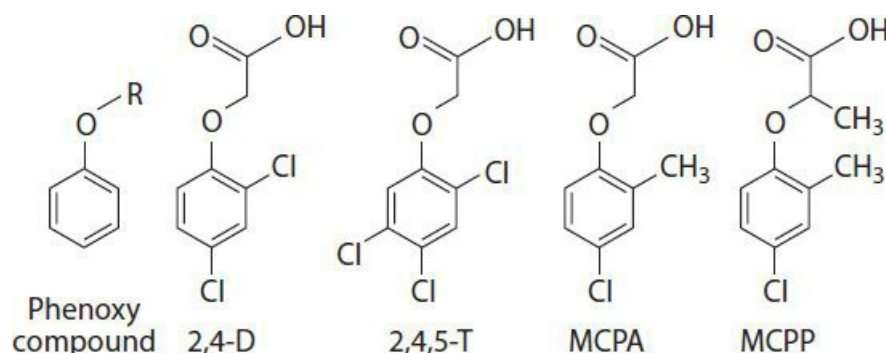


FIGURE 112–8 Structures of common phenoxy herbicides.

Agent Orange, a defoliant popularly used during the Vietnam War, was composed of an equal mixture of 2,4-D and 2,4,5-T. This product also contained the contaminant dioxin (2,3,7,8-tetrachlorodibenzodioxin), which was a byproduct of

the manufacture of phenoxy herbicides. Dioxin is a persistent organic pollutant that is alleged to induce chronic health conditions and cancer, although this has been debated. This chapter discusses only the outcomes of acute exposures to phenoxy herbicides.

Pharmacology

The mechanism of toxicity of phenoxy compounds is not well described. The formulation is irritating or corrosive, causing direct injury to the gastrointestinal tract. Patients with severe poisoning manifest multisystem effects, suggesting that the formulation is either nonspecific in its action or that it interferes with a physiological process common to a number of systems. As with other herbicide preparations, this may reflect the contribution of coformulants such as surfactants.

In rats, high plasma concentrations of MCPA damage cell membranes and induce toxicity, but the correlation between plasma concentrations, membrane damage, and toxicity is poor. Dose-dependent kidney injury from 2,4-D is observed in rats.

Uncoupling of oxidative phosphorylation also may contribute to the development of severe clinical toxicity. Phenoxyacetic derivatives demonstrate concentration-dependent uncoupling of rat mitochondria in vitro, although the specific process that is disrupted is not sufficiently described.^{10,133} Features of uncoupling of oxidative phosphorylation were observed antemortem in clinical studies of patients with large phenoxy herbicide exposures.⁹⁸

Phenoxy acid compounds inhibit the voltage-gated chloride channel CLC-1 in skeletal muscles, which is thought to contribute to the neuromuscular toxicity of these compounds. Dysfunction of CLC-1 induces myotonia due to hyperpolarization of the cell membrane. Other CLC channels are important for normal renal physiology. There are differences in the degree of inhibition between individual phenoxy acid compounds, which may contribute to the variability in animal LD₅₀ and possibly clinical features.

Other possible mechanisms of toxicity relate to their similarity to acetic acid, interfering with the utilization of acetylcoenzyme A (acetyl-CoA), or action as a false messenger at cholinergic receptors.⁸

Pharmacokinetics and Toxicokinetics

Animal studies and human case reports have shown nonlinear kinetics for the phenoxy herbicide compounds. Dose-dependent changes in absorption, protein binding, and clearance all occur, and each will influence the concentration-time profile.

Absorption is usually first order¹; however, the time to peak concentration may be delayed with increasing doses, which may suggest saturable absorption (this is supported by cell culture studies that demonstrate active absorption of these herbicides by a hydrogen ion-linked monocarboxylic acid transporter).^{55,61,101,123}

As the dose of MCPA increases there is a change in the semilogarithmic plasma concentration-time profile from linear to a biphasic convex profile. The inflection of this elimination curve in rats is approximately 200 mg/L,^{25,26,101,123} which appears to reflect saturation of albumin binding. As the plasma concentration exceeds this point the proportion of herbicide that is free (unbound) increases.¹⁰¹ This may increase the Vd and prolong the apparent plasma elimination half-life.

Another contributing mechanism to the observed biphasic convex concentration-time profile is saturation of renal clearance for which there is some interspecies variability. Dose-dependent renal clearance is attributed to saturation of an active transport process or direct nephrotoxicity. Renal clearance also varies with urine flow because of reabsorption from the distal tubule.

Similar to data from animal studies, the semilogarithmic plasma concentration-time curve of phenoxy herbicides in humans with acute poisoning is generally convex, with an apparent inflection from a longer (but highly variable) to shorter elimination half-life between 200 and 300 mg/L. The elimination half-lives are prolonged, which may explain the persistence of clinical toxicity and why death may occur a number of days postingestion of a phenoxyacetic herbicide.^{98,101}

Alterations in blood pH may also change tissue distribution because phenoxyacetic herbicides are weak acids (pKa ~ 3). Here, acidemia increases the proportion that is nonionized, and therefore lipophilic, which increases tissue binding and distribution. This has been observed in vitro and is similar to that observed for salicylates (Chap. 39). Similarly, an alkaline plasma pH is expected to decrease tissue (and probably receptor) binding and increase plasma concentrations.

Experience with acute human poisonings noted a poor correlation between plasma concentrations and peak toxicity.⁹⁸ This may reflect a discordance between plasma (measured) and intracellular (eg, mitochondrial) concentrations.

Pathophysiology

Direct injury to the gastrointestinal tract may cause vomiting and diarrhea, which induces hypovolemia and electrolyte abnormalities.⁸ Nonspecific cellular toxicity and uncoupling of oxidative phosphorylation interfere with normal function of ion channels and other cellular functions, preventing normal physiological processes.

Uncoupling of oxidative phosphorylation may be caused by chemicals that disrupt mitochondrial function, and causes

inefficiency in energy production. At a cellular level it describes an increase in oxygen consumption and heat production out of proportion to the generation of ATP due to mitochondrial dysfunction. Varying degrees of uncoupling of oxidative phosphorylation may occur. The initial physiological response to uncoupling is to increase mitochondrial respiration to maintain the supply of ATP, which increases heat production and respiratory rate. As ATP falls there is an increase in glycolysis, causing hypoglycemia and metabolic acidosis with an elevated lactic concentration. If the mitochondrial defect persists then there will be hyperthermia and insufficient ATP for essential cellular functions including active transport pumps such as $\text{Na}^+\text{-K}^+\text{-ATPase}$. This is followed by a loss of cellular ionic and volume regulation, which, if persistent, is irreversible and cell death occurs. Because mitochondria are the primary supplier of ATP for most physiologic systems, uncoupling of oxidative phosphorylation is expected to induce multisystem toxicity.

Clinical Manifestations

Vomiting, myotonia (confirmed on electromyography), and miosis are prominent features of 2,4-D poisoning in dogs. Severity varies in a dose-dependent manner, peaking 12 to 24 hours postingestion and persisting for a number of days.

Gastrointestinal toxicity including nausea, vomiting, abdominal or throat pain, and diarrhea are common. Other clinical features include neuromuscular findings (myalgia, rhabdomyolysis, weakness, myopathy, myotonia, and fasciculations), central nervous system effects (agitation, sedation, confusion, miosis), tachycardia, hypotension, kidney toxicity, and hypocalcemia. In some patients, these effects persist for a number of days.⁹⁸

Tachypnea with respiratory alkalosis occurs in patients with phenoxy herbicide poisoning, some of who died, which may be consistent with increased mitochondrial respiration from mild uncoupling. More severe poisoning may be characterized by metabolic acidosis, hyperventilation, hyperthermia, elevated creatine kinase, generalized muscle rigidity, progressive hypotension, pulseless electrical activity, or asystole.^{8,19,85,98}

The mortality from acute phenoxy herbicide poisoning is potentially high. A systematic review of all acute phenoxy herbicide poisoning described severe clinical toxicity in most patients, including death in one-third of the cases.⁸ Subsequently, a prospective study of MCPA exposures in Sri Lanka demonstrated minor toxicity in greater than 80% of patients and a mortality of 4.4% (eight of 181 patients).⁹⁸ When death occurs, it is usually delayed by 24 to 48 hours postingestion and results from cardiorespiratory arrest. The exact mechanism of death is inadequately described, but it may relate to uncoupling of oxidative phosphorylation or other metabolic dysfunction including acute kidney injury, as discussed above.

Diagnostic Testing

Commercial assays for the specific measurement of phenoxy herbicides are not available to assist in the diagnosis of acute poisoning. Further, their role in the management of acute poisoning is not confirmed because the relationship between plasma phenoxy herbicide concentration and clinical toxicity appears to be poor.⁹⁸ Sedation is reported with a plasma phenoxy concentration above 80 mg/L,⁹⁶ while concentrations more than 500 mg/L are associated with severe toxicity.²⁷ A patient survived severe MCPA poisoning (hypotension and limb myotonia) with a plasma concentration of 546 mg/L. The myotonia persisted for a number of days and resolved when the MCPA plasma concentration was less than 100 mg/L.¹⁰⁹ By contrast, death has been reported following MCPA poisoning at plasma concentrations as low as 107 mg/L to 230 mg/L.^{51,90,98}

Monitoring of electrolytes, kidney function, pulse oximetry, and blood gases is recommended to detect progression of organ toxicity. Hypoalbuminemia may predispose to severe poisoning.¹⁰¹ Creatine kinase should be determined since rhabdomyolysis may occur following acute poisoning. Urinalysis might be useful for identifying myoglobinuria. There are insufficient data describing the role of these measurements for prognostication.

Management

All patients with significant poisonings, particularly those with symptomatic oral ingestions, should be treated cautiously, including continuous monitoring for 24 to 48 hours preferably in an intensive care unit. Initial mild toxicity (eg, gastrointestinal symptoms but normal vital signs and level of consciousness at presentation) does not preclude subsequent severe toxicity and death.⁹⁸

Animal studies suggest that phenoxy herbicide toxicity increases when elimination is impaired. Empirically, this supports the use of treatments that reduce exposure by either decreasing absorption or increasing elimination. Unfortunately, there is insufficient evidence to recommend specific interventions in patients with acute phenoxy herbicide poisoning. However, an adequate urine output ($> 1 \text{ mL/kg/h}$) may optimize the renal excretion of phenoxy herbicides as well as decreasing renal toxicity from rhabdomyolysis. Since signs consistent with uncoupling of oxidative phosphorylation are likely to be associated with a poor outcome, more advanced treatments such as hemodialysis can be considered in these patients.^{8,98}

Resuscitation and Supportive Care. All patients should receive routine resuscitation, close observation, and supportive care. It is reasonable to correct electrolyte abnormalities and acidemia given that this may promote the distribution of weak acids and increase the intracellular concentration.

Gastrointestinal Decontamination. Gastrointestinal decontamination can be administered to patients per the guidelines listed in [Chap. 8](#). However, administration of activated charcoal beyond the usual time frame is reasonable given that absorption appears to be saturable.

Extracorporeal Removal. Because phenoxy compounds are small and water soluble, and subject to saturable protein binding with large exposures (increasing the free concentration), they are likely to be cleared by extracorporeal techniques. Extracorporeal elimination using resin hemoperfusion, hemodialysis, or plasmapheresis has been studied in a few cases, with clearances approaching 75 mL/minute. Hemodialysis should be considered in patients with severe poisoning if facilities are available.

Antidotes. There are no specific antidotes for phenoxy herbicides, but sodium bicarbonate or other alkalinizing agents may have a role in management by altering the kinetics of phenoxy herbicides.

Data from animal studies and case reports suggest that urinary alkalization increases the elimination of phenoxy herbicides. Increases in urinary pH increase clearance due to “ion trapping” of the phenoxy herbicide. For example, renal 2,4-D clearance was increased from 5.1 mL/minute to 63 mL/minute when urine pH increased from 5.0 to 8.0.⁹¹ Compared with a total clearance of approximately 30 mL/minute or less in volunteer studies,^{56,105} this increase in renal clearance has the potential to be clinically significant. Prospective, randomized studies are required to confirm the efficacy of urinary alkalization in humans.

Plasma alkalization may also limit the distribution of phenoxy compounds from the central circulation by “ion trapping.”

It is reasonable to consider plasma and urinary (urine pH > 7.5) alkalization in patients who are symptomatic, particularly if there are features of uncoupling of oxidative phosphorylation or metabolic acidosis. Alkalization is rarely associated with adverse effects when administered to patients with care and close observation (Antidotes in Depth: A5).

TRIAZINE COMPOUNDS, INCLUDING ATRAZINE

The 1,3,5-triazine or s-triazine compound ([Fig. 112–9](#)) is central to a large number of compounds, including herbicides, other pesticides (eg, cyromazine), resins (eg, melamine), explosives (RDX or C-4), and anti-infectives. Triazine herbicides are widely used, and in 2007 atrazine and simazine were among the 25 most used pesticides in the United States.³³ However, cases of acute poisoning are infrequent. Other herbicides included in this group are listed in [Table 112–1](#). These selective herbicides may be used pre- or postemergence for weed control.

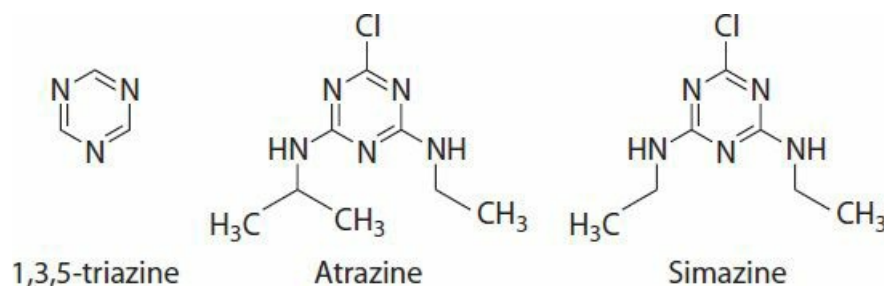


FIGURE 112–9 Structures of common triazine herbicides.

The safety of atrazine from an environmental health perspective is debated because of its persistence and propensity to spread across water systems and potential toxicity from chronic exposure. This led to restrictions on the use of triazine compounds in the European Union.

Pharmacology

The mechanism of toxicity is not fully determined, although it might relate to uncoupling of oxidative phosphorylation. Atrazine is a direct arteriolar vasodilator. Some metabolites of atrazine, particularly those remaining chlorinated, are thought to retain some biologic activity.² Similarly, clinical features of prometryn poisoning resolved posthemodialysis despite persistence of the parent herbicide, suggesting that toxic metabolites were eliminated.¹¹

Pharmacokinetics and Toxicokinetics

Approximately 60% of an oral atrazine dose is absorbed in rats and the concentration peaks beyond 3 hours.⁷⁸ The absorption phase of triazine compounds appears to be prolonged in humans where the serum or plasma concentration

continues to increase during treatment with hemodialysis.^{11,88} Atrazine is rapidly dealkylated to a metabolite that binds strongly to hemoglobin and plasma proteins, allowing it to be detected in the blood for months. Metabolites are excreted in the urine and around 25% of them are conjugated to glutathione.⁷⁸

The metabolism of atrazine has been studied in humans following occupational exposures, and animals, and a range of metabolites are described, in particular those derived from glutathione conjugation. Other metabolic products as a result of dealkylation and oxidation are also present.

Dermal absorption of atrazine is incomplete but increases with exposure to the proprietary formulation. Atrazine metabolites are readily measured in the urine of atrazine applicators.

Clinical Manifestations

There are limited cases of triazine herbicide poisoning. Vomiting, depressed level of consciousness, tachycardia, hypertension, acute kidney injury, and metabolic acidosis with elevated lactate concentration were described in a patient with acute prometryn and ethanol poisoning.¹¹ Similar clinical signs, in addition to hypotension with a low peripheral vascular resistance, were noted in a case of poisoning with atrazine, amitrole (Table 112–1), and other toxic compounds. This was followed by progressive multiorgan dysfunction and death due to refractory shock 3 days later.⁸⁸ Death following acute ametryn poisoning (coformulated with xylene and cyclohexanone) is reported, but the mechanism of death was not apparent.¹¹⁹

Diagnostic Testing

In a single case report, clinical toxicity did not directly relate to the concentration of prometryn, but the relationship to the concentration of metabolites has not been determined.¹¹ Routine biochemistry and blood gases are useful for monitoring for the development of systemic toxicity.

Management

Few publications of triazine herbicide poisoning are available to guide management of patients with acute triazine poisoning.

Resuscitation and Supportive Care. Routine resuscitation, close observation, and supportive care should be provided to all patients. Ventilatory support and correction of hypotension and metabolic disequilibria are reasonable.

Gastrointestinal Decontamination. It is reasonable to administer activated charcoal to patients beyond one hour because of the slow absorption of these compounds.

Extracorporeal Removal. Hemodialysis corrected metabolic acidosis in a case of prometryn poisoning without decreasing the serum concentration of prometryn, which might reflect ongoing absorption. In the absence of direct measurements of clearance, the efficacy of hemodialysis in removing prometryn cannot be determined, but is probably limited.¹¹ Hemodialysis clearance of atrazine was 250 mL/minute (extraction ratio 76%), but only 0.1% of the dose was removed after 4 hours of treatment. Further, similar to the previous case, atrazine concentrations continued to increase during the treatment.⁸⁸

Antidotes. No antidotes are available for the treatment of triazine herbicide poisoning.

SUMMARY

- A large number of heterogeneous xenobiotics are classified as herbicides; the toxicity in humans is not completely described for many of these xenobiotics.
- Coformulants, such as surfactants and solvents, probably contribute to clinical toxicity in commercial preparations.
- Many herbicides induce multisystem toxicity for which treatments are often unsatisfactory, although some compounds induce organ specific toxicity.
- All patients with acute intentional poisoning should be carefully observed for the development of poisoning.
- The priorities of treatment include prompt resuscitation, consideration of antidotes, a detailed history, ongoing monitoring, and supportive care.
- More research is required to better define the clinical syndromes associated with herbicide poisoning, the toxicokinetics of relevant compounds, and the efficacy of treatments including antidotes.

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113 INSECTICIDES: ORGANIC PHOSPHORUS COMPOUNDS AND CARBAMATES

Michael Eddleston

HISTORY AND EPIDEMIOLOGY

The first potent synthetic organic phosphorus anticholinesterase, tetraethylpyrophosphate (TEPP), was synthesized by Clermont in 1854. Clermont's report described the taste of the compound, a remarkable achievement because a few drops should be rapidly fatal.¹¹¹ In 1932, Lange and Krueger wrote of choking and blurred vision following inhalation of dimethyl and diethyl phosphorofluoridates. This account inspired Schrader in Germany to begin investigating these agents, initially as pesticides, and later for use in warfare (Chap. 132). During this research, Schrader's group synthesized hundreds of compounds, including the popular pesticide parathion and the chemical weapons sarin, soman, and tabun. Allied scientists were also motivated during the same period by the work and independently discovered other extremely toxic compounds such as diisopropylphosphofluoridate (DFP).²¹⁴ Since that time, it is estimated that more than 50,000 organic phosphorus compounds have been synthesized and screened for pesticidal activity, with dozens being produced commercially.⁴⁰

The history of carbamates was first recorded by Westerners in the 19th century when they observed that the Calabar bean (*Physostigma venenosum* Balfour) was used in tribal cultural practice in West Africa.¹¹² These beans were imported to Great Britain in 1840, and in 1864 Jobst and Hesse isolated an active alkaloid component they named "physostigmine." Vée and Leven (1865) claimed to have obtained physostigmine in crystallized form and named it eserine, from *ésère*, the African term for the ordeal bean. Physostigmine was first used medicinally to treat glaucoma in 1877.¹¹² In the 1930s, the synthesis of aliphatic esters of carbamic acid led to the development and introduction of carbamate pesticides, marketed initially as fungicides. In 1953, the Union Carbide Corporation developed and marketed carbaryl, the insecticide being prepared at the plant in Bhopal, India, during the catastrophic release of methyl isocyanate in 1984 (Chap. 2).^{8,193}

Organic phosphorus compounds (OPs) and carbamates are the two groups of cholinesterase-inhibiting pesticides that commonly produce human toxicity. Although the term organophosphate is often used in both clinical practice and in the literature to refer to all phosphorus-containing pesticides that inhibit cholinesterase, phosphates are compounds in which the P atom is surrounded by four O atoms, and there are other derivatives of phosphoric and phosphonic acids such as phosphonates that can exhibit cholinesterase inhibition. Some chemicals, such as parathion, contain thioesters, whereas others are vinyl esters. Those cholinesterase-inhibiting (anticholinesterase) insecticides that contain phosphorus will be collectively termed organic phosphorus compounds in this chapter. Those that contain the OC=ON linkage will be termed carbamates.

Anticholinesterase pesticides are broadly grouped according to their toxicity by the World Health Organization's Classification of Pesticides into five groups: Class Ia "Extremely hazardous," Class Ib "Highly hazardous," Class II "Moderately hazardous," Class III "Slightly hazardous," and "Active ingredients unlikely to present acute hazard in normal use" (Table 113–1). This classification is based upon comparative rat oral LD₅₀ data of the active ingredient. It seems useful to distinguish very toxic OPs (such as parathion, rat oral LD₅₀ 13 mg/kg) that have killed many thousands of people from relatively safe OPs (such as temephos, rat oral LD₅₀ 8600 mg/kg) that have not been reported to cause harm. However, the rat LD₅₀ seems to be less useful to distinguish between pesticides within the same class. Here, the differential toxicity may be due to differences in response to treatment, speed of onset, or coformulants.^{51,69}

TABLE 113–1. WHO Classification of Pesticide Toxicity²³⁶

		<i>LD₅₀ for the Rat (mg/kg body weight)</i>			
		<i>Oral</i>		<i>Dermal</i>	
	<i>Class</i>	<i>Solids</i>	<i>Liquids</i>	<i>Solids</i>	<i>Liquids</i>
Ia	Extremely hazardous	5 or less	20 or less	10 or less	40 or less
Ib	Highly hazardous	5–50	20–200	10–100	40–400
II	Moderately hazardous	50–500	200–2000	100–1000	400–4000
III	Slightly hazardous	Over 500	Over 2000	Over 1000	Over 4000

Reproduced with permission of World Health Organization. The WHO recommended classification of pesticides by hazard and guidelines to classification: 2009. Geneva: WHO; 2010.

Globally, anticholinesterase insecticides likely kill more people each year than acute poisoning by any other chemical. An estimated 200,000 die in rural Asia where intentional self-harm is common and extremely toxic organophosphorus insecticides are widely used in agriculture and therefore available in households at times of stress.^{62,99} Around 3000 to 6000 ventilators are constantly required in Asia alone to provide mechanical ventilation to poisoned patients.⁹⁹ Banning of the most toxic organic phosphorus insecticides has resulted in a 50% fall in total suicides in Sri Lanka, showing that regulation can be effective.¹⁰⁰ Severe occupational or unintentional poisoning also happens where such insecticides are used,²²⁷ but deaths are generally less common.

Anticholinesterase poisoning is less important in industrialized countries where access to toxic pesticides is much more controlled. However, when anticholinesterase poisoning does occur, patients often require intensive care with long hospital stays.^{79,180} A further threat is the terrorist use of organic phosphorus insecticides, such as parathion, to poison a water supply or flour used in bread baking. Such events occur regularly in rural India^{57,164} and might result in many hundreds of casualties being treated by clinicians with little experience of this potentially lethal toxic syndrome.

The case fatality for OP and carbamate poisoning will vary according to which pesticides are used in local agriculture and the health facilities available. Where fast acting, highly toxic pesticides are used in agriculture and therefore for self-harm (as in much of the rural developing world), deaths will occur before patients present to hospital. Hospital based data therefore has a falsely low case fatality, although often still high at 10% to 30%.⁶²

Before the ban of parathion in Germany, the case fatality in Munich's toxicology intensive care unit was approximately 40%.^{79,240} This was likely because the excellent ambulance services in Germany were able to get to patients early, before death, but after they had become symptomatic with this fast acting OP. Some had already aspirated or suffered hypoxic brain injury prior to arrival of the ambulance. Despite resuscitation at the scene, many of these patients died subsequently from complications of the pre-hospital events rather than from direct cholinergic effects of the OP insecticide. Few of these patients would have survived to hospital admission in the developing world.

During the 5-year period of 2002 through 2006, the American Association of Poison Control Centers (AAPCC) recorded almost 30,000 exposures to OP compounds and more than 14,000 exposures to carbamates. Although these totals are large, the number of reported exposures to both insecticides has each dropped annually since 2002, likely due in part to a phase out of their residential use during this period.²⁰¹ However, the number of fatalities reported to the AAPCC remained constant, during this time averaging about five per year. These insecticides still rank as the most lethal insecticides in use in the United States and are among the most lethal poisonings (Chap. 136).

Since the overall case fatality for OP and carbamate pesticide poisoning is on the order of 10% to 20%, the 200,000 deaths a year in rural Asia must represent 1 to 2 million poisonings. Respiratory failure is a major problem with OP and carbamate poisoning. Modeling suggests that the 20% to 30% of patients who develop respiratory failure will receive 1,147,000 to 2,294,000 days of ventilation every year.⁹⁹ This will require constant use of 3140 to 6280 ventilators worldwide solely for managing self-poisoning with pesticides.⁹⁹ These figures for acute poisoning undoubtedly omit numerous unreported and possibly unrecognized illnesses resulting from lower level environmental exposure to these chemicals.

Typically, patients present following unintentional or suicidal ingestion of anticholinesterase insecticides or after working in areas recently treated with these compounds. Children and adults can develop toxicity while playing in or inhabiting a residence recently sprayed or fogged with OP insecticides by a pesticide applicator.²⁴¹ Direct dermal contact with certain types of these insecticides may be rapidly poisonous.¹⁴⁵ Outbreaks of mass poisoning regularly occur in the developing world, and less commonly in the United States, from contamination of crops or food.^{30,41,56,57,78,181,217} Epidemics of toxicity are also reported among groups illegally importing and using the potent carbamate aldicarb.^{159,175} Unfortunately, OPs and carbamates have also been used for homicide.^{26,54,184,205,220}

PHARMACOLOGY

Organic Phosphorus Compounds

OP poisoning results in a rise in the concentration of acetylcholine (ACh) at muscarinic and nicotinic cholinergic synapses, which, in turn, leads to the syndrome of cholinergic excess. **Figure 113–1** shows the basic formula for cholinesterase inhibiting OP compounds.^{88,207} The “X” or “leaving group” determines many of the characteristics of the compound and provides a means of classifying OP insecticides into four main groups (**Table 113–2**). Group 1 compounds contain a quaternary nitrogen at the X position and are collectively termed phosphorylcholines. These chemicals were originally developed as weapons of war, are powerful cholinesterase inhibitors, and can directly stimulate cholinergic receptors, presumably because of their structural resemblance to ACh. Group 2 compounds are called fluorophosphates because they possess a fluorine molecule as the leaving group. Like group 1 compounds, these compounds are volatile and highly toxic, making them well-suited for chemical warfare. The leaving group of group 3 compounds is a cyanide molecule or a halogen other than fluorine. The most well-known agents in this group are cyanophosphates, such as the chemical weapon tabun.

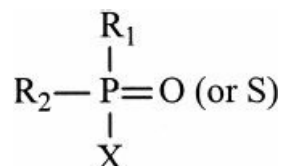


FIGURE 113–1 General structure of organic phosphorus insecticides. X represents the leaving group. R₁ and R₂ may be aromatic or aliphatic groups that can be identical.

TABLE 113–2. The Classification of Organic Phosphorus Compounds by Groups, Showing Leaving Groups and Examples of Each Group

Group 1—phosphorylcholines

Leaving group: substituted quaternary nitrogen

Echothiophate iodide

Group 2—fluorophosphates

Leaving group: fluoride

Dimetox, sarin, mipafox

Group 3—cyanophosphates, other halophosphates

Leaving group: CN⁻, SCN⁻, OCN⁻, halogen other than fluoride

Tabun

Group 4—multiple constituents

Leaving group:

Dimethoxy

Azinphos-methyl, bromophos, chlorothion, crotoxyphos, dikapthon, dichlorvos, dicrotophos, dimethoate, fenthion, malathion, mevinphos, parathion-methyl, phosphamidon, temephos, trichlorfon

Diethoxy

Carbophenothion, chlorfenvinphos, chlorpyrifos, coumaphos, demeton, diazinon, disulfoton, disulfoton, ethion, methidathion, parathion, phorate, phosolan, TEPP

Other dialkoxo

Isopropyl paraoxon, isopropyl parathion

Diamino

Schradan

Chlorinated and other substituted dialkoxo

Haloxon

Triethioalkyl

Merphos

Triphenyl and substituted triphenyl

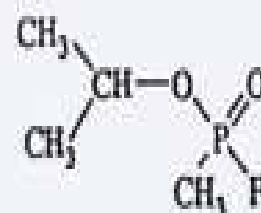
Triorthocresyl phosphate (TOCP)

Mixed substituent

Crofosfate, cyanofenphos



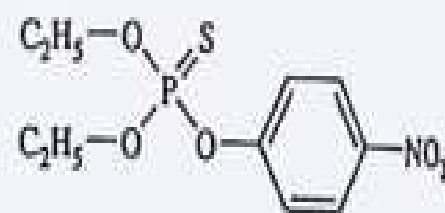
Echothiophate iodide



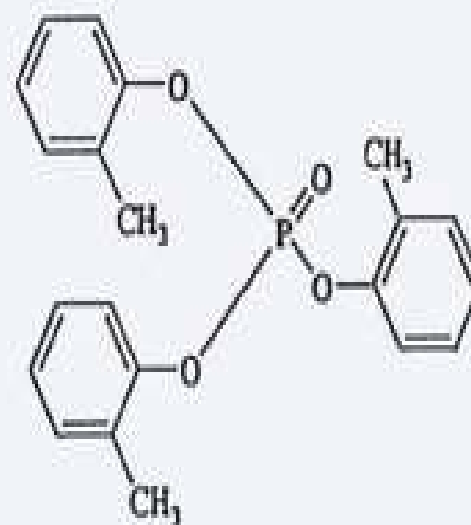
Sarin



Tabun



Parathion



Triorthocresyl phosphate (TOCP)

The fourth group is the broadest and comprises various subgroups based on the configuration of the R₁ and R₂ groups, with the majority falling into the category of either a dimethoxy or diethoxy compound. Most of the insecticides in use today fall into this last class.⁸⁸

“Direct”-acting OP insecticides (“oxons”) inhibit acetylcholinesterase (AChE) without being metabolized in the body. However, many pesticides, such as parathion and malathion, are “indirect” inhibitors (prodrugs or “thions”) requiring partial metabolism (to paraoxon and malaaxon, respectively) within the body to become active. Desulfuration to the oxon occurs in the intestinal mucosa and liver following absorption.^{131,202}

The OPs bind to a hydroxyl group at the active site of the AChE enzyme. As the leaving group of the OP insecticide is split off by AChE, a stable but reversible bond results between the remaining substituted phosphate of the OP and AChE, effectively inactivating the enzyme (Figs. 113–2 and 113–3).

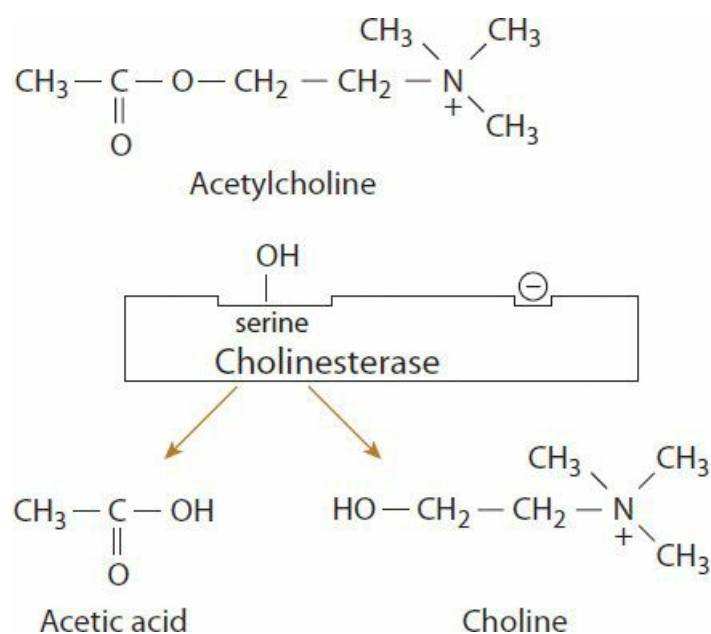


FIGURE 113–2 Normal metabolism of acetylcholine by acetylcholinesterase to choline and acetic acid.

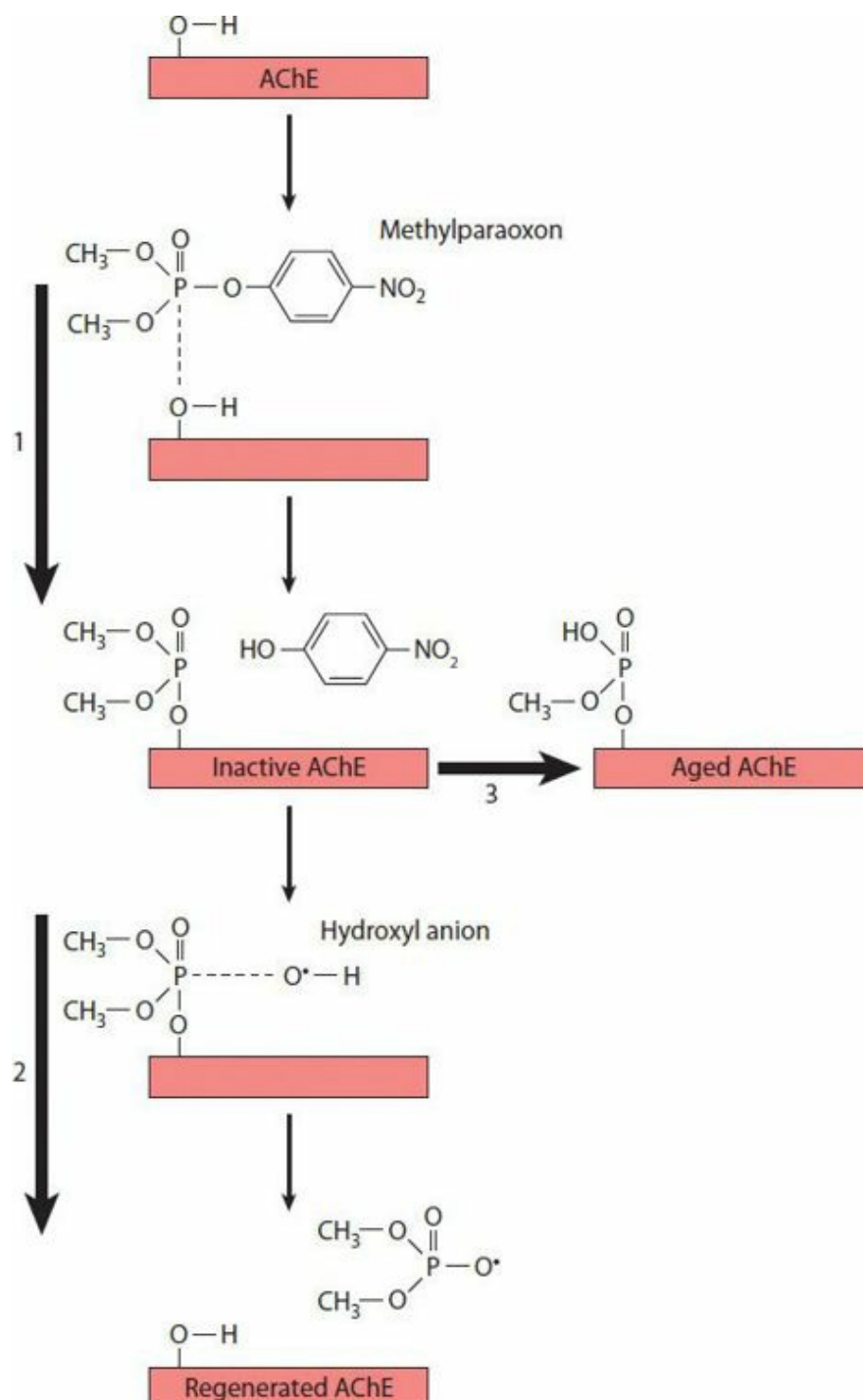


FIGURE 113–3 Mechanism of inhibition of acetylcholinesterase by an organic phosphorus compound.

A dimethylated organic phosphorous pesticide (for example, methylparaoxon) inhibits AChE function by phosphorylating the serine hydroxyl group at the active site of the enzyme (reaction 1). This reaction occurs very quickly. Active AChE is subsequently regenerated by a hydroxyl ion attacking the acetylated serine residue, removing the phosphate moiety, and releasing active enzyme (reaction 2). This regenerative process, however, is much slower than inhibition, requiring hours to days to occur (spontaneous reactivation $t_{1/2} \sim 0.7\text{--}86$ hours for dimethyl and $31\text{--}57$ hours for diethyl compounds).

While in the inactive state, the enzyme is prone to “aging” (reaction 3) in which one alkyl side chain of the phosphoryl moiety is removed non-enzymatically, leaving a hydroxyl group in its place. “Aged” AChE can no longer react with water, and regeneration no longer occurs. This reaction occurs considerably faster with enzymes that have been inhibited by dimethylated pesticides ($t_{1/2} \sim 3.3$ hours) than those inhibited by diethylated pesticides ($t_{1/2} \sim 30$ hours).

The slower the regenerative process, the greater the quantity of inactive AChE available for aging. Pralidoxime catalyses the regeneration of active acetylcholinesterase by exerting a nucleophilic attack on the phosphoryl group, transferring it from the enzyme to itself. By speeding up reaction 2, it reduces the quantity of inactive AChE available for aging. However, because aging occurs more rapidly with dimethylated pesticides, pralidoxime is only useful before about 12 hours with dimethylated enzyme.

Data from Eddleston M, Szinicz L, Eyer P et al. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. *Q J Med.* 2002;95:275–283.

Worek F, Backer M, Thiermann H et al. Reappraisal of indications and limitations of oxime therapy in organophosphate

poisoning. *Hum Exp Toxicol*. 1997;16:466–472.

Worek F, Diepold C, Eyer P. Dimethylphosphoryl-inhibited human cholinesterases: Inhibition, reactivation, and aging kinetics. *Arch Toxicol*. 1999;73:7–14.

Although splitting of the choline-enzyme bond in normal ACh metabolism is completed within microseconds, the severing of the OP compound-enzyme bond is prolonged. The half-life of this reaction depends on the chemistry of the substituted phosphate. The *in vitro* half-life for spontaneous reactivation of human AChE inhibited by dimethoxy OPs is 0.7 to 0.86 hours, while that of diethoxy inhibition is 31 to 57 hours.⁸¹ Spontaneous reactivation is therefore far quicker with dimethoxy OPs.

Oximes, such as pralidoxime or obidoxime, markedly speed up the rate of reactivation.⁸¹ However, if the phosphate is allowed to remain bound to the AChE, because of late or inadequate administration of oximes, an alkyl group is non-enzymatically lost (Fig. 113–3)—a process called “aging.” Once aging has occurred, the AChE can no longer be reactivated by oximes. Again, the half-life of this reaction is determined by the substituted phosphate. The *in vitro* half-life of human AChE after poisoning with dimethoxy OPs is 3.7 hours, compared to 31 hours after diethoxy poisoning.⁸¹ Clinically, this means that patients who present to a hospital 4 hours after poisoning with a dimethoxy OP will already have 50% of their AChE irreversibly inhibited; after 14 hours, the patients will be completely refractive to oxime therapy. In contrast, patients poisoned by diethoxy OPs presenting within 14 hours will have very little aged AChE and should be responsive to oximes. De novo synthesis of AChE is required to replenish its supply once aging has occurred (see Diagnostic Testing section below).²⁰⁷

OPs also vary by lipid solubility,²¹ rate of activation (conversion from thion to oxon), rate of AChE inhibition,⁸¹ and relative inhibition of the plasma enzyme butyrylcholinesterase. Some OPs do not fulfill the usual dimethoxy or diethoxy classification and have one of the alkyl groups linked to the phosphate by a sulfur molecule, rather than oxygen (eg, profenofos, methamidophos). Aging seems to be particularly rapid for these OPs.^{65,76}

Carbamates. Carbamate insecticides are N-methyl carbamates derived from carbamic acid (Fig. 113–4)¹⁸ Medicinal carbamate compounds include physostigmine, pyridostigmine, and neostigmine.²⁰⁷ Xenobiotics such as meprobamate and various urethanes are carbamate derivatives, but do not inhibit cholinesterase. Thiocarbamate fungicides and herbicides (eg, maneb, zineb, nabam, and mancozeb) also do not inhibit AChE and do not produce the cholinergic toxic syndrome (Chap. 112).

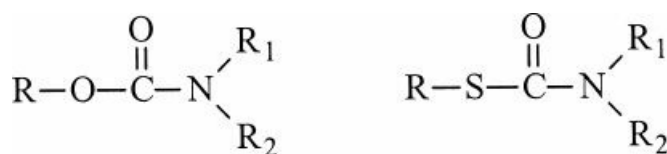


FIGURE 113–4 General structure of carbamate insecticides.

When exposed to carbamates, AChE undergoes carbamylation in a manner similar to phosphorylation by OPs,²³¹ allowing ACh to accumulate in synapses. Aging cannot occur, and the carbamate-AChE bond hydrolyzes spontaneously, reactivating the enzyme. As such, the duration of cholinergic symptoms in carbamate poisoning is generally less than 24 hours. However, complications that result from the cholinergic syndrome, in particular aspiration, can last much longer.

PHARMACOKINETICS AND TOXICOKINETICS

Organic Phosphorus Compounds

OP insecticides are well absorbed from the lungs, gastrointestinal tract, mucous membranes, and conjunctiva following inhalation, ingestion, or topical contact.⁸⁸ Although absorption through intact skin appears to be relatively low,⁹⁴ percutaneous exposure to highly toxic compounds can cause severe toxicity.^{43,45,145,226} The presence of broken skin and dermatitis and higher environmental temperatures further enhances cutaneous absorption.⁸⁸

Poisonings can be chronic or acute, although the differentiation has little clinical relevance. The difficulty in removing these compounds from the skin and clothing may explain some chronic poisonings; inadequate skin and respiratory protection during pesticide application is responsible for many cases of occupational exposures.

The time to peak plasma concentration after self-poisoning is unknown. Human volunteer studies, using very low doses of chlorpyrifos, found C_{max} to be around 6 hours after oral ingestion.¹⁶⁰ However, patients ingesting large amounts of oxon or fast acting thion OPs can become symptomatic within minutes,^{79,138} suggesting that the onset of absorption is rapid.

Most OPs are lipophilic²¹ and are therefore predicted to have a large volume of distribution and to rapidly distribute into tissue and fat where they are protected from metabolism. Radiolabeled parathion injected into mice distributes most

rapidly into the cervical brown fat and salivary glands, with high concentrations also measured in the liver, kidneys, and ordinary adipose tissue.⁸⁶ Adipose tissue gradually accumulates the highest concentrations. Redistribution from these stores may allow for measurement of circulating insecticide concentrations for up to 48 days post-ingestion.^{49,90,187}

Cholinergic crisis may recur in patients when unmetabolized OPs are mobilized from fat stores.⁸⁸ The more lipophilic compounds such as fenthion and dichlofenthion (both with a log P {octanol/water coefficient} >4.0) are particularly likely to cause this phenomenon.^{49,69,148} Dimethoate, methamidophos, and oxydemeton methyl are three common OPs that are not lipophilic (log P <1.0), with predicted small volumes of distribution and high plasma OP concentrations.⁵⁰

The distribution of OPs into fat will likely include both activated and unactivated compound. When released from the fat hours to days later, the unactivated thion will require activation to cause clinical features.

Thion OPs are activated by cytochrome P450 enzymes in the liver and intestinal mucosa. The precise CYP450s responsible appears to vary according to the concentration of OP. For example, chlorpyrifos, diazinon, parathion, and malathion are all activated by CYP1A2 and 2B6 at low concentrations.^{33,34} However, at the higher concentrations more likely to occur after self-poisoning, CYP3A4 becomes dominant. The particular enzymes involved in metabolism of the active oxon to inactive metabolites are less clear.

Studies have investigated possible relationships between human plasma paraoxonase (PON) activity and susceptibility to acute and chronic effects of OP poisoning.^{44,194,196} Paraoxonase is an A-esterase that can hydrolyze the active (oxon) metabolites of some OP insecticides. Activity differs significantly among animal species. Some animal models of OP poisoning demonstrate protection from toxicity when exogenous PON is administered, and greater susceptibility to poisoning when enzyme-deficient animals (such as genetically engineered knockout mice) are exposed.¹⁹⁴ Some authors have postulated that genetic polymorphisms in human PON activity may lead to variations in interindividual susceptibility to some OP insecticides.⁴⁴

Carbamates. Carbamate insecticides are absorbed across skin and mucous membranes, and by inhalation and ingestion. Peak cholinesterase inhibition occurs within 30 minutes of oral administration in rats.¹⁶² Most carbamates undergo hydrolysis, hydroxylation, and conjugation in the liver and intestinal wall, with 90% excreted in the urine within 3 to 4 days¹⁸.

There is a view that carbamates, unlike OPs, do not easily enter the brain. However, carbamates cause CNS depression in humans,¹⁷⁵ have lipophilic log P values,²¹ and rat studies show inhibition of brain cholinesterases with multiple carbamates.¹⁶² Furthermore, post mortem studies have shown high concentrations of carbamates in CSF and brain.^{109,150,151} The evidence at present therefore suggests that in this aspect they do not differ markedly from OPs. One important distinction between carbamates and OPs is that the carbamate-cholinesterase bond does not “age.” Thus AChE inhibition is reversible, with spontaneous hydrolysis occurring usually within several hours.

PATHOPHYSIOLOGY

Acetylcholine is a neurotransmitter found at both parasympathetic and sympathetic ganglia, skeletal neuromuscular junctions, terminal junctions of all postganglionic parasympathetic nerves, post-ganglionic sympathetic fibers to most sweat glands, and at some nerve endings within the central nervous system (Fig. 113–5).²²⁸ As the axon terminal is depolarized, vesicles containing ACh fuse with the nerve terminal, releasing ACh into the synapse or neuromuscular junction (NMJ). Acetylcholine then binds postsynaptic receptors leading to activation (G proteins for muscarinic receptors and ligand-linked ion channels for the nicotinic receptors). Activation alters the flow of K⁺, Na⁺, and Ca²⁺ ionic currents on nerve cells, and alters membrane potential of the postsynaptic membrane, resulting in propagation of the action potential.

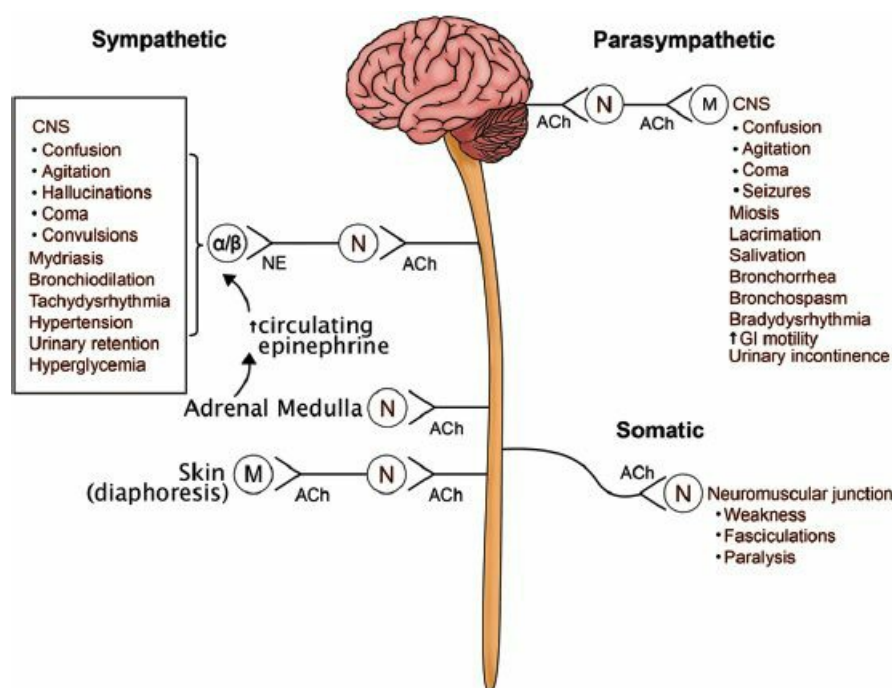


FIGURE 113–5 Pathophysiology of cholinergic syndrome as it affects the autonomic and somatic nervous systems. N = nicotinic; M = muscarinic.

OPs and carbamates are inhibitors of carboxylic ester hydrolases within the body, including variably acetylcholinesterase (AChE, EC 3.1.1.7), butyrylcholinesterase (plasma or pseudocholinesterase, BuChE, EC 3.1.1.8), plasma and hepatic carboxylesterases (aliesterases), paraoxonases (A-esterases), chymotrypsin, and other nonspecific proteases.³⁷

AChE hydrolyzes ACh into two inert fragments: acetic acid and choline. Under normal circumstances, virtually all ACh released by the axon is hydrolyzed almost immediately, with choline undergoing reuptake into the presynaptic terminal where it is reused to synthesize ACh.²²⁸ AChE is found in human nervous tissue and skeletal muscle, and on erythrocyte (RBC) cell membranes.¹⁴³ Acutely, RBC AChE activity correlates well with the function of nervous system AChE for some OPs.^{210,212} However, recent findings from profenofos poisoned humans⁷⁶ and dimethoate poisoned pigs⁷⁴ have raised questions about the validity of using AChE activity on RBCs as a marker of poisoning severity.⁸²

Butyrylcholinesterase is a hepatic derived protein that is found in human plasma, liver, heart, pancreas, and brain. Although the function of this enzyme is not well understood, its activity can be easily measured and has important clinical implications in anesthesia (Chap. 69).

Inhibition of AChE is generally thought to account for all, or the majority, of clinical features of both OP and carbamate poisoning. However, these compounds also inhibit many other enzymes.³⁷ The clinical effects of these interactions are not yet understood.

Patients also ingest formulated pesticides rather than the pure anticholinesterase compound or “active ingredient” (AI). OPs sold for agricultural use are typically emulsifiable concentrates (EC) in which the AI (eg, dimethoate) is mixed with an organic solvent such as xylene or cyclohexanone and a surfactant/emulsifier. Unfortunately, the compounds used for co-formulation are highly variable, being optimized by each pesticide manufacturer for each OP. As a result, co-formulants often differ between the same OP produced by two companies, and for two OPs produced by one company.

The clinical effect of poisoning with these co-formulants, in addition to the carbamate or OP, has not been completely evaluated and remains unclear. Complications of surfactant poisoning have been well described in glyphosate poisoning²⁸ (Chap. 112) but not with insecticides. The acute toxicity of the solvents appears to be low—for example, the rat oral LD₅₀s for xylene and cyclohexanone are 4000 to 5000 and 1620 mg/kg, respectively. However, in a minipig model of acute oral dimethoate EC40 poisoning, early respiratory arrest occurred at a point when red cell AChE was less than 30% inhibited, suggesting a non-AChE mechanism.⁷⁴ Early work showed that dimethoate toxicity could be increased markedly by changing the solvent³⁸; more recent work with chlorpyrifos has shown a modest change in toxicity after changing the solvent.²¹⁶ The minipig model has shown that the toxicity of dimethoate EC40 requires both the dimethoate AI and the cyclohexanone solvent. Changes in the solvent reduced toxicity.⁷⁴ While potentially important, the major differences in clinical syndrome noted in patients between dimethoate EC40, chlorpyrifos EC40, and fenthion EC50 cannot be attributed to the solvent since most pesticides are generic, using 40% xylene as the solvent.⁶⁹

A further effect of the solvents and surfactants occurs after aspiration. Ingestion of both OPs and carbamates can cause rapid loss of consciousness and respiratory arrest, increasing the risk of aspiration with pesticide AI, solvent, surfactant, and gastric contents. The relative role of gastric contents and pesticide is not yet clear. Aspiration pneumonitis is a major

clinical problem in OP poisoning and the treatment of the pneumonitis will not be achieved by the oximes and atropine.⁶³

Pesticides are frequently co-ingested with alcohol, particularly by men,^{130,219} raising questions about the effect of this alcohol on outcome after OP poisoning.⁶⁶ Analysis of a cohort of patients self-poisoned with dimethoate EC40 showed that the alcohol did not directly affect the clinical outcome of poisoning⁷¹; however, higher blood concentrations of alcohol were associated with higher blood concentrations of dimethoate, suggesting that inebriation caused people to drink larger amounts of pesticide, resulting in a worse outcome.

CLINICAL MANIFESTATIONS

Acute Toxicity—Organic Phosphorus Compounds

Clinical findings of acute toxicity from OPs derive from excessive stimulation of muscarinic and nicotinic cholinergic receptors by ACh in the central and autonomic nervous systems, and at skeletal neuromuscular junctions (Fig. 113–5). The classically described patient with severe OP poisoning is one who is unresponsive, with pinpoint pupils, muscle fasciculations, diaphoresis, emesis, diarrhea, salivation, lacrimation, urinary incontinence, and an odor of garlic or solvents. Less severe poisoning is often not so typical.

The timing of onset of symptoms varies according to the route, the degree of exposure, and particularly the OP. This is important since more rapid onset of poisoning will reduce the likelihood of the patient reaching health care safely, before need for intubation and ventilation, or onset of complications such as aspiration. Onset of respiratory failure outside of a hospital in most parts of the world will result in the patient's death.

Patients suffering massive ingestions can become symptomatic as quickly as 5 minutes following ingestion. Most patients with acute poisoning become symptomatic within a few hours of exposure, and practically all who will become ill show some features within 24 hours.

Oxon OPs (such as mevinphos and monocrotophos) are already active on exposure, and patients become symptomatic very soon after ingestion. One man was reported to have died within 15 minutes of mevinphos ingestion.¹³⁸ Some thion OPs are very rapidly converted to oxons and can similarly produce symptoms rapidly—patients ingesting parathion can be unconscious within minutes.⁷⁹ In contrast, patients ingesting thions that are slowly converted to active oxons (such as fenthion) may not show symptoms for hours.

The speed of onset will also be affected by the quantity ingested and the toxicity⁸¹ of the OP. Patients ingesting very large doses or less toxic pesticides or small doses of highly toxic pesticides will rapidly inhibit a clinically significant proportion of their AChE and exhibit features earlier.

Lipid solubility also likely affects time to onset. Fat soluble OPs (with log P of >3–4) will rapidly distribute to fat stores, in the process reducing their concentration in extracellular fluid where they impart their clinical effect (eg, fenthion⁶⁹). Significant poisoning with such OPs is commonly delayed as respiratory failure with fenthion, for example, typically occurs after 24 hours, in contrast to less fat soluble OPs.⁷³

Symptoms following OP exposure may last for variable lengths of time, again based on the compound and the circumstances of the poisoning. For example, the more lipophilic compounds, such as dichlofenthion or fenthion, can cause recurrent cholinergic effects for many days following oral ingestion as they are released from fat stores.^{49,148,172}

A variety of CNS findings are reported after exposure. Many patients present awake and alert, complaining of anxiety, restlessness, insomnia, headache, dizziness, blurred vision, depression, tremors, or other nonspecific symptoms.^{17,158} The level of consciousness may deteriorate rapidly to confusion, lethargy, and coma, and patients may display inappropriate behavior. Where careful observational studies have been done, convulsions appear to be uncommon in OP pesticide poisoning compared to OP nerve agent poisoning.^{69,122} The few convulsions that do occur may be due to hypoxia as a complication of acute cholinergic poisoning.

The effects of excessive ACh on the autonomic nervous system may be variable because cholinergic receptors are found in both the sympathetic and parasympathetic nervous systems (Fig. 113–5). Excessive muscarinic activity can be characterized by several mnemonics, including “SLUD” (salivation, lacrimation, urination, defecation) and “DUMBBELS” (defecation, urination, miosis, bronchospasm or bronchorrhea, emesis, lacrimation, salivation). Of these, miosis may be the most consistently encountered sign. Bronchorrhea can be so profuse that it mimics pulmonary edema.¹⁵⁸

Although muscarinic findings are emphasized in these mnemonics, muscarinic signs may not always be clinically dramatic or initially predominant. Parasympathetic effects can be offset by excessive autonomic activity from stimulation of nicotinic adrenal receptors (resulting in catecholamine release) and postganglionic sympathetic fibers.²⁰⁷ Mydriasis, bronchodilation, and urinary retention can occur as a result of sympathetic activity. Increased sympathetic activity usually precipitates white blood cell demargination, resulting in leukocytosis.^{156,158}

Excessive adrenergic influences on metabolism cause glycogenolysis²⁰⁸ with hyperglycemia and ketosis that have been mistaken for diabetic ketoacidosis.^{146,238} Hypoglycemia can also occur, although the mechanism is unclear.¹¹⁴ Disturbances

of glucose metabolism do not seem to be common. Two studies of patients with OP or carbamate poisoning showed hyperglycemia in 6% to 8%.^{105,195} It is possible that effects on glucose metabolism may be associated with specific OPs, such as the malathion¹¹⁴ and diazinon,¹⁸⁸ rather than all OPs. Larger cohorts of patients exposed to single OPs are required to determine whether such associations exist.

Hyperamylasemia appears to be relatively common in OP poisoning, occurring in 4/47 (9%) adults in one series¹⁸⁶ and 5/17 (29%) children in a second.²²⁵ However, both included various anticholinesterase pesticides; a series of only malathion poisoned patients reported hyperamylasemia in 47/75 (63%).⁴⁶ The amylase likely comes from the pancreas since animal studies show OP-induced damage¹¹⁵ and human poisoning cases show associated pancreatic edema and, rarely, necrotizing pancreatitis.^{29,103,165} The incidence of subclinical and clinical pancreatitis probably varies according to the OP ingested and perhaps the co-formulants. Elevations of hepatic enzymes can also occur following OP pesticide exposures.^{161,174,239}

Cardiovascular manifestations reflect mixed effects on the autonomic nervous system (including increased sympathetic tone), together with the consequences of OP-induced hypoxia and hypovolemia. Admission heart rate is usually normal, with relatively few patients expressing a tachycardia or bradycardia. Patients who have received atropine before admission may be tachycardic. The literature is filled with reports of QT prolongation and ventricular dysrhythmias.^{15,95,128,183,185} However, these reports are complicated by the fact that most patients had an ECG done before they received any atropine to counter the cholinergic syndrome or were so ill that atropine was ineffective. The first is illustrated by a description of 46 patients with OP or carbamate poisoning in which “ECG recordings [were] taken on arrival ... before the start of atropine treatment.”¹⁸⁵ The reported cardiac rhythms may be confounded by the hypoxia and hypovolemia that characterize the cholinergic syndrome. In another study, 29 of the 35 patients with such dysrhythmias died.¹⁴⁰ In contrast, when more than 1000 patients poisoned with WHO Class II OPs were evaluated, serious dysrhythmias were very rare in patients adequately resuscitated with oxygen, atropine, and fluids (Eddleston, unpublished data).

Hypotension may occur because of stimulation of vascular receptors by excessive circulating Ach, severe volume loss, or myocardial dysfunction.^{11,124} Severe hypotension is a particularly significant problem in poisoning with the unusually fat-insoluble OP dimethoate.^{50,69} Fatal poisoning is characterized by early respiratory failure followed by hypotension that can be treated only transiently with vasopressors. Such a syndrome was not found in poisoning with fat-soluble OPs such as chlorpyrifos and fenthion.⁶⁹ The exact role of direct cardiotoxicity and peripheral vasodilation is not yet clear, or whether this syndrome occurs with other fat-insoluble OPs, such as methamidophos and oxydemeton methyl.⁵⁰ Recent studies indicate that the solvent in branded dimethoate EC40, cyclohexanone, is partially responsible for this severe hypotension.⁷⁴

Respiratory complications of OP poisoning include the direct pulmonary effects of bronchorrhea and bronchoconstriction, neuromuscular junction failure in the diaphragm and intercostal muscles, and loss of central respiratory drive.⁵³ If severe and occurring before patients reach medical care, these effects will lead to hypoxemia and respiratory arrest, the most common cause of death after OP poisoning.⁸⁸ Both bronchorrhea and bronchoconstriction respond to adequate atropine therapy. Unfortunately, neither neuromuscular junction failure nor loss of central respiratory drive respond to atropine, and patients must be intubated and ventilated until respiratory function returns.

An additional early respiratory complication is hydrocarbon aspiration that may occur after ingestion of commercially formulated pesticides. The incidence of aspiration and the consequences of aspiration—whether chemical pneumonitis, pneumonia, or acute respiratory distress syndrome—are not yet known and likely differ according to the OP and formulation ingested.

Acetylcholine stimulation of nicotinic receptors also governs skeletal muscle activity. The effects of excessive cholinergic stimulation at these sites are similar to that of a depolarizing neuromuscular blocker (succinylcholine) and initially result in fasciculations or weakness. Although this effect is often considered to be the most reliable sign of parathion toxicity,¹⁵⁸ it is the author’s clinical experience that many patients severely poisoned with other OP insecticides do not display this sign. Acute cranial nerve abnormalities are uncommon.

Severe poisoning results in paralysis.²²³ Rarely, patients may present with paralysis from nicotinic effects without any other initial signs and symptoms suggestive of OP toxicity.^{84,92} Extraparal effects such as rigidity and choreoathetosis occur uncommonly after severe anticholinesterase poisoning but can persist for several days after cholinergic features have resolved.^{9,25,134,153}

Acute Toxicity—Carbamates. The acute effects of poisoning from carbamate insecticides appear identical to those of OP insecticides except for the relative short duration of cholinergic features due to rapid hydroxylation of the carbamate-AChE bond. Persistent cholinergic features are not reported for carbamate poisoning.

Chronic Toxicity

Illness may result from chronic exposure to excessive amounts of OP insecticides. Chronic exposure most commonly occurs in workers who have regular contact with OPs, but may also occur in individuals who have repeated contact with excessive

amounts of insecticides in their living environments. Cholinergic ophthalmic preparations can lead to toxicity in this manner.¹⁴¹ Although tolerance to acute cholinergic systemic effects of OP insecticides (including death in rats) may be observed with long-term exposures,⁸⁸ persons who have such repeated contact may begin to describe symptoms after substantial lengths of time. These effects can range from vague neurological complaints, such as weakness and blurred vision, to miosis, nausea, vomiting, diarrhea, diaphoresis, and other cholinergic effects.^{6,7,141,198} Butyrylcholinesterase activity is usually the most sensitive measure of exposure, and workers in contact with these chemicals should have baseline butyrylcholinesterase testing for comparison and monitoring.^{88,110}

Recent literature has linked Parkinson disease with chronic exposure to pesticides including OP insecticides.^{58,199} Some individuals may have a possible genetic susceptibility.²⁵ Additionally, significant acute exposures to OP insecticides can lead to self-limited movement disorders resembling Parkinson disease that resolve over weeks to months (see above). Although statistics derived from some epidemiologic studies suggest the connection,^{77,108} other studies have failed to find an association between OP compounds and Parkinson disease.²⁰⁶ All studies thus far have been retrospective in nature and therefore likely confounded by recall bias.

Delayed Syndromes

Neuromuscular Junction Dysfunction. A syndrome of delayed muscle weakness without cholinergic features or fasciculations resulting in respiratory failure was first reported by Wadia in 1974 as type II paralysis²²³ and further refined by Senanayake and Karalliedde in 1987 as the intermediate syndrome.¹⁹⁰ The syndrome is defined as occurring 24 to 96 hours after acute OP poisoning, and after resolution of the cholinergic crisis.^{125,190,223} Patients develop proximal muscle weakness, especially of the neck flexors, and cranial nerve palsies and progress to respiratory failure that may last for several weeks.¹²⁵ Consciousness is preserved unless complicated by hypoxia or pneumonia. The syndrome is important since apparently stable patients can suddenly develop a respiratory arrest; all patients must be evaluated for muscle weakness if deaths are to be prevented.^{20,166} The first sign is often weakness of neck flexion such that patients cannot lift their head off the bed.

Although the exact pathophysiology of the syndrome is unknown, it is clearly due to dysfunction of the neuromuscular junction, with respiratory failure resulting from weakness affecting the diaphragm and intercostal muscles. Preservation of consciousness suggests that the central respiratory drive is not involved. Clinicians have proposed that overwhelming NMJ stimulation causes downregulation of the NMJ synaptic machinery.^{52,190} This would require time to be repaired, even after the pesticide has been removed from the body, explaining the long duration of ventilation needed by many patients.⁷³

Cases and small case series are reported from around the world, with resulting comments that the intermediate syndrome is more common with certain OPs, such as parathion, methyl parathion, malathion, and fenthion. Unfortunately, large cohorts of poisoning with specific OPs receiving standardized treatments are rarely reported, making comparisons of incidence between OPs difficult. However, two cohorts have shown that the intermediate syndrome causing respiratory failure is more common in fenthion poisoning than chlorpyrifos, malathion, or fenitrothion poisoning.^{73,222}

Clinical examination remains the most reliable means of identifying the occurrence of intermediate syndrome.¹²⁵ Electromyograms will often show tetanic fade in these patients, and suggest both pre- and postsynaptic involvement.¹²⁵ Recent work has noted characteristic electrophysiological features that can be identified before onset of neurological features and respiratory paralysis.¹¹⁷ The majority of patients developing weakness in this series did not progress to respiratory failure, indicating that intermediate syndrome is a spectrum disorder.

Another study of severely poisoned patients suggested that the occurrence of intermediate syndrome strongly correlated with the initial degree of cholinergic crisis and seemed to be a continuum with the neuromuscular paralysis resulting from the early stages of poisoning.¹¹⁸ This view is supported by early work⁵² and a more recent study of dimethoate poisoning which showed that peripheral NMJ dysfunction can occur simultaneously with the cholinergic syndrome.⁷³ Patients with moderate to severe dimethoate poisoning typically require intubation for respiratory failure soon after ingestion, during the acute cholinergic syndrome. However, this is relatively short-lived, and patients recover consciousness after a few days. As the cholinergic syndrome settles and the patients regain consciousness, with recovery of the central respiratory drive, they are still unable to ventilate. Similar to patients with classical intermediate syndrome, they require ventilatory support for several weeks until their NMJ recovers function. In addition, this case series showed that the classic intermediate syndrome—respiratory failure after resolution of the cholinergic syndrome—can occur before 24 hours and after 96 hours.⁷³

These studies suggest that the original intermediate syndrome is just one important aspect of OP-induced peripheral NMJ dysfunction. It seems likely that the relative incidence and timing of the intermediate syndrome or delayed NMJ dysfunction for different OPs is determined by the rapidity and quantity of AChE inhibition. Where inhibition is intense, with fat-insoluble OPs like dimethoate that have very high plasma concentrations, NMJ dysfunction comes on early, before recovery from the cholinergic crisis. Fat-soluble OPs, such as fenthion, cause a more protracted AChE inhibition, likely

explaining why fenthion-induced NMJ dysfunction and respiratory failure occur later.⁷³

Some authors have suggested that insufficient oxime therapy explains the intermediate syndrome.²² Of note, AChE inhibited by dimethoate or fenthion responds poorly to oximes, in contrast to chlorpyrifos, which responds well to oximes and has a lower incidence of intermediate syndrome.^{69,73} The occurrence of NMJ dysfunction in chlorpyrifos poisoning may well be due to inadequate oxime therapy. However, adequate oxime therapy after, for example, malathion poisoning,²⁰⁰ may be irrelevant since this dimethyl OP responds poorly to oximes. Regardless, delayed NMJ dysfunction may be due to ineffective AChE reactivation, whether due to inadequate doses or to poisoning with OPs that do not respond to oxime therapy.

Recent animal studies of dimethoate poisoning may shed further light on this condition. These studies produced NMJ dysfunction and showed that it did not occur after poisoning with dimethoate active ingredient alone. However, it did occur after poisoning with the agricultural EC40 formulation that included both the dimethoate active ingredient and its solvent, cyclohexanone.⁷⁴ This raises the possibility that NMJ dysfunction is due to an interaction of solvent and active ingredient. All reported cases have occurred after poisoning with agricultural formulations of OP insecticides; further studies are required to clarify the role of solvents and the possible mechanisms of their effects.

The treatment of intermediate syndrome is supportive with airway protection and mechanical ventilation. There are no substantial data demonstrating that pralidoxime or atropine is effective in the treatment of this disorder, although patients may require these medications to control concurrent cholinergic symptoms. The weakness and paralysis commonly resolve in 5 to 18 days.^{73,106,117,118}

Organic Phosphorous Compound-Induced Delayed Neuropathy (OPIDN). Peripheral neuropathies can occur with chronic OP pesticide exposures days to weeks following acute exposures. OPIDN results from inhibition by phosphorylation of the enzyme neuropathy target esterase (NTE, now identified as a lysophospholipase) within nervous tissue.^{36,91,119,120} This enzyme catalyzes breakdown of endoplasmic reticulum-membrane phosphatidylcholine, the major phospholipid of eukaryotic cell membranes. Neuropathic OPs cause a transient loss of NTE activity, putatively disrupting membrane phospholipid homeostasis, axonal transport, and glial-axonal interactions.⁹¹

Such neuropathies may result from exposure to OPs that do not inhibit red blood cell cholinesterase or produce clinical cholinergic toxicity.³⁹ The more commonly implicated chemicals include triaryl phosphates, such as triorthocresyl phosphate (TOCP), and dialkyl phosphates, such as mephosfolan, mipafox, and chlorpyrifos.¹²⁰ Pathologic findings demonstrate effects primarily on large distal neurons, with axonal degeneration preceding demyelination.

Contaminated foods and beverages were responsible for epidemics of OP compound-induced delayed polyneuropathies and encephalopathy. In the 1930s, thousands of individuals in the United States became weak or paralyzed after drinking a supplement containing TOCP—an outbreak nicknamed “ginger Jake paralysis”^{10,149} (Chap. 2). Contaminated cooking and mineral oils were responsible for outbreaks of delayed polyneuropathies in Vietnam and Sri Lanka.^{56,189} Vague distal muscle weakness and pain are often the presenting symptoms and may progress to paralysis.⁹⁷ The administration of atropine or pralidoxime does not alter the onset and clinical course of these symptoms.²²¹ Pyramidal tract signs can appear weeks to months after acute exposures. Electromyograms and nerve conduction studies may be helpful in diagnosing this disorder by identifying the type of neuropathy (such as axonopathy, myelinopathy, or transmission neuropathy) and differentiating it from similar presentations such as Guillain-Barré syndrome.² Recovery of these patients is variable and occurs over months to years, with residual deficits common.^{149,189}

Delayed neuropathies are not usually associated with carbamate insecticides. One reason for this difference is presumed to be that aging of the neuropathy target esterase pesticide complex is a requirement for neuronal degeneration. Paradoxically, one study suggested that subgroups of carbamates may actually bind neuropathy target esterase and exert a protective effect against more toxic OP compounds.⁵ However, several cases of possible delayed neuropathy associated with carbamates have been reported.^{59,218,237} These cases involved ingestions of carbaryl, m-tolyl methyl carbamate, and carbofuran, included both sensory and motor tracts, and tended to resolve over 3 to 9 months. EMG findings were variable.

Behavioral Toxicity

Behavioral changes may also occur after acute or chronic exposure to OP compounds.⁸⁰ Signs and symptoms include confusion, psychosis, anxiety, drowsiness, depression, fatigue, and irritability. Electroencephalographic changes may be noted and can last for weeks.⁹⁶ Single photon emission computed tomography (SPECT) scanning revealed morphologic changes in the basal ganglia of one child following poisoning.²⁷ Recent studies have shown a deficit in cognitive processing after acute OP self-poisoning that lasts for at least 6 months and is not found in matched patients who had poisoned themselves with paracetamol.^{47,48} Thus far there appears to be no clear evidence for neuropsychiatric deficits resulting from subclinical exposure to OPs, although multiple small studies have suggested some effects.^{80,182}

DIAGNOSTIC TESTING

Organic Phosphorus Compounds

When confronted with a patient in cholinergic crisis who presents with a history of acute exposure to an OP cholinesterase inhibitor insecticide, the diagnosis is straightforward. Although textbooks list a variety of clinical signs for the cholinergic crisis (DUMBELS, SLUD—see above), most patients with significant poisoning can be simply identified by the presence of pinpoint pupils, excessive sweat, and breathing difficulty.⁶⁷ However, when the history is unreliable or does not suggest poisoning, the physician must turn to other means to confirm the diagnosis of OP or carbamate poisoning. Treatment of an ill patient with a cholinergic syndrome should not await confirmation of diagnosis.

The most appropriate laboratory tests for confirming cholinesterase inhibition by insecticides are tests that measure (1) specific insecticides and active metabolites in biologic tissues and (2) cholinesterase activity in plasma or blood. Unfortunately, although urine and serum assays for OP compounds and their metabolites are available,³ such testing is rarely obtainable within hours. Moreover “normal” ranges and toxic concentrations are not established for most compounds. Therefore, verifying cholinesterase inhibitor poisoning currently relies on measurement of cholinesterase activity.^{65,88}

Cholinesterase Activity. The two cholinesterases commonly measured are butyrylcholinesterase (BuChE, plasma cholinesterase, EC 3.1.1.8) and red cell acetylcholinesterase (AChE, EC 3.1.1.7). The former is produced by the liver and then secreted into the blood, where it metabolizes xenobiotics, including succinylcholine, pyrethroid insecticides, and cocaine. Red cell AChE is expressed from the same gene as the enzyme found in neuronal synapses. The main difference is in their mechanism of membrane attachment which is due to post-translational modification (red cell AChE is GPI-linked to the red cell while neuronal AChE forms dimers and tetramers that are attached to the postsynaptic membrane by other proteins¹⁴³). Inhibition of either red cell AChE or BuChE only serves as markers for cholinesterase inhibitor poisoning, as inhibition of these enzymes does not contribute to signs and symptoms of poisoning. However, in some cases, red cell AChE activity seems to reflect AChE activity in the NMJ soon after poisoning.²¹²

There is tremendous interindividual and interchemical variability in the degree and duration with which the OP insecticides affect particular cholinesterases. After a significant exposure, butyrylcholinesterase activity usually falls first, followed by a decrease in red blood cell AChE activity. The sequence may be highly variable, but by the time patients present with acute symptoms, activities of both cholinesterase have usually fallen well below baseline values.¹⁵⁸ Of note, the presence of BuChE, AChE, and other esterases varies markedly between species,¹³⁵ complicating the interpretation of animal studies. Furthermore, AChE occurs at very low concentrations in human plasma; therefore, papers citing human serum acetylcholinesterase activity^{13,215} are likely measuring serum BuChE.

Butyrylcholinesterase. BuChE activity usually recovers before red blood cell AChE activity, returning to normal within a few days after a mild exposure in the absence of a repeat exposure to the inciting agent.⁴⁵ However, BuChE activity is less specific for exposure than is red cell AChE activity.⁸⁸ Low BuChE activity can be found in patients with a number of disorders, including hereditary deficiency of the enzyme, malnutrition, hepatic parenchymal disease, chronic debilitating illnesses, and iron deficiency anemia.¹²⁶

The wide normal range of BuChE activity allows for patients with high normal values to suffer significant falls in activity, yet still register near normal BuChE activity on laboratory assay.⁴⁵ Additionally, day-to-day variation in the activity of this enzyme in healthy individuals may be as high as 20%.⁸⁸

Furthermore, since BuChE inhibition varies between OPs and does not cause clinical effects, an admission value by itself is of little value in predicting outcome. An admission value can only be used to predict outcome if the ingested OP is known and its clinical usefulness has been studied specifically for this OP.⁷⁰ For example, most patients who die with chlorpyrifos poisoning have a BuChE activity of around zero on admission; however, since chlorpyrifos is a very potent BuChE inhibitor, many other chlorpyrifos poisoned patients who do not die also present with very low BuChE activities. In contrast, since dimethoate is a poor inhibitor of BuChE, the majority of patients who die from dimethoate poisoning have a BuChE activity higher than many chlorpyrifos poisoned patients who remain clinically well.⁷⁰

Red Blood Cell Acetylcholinesterase. Red blood cell (RBC) AChE activity is thought to more accurately reflect nervous tissue AChE activity because the AChE in red blood cells is true AChE. Some authors suggest that clinical OP pesticide poisoning occurs when RBC AChE activity falls to below 50% of baseline values.¹⁵⁸ Neuromuscular dysfunction is typically associated with a value of 30% of normal or less.²¹² A major advantage of RBC AChE is that its activity can be related to blood hemoglobin (Hb) concentration, reducing variation due to varying hematocrits.²³⁴ Most people have a normal value of 600 to 700 mUnit/ μ mol Hb; a small study of Caucasians reported a mean of 651 with an SD of ± 18 mUnit/ μ mol Hb.²³⁴

After poisoning, and in the absence of oximes, RBC AChE may take many weeks to recover since erythrocytes in circulation at the time of OP exposure must be replaced. An average of 66 days may be necessary for RBC AChE activity to recover following severe inhibition (assuming no treatment with oxime), and activity may take up to 120 days to return to

normal. Rat studies suggest that neuronal AChE activity may return to normal more rapidly than RBC AChE.⁹⁸ Patients have been reported with normal NMJ activity and no cholinergic features, yet still have low RBC AChE laboratory values. For this reason, in subacute poisoning with OP agents, it is difficult to accurately predict the actual time of onset or duration of exposure when only the RBC AChE activity is known.

Depressed RBC AChE activity may be the result of exposures or conditions other than OP or carbamate poisoning, for example, in pernicious anemia and during therapy with antimalarial or antidepressant medicines (Table 113–3).^{127,152}

TABLE 113–3. Interpreting Cholinesterase Activity Values

	<i>Red Blood Cell Acetylcholinesterase</i>	<i>Butyrylcholinesterase</i>
Advantage	Better reflection of synaptic inhibition	Easier to assay, declines faster
Site	RBC (reflects CNS gray matter, motor end plate)	CNS white matter, plasma, liver, pancreas, heart
Regeneration (untreated)	1%/day	25%–30% in first 7–10 days
Normalization (untreated)	35–100 days	28–42 days
Use	Unsuspected prior exposure with normal butyrylcholinesterase	Acute exposure
False depression	Pernicious anemia, hemoglobinopathies, antimalarial treatment, oxalate blood tubes	Liver dysfunction, malnutrition, hypersensitivity reactions, drugs (succinylcholine, codeine, morphine), pregnancy, or deficiency

Recently, patients with acute profenofos poisoning have been noted to have complete inhibition of their RBC AChE activity without any cholinergic or neuromuscular signs.⁷⁶ Similarly, in an animal model, RBC AChE activity does not always reflect clinical severity, perhaps here due to the role of co-formulated solvents.⁷⁴ It is therefore unclear at present how useful RBC AChE activity is in grading poisoning severity.⁸²

Blood samples for cholinesterase activity must be obtained in the appropriate blood tubes. Tubes containing fluoride will permanently inactivate the enzymes, yielding falsely low activities, and should never be used. Specimens for RBC AChE are usually drawn into tubes containing a chelating anticoagulant such as EDTA to prevent clot formation. BuChE does not require an anticoagulant and can be drawn into a tube without chelators or anticoagulants.

Of note, OPs and oximes in collected blood samples will continue to interact with red cell AChE; small differences in time between sampling and assay can result in marked artificial variation in results. The most accurate way to take blood for AChE activity measurement is to immediately dilute it 1:20 or 1:100 into 0.9% sodium chloride solution or water cooled to 39°F (4°C) at the bedside, before rapidly freezing the sample. This process slows down both inhibitory and reactivating reactions in the tube, allowing more uniform results.^{65,234} Such rapid reactions do not occur with BuChE, and bedside dilution and cooling are therefore not required.

Protein Adducts. Current research is attempting to find ways of detecting OP exposure many weeks after the event. New techniques using mass spectrometry aim to identify phosphorylated proteins, such as albumin or BuChE, in blood samples.^{168,203}

Carbamates

Carbamates inhibit neuronal AChE, RBC AChE, and BuChE. The relative ease with which spontaneous decarbamylation of AChE takes place may result in the measurement of relatively normal RBC AChE activity despite severe cholinergic symptoms if the assay is not performed within several hours of sampling.¹⁵⁹ This emphasizes the importance of cooling and freezing the blood sample within minutes of collection (see above). As with OP pesticide poisoning, the wide “normal” range of BuChE activity makes interpretation of BuChE activity difficult at times when the patient’s baseline values are unknown. Unlike OP insecticides, carbamates generally do not produce persistently depressed RBC AChE and BuChE activities.

Atropine Challenge

An atropine challenge may be helpful in diagnosing cholinergic poisoning in a patient who presents with findings suggestive of this disorder, but in whom no history is available to suggest exposure to an OP or carbamate insecticide. In such individuals, a test dose of 1 mg of atropine in adolescents or adults, or 0.05 mg/kg in children up to an adult dose, should produce classic antimuscarinic findings, in particular tachycardia, mydriasis, and dry mucous membranes. Conversely, the persistence of cholinergic signs and symptoms after an atropine challenge strongly suggests the presence of anticholinesterase poisoning.¹⁵⁸ However, some patients suffering from mild anticholinesterase poisoning may respond to this dose of atropine. Therefore, the reversal of cholinergic findings does not completely exclude poisoning by one of these compounds.

Electromyogram (EMG) Studies

Although measuring cholinesterase activity is the test most often used to estimate tissue and neuronal AChE activity, studies support the use of repetitive nerve stimulation testing as an accurate method of quantifying AChE inhibition at the neuromuscular junction.^{12,23,117} Spontaneous repetitive potentials or fasciculations following single-nerve stimulation resulting from persistent ACh at nerve terminals can be a sensitive indicator of AChE inhibition at the motor endplate, and may be useful in the early diagnosis of anticholinesterase poisoning.²³ This type of evaluation may also be of benefit in early detection of rebound cholinergic crisis caused by continued insecticide absorption or redistribution from adipose, or onset of an intermediate syndrome.^{12,23,117}

Differential Diagnosis

The differential diagnosis for cholinergic poisoning includes three main categories (Table 113–4). The first comprises insecticides and other non-insecticidal cholinesterase inhibitors including the medicinal anticholinesterases neostigmine, pyridostigmine, physostigmine, and echothiophate iodide. The most common patients to suffer cholinergic poisoning syndrome from medicinal cholinesterase inhibitors are patients with myasthenia gravis who are given excessive doses of pyridostigmine. This entire group of xenobiotics should produce low butyrylcholinesterase and low RBC AChE activity. Newer agents used to treat Alzheimer disease, such as donepezil, may inhibit AChE, but symptomatic overdose of these agents appears rare.

TABLE 113–4. Categories of Cholinergic Poisoning

Cholinesterase inhibitors
Carbamate insecticides
Carbamate medicinals
Organic phosphorus insecticides
Organic phosphorus ophthalmic medications
Cholinomimetics
Acedidine
Bethanechol
Carbachol
Methacholine
Muscarine-containing mushroom
Pilocarpine
Nicotine alkaloids
Coniine
Lobeline
Nicotine

The second category of compounds that produce a syndrome of cholinergic poisoning includes agents with cholinomimetic activity. These compounds directly stimulate muscarinic or nicotinic cholinergic receptors, but do not inhibit AChE. In exposed individuals, BuChE and RBC AChE activity should be normal. Cholinomimetic medications include preparations of carbachol, methacholine, pilocarpine, and bethanechol. Nonpharmaceutical agents such as muscarine-containing mushrooms can be cholinomimetic (Chap. 120). Finally, a third group of xenobiotics, the nicotine alkaloids (eg, nicotine, lobeline, and coniine) cause CNS, autonomic, and skeletal muscle symptoms similar to those occurring in OP and carbamate toxicity (Chap. 85).

MANAGEMENT

Organic Phosphorus Insecticides

The primary cause of death after anticholinesterase poisoning is respiratory failure and hypoxemia. This results from muscarinic effects on the cardiovascular and pulmonary systems (bronchospasm, bronchorrhea, aspiration, bradydysrhythmias, or hypotension), nicotinic effects on skeletal muscles (weakness and paralysis), loss of central respiratory drive, and, rarely, seizures. Therefore, initial treatment for a patient exposed to OP compounds is directed at ensuring an adequate airway and ventilation, and at stabilizing cardiorespiratory function by reversing excessive muscarinic effects.^{65,67} Seizures not secondary to hypoxemia are treated with standard anticonvulsants such as benzodiazepines.

Maintenance of the patient's airway is best assured by early endotracheal intubation, and by positive pressure ventilation in patients who are comatose, have significant weakness, or who are unable to handle copious secretions that may accompany the poisoning. Only a neuromuscular blocker that is not primarily metabolized by cholinesterases should be used to induce pharmacologic paralysis if needed. The duration of action of the depolarizing agent succinylcholine and the nondepolarizing agent mivacurium, for example, will be extended in the presence of low BuChE activity, resulting in paralysis that can be prolonged for several hours.^{170,191,192}

Antimuscarinic Therapy. Simultaneously, excessive muscarinic activity should be controlled since this will aid respiration and oxygenation. Atropine competitively antagonizes ACh at muscarinic receptors to reverse excessive secretions, miosis, bronchospasm, vomiting, diarrhea, diaphoresis, and urinary incontinence^{87,107,158}

For adolescents and adults, intravenous doses should begin with boluses of 1 to 3 mg depending on the severity of symptoms; doses for children should start at 0.05 mg/kg up to adult doses. Although many authors state that repeat doses of 1 to 5 mg should be given every 2 to 20 minutes until "atropinization" occurs,⁶⁴ the most rapid method of obtaining control is to give doubling doses every 5 minutes if the response to the previous dose has been inadequate.⁶⁴⁻⁶⁷

This approach, of doubling or incremental doses, was tested against a standard bolus dose approach in a randomized controlled trial.¹ Patients were randomized to receive either 2 to 5 mg of atropine (depending on severity), repeated every 10 to 15 minutes as required, or 1.8 to 3 mg of atropine (depending on severity) followed by doubling doses every 5 minutes as required. Atropine doses were continued until all clinical signs of "atropinization" (see below) were clearly evident; atropine was given as further bolus doses at increasing intervals or as a constant infusion, respectively. All patients received pralidoxime (1–2 g q8–12h). The incremental approach was associated with reaching atropinization at 24 minutes versus 152 minutes with standard bolus dosing, despite administration of similar total doses of atropine (136 mg versus 109 mg, respectively). This faster administration of atropine was likely associated with more rapid resuscitation and stabilization as shown by the improved outcome: mortality with bolus atropine was 22.5% (18/80) and with incremental atropine was 8% (6/75) ($P < 0.05$). Incremental dosing was also associated with less atropine toxicity, less neuromuscular failure, and less requirement for ventilation.¹

"Atropinization" is classically said to occur when patients exhibit dry skin and mucous membranes, decreased or absent bowel sounds, tachycardia, reduced secretions, no bronchospasm (in absence of other causes such as aspiration), and usually, mydriasis.⁶⁴ However, patients die from cardiorespiratory compromise, not wet skin or miosis. Therefore, cardiorespiratory parameters, not pupil size or the presence of sweating, should guide administration of atropine. Atropine dosing should aim to reverse bronchorrhea and bronchospasm and to provide adequate blood pressure and heart rate for tissue oxygenation (for example, systolic BP >90 mmHg and heart rate >80 bpm). All can be easily and rapidly assessed.

Once atropinization occurs, it can be maintained by a constant infusion of atropine, typically initially giving 10% to 20% of the total loading dose per hour (usually maximum 2 mg/h). Regular checks for signs of under- or over-atropinization should guide the use of further boluses followed by changes in the infusion rate, or discontinuation of the infusion.⁶⁷ Continuous infusions have been used for as long as 32 days in patients severely poisoned by very fat soluble OPs that continue to redistribute from the fat and freshly inhibit AChE.⁹⁰

Many texts have previously recommended not giving atropine until oxygen has been administered due to the risk of inducing ventricular tachydysrhythmias.^{4,176} If true, this would have serious implications for patients in developing nations or remote regions where oxygen is frequently unavailable and where the advice would delay administration of potentially life-saving atropine. However, the data that drove this advice is weak, being based upon just two human case reports^{83,104} and one dog study.²²⁹ Overall, there is currently little evidence to support withholding atropine until after oxygen administration and clear possibilities for harm.

The presence of marked tachycardia (>120–140 beats/min in a well-hydrated patient not withdrawing from alcohol), mydriasis, absent bowel sounds, and urinary retention may indicate over-atropinization or atropine toxicity. This is unnecessary and possibly dangerous due to associated hyperthermia, confusion, and agitation.⁶⁷ Tachycardia is not, however, an absolute contraindication to atropine therapy since it can result from hypovolemia, aspiration pneumonitis, or agitation. Isolated pulmonary manifestations may respond to administration of nebulized atropine or ipratropium, and this treatment can accompany parenteral administration of these medications. However, the risk/benefit of this organ specific

treatment has not yet been assessed.

Large doses of atropine may be needed to reverse the bronchospasm, bronchorrhea, and bradycardia associated with severe OP pesticide toxicity.¹⁵⁸ Some patients with mild symptoms need only 1 or 2 mg of atropine to reverse cholinergic toxicity, but the moderately poisoned adolescent or adult commonly requires total doses as large as 40 mg.^{61,65} Some adults have received over 1000 mg of atropine in 24 hours (with adequate pralidoxime dosing) without demonstrating antimuscarinic effects,^{61,224} and total doses as high as 11,000 mg during the course of treatment are reported.¹¹³ However, the additional benefit of such extreme doses over more modest doses is unclear. One study reported that much smaller doses of around 1 mg/h were associated with adequate control of muscarinic features after initial atropinization.²¹³

Atropine does not reverse nicotinic effects. Therefore, patients who improve after receiving atropine should ideally be closely monitored in a high dependency setting for impending respiratory failure from delayed NMJ dysfunction. Patients should be clinically examined regularly for proximal muscle weakness (in particular neck flexor weakness); once noted, tidal volume or negative inspiratory force measurements should be made at least every 6 hours to detect impending respiratory failure and allow early instigation of ventilatory support.

When antimuscarinic CNS toxicity becomes evident, yet peripheral cholinergic findings necessitate the administration of more atropine (eg, bradycardia, bronchorrhea, vomiting), glycopyrrolate can be substituted for atropine because its quaternary ammonium structure limits CNS penetration.¹⁷⁷ One randomized clinical trial compared atropine with glycopyrrolate in ICU management of OP poisoning but was too small to detect any difference between regimens.¹⁶ The initial intravenous dose of glycopyrrolate for adults and adolescents is 1 to 2 mg, repeated as needed or in children 0.025 mg/kg up to adult doses. As with atropine, much higher doses of glycopyrrolate may be required to stabilize patients with severe poisonings. Although scopolamine (hyoscine) has been used in place of atropine,^{134,177} it may cause more pronounced CNS effects. If atropine supplies are exhausted during therapy, other antimuscarinic agents like diphenhydramine may be considered.

However, it is not clear that such an approach is required. In a large case series of patients treated by necessity outside of an ICU, atropinization without CNS toxicity could be safely accomplished by slowing atropine infusions whenever absent bowel sounds, confusion, or hyperthermia were detected.⁶⁷ It is therefore unclear whether glycopyrrolate or scopolamine is required for OP poisoning as long as the atropine regimen is adjusted for each patient.

Oximes

Phosphorylated AChE undergoes hydrolytic regeneration at a very slow rate. However, this process can be markedly enhanced by using an oxime such as pralidoxime chloride (2-PAM) or obidoxime (Fig. 113–3).⁸¹ Regeneration of AChE lowers ACh concentrations, improving both muscarinic and nicotinic effects. An immediate rise in RBC AChE activity, presumably paralleling a rise in neuronal AChE activity, can be seen after effective administration of oximes.^{69,211}

As discussed above, phosphorylated AChE becomes aged, and therefore unresponsive to oximes, at different rates according to the chemistry of the OP.⁸¹ Oximes therefore should be given early, within 3 to 4 hours of exposure, after dimethoxy OP poisoning. In contrast, they can still be highly efficacious 48 hours after diethoxy poisoning, with some effects even when given up to several days after exposure. Oximes can also be efficacious weeks after poisoning with a fat soluble OP. Therefore, some AChE may still be undergoing new inhibition for days or weeks after exposure in symptomatic patients, and such inhibition may be reversible by oximes.²³⁰ Case reports support this reasoning by noting dramatic effects in reversing paralysis, weakness, and cholinergic symptoms even after late administration of pralidoxime.^{148–157}

However, the clinical effectiveness of oximes in significant OP insecticide poisoning is still unclear. The first clinical experience with pralidoxime was reported in the late fifties by Namba who treated five patients with occupational parathion poisoning.¹⁵⁷ All patients responded well to around 1 g of pralidoxime IV. As expected from occupational inhalational exposure, none of the patients were very ill. Namba subsequently reported the use of much higher doses of pralidoxime, of 1 to 2 g bolus loading doses followed by 0.5 g/h, in patients with severe parathion poisoning.¹⁵⁵ He also noted that some OPs, including malathion, did not respond well to pralidoxime.¹⁵⁶ These caveats seem to have been lost subsequently, with most textbooks recommending the use of pralidoxime 1 g, followed by a second 1 g bolus after a few hours as necessary for all cases.

Extensive clinical experience of bolus pralidoxime regimens in Asia has led to widespread doubt about the efficacy of oximes.⁷⁵ Asian clinicians have traditionally used 1 g of pralidoxime every 4 to 6 hours for 1 to 3 days, producing high peaks and deep troughs in blood pralidoxime concentration. In a 1992 natural experiment, Sri Lankan doctors reported finding no difference in OP case fatality during a 6-month period when pralidoxime was not available in their hospital, compared to periods when it was available.⁵⁵ They argued that pralidoxime was of little clinical benefit, and since it was expensive, should not be routinely used for treating OP-poisoned patients. European clinician researchers responded that the doses being used in Asia were too low and that higher doses, more akin to Namba's second regimen, were required.¹²² Two further trials from south India reported no effect¹²³ or even harm⁴² from pralidoxime therapy.

All these clinical trials aimed for a plasma oxime concentration of around 4 µg/mL; unfortunately, this target was based on a single study with a single nerve agent in cats²⁰⁴ and should not have been extrapolated to human OP pesticide poisoning in general.⁸¹ In vitro studies with human RBCs suggest that a higher concentration of around 100 µmol (~20 µg/mL) is required for sustained reactivation,^{81,211} resulting in the recommendation from a WHO group that all patients receive a loading dose of at least 30 mg/kg pralidoxime chloride, followed by at least 8 mg/kg/h.¹²¹ A subsequent randomized clinical trial from India showed that very high doses of pralidoxime iodide, a 2 g loading dose followed by 1 g/h, reduced death and length of ventilation in moderately poisoned patients who presented early and were treated in an ICU.¹⁶⁷ However, similar doses of pralidoxime chloride did not reactivate AChE in severe poisoning with dimethoate and other dimethoxy pesticides.⁶⁹

Additionally, another randomized controlled trial from Sri Lanka was unable to demonstrate a benefit from similar high doses of pralidoxime.⁶⁸ This trial compared no pralidoxime chloride with a 2 g bolus over 20 minutes followed by 0.5 g/h for up to 7 days or when atropine was no longer required, in addition to standard therapy. Although the study was stopped earlier than planned, pralidoxime was associated with an adjusted hazard ratio (HR) of 1.69 (95% confidence interval 0.88 to 3.26, *p* = 0.12) for death.

A subsequent Cochrane review concluded that current evidence was insufficient to indicate whether oximes are harmful or beneficial.³¹ It is possible that some of the difference between the outcomes in the two major trials is due to the very high level of supportive care available in India. Despite being less severely poisoned, 66% of Indian patients were intubated at baseline compared to 17% of Sri Lankan patients. This high level of supportive care is not available in rural district hospitals that see the majority of OP-poisoned patients globally.

All the clinical trials included in the Cochrane review assessed pralidoxime salts. Obidoxime⁸¹ has been used in some countries, including Germany^{79,211} and Iran,¹⁴ with apparently beneficial effects. Although use of high dose obidoxime has been associated with liver injury,¹⁴ this does not seem to be the case with doses of 250 mg as a loading dose followed by 750 mg/24 h.⁸¹ The use of newer oximes such as HI-6 and HLo-7 has not yet been reported in pesticide poisoned patients. However, in vitro studies suggest that they will not be highly effective for human AChE inhibited by a range of OP pesticides.²³⁵

Currently, the exact role of oximes is unclear. However, they should be given as soon as possible after exposure to increase the chance of benefit. The difference between Indian and Sri Lankan studies indicates that high quality intensive care is probably required to reduce the risk of serious adverse effects. The duration of use is unclear; ideally, electrophysiological or clinical changes should be monitored to indicate whether oximes offer benefit to the patient.

Some effects of oximes are not well understood. Their quaternary ammonium compound structures are thought to reduce their passage across the blood–brain barrier and prevent CNS effects.²⁰⁷ However, obidoxime has been detected in CSF,⁸¹ and at least one case report describes pralidoxime-induced improvements in mental status and electroencephalograms not attributable to improved ventilation or perfusion.¹³⁹

Benzodiazepines

Animal studies demonstrate that administering benzodiazepines along with oximes in the treatment of poisoning with OP nerve agents or the insecticide dichlorvos can increase survival and decrease the incidence of seizures and neuropathy.^{60,154} Diazepam can also decrease cerebral morphologic damage resulting from OP compound–related seizures.^{24,144} One study suggests that diazepam may help attenuate OP-induced respiratory depression,⁶⁰ postulating that the benzodiazepines attenuate the overstimulation of central respiratory centers caused by OP insecticides. However, seizures have been uncommon in large case series of patients poisoned by OP insecticides,^{69,222} and no clinical studies have yet been performed to determine whether benzodiazepines offer benefit to humans.¹⁴² In the absence of this evidence, benzodiazepines should be used to treat OP-related seizures and agitation and to aid intubation but should not be given routinely to all cases.¹⁴²

Other Treatments

These therapies affect only limited mechanisms involved in OP poisoning. Multiple additional therapies have been tested in animals, but none have been shown to be beneficial in large clinical trials, and none are used widely in clinical practice.^{32,171} Future clinical trials may identify patients for whom they would be beneficial. Treatments that have been proposed include magnesium^{19,163} or clonidine¹⁶⁹ to reduce presynaptic acetylcholine release, fresh frozen plasma as a source of BuChE for scavenging OP pesticides,^{101,173} and sodium bicarbonate.¹⁷⁸

Decontamination

Cutaneous absorption of OP pesticides and carbamates necessitates removal of all clothing as soon as possible after

resuscitation and administration of atropine and oxygen. Medical personnel should avoid self-contamination by wearing neoprene or nitrile gloves. Double-gloving with standard vinyl gloves may be protective. Skin should be triple-washed with water, soap, and water, and rinsed again with water. Although alcohol-based soaps are sometimes recommended to dissolve hydrocarbons,⁸⁵ these products can be difficult to find, and expeditious skin cleansing should be the primary goal. Cutaneous absorption can also result from contact with OP and carbamate compounds in vomitus and diarrhea if the initial exposure was by ingestion. Oily insecticides may be difficult to remove from thick or long hair, even with repeated shampooing, and shaving scalp hair may be necessary. Exposed leather clothing or products should be discarded because decontamination is very difficult once impregnation has occurred.

Military institutions are now experimenting with cholinesterase sponges for cutaneous OP decontamination.⁹³ The sponge consists of a cholinesterase enzyme covalently linked and immobilized in a polyurethane matrix. Reportedly, the sponge is effective in removing OP compounds from skin and surfaces.⁹³

In substantial, potentially life-threatening acute ingestions, if emesis has not occurred and the patient presents within one hour, evacuation of stomach contents by lavage using a nasogastric tube can be done. Because the onset of coma, seizures, and paralysis can be rapid, airway protection is necessary to perform the procedure safely. Although there are data suggesting that activated charcoal (AC) may adsorb some OP insecticides, a study of 1310 Sri Lankan patients with OP or carbamate poisoning found no benefit from the use of multiple dose AC.⁷² Thus, the present recommendation is that patients with anticholinesterase poisoning receive a single dose of 1 g/kg AC.

Health care providers must always maintain caution when coming into contact with stomach contents or other body fluids when managing these cases.¹³⁷ Bystanders have been poisoned by providing mouth-to-mouth resuscitation to a victim of an intentional ingestion of diazinon.¹²⁹ There have also been reports of nosocomial poisoning in ED staff.^{35,89,197} However, in only one paper were BuChE activities tested³⁵ to support the hypothesis of nosocomial poisoning, and none showed any evidence of inhibition. Clinical experience from South Asia suggests that nosocomial poisoning with OP pesticides is unlikely as long as standard universal precautions are followed.¹⁷⁹ It is more likely that the nonspecific illnesses and anxiety reported are due to the solvents co-formulated with the pesticides.¹³⁷ An Australian consensus statement on nosocomial poisoning found little evidence that health care workers were at risk of such poisoning and noted that decontamination should not take place to the detriment of timely resuscitation and medical assessment.¹³⁷

Disposition

After atropinization, patients with cholinesterase inhibitor poisoning should be frequently observed for evidence of (1) deteriorating neurologic function and potential paralysis and (2) need for increases or reductions in atropine dosing.

RBC AChE and BuChE activities can be measured intermittently after the institution of pralidoxime therapy.^{79,81,209,230} Effective oxime therapy will normalize RBC AChE activity but usually does not affect BuChE activity. In the absence of effective oxime therapy, RBC AChE activity may be markedly depressed long after neuronal AChE activity has returned to normal. Therefore, an individual who remains asymptomatic may be discharged home with subnormal cholinesterase activity. BuChE begins to rise when no more OP is left in the body.⁶⁵ A sudden fall in BuChE activity suggests that OP is being redistributed from fat stores. The relevance of a fall in BuChE activity that is not clinically apparent is uncertain. Overall, there is little evidence at present that repeated testing of AChE or BuChE activity improves management and outcome over clinical monitoring alone. Such testing is, however, important for research assessing new interventions.

When available, electromyographic studies to detect signs of motor endplate dysfunction and early AChE inhibition may be a more sensitive method for identifying recurrent cholinergic toxicity.²³ Again, the clinical usefulness of this approach has not yet been studied.

A patient who becomes asymptomatic, not requiring pralidoxime or atropine for 1 to 2 days, may be discharged. Although recurrent cholinergic crises and/or respiratory failure can occur after several days, usually such patients have previously shown clinical signs of some form. Patients should not be allowed to go home wearing clothing that was worn when the poisoning occurred.

Carbamates

The treatment of patients with carbamate poisoning is identical to that of OP compound poisoning, with two exceptions. First, the use of oxime in monomethyl carbamate exposure is controversial, and many providers will not administer it because animal data imply that pralidoxime may increase AChE inactivation in carbaryl poisoning.^{133,136} More recent reports suggest aldicarb poisoning may benefit from oxime therapy¹⁷⁵ and that the dose of pralidoxime may be important in carbaryl poisoning.¹⁴⁷ Comparative human data investigating the use of oximes in carbamate poisonings are currently lacking. Fortunately, because of the rapid hydrolysis of the carbamate-AChE complex, symptoms, including weakness and paralysis, usually resolve within 24 to 48 hours without pralidoxime therapy. However, administering pralidoxime to a poisoned patient in a cholinergic crisis is appropriate when it is not known whether the patient is suffering from OP or carbamate pesticide poisoning. If the poisoning is from a carbamate pesticide, pralidoxime therapy may not be necessary,

but if used will likely not prove detrimental.

Second, significant inhibition of RBC AChE and BuChE by carbamates generally does not last for more than 1 to 2 days, assuming absorption is complete. Patients exposed to carbamates usually have normal cholinesterase activities by the time of discharge. There are no reported cases of recurrent or delayed poisonings following carbamate insecticide poisoning. Therefore, repeating cholinesterase tests after patients are asymptomatic is usually unnecessary. However, of note, complications of poisoning with carbamates—such as aspiration and hypoxic brain injury—can last many days.

SUMMARY

- OP and carbamate insecticides kill hundreds of thousands of people each year.
- Poisoning with these pesticides is not uniform—they differ markedly in their human toxicity, pharmacokinetics, clinical syndrome, and response to therapy.
- Symptoms result from inhibition of AChE and overstimulation of muscarinic and nicotinic receptors in synapses of the autonomic and central nervous systems and at the neuromuscular junction.
- Patients with substantial poisoning present with the cholinergic crisis and show pinpoint pupils, excessive sweating and salivation, and respiratory failure due to bronchospasm, bronchorrhea, loss of central respiratory drive, and dysfunction of neuromuscular junction.
- For severe poisoning, atropine should be administered in doubling doses to attain atropinization before being continued as an infusion at a dose individualized for the patient.
- Patients may develop neuromuscular junction dysfunction that progresses to respiratory failure; such patients often require ventilatory support for weeks.
- Cholinergic features can recur many days after ingestion of very fat-soluble compounds such as fenthion due to redistribution from fat stores.

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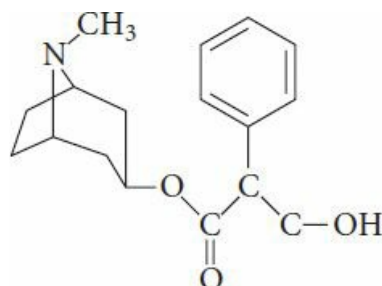
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A32 ANTIDOTES IN DEPTH

Atropine

Mary Ann Howland



INTRODUCTION

Atropine is the prototypical antimuscarinic xenobiotic. It is a competitive antagonist at both central and peripheral muscarinic receptors, that is used to treat patients with symptoms following exposures to muscarinic agonists such as pilocarpine, Clitocybe mushrooms, and acetylcholinesterase inhibitors. The latter group includes pesticides, such as carbamate and organic phosphorous compounds, chemical warfare nerve agents, and some xenobiotics used to treat patients with Alzheimer disease, such as donepezil and rivastigmine.

HISTORY

Many plants contain the alkaloids atropine and or scopolamine. One notable example is *Atropa belladonna*, named by Linnaeus after Atropos, the goddess of fate in Greek mythology who could cut short a person's life. Belladonna means beautiful woman in Italian and comes from the practice by Italian women of placing belladonna extract in their eyes to produce aesthetically pleasing dilated pupils.¹⁰ In the early 1800s, atropine was isolated and purified from plants. In the 1860s, Fraser experimented with the dose-response relationship between atropine and physostigmine involving various organs such as the heart and the eye.²⁰ Experiments in the 1940s with cholinesterase inhibitors demonstrated that atropine reversed many of the effects of these xenobiotics and protected animals against doses two to three times the LD₅₀.^{50, 50}

PHARMACOLOGY

Chemistry

Atropine (dl-hyoscyamine), like scopolamine (l-hyoscine), is a tropane alkaloid with a tertiary amine structure that allows central nervous system (CNS) penetration. Quaternary amine antimuscarinics such as glycopyrrolate, ipratropium, tiotropium, methylhomatropine bromide, and methylatropine bromide do not cross the blood-brain barrier into the CNS. Tropane alkaloids are bicyclic nitrogen containing compounds that are naturally found in the plants of the families Solanaceae (eg, deadly nightshade, *Datura*) and Erythroxylaceae (eg, coca) and have a long history of use as poisons and medicinals. Only l-hyoscyamine is active and found in nature. The process of isolation results in racemization and forms dl-hyoscyamine.

Mechanism of Action

Cholinergic receptors consist of muscarinic and nicotinic subtypes. Muscarinic receptors are coupled to G proteins and either inhibit adenylyl cyclase (M₂, M₄) or increase phospholipase C (M₁, M₃, M₅). Muscarinic receptors are widely distributed throughout the peripheral and central nervous systems.²³

The competitive blockade of muscarinic receptors in normal individuals results in dose-dependent clinical effects that

vary by organ system based on the degree of endogenous parasympathetic tone.^{10,23} In adults, low doses (0.5 mg) of atropine sometimes causes a paradoxical bradycardia of about 4 to 8 beats per minute, not evident with rapid IV administration. Higher doses of atropine (2 mg) produce noticeable dryness of the mouth and sweat glands, feeling of warmth, flushing, tachycardia, reactive dilated pupils, blurred near vision, drowsiness, postural hypotension, and urinary hesitation. At higher doses (3 to 5 mg) of atropine, all the aforementioned symptoms are exaggerated, with escalating degrees of hyperthermia, tachycardia, drowsiness, difficulty voiding, prolonged gastrointestinal transit time, and decreased peristalsis. Doses of greater than or equal to 10 mg of atropine produce incapacitation with hot, dry, flushed skin, dilated pupils, blurred vision, very dry mouth, tachycardia, urinary retention, constipation, increased drowsiness or disorientation, hallucinations, stereotypical movements, bursts of laughter, delirium, and finally, coma, and rarely death.^{10,22}

The paradoxical bradycardia produced at low doses of atropine is thought to be a consequence of the inhibition of peripheral M₁ presynaptic postganglionic parasympathetic neurons. Stimulation of these receptors by acetylcholine inhibits the further release of acetylcholine, and atropine interferes with this negative feedback.^{10,48} Not all studies, however, have shown this paradoxical decrease in heart rate.²⁷

Centrally acting muscarinic antagonists include atropine, scopolamine, and homatropine. Glycopyrrolate, ipratropium, and tiotropium act peripherally. Scopolamine is approximately 10 times more potent than atropine.³¹ Homatropine is approximately one-tenth as potent as atropine, depending on the measured outcome and route of administration.²⁹

Cholinesterase inhibitors prevent the breakdown of acetylcholine by acetylcholinesterase, thereby increasing the amount of acetylcholine available to stimulate cholinergic receptors at both muscarinic and nicotinic subtypes, although the degree of effect varies widely among the class. Atropine is a competitive antagonist of acetylcholine only at muscarinic receptors and not nicotinic receptors.¹³

Miosis from the topical instillation of a cholinesterase inhibitor into the eye will not be reversed by the systemic administration of atropine.²² The systemic administration of 354 mg of atropine made one patient floridly anticholinergic but did not counteract the ophthalmic effects of a previously instilled topical cholinesterase inhibitor.²²

Pharmacokinetics and Pharmacodynamics

Atropine is absorbed rapidly from most routes of administration including inhalation, oral, and intramuscular (IM).³ Ingestion of 1 mg of atropine produces maximal effects on heart rate and on salivary secretions in 1 and 3 hours, respectively. The duration of action may last from 12 to 24 hours, depending on the dose.

The distribution half-life of atropine following intravenous (IV) administration is approximately one minute. The apparent volume of distribution (V_d) is about 2 to 2.6 L/kg.²⁹ As a result of the rapid distribution, 10 minutes after IV administration less than 5% of the dose remains in the serum. The serum concentrations of atropine are similar at 1 hour following either 1 mg IV or IM in adults.^{3,7} The elimination half-life is 6.5 hours.⁴¹

Following IM administration of 0.02 mg/kg in adults, the absorption rate and elimination rates are comparable for the racemic dl-hyoscyamine and the active l-hyoscyamine at 8 minutes and 2.5 hours, respectively. The mean peak serum concentration and the area under the curve (AUC) are higher for the racemic mixture indicating a stereochemical difference in pharmacokinetics.²⁹ Renal elimination accounts for 34% to 57% of the excretion of the dose, and the majority of renal elimination occurs within 6 hours.³ Serum concentrations of l-hyoscyamine correlate with effects on heart rate and the antisialagogue effects. Serum concentrations below 0.5 µg/L may cause bradycardia in adults, whereas higher concentrations cause tachycardia.²⁹

A study of intraosseous (IO) administration in minipigs demonstrated a pharmacokinetic profile similar to IV atropine.³⁵ The time to maximum concentration following a dose of 0.25 mg/kg was 2 minutes with both IV and IO injection, compared to 3.5 minutes for IM injection.

Atropine autoinjectors are now given to first responders for use during chemical terrorist attacks. The administration of 2 mg of atropine by autoinjector was compared with 2 mg administered by conventional needle and syringe into the deltoid of six adult subjects.⁴⁶ The onset of tachycardia and the time to maximal increase in heart rate occurred sooner with the autoinjector (16 minutes versus 23 minutes, and 34 minutes versus 41 minutes, respectively). An analysis of radiographs of contrast material injected by autoinjector or conventional IM administration into the leg of a dog demonstrated that the autoinjector appeared to “spray” the material into a larger tissue area, accounting for a faster rate of absorption.⁴⁶

Ophthalmic instillation of atropine causes cyclopegia and mydriasis by blocking the M₃ muscarinic receptor on the iris sphincter muscle.³⁴ The peak mydriatic effect occurs within 30 to 40 minutes and persists for 7 to 10 days. In contrast, the effects of topical homatropine on the eye occur sooner than topical atropine (10–30 minutes for mydriasis and 30–90 minutes for cyclopegia) and are shorter in duration (6–48 hours).

The effects on pupillary dilation after systemic atropine administration depend on the dose and route of administration. An IM dose of 0.01 mg/kg into the thigh of healthy adults produced no change in pupil size,¹⁴ while subcutaneous administration into the upper arm of doses of 0.5 mg, 1 mg, and 2 mg per 70 kg person produced a dose dependent increase

in pupil size. An oral dose of 0.02 mg/kg also produced pupillary dilation.^{12,27}

An investigation of the bioavailability of atropine eye drops in healthy adults revealed approximately a 65% systemic absorption, but with a wide individual variability.²⁸ The time to maximum serum concentration was 30 minutes, and the apparent elimination half-life was 2.5 hours.

The pharmacokinetics of three inhaled doses of atropine from a metered dose nebulizer was compared with 2 mg of IM atropine in healthy adults.²⁴ Peak concentrations were comparable for the 2 mg inhaled and 2 mg IM atropine doses. The time to peak concentration following inhalation averaged 1.3 hours. A novel nanoatropine dry powder inhaler is being evaluated to rapidly achieve blood concentrations of atropine in the hopes of circumventing IM administration.²

ROLE IN ORGANIC PHOSPHOROUS AND CARBAMATE TOXICITY

One of the earliest descriptions of the effectiveness of atropine in parathion and tetraethylpyrophosphate insecticide poisoning was published in 1955.²¹ Atropine improved survival when administered early and continued with adequate maintenance doses, intubation, and ventilation. Parathion and tetraethylpyrophosphate insecticide exposure led to heart block and bronchoconstriction in dogs, whereas humans were more likely to develop a relative bradycardia. Humans were more likely to die from respiratory causes resulting from central apnea, diaphragmatic weakness, and bronchorrhea.

In 1971, a landmark case series and review of organic phosphorus compound (OP) insecticide poisonings was published. Included was a table classifying the severity of poisoning along with treatment protocols for each level of severity.³⁶ This regimen served as the foundation of treatment regimens (atropine and pralidoxime) for many years.

In the 1930s and 1940s, the Germans synthesized OP insecticides (acetylcholinesterase inhibitors) that were further developed as chemical warfare nerve agents ([Chap. 132](#)).⁴⁵ Although these xenobiotics inhibit acetylcholinesterase in a manner similar to traditional OP insecticides, these so-called “nerve agents” also affect other cholinesterases, and at high doses directly affect nicotinic and muscarinic receptors. Atropine was chosen in the late 1940s as the standard antidote for these nerve agents. The dose of atropine needed to antagonize these nerve agents is much less than that needed to effectively antagonize traditional OP insecticides, largely because of differences in pharmacokinetics. The benefits of adding pralidoxime to atropine were noted in the 1950s, and in the 1960s, pralidoxime was established as a standard antidote in addition to atropine for these xenobiotics ([Antidotes in Depth: A33](#)).

ADVERSE EFFECTS AND SAFETY ISSUES

When atropine is used in the absence of a xenobiotic that increases or mimics acetylcholine, adverse effects begin at 0.5 mg IV in the adult and include dry mouth and decreased sweat. However, in the presence of muscarinics or anticholinesterases, these effects may not occur until many milligrams of atropine are administered.

Intravenous doses of greater than 10 mg of atropine and oral doses of 500 to 1000 mg have been administered with full recovery. Deaths from atropine use are usually correlated with hyperthermia.

An unintentional atropine dose of one thousand milligrams orally resulted in typical manifestations of anticholinergic poisoning that began within a short time and lasted 4 days.¹ In 2 hours the patient went from feeling hot and flushed with blurred vision to stupor. Over the ensuing 24 hours he became tachycardic, hyperthermic, and comatose with dilated, nonreactive pupils and shallow respirations. By 40 hours he started to respond to his name and his temperature had normalized, but he had dry mucous membranes with dilated and nonreactive pupils. He went from coma to restlessness, hallucinations, and paranoia. At 4 days he regained a normal mental status with amnesia for the previous 4 days.

A survey of pediatric emergency departments in Israel reported on 240 children who were unintentionally injected by atropine autoinjections or autoinjector systems, triggering unintended administration, self administration, needle injury, or delivery to an unintended site during the Persian Gulf crisis.⁴ Half of the children developed systemic effects that correlated with the doses of atropine administered. Eight percent of effects were serious, but there were no seizures or deaths.

Systemic atropine toxicity may occur when too large a dose of atropine, scopolamine, or homatropine is instilled in the eye, especially in children.³⁸ Excessive absorption from other routes of administration such as rectal or inhalation would also be expected to result in toxicity.⁴⁴ In the event of an atropine overdose, physostigmine, a reversible, CNS active, cholinesterase inhibitor, is the antidote of choice ([Antidotes in Depth: A9](#)).³⁷ Schizophrenic patients in the 1950s were often given atropine as a treatment. Within 15 to 20 minutes of getting 32 to 212 mg of IM atropine, patients become restless and often confused. This progressed to muscular incoordination, ataxia, weakness, and garbled speech.¹⁹ The patients then progressed to disorientation with illusions, visual hallucinations, and delirium, to coma. The coma often lasted for 4 to 6 hours, and then patients recovered in a manner that in some respects is the reverse of poisoning. Regardless of the dose of atropine required to induce the coma, physostigmine 4 mg IM completely reversed the toxicity within 20 minutes, although the reversal only lasted for 30 to 45 minutes.^{19,37}

Other precautions or contraindications to consider when administering atropine include those associated with all antimuscarinics and include narrow angle closure glaucoma, obstructive uropathy, gastroparesis, pylorospasm, relaxation of the lower esophageal sphincter, and myasthenia gravis. Of course these complications must be weighed against the possible life-threatening nature of OP, carbamate, and chemical nerve agent poisoning.

PREGNANCY AND LACTATION

Atropine is classified by the Food and Drug Administration (FDA) as pregnancy category C. Atropine crosses the placenta and may cause tachycardia in the fetus near term. Human data suggest low risk, and atropine should be used when indicated.^{9,47} The American Academy of Pediatrics classifies atropine to be as compatible with breast-feeding.⁹

DOSING AND ADMINISTRATION

The dosage regimen of atropine for pesticide poisoning in adults has never been evaluated in a randomized, controlled trial, and there is considerable variation in recommendations in the literature.¹⁶ A prospective, observational study suggested that a dose doubling, titrated protocol provided equal efficacy with less atropine toxicity compared with a less preplanned ad hoc dosing protocol.⁴⁰ Experience suggested that atropine should be initiated in adults in doses of 1 to 2 mg IV for mild to moderate poisoning and 3 to 5 mg IV for severe poisoning with unconsciousness.³⁶ This dose can be doubled every 3 to 5 minutes until improvement has begun, at which time dose doubling can stop and similar or smaller doses can be used.^{17,42} We believe that the most important end point for adequate atropinization is the resolution of bronchorrhea and the reversal of the muscarinic toxic syndrome. However, it is important not to confuse abnormal focal auscultatory sounds associated with pulmonary aspiration with those of extensive bronchorrhea.^{17,42} Some authors suggest clear lungs, heart rate greater than or equal to 80 beats/min, and systolic blood pressure exceeding 80 mm Hg as the most important goals of therapy, and dry axillae and wider than pinpoint pupils as additional goals.¹⁸ Once these end points are achieved, a maintenance dose of atropine needs to be started. One group suggests administering 10% to 20% of the loading dose as an IV infusion every hour as a starting point with meticulous, frequent reevaluation and titration.^{16,17} Atropine can be diluted in 0.9% sodium chloride, with rates of 0.5 to 1.5 mg/h of atropine commonly used.⁴⁰ For example, if a patient received atropine 2 mg IV, then 4 mg in 5 minutes, and 8 mg in 5 minutes, when improvement in bronchorrhea is noticeable, the total loading dose to initial control would be 14 mg in 10 minutes. The initial IV infusion dose of atropine would be 1.4 mg/h. This could be achieved by mixing 10 mg of atropine in 100 mL of 0.9% sodium chloride to make a concentration of 0.1 mg/mL and infusing it at 14 mL (1.4 mg)/h. If too much atropine is administered, the patient demonstrates classic signs of peripheral and central anticholinergic toxicity as described above.

The IV/IO starting dose of atropine in children is 0.02 mg/kg up to the adult dose.^{39,42,49} A continuous infusion of 0.025 mg/kg/h was successfully used in a 2 year-old child following a fenthion poisoning.⁸ Although a minimum dose of 0.1 mg has been advocated, this dose would be toxic to infants <5 kg and is not recommended.⁶

In the event that a person is exposed to a chemical warfare nerve agent, atropine should be administered in a dosage suitable for both the severity of the poisoning and the age of the patient. In a conscious adult with mild to moderate cholinergic effects, 2 mg of atropine IV or IM should be administered every 5 to 10 minutes until shortness of breath improves and drying of secretions occurs.⁴⁵ One adult autoinjector of atropine for IM administration, Mark 1 Nerve Agent Antidote Kit (NAAK), contains 2 mg of atropine, and therefore multiple injectors may be required. Total doses of 2 to 4 mg of atropine are usually all that is needed, which is much lower than the dose for most OP pesticide exposures. Patients who are unconscious or apneic require higher total doses, with 5 to 15 mg usually sufficing.⁴⁵

The appropriate total Mark 1 autoinjector doses of atropine for children depend on age and weight.^{25,32} For ages 3 to 7 (13–25 kg), one autoinjector (2 mg) of atropine and one autoinjector of pralidoxime (600 mg) should be administered, resulting in a projected atropine dose of 0.08 to 0.15 mg/kg. For ages 8 to 14, two autoinjectors of atropine and two autoinjectors of pralidoxime should be administered, resulting in a projected atropine dose of 0.08 to 0.15 mg/kg. For patients older than 14 years of age, three autoinjectors of atropine and pralidoxime should be administered, resulting in a projected dose of atropine of less than 0.11 mg/kg. In an emergency for children younger than 3 years of age, a risk-to-benefit analysis would suggest injecting one autoinjector of atropine and one of pralidoxime. If time permits and only one autoinjector is available for use, its contents may be transferred to a small sterile vial for traditional IM administration with a needle and syringe.²⁶ Some experts recommend that children under the age of one year be administered one pediatric atropine autoinjector (0.5 mg), such as AtroPen (Meridian Medical Technologies, Inc.), if available, and children over the age of one year be administered the Mark 1 autoinjector as described above.

When IV administration is not feasible, atropine may also be administered IO at the standard IV dose. However, the dose for endotracheal administration in adults should be two to two-and-a-half times the IV dose, diluted in 5 to 10 mL of 0.9% sodium chloride solution or sterile water. For children, the 2010 American Heart Association guidelines for

pediatric advanced life support recommend 0.04 to 0.06 mg/kg in a child endotracheally, followed by a flush of 5 mL of 0.9% sodium chloride solution and then five manual ventilations to enhance absorption.³⁹

FORMULATION AND ACQUISITION

Atropine sulfate injection is available in many different strengths, with the following concentrations in each 1 mL vial or ampule: 50 µg, 300 µg, 400 µg, 500 µg, 800 µg, and 1 mg. Atropine sulfate is also available in prefilled 5 mL or 10 mL syringes with a concentration of 0.1 mg/mL for adults and in 5 mL syringes with a concentration of 0.05 mg/mL for pediatrics.

The AtroPen Auto-Injector is a prefilled syringe designed for IM injection by an autoinjector into the outer thigh.⁵ It is available in four strengths: 0.25 mg, 0.5 mg (blue label), 1 mg (dark red label), and 2 mg (green label).

Atropine is also packaged in a kit designed for IM injection with a second autoinjector containing 600 mg of pralidoxime in 2 mL of sterile water for injection with 40 mg benzyl alcohol and 22.5 mg glycine. The pralidoxime injector is accompanied by an atropine autoinjector containing 2.1 mg of atropine in 0.7 mL of a sterile solution containing 12.47 mg glycerin and not more than 2.8 mg phenol. This particular combination kit is called a “Mark 1 Nerve Agent Antidote Kit” and is designed for IM use in case of a nerve agent attack. The needles are 0.8 inches in length.³³ The Mark 1 NAAK has recently been replaced by the DuoDote Autoinjector System and the analagous, military designated antidote treatment nerve agent, autoinjector (ATNAA), which use technology that sequentially administers 2.1 mg in 0.7 mL atropine followed by 600 mg in 2 mL pralidoxime chloride IM through the same syringe. The 23 gauge needle is 0.8 inches in length.

Atropine is available orally in 300 µg, 400 µg, and 600 µg tablets.

In case of a shortage during an emergency, large quantities of atropine syringes can be compounded by a pharmacist from atropine powder utilizing standard syringe batching system.³⁰ In vitro evidence suggests that outdated atropine retains its potency and that an extemporaneously prepared atropine solution from powder is stable for at least 3 days.^{15,43} Other sources of atropine to consider in an emergency during a shortage would be atropine eye drops, which come as a 1% concentration (10 mg/mL). Homatropine, available as eye drops in a 2% or 5% concentration, compared favorably with atropine in preventing lethality when administered IM in a pretreatment rodent model using dichlorvos. In this experimental model, homatropine appeared to be half as potent as atropine.¹¹ Atropine is maintained as part of the Strategic National Stockpile (SNS) for formulary in repositories in numerous locations throughout the United States.

SUMMARY

- Atropine has many clinical uses as a competitive antagonist at both central and peripheral muscarinic receptor sites.
- The use of atropine is extensive for patients with bradycardias, in advanced cardiac life support, and in those exposed to acetylcholinesterase inhibitors in the workplace, in the home, and potentially on the battlefield.
- Atropine should be dosed to the resolution of bronchorrhea caused by the muscarinic toxidrome using a dose-titrated doubling protocol.

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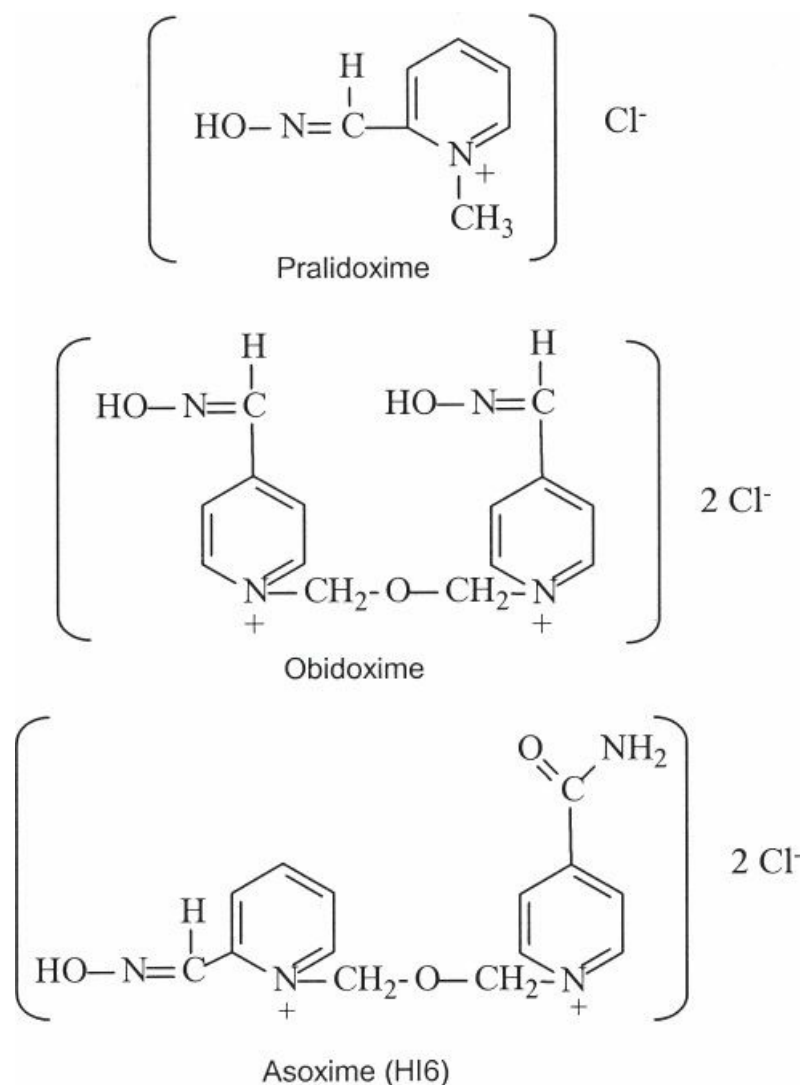
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A33 ANTIDOTES IN DEPTH

Pralidoxime

Mary Ann Howland



INTRODUCTION

Pralidoxime chloride (2-PAM) is the only cholinesterase-reactivating xenobiotic currently available in the United States. It is used concomitantly with atropine in the management of patients poisoned by organic phosphorus (OP) compounds. Administration should be initiated as soon as possible after exposure, but can be effective even days after an exposure and therefore should be administered to all symptomatic patients independent of delay. Continuous infusion is preferable to intermittent administration for patients with serious toxicity, and a prolonged therapeutic course may be required.

HISTORY

It was recognized in the 1950s that certain phosphate esters were potent and irreversible inhibitors of acetylcholinesterase (AChE).^{84,85} Identification of an anionic site on AChE led to the theory that a compound could be developed that would bind to this site and remove the phosphate ester, thereby reactivating AChE. A few hydroxylamine derivatives were studied and led to the design of pralidoxime.⁸⁵

PHARMACOLOGY

Chemistry

Pralidoxime chloride is a quaternary pyridinium oxime with a molecular weight of 173 Da. The chloride salt exhibits excellent water solubility and physiologic compatibility. Pralidoxime iodide has a molecular weight of 264 Da, is less water soluble, and can potentially induce iodism.³

Related Xenobiotics

Organic phosphorous pesticides and nerve agents both cross the CNS. A disadvantage of pralidoxime is that in vivo rat studies it demonstrates only a 10% CNS penetration.⁶⁶ Strategies to enhance the penetration of oximes across the blood–brain barrier (BBB) include enhancing lipophilicity by adding a fluorine atom into the ring structure, designing a glucose-oxime drug which could use facilitated glucose transporters to cross the BBB, designing a prodrug of pralidoxime that could be oxidized to the active drug once it had crossed the BBB, conjugating the oxime with amidine, and by using a targeted nanoparticle drug delivery system.⁵⁰

Obidoxime (Toxogonin, LuH-6) is an oxime used outside the United States that contains two active sites per molecule and is considered by some to be more effective than pralidoxime.^{23,24,88} An in vitro study using human erythrocyte AChE supported the superiority of obidoxime to pralidoxime in reactivating AChE inhibited by the dimethyl phosphoryl (malaaxon, mevinphos) and diethyl phosphoryl OP compounds (paraoxon). On a molar basis, obidoxime is approximately 10 to 20 times more effective in reactivating AChE than pralidoxime.⁸⁸ A potential disadvantage is the concern that the phosphorylobidoxime generated from the reactivation of AChE by obidoxime could reinhibit AChE if not metabolized by a plasma enzyme similar or identical to human paraoxonase 1 (PON1). PON1 exhibits polymorphism²¹ and one in 20 patients may not be able to metabolize this phosphorylobidoxime compound. Phosphorylpralidoxime is unstable and does not accumulate. A molecular docking simulation study demonstrated that pralidoxime had better positioning at the oxyanion hole compared to obidoxime, allowing better reactivation of methamidophos inhibited AChE.⁴³ The H series of oximes (named after Hagedorn; HI-6, HLo-7) were developed to act against the chemical warfare nerve agents⁶ (Chap. 132). These oximes have superior effectiveness against sarin, VX, and certain types of newer pesticides (eg, methyl-fluorophosphonylcholines).^{3,11,37,40,44,65,88,89} Unfortunately, they are less efficacious for traditional OP insecticide poisoning, and their toxicity profile is inadequately defined.^{11,37,40,44,65,88,89} In addition to reactivating AChEs, the Hagedorn oximes demonstrate direct central and peripheral anticholinergic effects at supratherapeutic concentrations.⁶⁵

Mechanism of Action

Organic phosphorus compounds are powerful inhibitors of carboxylic esterase enzymes, including acetylcholinesterase (AChE; true cholinesterase, found in red blood cells, nervous tissue, and skeletal muscle) and plasma cholinesterase or butyrylcholinesterase (found in plasma, liver, heart, pancreas, and brain).⁵⁵ The OP binds firmly to the serine-containing esteratic site on the enzyme, inactivating it by phosphorylation (Fig. 113–3).^{36,56,76} This reaction results in the accumulation of acetylcholine at muscarinic and nicotinic synapses in the peripheral and central nervous systems, leading to the clinical manifestations of OP poisoning. Following phosphorylation, the enzyme is inactivated and can undergo one of three processes; endogenous hydrolysis of the phosphorylated enzyme, reactivation by a strong nucleophile, such as pralidoxime, and aging, which involves biochemical changes that stabilize the inactivated phosphorylated molecule and render it incapable of reactivation by oximes.

Endogenous hydrolysis of the bond between the enzyme and the OP is generally extremely slow and is considered insignificant. This is in contrast to the rapid hydrolysis of the related bond between the enzyme and many carbamates. The positively charged quaternary nitrogen of pralidoxime is attracted to the negatively charged anionic site on the phosphorylated enzyme, bringing it in close proximity to the phosphorous moiety (Fig. 113–3). Pralidoxime then exerts a nucleophilic attack on the phosphate moiety, successfully releasing it from the AChE enzyme.⁸³ This action liberates the enzyme to a variable extent depending on the OP in question and restores enzymatic function.⁴⁵ Diethylorganophosphates (eg, parathion, chlorpyrifos, phorate) take days to age in comparison to 12 hours for dimethylorganophosphates (eg, dimethoate, dichlorvos, monocrotophos).^{17,25}

Pralidoxime is important at nicotinic sites where atropine is ineffective, most often typically improving muscle strength within 10 to 40 minutes after administration.^{56,76} This effect is vital to maintaining the muscles of respiration. Pralidoxime is also synergistic with atropine; it liberates cholinesterase enzyme so that additional acetylcholine can be metabolized while atropine inhibits the effects of acetylcholine at cholinergic receptors. This suggests that pralidoxime should always be used with atropine.^{24,56} Some OP compounds respond much better to pralidoxime than others, depending on the affinity of pralidoxime for the particular type of phosphorylated enzyme, its reactivating ability, concentrations of both the oxime and the OP, aging, and OP redistribution from a depot site such as fat.^{23,88}

The central nervous system (CNS) benefits of pralidoxime are controversial, as the molecule is a quaternary nitrogen compound and not expected to cross the blood–brain barrier.^{47,56} A rat experiment using a microdialysis technique demonstrated only 10% CNS penetration of pralidoxime.⁶⁶ Following exposure to IV fenitrothion, IV administration of pralidoxime in rats failed to improve survival or to reactivate brain cholinesterase, whereas with direct brain instillation pralidoxime partially restored brain cholinesterase and eliminated fatalities.⁷⁹ Clinical observations, however, have certainly suggested a CNS action of pralidoxime with a prompt return of consciousness reported in some cases.^{55,56,63,83} A 3 year-old child who was comatose from parathion was given 500 mg of 2-PAM IV over 15 minutes with continuous electroencephalographic (EEG) monitoring. Within 2 minutes there was a dramatic response on the EEG, followed rapidly by normalization of consciousness.³⁵

Early work with feline models led to a proposal that a serum concentration of greater than or equal to 4 µg/mL was a desired therapeutic concentration for pralidoxime.⁷⁵ However, more recent in vitro work with human erythrocytes and a mouse hemidiaphragm model suggests that higher serum concentrations are actually needed.⁸⁸ Twenty percent reactivation was achieved in 5 minutes with serum concentrations of 10 µg/mL.⁸⁸ A simulation and analysis suggests that serum concentrations between 10 and 15 µg/mL (50–100 µmol/L) are necessary for optimal treatment of severely poisoned patients.^{21,90} These recommendations await validation in poisoned patients. Serum concentrations are not available in a timely manner, but may help in the design of future pralidoxime dosing protocols.

Organic phosphorous compounds inhibit butyrylcholinesterase (plasma cholinesterase) and AChE to different extents.¹⁸ If performed correctly, butyrylcholinesterase may act as a surrogate marker for OP or carbamate elimination from the body.³⁸ Likewise, the reactivation of butyrylcholinesterase by pralidoxime is dependent on the concentration of pralidoxime and often has a flat dose response. For example, in an in vitro model of human blood taken from healthy volunteers and treated with paraoxon, pralidoxime was able to reactivate 1.3% and 18.1% of AChE at pralidoxime concentrations of 10 µmol and 100 µmol, respectively, compared with only 1% and 5.5% of butyrylcholinesterase with 10 and 100 µmol concentrations of pralidoxime.³⁵ Unless the effect of the specific OP on butyrylcholinesterase is known, there is no role for following serial butyrylcholinesterase concentrations.

In contrast to the usefulness of pralidoxime in the management of the cholinergic syndrome, current understanding of the pathophysiology of the intermediate syndrome is inadequate to determine whether pralidoxime can prevent the development of the syndrome (Chap. 113).⁷⁴ However, if cholinergic receptor desensitization is responsible for the cause of the muscle weakness, then pralidoxime would be unlikely to prevent the syndrome, especially after large intentional ingestions.¹² Additionally, certain OP pesticides may lead to the development of delayed onset neurotoxicity, which involves inhibition of neurotoxic esterases that cannot be prevented or treated by pralidoxime.^{19,48}

Pharmacokinetics and Pharmacodynamics

Pralidoxime chloride pharmacokinetics are characterized by a two-compartment model. Pharmacokinetics values vary depending on whether calculations are determined in healthy volunteers or poisoned patients. The volume of distribution (Vd) is larger in poisoned patients and most likely accounts for the prolonged elimination phase.²¹

In volunteers, the Vd is about 0.8 L/kg and the $t_{1/2}$ is 75 minutes.^{33,61,72} Pralidoxime is renally excreted, and within 12 hours, 80% of the dose is recovered unchanged in the urine.^{34,71}

A dose of 10 mg/kg of pralidoxime administered intramuscularly (IM) to volunteers results in peak serum concentrations of 6 µg/mL (reached 5–15 minutes after IM injection) and a half-life of approximately 75 minutes.⁷¹ Following a standard 30 minute IV infusion dose of 1 g of pralidoxime in a 70 kg man, the serum concentration fell to less than 4 µg/mL (no longer thought to be considered a goal serum concentration) at 1.5 hours. In a simulated model, a continuous infusion of 500 mg/h of pralidoxime led to a concentration greater than 4 µg/mL after 15 minutes, which could be maintained throughout the infusion.⁷⁷ In a human volunteer study, an IV loading dose of 4 mg/kg over 15 minutes followed by 3.2 mg/kg/h for a total of 4 hours maintained serum pralidoxime concentrations greater than 4 µg/mL for 4 hours. The approximately same total dose, 16 mg/kg, administered over 30 minutes only maintained those concentrations for 2 hours.⁴⁹ In poisoned patients receiving continuous infusions of pralidoxime as opposed to intermittent infusions, both the Vd and the $t_{1/2}$ are increased.⁷⁸ A Vd of 2.77 L/kg, an elimination $t_{1/2}$ of 3.44 hours, and a clearance of 0.57 L/kg/h were reported in poisoned adults given a mean loading dose of 4.4 mg/kg followed by an infusion of 2.14 mg/kg/h.⁸³ In poisoned children and adolescents, the Vd varied with severity of poisoning from 8.8 L/kg in the severely poisoned patients to 2.8 L/kg in moderately poisoned patients.⁶⁸ After a mean loading dose of 29 mg/kg followed by a continuous infusion of about 14 mg/kg/h, a steady-state serum concentration of 22 µg/mL, a $t_{1/2}$ of 3.6 hours, and a clearance of 0.88 L/kg/h were calculated.⁶⁸

Oral administration of salts of pralidoxime (not used clinically because of OP poisoning–induced vomiting) demonstrated a peak concentration at 2 to 3 hours, a $t_{1/2}$ of 1.7 hours, and an average urine recovery of 27% of unchanged

pralidoxime in humans.³⁹ Oral administration demonstrated clinical efficacy in a mice model.⁸

Autoinjector administration of 600 mg of pralidoxime chloride in an adult man (9 mg/kg) produced a concentration above 4 µg/mL at 7 to 16 minutes, a maximum serum concentration of 6.5 µg/mL at about 28 minutes, and a $t_{1/2}$ of 2 hours.^{61,70} Using traditional needle and syringe IM administration requires a longer time to achieve comparable serum concentrations. The autoinjectors more widely disperse the medication in the tissues resulting in faster absorption.^{64,72}

ROLE IN ORGANIC PHOSPHORUS COMPOUND TOXICITY: EFFICACY RELATED TO TIME OF ADMINISTRATION AFTER POISONING

The sooner after exposure to an OP, the more likely pralidoxime is to be effective. Timely administration reduces the likelihood that aging of the OP–AChE complex has occurred and is completed. However, there is no absolute time limitation on reactivation function, as long as the patient remains symptomatic.

Early in vitro evidence suggested that the successful use of cholinesterase reactivators depended on administration within 24 to 48 hours of exposure to the OPs; afterward, the acetylcholinesterases would be irreversibly inactivated.^{4,14,31,32,67} The 48 hour limit was derived from in vitro experiments using a small number of tightly bound compounds and reactivators and data from plasma cholinesterase enzyme activity, which is now recognized to be relatively resistant to oxime-nucleophilic attack. These early data were accepted without consideration of their relevance to human systems, the use of newer and less tightly bound OP compounds, temperature and pH variation, blood flow, fat solubility, active metabolites, and species specificity. Fat soluble OP compounds redistribute from fat stores over time and can continue to newly inhibit AChE for days.

An in vitro experiment assessed the effect of aging on the ability of pralidoxime to regenerate rat erythrocyte and brain cholinesterases using three different OP compounds.⁸⁰ The rate of reactivation of erythrocyte and brain cholinesterases was significantly decreased over time for fenitrothion and methyl parathion, with no reactivation occurring at 48 hours. This is partly because dimethylated (dimethyl, dimethoxy) OP pesticides age more quickly than diethylphosphorylated pesticides.¹⁹ In contrast, a very high reactivation rate for ethyl parathion was still apparent at 48 hours. Thus the structure of the OP compound is important in the rates of aging and reactivation with pralidoxime. Fenitrothion and methyl parathion are both O,O-dimethyl OP compounds as is dimethoate, whereas ethyl parathion is an O,O-diethyl OP compound.⁸⁰ Other studies also suggest that pralidoxime remains effective for more than 48 hours following exposure.^{2,5,8,13,16,19,21,53,62,82}

ROLE IN ORGANIC PHOSPHOROUS COMPOUND TOXICITY: HUMAN TRIALS

There are four randomized clinical trials examining the efficacy of pralidoxime for the management of OP poisoning. Two of these trials were done in the 1990s in India using doses of pralidoxime now considered to be inadequate.¹⁹ Neither study demonstrated a benefit for pralidoxime and, in fact, suggested an increase in mortality in patients receiving the higher but still inadequate dose of pralidoxime. Other criticisms include a delay in administration and an inadequate duration of treatment. The third clinical trial included 200 patients in India who were moderately to severely poisoned with an OP pesticide.⁵⁸ All patients received a 2 g loading dose of pralidoxime iodide over 30 minutes before being randomized to receive 1 g over 1 hour every 4 hours for 48 hours or a continuous infusion of 1 g/h for 48 hours. Beyond 48 hours, all patients received 1 g every 4 hours until no longer ventilator dependent. In the continuous pralidoxime infusion arm, the authors demonstrated reduced atropine requirements, a smaller number of patients requiring intubation, fewer days of intubation, and a reduction in mortality from 8% to 1%. It should be noted that the iodide salt of pralidoxime was used and would equate to about 650 mg/h of the chloride salt.²² Even though the majority of the patients by history ingested dimethoate, a dimethoxy compound with high lethality and rapid aging, the time to admission and administration of pralidoxime was very short with a median time of 2 hours. Criticisms of the study include a lack of blinding, no measurement of AChE or pesticide concentrations, and no objective monitoring of neuromuscular function.²² In contrast, the most recent trial performed in Sri Lanka was unable to demonstrate a beneficial effect of pralidoxime in 121 patients compared to 114 patients treated with placebo.²⁰ There was no difference in mortality between groups, although pralidoxime effectively reactivated red cell AChE inhibited by diethyl OP insecticides. It also reactivated red cell AChE inhibited by dimethyl OP insecticides, but less so, as expected. In comparison to the third study,⁵⁸ these patients arrived later (4.4 versus 2 hours), and the extent of supportive care was inferior. The exact reasons for these disparate results are unclear.

ROLE IN CARBAMATE TOXICITY

Acetylcholinesterases inactivated by most carbamates spontaneously reactivate with half-lives of 1 to 2 hours, and typical clinical recovery occurs in several hours. However, in severe cases, cholinergic findings may persist for 24 hours.^{10,28} Pralidoxime is rarely indicated for carbamate poisoning, but it is not contraindicated as previously suggested. This erroneous conclusion was based solely on data regarding a single carbamate, carbaryl, and inappropriately applied to all carbamates. Pralidoxime decreased the rate of carbamylation of 16 insecticidal carbamates, though it modestly increased the rates for three, one of which was carbaryl.¹⁵ In another experiment, pralidoxime had no effect on the reactivation of human erythrocyte AChE carbamylated by aldicarb, methomyl, and carbaryl.⁴¹ Furthermore, animal studies demonstrated the beneficial effects of pralidoxime in decreasing the lethality of several carbamate insecticides,^{57,73} though worsened the toxicity of carbaryl. It was suggested that this is possibly because the carbamate-oxime complex may actually be a more potent cholinesterase inhibitor than carbaryl alone.^{28,57,73} However, even in the presence of carbaryl, the combination of atropine plus an oxime, a more clinically relevant situation, resulted in survival data comparable to that of atropine alone.²⁸ Previous animal data may also be confounded by the use of excessive doses of pralidoxime.⁵¹ This evidence suggests that pralidoxime is not usually a necessary adjunct to atropine for a patient with a pure carbamate overdose. However, there are cases reports, particularly with aldicarb, where pralidoxime appears to improve outcome.¹⁰ Thus pralidoxime should never be withheld in a seriously poisoned patient out of concern that a cholinergic xenobiotic may be a carbamate.⁴¹ Pralidoxime should be used in conjunction with atropine and rarely as the sole therapy in OP or carbamate poisoning.

ADVERSE EFFECTS AND SAFETY ISSUES

At therapeutic doses of pralidoxime in humans, adverse effects are minimal.^{26,27,54–56,63,77} Transient dizziness, blurred vision, and elevations in diastolic blood pressure may be related to the rate of administration.^{33,49} Doses of 45 mg/kg produce blood pressure elevations that may persist for several hours, but may be reversed with IV phentolamine.⁷⁰ The most recent randomized clinical trial revealed a higher percentage of patients with tachycardia and hypertension associated with pralidoxime compared to placebo after both the loading dose and the continuous infusion (75% versus 49% and 30% versus 14%). Rapid IV administration has produced sudden cardiac and respiratory arrest due to laryngospasm and muscle rigidity,^{59,69,86} whereas IM administration in volunteers produced diplopia, dizziness, headache, drowsiness, nausea, tachycardia, increased systolic blood pressure, hyperventilation, decreased kidney function, muscular weakness, and pain at the injection site.⁶¹ Elevations in liver enzyme concentrations were observed in volunteers administered autoinjector doses of 1200 to 1800 mg; these enzyme concentrations returned to normal in 2 weeks.⁶¹ An important safety issue is inadvertent provider or patient contact with the “active” needle end of autoinjectors or autoinjector systems, triggering unintended administration, self-administration, needle injury, or delivery to an unintended site.

PREGNANCY AND LACTATION

Pralidoxime is FDA pregnancy risk category C. Reproduction studies have not been done, and human case reports are limited. However, considering the maternal benefit of pralidoxime, it should be used as clinically indicated to protect the maternal fetal dyad. The use of pralidoxime should not be withheld because of pregnancy.⁹ It is unknown whether pralidoxime is excreted into breast milk.

DOSING AND ADMINISTRATION

The optimal dosage regimen for pralidoxime is unknown. A maintenance dose in adults of 1 g/h of the iodide salt of pralidoxime was used in the study from India and is approximately equal to 650 mg of pralidoxime chloride.⁵⁸ The package insert, last updated in 2010, recommends a pediatric loading dose of 20 to 50 mg/kg (not to exceed 2000 mg/dose) over 15 to 30 minutes followed by a continuous infusion of 10 to 20 mg/kg/h.⁶² It recommends an adult dose of 1 to 2 g in 100 mL of 0.9% sodium chloride given intravenously over 15 to 30 minutes, with additional doses given every 3 to 8 hours as long as signs of poisoning recur.⁶² However, it does give the pharmacokinetics of a loading dose followed by a continuous infusion and comments that a loading dose followed by a continuous infusion is more likely to maintain therapeutic serum concentrations as compared to intermittent dosing.⁶² Difficulties arise because a target serum concentration in humans has not been established, although in vitro studies suggest a target concentration closer to 17 µg/mL compared with the 4 µg/mL previously suggested.^{21,23,35} This is complicated by the possibility that there is a ceiling dose and that some OP compounds are likely to be more easily reactivated than others. In addition, pharmacokinetic studies in volunteers suggest that a continuous infusion maintains a target concentration with less variation compared with intermittent boluses. Based on all of the above, we recommend a loading dose of pralidoxime chloride of 30 mg/kg (up to 2 g) over 15 to 30 minutes followed by a maintenance infusion of 8 to 10 mg/kg/h for adults (up to 650 mg/h) and 10 to 20 mg/kg/h for children (up to 650 mg/h).

The addition of 20 mL of sterile water for injection to the 1 g vial of pralidoxime results in a 5% solution (50 mg/mL). Following reconstitution, the pralidoxime should be used within several hours. This solution can be further diluted to a volume of 100 mL of 0.9% sodium chloride solution for IV infusion, or a concentration of 10 to 20 mg/mL. The loading dose can be infused over 15 to 30 minutes. If fluid overload is a concern, the 1 g of pralidoxime in 20 mL can be infused slowly over not less than 5 minutes.⁶²

Although IV administration is preferred, IM administration is acceptable using a 1 g vial of pralidoxime reconstituted with 3 mL of sterile water or 0.9% sodium chloride for injection to provide a solution containing 300 mg/mL (concentrations above 35% weight/volume produce muscle necrosis in animals).⁷¹ This could be used until an IV site is established. Patients with reduced kidney function may require dosage adjustment, but there are no specific recommendations on how to accomplish this. In patients with ARDS, the dose can be given as a 5% solution by a slow IV injection over at least 15 to 30 minutes.⁷¹

Depending on the severity of a nerve agent exposure, one to three injections with a pair of autoinjectors containing atropine and pralidoxime should be administered. The number of autoinjector doses administered to a child depends on the age and weight of the child.^{29,46} For children aged 3 to 7 (13–25 kg), one autoinjector of atropine and one autoinjector of pralidoxime should be administered, which should result in a projected pralidoxime dose of 24 to 46 mg/kg. For children aged 8 to 14, two autoinjectors of atropine and two autoinjectors of pralidoxime should be administered. These injections should result in a projected pralidoxime dose of 24 to 46 mg/kg. For anyone older than 14 years of age, three autoinjectors of atropine and pralidoxime should be administered. This results in a projected dose of pralidoxime of less than 35 mg/kg. For children younger than 3 years, during an emergency, one autoinjector of atropine and one of pralidoxime may be administered in accordance with a risk-to-benefit analysis. If time permits and only autoinjector doses are available, its contents may be transferred to a small sterile vial for traditional IM administration with a needle and syringe.³⁰

Duration of Treatment

The signs and symptoms of OP poisoning usually manifest within minutes but may be delayed up to 24 hours.⁵⁶ Delayed manifestations occur with the fat soluble compounds, such as fenthion or chlorfenthion. The route of exposure may also influence the onset of systemic symptoms. For example, there may be a delay following dermal contact, which does not occur following ingestion or inhalation. When symptoms are either delayed or prolonged, or when treatment is delayed, extended therapy with pralidoxime may be indicated.^{1,7,53} In one case of poisoning with the fat soluble compound fenthion, 5 days elapsed before cholinergic symptoms appeared, and some symptoms then persisted for 30 days.⁵³ Pralidoxime and atropine were administered continuously in varying doses for the time that the patient was symptomatic. Therefore, the most practical recommendation is to continue the pralidoxime until symptoms have resolved and atropine has not been needed for 12 to 24 hours.¹⁸ Other recommendations for estimating the duration of pralidoxime therapy include; (1) measuring the serum or urinary concentration of the OP compound, (2) measuring serial determinations of plasma cholinesterase (increasing concentrations suggests the elimination of the OP compound), (3) incubating the patient's serum with an exogenous source of AChE or butyrylcholinesterase to assess inhibition, (4) incubating the patient's inhibited red blood cell cholinesterase with a high concentration of oxime in vitro, to assess reactivation.²¹ However, measurements of urinary concentrations of OP or AChE or plasma cholinesterase are not likely to happen in real time. Furthermore, plasma cholinesterase is not always a good surrogate for OP inhibition. In all cases, patients should be observed for the recrudescence of toxicity after termination of pralidoxime. If symptoms return, therapy should be continued for at least an additional 24 hours.

FORMULATION AND ACQUISITION

Pralidoxime chloride (Protopam) is supplied in 20 mL vials containing 1 g of powder, ready for reconstitution with sterile water or 0.9% sodium chloride for injection.^{60,62}

As noted above, pralidoxime chloride is also available for IM administration by an autoinjector containing 600 mg of pralidoxime in 2 mL of sterile water for injection with 20 mg of benzyl alcohol and 11.26 mg of glycine. The 2-PAM autoinjector is also packaged in a kit containing 600 mg of pralidoxime in 2 mL of sterile water for injection with 40 mg of benzyl alcohol and 22.5 mg of glycine, accompanied by an autoinjector containing 2.1 mg of atropine in 0.7 mL of a sterile solution containing 12.47 mg of glycerin and not more than 2.8 mg of phenol. This kit is called a "Mark 1 Nerve Agent Antidote Kit (NAAK)" and is designed to be used IM by first responders in case of a nerve agent attack. The needles extend 0.8 inch in length. The Mark 1 NAAK was recently replaced by the DuoDote Autoinjector System and the analogous, military designated Antidote Treatment Nerve Agent Autoinjector (ATNAA), which use technology that sequentially administers 2.1 mg of atropine in 0.7 mL followed by 600 mg of pralidoxime chloride in 2 mL IM through the same syringe.^{15a} The 23 gauge needle is 0.8 inches in length. Pralidoxime is maintained as part of the the Strategic National Stockpile (SNS) formulary in repositories in numerous locations throughout the US.

SUMMARY

- Pralidoxime is an effective reactivator of AChE in many OP compound poisonings primarily reversing neuromuscular manifestations.
- The sooner pralidoxime is administered after OP toxicity, the more effective it is likely to be, although there is no absolute time limitation on reactivation function.
- Pralidoxime and atropine are synergistic and should be used together in the management of patients with OP poisonings.
- If a patient requires multiple doses of atropine for muscarinic symptoms or has neuromuscular weakness, then the use of 2-PAM is indicated.
- The resolution of all signs or symptoms does not indicate that the enzyme systems are fully active; patients may still benefit from enzyme regeneration with the safe and effective antidote pralidoxime.
- Because newer highly fat soluble OP pesticides are currently available, it may be necessary to administer atropine and 2-PAM for more prolonged periods of time than previously suggested.

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114 INSECTICIDES: ORGANIC CHLORINES, PYRETHRINS/PYRETHROIDS, AND INSECT REPELLENTS

Michael G. Holland

ORGANIC CHLORINE PESTICIDES

History and Epidemiology

Until the 1940s, commonly available pesticides included highly toxic arsenicals, mercurials, lead, sulfur, and nicotine. When Nobel Prize-winning chemist Paul Müller demonstrated the insecticidal properties of dichlorodiphenyltrichloroethane (DDT) in the early 1940s, a whole new class of pesticides was introduced. The organic chlorine insecticides were inexpensive to produce, nonvolatile, environmentally stable, and had relatively low acute toxicity when compared to previous insecticides. Most organic chlorines have a negative temperature coefficient, making them more insecticidal at lower temperatures and less toxic to warm-blooded organisms (Table 114–1).¹⁶⁴ Widespread use of these xenobiotics occurred from the 1940s until the mid 1970s. They were highly effective and revolutionized modern agriculture, allowing unprecedented crop output from each acre of arable land. Because of their stability, organic chlorines were used extensively in structural protection (termites, carpenter ants) and soil treatments. Medical and public health applications of DDT and its analogues were also found in the control of typhus and eradication of malaria by eliminating the mosquito vector.³⁴ By 1953, DDT alone was credited for saving an estimated 50 million lives and with averting one billion cases of human disease. It has also been credited with eliminating malaria from the United States and Europe. It is suggested that because of this consequential impact on human health, DDT is the single most important factor in the population explosion that occurred between 1950 and 1970.⁴⁶

TABLE 114–1. Classification of Organic Chlorine Pesticides

<i>Classes of Organic Chlorines</i>	<i>Specific Organic Chlorine; CAS Registry#</i>	<i>Brand Name(s)</i>	<i>Current EPA Registration (US)</i>	<i>Acute Oral Toxicity (Man)</i>	<i>Dermal Absorption</i>	<i>Lipid Storage</i>	<i>Specific Characteristics</i>
Hexachloro-cyclohexanes	Lindane (γ isomer) 58–89–9	Kwell; Gustafson Flowable; Sorghum Guard	Topical scabicide; Agricultural use cancelled 2006	Moderate	High	Low	Topical scabicide; Seizures; CNS excitation; musty odor
DDT and analogues	DDT-Dichlorodiphenyltrichloroethane 50–29–3	Neocid, Ioxodex, Anofex, others	Cancelled 1972	Low to moderate	Low	Highest	Tremors, CNS excitation; odorless
	Methoxychlor 72–43–5	Marlate	Cancelled 2003	Low	Low	Moderate	Less toxic DDT substitute
	Dicofol 115–32–2	Kelthane	Residential Use Banned 1998; Cotton, Citrus, Apple	Low	Low	Low	
	Chlorobenzilate 510–15–6	Benzilan, BenzoChlor	Cancelled 1983	Low	Low	Low	Much less environmental persistence than DDT
Cyclodienes and related compounds	Aldrin 309–00–2	Aldrex, Octalene, Toxadrin	Cancelled 1974	High	High	High	Rapidly metabolized to Dieldrin; mild “chemical” odor
	Dieldrin 60–57–1	Dieldrine, Octalox, Quintox	Cancelled 1974	High	High	High	Stereoisomer of Endrin; early and late seizures; odorless
	Endrin 72–20–8	Hexadrin	Cancelled 1974	Highest	High	None	Most toxic organic chlorine; rapid onset seizures, status epilepticus
	Chlordane 57–74–9	Octachlor, Toxichlor, others	Cancelled 1988	Moderate	High	High	Early and late seizures occur
	Endosulfan 115–29–7	Thiodan, Cyclodan, others	RED ^a 2002	High	High	Low	Strong sulfur odor
	Heptachlor 76–44–8	Drinox	Restricted: fire ant control, soil treatment	Moderate	High	High	Toxic metabolite heptachlor epoxide; odor of camphor
	Isobenzan 297–78–9	Telodrin	Never Registered	High	Moderate	High	Also inhibits Mg ⁺⁺⁺ -ATPase; mild “chemical” odor
	Thenachlor 2227–17–0 Toxaphene (Polychlorinated Camphene) 800–35–2	Pentac Alltox, Chemphene, Toxakil, others	Cancelled Cancelled 1982	NA Moderate to high	Low Low	Low Low	Toxic metabolite binds to GSH Seizures; turpentine-like odor, often mixed with parathion
Chlordecone and Mirex	Chlordecone 143–50–0	Kepone	Cancelled 1977	Moderate	High	High	“Kepone shakes”; seizures not seen, structurally similar to mirex
	Mirex 2385–85–5	Dechlorane	Cancelled 1976	Low	High	High	(?) Converted to chlordecone, toxicity identical

^aChemical Abstracts Service # provided here to facilitate Toxline, Medline database searches. ^bRED = Re-registration eligibility decision.

However, the properties that made these chemicals such effective insecticides also made them environmental hazards; they are slowly metabolized, lipid soluble, chemically stable, and environmentally persistent. In her 1962 book, *Silent Spring*, Rachel Carson, a biologist with the US Fish and Wildlife Service, demonstrated that organic chlorines are bioconcentrated and biomagnified up the food chain.¹⁹ She alleged that this persistence could eventually lead to increases in cancer in the future. Extensive environmental research demonstrates that organic chlorine residues caused eggshell thinning and decreased reproductive success in predatory birds, most notably grebes, peregrine falcons, bald eagles, and pelicans.⁴⁵ However, conflicting results were seen when DDT-laced feedstuffs were administered in high concentrations to experimental birds. Testing on domesticated birds, such as Japanese quail^{21,26,121} and chickens,¹⁶² showed little or no eggshell thinning, whereas testing on mallard ducks showed thinning.^{40,41} Hearings before the Environmental Protection Agency (EPA) regarding DDT registration focused also on the unproven fear of placing future generations at risk of cancer. This fear, and the demonstration of persistent DDT residues in all humans, even those living in areas where DDT was never utilized (eg, Eskimos), led to the severe restriction or total ban of DDT and most other organic chlorines in North America and Europe.³⁴ There is considerable evidence that since DDT was banned, less-effective replacements have placed many more millions of people at risk for malaria and are responsible, at least in part, for millions of deaths from this disease.^{95,118,119} Not surprisingly, DDT is still considered a highly effective mosquito control agent with a low order of acute toxicity, and it is very inexpensive compared to newer replacement insecticides. For these reasons, the World Health Organization (WHO) exempted DDT from its list of banned pesticides, and it is still widely used for malaria control

programs in many countries since alternatives are more expensive and must be applied more often. Current use of DDT for indoor residual spraying is ongoing in endemic areas in Africa and has been shown to be safe and effective as a public health initiative to control malaria, even in areas with resistant strains.¹²⁷ In 2006, the EPA officially cancelled the registration for lindane and all use in agriculture ceased in 2009.¹⁵⁷

Organic chlorine pesticides are complex, cyclic polychlorinated hydrocarbons having molecular weights generally in the range of 300 to 550 Da. They are nonvolatile solids at room temperature. Most act as central nervous system stimulants. In contrast, chlorinated hydrocarbon solvents and fumigants are low molecular weight, alkyl compounds that are volatile liquids or gases and generally have CNS depressant effects (Chap. 108).

The organic chlorine pesticides can be grouped into four categories based on their chemical structures and similar toxicities: (a) DDT and related analogues; (b) cyclodienes (the related isomers aldrin, dieldrin, and endrin; and heptachlor, endosulfan), and related compounds (toxaphene, dienochlor); (c) hexachlorocyclohexane, the primary organochlorine pesticide still in clinical use as a pediculocide (more commonly termed lindane, the γ isomer; also referred to by the misnomer γ -benzene hexachloride). Specifying the exact isomer is important with this compound, because the β and δ isomers are CNS depressants and have no insecticidal properties,^{3,32,108} and (d) mirex and chlordane (Table 114–1; Fig. 114–1). These organic chlorine insecticide compounds differ substantially, both between and within groups, with respect to toxic doses, skin absorption, fat storage, metabolism, and elimination.³⁴ The signs and symptoms of toxicity in humans, however, are remarkably similar within each group.

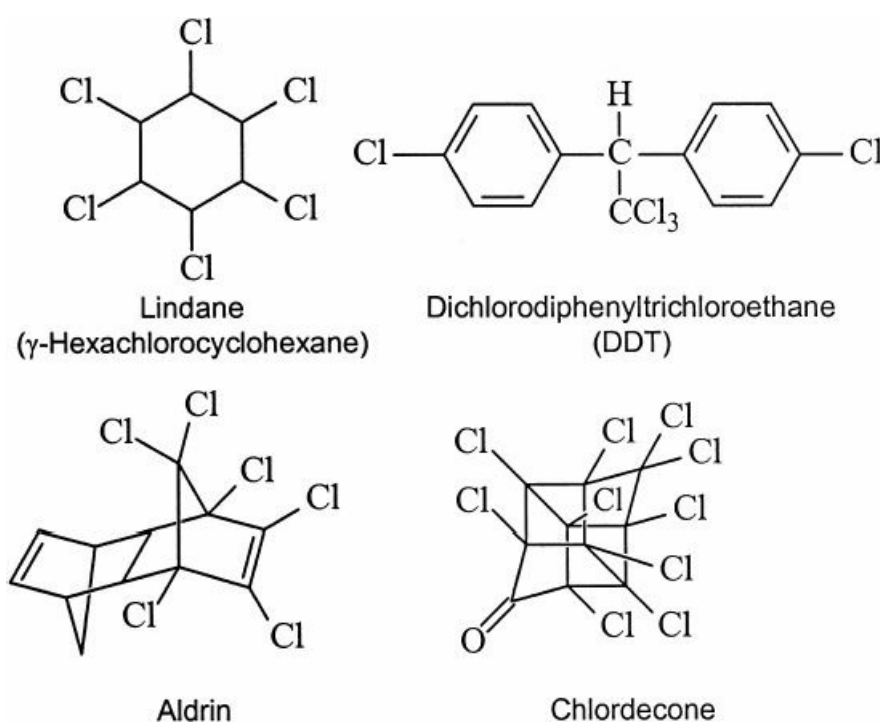


FIGURE 114–1. Structures of various organic chlorine pesticides.

Toxicokinetics

Absorption. All the organic chlorine pesticides are well absorbed orally and by inhalation; transdermal absorption is variable, depending on the particular xenobiotic. Absorption by any route may be affected by the vehicle and the physical state (solid or liquid) of the pesticide. Organic chlorines are not water-soluble, and they are usually either dissolved in organic solvents or manufactured as powders for dusting.

DDT and its analogues, methoxychlor, dicofol, and chlorobenzilate, are very poorly absorbed transdermally, unless the pesticide is dissolved in a suitable hydrocarbon solvent.¹¹⁶ DDT has limited volatility, so air concentrations are usually low, and toxicity by the respiratory route is unlikely.

All the cyclodienes have significant transdermal absorption rates. Cutaneous absorption of dieldrin is approximately 50% of the oral route. Oral absorption of the cyclodienes is also high, and significant poisonings have occurred when foodstuffs were contaminated with these pesticides.^{17,23} Toxaphene is poorly absorbed through the skin in both acute and chronic exposures.¹³²

Lindane is well absorbed after skin application, and in adults it has a documented forearm skin absorption rate of 9.3% of a topically applied dose over 24 hours.⁵⁴ Anatomic sites vary in their absorptive capacities: axillary rates are 3.6 times greater, and scrotal absorption is 42 times greater than that of forearm rates.^{14,58,73,142} Animal studies and case reports suggest that the young, the malnourished, and those who receive repeated topical doses may have increased accumulation and increased toxicity.¹⁰⁹ Hot baths, occlusive clothing or bandages, the vehicle for the lindane, and a disturbed cutaneous

integrity, such as eczema, fissures, and other violations of the skin, all enhance dermal penetration.^{141,142} The state of hydration of the skin also affects the amounts absorbed, so bathing just prior to application can enhance absorption and increase the likelihood of toxicity.^{93,142} Lindane is a stable compound and volatilizes easily when heated. It was previously used extensively in home vaporizers, and toxicity was common via inhalation and when vaporizer tablets were unintentionally ingested by children. Review of data when lindane was ingested therapeutically as an anthelmintic demonstrates that 40 mg/d for 3 to 14 days generally produced no symptoms.³⁴ Mirex and chlordecone are efficiently absorbed via skin, by inhalation, and orally.⁵³

Distribution. All organic chlorines are lipophilic, a property that allows penetration to their sites of action.²⁸ The fat-to-serum ratios at equilibrium are high, in the range of 660:1 for chlordane,⁶² 220:1 for lindane,¹³³ and 150:1 for dieldrin.³⁵ Central nervous system redistribution of the organic chlorines to the blood and then to fat may account for the apparent rapid CNS recovery despite the persistent substantial total body burden. In the rat model, there is a direct correlation between the concentration of DDT or dieldrin in the brain and the clinical signs produced after a single dose of the insecticide.^{34,38}

Metabolism. The high lipid solubility and very slow metabolic disposition of DDT, DDE (dichlorodiphenyl dichloroethylene, a metabolite of DDT), dieldrin, heptachlor, chlordane, mirex, and chlordecone causes significant adipose tissue storage and increased body burdens in chronically exposed populations.⁵³ Organic chlorines that are rapidly metabolized and eliminated, such as endrin (an isomer of dieldrin), endosulfan, lindane, methoxychlor, dienochlor, chlorobenzilate, dicofol, and toxaphene tend to have less persistence in body tissues, despite being highly lipid soluble.¹¹⁶

Most organic chlorines are metabolized by the hepatic microsomal enzyme systems by dechlorination, oxidation, with subsequent conjugation. However, metabolism may result in the production of a metabolite with more toxicity than the parent compound, such as heptachlor to heptachlor epoxide, chlordane to oxychlordane, and aldrin to dieldrin.

In animals, most organic chlorine pesticides are capable of inducing the hepatic microsomal enzyme systems.^{33,166} Enzyme induction changes the biodegradation of the pesticide in rodents,¹⁴⁸ and in certain animal models the acute toxicity of organic phosphorus compounds and carbamates may be reduced by the administration of organic chlorines. This protective effect is presumably induced by the hepatic microsomal metabolism of the organic phosphorus compound because this effect is ameliorated by administering piperonyl butoxide, an inhibitor of the liver microsomal enzyme system.^{34,166} However, induction of hepatic enzymes has not been described in humans, except in rare cases of massive exposure with concomitant neurologic findings.^{53,62}

Elimination. The half-lives of fat-stored compounds and poorly metabolized organic chlorines, such as DDT and chlordecone, are measured in months or years, compared to the elimination half-life of lindane, which is 21 hours in adults.⁹⁴ The primary route of excretion of organic chlorines is in the bile, but most also have detectable urinary metabolites. However, as with other compounds excreted in bile, most organic chlorines, such as mirex and chlordecone, have significant enterohepatic or enteroenteric recirculation.^{12,31,53} All the lipophilic compounds are excreted in maternal milk.¹²²

Mechanisms of Toxicity

The same neurotoxic properties that make organic chlorines lethal to target insects make them potentially toxic to higher forms of life. Organic chlorines exert their most important effects on the central nervous system. Electrophysiologic studies demonstrate that organic chlorine insecticides affect the neuronal membrane by either interfering with repolarization, by prolonging depolarization, or by impairing the maintenance of the polarized state of the neuron. The end result is hyperexcitability of the nervous system and repetitive neuronal discharges.⁴⁶

The voltage-gated Na⁺ channel is a common site of action for neurotoxins, both natural and synthetic. There are at least 10 separate binding sites on the Na⁺ channel, including those for local anesthetics and anticonvulsants. DDT, as well as the pyrethroids (see below), bind at the same site on these channels. They preferentially bind when the channel is in the open state, allowing prolonged inward sodium conductance, repetitive action potentials, and extended tail currents. Prolonged axonal firing and repetitive stimulus eventually leads to nerve paralysis and death in target insects, whose Na⁺ channels have much greater affinity for these insecticides than those in mammals.^{98,99,143,102} In mammals, low-level stimuli cause exaggerated responses, manifested clinically as prominent tremors and abnormal startle reflexes observed in test animals.^{70,155} Evidence of this as the primary mechanism of action is the amelioration of DDT-induced tremor by pretreatment with phenytoin, a Na⁺ channel blocker, which reduces the ability of voltage-dependent Na⁺ channels to recover from inactivation.^{70,156}

The cyclodienes and lindane act as γ -aminobutyric acid (GABA) antagonists. They inhibit GABA binding at the GABA_A receptor-chloride ionophore complex in the CNS, by interacting at the picrotoxinin binding site.^{3,9,32,61,66,101,108} In fact, the degree of binding at this site correlates well with the amount of Cl⁻ influx inhibited and the relative neurotoxicity

of each insecticide^{9,61} (Figs. 14–9, 14–10, and 114–2). Indeed, development of cyclodiene resistance seems to be related to alterations of the GABA_A-receptor-chloride ionophore complex in these affected insects.^{10,99} This also explains the efficacy of GABA agonists, such as benzodiazepines and phenobarbital, in treating the seizures and neurotoxicity of the cyclodienes⁶⁷ and lindane.¹⁷⁰ Toxaphene also inhibits GABA binding at the GABA_A receptor-chloride ionophore complex.¹³²

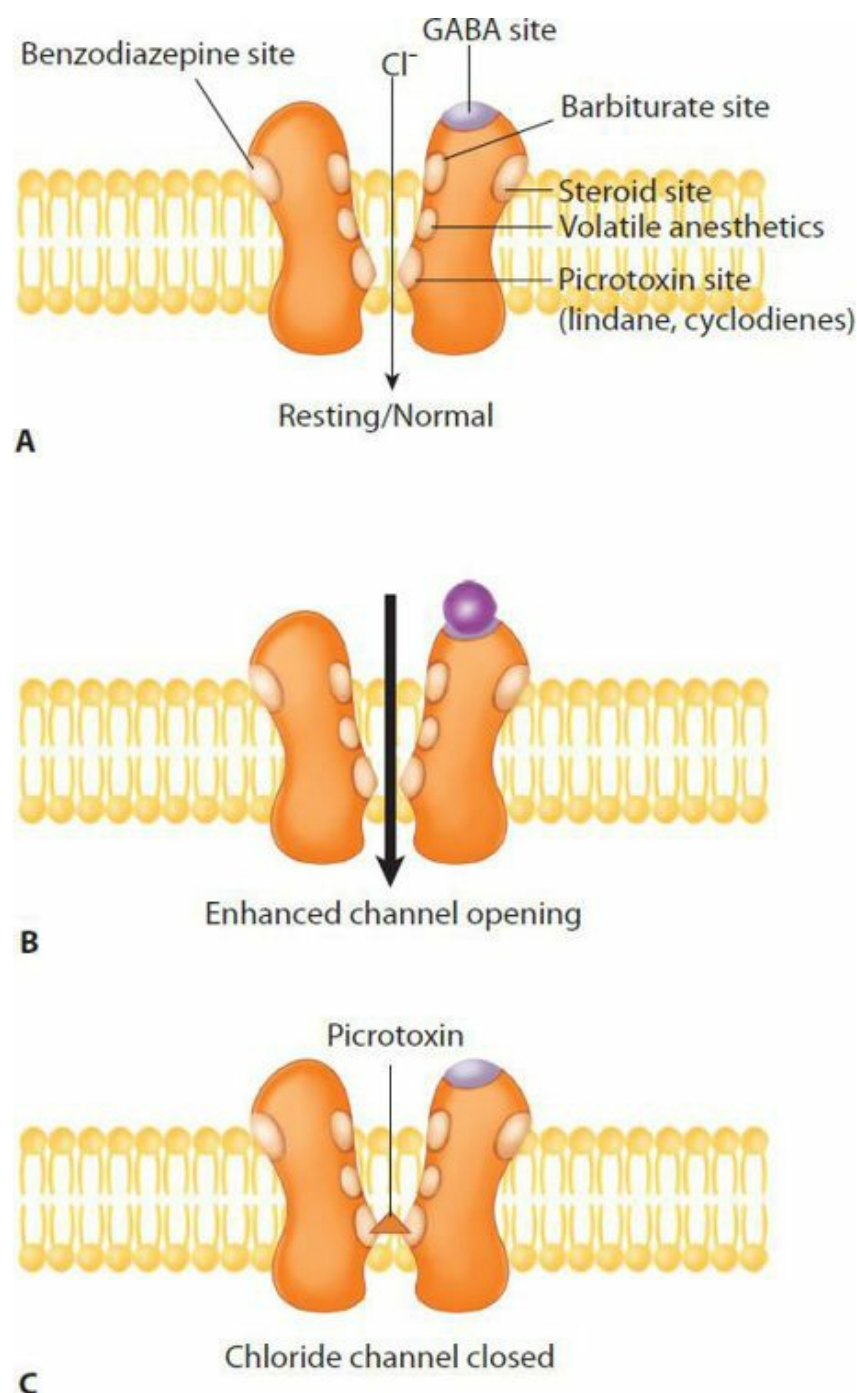


FIGURE 114–2. Chloride channel. Under resting conditions, a tonic influx of chloride maintains the nerve cell in a polarized state. Binding of GABA or an indirect-acting GABA agonist (benzodiazepine, barbiturate, volatile anesthetic) opens the chloride channel. The subsequent chloride influx hyperpolarizes the cell membrane, making the neuron less likely to propagate an action potential in response to a stimulus. GABA antagonists, such as picrotoxin, close the chloride channel, reducing chloride influx. The resulting decreased membrane polarity causes the neuron to become hyperexcitable to even those stimuli that are normally subthreshold in nature (Chap. 14).

The mechanisms of action of mirex and chlordecone are not as well understood. They inhibit Na⁺-K⁺-ATPase and Ca²⁺-ATPase. However, lindane, DDT, and the cyclodienes also inhibit these enzymes yet produce very different symptoms of toxicity, suggesting that these effects are not responsible for the clinical manifestations seen in mirex and chlordecone toxicity. Phenytoin and serotonin agonists exacerbate the prominent tremor that occurs with chlordecone intoxication, but conversely attenuate the tremors in DDT poisoning, which further supports a different mechanism than the Na⁺ channel effects of DDT.⁴⁶ Mirex and chlordecone are poor inhibitors of GABA binding at the GABA_A-receptor-chloride ionophore complex; therefore, their mechanism of action is likely not at this site,⁵³ and seizures are not described

with mirex or chlordane. Organic chlorines can predispose test animals to cardiac dysrhythmias,¹¹⁶ presumably via myocardial sensitization, similar to chlorinated hydrocarbon solvents (Chap. 108).

Drug Interactions

There are theoretical consequences of liver enzyme induction, such as enhanced metabolism of therapeutic drugs and reduced efficacy. Dysfunctional uterine bleeding was attributed to enhanced oral contraceptive metabolism induced by chlordane, but this report involved a single patient with weeks of excessive exposure to chlordane.⁶² A large group of workers poisoned by chlordane over many months had some increased hepatic microsomal activity, but there was no evidence of drug interactions or adverse clinical effects.⁵³ Thus, induction of the hepatic microsomal enzyme system by organic chlorines probably occurs only with extended, substantial exposure.¹¹⁶ There are no definitive reports of enhanced metabolism of therapeutic drugs or adverse reactions because of microsomal enzyme induction in humans.

Clinical Manifestations

Acute Exposure. In sufficient doses, organic chlorines lower the seizure threshold (DDT and related Na⁺ channel agents) or remove inhibitory influences (antagonism to GABA effects) and produce CNS stimulation, with resultant seizures, respiratory failure, and death^{20,23,29,66,67,80,81,125,126} After DDT exposure, tremor may be the only initial manifestation. Nausea, vomiting, hyperesthesia of the mouth and face, paresthesias of face, tongue, and extremities, headache, dizziness, myoclonus, leg weakness, agitation, and confusion may subsequently occur. Seizures only occur after very high exposures, usually following large ingestions^{46,67} DDT has a relatively low order of acute toxicity, and high doses of DDT (>10 mg/kg or more) are usually necessary to produce symptoms⁶⁷ However, with lindane, the cyclodienes, and toxaphene, there often are no prodromal signs or symptoms, and more often than not, the first manifestation of toxicity is a generalized seizure^{20,23,46,45,67,81,125,145} If seizures develop, they often occur within 1 to 2 hours of ingestion when the stomach is empty, but they may be delayed as much as 5 to 6 hours when the ingestion follows a substantial meal⁶⁷

Seizures related to dermal application of 1% lindane for treatment of ectoparasitic diseases may occur following a single inappropriate application,^{86,109,153} or, more commonly, after repetitive and prolonged exposures.^{83,113} The time from application to seizure onset can vary from hours to days. The seizures are often self-limited, but may recur or result in status epilepticus. Analysis of an epidemic of lindane poisoning related to the unintentional substitution of lindane powder for sugar used in coffee demonstrated a delay of 20 minutes to 3 hours before the onset of nausea, vomiting, dizziness, facial pallor, severe cyanosis of the face and extremities, collapse, convulsions, and hyperthermia. Affected patients ingested an average of 86 mg/kg of lindane in a single dose.³⁴

The cyclodienes are also notable for their propensity to cause seizures that may recur for several days following an acute exposure. If the seizures are brief and hypoxia has not occurred, recovery is usually complete. Electroencephalographic (EEG) abnormalities have been recorded before, during, and following seizures.⁸¹ Hyperthermia secondary to central mechanisms, increased muscle activity, or aspiration pneumonia is common.⁴⁶

Status epilepticus is a common occurrence in patients with intentional endosulfan ingestions. A recent abstract summarized 25 cases of endosulfan self-poisonings with resultant status epilepticus in Nepal. More than half of the patients developed refractory status epilepticus, and eight patients died.⁸⁸

The ingestion of combinations of xenobiotics may result in significantly increased toxicity—probably the result of synergy. This has been demonstrated for DDT and lindane.⁶⁷

Lindane: Specific Risks. Patients are at risk for developing central nervous system toxicity from improper topical therapeutic use, such as exceeding recommended application times or amounts, repeated applications, application following hot baths, and use of occlusive dressings or clothing shortly after application. Toxicity also occurs after unintentional oral ingestion of topical preparations. Young children appear at greatest risk, possibly because of greater skin permeability, increased ratio of body surface area to mass, or immature liver enzymes^{113,152,153} The elderly may also be at increased risk because of impaired hepatic metabolism, atrophic skin, and perhaps age-related increased sensitivity. Patients at increased risk also include those with preexisting conditions that cause increased risk of seizures, such as treatment with antipsychotics, which lower the seizure threshold, CNS disease, or skin absorption changes^{4,36,55,83,86,103,109,113,141,142,152,153}

Despite the availability of safer and equally or more effective treatments such as permethrin, lindane had continued to be used because of its lower cost than permethrin and generally good safety profile, when used according to directions. However, now that permethrin products are available in less-expensive generic forms, the cost advantage of lindane is gone, and it is being used less each year.

An evaluation of published English-language case reports and those submitted to the US Food and Drug Administration (FDA) divided toxicity into those associated with concentrations of lindane greater than or less than 1%.⁸³ Only 6 of 26 cases could be considered related to 1% lindane;⁴ six of these cases were the result of ingestion or inappropriate skin

application.⁴ However, a recent comprehensive review of all published adverse events associated with topical lindane (67 cases) showed that while most of the serious adverse reactions (16 deaths, 11 seizures) occurred in ingestions or excessive use, labelled use accounted for a substantial portion of serious adverse reactions (4 deaths, 11 seizures).¹⁰⁰ The sale of lindane-containing products for use in humans was banned in California in 2004 because of its toxicity and environmental concerns.¹⁷ In 1995, the FDA changed the labeling requirements for lindane, adding a black-box warning and relegating it to second line therapy for ectoparasitic skin infections, due to its toxicity and to the superior safety and efficacy of other products.¹⁵⁸

Chronic Exposure. Chlordecone (Kepone), unlike the other organic chlorines, produces an insidious picture of chronic toxicity related to its extremely long persistence in the body. Because of poor industrial hygiene practices in a makeshift chlordecone factory in Hopewell, Virginia, 133 workers were heavily exposed for 17 months between 1974 and 1975. They developed a clinical syndrome which became known as the “Hopewell epidemic,” which consisted of a prominent tremor of the hands, a fine tremor of the head, and trembling of the entire body, known as the “Kepone Shakes.” Other findings included weakness, opsoclonus (rapid, irregular, dysrhythmic ocular movements), ataxia, altered mental status, rash, weight loss, and elevated liver enzymes. Idiopathic intracranial hypertension, oligospermia, and decreased sperm motility were also found in some of these workers. Severely affected workers even exhibited an exaggerated startle response, remarkably similar to that seen in animal studies. The exposures were so intense that some workers went home covered with chlordecone, and several workers’ wives developed neurologic symptoms, presumably from exposures while laundering their husbands’ work clothes.^{53,31}

There is much concern in environmental health centers on persistent organic chemicals, organic chlorine residues and PCBs being prime examples. A recent review of the world literature reveals that since being outlawed in many processes and countries, human burden appears to be decreasing.⁹⁰

DDT and Breast Cancer. DDT and other organic chlorine insecticides have estrogenic effects.^{37,144} Since breast cancer incidence rates in the United States have steadily climbed 1% per year since the 1940s, coinciding with the worldwide use of DDT, it has been postulated that women who have higher concentrations of estrogenic organic chlorines compounds (eg, DDT, polychlorinated biphenyls {PCBs}) may be at risk for developing breast cancer.^{128,129,130,130,168}

Several small case-control studies of women with breast cancer showed that women with the disease had higher average body burdens of DDT, DDE, and PCBs than their age-matched controls. These studies implicated organic chlorines as a possible cause of human breast cancer. Recently, however, larger studies have shown no increased risk of breast cancer because of exposure to organic chlorines¹⁸ and that currently accepted hereditary and lifestyle risk factors were present in the patients with cancer.^{71,84,130,129,128} In fact, other natural dietary estrogens, such as flavonoids, lignans, sterols, and fungal metabolites, are present in the human diet and have much higher estrogenic potency; the organic chlorine contribution is probably minimal by comparison.⁶⁰ One interesting report suggests age at first exposure, that is, age <14 years (prior to menarche) as having an association with later breast cancer,³⁰ but most case-control studies recently published have not supported an association between DDT and breast cancer.^{15,63,72,74,138,139} A meta-analysis of 22 studies found strong evidence to discard the putative relationship between p, p'-DDE levels and breast cancer risk.⁸⁹

Diagnostic Information

The history of exposure to an organic chlorine pesticide is the most critical piece of information because exposure is otherwise rare. By law, the package label of these products must list the ingredients, the concentrations, and the vehicle. The EPA-registered use of the insecticide may be helpful in determining which agent is involved. The presence of an unusual odor in the mouth, in the vomitus, or on the skin may be helpful. Toxaphene, a chlorinated pinene, has a mild turpentinelike odor, and endosulfan has a unique “rotten egg” sulfur odor (Table 114–1). Following ingestion, an abdominal radiograph may reveal the presence of a radiopaque chlorinated pesticide, since chlorine increases the radiopacity of the xenobiotics (Chap. 5). A large number of other xenobiotics lead to seizures as the first manifestation of toxicity and must be considered in the differential of an unknown exposure (Chaps. 14 and 24).

Laboratory Testing

Gas chromatography can detect organic chlorine pesticides in serum, adipose tissue, and urine.^{35,71} If confirmation is necessary for purposes of documentation of source, it may be necessary to measure concentrations of organic chlorines. If the patient’s history and toxidrome are obvious, then laboratory evaluation is unnecessary, as this determination will not alter the course of management, and these blood tests are not available on an emergent basis. At present, there are no data correlating health effects and tissue concentrations. Routine surveillance of serum concentrations in the occupationally exposed is not currently performed.³⁵

Most humans studied have measurable concentrations of DDT in adipose tissue. In a study of a community with a very large exposure to DDT, serum DDT concentrations increased proportionally with age. These increasing concentrations were not associated with any apparent adverse health effects, but there was an association with increasing concentrations

of the liver enzyme γ -glutamyltransferase (GGT), although significant hepatotoxicity did not occur. The CDC's Third National Report on Human Exposure to Environmental Chemicals demonstrated the presence of numerous organic chlorine pesticide residues in lipid fraction of serum of US residents. These concentrations tend to increase with patient age, consistent with the bioaccumulation and fat-storing properties of the chemicals.²⁴ More recently, studies of occupationally-exposed pesticide applicators and persons living in targeted regions confirmed higher serum concentrations over those not exposed, but no ill health effects are documented.¹²⁷

Serum lindane concentrations can be used to document exposure, and clinical signs and symptoms of toxicity correlated with blood concentrations.³¹ Lindane-exposed workers with chronic neurologic symptoms showed blood lindane concentrations of 0.02 mg/L.^{4,67} A limited series of patients with acute lindane ingestion suggests that a serum concentration of 0.12 mg/L correlates with sedation, and that 0.20 mg/L is associated with seizures and coma.⁴ After cutaneous application, lindane concentrations in the CNS are 3 to 12 times higher than serum concentrations.^{39,142}

Management

As with any patient who presents with an altered mental status, the administration of dextrose and thiamine in an adult should be considered. Skin decontamination is essential. Clothing should be removed, placed in a plastic bag, and disposed of appropriately as a biohazardous waste; the skin must be washed with soap and water. Health care providers should be protected with rubber gloves and aprons. Because these pesticides are almost invariably liquids, a nasogastric tube can be used to suction and lavage gastric contents, if clinically indicated. This is most appropriate only with very recent ingestion (Chap. 8). Activated charcoal (AC) can be used after or instead of gastric lavage, when lavage is not indicated.^{67,92} However, the ability of AC to adsorb the various organic chlorines is not adequately studied, and mixtures containing petroleum distillates would obviously preclude the use of AC (Chap. 20). Because organic chlorines are all neurotoxins, the risk of complications associated with seizures probably outweighs the risk of any of the GI decontamination strategies in most acute settings. A murine model of lindane toxicity following intragastric administration showed a trend, but not a statistically significant benefit, of AC. The use of cholestyramine, a nonabsorbable bile acid-binding anion exchange resin, in the same murine model did show a statistically significant benefit by raising both the convulsive dose and the lethal dose.⁷⁸ Oil-based cathartics should never be used, as they may facilitate absorption. There is some evidence that sucrose polyester (olestra, a nonabsorbed synthetic dietary oil substitute) can increase excretion of a wide variety of fat-soluble organic chlorine chemicals.^{75,96} This effect was demonstrated in dioxin-poisoned patients when administered in potato chips,⁶⁴ and was recently employed in treating Ukrainian President Viktor Yushenko.¹⁴⁶ Sucrose polyester might be an inexpensive and more palatable alternative to cholestyramine to increase excretion in patients with increased body burdens from chronic organic chlorine toxicity.

Seizures should be controlled with a benzodiazepine followed by pentobarbital or a propofol infusion and, if necessary, neuromuscular blockade to control the peripheral manifestations of seizures, thereby preventing metabolic acidosis and rhabdomyolysis. As has been shown in other toxic exposures, phenytoin is much less effective in these cases, particularly with the GABA-chloride ionophore antagonists lindane, toxaphene, and the cyclodienes.¹¹⁶ Hyperthermia should be managed aggressively with external cooling.

Cholestyramine should be administered to all patients symptomatic from chlordecone, and possibly other organic chlorines. Chlordecone undergoes both enterohepatic and enteroenteric recirculation, which can be interrupted by cholestyramine at a dosage of 16 g/d. Cholestyramine increased the fecal elimination of chlordecone 3-to 18-fold in industrial workers exposed during the Hopewell epidemic, resulting in clinical improvement.³¹ Sucrose polyester may also be an option for enhancing excretion.

PYRETHRINS AND PYRETHROIDS

The pyrethrins are the active extracts from the flower *Chrysanthemum cinerariaefolium*. These insecticides are important historically, having been used in China since the 1st century A.D.³⁴ and developed for commercial application by the 1800s. They are produced by organic solvent extraction from ground *Chrysanthemum* flowers. The resulting concentrates have greater than 90% purity. Pyrethrum, the first pyrethrin identified, consists of six esters derived from chrysanthemic acid and pyrethric acid. These insecticides are highly effective contact poisons, and their lipophilic nature allows them to readily penetrate insect chitin (exoskeleton) and paralyze the nervous system through Na^+ channel blockade.^{28,97,143,116} When applied properly, they have essentially no systemic mammalian toxicity because of their rapid hydrolysis. Pyrethrins break down rapidly in light and in water, and therefore have no environmental persistence or bioaccumulation. This fact makes them extremely safe after human exposures, but unsuitable for commercial agriculture, since the constant reapplication would be cost prohibitive.

The pyrethroids are the synthetic derivatives of the natural pyrethrins¹⁴⁰ (Table 114–2 and Fig. 114–3). They were developed in an effort to produce more environmentally stable products for use in agriculture. Originally, the pyrethroids

were divided into two groups based on the toxic syndromes they elicited in test animals. The T syndrome (for tremor seen in rats) was produced by intravenous administration of pyrethrin and most (15 of 18) of the pyrethroids that did not contain a cyano group at the central ester linkage (see below). The CS syndrome (for choreoathetosis and salivation) was produced by 12 of the 17 pyrethroids that had an α -cyano group at the ester linkage. The original studies delineating the T or CS method of classification did not test several new currently registered pyrethroid pesticides, and the testing methods involved intravenous or intracerebral administration, which are not relevant to human exposures.¹⁴⁰

TABLE 114-2. Synthetic Pyrethroids in Common Use

Pyrethroid Class	Generic Name, CAS #	Trademark Brand Names	Generation of Pyrethroid, Dates Introduced (if Available)
Type I	Allethrin 584-79-2	Pynamin	1st generation; first synthetic pyrethroid, 1949
	Bioallethrin 584-79-2	D-Trans	2nd generation, 1969; trans isomer of allethrin
	Dimethrin 70-38-2	Dimetrix	
	Phenothrin 26002-80-2	Fenothrin, Forte, Sumithrin	2nd generation, 1973
	Resmethrin 10453-86-8	Benzofluorene, Chrysion, Crossfire, pyrethrum Premgard, Pynosect, Pyrethrin, Synthrin	2nd generation, 1967; 20X strength of pyrethrum
	Bioresmethrin 28434-01-7		2nd generation, 1967; 50X strength of pyrethrum, isomer of resmethrin
	Tetramethrin 7696-12-0	Neo-Pynamin	2nd generation, 1965
	Permethrin 52645-53-1	Ambush, Biomist, Dragnet, Ectiban, Elmite, Iptox, Ketokill, Nix, Outflank, Perigen, Permasect, Persect, Pertox, Pounce, Prames, etc	3rd generation, 1972; effective topical scabicide and miticide, low toxicity
	Bifenthrin 82657-04-3	Capture, Talstar	4th generation
	Prallethrin 23031-36-9	SF, Etox	4th generation
	Imiprothrin 72963-72-5	Multicide, Pralle, Raid Ant & Roach	3rd generation, 1998
Type II	Fenvalerate 51630-58-1	Belmark, Evercide, Extrin, Fenkill, Sanmarton, Sumicidin, Sumilly, Sumipower, Sumitox, Tribute	3rd generation, 1973
	Azinathrin 103833-18-7	Rufast	4th generation
	Cyfluthrin 68359-37-5	Baythroid, Countdown, Cylense, Laser, Tempo, Bulldock, Cyfloxylate, Eulan SP, Solfac	4th generation
	Cyhalothrin 91465-08-6	Demand, Karate, Ninja 10WP, Scimitar, Warrior	4th generation
	Cypermethrin 52315-07-8	Ammo, Barricade, CCNS2, Cymbush, Cyperator, Cynoff, Cypercopal, Cyperkill, Cynuc, Demon, Electron, Kahl/Super, Ripcord, Siperin, Mustang & Fury	4th generation
	Deltamethrin 52918-63-5	Butolin, Butox, Crackdown, Decis, DeltaDust, DeltaGard, Deltex, K-Othrine, Striker, Suspend	4th generation
	Esfenvalerate 66230-04-4	Asana, Asana-XL, Hallmark, Sumi-alpha	4th generation
	Fenpropathrin 39515-41-8	Danitol, Herald, Meothrin, Rody	4th generation, 1989
	Flucythrinate 70124-77-5	AASTAR, Cybolt, Floent, Payoff, Guardian, Cythrin, StockGuard	4th generation
	Fluvalinate 102851-06-9	Apistan, Klaran, Mavrik, Mavrik Aqua Flow, Spur, Taufluvalinate, and Yandex	4th generation
	Imiprothrin 72963-72-5	Pralle; Multicide (mixture with d-phenothrin)	4th generation, 1998
	Tefluthrin 79538-32-2	Demand, Force, Karate, Scimitar, Evict, Fireban, Force & Raze	4th generation
	Tralomethrin 66841-25-6	Dethmor, SAGA, Scout, Scout X-TRA, Tralex	4th generation

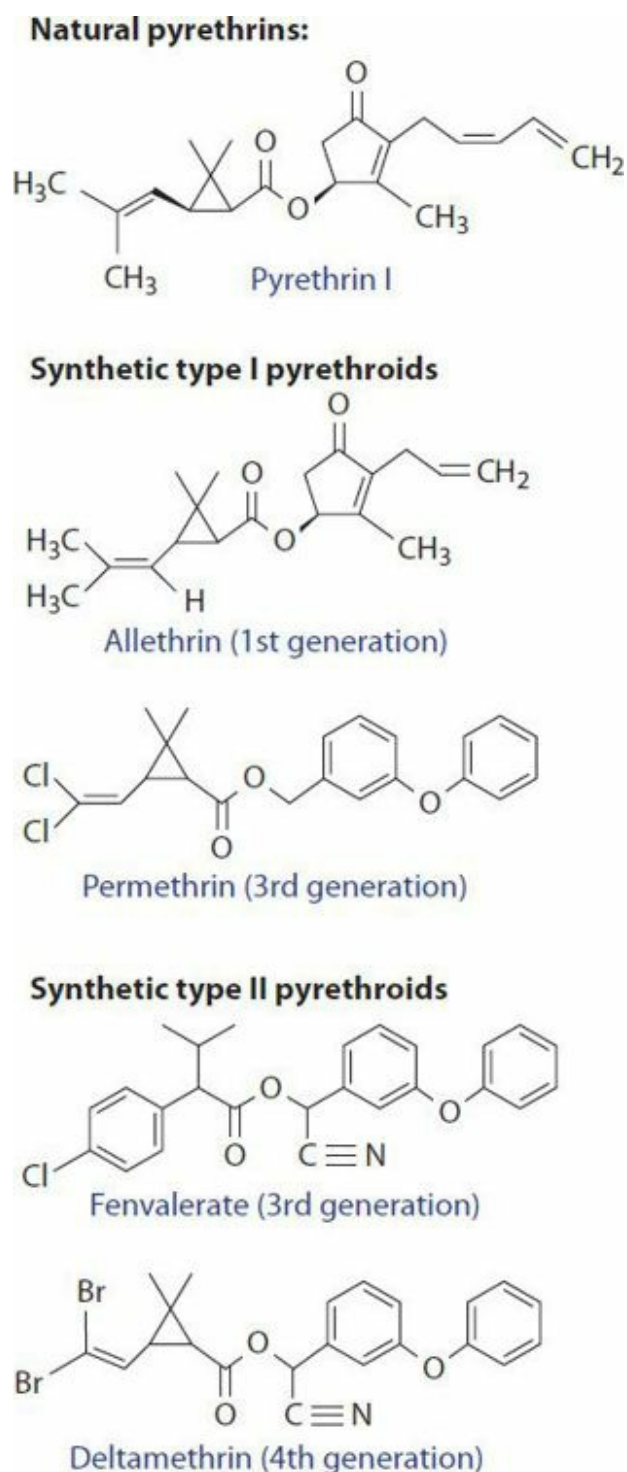


FIGURE 114–3 Representative structures of pyrethrin and pyrethroids.

The predominant classification scheme used today is based on the structure of the pyrethroid, its clinical manifestations in mammalian poisoning, its actions on insect nerve preparations, and its insecticidal activity. Type I pyrethroids have a simple ester bond at the central linkage without a cyano group. Commonly used type I pyrethroids include permethrin, allethrin, tetramethrin, and fenothrin. The type II pyrethroids have a cyano group at the carbon of this ester linkage. Type II pyrethroids in common use include cypermethrin, deltamethrin, fenpropathrin, fluvalinate, and fenvalerate. The cyano group greatly enhances neurotoxicity of the type II pyrethroids in both mammals and insects, and type II pyrethroids tend to produce the CS syndrome in test animals and are generally considered more potent and toxic than the type I pyrethroids (Fig. 114–3).^{45,91,115,116,140}

The development of the pyrethroids can also be divided into “generations,” based on efficacy and dates of introduction.¹⁶⁴ The first generation began in 1949, with the development of allethrin. The second generation began in 1965, with the introduction of tetramethrin. The major advance of the second generation was a dramatic increase in potency compared with the pyrethrins. The third generation, introduced in the 1970s and including fenvalerate and permethrin, were the first pyrethroids with practical agricultural use. They were more potent, and more environmentally stable, with efficacious crop residues lasting 4 to 7 days. The current fourth generation includes mostly type II pyrethroids, which have even greater insecticidal activity, are photostable (do not undergo photolysis, “splitting,” in sunlight), have minimal volatility, and provide extended residual effectiveness for up to 10 days under optimum conditions.^{91,164}

There are more than 1000 pyrethroids, of which 16 to 20 are in widespread use today.^{34,13} Pyrethrins and pyrethroids

are found in more than 2000 commercially available products. These insecticides have a rapid paralytic effect (“knock down”) on insects. Most mammalian species are relatively resistant because the pyrethrins can be rapidly detoxified by ester cleavage and oxidation.¹⁰⁷ Toxicity of the pyrethrins and pyrethroids is enhanced in insects by combination with microsomal enzyme inhibitors such as piperonyl butoxide (a synthetic analogue of sesamin, the methylenedioxyphenyl component of sesame oil) or N-octyl bicycloheptene dicarboximide.^{8,111}

Permethrin, a type I pyrethroid, is used medicinally for topical treatment of ectoparasitic conditions in humans, and it is impregnated in clothing and mosquito netting for its insect repellent properties. It has an excellent safety profile, with approximately 2% or less absorbed systemically through the skin.⁹³ Recent comprehensive reviews have confirmed that 5% permethrin is the drug of choice for scabies treatment, with the best efficacy versus safety profile of topical treatments for scabies and lice.^{123,163}

West Nile Virus was first identified in the United States in 1999 and rapidly spread to most of the United States by 2006. Outbreaks of encephalitis caused by West Nile virus (WNV) have occurred in the late summer and early autumn months in the United States since 1999. Although birds are the reservoirs for WNV, transmission to humans occurs via mosquito bites, and hence many states and municipalities have increased their aerial spraying in an effort to control mosquitoes vectors of this disease. Most spraying programs use pyrethroid insecticides because of their favorable safety profile and their efficacy against the adult mosquito. These widespread spraying programs have increased the potential for human exposures to these xenobiotics. A Centers for Disease Control and Prevention study of pyrethroid spraying did not reveal an increase in detectable pyrethroid metabolites in the general public living in the sprayed areas.⁷ Another study of asthma surveillance showed no increases in emergency department visits because of asthma-related conditions for the periods after pyrethroid spraying.⁷⁶

Toxicokinetics

Absorption. Pyrethrins are well absorbed orally and via inhalation, but skin absorption is poor. Piperonyl butoxide is also well absorbed orally, but likewise has poor dermal penetration.¹¹¹ The oral toxicity of pyrethrins in mammals is extremely low because they are so readily hydrolyzed into inactive compounds. Their dermal toxicity is even lower, owing to their slow penetration and rapid metabolism.^{46,107}

The pyrethroids are more stable than the natural pyrethrins, and significant systemic toxicity occurs following ingestion.⁶⁸ An average of 35% (range 27%–57%) of orally administered cypermethrin is absorbed in human volunteers.¹⁶⁹ Most exposures are from dermal absorption, the rate of which may vary depending on the solvent vehicle. In the same volunteer study noted above, a mean of 1.2% (range 0.85%–1.8%) of dermally applied cypermethrin in soybean oil vehicle was absorbed systemically.¹⁶⁹ Intradermal metabolism of pyrethroids is documented in test animals and likely further limits systemic absorption.¹³ Direct absorption of pyrethroids through the skin to the peripheral sensory nerves probably accounts for the facial paresthesias that occur in these cases, as symptoms were prominent in areas of direct contact.^{27,85} Absorption probably also occurs through the oral mucosa, as noted by a large study of Chinese insecticide sprayers who frequently used their mouths to clear clogged spray nozzles. The pyrethroids are also absorbed via inhalation; however, in these same sprayers, inhalation was not found to be a clinically significant route of exposure as analyzed by breathing zone assays.²⁷ The pyrethroids are not volatile compounds, so inhalation is always due to powders or sprayed mists, and mucosal and pulmonary toxicity may be due to hydrocarbon solvent vehicles. Systemic absorption and resultant effects may follow massive exposures, such as occurs in enclosed spraying or other extreme conditions.

Distribution. The pyrethroids and pyrethrins are lipophilic and as such are rapidly distributed to the central nervous system. Because they are rapidly metabolized, there is no storage or bioaccumulation, which limits chronic toxicity.^{46,45}

Metabolism. Natural pyrethrins are readily metabolized by mammalian microsomal enzymes, and hence are essentially nontoxic to humans. They can induce CYP3A and CYP2B isoforms in vitro in human cultured hepatocytes, but clinical significance is doubtful.¹¹⁰

The synthetic pyrethroids are readily metabolized in animals and humans by hydrolases and the CYP microsomal system. The metabolites are of lower toxicity than the parent compounds.¹⁴⁰ Piperonyl butoxide, a P-450 inhibitor, enhances the potency of pyrethrins and pyrethroids 10- to 300-fold to target insects. It is often added to insecticide preparations to ensure lethality, as the initial “knock down” effect of a pyrethroid alone is not always lethal to the insect.⁴⁵ Testing of piperonyl butoxide on antipyrine metabolism (measure of CYP enzyme function) in humans at a dose exceeding 50 times that received in all-day confined space pesticide spraying revealed no effect on this enzyme system in humans.¹¹¹

Elimination. There is no evidence that the pyrethroids undergo enterohepatic recirculation. Deltamethrin disappeared from the urine of exposed workers within 12 hours, and fenvalerate disappeared within 24 hours.²⁷ Parent compounds, and metabolites of the pyrethroids, are found in the urine.¹¹⁶ The most commonly assayed metabolites are 3-PBA (3-phenoxybenzoic acid, a nonspecific metabolite of multiple pyrethroids), cis-DCCA (cis-3-{2,2-dichloroethenyl}-dimethyl cyclopropane carboxylic acid, a metabolite of cis-permethrin, cypermethrin, and cyfluthrin), trans-DCCA (trans-3-{2,2-

dichloroethenyl}-dimethyl cyclopropane carboxylic acid, a metabolite of trans-permethrin, cypermethrin, cyfluthrin), and Br2CA (3-{2,2-dibromovinyl}-2,2-dimethylcyclopropanecarboxylic acid, a metabolite of deltamethrin). The metabolite CDCA (chrysanthemumdicarboxylic acid) is also a nonspecific metabolite of natural pyrethrin I and the synthetic pyrethroids allethrin, resmethrin, and tetramethrin^{87,149} Monitoring of these metabolites is used in population-based studies for pesticide exposures. However, a recent review revealed that commonly assayed pyrethroid metabolites also occur in the environment from natural degradation. Therefore, the detection of these metabolites in the urine may be from a subject's exposure to the parent compound or from its metabolite in the environment

Pathophysiology

Like DDT, pyrethrins and pyrethroids prolong the activation of the voltage-dependent Na⁺ channel by binding to it in the open state, causing a prolonged depolarization, as evidenced by an extended tail current seen with squid axon voltage clamp experiments.^{98,99} Indeed, DDT and pyrethrin/pyrethroids bind to the same site on insect Na⁺ channels, and resistance to one class causes cross-resistance to the other class as well.¹⁰² The voltage-sensitive Na⁺ channel binding is responsible for the insecticidal activity and the toxicity of the pyrethroids to nontarget species. Natural pyrethrins and type I synthetic pyrethroids induce repetitive or "burst discharges" following a single stimulus because they hold the Na⁺ channel in its open state for shorter periods. The actual amplitude of the tail current is determined by the concentration of the pyrethroids, regardless of type. Type II pyrethroids cause the Na⁺ channel to remain open longer and allow a prolonged period of depolarization of the resting membrane potential, causing a longer duration of the tail current.^{143,161} Type II pyrethroids are thus more potent and lead to significant after-potentials and eventual nerve conduction block. The mammalian voltage-dependent Na⁺ channel, unlike the insect, has many isoforms, and may help explain the relative resistance in mammalian species. Different pyrethroids have varied effects on these mammalian Na⁺ channels, and the effects are not additive, and in fact may be antagonistic. Structure-activity relationship is important as well because some pyrethroid trans isomers at the ester linkage are not insecticidal, but the cis isomers are, and some isomers are insecticidal but lack mammalian toxicity because of this isomeric specificity.¹⁴⁰

Pyrethroids also have activity at certain isoforms of the voltage-sensitive calcium channel, which may explain the neurotransmitter release that occurs in pyrethroid intoxication. Additionally, pyrethroids block voltage-sensitive chloride channels in test animals, producing the salivation as part of the CS syndrome. These effects may contribute to enhanced CNS toxicity¹⁴⁰ and are likely responsible for the choreoathetosis that occurs in animal models of severe type II poisonings.¹¹⁴ Some studies show some interference of the type II pyrethroids with the GABA_A-mediated inhibitory chloride channels, but only in high concentrations.^{28,97} Antagonism of the GABA_A chloride channels likely has a significant role in human pyrethroid exposures and probably contributes to the seizures following severe poisoning by type II agents.^{97,114} The pyrethroids may also act at the peripheral benzodiazepine receptor, as evidenced by decreased salivation in test animals when this receptor was blocked. The clinical significance of this is currently unknown.¹³

Natural pyrethrins and type I pyrethroids have a negative temperature coefficient, similar to DDT, and are more selectively toxic to non- warm-blooded target species, but also less effective at warmer environmental temperatures. Type II pyrethroids have a positive temperature coefficient, which makes them more insecticidal at higher ambient temperatures, and thus more useful in agricultural applications.^{97,164} However, this may also partly explain the greater toxicity of type II pyrethroids to warm-blooded species as compared to type I.⁹⁷

Clinical Manifestations

Pyrethrum probably has an LD₅₀ of well over 1 g/kg in humans, as extrapolated from animal data. Most cases of toxicity associated with the pyrethrins are the result of allergic reactions.^{107,165} Theoretically, those at highest risk for allergic reactions would be patients who are sensitive to ragweed pollen, 50% of whom may cross-react with chrysanthemums (ragweed and chrysanthemum are in the same botanical family). These allergic reactions are postulated to be due to residual natural components present in the extracts.¹¹⁶ However, recent reviews have cast some doubt on this explanation. First, there have been only four cases of life-threatening respiratory reactions reported in the literature, three of which were in known asthmatics.¹¹¹ Second, the presence of residual natural proteins is unlikely, as the purification procedures would allow little, if any, residuals.⁵⁹ Third, most reported cases of contact urticaria have been erroneously classified as type I hypersensitivity reactions.⁵⁹ The synthetic pyrethroids can cause histamine release in vitro⁴² but generally do not induce IgE-mediated allergic reactions.¹⁷

In animals, type I pyrethroid poisoning most closely resembles that of DDT, with extensive tremors, twitching, increased metabolic rate, and hyperthermia. Excluding the rare possibility of skin irritation or allergy, the type I pyrethroids are unlikely to cause systemic toxicity in humans. It has been shown experimentally that pyrethroids have greater than 1000-fold more affinity for insect Na⁺ channels than for those of mammals, explaining their low toxicity in higher life forms. This

selectivity, along with the negative temperature coefficient and slower insect metabolism, combines to make the type I pyrethroids approximately 15,000 times more toxic in insects than humans.⁹⁹ The type II pyrethroids are generally more potent and cause profuse salivation, ataxia, coarse tremor, choreoathetosis, and seizures in animals. In humans, poisoning with type II pyrethroids can cause paresthesias (secondary to Na⁺ channels effects in cutaneous sensory nerves after topical exposure),⁸⁵ salivation, nausea, vomiting, dizziness, fasciculations, altered mental status, coma, seizures, and acute lung injury.⁶⁸ A review of more than 500 cases of acute pyrethroid poisoning from China highlights some similar manifestations between a massive acute type II pyrethroid overdose and an organic phosphorus compound overdose. However, serious atropine toxicity and death has resulted when poisoning from a type II pyrethroid was mistaken for an organic phosphorus compound, and treatment was directed at these seemingly muscarinic signs.⁶⁸ Features such as acute respiratory distress syndrome may be caused by solvents and surfactants present in the agricultural products.⁸ Although the type II pyrethroids contain a cyanide moiety, cyanide poisoning does not occur, and cyanide antidotal therapy is not indicated.

Most significant unintentional exposures are dermal, especially in occupational settings, and local symptoms predominate in the majority of these cases. Systemic effects from insecticidal sprayings have been reported from wind drift or inappropriate handling, and the more potent type II pyrethroids predominate in case reports. An exposure of workers possibly affected by wind drift from a mixture of 32 ounces of the type II pyrethroid cyfluthrin mixed with 18.5 gallons of petroleum oil and 1800 gallons of water was reported in California in 2006. Spraying occurred in a citrus grove, and 23 female workers in an adjacent vineyard were possibly exposed. These workers complained of a “chemical” odor and felt ill with headaches, nausea, eye irritation, weakness, anxiety, and shortness of breath. They were all evaluated in local EDs and discharged home. Despite the fact that no cyfluthrin was detected on these²⁵ workers’ clothing or on foliage in the field where they were alleged to have been exposed, the report concluded that cyfluthrin was the cause; no estimate of the contribution of the petroleum vehicle to the symptoms was posited.²⁵ The predominant feature after significant cutaneous exposures is local paresthesias in the areas of skin contact, due to Na⁺ channel effects on cutaneous sensory nerves. Local skin irritation was seen in up to 10% of workers spraying pyrethroid insecticides, but it is rarely seen after medicinal use of the pyrethroid creams and shampoos. Ocular contact causes more severe symptoms, including immediate pain, lacrimation, photophobia, and conjunctivitis.¹³

Intentional ingestions represent the most serious exposures, due to the higher doses involved and the greater exposures to vehicles and solvents. However, a study of 48 cases of permethrin/xylene/surfactant mixtures (38 were suicidal ingestions) revealed that mild GI signs and symptoms predominated (73%: sore throat, mouth ulcerations, dysphagia, epigastric pain, vomiting). Pulmonary signs and symptoms were documented in 29%, and eight patients (including one death) had aspiration pneumonia. Thirty three percent had CNS symptoms: confusion (13%), coma (21%), and seizures (8%). The involvement of the central nervous system and lungs were less common, but clinically more significant.¹⁷² The relative contributions of the 70% xylene and 10% surfactant were likely responsible for much of the GI and pulmonary effects, though it was not discussed in the report.

Chronic Exposures

Since the pyrethroids are rapidly metabolized and are not biopersistent compounds, they have not been shown to cause cumulative toxicity. A single case of motor neuron disease resulted from heavy daily inhalation exposure to pyrethroid mixtures in a combined space for 3 years, which resolved after exposure ceased.⁴³ Some investigators have expressed concerns regarding possible neurotoxicity of the pyrethroids. However, a recent review noted that regulatory studies in multiple species have shown no evidence supporting gross neurodevelopmental toxicity or adult neuronal loss in man.¹¹⁴ In Germany, a unique situation exists where numerous civil lawsuits allege multiple chemical sensitivity (MCS) was caused by pyrethroid exposures. Scientific study of this phenomenon yields no scientific data to support this contention,¹¹ and the controversy is fueled by civil litigation, popular media sensationalizing, and subsequent public fear.⁵

Treatment

Initial treatment should be directed toward skin decontamination, as most poisonings occur from exposures by this route. Patients with intentional oral ingestions of a type II pyrethroid should be treated with a single standard dose of AC, provided the diluent of the pyrethroid does not contain a petroleum solvent. Contact dermatitis and acute systemic allergic reactions should be treated in the usual manner, utilizing histamine blockers, corticosteroids, and β -adrenergic agonists as clinically indicated.

Treatment of systemic toxicity is entirely supportive and symptomatic because no specific antidote exists. Benzodiazepines should be used for tremor and seizures. Topical vitamin E oil (dl- α -tocopherol) is especially effective in preventing and treating cutaneous paresthesias due to topical pyrethroid exposures.^{13,116}

INSECT REPELLENTS

Mosquitoes transmit more diseases to humans than any other biting insect. Worldwide, more than 700 million people are infected yearly by mosquito bites that transmit such diseases as malaria, viral encephalitis, yellow fever, dengue fever, bancroftian filariasis, and epidemic polyarthritis. Novel approaches to mosquito control also includes impregnation of indoor house paints with various insecticides (organic phosphorus compounds) and insect growth regulators. The WHO estimates that in 2010 there were about 219 million malaria cases and an estimated 660,000 malaria deaths worldwide.⁶ In the United States, eight people died from West Nile Virus (WNV) in NYC in 1999, and by January 2005, the virus, carried by mosquitoes from infected birds, had spread to all lower 48 states. Therefore, mosquito repellants have become important public health tools, and DEET has been the time-tested primary weapon for the past five decades. However, much controversy continues to surround DEET despite a remarkable safety profile with over a half-century of global use by billions of people. A growing trend in the United States and many western cultures has been a chemophobia against synthetic products like DEET. Many people favor plant-based “natural” or “organic” repellents, paralleling the increasing consumer preference for natural or organic foods. Several xenobiotics are proposed, but thus far few have been shown by objective blinded studies to even approach the efficacy of DEET, much less surpass it. Numerous comprehensive reviews of the subject have demonstrated superiority of DEET in most cases, and it remains the insect repellent standard by which all others are measured (Table 114–3).

TABLE 114–3 Comparative Efficacy and Toxicity of Commonly Available Insect Repellents

<i>Insect Repellent</i>	<i>EPA Approval</i>	<i>EPA Toxicity Rating^a</i>	<i>Efficacy in Lab and Field studies^b</i>	<i>Notes</i>
DEET	1957 (1980)	III	Most efficacious in lab and field studies; proven protection against ticks and mosquitoes	>50 years of experience, billions of users 10%–30% soln: safe, effective when used as directed
Picaridin (Bayrepel)	2001	IV	20% soln: Lab: Equivalent to DEET Field: Essentially equivalent to DEET	All studies done on 20% picaridin; no studies done with 7% US formula Recommended by CDC as a DEET alternative
IR3535 (Substituted β amino acid)	1999	IV	Lab: Inferior to DEET Field: None available	Recommended by CDC as a DEET alternative
Oil of Lemon Eucalyptus (p-menthane diol)	2000	IV (I, ocular)	Equivalent to DEET for mosquitoes; not tested for tick bite prevention	Recommended by CDC as a DEET alternative
BioUD (2-undecanone)	2007	IV	Lab: Equivalent to 7% DEET Field: Equal to 25% and 30% DEET	Studies performed by patent holders and developers of IR, no impartial evidence
Citronella oil	1948	IV	Lab study: Ineffective	Candles only provide some repellency when within 1 meter

^aEPA Acute Toxicity Ratings: Category I = very highly or highly toxic; Category II = moderately toxic; Category III = slightly toxic; Category IV = practically nontoxic. ^bLab tests: arm in cage studies for mosquito repellency; Field studies: actual biting or tick attachment assays in natural conditions.

DEET

The topical insect repellent, N,N-diethyl-3-methylbenzamide (DEET, former nomenclature N,N-diethyl-meta-toluamide), was patented by the US Army in 1946 and has been commercially marketed in the United States since 1956. Currently, it is used worldwide by more than 200 million persons annually. The EPA estimates that 38% of the US population uses DEET each year. Despite the current search for alternatives, DEET is still the most effective repellent available and has the most clinical toxicity information.^{56,57}

DEET can be purchased without prescription in concentrations ranging from 5% to 100%, and in multiple formulations of solutions, creams, lotions, gels, and aerosol sprays. Mosquitoes are attracted to their hosts by temperature and chemical attractants, principally CO₂ and lactate. The mechanism by which DEET repels insects was thought to be due to some interference with the chemoreceptors that detect lactic acid and CO₂.^{56,112} However, recent work has demonstrated that DEET itself is actually detected by the mosquito’s olfactory receptors and repels them independently of whether the normal physical or chemical attractants are present.¹⁵¹ DEET formulations can feel greasy or sticky and can dissolve or damage some plastics (eyeglass frames, watches) and synthetic fabrics.

Toxicokinetics

DEET is extensively absorbed via the gastrointestinal tract.¹⁵⁹ Skin absorption is significant, depending on the vehicle and the concentration. Transdermal absorption of 30 to 45% DEET in ethanol is significantly higher than 100% DEET solution

in an in vitro human skin model.¹⁴⁷ This has led to development of microencapsulated liposphere formulas and polyethylene glycol-based solutions that reduce absorption and increase repellent time and efficacy in animal models.⁴⁴

DEET does not bind to stratum corneum, and only 0.08% or less of a dose remains in the skin 8 hours after application.¹¹² DEET is lipophilic, and skin absorption usually occurs within 2 hours, although it is eliminated from plasma within 4 hours. The volume of distribution is large, in the range of 2.7 to 6.2 L/kg in animal studies. DEET is extensively metabolized by oxidation and hydroxylation by the hepatic microsomal enzymes, primarily by the isozymes CYP2B6, 3A4, 2C19, and 2A6.¹⁵⁹ DEET is excreted in the urine within 12 hours, mainly as metabolites, with 15% or less appearing as the parent compound.^{57,112}

DEET toxicity reports and studies have been extensively reviewed in terms of acute and chronic toxicity. It has been found safe for use in pregnant and lactating women⁸²; it was found to have no specific target organ toxicity or oncogenicity in any observed rat, mouse, or dog studies¹³⁶; and chronic DEET exposure together with other insecticides showed no increased cancer risks.¹⁰⁶

Pathophysiology

The exact mechanism of DEET toxicity is unknown. Recent reviews of adverse reactions to DEET reported 26 cases with major morbidity including encephalopathy, ataxia, convulsions, respiratory failure, hypotension, anaphylaxis, or death, particularly after ingestion or dermal exposure to large amounts.^{22,57,104,105,154,160} These primarily neurologic adverse reactions occurred mainly in children, and most involved prolonged use and excessive dosing beyond what is currently recommended. One fatal case involved a child who was known to be heterozygous for ornithine carbamoyl transferase (OCT) deficiency, and death was because of a Reye-like syndrome with hyperammonemia. This child had experienced prior episodes of hyperammonemia unrelated to DEET use, and DEET does not appear to affect, or be affected by, OCT activity in humans.¹⁰⁴ Currently, there is no evidence that enzyme polymorphism affects DEET metabolism or influences individual susceptibility to toxicity.

Although single, large, acute oral doses (1–3 g/kg) in rats produced seizures and CNS damage,^{134,135} smaller acute doses (500 mg/kg and less) and chronic multigenerational dosing in another rat study produced no obvious toxicity.¹³⁴ Teratogenicity studies in rats and rabbits failed to demonstrate toxicity except at the highest doses,^{136,171} and DEET was not found to be carcinogenic.^{112,136} In view of the billions of applications, the number of reports of toxicity appears exceedingly small and suggests a remarkably wide margin of safety.^{57,65,104,105,120,150,160}

Clinical Manifestations

Most calls to poison control centers regarding DEET exposures involve minor or no symptoms, and symptomatic exposures occur primarily when DEET is sprayed in the eyes or inhaled.¹⁶⁰ Except for suicidal ingestions, most serious reactions consist of seizures in children overexposed via the dermal route; in fact, some of these cannot be definitely attributed to DEET.^{65,104} Most symptoms resolve without treatment, and the majority of patients with serious toxicity recover fully with supportive care. A case report of severe poisoning developed in a man with extreme exposure. He used 30% DEET on his entire body several times daily for a prolonged time period, with an entire bottle used the day prior to admission. He developed weakness and nausea which progressed to confusion and shortness of breath. Metabolic acidosis, elevated lactate concentration, acute kidney injury requiring hemodialysis, and worsening weakness requiring mechanical ventilation developed. His blood DEET concentration was 130 ppb (µg/L). No seizures developed, and he experienced a full neurological recovery after a prolonged hospitalization.¹¹⁷

Treatment

Patients with DEET exposures are treated with supportive care aimed at primarily neurologic symptoms. In cases of dermal exposures, skin decontamination should be a priority to prevent further absorption. Patients with intentional oral ingestions should receive a single dose of AC if clinically indicated.

An extensive review of the safety risk of DEET repellent use confirms its safe use for all populations when used according to labeling guidelines.¹⁵⁰ Despite its good safety profile, avoiding the overuse of DEET seems prudent. The American Academy of Pediatrics (AAP) revised its recommendations for insect repellent (IR) use due to the emergence of WNV infections (prior recommendations were for use of products with DEET <10%).¹³⁷ They found that DEET-containing products are the most effective mosquito repellents available and are also effective against a variety of other insects, including ticks. IR with a DEET concentration from 10% to 30% (the maximum recommended for children) appear to be equally safe when used according to the directions on the product labels. The safety of DEET does not appear to relate to differences in these concentrations, and higher concentrations have longer durations of effects.¹ As indicated in the AAP handbook, repellents are not recommended for children younger than 2 months of age.²

The higher concentrations prolong the repellency period, but there is a plateau at about 50% DEET concentration, and about 6 hours may be the maximum protection time from any single application. Newer, longer-acting DEET formulations in lipids or polymers cause the DEET to evaporate more slowly, which affords protection for > 6 hours and also less systemic absorption.^{79,131} Since the lower concentrations recommended for children last approximately 2 hours, frequent reapplication is usually unnecessary. Since mosquitoes are most active for a few hours preceding and following dusk, DEET should be promptly washed off the child's skin when protection is no longer needed. Soaking the skin is not more effective and may contribute to toxicity. DEET should be applied only to exposed skin. One should avoid abraded skin or skin with rashes. Care should be taken to avoid exposure to eyes and sensitive skin areas. Avoid use on children's hands, so that the child does not wipe on eyes, mouth, genitalia, and so on. Adults should apply DEET to their own hands and then wipe onto the child's face, rather than spraying onto a child's face.

DEET combination products which include sunscreen should not be used together for mosquito repellency, since these combination products mutually enhance the percutaneous absorption of each component in both a porcine in vivo study⁷⁷ and in an in vitro mouse skin model.¹²⁴ Since mosquitoes are most active near dusk, there is clearly no need for the sunscreen component when repelling mosquitoes. These new combination products may be useful for tick repellency, however. Other options for protection include mechanical means, such as mosquito netting, as well as permethrin-impregnated clothing for tick prevention.

Newer Insect Repellents

The efficacy of any drug, treatment, or repellent is directly related to compliance with the treatment. Despite its demonstrated efficacy and safety, many people view chemical insect repellents such as DEET as potentially harmful and avoid their use. Several survey results in the United States and Canada revealed that 56% of people believe repellents are likely to be harmful to children, and 45% believed insect repellents are likely to sicken adults.¹⁶⁷ This has led to an intense search for effective alternatives to DEET-based repellents. Although their efficacy is not superior to DEET, their safety is likely at least equivalent to that of DEET, since the most recent data from NPDS revealed out of more than 1300 reported exposures, most reported no or minor effects.¹⁶

Picaridin (Bayrepel, KBR3023; CASRN: 119515-38-7). Picaridin (chemical name: 2-{2-hydroxyethyl}-1-piperidinecarboxylic acid 1-methylpropyl ester) is also known as Bayrepel and KBR 3023 in Europe. It is a piperidine derivative and has low acute oral, dermal, and inhalation toxicity. The EPA classifies it as Toxicity Category IV for acute inhalation toxicity and primary dermal irritation, the lowest rating available (Class III for oral ingestion). It is not a dermal sensitizer, and no developmental toxicity was observed in chronic animal feeding studies. It was also not shown to be mutagenic in a battery of tests and is not considered carcinogenic.⁴⁷ Picaridin is nearly as efficacious as DEET in comparison studies of the 20% solution used in Australia and Europe, but unfortunately no studies have compared the 7% formula marketed in the United States (Cutter Advanced; Avon Skin So Soft with Picaridin). Since duration of protection is generally related to concentrations of the repellent (clearly shown with DEET), it would be reasonable to assume the 7% US formula would not have as long a duration of effect. A comprehensive MedLine search performed in February 2013 revealed no reports of human toxicity of picaridin insect repellents

2-Undecanone (BioUD; Methyl Nonyl Ketone; CAS#: 112-12-9). A newly formulated natural repellent, 2-undecanone, was approved for use as an IR by the EPA in 2007 and is known by the brand name of BioUD. Its active ingredient is derived from the wild tomato plant *Lycopersicon hirsutum* Dunal f *glabratum* C. H. Mull.¹⁶⁷ 2-Undecanone (also known as methyl nonyl ketone) was originally registered in 1966 as a dog and cat repellent and training aid and as an iris borer deterrent. It received EPA approval as a topical insect repellent in 2007. The EPA RED documents that in studies using laboratory animals, methyl nonyl ketone exhibited no toxicity via the oral and inhalation routes and was placed in Toxicity Category IV. Methyl nonyl ketone was slightly toxic (Toxicity Category III) for dermal toxicity, eye irritation, and dermal irritation and was a weak dermal sensitizer. Since it has a long history of safe use, is from a natural source, and is an approved food additive, it is considered essentially nontoxic. Methyl nonyl ketone is currently found in only one insect repellent in the form of both a lotion and a spray known as HOMS BiteBlocker Insect Repellent.⁵¹ The manufacturer lists a nonpublished study on its website of a field test showing protection from mosquito bites surpassing that of a DEET 30% at 6 hours, and equivalent at 4 hours.⁶⁹ A 2008 study done by the inventors and patent holders showed it was only as efficacious as lower DEET concentration products in laboratory arm-in-cage trials, but field trials revealed efficacy equivalent to 25% to 30% DEET formulations.¹⁶⁷ A comprehensive MedLine search performed in February 2013 revealed no reports of human toxicity of 2-undecanone insect repellents

Oil of Lemon Eucalyptus (PMD; p-menthane-3,8-diol; CAS 42822-86-6). Oil of Lemon eucalyptus occurs naturally in the lemon eucalyptus plant (*Eucalyptus citriodora* also known as *Corymbia citriodora*). It is marketed in the USA under the brand name "OFF! Botanicals Insect Repellent®". The natural oil can be extracted from the eucalyptus leaves and twigs; commercially the active ingredient, p-menthane-3,8-diol (PMD), is chemically synthesized, and is structurally similar to menthol. In its pure form, it is a solid at room temperature, and has a faint mint-like odor. PMD is placed into Toxicity Category IV for acute oral toxicity, dermal toxicity and skin irritation, and Toxicity Category I for eye irritation (Toxicity

Category II for the end-use product). It is not a skin sensitizer. The EPA has determined that there is reasonable certainty of no harm to the U.S. population or subpopulations, including infants and children, as the result of the uses of PMD to formulate insect repellents.⁴⁸ This compound is not to be confused with eucalyptus oil, a toxic essential oil containing 1,8 cineole (CAS#470-82-6), which has no insect repellent properties. A comprehensive MedLine search performed February 2013 revealed no reports of human toxicity of PMD insect repellents.

Oil of Citronella. Plant-derived essential oil products are considered minimum-risk pesticides and are exempt from Environmental Protection Agency registration under Section 25(b) of the Federal Insecticide Fungicide and Rodenticide Act. Oil of Citronella has been used for over 50 years as an insect repellent and as an animal repellent in candles and topical skin products. These products, which have little efficacy, are not expected to cause harm to humans, pets, or the environment when used according to the label.⁵² A comprehensive MedLine search performed in February 2013 revealed no reports of human toxicity of citronella-containing insect repellents

Legal Standards for an Insecticide Label

The Federal Insecticide, Fungicide, and Rodenticide Act of 1962 established criteria for a “signal word” on an insecticide label, which implies the degree of toxicity based on an oral LD₅₀. Also, the label on the original container of these products is usually instructive and should always be brought to the medical facility (Table CS9–1).

SUMMARY

- Organic chlorine insecticide agricultural use has largely been eliminated in the United States and Europe but remains a problem in the developing countries. DDT remains an important tool for control of malaria vector mosquitoes. These xenobiotics classically cause neurological toxicity (tremors, seizures) when ingested.
- Pharmaceutical use of lindane for topical ectoparasitic infestations has decreased greatly in favor of less toxic permethrin preparations. Lindane is still available in most of the United States.
- Pyrethroid insecticides are the most commonly used insecticides for home use and have a lower order of toxicity than organic chlorine or organic phosphorus insecticides. The Type II pyrethroids are more potent and can cause systemic toxicity (CNS, pulmonary) when ingested, but toxicity may be due to solvents and surfactants in the formulations.
- DEET containing insect repellents are still the most efficacious formulas and have many years of safe use in billions of people worldwide when used as directed. Neurological toxicity has been described with extreme exposure situations.
- Some newer insect repellents have efficacy approaching that of DEET, and few reported toxicities. As these newer repellents become more commonly used, it is not expected that significant toxicities will be manifested.

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115 SODIUM MONOFLUOROACETATE AND FLUOROACETAMIDE

Fermin Barrueto Jr.

HISTORY AND EPIDEMIOLOGY

Sodium monofluoroacetate (SMFA) occurs naturally in plants native to Brazil, Australia, and South and West Africa (eg, gifblaar {*Dichapetalum cymosum*}).¹¹ The highest concentration (8.0 mg/g) is found in the seeds of a South African plant, *Dichapetalum braunii*.¹¹ In the 1940s, SMFA was released as a rodenticide (CAS No. 62-74-8) and assigned the compound number 1080, which was registered as its trade name. Fluoroacetamide, a similar pesticide, is known as Compound 1081. These compounds are widely effective as poisons against most mammals and some amphibians.²⁶ Both products were banned in the United States in 1972, except to protect sheep and cattle from coyotes. Collars embedded with SMFA are placed around the neck of livestock, the typical point of attack for coyotes.

Sodium monofluoroacetate is used extensively in New Zealand and Australia to control the possum population and other animal species considered pests that have no natural predators. Its continued use is extremely controversial, but following a recent review of the ramifications of the use of the compound, the government of New Zealand retained both the aerosolized and collar applications. Reported cases of human poisoning with SMFA are uncommon and the epidemiology is poorly understood. There have been only 65 reported cases from 1999 to 2010 with no deaths in the National Poisoning Database System of the American Association of Poison Control Centers ([Chap. 136](#)).

TOXICOKINETICS AND TOXICODYNAMICS

Sodium monofluoroacetate is an odorless and tasteless white powder with the consistency of flour. When it is dissolved in water, it is said to have a vinegarlike taste. Sodium monofluoroacetate and fluoroacetamide (CAS No. 640-19-7) are well absorbed by the oral and inhalational routes.^{10,11,12,27} Detailed toxicokinetic data are lacking in humans, but in sheep, up to 33% of an ingested dose is excreted unchanged in the urine over 48 hours. Glucuronide and glutathione conjugates have been isolated.¹¹ Substantial defluorination is not thought to occur in vivo. The serum half-life is estimated to be 6.6 to 13.3 hours in sheep.¹⁰ Sodium monofluoroacetate has an LD₅₀ of 0.07 mg/kg in dogs.¹⁹ The oral dose thought to be lethal to humans is 2 to 10 mg/kg.³

PATHOPHYSIOLOGY

Sodium monofluoroacetate, a structural analog of acetic acid ([Fig. 115–1](#)), is an irreversible inhibitor of the tricarboxylic acid cycle ([Fig. 13–3](#)). Monofluoroacetic acid enters the mitochondria, where it is converted to monofluoroacetyl-coenzyme A (CoA) by acetate thiokinase. Mitochondrial citrate synthase is then joined with the monofluoroacetyl-CoA complex with oxaloacetate to form fluorocitrate. Fluorocitrate then covalently binds aconitase, preventing the enzyme from any further metabolic activity in the tricarboxylic acid cycle.¹⁷ Thus, fluorocitrate acts as a “suicide inhibitor” of aconitase, producing a biochemical dead end. The net toxicity caused by fluorocitrate results from the increase in tricarboxylic acid cycle substrates proximal to inhibition of aconitase and the depletion of substrates distal to the step catalyzed by aconitase. This inhibition of aconitase impairs energy production, leading to anaerobic metabolism and metabolic acidosis with an elevated lactate concentration. Additionally, other tricarboxylic acid cycle intermediates increase in concentration, contributing to the toxicity. α -Ketoglutarate depletion, caused by the lack of isocitrate, leads to glutamate depletion since α -ketoglutarate is a precursor of glutamate synthesis. Glutamate depletion leads to urea cycle disruption and ammonia accumulation. Impaired fatty acid oxidation leads to ketosis. Excess citrate binds to divalent cations such as calcium causing hypocalcemia.

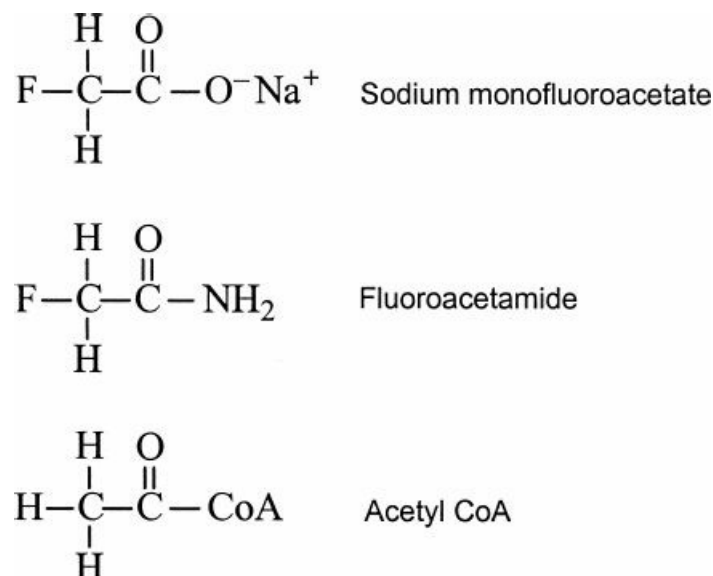


FIGURE 115–1. Structural similarities among acetyl-CoA, sodium monofluoroacetate, and fluoroacetamide.

Disruption of the tricarboxylic acid and urea cycles affects every system in the human body, but the most consequential effects occur in the central nervous system and the cardiovascular system. Fluoride toxicity from enzymatic defluorination of sodium monofluoroacetate and fluoroacetamide does not occur substantially *in vivo* and is of minor significance.

CLINICAL MANIFESTATIONS

The majority of the clinical experience with SMFA is associated with intentional self-poisoning; fluoroacetamide poisoning is presumed to have a similar presentation.^{9,16,18,29} Most patients develop symptoms within 6 hours after exposure. In the largest case series of 38 Taiwanese patients who ingested SMFA, 7 died.⁶ The most common clinical findings recorded at the time of emergency department (ED) presentation were nausea and vomiting (74%), diarrhea (29%), agitation (29%), and abdominal pain (26%).⁶ The mean time to presentation to the hospital was 10.9 ± 5.7 hours for those who died and 3.4 ± 0.6 hours for the survivors. All deaths occurred within 72 hours of admission to the hospital. The presence of respiratory distress or seizures was a poor prognostic indicator of death. All seven patients who died had systolic blood pressures less than 90 mm Hg on presentation to the ED, a finding noted in only 16% of the survivors.⁶

In a case series involving two patients, invasive hemodynamic monitoring revealed persistent low systemic vascular resistance and increased cardiac output despite adequate fluid resuscitation.⁷ The authors theorized that the cardiovascular response may have been triggered by ATP depletion and inhibition of gluconeogenesis.⁷ Anaerobic metabolism, mitochondrial inhibition, and sensitivity of the vasculature to SMFA are also confounding factors.

The initial neurologic manifestations consist of agitation and confusion with progression to seizures. Neurologic sequelae such as cerebellar dysfunction may be permanent.^{30,15} One report describes a 15 year-old girl who survived an initial exposure to SMFA but later developed cerebellar dysfunction and cerebral atrophy, demonstrated by brain computed tomography.³⁰ QT interval prolongation, premature ventricular contractions, ventricular fibrillation, ventricular tachycardia, and other dysrhythmias are documented.⁶ SMFA has negative inotropic effects, except in one case report that described episodic hypertension.²⁵ Signs and symptoms associated with severe poisoning are seizures, respiratory distress, and hypotension.

DIAGNOSTIC TESTING

The presence of SMFA and fluoroacetamide can be confirmed in the blood and urine with gas chromatography–mass spectrometry and thin-layer chromatography.^{1,5,20} Simultaneous analysis for other rodenticides that can induce seizures, for example, fluoroacetamide and “tetramine,” has been performed by gas chromatography in China, where exposure to these xenobiotics is more probable.^{2,4,31} Like tetramine, SMFA is considered a potential weapon of mass destruction.¹³ An elevated serum citrate concentration has been proposed as a useful marker for exposure to SMFA.⁴ However, none of these studies can be performed in a clinically relevant period. A combination of history, signs, symptoms, and common laboratory tests can assist with the diagnosis.

Hypokalemia, anion gap metabolic acidosis, and an elevated creatinine concentration⁸ are associated with severe poisoning but are very nonspecific.⁶ The predominant electrolyte abnormality will be hypocalcemia, although hypokalemia can result from acute kidney injury and gastrointestinal losses. Creatinine, liver enzyme, and bilirubin concentrations may also be elevated as a result of multisystem organ toxicity. Ketones may be present in urine and serum. A complete blood

cell count may reveal leukocytosis. An electrocardiogram is valuable in the diagnosis of SMFA exposure; a prolonged QT interval, atrial fibrillation with a rapid ventricular response, ventricular tachycardia, and other dysrhythmias may be present.^{6,28} An initial computed tomography scan of the brain may be normal, but subsequent scans may reveal cerebral atrophy.³⁰ Diffusion weighted magnetic resonance imaging (MRI) has shown reversible symmetric high signal intensity in the cerebellar peduncles, corpus callosum, internal capsules, and corona radiata in an SMFA poisoned patient with a sublethal ingestion. MRIs were performed on the day of ingestion and 7 days later.¹⁵ Brain single photon emission computed tomogram (SPECT) was also normal 14 days later.

TREATMENT

Initial decontamination should include removal of clothes and cleansing of skin with soap and water. Because there is no proven antidote for SMFA or fluoroacetamide poisoning, orogastric lavage should be considered for exposed patients who present to the ED prior to significant emesis. Appropriate patients should receive 1 g/kg of activated charcoal (AC) orally. A rat study showed that colestipol is more effective than AC in binding SMFA.²¹ By extension, it seems reasonable to consider the use of colestipol, if available, for the treatment of life-threatening exposures in humans, although there are no human data to support this therapy. A suggested initial dose would be 5 g.

In a cat model, glycerol monoacetate (monacetin) at a dose of 0.5 mL/kg every 30 minutes prolonged survival. In this context, monacetin functions as an acetate donor for ultimate incorporation into citrate in place of fluoroacetate.²⁹ Both ethanol and glycerol monoacetate are converted to acetyl-CoA and compete with monofluoroacetyl-CoA for binding of citrate synthase. This may prevent the “suicide-inhibition” of aconitase, subsequent increase in citrate, and the formation of the toxic metabolite fluorocitrate.²⁹ Availability of monacetin for human use is limited, and appropriate human dosing is unknown.

Ethanol has been used in human cases, although the appropriate dose is unknown and there is not enough evidence to support its use as a single antidote.^{6,7,24} A reasonable therapeutic dose is the amount of ethanol required to obtain and sustain an ethanol serum concentration of 100 mg/dL (Antidotes in Depth: A31). One intriguing case report involves a patient who ingested 240 mg of SMFA (typically a lethal dose) mixed with a Taiwanese wine (30% ethanol) and survived.⁶ It is possible that the ethanol decreased or delayed the toxicity of SMFA.

In a mouse model, use of a combination of calcium salts, sodium succinate, and α -ketoglutarate improved survival.²² The rationale of using these antidotes is to provide tricarboxylic acid cycle intermediates distal to the inhibited aconitase in an attempt to improve energy production. These antidotes were not effective unless calcium was coadministered, emphasizing the importance of replenishing electrolytes, particularly the divalent cations that are chelated by citrate.^{14,28,23}

If a patient develops hypotension and shock, rapid administration of intravenous 0.9% NaCl should be followed by a vasopressor, such as norepinephrine or vasopressin. Supportive care, correction of electrolyte abnormalities (especially calcium and potassium), ethanol infusion, and monitoring for dysrhythmias (prolonged QT interval) and seizures are the practical mainstays of treatment.

SUMMARY

- Sodium monofluoroacetate and fluoroacetamide are potent pesticides that inhibit the tricarboxylic acid cycle, disrupting cellular energy production.
- Patients who are exposed to SMFA typically present with nausea, vomiting, agitation, and abdominal pain, which may be followed by hypotension, respiratory distress, shock, seizures, and death.
- Lactate accumulation, hypokalemia, hypocalcemia, metabolic acidosis, and elevation of serum creatinine also occur.
- Treatment of SMFA and fluoroacetamide poisoning largely involves replenishing electrolytes, correcting hypotension with intravenous fluids and vasopressors if necessary, monitoring for dysrhythmias, and treating seizures.
- Ethanol, although not well studied as an antidote, is relatively familiar, readily available, and can be administered safely. The efficacies of other experimental antidotes are unknown.

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116 PHOSPHORUS

Michael C. Beuhler

Phosphorus (P)

Atomic number = 15

Atomic weight = 30.97 Da

Normal concentration

Serum = 3–4.5 mg/dL (1–1.4 mmol/L)

HISTORY AND EPIDEMIOLOGY

Phosphorus is a nonmetallic element not naturally found in its elemental form; it was isolated from distilled urine by Hennig Brandt in 1669. White phosphorus has been used in munitions (mortar rounds, grenades, artillery shells, bombs) since World War I for its antipersonnel effect as well as its warning, incendiary, and smoke producing properties. It is also used in fireworks made in countries other than the United States and China and for selected chemical synthetic processes (including some pesticides). White phosphorus was used extensively in the past as a rodenticide but is no longer employed for this purpose in the United States. Because of the potential use of red phosphorus for illicit drug manufacture (methamphetamine), its sale is monitored by the US Drug Enforcement Administration, which limits its availability in the United States. Before modern regulation, it was used in scientifically unsubstantiated remedies primarily because its phosphorescent and reactive qualities suggested potency. Its occasional use for homicides was limited by its glowing, smoking qualities. It remains a common method of suicide in some countries.

At the beginning of the 20th century, phosphorus was used in millions of “strike anywhere” matches (lucifers). However, safety concerns with the matches and illnesses in the workers producing the matches prompted a shift from using the more dangerous white phosphorus in the match heads to substituting the safer red phosphorus in the strikers. Workers chronically exposed to white phosphorus developed “phossy jaw,” an illness characterized by disfiguring osteonecrosis of the mandible along with multiple draining abscesses.

CHEMISTRY

Phosphorus, atomic number 15, is in a group of 15 nonmetallic elements sharing chemical properties with nitrogen (above) and arsenic (below) in the periodic table. Elemental phosphorus can exist in several different allotropes (polymorphs); the two common forms considered here are red phosphorus and the highly reactive white phosphorus. The relatively nontoxic and nonreactive black form will not be considered further.

White phosphorus is a waxy whitish to yellow solid with a melting point of 111.4°F (44.1°C). Often there is a small amount of red phosphorus in samples of white phosphorus, resulting in discoloration and explaining the term, “yellow” phosphorus. The word “phosphorus” means light-bearer, which originates from its property of glowing when exposed to air, due to the formation of reactive luminescent phosphorus oxides on its surface. Phosphorus is insoluble in water and often stored under it, but soluble in carbon disulfide and other organic solvents. White phosphorus is very reactive, igniting spontaneously in air at approximately 93°F (34°C), oxidizing to form phosphorus pentoxide (P_4O_{10}), which usually appears as a white fume having a garliclike smell. Phosphorus pentoxide is hygroscopic and reacts with water to form phosphoric acid (H_3PO_4) and reacts with organic molecules in dehydrating reactions.

Red phosphorus is a red powdery compound of limited toxicologic significance. It is not luminescent, it does not combust in air, and its toxicity is orders of magnitude less than that of white phosphorus.

TOXICOKINETICS

White phosphorus is well absorbed from the intestinal tract, and coingestion with fats, alcohol, and liquids increases toxicity, probably from increased absorption.^{6,7} White phosphorus is also well absorbed through the skin, with burns contributing to the absorption; significant morbidity and mortality occurring from large surface area burns. White

phosphorus can also be absorbed by inhalation, although this exposure route is rare with current industrial hygiene practices. After ingestion, phosphorus is found in high concentrations within 3 hours in the blood, liver, and kidneys.^{4,12}

Internally absorbed white phosphorus has significant toxicity. A dose of only about 1 mg/kg in adults is likely to cause significant morbidity, but a lethal dose of 3 mg is reported in a child.³ The mortality from white phosphorus ingestion is difficult to estimate, because the majority of reported cases occurred prior to the development of critical care. Historically, significant ingestions carried a 25% mortality rate.¹⁰

PATHOPHYSIOLOGY

The mechanism of dermal injury from white phosphorus differs significantly from that of ingested white phosphorus. Externally, white phosphorus reacts with oxygen to form phosphorus pentoxide and other phosphorus oxides. Phosphorus pentoxide readily reacts with water in an exothermic reaction, producing corrosive phosphoric acid.¹³ Additionally, phosphorus pentoxide reacts with (dehydrates) some organic molecules. These three mechanisms (exothermic, acid-producing, and dehydrating reactions) all contribute to the tissue injury observed, although the most damaging mechanism is the thermal injury from the heat of the reaction, as evidenced by the relatively short distance of tissue penetration by the acid and the relatively large amount of available water.^{5,20} The evidence for describing white phosphorus as a cytoplasmic toxin is mostly derived from electron microscopy, which demonstrates an initial cytoplasmic injury of the rough endoplasmic reticulum rather than initial nuclear or mitochondrial changes; but white phosphorus may also have an effect on mitochondrial energetics.¹¹

Red phosphorus has limited direct toxicological significance. It can cause gastrointestinal (GI) irritation when ingested in significant amounts, but it is orders of magnitude less toxic than white phosphorus.

A resurgence of toxicity and human injury indirectly related to red phosphorus has resulted from the increase in North American domestic methamphetamine production. Red phosphorus is used in conjunction with elemental iodine to produce hydroiodic acid, the ultimate reducing agent required to convert ephedrine to methamphetamine. In this situation, red phosphorus contributes to human injury by causing fire due to its unintentional conversion to highly flammable white phosphorus. Additional pathology occurs because during heating, the reaction products of iodine and red phosphorus often generate phosphine (PH_3), a pulmonary irritant and metabolic inhibitor gas (Chap. 124). Phosphine is only produced in significant amounts during an active methamphetamine “cook” using the red phosphorus method. This gas most likely contributes to some of the pulmonary effects occurring with chronic exposures in methamphetamine laboratories, as well as several of the deaths resulting from performing the synthesis in an area with limited ventilation in order to hide the characteristic odors.²¹ Unless specifically stated, all further references to phosphorus in this chapter refer to white phosphorus.

CLINICAL MANIFESTATIONS

General

The clinical manifestations of oral phosphorus poisoning are classically described in three stages. The initial effects may be delayed for a few hours, and the degree of delay depends on the dose. During the first phase, patients experience vomiting, hematemesis, and abdominal pain, with hypotension and death occurring within 24 hours after large ingestions.⁷ During the second stage, there is transient resolution of the toxic effects. During the third stage, the patient develops hepatic injury with coagulopathy and jaundice and acute kidney injury with oliguria and uremia. Mental status changes and seizures (independent of electrolyte changes) are also reported. However, clinical experience demonstrates that three distinct phases are the exception rather than the rule, with significant overlap or absence of the “quiescent” second stage and death potentially occurring within hours of ingestion.^{6,15} In the first 6 hours postexposure, poor prognostic signs include altered sensorium, cyanosis, hypotension, metabolic acidosis, elevated prothrombin time, and hypoglycemia.⁶ Survival to 3 days serves as a good prognostic sign. However, deaths occur later in the clinical course.⁷ Recovery usually occurs over 1 to 2 weeks.

Gastrointestinal

Initial symptoms after ingestion of phosphorus include nausea, vomiting, and abdominal pain. Both diarrhea and constipation are reported but are much less common. The breath and vomitus are sometimes described as having a garlic or musty sweet odor. The vomitus and diarrhea are sometimes luminescent and smoking, but this specific finding occurs infrequently. The smoking material is caused by the combustion of phosphorus upon its reexposure to air after being eliminated from the GI tract. Phosphorus causes an inflammatory injury to the GI tract characterized by local hemorrhage and hematemesis, but generally perforation does not occur. Massive GI bleeding may occur later in the clinical course, particularly when hepatic failure and coagulopathy are present.¹⁰

Renal/Electrolytes

In a rat model of dermal burns from phosphorus, an initial diuresis occurs followed by acute kidney injury manifested by hyperkalemia, hyponatremia, and hyperphosphatemia.¹ Renal cell swelling and necrosis with vacuolar degeneration of proximal convoluted tubules was also observed.¹ Poisoned patients demonstrated an increase in urinary white and red blood cells with casts and proteinuria.³ In humans, acute kidney injury from phosphorus is most likely acute tubular necrosis resulting from hypotension, salt and water depletion, and a direct toxic effect.⁷

Significant electrolyte disturbances may result from both ingestion and dermal absorption of phosphorus. Hypocalcemia is common, but hypercalcemia is also occasionally reported.¹³ Hyperphosphatemia may accompany the hypocalcemia but is not universal and can occur at any time in the clinical course.³ The hyperphosphatemia is partially due to the conversion of absorbed phosphorus to phosphate. In an animal model, those that died had increased concentrations of phosphorus, decreased concentrations of calcium, and hyperkalemia as early as one hour postexposure.² Hyperkalemia is occasionally reported in humans and may be secondary to tissue injury and acute kidney injury.¹ The electrolyte disturbances are likely a leading cause of early mortality from phosphorus.

Cardiovascular

Death within 24 hours of the ingestion is likely the result of cardiovascular collapse. One series of 41 patients who attempted suicide demonstrated a variety of initial electrocardiographic (ECG) abnormalities. T wave changes predominated in 24 patients, and there were also two cases of ventricular fibrillation. An increasing number of ECG abnormalities occurred in patients with larger ingestions, although the electrolyte abnormalities were not described in many patients.⁷ An animal model of phosphorus exposure demonstrated prolonged QT interval and ST segment changes along with electrolyte abnormalities, suggesting that many of the ECG changes might be due to electrolyte abnormalities.² A small study of phosphorus exposure in rats observed a decrease in amino acid uptake in myocytes suggesting a direct toxic effect. Human autopsies of several poisoned patients demonstrated fatty degeneration of the myocardium and vacuolated cytoplasm many hours postingestion.¹⁹

Hepatic

Phosphorus is a potent hepatotoxin. Increase in prothrombin time, hyperbilirubinemia, and hypoglycemia usually occur within 3 days, with earlier signs of hepatic failure such as jaundice and coagulopathy indicative of a poor prognosis.^{7,14} The increase in hepatic aminotransferases occurs over several days, usually peaking at or below 1000 IU/L and almost invariably less than 3000 IU/L.¹⁰ Other biochemical effects demonstrated by experimental phosphorus toxicity include an increase in glucose-6-phosphate activity and impairment of triglyceride metabolism and protein synthesis. When death occurs after several days (as opposed to within 24 hours), hepatic injury is usually implicated. If survival occurs, the hepatic damage usually resolves over several months, although persistent periportal fibrosis is reported.¹⁴

With absorption of sufficient quantities, phosphorus causes a dose-related zone 1 or periportal hepatic injury, in contrast to the centrilobular pattern (zone 3) that occurs with other hepatotoxins, such as acetaminophen and carbon tetrachloride ([Chap. 23](#)). Fatty degenerative changes and fatty infiltrates are also observed within 6 hours of ingestion.⁶ Other histological changes include acute necrosis with large vacuoles and inflammatory changes. Electron microscopy in a rat model demonstrated an increase in the rough endoplasmic reticulum and an increase in the cytoplasmic fat without initial mitochondrial or nuclear injury.¹¹ Although the early pathological effects appear to be predominantly cytoplasmic, the formation of nuclear vacuoles can occur.¹⁴

Nervous System

Central nervous system effects include headache, altered mental status, coma, and rarely seizures. The altered mental status is probably due partially to the presence of other organ dysfunction and shock; one example of the former is the encephalopathy secondary to hepatic injury. Patients with initial alterations in mental status or coma have an increased mortality rate independent of the presence of any electrolyte abnormalities.¹⁵

Dermal/Mucous Membranes

Dermal phosphorus exposure causes extensive burns, and this occurs most frequently in the military setting. The burns are described as emitting a garlic odor and displaying a yellow color that fluoresces under ultraviolet light. Necrosis of the wounds is common when wound decontamination is incomplete. Depending on the release conditions, white phosphorus can be a solid or liquid. Liquid white phosphorus splatters and can penetrate clothing; burning clothing commonly exacerbates the burn area.^{13,16} Dermal penetration may be partially due to its lipophilicity and a compromised dermal barrier caused by the burn injury. The smoke produced by burning white phosphorus contains phosphorus pentoxide and is

irritating to the conjunctiva and mucosa of the oropharynx and lungs.

Following a large burn, systemic illness manifested by electrolyte, cardiovascular, and hepatic abnormalities may result from absorbed phosphorus.^{1,2} A 12% to 15% body surface area burn in a rat was lethal 50% of the time; human morbidity from large skin burns is similarly high. Rats with dermal burns from phosphorus subsequently developed kidney and liver injury. Healing time from phosphorus burns is prolonged when compared with thermal burns.⁷

DIAGNOSTIC TESTING

Serum elemental phosphorus concentrations are not clinically available, and a serum phosphate concentration does not reflect the serum elemental phosphorus concentration. The diagnosis of phosphorus poisoning must rely on the history and physical examination. However, for optimal supportive care of the patient, many laboratory factors must be monitored such as ECG, electrolytes, serum pH, hepatic function, glucose, renal function, and coagulation parameters.

MANAGEMENT

Protection of Health Care Workers

Caution should be exercised in decontamination and subsequent storage of contaminated clothing. Vomitus and diarrhea must be considered potentially hazardous due to fire risk and should be carefully handled. Any phosphorus fragments removed from the patient as well as all potentially contaminated clothing items should be kept under water. Fires and explosions are reported during GI decontamination efforts, and the smoke from burning white phosphorus is irritating to the eyes and pulmonary system.¹⁷

General

General supportive care is the mainstay of treatment. Cardiac monitoring; frequent analysis of calcium, phosphate, and potassium concentrations, and serial ECGs are essential for patients with a history of significant ingestion or overt toxicity as dysrhythmias may occur rapidly.⁷ Electrolyte disturbances such as hyperkalemia, hypocalcemia, and hypercalcemia should be corrected. With significant exposure to phosphorus, hepatic injury will occur, and thus directed supportive care should be provided such as fresh-frozen plasma and vitamin K, when indicated. Adequate serum glucose concentrations are required to provide reducing equivalents through glycolysis and the glucose-6-phosphate dehydrogenase (G6PD) pathways, especially when there is evolving hepatic injury. Increased glucose concentrations may also theoretically offer protection by competing with phosphorus reuptake in the kidney, but the contribution to human morbidity is unclear. Corticosteroids have not been shown to improve outcome following ingestions of white phosphorus.¹⁴ Direct contact of phosphorus with the eye can result in serious ophthalmic injury. Immediate copious ophthalmic decontamination with water rather than with copper sulfate is recommended (see Dermal Exposure).¹⁸ A careful examination should be conducted by an ophthalmologist whenever possible.

Dermal Exposure

Initial treatment is to halt continuing injury by extinguishing combustion of the phosphorus. This is performed by submerging the affected area in cool water or, more practically, covering any areas with clean materials soaked in water or a 0.9% sodium chloride solution to limit the white phosphorus contact with atmospheric oxygen. Decontamination is undertaken by removing clothing and using large amounts of cool water to remove any phosphorus fragments. In the past, sodium bicarbonate decontamination solution was recommended, but because the tissue injury is not due to the production of acid and because no clinical benefit was demonstrated, there is no current role for specific neutralization fluids.^{5,20} Water dilutes any phosphoric acid present and reacts with the phosphorus pentoxide to limit the damaging dehydrating reactions.

Careful débridement is the next critical step as wounds that have not undergone adequate decontamination heal poorly, requiring additional débridement. Smoking pieces of phosphorus are not necessarily hot enough to cause thermal burns, but the oxidation process must be arrested. Fragments of phosphorus from the wound should be placed under water to prevent a fire hazard. Particles of phosphorus can be visualized by using a Woods lamp as the chemical burns have a yellowish fluorescence. One author recommends turning off the lights to look for the glow of the phosphorescent particles; presumably this will work only if there has not been any copper or silver metal wash solution used, but others have questioned if the amount of glow will be enough to locate fragments under real world conditions (see following paragraphs).⁸ Because of the increased solubility of phosphorus in hydrophobic solvents, it is important not to use ointments until the wound is completely decontaminated.

A copper (II) sulfate solution was previously recommended for “decontamination.” Copper sulfate reacts with phosphorus to produce copper phosphide, a dark compound that is much more easily visualized in the tissues. This dark material coats the particle, but the entire particle is not converted to copper phosphide. Additionally, this coating decreases

the reaction of phosphorus with oxygen for a limited time. The use of high concentrations of copper sulfate solutions on exposed human flesh is no longer recommended because of potential systemic toxicity such as hemolysis caused by the copper (Chap. 95).¹⁸ This is especially concerning in patients at increased risk for oxidant injury, such as those with G6PD deficiency. The solutions of copper sulfate historically used ranged from 2% to 5% and were applied for several hours to the wounds, resulting in substantial amounts of copper absorption and morbidity.

However, copper sulfate solutions still may have a role in the complete approach to the treatment of phosphorus wounds. A dilute copper sulfate solution (0.5%–1.0%) applied once to the wound and then rinsed off with water may not result in the morbidity that occurs with the more concentrated rinses and may provide temporary neutralization of the outer surface of the phosphorus. This approach may assist in identification of the small pieces of phosphorus that are difficult or impossible to visualize by darkening the fragments, especially in those with less experience débriding these wounds. Wounds that are not treated with a copper solution may be at greater risk of requiring repeat débridement because of the persistence of small phosphorus particles missed during the initial decontamination efforts. Animal models have suggested improved healing from the initial treatment with a dilute copper solution, but a relatively large human case series did not find a difference in those who were treated with copper sulfate compared with those who were not.⁵ The copper phosphide-coated particles must be removed as they still react slowly and can cause toxicity. It is important to remember that the dilute copper sulfate solution is not a decontamination therapy but a temporizing treatment that allows for better visualization for physical débridement, and this solution must be rinsed away immediately after application.⁸ The use of pads soaked in copper sulfate is not recommended.

Silver nitrate has been suggested as a potential solution to replace the use of copper sulfate. It forms an insoluble, minimally reactive silver phosphide. Its use and preparation is similar to that described above and as such silver nitrate (1%–2% solution) should be considered as a temporary neutralization tool and not a decontamination therapy. It does not have the detrimental physiologic effects that internalized copper ions cause. However, there is very limited experience with this approach and no detailed human data. Silver forms an insoluble precipitate with chloride and cannot be combined with 0.9% sodium chloride solutions; therefore, the amount of soluble silver ion that reaches the imbedded phosphorus may be more limited than with copper because of the presence of relatively large amounts of chloride ion in living tissues.²²

A reasonable approach is to begin by decontaminating the wound using a Woods lamp and or a darkened room looking for phosphorescence. Only then applying a transient dilute copper sulfate or silver nitrate wash as described above is indicated to improve visualization and possibly neutralize very small phosphorus particles. After decontamination, good wound care and burn management is required, because these burns (like other chemical burns) can require an extended period of time to heal. As discussed, incomplete decontamination is a common reason for delayed wound healing. For significant burns, the patient should be admitted to a burn intensive care unit for close monitoring of cardiovascular, renal, and electrolyte status for several days at the minimum. Because of the potential instability of these patients, it is important to weigh the risk-to-benefit ratio of transfer to a specialized center. The experience of the receiving center with phosphorus burns in addition to the acuity and severity of the injury are important factors in making this decision.

Gastrointestinal Exposure

There is no evidence that GI decontamination or antidotal therapy following phosphorus ingestion is efficacious. In the past, several different lavage fluids were recommended, ranging from the mostly benign (sodium bicarbonate) to the potentially dangerous (potassium permanganate). Milk might also be potentially harmful because of its lipophilic components. Some authors postulate better outcome with earlier GI decontamination, but no reliable studies are available.¹⁴ Activated charcoal may bind to white phosphorus and could be considered, although there are no human data to support its use. However, despite the lack of data of efficacy, given the poor outcome of patients with large ingestions of phosphorus, decontamination efforts should be strongly considered. If lavage is considered, a nasogastric tube would not be expected to remove substantial quantities due to the insoluble, solid nature of phosphorus. The tissue injury caused by phosphorus is not expected to cause early esophageal perforation, and the use of an orogastric (OG) tube would therefore be best. Caution to protect caregivers should be exercised with any lavaged material. Due to the risk of fire and explosion, one author recommends keeping the free end of the OG tube under water while inserting and instilling small amounts of water (not air) to check for proper placement.¹⁷

It appears that the hepatic injury is much more likely with ingested phosphorus exposure than following dermal exposure. N-acetylcysteine (NAC) is suggested as a potential adjunct in the treatment of phosphorus toxicity. Although NAC was used in a limited human series, the numbers were small.¹⁰ The use of superoxide dismutase in an animal model suggested benefit but did not limit morbidity, and a separate animal model suggested benefit from glutathione; therefore, limiting oxidant injury may play a role in treatment.⁹ There is no theoretical harm in using NAC for phosphorus toxicity, and so it should be added to the treatment regimen. Methionine was used many years ago in the treatment of a few patients, but the number of treated patients was too few to draw any conclusions.⁶ When liver transplantation was performed for phosphorus induced hepatic failure outcomes have been suboptimal, likely due to toxicity occurring in the central nervous and cardiovascular systems.

SUMMARY

- White phosphorus was most commonly used in warfare, causing morbidity through dermal burns.
- These burns require large amounts of water irrigation and adequate débridement while protecting health care workers.
- Following ingestion, typically in suicide attempts, morbidity remains quite high, and treatment options are limited to unproven decontamination therapies.
- Signs and symptoms of white phosphorus toxicity include vomiting, abdominal pain, confusion, dysrhythmias, hepatic injury, and acute kidney injury.
- As early mortality is believed to be due to electrolyte abnormalities and cardiac dysrhythmias, vigilant critical care is the mainstay of therapy.
- NAC may be used, but it has not been shown to alter human outcomes.

Acknowledgments

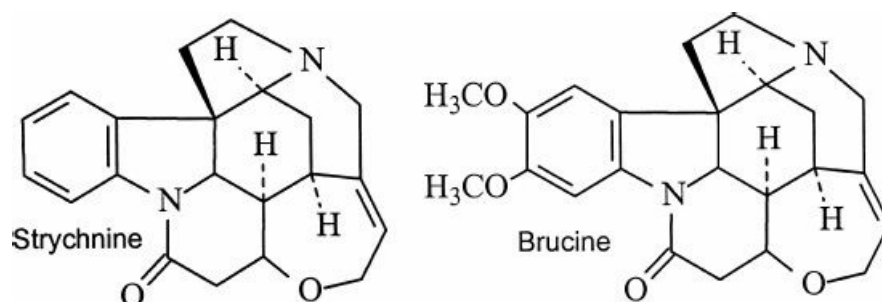
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117 STRYCHNINE

Yiu-Cheung Chan



HISTORY AND EPIDEMIOLOGY

Strychnine alkaloid occurs naturally in *Strychnos nux-vomica*, a tree native to tropical Asia and North Australia, and in *Strychnos ignatii* and *Strychnos tiente*, trees native to South Asia. The alkaloid was first isolated in 1818 by Pelletier and Caventou.^{5,15} It is an odorless and colorless crystalline powder that has a bitter taste when dissolved in water. Besides strychnine, the dried seeds of *S. nux-vomica* contain brucine, a structurally similar, although less potent, alkaloid.⁸⁸ Strychnine is available from commercial sources in its salt form, usually as nitrate, sulfate, or phosphate.

Strychnine was first introduced as a rodenticide in 1540, and in subsequent centuries was used medically as a cardiac, respiratory, and digestive stimulant,⁴⁵ as an analeptic,⁹² and as an antidote to barbiturate⁹¹ and opioid overdoses.⁵⁹ Nonketotic hyperglycemia,^{9,36,80} sleep apnea,⁷⁶ and snake bites¹⁵ were also once considered indications for strychnine use. In 1982, at least 172 commercial products were found to contain strychnine, including 77 rodenticides, 25 veterinary products, and 41 products made for human use.⁸³ However, the use of strychnine was substantially decreased; some countries such as the European Union banned its use as a rodenticide in 2006, and most of its prior medicinal indications are no longer utilized. Currently, strychnine is used as a rodenticide (for moles, gophers, and pigeons) and a research tool for the study of glycine receptors. Most commercially available strychnine-containing products contain about 0.25% to 0.5% strychnine by weight.⁸³

Between 1926 and 1928, strychnine killed more than three Americans every week.^{5,27} In 1932, it was the most common cause of lethal poisoning in children,^{5,83,98} and one-third of the unintentional poison-related deaths in children younger than 5 years were attributed to strychnine.⁶⁰ Currently, strychnine poisoning is rare and continues to decrease in the United States, although deaths are still reported. The Toxic Exposure Surveillance System (TESS) and National Poison Data System (NPDS) data of the American Association of Poison Control Centers (AAPCC) reported 1414 strychnine exposures during the past 10 years (2002–2011), with only eight deaths (Chap. 136).

Strychnine poisoning has resulted from deliberate exposure with suicidal and homicidal intent,^{27,50} as well as from unintentional poisoning by a Chinese herbal medicine (Maqianzi)¹⁶ and a Cambodian traditional remedy (slang nut).^{47,49,51,86} Maqianzi is used to treat limb paralysis, severe rheumatism, and inflammatory disease, whereas slang nut is used to treat gastrointestinal illness. The bitter taste of strychnine allows it to be used to adulterate heroin⁴³ and cocaine.^{13,22,64} There are also reports of strychnine poisoning from adulterated amphetamines,²² 3,4-methylenedioxymethamphetamine (MDMA),²⁵ Spanish fly,¹² and from the ingestion of gopher bait.⁵²

TOXICOKINETICS

Standard references list the lethal dose of strychnine as approximately 50 to 100 mg^{18,33,34,70,94} (1–2 mg/kg). However, mortality resulting from doses as low as 5 to 10 mg and, alternatively, survival following ingestions of 1 to 15 g of strychnine are reported.^{6,18,82,97} Some of this variation may be attributed to the route of administration, with parenteral administration being more toxic than oral, and the limitations of self-reported exposure quantities.

Strychnine is rapidly absorbed from the gastrointestinal tract and mucous membranes. There is a case of reported

poisoning as a result of dermal absorption of strychnine from an alkaline solution, in which strychnine exists in the nonionized, alkaloid form.³⁵ Protein binding is minimal, and strychnine is rapidly distributed to peripheral tissues⁹³ with a large volume of distribution (13 L/kg).⁴⁰ Based on postmortem findings, the highest concentrations of strychnine are found in the liver,^{57,70,78} bile,⁷⁰ blood,⁷⁰ and gastric contents.^{70,78} Relatively less strychnine is identified in kidney, urine, and brain.⁷⁸

Strychnine is metabolized by hepatic cytochrome P450 isozymes, mainly CYP3A4,^{1,53,61} producing strychnine-N-oxide as the major metabolite,¹ the toxicity of which is about one-tenth of that of the original alkaloid.⁵⁵ This metabolism is increased by P450 induction.^{44,48} Several urinary metabolites are identified,⁶⁵ and 1% to 30% of strychnine is excreted unchanged in urine,^{10,39,69} in decreasing proportions when larger amounts are ingested.^{81,93} Strychnine follows first-order kinetics with an elimination half-life of 10 to 16 hours.^{26,69,95}

PATHOPHYSIOLOGY

Glycine, one of the major inhibitory neurotransmitters in the spinal cord, opens a ligand-gated chloride (Cl^-) channel, thus allowing the inward flow of Cl^- (Fig. 14–12).²⁰ As Cl^- moves inward, the cell becomes hyperpolarized, reducing neuronal excitability. Strychnine competitively inhibits the binding of glycine to the α -subunit of the glycinergic chloride channel.^{13,19,96,98} Although strychnine affects all parts of the central nervous system in which glycine receptors are found, the most significant effect is in the spinal cord. With loss of the glycine inhibition at the motor neurons in the ventral horn, there is a loss of inhibitory influence on the normally suppressed reflex arc. The result is increased impulse transmission to the muscles, producing generalized muscular contraction. Rabbits pretreated with glycine had a 40% increase in the strychnine “seizure” threshold, illustrating the competitive nature of strychnine and glycine activity on the glycinergic chloride channel.^{17,77} Tetanus toxin (tetanospasmin) causes an identical clinical syndrome of muscular contractions but does so by preventing the release of presynaptic glycine and does not function as a competitive antagonist. In dogs, strychnine also has positive chronotropic and inotropic effects on the heart,⁸⁴ but this effect is unlikely to exert a major effect in human poisoning.

CLINICAL MANIFESTATIONS

Oral strychnine poisoning is characterized by a rapid onset of signs and symptoms beginning within 15 to 60 minutes of ingestion³² and, although less well documented, effects begin even sooner after parenteral or nasal administration. Delayed onset of clinical effects are rarely reported.^{23,34} The typical findings of poisoning are involuntary, generalized muscular contractions resulting in neck, back, and limb pain. The contractions are easily triggered by trivial stimuli (such as turning on a light), and each episode usually lasts for 30 seconds to 2 minutes.⁸³ These episodes may recur for as long as 12 to 24 hours. Differences in the strength of various opposing muscle groups result in the classic signs of opisthotonus, facial trismus, and risus sardonicus, with flexion of the upper limbs and extension of lower limbs predominating. Hyperreflexia, clonus, and nystagmus^{11,62} are also evident on examination. Because strychnine affects glycine inhibition mainly in the spinal cord, the patient typically remains fully alert until metabolic complications arise. The combination of convulsive motor activity involving both sides of the body in the conscious patient has often resulted in imprecise descriptions such as “conscious seizure” or “spinal seizure.” Hemodynamically, both hypotension,^{24,26,64} or hypertension^{13,29,63} in the presence of bradycardia^{14,24,26,64} or tachycardia^{13,14} are reported. Hyperthermia, presumably from increased muscular activity, is typical, and temperatures as high as 109.4°F (43°C) are reported.¹³ Other nonspecific signs and symptoms include dizziness, vomiting, and chest and abdominal pain.⁶²

Early in the course of strychnine poisoning, mortality is mainly due to hypoventilation and hypoxia secondary to muscular contractions.²⁹ Life-threatening complications include rhabdomyolysis with subsequent myoglobinuria and acute kidney injury,¹⁴ hypoxia or hyperthermia-induced multiorgan failure, aspiration pneumonitis,⁸⁵ anoxic brain injury, and pancreatitis.⁴² Rarely, local neuromuscular sequelae such as weakness, myalgia, and anterior tibial compartment syndrome are reported.¹³ As might be expected, the prognosis is related to the duration and extent of the episodes of muscle contractions.³¹

DIFFERENTIAL DIAGNOSIS

The diagnosis of strychnine poisoning is mainly established on clinical grounds, based on exposure history and compatible clinical manifestations, but can be confirmed by detection of strychnine in biological specimens. Several diagnoses need to be considered, the most important of which is tetanus because it produces similar muscular hyperactivity. In a patient with tetanus, however, the onset of symptoms is more gradual and the duration much longer than in the case of strychnine

poisoning. Frequently, the diagnosis of tetanus is suggested by a history of recent injury, or the finding of an obvious wound. In general, patients with tetanus have either undocumented or incomplete tetanus immunization.

Strychnine poisoning can be differentiated from generalized seizures by the presence of a normal sensorium during the period of diffuse convulsions. That is, most patients with bilateral convulsions are having generalized seizures, which by definition involve the reticular activating system, producing unconsciousness. It is conceivable, although extraordinarily rare, to have bilateral focal seizures producing apparent “generalized” convulsions. In this case, because the reticular activating system may not be involved, the mental status of the patient may be preserved. The presence of consciousness in a patient with a generalized convulsion may be sufficient to establish the diagnosis of strychnine poisoning or tetanus at least in the early phase of the clinical course. As time progresses and management is delayed this finding may be obscured by metabolically induced alterations in sensorium.¹⁷ When there is an alteration in the level of consciousness, an electroencephalogram may be helpful, to document the presence or absence of a seizure focus. A computed tomography scan of the head can help to exclude structural brain lesions, and a lumbar puncture is helpful to exclude meningitis or encephalitis. Hypocalcemia, hyperventilation, and myoclonus secondary to kidney or liver failure are evaluated by appropriate routine laboratory testing. Although a drug induced dystonic reaction should be considered when there is a relevant history, dystonic reactions are usually static, whereas strychnine poisoning results in dynamic muscular activity. Serotonin toxicity, malignant hyperthermia, neuroleptic malignant syndrome, and stimulant associated toxicity should be considered if the medical history is supportive.

DIAGNOSTIC TESTING

Respiratory and metabolic acidosis both occur commonly in strychnine-poisoned patients. Metabolic acidosis is associated with elevated serum lactate concentrations,¹³ whereas respiratory acidosis secondary to hypoventilation results from diaphragmatic and respiratory muscle failure. Survival of patients with serum pHs in the range of 6.5 to 6.6 is well documented.^{13,29,30,32,54,95} The lowest pH and highest lactate concentration reported in a patient who subsequently had full recovery was 6.5 and 32 $\mu\text{mol/L}$,^{13,95} respectively. Thus, profound acidemia in strychnine poisoning is not necessarily associated with a poor prognosis.^{7,8,13,73} In contrast to the metabolic acidosis with elevated lactate concentration that occurs in shock, the elevated lactate concentration of strychnine poisoning results from overactivity of the muscle instead of undersupply or underutilization of oxygen and nutrients.

Besides acidemia, other laboratory abnormalities expected from prolonged muscular activity include hyperkalemia and those associated with rhabdomyolysis and acute kidney injury.¹³ There is also stress-induced leukocytosis,^{13,42} elevated liver enzyme concentrations,^{42,62,90} hypocalcemia,^{13,40} hypernatremia,³² and hypokalemia.^{28,62,85} The electrocardiogram is expected to remain normal or reflect changes consistent with the above electrolyte disturbances.⁴⁰ Chest radiography may show evidence of aspiration pneumonitis or acute respiratory distress syndrome.

Strychnine can be detected by a variety of methods such as thin-layer chromatography,^{66,89} high-performance liquid chromatography,² ultraviolet spectrometry,⁶⁶ a simple colorimetric reaction,⁶⁶ gas chromatography–mass spectrometry,^{14,57,69,78} gas chromatography flame ionization detector,⁹⁴ and capillary electrophoresis.⁹⁹ With the exception of the bedside colorimetric reaction, none of these tests are routinely available in a time frame useful to assist in clinical decisions. Strychnine is also detectable in amounts as low as 0.01 mg/L in tissue,^{2,21,58,72} and strychnine resists postmortem putrefaction. Additionally, even when available, quantitative concentrations do not correlate with clinical toxicity. Reported blood strychnine concentrations in fatal poisoning ranged from 0.5 to 61 mg/L.⁹⁴ Conversely, the highest initial blood concentration associated with survival was 4.73 mg/L from blood drawn 1.5 hours postingestion⁹⁵; a concentration as low as 0.06 mg/L was found in a patient who solely had muscular irritability.²⁶

MANAGEMENT

In patients with strychnine poisoning, inducing vomiting is absolutely contraindicated because of the risk of aspiration and loss of airway control following rapid onset of muscle contractions. Gastric lavage should be considered on an individual basis after evaluating potential benefits and risks.³ When gastric lavage is thought to be indicated, it may be important to protect and secure the airway with an endotracheal tube before attempting lavage. Activated charcoal (AC) binds strychnine effectively at a ratio of approximately 1:1; 1 g of AC will bind 950 mg of strychnine.^{4,88} In animal models, pretreatment⁶⁷ and posttreatment⁷¹ with AC increase the median lethal dose in 50% of test subjects (LD_{50}) for strychnine. Clinical evidence of the effectiveness of AC for strychnine ingestion was first demonstrated in 1831, when Professor Touery survived the ingestion of a lethal dose of strychnine by using AC in a demonstration before the French Academy of Medicine.

Currently, there is no evidence to recommend the use of multiple-dose AC or whole-bowel irrigation for strychnine poisoning. Although forced diuresis was once suggested as an effective means of enhancing the elimination of strychnine,⁸⁸

subsequent data failed to demonstrate an increase in clearance⁸¹ and it is therefore no longer recommended. Peritoneal dialysis, hemodialysis, and hemoperfusion have not been extensively studied. However, because strychnine is rapidly distributed to the tissues⁹³ with a large volume of distribution (13 L/kg), extracorporeal drug elimination procedures are unlikely to be useful and therefore not justified given their risks.

Supportive treatment remains the most important aspect of management in the majority of cases. The focus of care is to stop the muscular hyperactivity as soon as possible to prevent the metabolic and respiratory complications. At all times, unnecessary stimuli and manipulation of the patient should be avoided, as these activities trigger muscle contractions. Benzodiazepines remain the first line treatment for strychnine induced muscular hyperactivity.^{83,95} Although much of the evidence concerning the efficacy of benzodiazepines is based on clinical experience with diazepam,^{38,46,64} any of the other commonly used benzodiazepines (midazolam or lorazepam) would likely have similar effects. The initial dose of the benzodiazepine chosen should be the standard dose used for other indications, although doses of more than 1 mg/kg diazepam or its equivalent may be needed.^{41,56} In case of failed intravenous access, lorazepam or midazolam can be given intramuscularly or intraosseously. Dosing should be repeated until the patient demonstrates muscle relaxation and the contractions cease. In addition to benzodiazepines, barbiturates and propofol are also effective, although considered secondary therapies, in stopping the strychnine-induced hyperactivity.^{37,51,74,87} Benzodiazepines and barbiturates both work through agonism of γ -aminobutyric acid (GABA) receptor chloride complexes to increase the inhibitory neurotransmission to the spinal cord from the brain, and thus raise the reflex arc threshold.⁷⁹ If these measures fail to control the muscular hyperactivity, a nondepolarizing neuromuscular blocker (NMB) should be administered. Only nondepolarizing NMBs should be used, as succinylcholine itself, a depolarizing NMB, induces muscle contractions.^{13,26,51,64,81} It is important to remember that strychnine has no direct effects on consciousness, so that sedation must always accompany neuromuscular blockade. Generally, therapy is continued for about 24 hours, at which time the benzodiazepines and or NMBs can be tapered as tolerated.

The most important therapy for the metabolic complications of strychnine poisoning is to expeditiously stop the production of metabolic byproducts by terminating the muscular hyperactivity. Hyperthermia should be treated rapidly by active cooling with ice water immersion, cooling blanket, or mist and fan, depending on the magnitude of temperature elevation. Means to prevent rhabdomyolysis induced acute kidney injury include adequate fluid administration to ensure good urine output (> 1 mL/kg/h), the potential use of urinary alkalization with sodium bicarbonate,⁷⁵ and temporary renal replacement therapy, if acute kidney failure occurs. Metabolic acidemia rapidly resolves when muscular activity is controlled.^{13,68}

Effective management in the first few hours of strychnine poisoning is crucial for survival. If the patient can be supported adequately for the first 6 hours, this may be considered a good prognostic sign.^{13,34} All significantly poisoned patients should be managed in an intensive care unit with the help of a regional poison center or a medical toxicologist. For patients unintentionally exposed to strychnine who remain asymptomatic, an observation period of 12 hours is sufficient to exclude significant risk.

SUMMARY

- Strychnine is a lethal poison that is no longer frequently encountered, except in areas where it is used as a rodenticide.
- A “conscious seizure” is the characteristic presentation of strychnine toxicity, and is rapidly followed by life threatening metabolic and respiratory consequences.
- The mainstay of treatment is supportive care with the goal of rapidly terminating muscular contractions, providing adequate airway management, and rapidly treating hyperthermia and or metabolic abnormalities.
- Although benzodiazepines are generally sufficient, neuromuscular paralysis with a nondepolarizing NMB may be required.
- Generally, the prognosis of strychnine poisoning is good, if the patient can be adequately supported and survives the first few hours of toxicity.

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L. NATURAL TOXINS AND ENVENOMATIONS

CASE STUDY 10

History A 32 year-old woman with no past medical history presented to the emergency department with a 2 day history of a painless, rapidly expanding lesion on her back. She first noticed the lesion 2 days prior but did not recall any trauma or other inciting factors. The woman denied headache, shortness of breath, chest pain, nausea, vomiting, diarrhea or dysuria, but she reported subjective fever and malaise for 2 days. She was not taking any medications, she drank alcohol socially, and she denied intravenous drug use. She worked as an accountant in New York City and traveled frequently to a vacation home in Montauk, Long Island.

Immediate Assessment and Management On presentation to the emergency department, the patient was well appearing and in no apparent distress. Vital signs were: blood pressure, 102/52 mm Hg; pulse, 92 beats/min; respiratory rate, 16 breaths/min; tympanic temperature, 98.7°F (37.1°C); and oxygen saturation, 100% on room air. A complete physical examination was entirely within normal limits, except for her skin examination. This was notable for a solitary 9 cm annular plaque on the upper back with central hemorrhagic crust overlying a 5 cm violaceous plaque surrounded by a ring of erythema (Fig. CS10–1). The lesion was only mildly tender to palpation, and there was no underlying fluctuance.



FIGURE CS10-1 The lesion on the woman's back, reproduced with her permission.

What Is the Differential Diagnosis? The only remarkable finding in this patient is the 2 day old skin lesion, associated with subjective fever and malaise. The differential diagnosis includes infectious diseases such as cellulitis or a bacterially superinfected cyst or arthropod bite, sporotrichosis, lyme disease, and anthrax (Chap. 133); drug reactions such as a fixed-drug eruption, or given the necrotic appearance of the lesion, necrosis due to warfarin or heparin therapy (Chaps. 18 and 60); and necrotic spider bites (Chap. 118).

Immediate Assessment and Management A more detailed history failed to reveal any clues. The woman specifically denied knowledge of tick or spider bites, and she neither worked, lived, nor vacationed in an area known to be inhabited by brown recluse spiders. However, she frequented an area of Long Island where ticks are endemic. An intravenous line was inserted and a complete blood count, basic metabolic panel, and liver function tests were sent; all were within normal limits. The patient was started on vancomycin to provide *Staphylococcus aureus* and methicillin-resistant *S. aureus* coverage for a presumed bacterial infection or necrotizing soft tissue infection.

Cases such as these require an immediate assessment for potential public health implications. Once a diagnosis of cutaneous anthrax is considered, the possibility of malicious exposure mandates a coordinated effort to establish a definitive diagnosis. It is important to recall that one of the cases of cutaneous anthrax that occurred following the malicious letters in New York in 2001 involved the case of a small child who was initially diagnosed with brown recluse spider envenomation. Additionally, while spider envenomation may occur outside of regions considered to be endemic as movement of spiders in suitcases, packages, or vehicles may occasionally occur, a new pattern of envenomation may represent a local infestation or the expansion of an endemic area resulting from climate changes. All of these scenarios may require public health interventions.

What Further Diagnostic and Therapeutic Interventions Are Indicated? A dermatology consult was called, and a biopsy was taken for histologic evaluation of a permanent section as well as Gram stain. An acid-fast bacillus stain was also done on the tissue for mycobacterial infection and was negative. Extensive laboratory testing was ordered to help exclude uncommon etiologies for the skin lesion. The biopsy demonstrated epidermal necrosis and dermal abscess, which are nonspecific findings. A wound Gram stain and culture failed to show white blood cells or microorganisms.

Case Resolution Serologies including a Lyme western blot, Rocky Mountain spotted fever antibodies, and *Francisella tularensis* were all negative. The vancomycin was stopped, and the woman was discharged on a 21 day course of oral doxycycline for presumed Lyme disease given the history and morphology of the lesion. The lesion began to regress on oral doxycycline. Although a final diagnosis was never established, the working diagnosis was that of either Lyme disease or a necrotic spider envenomation, and the patient's Lyme Western blot was to be repeated in 3 to 4 weeks in order to further clarify between the two leading diagnoses: Lyme or necrotic spider envenomation.

118 ARTHROPODS

In-Hei Hahn

TAXONOMY

Arthropoda means “joint-footed” in Latin and describes arthropods’ jointed bodies and legs connected to a chitinous exoskeleton.⁵ The majority of arthropods are benign to humans and environmentally beneficial. Some clinicians regard bites and stings as inconsequential and more of a nuisance than a threat to life. However, some spiders have toxic venoms that can produce dangerous, painful lesions or significant systemic effects. Important clinical syndromes are produced by bites or stings from animals in the phylum Arthropoda, specifically the classes Arachnida (spiders, scorpions, and ticks) and Insecta (bees, wasps, hornets, and ants) (Table 118–1). Infectious diseases transmitted by arthropods, such as the various encephalitides, Rocky Mountain spotted fever, human anaplasmosis, babesiosis, and Lyme disease, are not discussed in this chapter.

TABLE 118–1. Insects and Other Arthropods That Bite, Sting, or Nettle Humans	
Arthropod	Description
Honeybee (<i>Apis mellifera</i>)	Hairy, yellowish brown with black markings
Bumblebee and carpenter bee (<i>Bombus</i> spp and <i>Xylocopa</i> spp)	Hairy, larger than honeybees and colored black and yellow
Vespids (yellow jackets, hornets, paper wasps)	Short-waisted, robust, black and yellow or white combination
Schecoids (thread-waisted wasps)	Threadlike waist
Nettling caterpillars (browntail, lo, hag, and buck moths, saddleback and puss caterpillars)	Caterpillar shaped
Southern fire ant (<i>Solenopsis</i> spp)	Ant shaped
Spiders (<i>Arachnida</i>) black widow, brown recluse	Body with two regions: cephalothorax and abdomen; eight legs
Scorpions (<i>Centruroides</i>)	Eight legged, crablike, stinger at the tip of the abdomen; pedipalps (pincers) highly developed (not a true insect)
Centipedes (<i>Chilopoda</i>)	Elongated, wormlike, with many jointed segments and legs; one pair of poison fangs behind head

Arthropoda comprises the largest phylum in the animal kingdom. It includes more species than all other phyla combined (Fig. 118–1).⁵ At least 1.5 million species are identified, and half a million or more are yet to be classified. Araneism (pertaining to spiders) or arachnidism (spiders including other arachnids) results from the envenomation caused by a spider bite. “Bites” are different from “stings.” Bites are defined as creating a wound using the oral pole with the intention for either catching or envenomating prey or blood feeding,^{96,195} or for the purpose of feeding such as in arthropods that have mouthparts for chewing or sucking (plant sucking). “Stings” occur from a modified ovipositor at the aboral pole that is also able to function in egg laying as in bees and wasps. In scorpions the sting is not a modified ovipositor and the “tail” is not a tail but the metasoma section of the abdomen. Stinging behavior typically is used for defense. Most spiders are venomous, and the venom weakens the prey, enabling the spider to secure and digest their prey. However, there is one family of spiders, Uloboridae, which do not have a venom gland, a venom duct, or duct opening in the fangs. Spiders in general are

not aggressive toward humans unless they are provoked. The chelicerae (mouthparts comprised of basal section and hinged fang) of many species have fangs that are too short to penetrate human skin.

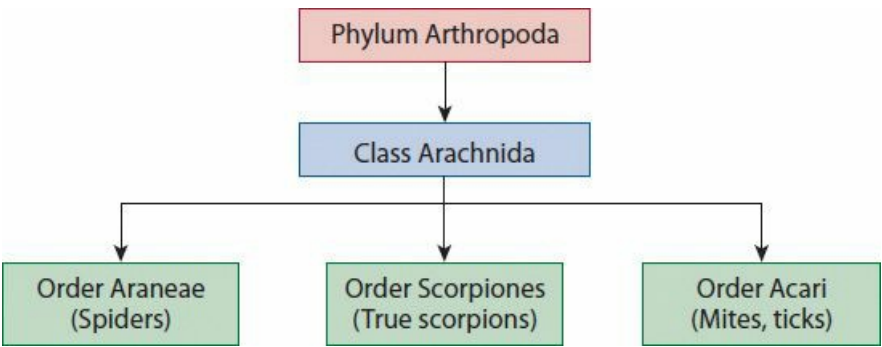


FIGURE 118-1 Taxonomy of the phylum Arthropoda.

Spiders can be divided into categories based on whether they pursue their prey as hunters or trappers. Trappers snare their prey by spinning webs, then feed on their prey and enshrine excess victims in a cocoon silk to be eaten later. The order of spiders (Araneae) differs from other members of the class (Arachnida) because of various anatomic differences best assessed by an entomologist/arachnologist. Simplistically, the arachnids have four pairs of joined legs whereas insects have three pairs. The arachnid’s body is divided into two parts (cephalothorax and unsegmented abdomen, except for some spiders in Mesothelae and also some Mygalomorph {tarantula-type} relatives that have abdominal plates) connected by a small pedicel and two, three, or four pairs (Mesothelae contain up to six pairs) of spinnerets from which silk is spun. Two pedipalps are attached anteriorly on the cephalothorax on either side of their chelicerae and are used for sensation, manipulation of food and objects, and in males are modified for sperm transfer. Spiders have eight eyes, although there are instances when they have two, four, six, or even no eyes and are quite myopic. Prey is localized by touch as they land in the spider’s web, though not all spiders produce webs and use silk to capture prey. Most spiders use venom to kill or immobilize their prey. The spiders of medical importance in the United States include the widow spiders (*Latrodectus* spp), the violin spiders (*Loxosceles* spp), and the hobo spider (*Tegenaria agrestis*). Although there is some disagreement as to the extent of the danger of hobos in the United States, hobos are not considered dangerous in Europe. In Australia, the funnel web spider (*Atrax robustus*) and *Hadronyche* species can cause serious illness and death. In South America, the Brazilian Huntsmen (*Phoneutria fera*) and *Arantia Armeadeira* (*Phoneutria nigriventer*) are threats to humans.

HISTORY AND EPIDEMIOLOGY

Since the time of Aristotle, spiders and their webs were used for medicinal purposes. Special preparations were concocted to cure a fantastic array of ailments, including earache, running of the eyes, “wounds in the joints,” warts, gout, asthma, “spasmodic complaints of females,” chronic hysteria, cough, rheumatic afflictions for the head, and stopping blood flow.²²⁷

One *Latrodectus* species has an infamous history of medical concern, hence the name mactans, which means “murderer” in Latin.¹⁸³ Hysteria regarding spider bites peaked during the 17th century in the Taranto region of Italy. The syndrome tarantism, which is characterized by lethargy, stupor, and a restless compulsion to walk or dance, was blamed on *Lycosa tarantula*, a spider that pounces on its prey like a wolf. Deaths were associated with these outbreaks. Dancing the rapid tarantella to music was the presumed remedy. The real culprit in this epidemic was *Latrodectus tredecimguttatus*.¹⁸³ Other epidemics of arachnidism occurred in Spain in 1833 and 1841.¹⁵⁶ In North America, there was an increase in spider exposures during the late 1920s; Rome reported large numbers in 1953; Yugoslavia reported a large number of cases between 1948 and 1953.^{33,156} These epidemics may be related to actual reporting biases as well as climatic variations.¹⁸³ Spider bites are more numerous in warmer months, presumably because both spiders and humans are more active during that season.

Approximately 200 species of spiders are associated with envenomations.^{192,196} Eighteen genera of North American spiders produce poisonings that require clinical intervention (Table 118–2). In one series of 600 suspected spider bites, 80% were determined to result from arthropods other than spiders, such as ticks, bugs, mites, fleas, moths, butterflies, caterpillars, flies, beetles, water bugs, and some members (ants, bees, wasps) of order Hymenoptera. Ten percent of the presumed bites actually were manifestations of other nonarthropod disorders.^{194,196}

TABLE 118–2. North American Spiders of Medical Importance

<i>Genus</i>	<i>Common Name</i>
<i>Araneus</i> spp	Orb weaver
<i>Argiope aurantia</i>	Orange argiope
<i>Bothriocyrtum</i> spp	Trap door spider
<i>Chiracanthium</i> spp	Running spider
<i>Drassodes</i> spp	Gnaphosid spider
<i>Heteropoda</i> spp	Huntsman spider
<i>Latrodectus</i> spp	Widow spider
<i>Liocranoides</i> spp	Running spider
<i>Loxosceles</i> spp	Brown, violin, or recluse spider
<i>Lycosa</i> spp	Wolf spider
<i>Misumenoides</i> spp	Crab spider
<i>Neoscona</i> spp	Orb weaver
<i>Peucetia viridans</i>	Green lynx spider
<i>Phiddipus</i> spp	Jumping spider
<i>Rheostica (Aphonopelma)</i> spp	Tarantula
<i>Steatoda grossa</i>	False black widow spider
<i>Tegenaria agrestis</i>	Hobo spider
<i>Ummidia</i> spp	Trap door spider

From 2006 to 2007, an annual average of 14,000 spider exposures and 44,000 insect exposures were reported to US poison centers.^{36,40} No more than two fatalities were reported per year. One was from the Hymenoptera category, and the other was an unknown spider exposure.³⁶ However, from 2008 to 2011 the annual average of spider and insect exposures declined to 10,900 and 39,600 exposures, respectively.^{37,38,39,41} Fatalities again were low. In 2008, one death was reported as caused by scorpion exposure; in 2009, one death was reported as caused by an “other insect bite/sting”; in 2010, two deaths were reported from bee stings and one death from an “other spider bite”^{37,38,39} (Chap. 136).

Most information on the clinical presentation of spider bites continues to be unreliable because it is based on case reports and case series. Frequently, the cases do not have any expert confirmation of the actual spider involved, which can lead to propagation of misinformation about different spiders, particularly with necrotic arachnidism. For example, cutaneous anthrax was mistaken for a cutaneous necrotic spider bite.¹⁹¹ Additionally, the white tail spider (*Lampona* spp) was suspected for more than 20 years to cause necrotic lesions. Only recently has a prospective study of confirmed spider bites refuted this myth by reporting more than 700 confirmed spider bites in Australia.^{127,128,129} Because most arthropod-focused research involves characterizing the structure of spider toxins rather than verifying clinical presentations, it is important to produce clinical studies that have bites confirmed by the presence of the spider that is identified by an expert. Definite spider bites or stings are defined as the following: (1) evidence of a bite or sting soon after the incident or the creature can be seen to bite or sting, (2) collection of the particular creature, either alive or dead, with positive identification of the creature by an expert biologist/taxonomist in the field relating to the creature.^{128,130}

BLACK WIDOW SPIDER (*LATRODECTUS MACTANS*; HOURGLASS SPIDER)

Five species of widow spiders are found in the United States: *Latrodectus mactans* (black widow; Fig. 118–2A), *Latrodectus hesperus* (Western black widow), *Latrodectus variolus* (found in New England, Canada, south to Florida, and west to eastern Texas, Oklahoma, and Kansas), *Latrodectus bishopi* (red widow of the South), and *Latrodectus geometricus* (brown widow or brown button spider; Fig. 118–2B). They are present in every state except for Alaska. Dangerous widow

spiders in other parts of the world include *L. geometricus* and *Latrodectus tredecimguttatus* (European widow spider found in southern Europe), *Latrodectus hasselti* (red-back widow spider found in Australia, Japan, and India; [Fig 118-2C](#)), and *Latrodectus cinctus* (found in South Africa). These spiders live in temperate and tropical latitudes in stone walls, crevices, wood piles, outhouses, barns, stables, and rubbish piles. They molt multiple times and as a result can change colors. The ventral markings on the abdomen are species specific, and the classic red hourglass-shaped marking is noted in only *L. mactans*. Other species may have variations on their ventral surface, such as triangles and spots.



FIGURE 118-2 Widow spiders. (A) The North American black widow spider, *Latrodectus mactans*. Note the hourglass on the abdomen. (B) The brown widow spider, *Latrodectus geometricus*. (C) The Australian redback spider, *Latrodectus hasselti*. (Used with permission of The American Museum of Natural History.)

Typically, the female *L. mactans* is shiny, jet-black, and large (8–10 mm), with a rounded abdomen and a red hourglass mark on its ventral surface. Her larger size and ability to penetrate human skin with her fangs make her more venomous and toxic than the male spider, which resembles the immature spider in earlier stages of development and is smaller, lighter in color, and has a more elongated abdomen and fangs that usually are too short to envenomate humans ([Table 118-3](#)). Black widow females are trappers and inhabit large, untidy, irregularly shaped webs. Webs are placed in or close to the ground and in secluded, dimly lit areas that can trap flying insects, such as outdoor privies, barns, sheds, and garages.⁵

TABLE 118-3. Brown Recluse and Black Widow Spiders: Comparative Characteristics

	<i>Brown Recluse (Larsscoles spp)</i>	<i>Black Widow (Latrodectus spp)</i>
Description	Female brown, 6–20 mm, violin shaped mark on dorsum of cephalothorax; female greater toxicity than male	Female jet black, 8–10 mm, red hourglass mark on ventral surface, female greater toxicity than male
Major venom component	Sphingomyelinase D	α -Latrotoxin
Pathophysiology of envenomation	Vascular injury, dermatonecrosis, hemolysis	Massive presynaptic discharge of neurotransmitters; lymphatic and hematogenous spread, neurotoxicity
Epidemiology	Bites more common in warmer months North America (southern and midwestern states): <i>L. reclusa</i> South America: <i>L. loati</i> , <i>L. guschi</i> Europe: <i>L. rufescens</i> Africa (southern): <i>L. parum</i> , <i>L. spiniceps</i> , <i>L. pilosa</i> , <i>L. bergeri</i> Asia/Australia: Rare	Bites more common in warmer months in subtropical and temperate areas; perennial in tropics North America: <i>L. mactans</i> , <i>L. hesperus</i> , <i>L. geometricus</i> Europe: <i>L. tenebrosus</i> Africa (southern): <i>L. indistinctus</i> Australia: <i>L. hasselti</i> Asia/South America: Rare
Clinical effects	Cutaneous Initial (0–2 hours after bite): Painless, erythema, edema 2–8 hours: Hemorrhagic, ulcerates, painful 1 week: Eschar Months: Healing Hematologic Methemoglobinemia, hemolysis, thrombocytopenia, disseminated intravascular coagulopathy Renal: Kidney failure, acute tubular necrosis	Cutaneous Initial (5 minutes–1 hour after bite): Local pain 1–2 hours: Puncture marks Hours: Regional lymph nodes swollen, central blanching at bite site with surrounding erythema CVS: Initial tachycardia followed by bradycardia, dysrhythmias, initial hypotension followed by hypertension GI: Nausea, vomiting, mimic acute abdomen Hematologic: Leukocytosis Resolution over several days Metabolic Hyperglycemia (transient) Musculoskeletal: Hypertonia, abdominal rigidity, "facies latrodectimica" Neurologic CNS: Psychosis, hallucinations, visual disturbance, seizures Peripheral nervous system: Pain at the site Autonomic nervous system: Increased secretions; sweating, salivation, lacrimation, diarrhea, bronchorrhea, mydriasis, miosis, priapism, ejaculation Renal: Glomerulonephritis, oliguria, anuria Respiratory: Bronchoconstriction, acute respiratory distress syndrome
Treatment	Analgesia Wound care Dapsone (?) Hyperbaric oxygen (local) (?) Antivenom (?) not available universally Corticosteroids	Analgesia Muscle relaxants Antivenom

Pathophysiology

The venom is more potent on a volume-per-volume basis than the venom of a pit viper and contains six active components with molecular weights of 5000 to 130,000 Da.⁵ The six components are five latroinsectotoxins (α -, β -, γ -, δ -, ϵ -LITs) (insect-specific neurotoxins), and α -latrocrustatoxin (α -LCT) (crustacean-specific neurotoxin).¹⁰⁵ α -Latrotoxin binds, with nanomolar affinity, to the specific presynaptic receptors neurexin I- α and Ca^{2+} -independent receptor for α -latrotoxin (CIRL), otherwise known as latrophilin.^{30,114,126} The binding triggers a cascade of events: conformational change allowing

pore formation by tethering the toxin to the plasma membrane; Ca^{2+} ionophore formation; translocation of the N-terminal domain of α -LTX into the presynaptic intracellular space, and intracellular activation of exocytosis of norepinephrine, dopamine, neuropeptides, acetylcholine, glutamate, and γ -aminobutyric acid (GABA), respectively. This massive release of neurotransmitters is what causes the clinical envenomation syndrome known as latrodectism.^{5,171,174}

Clinical Manifestations

Widow spiders are shy and nocturnal. They usually bite when their web is disturbed or upon inadvertent exposure in shoes and clothing. A sharp pain typically described as a pinprick occurs as the victim is bitten. A pair of red spots may evolve at the site, although the bite is commonly unnoticed.^{53,155} The bite mark itself tends to be limited to a small puncture wound or wheal and flare reaction that often is associated with a halo (Table 118–3). However, the bite from *L. mactans* may produce latrodectism, a constellation of signs and symptoms resulting from systemic toxicity. Some cases do not progress; others may show severe neuromuscular symptoms within 30 to 60 minutes. The effects from the bite spread contiguously. For example, if a person is bitten on the hand, the pain progresses up the arm to the elbow, shoulder, and then toward the trunk during systemic poisoning. Typically, a brief time to symptom onset denotes severe envenomation. One patient developed latrodectism following the intentional intravenous injection of a crushed whole black widow spider.⁴⁷

One grading system divides the severity of the envenomation into three categories.⁶⁰ Grade 1 envenomations range from no symptoms to local pain at the envenomation site with normal vital signs. Grade 2 envenomations involve muscular pain at the site with migration of the pain to the trunk, diaphoresis at the bite site, and normal vital signs. Grade 3 envenomations include the grade 2 symptoms with abnormal vital signs; diaphoresis distant from the bite site; generalized myalgias to back, chest, and abdomen; and nausea, vomiting, and headache.

The myopathic syndrome of latrodectism involves muscle cramps that usually begin 15 minutes to 1 hour after the bite. The muscle cramps initially occur at the site of the bite but later may involve rigidity of other skeletal muscles, particularly muscles of the chest, abdomen, and face. The pain increases over time and occurs in waves that may cause the patient to writhe. Large muscle groups are affected first. Classically, severe abdominal wall spasm occurs and may be confused with a surgical abdomen, especially in children who cannot relate the history with the initial bite.⁴⁴ Muscle pain often subsides within a few hours but may recur for several days. Transient muscle weakness and spasms may persist for weeks to months.

Additional clinical findings include “*facies latrodectismica*,” which consists of sweating, contorted, grimaced face associated with blepharitis, conjunctivitis, rhinitis, cheilitis, and trismus of the masseters.¹⁵⁵ A fear of death, *pavor mortis*, is described.¹⁵⁵ Nausea, vomiting, sweating, tachycardia, hypertension, muscle cramping, restlessness, compartment syndrome at the site of the bite, and, rarely, priapism are also reported.^{5,61,119,214} The mechanism of compartment syndrome developing after a black widow spider envenomation is unclear, but two postulated theories include rhabdomyolysis and the venom affecting the blood vessels leading to engorgement and obstruction of the venous outflow. In one case, the compartment syndrome was treated with antivenom, and the patient recovered without the need for a fasciotomy.⁶¹ Recovery usually ensues within 24 to 48 hours, but symptoms may last several days with more severe envenomations. Life-threatening complications include severe hypertension, respiratory distress, myocardial infarction, cardiovascular failure, and gangrene.^{47,60,61,81,165,179,183} In the past 20 years, more than 40,000 presumed black widow spider bites have been reported to the American Association of Poison Control Centers. Death is rarely reported. There have been two fatalities in Madagascar from envenomation by *L. geometricus*, one from cardiovascular failure and the other from gangrene of the foot.¹⁸³ The most recent fatality reported from Greece resulted from myocarditis secondary to envenomation by *L. tredecimguttatus*,¹⁸² confirmed by a local veterinarian. The patient developed severe dyspnea, hypoxemia, cyanosis, cardiomyopathy, and global hypokinesia of the left ventricle confirmed by echocardiography, followed by death 36 hours later; antivenom was not available. On autopsy, diffuse interstitial and alveolar edema, with mononuclear infiltrate of the myocardium and degenerative changes, were noted, and toxicologic analysis for xenobiotics, as well as all blood, urine, bronchial, and serologic viral cultures, were negative. The paucity of mortalities is presumed to result from the improvement in medical care, the availability of antivenom, or the limited toxicity of the spider.

Diagnostic Testing

Laboratory data generally are not helpful in management or predicting outcome. According to one study, the most common findings include leukocytosis and increased creatine phosphokinase and lactate dehydrogenase concentrations.⁶⁰ Currently, no specific laboratory assay is capable of confirming latrodectism. However, the clinical situation may warrant the need to check laboratory tests and other studies to evaluate the sequelae of the black widow spider envenomation.

Management

Treatment involves establishing an airway and supporting respiration and circulation, if indicated. Wound evaluation and local wound care, including tetanus prophylaxis, are essential.²³⁶ The routine use of antibiotics is not recommended.

Pain management is a substantial component of patient care and depends on the degree of symptomatology. Using the grading system, grade 1 envenomations may require only cold packs and orally administered nonsteroidal antiinflammatory agents. Grade 2 and 3 envenomations probably require intravenous (IV) opioids and benzodiazepines to control pain and muscle spasm.

Traditionally, 10 mL 10% calcium gluconate solution was given IV to decrease cramping. However, a retrospective chart review of 163 patients envenomated by the black widow concluded that calcium gluconate was ineffective for pain relief compared with a combination of IV opioids (morphine sulfate or meperidine) and benzodiazepines (diazepam or lorazepam).^{60,141} Another study found greater neurotransmitter release when extracellular calcium concentrations were increased, suggesting that administration of calcium is irrational in patients suffering from latrodectism.¹⁹² The mechanism of action of calcium remains unknown, and its efficacy is anecdotal; therefore, we do not recommend calcium administration for pain management.

Although often recommended, methocarbamol (a centrally acting muscle relaxant) and dantrolene also are ineffective for treatment of latrodectism.^{141,197} A benzodiazepine, such as diazepam, is more effective for controlling muscle spasms and achieves sedation, anxiolysis, and amnesia. Management should primarily emphasize supportive care, with opioids and benzodiazepines for controlling pain and muscle spasms, because the use of antivenom risks anaphylaxis and serum sickness.

Latrodectus antivenom (Wyeth) is rapidly effective and curative. In the United States, the antivenom formulation is effective for all species but is available as a crude hyperimmune horse serum that may cause anaphylaxis and serum sickness. The morbidity of latrodectism is high, with pain, cramping, and autonomic disturbances, but mortality is low. Hence controversy exists over when to administer the black widow antivenom. The antivenom can be administered for severe reactions (eg, hypertensive crisis or intractable pain), to high-risk patients (eg, pregnant women suffering from a threatened abortion), or for treatment of priapism.^{141,183} Use of antivenom probably should not be considered for patients unless systemic effects are designated as grade 3.⁶¹ The usual dose is one to two vials diluted in 50 to 100 mL 5% dextrose or 0.9% sodium chloride solution, with the combination infused over 1 hour (Antidotes in Depth: A34). Skin testing may identify a highly allergic individual but does not eliminate the occurrence of hypersensitivity reactions; therefore, we do not recommend skin testing. Recently, an anaphylactoid reaction to the black widow spider antivenin was reported after a negative skin test in both a boy and a man^{124,168} who subsequently died from the anaphylactoid reaction. Both were being treated for intractable pain after failing intravenous opioid management. Pretreatment with histamine H₁- or H₂-blockers, or both, and epinephrine may be beneficial in preventing histamine release and anaphylaxis. Patients with allergies to horse serum products and those who have received antivenom or horse serum products are at risk for immunoglobulin IgE-mediated hypersensitivity reactions and, though efficacy is largely unproven, may benefit from the pretreatment with antihistamines and corticosteroids.

A purified F(ab)₂ fragment *Latrodectus mactans* antivenom, Analatro®, is currently undergoing clinical trials (Antidotes in Depth: A34).

In Australia, a purified equine-derived IgG-F(ab)₂ fragment antivenom for the red-back spider *L. hasselti* (RBS-AV) is available. The RBS-AV (CSL, Melbourne, Australia) is administered intramuscularly and given as first-line therapy to patients presenting with systemic signs or symptoms in Australia. Since its introduction in 1956, no deaths are reported, and the incidence of mild allergic reactions to RBS-AV is only 0.54% in 2144 uses.²²³

However, an underpowered prospective cohort study of confirmed red-back spider bites failed to show that intramuscular antivenom was better than no treatment when all patients were followed up over one week.¹²⁹ This study did note that only 17% of patients were pain-free at 24 hours with antibody treatment. Therefore, intramuscular antivenom appears to be less effective than previously thought, and the route of administration requires review. Recently in Italy, an FM₁ Fab fragment specific for the α-latrotoxin has been highly effective in neutralizing the toxin in vivo in mice and shows some promise for possible use in humans.^{12,45} This single monoclonal antibody shows great promise in the treatment for severe black widow envenomation. Inadvertent use of RBS-AV successfully treated envenomations from the comb-footed spider (*Steatoda* spp),¹³⁰ and the *Steatoda* venom and clinical effects are similar to the *Latrodectus* venom but milder in clinical presentation.¹⁰³

BROWN RECLUSE SPIDER (*LOXOSCELES RECLUSA*; VIOLIN OR FIDDLEBACK SPIDER)

Loxosceles reclusa was confirmed to cause necrotic arachnidism in 1957, although reports of systemic symptoms following brown spider bites have appeared since 1872.¹⁰ This spider has a brown violin-shaped mark on the dorsum of the cephalothorax, three dyads of eyes arranged in a semicircle on top of the head, and legs that are five times as long as the body. It is small (6–20 mm long) and gray to orange or reddish brown (Fig. 118–3A). *Loxosceles* spiders weave irregular white, flocculent adhesive webs that line their retreats.⁹² Spiders in the genus *Loxosceles* have a worldwide distribution. In

the United States, other species of this genus, which include *L. rufescens*, *L. deserta*, *L. devia*, and *L. arizonica*, are prominent in the Southeast and Southwest.⁹ *L. rufescens* was inadvertently introduced in several buildings in New York City. Though it is unclear how they initially arrived there, they were most likely transported on personal belongings and cartons of materials (confirmed by Lou Sorkin BCE, arachnologist, American Museum Natural History, New York).²¹¹ They are hunter spiders that live in dark areas (wood piles, rocks, basements), and their foraging is nocturnal. They are not aggressive but will bite if antagonized (Table 118-3). These spiders live up to 2 years and maybe even longer. They are resilient and can survive up to 6 months without water or food and can tolerate temperatures from 46.4° to 109.4°F (8°–43°C).⁹⁶ Like the black widow spider, the female is more dangerous than the male. *Loxosceles* venom has variable toxicity, depending on the species, with *Loxosceles intermedia* venom causing more severe clinical effects in humans.^{15,16} The peak time for envenomation is from spring to autumn, and most victims are bitten in the morning. However, the brown recluse spider is often misdiagnosed as the culprit for a necrotic wound and has been identified as the biting spider when *L. rufescens* was the actual species. One study examined 182 patients enrolled over 23 months who presented to the emergency department (ED) for a chief complaint of spider bite. The study found that only 3% (7/182) were ultimately confirmed by their treating physician to have the diagnosis of a spider bite, whereas 84% (152/182) had a skin and soft tissue infection (SSTI), nine patients were bitten by other animals, six patients were given other non-bite diagnoses, such as erythema multiforme, subcutaneous nodules, folliculitis from a razor cut, and eight patients had no diagnostic category recorded. Of the seven patients that had a confirmed spider bite, only one brought the spider in for identification, while the others saw a spider or witnessed a bite, and one patient did not witness or feel a bite.²¹⁷ Community-acquired MRSA was the most common cause of SSTI's, accounting for 70% of positive wound cultures when performed. Hence the spider bite diagnosis is often frequently misused, and a diagnosis of dermatonecrotic wound of uncertain etiology would be more accurate.²¹⁷



FIGURE 118-3 Brown recluse spider. (A) *Loxosceles reclusa*. Note the image of the violin, which gives the spider its common name, “the fiddle back spider.” (Image contributed by Progeny Products, www.brown-recluse.com.) (B) A typical

envenomation from the brown recluse spider. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Pathophysiology

The venom is cytotoxic. The two main constituents of the venom are sphingomyelinase-D and hyaluronidase, though other subcomponents include deoxyribonuclease, ribonuclease, collagenase, esterase, proteases, alkaline phosphatase, and lipase.^{70,146,232} Hyaluronidase is a spreading factor that facilitates the penetration of the venom into tissue but does not induce lesion development.¹⁴⁶ Sphingomyelinase-D is the primary constituent of the venom that causes necrosis and red blood cell hemolysis and also causes platelets to release serotonin.¹⁴⁶ Sphingomyelinase also reacts with sphingomyelin in the red blood cell membrane to release choline and N-acylsphingosine phosphate, which triggers a chain reaction releasing inflammatory mediators, such as thromboxanes, leukotrienes, prostaglandins, and neutrophils, leading to vessel thrombosis, tissue ischemia, and skin loss.¹⁴⁶ Early perivascular collections of polymorphonuclear leukocytes with hemorrhage and edema progress to intravascular clotting. Coagulation and vascular occlusion of the microcirculation occur, ultimately leading to necrosis.²⁰⁷

Clinical Manifestations

The clinical spectrum of loxoscelism can be divided into three major categories. The first category includes bites in which very little, if any, venom is injected. A small erythematous papule may be present that becomes firm before healing and is associated with a localized urticarial response. In the second category, the bite undergoes a cytotoxic reaction. The bite initially may be painless or have a stinging sensation but then blisters and bleeds and ulcerates 2 to 8 hours later (Table 118–3). The lesion may increase in diameter, with demarcation of central hemorrhagic vesiculation, then ulcerates and develops violaceous necrosis, surrounded by ischemic blanching of skin and outer erythema and induration over 1 to 3 days. This is also known as the “red, white, and blue” reaction (Fig. 118–3B).^{142,242} Necrosis of the central blister occurs in 3 to 4 days, with eschar formation between 5 and 7 days. After 7 to 14 days, the wound becomes indurated and the eschar falls off, leaving an ulceration that heals by secondary intention. Local necrosis is more extensive over fatty areas (thighs, buttocks, and abdomen).¹⁴⁶ The size of the ulcer determines the time for healing. Large lesions up to 30 cm may require months or more to heal.

Upper airway obstruction was reported in a child who was bitten on his neck and subsequently developed progressive cervical soft tissue edema with airway obstruction and dermatonecrosis 40 hours later.¹⁰⁰ Another case reported stridor and respiratory distress following a brown recluse envenomation of the ear. Although the presentation is rare, respiratory compromise should be considered when an envenomation occurs near the airway.⁹⁵

The third category consists of systemic loxoscelism, which is not predicted by the extent of cutaneous reaction, and occurs 24 to 72 hours after the bite. The young are particularly susceptible.^{99,198} The clinical manifestations of systemic loxoscelism include fever, chills, weakness, edema, nausea, vomiting, arthralgias, petechial eruptions, rhabdomyolysis, disseminated intravascular coagulation, hemolysis that can lead to hemoglobinemia, hemoglobinuria, acute kidney injury, and death.^{27,49,88,99,153,202,239} However, in North America, the incidence of systemic illness is rare, and mortality is low.⁷

Diagnostic Testing

Bites from other spiders, such as Cheiracanthium (sac spider), Phidippus (jumping spider), and Argiope (orb weaver), can produce necrotic wounds. These spiders are often the actual culprits when the brown recluse is mistakenly blamed. Definitive diagnosis is achieved only when the biting spider is positively identified. No routine laboratory test for loxoscelism is available for clinical application, but several techniques are presently used for research purposes. The lymphocyte transformation test measures lymphocytes that have undergone blast transformation up to one month after exposure to *Loxosceles* venom. The lymphocytes incorporate thymidine into the nucleoprotein, providing a quantitative response.⁸ A passive hemagglutination inhibition test (PHAI) has been developed in guinea pigs. The PHAI assay is based on the property of certain brown recluse spider venom components to spontaneously adsorb to formalin-treated erythrocyte membranes and the ability of the brown recluse spider venom to inhibit antiserum-induced agglutination of venom-coated red blood cells.¹⁸ The test is 90% sensitive and 100% specific for 3 days postenvenomation and may prove useful for early diagnosis of brown recluse spider envenomation.¹⁸ An enzyme-linked immunoassay (ELISA) specific for *Loxosceles* venom in biopsied tissue can confirm the presence of venom for 4 days postenvenomation,¹⁸ and in an experimental model using rabbits, the antigen was recoverable using the ELISA assay from 14 to 21 days.¹⁵⁸ The drawbacks of using a skin biopsy are the invasive nature of the procedure, which can result in further scarring with an increased potential for infection, and the lack of proof that skin biopsy can diagnose early envenomations prior to the development of dermatonecrosis. Another ELISA utilizing serum for detection of venom antigens has been developed that correctly discriminates the mice inoculated with antigens from *L. intermedia* venom. The ELISA immunoassay and antivenom may

become useful diagnostic tools if envenomation can be proved or disproved early.⁵⁷ A venom-specific enzyme immunoassay that uses hair, skin biopsies, or aspirated tissue near a suspected lesion to detect the presence of venom up to 7 days after injury is under investigation.^{145,161} In Brazil, ELISA is used to detect the venom of *Loxosceles gaucho* in wounds and patient sera, but the technique is not in widespread clinical use.⁵³

Clinical laboratory data may be remarkable for hemolysis, hemoglobinuria, and hematuria. Coagulopathy may be present, with laboratory data significant for elevated fibrin split products, decreased fibrinogen concentrations, and a positive D-dimer assay. Other tests may show increased prothrombin time (PT) and partial thromboplastin time (PTT), leukocytosis (up to 20,000–30,000 cells/mm³), spherocytosis, Coombs-positive hemolytic anemia, thrombocytopenia, or abnormal kidney and liver function tests.^{5,12,92,194,196,198,237}

Treatment

Optimal local treatment of the lesion is controversial. The most prudent management of the dermatonecrotic lesion is wound care, immobilization, tetanus prophylaxis, analgesics, and antipruritics as warranted (Table 118–4).^{5,92,234,237} Early excision or intralesional injection of corticosteroids appears unwarranted.¹⁸⁹ Corrective surgery can be performed several weeks after adequate tissue demarcation has occurred. In one case series the use of curettage of the lesion to remove necrotic and indurated tissue from the lesion, thus eliminating any continuing action of the lytic enzymes on the surrounding tissue, showed promising results.¹¹⁷ These patients had wound healing without further necrosis and minimal scarring. Vacuum-assisted closure, otherwise known as negative pressure wound therapy, is also described in a series of clinical cases in the surgical literature as a means to treat necrotic wounds caused by presumed brown recluse spider bites more quickly than the traditional methods, due to increased bacterial clearance and dermal perfusion, modulating the inflammatory response, extracting toxic substances, and accelerated rate of granulation tissue formation.²⁴⁰ Electric shock delivered via stun guns was not found to be useful in a guinea pig envenomation model.¹⁸ Cyproheptadine, a serotonin antagonist, was not beneficial in a rabbit model.¹⁷⁶ A randomized, controlled study evaluating the efficacy of topical nitroglycerin for envenomated rabbits showed no difference in preventing skin necrosis and suggested the possibility of increased systemic toxicity.¹⁵⁰ Antibiotics should be used to treat cutaneous or systemic infection, but they should not be used prophylactically.

TABLE 118–4. Management of Brown Recluse Spider Bite

General Wound Care	Local Wound Care	Systemic
Clean	Serial observations	Antipruritic/antianxiety and/or analgesics
Tetanus prophylaxis as indicated	Natural healing by granulation	Antibiotics for secondary bacterial infection
Immobilize and elevate bitten extremity	Delayed primary closure	Polymorphonuclear white blood cell inhibitors (?): dapsone, colchicine
Apply cool compresses; avoid local heat	Delayed secondary closure with skin graft Gauze packing, if applicable	Antivenom (experimental) Hyperbaric oxygen (local) (?)

Early use of dapsone (in patients who develop a central purplish bleb or vesicle within the first 6–8 hours) may inhibit local infiltration of the wound by polymorphonuclear leukocytes.¹⁴² The dosage recommended is 100 mg twice daily for 2 weeks.¹⁸⁷ However, prospective trials with large numbers of patients are lacking. One study compared the efficacy of erythromycin and dapsone therapy, erythromycin and antivenom therapy, and erythromycin, dapsone, and antivenom therapy (developed in rabbits based on a previous study).¹⁸⁶ Although the treatment groups were very small, all groups showed wound healing at approximately 20 days despite the different therapies used. This study’s biggest limitation includes the definition of a spider bite diagnosis (the study used the following criteria: a patient feeling the spider bite, seeing the spider, or having a clinically plausible necrotic lesion). The study suggests that the use of dapsone may eliminate the need for surgery following bites and that antivenom therapy was most effective clinically if the patient never developed the necrotic lesion. Hence, the use of dapsone in the management of a local lesion should be considered experimental until its use is validated by randomized, controlled clinical trials. Hepatitis,¹⁹⁰ methemoglobinemia (Chap. 127), and hemolysis are associated with dapsone use. If dapsone therapy is used, a baseline glucose-6-phosphate dehydrogenase and weekly complete blood counts should be performed.

An underpowered animal study evaluated the effects on the size of skin lesions induced by *Loxosceles* envenomation by treatment with hyperbaric oxygen therapy, dapsone, and combined hyperbaric oxygen therapy and dapsone.¹¹⁵ The study concluded that there was no clinically significant change in necrosis or induration by these treatment modalities. Further evaluation of these interventions remains appropriate. Another study using hyperbaric oxygen for treatment of *Loxosceles*-induced necrotic lesions in rabbits revealed no clinical improvement in the size of the lesion; however, the histology of the lesions improved. Whether this finding is of value in humans has not been determined.^{115,216} Use of 1.2 mg colchicine, a leukocyte inhibitor, followed at 2-hour intervals with 0.6 mg for 2 days, then 0.6 mg every hours for 2 additional days is sometimes recommended, but we do not advocate this treatment because of potential colchicine toxicity.¹⁹⁴ Rabbit-derived intradermal anti-*Loxosceles* Fab (α -Loxd) fragments attenuated the dermatonecrotic inflammation of rabbits injected with *L. deserta* venom in a time-dependent fashion.⁹⁷ At time 0 after envenomation, lesion development was blocked. At time 1 and 4 hours after envenomation, the α -anti-Loxd Fab antivenom continued to suppress the lesion areas, although the longer the delay in treatment, the smaller the difference in treatment and control lesion areas. At time 8 and 12 hours postenvenomation, there was no difference in lesion size. The typical 24-hour delay in lesion development makes the diagnosis difficult, and the antivenom would likely be useless if administered so late in the clinical course. Currently this antivenom is not available for commercial use.

One preclinical study shows promise for the treatment of *Loxosceles* envenomations using an antiloxoscelic serum that was produced from recombinant sphingomyelinase D that was derived from the sphingomyelinase of the *L. intermedia* and *L. laeta* spiders. The isolated sphingomyelinase from the respective *Loxosceles* species carried the full biological effects of the entire venom. This antiloxoscelic serum when administered IV into rabbits that were given intradermal injections of the loxoscelic venom from *L. laeta* and *L. intermedia* had greater neutralizing activity than when compared to the existing antiarachnid serum, which is made by hyperimmunizing horses against the venom of *L. gaucho*, *P. nigriventer*, and the scorpion *Tityus serrulatus*. In Brazil and South America, most of the envenomations occur with the *L. laeta* and *L. intermedia*, not *L. gaucho*. Knowing which species envenomated the patient could help determine which antiserum should be used.⁷³

Patients manifesting systemic loxoscelism or those with expanding necrotic lesions should be admitted to the hospital. All patients should be monitored for evidence of hemolysis, acute kidney injury, or coagulopathy. If hemoglobinuria ensues, increased IV fluids and urinary alkalization can be used in an attempt to prevent acute kidney injury. Hemolysis, if significant, can be treated with transfusions. Patients with coagulopathy should be monitored with serial complete blood cell count, platelet count, PT, PTT, fibrin split products, and fibrinogen. Disseminated intravascular coagulopathy may require treatment, based on severity.

HOBO SPIDER (TEGENARIA AGRESTIS, NORTHWESTERN BROWN SPIDER, WALCKENAER SPIDER)

The hobo spider is native to Europe and was introduced to the northwestern United States (Washington, Oregon, Idaho) in the 1920s or 1930s.²³³ These spiders build funnel-shaped webs within wood piles, crawl spaces, basements, and moist areas close to the ground. They are brown with gray markings and 7 to 14 mm long. They are most abundant in the midsummer through the fall. They bite if provoked or threatened but otherwise retreat quickly with disturbance.²³ The medical literature is sparse in reported hobo spider bites that are verified by a specialist. There is only one confirmed Hobo spider bite resulting in a necrotic lesion.⁶³ A 42 year-old woman with a history of phlebitis who felt a burning sensation on her ankle rolled her pants and found a crushed brown spider, which was later confirmed (unpublished source cited by MMWR) to be *T. agrestis*. She complained of persistent pain, nausea, and dizziness, and a vesicular lesion developed within several hours. The vesicle ruptured and ulcerated the next day. The lesion initially was 2 mm, but over the next 10 weeks enlarged to 30 mm in diameter and was circumscribed with a black lesion, at which time she sought medical advice. She was given a course of antibiotics, which did not limit the progression of this ulcer. Subsequently, the patient was unable to walk, and she was found to have a deep venous thrombosis. The other cases implicating Hobo spiders as a cause for dermatonecrotic injuries are based on proximity of the Hobo spider or other large brown spiders that are unidentified. *T. agrestis* venom implanted into rabbit skin can produce hemorrhagic necrotic lesions dermally and systemically.^{233,234}

The venom from European Hobo spiders and US Hobo spiders was analyzed using liquid chromatography to address the question of variability between the two spiders. *T. agrestis* originating from Europe is considered medically harmless. Liquid chromatography (European Hobo *T. agrestis* from the United Kingdom and American Hobo *T. agrestis* from Washington State, United States) found little variability between the two venoms to account for their differential necrotic effects.²⁸ The authors suggest four possibilities for the discrepancy between the European Hobo and American Hobo spiders: (1) an evolutionary change may have accounted for the novel necrotic effects; (2) venom chemistry may be similar but the habitat might account for the difference in behavior; (3) venom chemistry and habitat may be similar but an extrinsic factor such as a bacterium found in the US Hobo spider might be the cause for the necrotic effects; (4) *T. agrestis* do not

directly or indirectly cause necrotic arachnidism and have been falsely accused.²⁸ The authors suggest that either a bacterium such as *Mycobacterium ulcerans*, known to cause slow-developing ulcers on human skin, might coexist on the chelicerae of the *T. agrestis*, which is highly unlikely because of the presence of antibacterial peptides in the venom,^{113,241} or the more likely circumstance that *T. agrestis* has been falsely accused as being a cause for necrotic arachnidism. Further evidence to suggest that the *T. agrestis* is not likely to be a culprit for necrotic arachnidism is based on a study that evaluates the possibility of the spider's ability to carry and transfer pathogenic bacteria including the methicillin-resistant *Staphylococcus aureus* (MRSA) and analyzes the venom's hemolytic properties.⁹¹ One hundred two *T. agrestis* adult spiders were collected, and a bacterial diversity assay was conducted to find a total of six Gram-positive and four Gram-negative bacteria genera identified which was consistent with the bacteria found in the fauna of the natural environment of the Pacific Northwest and several occurring on human and animal skin. Spiders were then exposed to MRSA on polyethylene disks since the tissue lesions caused by this bacterium is often confounded with a necrotic arachnidism. No MRSA was found on either the spiders or the surfaces to which the MRSA exposed spiders were subjected, although the MRSA was found to persist on the polyethylene disks. Finally, the Hobo Spider venom was analyzed to determine its hemolytic activity in vertebrate blood. Compared to the known *Loxocles reclusa* hemolytic activity of 37%, the potential of *T. agrestis* venom hemolysis activity was negligible at 0.62 and 0.93% for male ($n = 5$) and female ($n = 7$) spiders, respectively. Misdiagnosis of spider bites is common. Wounds can be misleading and can occur from the reaction of other organisms such as ticks and other arthropods, superinfection with anthrax, or underlying medical conditions like diabetes and leukemia or bacterial infections. The need to revisit the Hobo spider toxicity syndrome with further studies that show direct evidence of *T. agrestis* causing necrotic arachnidism in humans is warranted before one can conclude that any necrotic arachnidism in the Pacific Northwest is caused by *T. agrestis*.

Pathophysiology

The toxin has been fractionated, with three peptides identified as having potent insecticidal activity and no discernible effects in mammalian in vivo assays.¹³⁴ The peptide toxins TaITX-1, TaITX-2, and TaITX-3 exhibit potent insecticidal properties by acting directly in the insect central nervous system and not at the neuromuscular junction.¹³⁴ Insects envenomated with *T. agrestis* venom and the insecticidal toxins purified from the venom developed a slowly evolving spastic paralysis. Currently, little is known about the toxin and its mechanism of action in humans.

Clinical Manifestations

The toxicity of Hobo spider venom is questionable; however, it occasionally causes necrosis secondary to infection. Other causes of dermatonecrotic lesions should be considered. The most common symptom associated with the spider bite is a headache that may persist for one week.⁶³ Other symptoms, including nausea, vomiting, fatigue, memory loss, visual impairment, weakness, and lethargy, are reported.^{63,234}

Diagnostic testing

No specific laboratory assay confirms envenomation with *T. agrestis* spider.

Treatment

Treatment emphasizes local wound care and tetanus prophylaxis, although systemic corticosteroids for hematologic complications may be of value. Surgical graft repair for severe ulcerative lesions may be warranted when there is no additional progression of necrosis.⁶³

TARANTULAS

Tarantulas are primitive mygalomorph spiders that belong to the family Theraphosidae, a subgroup of Mygalomorphae (Greek word mygale for field mouse).^{58,200} There are more than 1500 species, with 54 species found in the deserts of the western United States.¹⁷⁸ Because of their great size and reputation, tarantulas are often feared. They are the largest and hairiest spiders, popular as pets, and can be found throughout the United States as well as in tropical and subtropical areas (Fig. 118–4). The lifespan of the female can exceed 15 to 20 years. They have poor eyesight and usually detect their victims by touch and vibrations. Their defense lies in either their painful bite with erect fangs or by barraging their victim with urticating hairs that are released on provocation.⁵⁸ Only the New World tarantulas (tarantulas indigenous to the Americas) have and use the urticating hairs to defend themselves.⁵⁸



FIGURE 118-4 The Mexican redknee tarantula, *Brachypelma smithi*. (Used with permission of The American Museum of Natural History.)

Tarantulas may bite when provoked or roughly handled. Based on the few case reports, their venom has relatively minor effects in humans but can be deadly for canines and other small animals, such as rats, mice, cats, and birds.^{44,131} Small prey might actually be killed by the physical nature of having fangs impaled many times through their bodies. A study from Australia covering a 25 year span reported only nine confirmed bites by Theraphosid spiders in humans and seven confirmed bites in canines—in two cases the owner was bitten after the dog.^{19,131} At least four genera of tarantulas (*Lasiadora*, *Grammostola*, *Acanthoscurria*, and *Brachypelma*) possess urticating hairs that are released in self-defense when the tarantulas rub their hind legs against their abdomen rapidly to create a small cloud.⁹⁶ There are seven different types of urticating hairs. Type 1 hairs are found on tarantulas in the United States and are the only hairs that do not penetrate human skin. Type 2 hairs are incorporated into the silk web retreat but are not thrown off by the spider. Type 3 hairs can penetrate up to 2 mm into human skin. Type 4 hairs belong to the South American *Grammostola* spider and can cause severe respiratory inflammation. Urticarial hairs or setae are composed of chitin, lipoproteins, and mucopolysaccharides, which are recognized as foreign bodies triggering a humoral response in the mammalian immune system. Chitin is proinflammatory and activates T helper cells to stimulate activated macrophages to produce chitinases, which will break down the chitin but also trigger inflammation. Besides cell-mediated inflammation, spider setae can also trigger immunoglobulin E-mediated hypersensitivity.^{19,55}

Pathophysiology

Tarantula venom, specifically the venoms of *Aphonopelma hentzi* (synonym of *Dugesia hentzi* {Arkansas tarantula}) and other members of the genus *Aphonopelma* (Arizona or Texas brown tarantula), contains hyaluronidase, nucleotides (adenosine triphosphate {ATP}, adenosine diphosphate, and adenosine monophosphate), and polyamines (spermine, spermidine, putrescine, and cadaverine) that are used for digesting their prey.^{48,139,200} The role of spermine is unclear, but hyaluronidase is a spreading factor that allows more rapid entrance of venom toxin by destruction of connective tissue and intercellular matrix. ATP potentiates death in mice exposed to the *A. hentzi* venom and lowers the LD₅₀ in comparison to venom without ATP.^{56,155} Both venoms cause skeletal muscle necrosis when injected intraperitoneally into mice.⁹⁰ The primary injury results in rupture of the plasma membrane, followed by the inability of mitochondria and sarcoplasmic reticulum to maintain normal concentrations of calcium in the cytoplasm leading to cell death. *Aphonopelma* venom is similar to scorpion venom in composition and clinical effects. Novel toxins have been discovered in the venom that can act on potassium channels, calcium channels, and the recently discovered acid-sensing ion channels that may elucidate the molecular mechanism of voltage-dependent channel gating and their respective physiologic roles.^{82,83}

Clinical Manifestations

Although relatively infrequent in occurrence, bites present with puncture or fang marks. They range from being painless to a deep throbbing pain that may last several hours without any inflammatory component.¹³¹ Fever occurs in the absence of

infection, suggesting a direct pyrexia action of the venom. Rarely, bites create a local histamine response with resultant itching, and hypersensitive individuals could have a more severe reaction and, less commonly, mild systemic effects such as nausea and vomiting.^{96,131} Contact reactions from the urticating hairs are more likely to be the health hazard than the spider bite. The urticating hairs provoke local histamine reactions in humans and are especially irritating to the eyes, skin, and respiratory tract. Tarantula urticating hairs cause intense inflammation that may remain pruritic for weeks. Inflammation can occur at all levels from conjunctiva to retina. An allergic rhinitis can develop if the hairs are inhaled.¹³⁹ Tarantula hairs resemble sensory setae of caterpillars: both are type 3 that can migrate relentlessly and cause multiple foci of inflammation at all levels of the eye.¹²¹ Ophthalmia nodosa, a granulomatous nodular reaction to vegetable or insect hairs, is reported with casual handling of tarantulas.^{22,26} Other eye findings include setae in the corneal stroma, anterior chamber inflammation, migration into the retina, and secondary glaucoma and cataracts.³¹

Treatment

Treatment is largely supportive. Cool compresses and analgesics should be given as needed. All bites should receive local wound care, including tetanus prophylaxis if necessary. If the hairs are barbed, as in some species, they can be removed by using adhesive such as duct tape or cellophane tape followed by compresses or irrigation with 0.9% sodium chloride solution. If the hairs are located in the eye, then surgical removal may be required, followed by medical management of inflammation. If the hairs are difficult to remove and the patient has persistent ocular pain and discomfort, then a therapeutic pars plana vitrectomy may be necessary to reduce the antigenic load and to improve clinical symptomatology.¹¹⁸ Urticarial reactions should be treated with oral antihistamines and topical or systemic corticosteroids.

FUNNEL WEB SPIDERS

Australian funnel web spiders are a group of large Hexathelidae mygalomorphs that can cause a severe neurotoxic envenomation syndrome in humans. The fang positions of funnel web spiders (as well as the tarantulas) are vertical relative to their body, which requires the spider to rear back and lift the body to attack. The length of fangs can reach up to 5 mm. This spider can bite tenaciously and may require extraction from the victim.¹⁶³ Atrax and Hadronyche species are found along the eastern seaboard of Australia. *A. robustus*, also called the Sydney funnel web spider, is the best known and is located around the center of Sydney, Australia.¹⁶³ Funnel web spiders tend to prefer moist, temperate environments.¹⁶³ They are primarily ground dwellers and live in burrows, crevices in rocks, and around foundations of houses. They build tubular or funnel-shaped webs.⁹⁶ At night, the spiders ascend the tubular web and wait for their prey. The Sydney funnel web spider is considered one of the most poisonous spiders. It was responsible for 14 deaths between 1927 and 1980, at which time the antivenom was introduced.^{220,221}

Pathophysiology

Originally called robustotoxin from *A. robustus* spider and versutoxin from the *Hadronyche versuta* spider, the toxin which is now referred to as atracotoxin or atraxin (δ -ACTX-Arl and δ -ACTX-Hvla, respectively) is the lethal protein component of *A. robustus* venom and is unique in its toxicity affecting primates and newborn mice in biological doses, although other mammals are susceptible in higher doses.^{163,219,221,238} δ -ACTX is a 42 amino acid peptide that targets mammals by increasing the ion conductance at voltage-gated sodium channels via trapping the channel's voltage sensor domain IV S4 segment in an inward conformational change, preventing the closure of the ion channel, thereby evoking a fulminant neurotransmitter release at the autonomic and/or somatic synapses.^{151,172} Hence δ -ACTX produces an autonomic storm, releasing acetylcholine, noradrenaline, and adrenaline. In monkeys, a 5 μ g/kg intravenous infusion dose of robustotoxin from male *A. robustus* spiders causes dyspnea, blood pressure fluctuations leading to severe hypotension, lacrimation, salivation, skeletal muscle fasciculation, and death within 3 to 4 hours.¹⁶⁹ Versutoxin, a toxin from the Blue Mountain funnel web spider, is closely related to robustotoxin and has demonstrated voltage-dependent slowing of sodium channel inactivation.¹⁷³

Clinical Manifestations

A biphasic envenomation syndrome is described in humans and monkeys.^{220,221} Phase 1 consists of localized pain at the bite site, perioral tingling, piloerection, and regional fasciculations (most prominent in the face, tongue, and intercostals). Fasciculations may progress to more overt muscle spasm; masseter and laryngeal involvement may threaten the airway.²¹⁹ Other features include tachycardia, hypertension, cardiac dysrhythmias, nausea, vomiting, abdominal pain, diaphoresis, lacrimation, salivation, and acute respiratory distress syndrome (ARDS), which often is the cause of death in phase 1.²³⁸ Phase 2 consists of resolution of the overt cholinergic and adrenergic crisis; secretions dry up, and fasciculations, spasms, and hypertension resolve. This apparent improvement can be followed by the gradual onset of refractory hypotension,

apnea, and cardiac arrest.²²¹

Treatment

Pressure immobilization using the crepe bandage to limit lymphatic flow and immobilization of the bitten extremity may inactivate the venom and should be applied if symptoms of envenomation are present. Funnel web venom is one of the few animal toxins known to undergo local inactivation. Monkey studies and a human case report support the utility of pressure immobilization.^{101,222} After injecting *A. robustus* venom subcutaneously in monkeys, pressure-immobilization technique increased survival by retarding the venom movement and also by allowing the local peripheral enzymes inactivating the venom.^{220,222}

The patient should be transferred to the nearest hospital with the bandage in place and then stabilized and placed in a resuscitation facility with adequate ampules of antivenom readily available before the bandage is removed; otherwise, a precipitous envenomation may occur during the removal of the pressure bandage. A purified IgG antivenom protective against *Atrax* envenomations was developed in rabbits.²²⁰ One ampule of the antivenom contains 100 mg purified rabbit IgG or 125 units of neutralizing capacity per ampule.²³⁸ It has been effective for more than 40 humans bitten by the *Atrax* species.²²² The starting dose is two ampules if systemic signs of envenomations are present, and four ampules if the patient develops ARDS or decreased mental status. Doses are repeated every 15 minutes until clinical improvement occurs.²³⁸ Up to eight ampules is common in a severe envenomation. Since anaphylaxis has not been reported,²²² the manufacturer no longer recommends premedication. Serum sickness is rare after funnel web antivenom administration, with only one reported case in a patient who received five ampules of antivenom.¹⁶²

SCORPIONS

Scorpions are invertebrate arthropods that have existed for more than 400 million years.⁶² Of the 650 known living species, most of the lethal species are in the family Buthidae (Table 118–5). The genera of the family Buthidae include *Centruroides*, *Tityus*, *Leiurus*, *Androctonus*, *Buthus*, and *Parabuthus*.⁶² Scorpions envenomate humans by stinging rather than biting. Their five-segmented metasoma (“tail”) contains a terminal bulbous segment called the telson that contains the venom apparatus (Fig. 118–5). More than 100,000 medically significant stings likely occur annually worldwide, predominantly in the tropics and North Africa.^{1,25,73,106,132,144} According to American Association of Poison Control Centers data from 1995 to 2011, approximately 11,000 to 19,000 scorpion annual exposures occurred in the United States, mostly in the southwestern region, but no deaths have been reported. These members of the class Arachnida rarely cause mortality in victims older than 6 years.¹⁸⁹ The venomous scorpions in the United States are *Centruroides exilicauda* and *Centruroides vittatus*. The most important is *C. exili cauda*, previously called *Centruroides sculpturatus* Ewing and *Centruroides gertschii* (bark scorpion; Table 118–6).⁸⁶

TABLE 118–5. Scorpions of Toxicologic Importance^{74,84}

Australia:	<i>Lychas marmoreus</i> , <i>Lychas</i> spp, <i>Isometrus</i> spp, <i>Cercophonius squama</i> , <i>Urodacus</i> spp
India:	<i>Buthus tamulus</i>
Mexico:	<i>Centruroides suffusus</i>
Middle East:	<i>Androctonus crassicauda</i> , <i>Androctonus Australis</i> , <i>Buthus minax</i> , <i>Androctonus Australis</i> , <i>Buthus occitanus</i> , <i>Leirus quinquestriatus</i>
Spain:	<i>Buthus occitanus</i>
South Africa:	<i>Androctonus crassicauda</i>
South America:	<i>Tityus serrulatus</i>
United States:	<i>Centruroides exilicauda</i>



FIGURE 118-5 The Brazilian scorpion, *Tityus serrulatus*, shown here to demonstrate the typical features of scorpions. Note the telson (stinger) located on the tail. (Used with permission of The American Museum of Natural History.)

TABLE 118–6. Envenomation Gradation for *Centruroides exilicauda* (Bark Scorpion)

Grade	Signs and Symptoms
I	Site of envenomation Pain and/or paresthesias Positive tap test (severe pain increase with touch or percussion)
II	Grade I in addition to Pain and paresthesias remote from sting site (eg, paresthesias moving up an extremity, perioral “numbness”)
III	One of the following: Somatic skeletal neuromuscular dysfunction: jerking of extremity(ies), restlessness, severe involuntary shaking and jerking, which may be mistaken for seizures Cranial nerve dysfunction: blurred vision, wandering eye movements, hypersalivation, trouble swallowing, tongue fasciculation, upper airway dysfunction, slurred speech
IV	Both cranial nerve dysfunction and somatic skeletal neuromuscular dysfunction

Pathophysiology

Components of scorpion venom are complex and species specific.^{109,181,189,190} Buthidae venom is thermostable and consists of phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins. Four neurotoxins, designated toxins I to IV, have been isolated from *C. exilicauda*. Some of the toxins target excitable membranes,^{71,85,107,159,199} especially at the neuromuscular junction, by opening sodium channels. The results are repetitive depolarization of nerves in both sympathetic and parasympathetic nervous systems causing catecholamine and acetylcholine release, respectively, and associated cardiac hypoxia, and action at the juxtaglomerular apparatus, causing increased renin secretion.^{68,189} The clinical effects of *Tityus* scorpion sting are related to elevated concentrations of interleukin (IL)-1 β , IL-6, IL-8, IL-10, kinins,⁸⁹ and tumor necrosis factor (TNF)- α , which correlate with the severity of envenomation and hyperamylasemia.^{67,90}

Clinical Manifestations

Scorpion stings produce a local reaction consisting of intense local pain, erythema, tingling or burning, and occasionally discoloration and necrosis without tissue sloughing (Table 118–6). Depending on the scorpion species involved, systemic effects may occur, including autonomic storm consisting of cholinergic and adrenergic effects. Cardiotoxic effects include myocarditis, dysrhythmias, and myocardial infarction.^{71,85,107,159,199} Electrocardiographic (ECG) abnormalities may persist for several days and include sinus tachycardia, sinus bradycardia, bizarre broad notched biphasic T-wave changes with additional ST elevation or depression in the limb and precordial leads, appearance of tiny Q waves in the limb leads consistent with an acute myocardial infarction pattern, occasional electrical alternans, and prolonged QT interval.^{107,109} Other reported effects include pancreatitis, coagulation disorders, acute respiratory distress syndrome (ARDS), massive hemoptysis, cerebral infarctions in children, seizures, and a shock syndrome that may precede but usually follows the hypertensive phase.^{24,76,85,107,108,199,209}

In the United States, *C. exilicauda* stings produce local paresthesias and pain that can be accentuated by tapping over the envenomated area (tap test) without local skin evidence of envenomation.^{62,189} Symptoms begin immediately after envenomation, progress to maximum severity in 5 hours, and may persist for up to 30 hours.^{62,189} Autonomic findings include hypertension, tachycardia, diaphoresis, emesis, and bronchoconstriction. The somatic motor symptoms reported include ataxia, muscular fasciculations, restlessness, thrashing, and opsoclonus; rarely, children require respiratory support (Table 118–6).^{68,181}

Treatment

Because most envenomations do not produce severe effects, local wound care, including tetanus prophylaxis and pain management, usually is all that is warranted. In young children or patients who manifest severe toxicity, hospitalization may be required. Treatment emphasizes support of the airway, breathing, and circulation. Corticosteroids, antihistamines, and calcium have been administered without any known benefit.⁶⁷ Continuous IV midazolam infusion is often used for *C. exilicauda* scorpion envenomation until resolution of the abnormal motor activity and agitation occurs.⁹⁴

The severity of envenomation dictates the need to use antivenom, with antivenom indicated for grade III and grade IV envenomations. (Table 118–6).⁶⁷ When an equine-derived F(ab')₂ product called Alacramyn, developed in Mexico against the *Centruroides limpidus* venom, was administered to critically ill US children with neurotoxicity from scorpion stings, there was a rapid resolution of symptoms, decreased need for sedation, and reduced concentrations of circulating unbound venom.³⁴ This antivenom was subsequently approved in the United States in 2011 and called Anascorp (Bioclon, Mexico)⁷³ (Antidotes in Depth: A35). Because the neurotoxic syndrome occurs almost exclusively in children < 10 years of age, antivenom use is most likely to be considered in children. However, intractable pain in adults not responding to reasonable doses of opioids or other systemic effects that may pose a danger to the patient or a fetus should be considered potential indications for antivenom therapy.

Atropine has been used to reverse the excessive oral secretions in *C. exilicauda* scorpion envenomation, with some success in healthy children.²¹⁸ Routine use is not recommended and should be limited to species such as *Parabuthus transvaalicus* in southern Africa,²¹⁸ whose envenomations cause a prominent cholinergic crisis. Potentiation of the adrenergic effects causing cardiopulmonary toxicity is reported.²¹ Atropine use to reverse the effects of stings from scorpions from India, South America, the Middle East, and Asia is contraindicated because these scorpions cause an “autonomic storm” with transient cholinergic stimulation followed by sustained adrenergic hyperactivity.^{20,218}

TICKS

In 1912, Todd described a progressive ascending flaccid paralysis after bites from ticks.²²⁹ Three families of ticks are recognized: (1) Ixodidae (hard ticks), (2) Argasidae (soft ticks), and (3) Nuttalliellidae (a group that has characteristics of both hard and soft ticks and not thought to be parasitic compared to ixodids and argasids). The terms hard and soft refer to a dorsal scutum or “plate” that is present in the Ixodidae but absent in the Argasidae. Both types are characteristically soft and leathery, and both have clinical importance. Ixodidae females are capable of enormous expansion up to 50 times their weight in fluid and blood.⁹³ The paralytic syndrome can be induced following envenomation during the larva, nymph, and adult stages and is related to the tick obtaining a blood meal. The following discussion focuses only on tick paralysis (TP) or tick toxicosis and not on any of the infectious diseases associated with tick bites. Most of the major tick-borne diseases in North America are transmitted by Ixodid ticks except for relapsing fever, which is spread by the soft tick of the genus *Ornithodoros* or *Pediculus humanus* (human louse).

In North America, *Dermacentor andersoni* (Rocky Mountain wood tick) and *Dermacentor variabilis* (American dog tick), and *Amblyomma americanum* (Lone Star tick) are the most commonly implicated causes of TP.^{99,229} Typically, tick toxicosis occurs in the Southeast, Rocky Mountain, and Pacific Northwest regions of the United States, but cases are also reported in the Northeast.⁷² In Australia, the *Ixodes holocyclus* or Australian marsupial tick is the most common

offender.^{99,229} I. holocyclus also seems to be the most potent of the world's paralyzing ticks and has been known to paralyze dogs, cats, sheep, mice, foals, pigs, chickens, and humans.¹⁵⁴

Pathophysiology

Venom secreted from the salivary glands during the blood meal is absorbed by the host and systemically distributed. To allow successful feeding over several days, ticks need to overcome the host's hemostatic, inflammatory, and immune mechanisms by producing anticoagulants, fibrinolytic enzymes, antiplatelet and vasodilator substances.^{140,188} The saliva also contains some cement to anchor the tick to the host, the hypostome of the I. holocyclus reaches up to 980 microns into the host's skin and does not need cement support.⁶ Paralysis results from the neurotoxin "ixobotoxin,"¹⁶⁷ which inhibits the release of acetylcholine at the neuromuscular junction and autonomic ganglia, very similar to botulinum toxin.^{102,167} Both botulinum toxin and ixobotoxin demonstrate temperature dependence in rat models and show increased muscular twitching activity as the temperature is reduced.^{64,154} The salivary toxin of I. holocyclus directly affects vascular and cardiac potassium channels by blockade, and this action differed from the respiratory distress caused by progressive muscle paralysis.¹¹ Cardiovascular function was decreased in dogs with TP. The dogs developed acute left-sided congestive heart failure and prolonged QT intervals were noted.⁵¹

Clinical Manifestations

Usually the tick must remain on the person for 5 to 6 days in order to result in systemic effects. Several days must pass before tick salivary glands begin to secrete significant quantities of toxin. Once secreted, the toxin does not act immediately and may undergo binding and internalization, in a similar sequence to botulinum toxin.^{18,64,136} Ticks typically attach to the scalp but can be found on any part of the body, including the ear canals and anus. Children, particularly girls, and adult men in tick-infested areas are predominantly affected. One large series of 305 cases in Canada reported that 21% were adults older than 16 years.²⁰⁴ Among the children, 67% were girls; in adults, 83% were male. The distribution was attributed to the difficulty of detecting ticks in long hair and the possible greater exposure of adult men to tick-infested environments. Children may appear listless, weak, ataxic, and irritable for several days before they develop an ascending paralysis that begins in the lower limbs. Fever usually is absent. Other manifestations include sensory symptoms such as paresthesias, numbness, and mild diarrhea. These symptoms are followed by absent or decreased deep-tendon reflexes and an ascending generalized weakness that can progress to bulbar structures involving speech, swallowing, and facial expression within 24 to 48 hours, as well as fixed, dilated pupils and disturbances of extraocular movements.^{102,204} Other atypical presentations are reported and include the following: a child presenting with double vision and being unable to see before the neuromuscular changes occurred, and a healthy elderly man presenting with unilateral weakness and numbness in the left arm for 2 days. Both patients fully recovered after the removal of the tick.⁷² If the tick is not removed, respiratory weakness can lead to hypoventilation, lethargy, coma, and death. Unlike the Dermacentor spp of North America, removal of the I. holocyclus tick does not result in dramatic improvement for several days to weeks. The maximal weakness may not be reached until 48 hours after the tick has been removed or drops off.¹⁰² It is imperative to closely observe patients for possible deterioration. A recent 60-year meta-analysis of TP in the United States reviewed 50 well-documented cases from 1946 to 2006 supporting the above findings.⁷⁸ The demographics were analyzed and the following remained the same: (1) TP is highly predictable regional disease found in the US Pacific Northwest (WA), the West (CA, CO), and the Southeast (GA, MS, NC, SC, VA), and very few cases occurred outside those areas; (2) TP remains a highly predictable seasonal disease occurring during the spring to summer seasons; (3) TP remains more common in females of all ages (80% female/male 4.9:1); (4) Tick attachment sites on the head and scalp continued to predominate over all other attachment sites, representing 48% of the reported attachment sites, 20% occur behind the ear; (5) The Rocky Mountain wood tick (D. Andersoni) was the only TP vector in the western United States (CA, WA, CO) when reported, and D. variabilis, the American dog tick, was the only TP vector from the southeastern United States (GA, NC) when reported.

The differential diagnosis is extensive and includes Guillain-Barré syndrome (GBS), the Miller-Fisher variant of Guillain-Barré, poliomyelitis, botulism, transverse myelitis, myasthenia gravis, periodic paralysis, elapid snakebites, marine neurotoxin poisoning, acute cerebellar ataxia, and spinal cord lesions. The cerebrospinal fluid remains normal, and the rate of progression is rapid, unlike GBS and poliomyelitis.^{78,84,201} The edrophonium test is negative. Nerve conduction studies in patients with TP may resemble those of patients with early stages of GBS: findings in both conditions include prolonged latency of the distal motor nerves, diminished nerve conduction velocity, and reduction in the amplitudes of muscle and sensory-nerve action potentials.⁸⁴ With GBS, there is a prolongation of the F wave, however, which does not occur with TP, reflecting the more proximal demyelination of the nerve root.¹⁰⁴ The other causes for acute ascending flaccid paralysis should be eliminated by a complete history, including environmental exposure, hobbies, workplace, travel, ingestions, obtaining appropriate laboratory testing, psychiatric evaluations if needed, and of course a thorough physical examination.

Treatment

Other than removal of the entire tick, which is curative, treatment is entirely supportive. Proper removal of the tick is very important, otherwise infection or incomplete tick removal may occur. The tick should be grasped as close to the skin surface as possible with blunt curved forceps, tweezers, or gloved hands. Steady pressure without crushing the body should be used; otherwise, expressed fluid may infect the patient and lead to inoculating the patient with a higher dose of toxin or infectious agent. After tick removal, the site should be disinfected. Traditional methods of tick removal using petroleum jelly, topical lidocaine, fingernail polish, isopropyl alcohol, or a hot match head are ineffective and may induce the tick to salivate or regurgitate into the wound.¹⁷⁰ It should be remembered that the very same vectors responsible for tick toxicosis can also cause infectious illnesses such as babesiosis, Rocky Mountain spotted fever, anaplasmosis, tularemia, Colorado tick fever, tick-borne relapsing fever, and Lyme disease. Since *I. holocyclus* of Australia is considerably more toxic and patients are more likely to deteriorate before they improve, close observation is required for several days until improvement is certain.⁸⁴ A hyperimmune serum prepared from dogs is the usual treatment for paralyzed animals, but it has been used sparingly in severely ill humans because of the risk of acute reactions and serum sickness.⁸⁴

HYMENOPTERA: BEES, WASPS, HORNETS, YELLOW JACKETS, AND ANTS

Within the order Hymenoptera are three families of clinical significance: Apidae (honeybees and bumblebees), Vespidae (yellowjackets, hornets, and wasps), and Formicidae (ants, specifically fire ants). These insects (Fig. 118–6) are of great medical importance because their stings are the most commonly reported and can cause acute toxic and fatal allergic reactions. In the 1960s and 1970s, an estimated 40 deaths per year were attributed to anaphylaxis secondary to hymenoptera stings in the United States.^{17,208} However, from 2008 to 2011 there have been only two deaths related to envenomations from bees, wasps, and hornets reported to the National Data Poisons System, probably due to increased public awareness of allergic reactions and easier access to medical care.^{37,38,39,41}

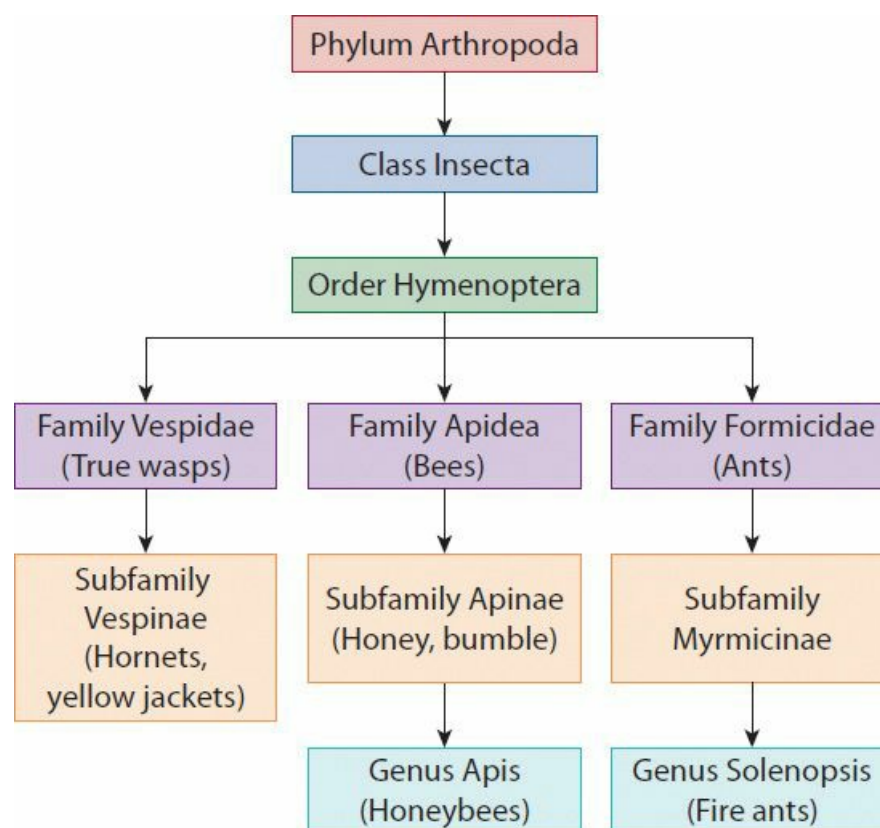


FIGURE 118-6 Taxonomy of the order Hymenoptera.

Apis and *Bombus* species (honeybees and bumblebees) generally build nests away from humans and are passive unless disturbed, but nests of both the honeybees and bumblebees have been found in walls and rodent burrows near homes. Honeybee workers can only sting once because their stinger is a modified ovipositor that resides in the abdomen and its shaft is barbed and has a venom sac attached. Once the stinger embeds into the skin, the stinger disembowels the bee. Bumblebees, however, can sting multiple times. Vespids, on the other hand, are more aggressive and build nests in human living areas, such as in trees and under awnings; yellow jackets inhabit shrubs, trees, and the ground. They, too, are able to sting multiple times.⁹⁶ The introduction of the Africanized honeybee in Brazil (because originally they were thought to be a

more efficient honey producer) has caused significant economic and health issues. The bees have migrated toward the southern border of the United States and pose a greater threat to humans. Africanized honeybees are characterized by large populations, can make nonstop flights of at least 20 km, and have a tendency toward mass attack with little provocation.¹⁶⁴

Pathophysiology

Several allergens (Table 118–7) and pharmacologically active compounds are found in honeybee venom. The three major venom proteins are found in the honeybee: melittin, phospholipase A₂, and hyaluronidase.¹⁴⁹ Other proteins include apamin, acid phosphatase, and other unidentified proteins. Phospholipase A₂ is the major antigen/allergen in bee venom.³²

TABLE 118–7. Composition of Hymenoptera Venom

<i>Vespid (Wasps, Hornets, Yellow Jackets)</i>	<i>Apids (Honeybees)</i>	<i>Formicids (Fire Ants)</i>
Biogenic amines (diverse)	Biogenic amines (diverse)	Biogenic amines (diverse)
Phospholipase A, phospholipase B	Phospholipase A, phospholipase B (?)	Phospholipase A
Hyaluronidase	Hyaluronidase	Hyaluronidase
Acid phosphatase	Acid phosphatase	Piperidines
Mast cell degranulating peptide	Minimine	
Kinin	Mellitin	
	Apamin	
	Mast cell degranulating peptide	

Melittin is the principal component of honeybee venom. It acts as a detergent to disrupt the cell membrane and liberate potassium and biogenic amines.¹⁴ Histamine release by bee venom appears to be largely mediated by mast cell degranulation peptide. Apamin is a neurotoxin that acts on the spinal cord. Apamin binds to the Ca⁺²-triggered K⁺ channel and depresses delayed hyperpolarization to cause its toxicity, which is seen in the mouse model as uncoordinated movements leading to spasms, jerks, and convulsions of a spinal origin.¹¹² Adolapin inhibits prostaglandin synthase and has antiinflammatory properties that may account for its use in arthritic therapy.²⁰⁶ Phospholipase A₂ and hyaluronidase are the chief enzymes in bee venom.

The three major proteins in vespid venoms serve as allergens and are accompanied by a wide array of vasoactive peptides and amines.¹⁴⁹ The intense pain following vespid stings is largely caused by serotonin, acetylcholine, and wasp kinins. Antigen 5 is the major allergen in vespid venom.¹⁶⁵ Its biologic function is unknown. Mastoparans have action similar to mast cell degranulation peptide, but weaker.¹⁴ Phospholipase A₂ may be responsible for inducing coagulation abnormalities.¹⁷⁵

Clinical Manifestations

Normally, the honeybee sting is manifested as immediate pain, a wheal-and-flare reaction, and localized edema without a systemic reaction. Vomiting, diarrhea, and syncope can occur with a higher dose of venom resulting from multiple stings.³⁵ Rarely, a sting in the oropharynx produces airway compromise.²⁰⁸

Toxic reactions occur with multiple stings (more than 500 stings are described as possibly fatal and occur with Africanized honeybees)⁹⁶ and include gastrointestinal (GI) symptoms, headache, fever, syncope and, rarely, rhabdomyolysis, acute kidney injury, and seizures.³⁵ Other rare complications include idiopathic intracranial hypertension,²²⁶ cerebral infarction, and ischemic optic neuropathy²⁰³ and Parkinsonism¹⁴⁸ and are thought to occur because of the proximity of the sting near the head and neck. Bronchospasm and urticaria are typically absent.

This type of toxic reaction is different from the hypersensitivity reactions or anaphylactic reactions because it is not an IgE-mediated response, but rather a direct effect from the venom itself. Hypersensitivity reactions, including anaphylaxis, occur from Hymenoptera stings. These reactions are IgE mediated. The IgE antibodies attach to tissue mast cells and basophils in individuals who have been previously sensitized to the venom. These cells are activated, allowing for progression of the cascade reaction of increased vasoactive substances, such as leukotrienes, eosinophil chemotactic factor-A, and histamine. An anaphylactic reaction is not dependent on the number of stings. Patients who are allergic to hymenoptera venom develop a wheal-and-flare reaction at the site of the inoculum. The shorter the interval between the

sting and symptom onset, the more likely the reaction will be severe. Fatalities can occur within several minutes; even initially mild symptoms may be followed by a fulminant course. Generalized urticaria, throat and chest tightness, stridor, fever, chills, and cardiovascular collapse can ensue.

Treatment

Application of ice at the site usually is sufficient to halt discomfort. Stingers from honeybees should be removed by scraping with a credit card or scalpel, as opposed to pulling, which may release additional retained venom. Since the stinger in other bee species typically stays within the insect, this removal technique would not be necessary if other bee species are involved. Therapy is aimed at supportive care that includes standard therapy for anaphylaxis with epinephrine, diphenhydramine, and corticosteroids.

FIRE ANTS

There are native fire ants in the United States, but the imported fire ants *Solenopsis invicta* and *Solenopsis richteri* are significant pests that have no natural enemies. They are native to Brazil, Paraguay, Uruguay, and Argentina but were introduced into Alabama in the 1930s. They have spread rapidly throughout the southern United States, damaging crops, reducing biologic diversity, and inflicting severe stings to humans.²²⁴ *S. invicta*, the most aggressive species, now infests 13 southern states and has been introduced into Australia.^{210,213} Allergic reactions to ant stings were limited to the jumper ant (*Myrmecia pilosula*, other *Myrmecia* spp) and the greenhead ant (*Rhytidoponera metallica*; *Odontomachus*, *Cerapachys*, and *Brachyponera* spp) in Australia until February 2001, when the imported red fire ant was identified at two sites in Brisbane.²¹⁰ The mode of introduction is unknown but may have originated from the transport of infested cargo. Fire ants range from 2 to 6 mm in size. They live in grassy areas, garden sites, and near sources of water. The nests are largely subterranean and have large, conspicuous, dome-shaped above-ground mounds (up to 45 cm above the ground), with many openings for traffic. The mounds can contain 80,000 to 250,000 workers and one or more queens that live for 2 to 6 years and produce 1500 eggs daily.²³⁵ Fire ants are named for the burning pain inflicted after exposure, and necrosis can result at the site. The imported fire ant attacks with little warning. By firmly grasping the skin with their mandibles, both the fire ant and the jumper ant can repeatedly inject venom from a retractile stinger at the end of the abdomen. Pivoting at the head, the fire ant injects an average of seven or eight stings in a circular pattern.²¹³

Pathophysiology

The venom inhibits sodium and potassium adenosine triphosphatases, reduces mitochondrial respiration, uncouples oxidative phosphorylation, adversely affects neutrophil and platelet function, inhibits nitric oxide synthetase, and perhaps activates coagulation.^{133,135} Unlike the venoms of wasps, bees, and hornets that contain mostly aqueous-containing proteins, the imported fire ant venom is 95% alkaloid, with a small aqueous fraction that contains soluble proteins.¹⁵² Of the alkaloids, 99% is a 2,6-disubstituted piperidine that has hemolytic, antibacterial, insecticidal, and cytotoxic properties.⁷⁴ There is also some in vivo evidence that the Solenopsin alkaloids can inhibit nitric oxide synthetase activity and has direct cardiotoxic, convulsant, and respiratory depressant activities.^{123,243} These alkaloids do not cause allergic reactions, but they produce a pustule and pain. The aqueous portion of the venom contains the allergenic activity of fire ant venom, Sol i I to IV.^{116,213} The proteins identified in the venom include a phospholipase, a hyaluronidase, and the enzyme N-acetyl- β -glucosaminidase.^{75,213}

Clinical Manifestations

In the United States, residents of health care facilities who are immobile or cognitively impaired are at risk for fire ant attacks, especially when the facility lacks pest control techniques for fire ants.⁷⁵ Three categories are suggested based on the reactions to the imported fire ant: local, large local, and systemic.²¹³ Local reactions occur in nonallergic individuals. Large local reactions are defined as painful, pruritic swelling at least 5 cm in diameter and contiguous with the sting site. Systemic reactions involve signs and symptoms remote from the sting site. The sting initially forms a wheal that is described as a burning itch at the site, followed by the development of sterile pustules. In 24 hours, the pustules umbilicate on an erythematous base. Pustules may last 1 to 2 weeks.⁹⁶ Late cutaneous allergic reactions can occur in some persons who experience indurated pruritic lumps at the site of subsequent stings.⁷⁴ Large reactions may lead to tissue edema sufficient to compromise blood flow to an extremity. Anaphylaxis occurs in 0.6% to 6% of persons who have been stung.²¹³ Often, healing occurs with scarring in 10 to 14 days.

The majority of individuals who die after fire ant attacks succumbed to heart failure.⁷⁵ These individuals came from nursing homes primarily; however, the solenopsins were found to strongly inhibit myocardial contractility which might explain the heart failure that occurred after massive envenomations.^{75,123}

Diagnosis

Clinical clues such as pustule development at the sting site after 24 hours, species identification, and history may help to identify fire ant exposure. No laboratory assays to determine exposure are available. Fire ant allergy can be determined by correlating the clinical manifestation of fire ant sting reactions with imported fire ant–specific IgE determined by skin testing or radioallergosorbent test.

Treatment

Local reactions require cold compresses and cleansing with soap and water. Some authors recommend topical or injected lidocaine with or without 1:100,000 epinephrine, and topical vinegar and salt mixtures to decrease pain at the site of the bite and sting.^{43,120,157,193}

Large local reactions can be treated with oral corticosteroids, antihistamines, and analgesics. Secondary infections should be treated with antibiotics. Systemic reactions should be treated with subcutaneous or intravenous epinephrine

BUTTERFLIES, MOTHS, AND CATERPILLARS

Butterflies and moths are insects of the order Lepidoptera. Several moth and butterfly families have species whose caterpillars are clinically important, that is, they contain spines or urticating hairs that secrete a poison that is irritating to humans on contact. Lepidopterism is a general term that describes the systemic adverse effects such as generalized urticaria, headache, pharyngitis, conjunctivitis, nausea, vomiting, bronchospasm, wheezing, and dyspnea that occur when humans are exposed to moths and butterflies.¹⁶⁶ Erucism is the term used when a cutaneous dermatitis results from contact with urticating caterpillars, the larval forms of the insect order Lepidoptera (moths and butterflies).⁷⁹ Caterpillar species from about 12 families of moths and rarely butterflies worldwide can inflict serious human injuries, including urticarial dermatitis, allergic reactions, consumptive coagulopathy, acute kidney injury, intracerebral hemorrhage, arthritis, joint deformity, and even altered mental status, ataxia, and dysarthria.^{79,122}

Caterpillar, which means hairy cat in Latin, is the larval stage for moths and butterflies. In the United States, several significant stinging caterpillars are of note. Often the puss caterpillar (*Megalopyge opercularis*) is considered one of the most important and toxic of the caterpillars in the United States because of the frequency with which reactions have been reported, especially in Texas.²¹⁵ Other names for the puss caterpillar are woolly/hairy worm, wooly slug, opossum bug, tree asp, Italian asp, and “el perrito” in Spanish.²¹⁵ The caterpillars look furry and are covered in silky tan to brownish hairs that hide short spines containing an urticarial toxin. The spines are yellowish with black tips, and the hairs vary in color ranging from pale yellow and gray to brown.²⁹ Other significant stinging caterpillars in the United States are the flannel moth caterpillar (*Megalopyge crispata*), the Io moth (*Automeris io*), the saddleback caterpillar (*Sibine stimolata*), and the hickory tussock caterpillar (*Lophocampa caryae*).¹⁴⁷ In South America, especially Brazil, *Lonomia obliqua* caterpillars are notorious for causing severe pain and a hemorrhagic syndrome.^{52,69} In Australia, several caterpillars are of medical importance: mistletoe brown tail moth (*Euproctis edwardsi*), processionary caterpillars (*Ochrogaster lunifer*), cup moths (*Doratifera* spp), and the white-stemmed gum moth (*Chelepteryx collesi*).¹³ Pine processionary caterpillars (*Thaumetopoea pityocampa*) are the most important defoliator of pine forests in the Mediterranean and central European countries, with significant consequential economic and occupational repercussions for workers who frequent these pine forests.²³⁰ In Nigeria, the *Anaphe venata* caterpillar is an important resource for protein that can cause thiamine deficiency syndrome similar to dry beriberi. Finally, the dendrolimus caterpillars of China and the *Preolis semirufa* caterpillars in Brazil cause significant joint disease.

Pathophysiology

The pathophysiology of dendrolimiasis is not understood, but the tegument-produced venom contains formaldehyde and several uncharacterized histamine analogs with a tropism for receptors in bone, joints, and cartilage and during the acute phase may result from IgE-mediated allergy to foreign proteins, and the chronic bone and joint disease may be autoimmune mediated.¹²⁵ The composition of the venom varies according to the different caterpillar species. Some toxins contain proteins that cause histamine release, such as thaumetopoein isolated from *T. pityocampa* or pine processionary caterpillar.^{230,231} Another protein isolated from the *L. obliqua* caterpillar causes coagulopathy. It is called lonomin V and is a proteolytic enzyme, which is isolated in the hairs, spines, and hemolymph of the *L. achelous*.¹¹¹ Its mechanism of action is not fully known, but it somehow activates factors X and II, and there is some evidence that collagen degradation might be responsible for platelet inhibition.^{80,110,138} The venom and hair structure of *Lagoa crispata*, which has often been confused with the southern Texas puss caterpillar, has been characterized.¹⁴⁷ The venom is stored at the base of the hollow setae (spines) where the poison sac and nervous tissue are located. Upon contact with these spines, the toxin is released. The toxin may be a protein or a substance that conjugates with proteins.⁸⁷ The varying differences of caterpillar venom and their

clinical effects emphasize the importance of positive identification of caterpillars.

Clinical Manifestations

The pathophysiologic effects of venomous caterpillar exposures can be classified into seven distinct clinical syndromes to guide clinicians in making earlier, more species-specific diagnoses to direct therapies, including: (1) erucism, (2) lepidopterism, (3) dendrolimiasis, (4) ophthalmia nodosa, (5) consumptive coagulopathy with secondary fibrinolysis,⁷⁹ (6) seasonal ataxia, and (7) paramorse.¹²² Erucism is the preferred term for caterpillar dermatitis caused by contact with caterpillar urticating hairs, spines, or toxic hemolymph. Lepidopterism is a systemic illness caused by a constellation of adverse effects resulting from direct or aerosol contact with caterpillar, cocoon, or moth urticating hairs, spines or body fluids and is characterized by generalized urticaria, headache, conjunctivitis, pharyngitis, nausea, vomiting, bronchospasm, wheezing, and, rarely, dyspnea. Dendrolimiasis is a chronic form of lepidopterism caused by direct contact with urticating hairs, spines, or hemolymph of living or dead central Asian pine-tree lappet moth caterpillars or their cocoons and is characterized by urticating maculopapular dermatitis, migratory inflammatory polyarthritis, migratory inflammatory polychondritis, chronic osteoarthritis, and, rarely, acute scleritis.¹²⁵ Ophthalmia nodosa is a chronic ocular condition characterized by initial conjunctivitis with subsequent panuveitis caused by corneal penetration and subsequent intraocular migration of urticating hairs from lymantriid caterpillars and moths and therapsid spiders (tarantulas).

The South American *Lonomia saturniid* moth caterpillars range from Venezuela to northern Argentina and pose a threat in Brazil due to the high fatality rates from venom-induced consumptive coagulopathy, intracerebral hemorrhage, and acute renal failure, possibly due to a combination of venom nephrotoxicity and microcirculatory fibrin deposition.⁴⁶ The hemorrhagic syndrome can present as a disseminating intravascular coagulopathy and as a secondary fibrinolysis with skin, mucosal, and visceral bleeding, acute kidney injury, and intracerebral hemorrhage.^{52,138}

Seasonal ataxia is a syndrome of unsteady gait and dysarthria, which occurs after the ingestion of the caterpillar of *Anaphe venata*. This occurs in areas of Nigeria where they are a source of protein.^{3,4} Ingestion of the roasted larvae causes nausea and vomiting and progresses to dizziness, ataxia, and unsteady gait in more than 90% of victims. These symptoms may take weeks to months for resolution. Dysarthria and impaired consciousness have also been reported. The pathogenesis is related to thiamine deficiency induced by the caterpillars.

Paramorse is similar to dendrolimiasis with pruritic or painful dermatitis associated with arthritis and joint deformity, arising from contact with the caterpillar of *Premolis semirufa*, which are found in the Brazilian Amazon rain forests. Rubber tree plantation workers are particularly at risk even when wearing protective gloves.^{66,77}

The clinical effects of caterpillar exposure can generally be separated into two types—stinging reaction and pruritic reaction—although overlap may occur. Stinging caterpillars, such as *M. opercularis*, envenomate by contact with their hollow spines containing venom. The reaction is characterized as a painful, burning sensation with local effects and, less commonly, systemic effects. The area may become erythematous and swollen, and papules and vesicles may appear. The classic gridlike pattern develops within 2 to 3 hours of contact. Reported symptoms include nausea, vomiting, fever, headache, restlessness, tachycardia, hypotension, urticaria, seizures, and even radiating lymphadenitis and regional adenopathy.¹⁷⁷ Pruritic reactions occur upon exposure to the itchy caterpillars that have nonvenomous urticating hairs, which can produce a mechanical irritation, allergic reaction, or a granulomatous reaction from the chronic presence of the hairs. Several species that cause allergic reactions are the white-stemmed moth (*C. collesi*), Douglas fir tussock moth (*Orgyia pseudotsugata*), and gypsy moth caterpillar (*Lymantria dispar*).¹⁶⁶ Caterpillar hairs can cause ocular trauma, otherwise known as ophthalmia nodosa.²¹² The range of ocular pathology depends on the penetration factor and the effect of the released urticating toxins.⁵⁰ The ocular spectrum has been classified into five types.⁵⁰

Type 1: Brief exposure time of 15 minutes. Symptoms of chemosis, inflammation, epiphora, and foreign body sensation may last for weeks.

Type 2: Chronic mechanical keratoconjunctivitis (hairs in bulbar/palpebral conjunctivitis). Foreign body sensation is relieved by removal of hairs. Corneal abrasions may be present.

Type 3: Gray-yellow nodules or asymptomatic granulomas.

Type 4: Severe iritis with or without iritis nodules; hairs are in the anterior chamber and possible intralenticular foreign body.

Type 5: Vitreoretinal involvement. Hairs may enter through the anterior chamber or iris lens or by transscleral migration. May cause vitreitis, cystoid macular edema, papillitis, or endophthalmitis.

Treatment

Management for most dermal caterpillar envenomations is entirely supportive and includes washing the area with soap and water; “no touch” drying of the sting site with a hair dryer; gentle stripping of the bite site with cellophane or adhesive duct

tape; and application of ice packs with cooling enhanced by initial topical swabbing with isopropyl alcohol. Rings should be removed in anticipation for potential swelling of the extremity, and tetanus prophylaxis should be updated accordingly.⁷⁹

Treatment of ocular lesions depends upon the exposure classification and should be managed by the ophthalmologist. Most patients can be classified as type 1 or 2. Irrigation with 0.9% sodium chloride solution should be followed by meticulous removal of setae, followed by topical steroids and antibiotics. Type 3 requires surgical excision of the nodules. Type 4 requires topical steroids with or without iridectomy for nodules or operative removal of setae. Type 5 requires local treatment with or without systemic steroids. Resistant cases may require vitrectomy with removal of setae.

Opioids may be necessary, if minor analgesics do not provide relief. If muscle cramps develop, benzodiazepines should be administered. One study recommended the use of 10 mL 10% calcium gluconate administered IV, which provided pain relief.¹⁶⁰ Topical corticosteroids can be used to decrease local inflammation. Antihistamines such as diphenhydramine (25–50 mg for adults and 1 mg/kg, maximum 50 mg, in children) can be used to relieve pruritus and urticaria.^{160,177} Nebulized β -agonists and epinephrine administered subcutaneously may be required for more severe respiratory symptoms and anaphylactoid/anaphylactic-type reactions. Dendrolimiasis treatment consists of mostly supportive care with early surgical intervention recommended to excise draining sinus tracts and infected cartilage and to prevent permanent bone and joint deformities.¹²⁵ For hemorrhagic syndrome resulting from exposure to *L. obliqua* caterpillar, besides restoration of clotting factors, platelet, and cryoprecipitate infusions, an antidote called the antilonomic serum (SALon) is available and is used for treatment of the hemorrhagic syndrome in Brazil.⁶⁹ It is important to involve an experienced hematologist for suspected *Lonomia* envenomation and very important to distinguish *Lonomia obliqua* from *Lonomia achelous* because the cryoprecipitate, purified fibrinogen, and antifibrinolytic drugs, such as aprotinin and ϵ -aminocaproic acid, have been successfully used in *Lonomia achelous* but may exacerbate the hemorrhagic symptoms in *Lonomia obliqua* with fatal consequences.^{59,98} Patients exposed to either species should neither receive whole blood nor fresh plasma or they may worsen clinical symptoms. Treatment for the seasonal ataxia includes supportive care with the administration of thiamine 100 mg orally every 8 hours, which found reversal of symptoms within 48 hours without long term sequelae in a double blinded placebo controlled trial.²

BLISTER BEETLES

Blister beetles are plant-eating insects that exude a blistering agent for protection. They can be found in the eastern United States, southern Europe, Africa, and Asia. Most are from the order Coleoptera, family Meloidae. *Epicauta vittata* is the most common of more than 200 blister beetles identified in the United States.¹³⁷ When the beetles sense danger, they exude cantharidin by filling their breathing tubes with air, closing their breathing pores, and building up body fluid pressure until fluid is pushed out through one or more leg joints.⁹⁶ Cantharidin is a potent blistering agent found throughout all 10 stages of life of the blister beetle.⁵⁴ Cantharidin is produced only by the male blister beetle and is stored until mating. In the wild, the female repeatedly acquires cantharidin as copulatory gifts from her mates. However, the female blister beetle loses most of her reserves as she matures.⁵⁴ Cantharidin, also known popularly as Spanish fly, takes its name from the Mediterranean beetle *Cantharis vesicatoria*. It has been ingested as a sexual stimulant for millennia. The aphrodisiac properties are related to the ability of cantharidin to cause vascular engorgement and inflammation of the genitourinary tract upon elimination, hence the reports of priapism and pelvic organ engorgement.²²⁸ Cantharidin was once used for treatment of bladder and kidney infections, stones, stranguria (bladder spasm), and various venereal diseases.¹³⁷ In the last century, cantharidin was commonly used for treatment of pleurisy, pneumonia, arthritis, neuralgias, and various dermatitides. A topical 1% commercial preparation can be used for removal of warts and molluscum contagiosum.^{65,205} Cantharidin poisoning is reported by cutaneous exposure,⁴² unintentional inoculation,¹⁸⁰ and inadvertent ingestion of the beetle itself.²²⁵ There is one case report of a child being treated for molluscum contagiosum with cantharidin preparation that included podophyllin and salicylic acid, also called Canthacur PS or Canthacur Plus.²⁰⁵ The child developed varicelliform vesicular dermatitis in the distribution of the application of petrolatum. It is thought that the petrolatum used by the parents to moisturize her skin spread the lipophillic cantharidin preparation to the nearby areas causing the blistering reaction. Canthacur PS should not be used for molluscum contagiosum but is reserved for verrucae vulgaris on acral areas. Canthacur or Cantharone contains plain cantharidin and can be used for the treatment of molluscum contagiosum. Fewer than 30 cases of Spanish fly poisoning have been reported since 1900.¹³⁷

Pathophysiology

Cantharidin is a natural, defensive, highly toxic terpenoid (lethal dose for humans 0.5 mg/kg) produced by blister beetles and shares a structural similarity with the herbicide Endothall.¹⁴⁹ Endothall causes corrosive effects to the GI tract; cardiomyopathy and vascular permeability lead to shock. A single case report of lethal poisoning with 7 to 8 g of endothall has been reported, and the healthy young male died of hemorrhage of the GI tract and lung, which is clinically similar to the cantharidin exposures. Although the mechanism of action has not been elucidated, one mechanism based on an in vitro study

suggests that cantharidin inhibits the activity of protein phosphatases type 1 and 2A. This inhibition alters endothelial permeability by enhancing the phosphorylation state of endothelial regulatory proteins and results in elevated albumin flux and dysfunction of the barrier.¹⁴³ Enhanced permeability of albumin may be responsible for the systemic effects of cantharidin, which lead to diffuse injury of the vascular endothelium and resultant blistering, hemorrhage, and inflammation.

Clinical Manifestations

The clinical effects can mostly be attributed to the irritative effects on the exposed organ systems. The secretions of cantharidin from the beetle's leg joints cause an urticarial dermatitis that is manifested several hours later by burns, blisters, or vesiculobullae.⁴² Symptoms may be immediate or delayed over several hours. In addition to the local effects, cantharidin can be absorbed through the lipid bilayer of the epidermis and cause systemic toxicity, with diaphoresis, tachycardia, hematuria, and oliguria from extensive dermal exposure.²²⁸ If the periorbital region is contaminated, edema and blistering can evolve. Ocular findings from direct contact with the beetle or hand contamination include decreased vision, pain, lacrimation, corneal ulcerations, filamentary keratitis, and anterior uveitis.¹⁸⁰ Most human exposures involve inadvertent contact with the beetle or its secretions, resulting in dermatitis, keratoconjunctivitis, and periorbital edema secondary to hand-eye involvement, also called the Nairobi eye.¹⁸⁰

When cantharidin is ingested, severe GI disturbances and hematuria can occur. Initial patient complaints may include burning of the oropharynx, dysphagia, abdominal cramping, vomiting, hematemesis followed by lower GI tract hematochezia, and tenesmus. An inadvertent blister beetle ingestion by a child who thought it was the edible *Eulepida mashona* or white grub resulted in hematuria and abdominal cramping.²²⁵ Genitourinary effects include dysuria, urinary frequency, hematuria, proteinuria, and renal impairment. Most symptoms resolved over several weeks. However, death from renal failure with acute tubular necrosis is reported.²²⁸

Diagnostic Testing

Cantharidin toxicosis has been identified for equine and ruminant exposures by screening urine and gastric contents with high-performance liquid chromatography and gas chromatography-mass spectrometry.^{184,185} This method has not been used in clinical practice.

Treatment

Treatment is largely supportive. Wound care and tetanus status should be assessed. For keratoconjunctivitis, an ophthalmologist should be consulted early in the clinical course and the patient treated with topical corticosteroids (prednisolone 0.125%), mydriatics (cyclopentolate 1%), and antibiotics (ciprofloxacin 0.3%).

SUMMARY

- Health care providers should have an extensive knowledge regarding the identification of arthropods and their bites and stings so they can provide optimal care to their patients.
- Black widow: Lactrodectism is a painful neurotoxic condition best known for causing intense muscle spasms associated with short term autonomic and central nervous system dysfunction.
- Brown recluse: Loxoscelism is manifested by necrotic tissue loss, which is less often accompanied by systemic reactions such as hemolysis, coagulopathy, renal failure, and death.
- Scorpions: Envenomation releases a neurotoxin that opens the sodium channels to cause an array of effects the envenomation leads to local as well as systemic effects that activate the sympathetic and parasympathetic branches of the nervous system leading to intense pain, edema, and erythema as well as severe hypertension and tachy- or brady-dysrhythmias.
- Ticks: Ticks are vectors that are commonly known to transmit disease but in the setting of envenomations, one must remember tick toxicosis in the differential as a cause of progressive ascending flaccid paralysis that can be fatal if the tick is not removed.
- Caterpillars: Lepidopterism is another cause of common human envenomations that typically cause dermal and ocular symptoms.

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A34 ANTIDOTES IN DEPTH

Antivenom: Spider

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INTRODUCTION

The terms “antivenom” and “antivenin” often are used interchangeably. Although the origin of the term “antivenom” is obvious, “venin” is French for venom and “antivenin” is traditionally used in certain parts of the world. Wyeth Pharmaceuticals, the maker of Crotaline and Micrurus antivenom, and Merck & Co., Inc., the maker of Latrodectus antivenom, adopted “antivenin” in the brand names for their products. Brand name recognition has largely been responsible for the use of the term “antivenin” in place of “antivenom”. In 1981, the World Health Organization determined the preferred terms for the English language to be “venom” and “antivenom.”

HISTORY

Of the species of spiders of medical importance in the United States, two of the most notable are Latrodectus (*L. mactans*, *L. geometricus*, *L. vaiolus*, *L. hesperus*, and *L. bihopi* are native, while *L. geometricus* was introduced) and Loxosceles. Although commercially available antivenom exists in the United States for treatment of Loxosceles envenomation, antivenom produced for South American Loxosceles spiders demonstrates cross-reactivity with North American species like *L. reclusa*.¹² Currently, one commercially available Latrodectus antivenom exists in the United States. Black widow spider antivenin (Merck & Co., Inc.) (Merck BW-AV) has been available in the United States since its U.S. Food and Drug Administration (FDA) approval in 1936.³ The use of this antivenom in the treatment of Latrodectus envenomations remains controversial, as mortality from these bites is low in the United States,^{7,8,30,32} and complications including death following antivenom administration are rarely reported.^{7,20,31} Most recently, severe production shortages have necessitated emergency release of the product by the manufacturer within 24 hours of notification of a patient with symptoms from a presumed envenomation.¹ Ongoing research and development of an F(ab')₂ antivenom may ameliorate concerns and limitations related to potential adverse events resulting from administration of the Merck antivenom and production shortages limiting availability.¹¹

PHARMACOLOGY

Chemistry, Preparation, and Mechanism of Action

Antivenom for spiders is prepared in a similar manner as other antivenom products by first immunizing animals with non-toxic amounts of venom.^{5,25} Monkeys, horses, goats, sheep, chicken, camels, and rabbits have been used historically to source antivenom.²⁸ The animals are placed on an inoculation schedule to allow gradual production of immunoglobulins, most importantly IgG. Sufficient antibody production usually requires up to 6 weeks. Animal choice for immune serum production is more often dictated by the species availability, financial considerations, and tradition rather than scientific modeling. Horses are used by the majority of antivenom producers, since they are relatively easy to maintain, and large volumes of serum can be obtained at one time without harm. Varying efforts are made during antivenom production to remove animal proteins such as albumin. Antivenoms target, bind, neutralize, and promote elimination or redistribution of toxins from body tissues. To date, no studies have compared immune sera of different animals for human compatibility or tolerance.

The antidotal fraction of an antivenom exists as either whole IgG, Fab, or F(ab')₂. The IgG molecule is composed of two antigen-binding fragments (Fab fragments) that are fused together and attached to the larger complement binding fragment (Fc fragment). It is the larger Fc portion that is generally considered to be the most responsible for immune mediated reactions. Digestion of the disulfide bonds of an IgG molecule with the enzyme pepsin will cleave the Fc fragment, allowing isolation of pure F(ab')₂ fragments (two fused Fab fragments). In contrast, digestion with papain cleaves

the molecule more distally such that a larger Fc portion is removed from two separate Fab fragments. Both Fab and F(ab')₂ molecules can be isolated with affinity chromatography, and the highly antigenic Fc portion discarded. Although Fab and F(ab')₂ are more expensive to produce than their whole immunoglobulin counterparts, they are generally regarded as less allergenic and therefore safer products.

Whole IgG antivenom is the easiest and least expensive to produce. It has a molecular weight of approximately 150 kDa, and is the largest of the three antivenom types. Because of its size, it is the least filterable at the glomerulus and has the smallest volume of distribution. IgG has a longer elimination half-life than either Fab or F(ab')₂.¹⁷

F(ab')₂ has an intermediate size (~100 kDa) and elimination half-life. While lowering the risk of anaphylaxis compared to whole IgG, the F(ab')₂ portion retains much of the allosteric configuration of the original IgG molecule that is lost in when Fab are formed. This configuration theoretically allows for tighter binding to venom. Fab is the smallest (~50 kDa) antivenom molecule in size and is eliminated by the kidneys. It has the largest volume of distribution and a greater ability to reach extravascular compartments. Arachnid venoms that affect the central nervous system have low molecular weights and large volumes of distribution. Fab and F(ab')₂ based antivenoms may therefore be best suited for this function.¹⁷

Immunoglobulin based antivenoms can be given by the intramuscular (IM), intravenous, or subcutaneous route. Intravenous administration achieves rapid peak serum concentrations, and the infusion can be stopped in the event of an allergic reaction.¹⁸ Intramuscular injection has been used when intravenous access is unobtainable.

Pharmacokinetics and Pharmacodynamics

Currently, there is no published pharmacokinetic or pharmacodynamic information available on Merck BW-AV in humans or animals. Graudins and colleagues demonstrated western blot binding of *L. hasselti* (Red Back Spider) Antivenom (RBS-AV) to purified α -latrotoxin and similar protein bands derived from multiple widow spiders (*L. mactans*, *L. hesperus*, *L. lugubris*, *L. tredecimguttatus*, and *L. hasselti*). When co-mixed with the venoms from these species prior to administration, RBS-AV prevented the development of a reproducible and rapid muscle contracture of an in vitro chicken nerve-muscle preparation. A dose-response relationship was observed with varying doses of RBS-AV administration.¹⁶ This confirms a direct in vitro binding effect of RBS-AV against widow spider venoms.

Previous animal studies have demonstrated that intramuscular administration of antivenom demonstrated very low serum venom concentrations.^{35,36} In these rabbit studies of intramuscular administration, F(ab')₂ and IgG had poor bioavailability (36%–42%) and delayed time to peak concentrations of 48 to 96 hours.

Pharmacokinetic and pharmacodynamic characteristics of equine derived antivenoms may differ between species studied. Equine derived antivenom maximum concentrations were greater in cows than in horses, and steady state distribution volumes were higher in cows than in horses in one study. Similar results were observed in rabbit models.³⁷ Pharmacokinetic and pharmacodynamic parameters observed in animal models should therefore be interpreted with caution with regard to behavior of antivenoms in humans.

RBS-AV has been administered intramuscularly to treat human envenomations and clinical effectiveness equivalent to intravenous administration was previously reported.²¹ Subsequent studies, however, demonstrated the absence of RBS-AV in circulating serum up to 5 hours following intramuscular administration. Serum concentrations of RBS-AV were detected within 30 minutes of administration following intravenous administration.²⁴ These results are consistent with animal studies demonstrating little if any effect on circulating venom when antivenoms are given intramuscularly. Additional studies on the pharmacokinetic and pharmacodynamic properties of RBS-AV, Merck Black Widow Antivenom, and F(ab')₂ black widow antivenom (in development) are needed.

ROLE IN LATRODECTUS SPECIES (*L. MACTANS*, *L. HESPERUS*, *L. BISHOPI*, *L. GEOMETRICUS*, *L. VARIOLUS*, *L. INDISTINCTUS*)

Although black widow bites are associated with severe muscle pain, cramping, and autonomic disturbances, mortality remains low.^{7,8,30,33} Symptomatic treatment with muscle relaxants and opioid analgesics is generally effective, although the duration of symptoms following severe envenomation may necessitate hospitalization for 1 to 2 days or more.

The use of Merck Black Widow antivenom may shorten the length of symptoms dramatically, allowing outpatient care in some cases.^{7,30,32,33,39} Studies of reported *Latrodectus* envenomated patients in Australia, however, have demonstrated little clinical difference between *Latrodectus* antivenom and placebo.²¹ In addition, anaphylaxis and other adverse events following the administration of *Latrodectus* antivenom are reported.^{7,20,30,31}

Because of low mortality and potential for adverse events following administration, some authors question the use of black widow antivenom.³⁶ Many toxicologists still believe *Latrodectus* antivenom is safe and effective when used appropriately, and it is generally indicated in cases of severe envenomation where muscle cramping, hypertension,

diaphoresis, nausea, vomiting, and respiratory difficulty are present.⁸

Latrodectus antivenom is also reported to successfully treat priapism complicating severe envenomation.¹⁹ Although the safety of antivenom is not clearly established in the developing fetus, pregnancy is suggested as a consideration for Latrodectus antivenom administration, as the stress of severe pain and muscle cramps may have adverse fetal effects.^{4,38}

Antivenoms for a number of Latrodectus spiders are available worldwide (Table A34–1). A shortage of Merck antivenom prompted the finding that antivenom against *L. hasseltii* (RBS-AV) also neutralizes venom of *L. mactans* in a mouse model.¹⁰ Analatro, a polyvalent F(ab)₂, is an equine-derived antivenom created for *L. mactans* in both Argentina and Mexico that is currently undergoing multi-center clinical trials in Latrodectus envenomated patients in the United States.

TABLE 118–1. Worldwide Availability of Spider Antivenom

Atrax species, Hadronyche species

(Funnel Web Spider)

Australia: Funnel Web Spider Antivenom, CSL Ltd. Rabbit IgG

Latrodectus species

(Black widow spider, Red-backed spider)

Argentina: Anti Latrodectus Antivenom, Instituto Nacional de Produccion de Biologicos, Equine IgG

Australia: Red-backed spider Antivenom, CSL Ltd. Equine F(ab')₂

USA: Antivenin Latrodectus mactans, Merck & Company, Equine IgG

South Africa: SAIMR Spider Antivenom, SAIMR, Equine IgG

Mexico: Aracmyn, Instituto Bioclon, Equine F(ab')₂

Croatia: Antilatrodectus Mactans Tredecimguttatus Serum, Institute of Immunology, Equine IgG

Loxosceles species

(Brown spiders)

Brazil: Antiloxosceles Serum, Centro de Producao e Pesquisas de Immunbiologicos. Equine IgG

Brazil: Soro Antiarachnidico, Instituto Butantan (contains Loxosceles sp, Tityus sp and Phoneutria sp. Antivenom), Equine IgG

Peru: Antiloxosceles Serum, Instituto Nacional de Salud, Centro Nacional de Production de Biologicos, Equine IgG

In a review of 163 cases of presumed *L. hesperus* and *mactans* envenomations, antivenom reduced the mean duration of symptoms from 22 to 9 hours. Symptoms usually subsided within 1 to 3 hours of antivenom administration. The hospital admission rate fell from 52% in those who were managed with opioids and muscle relaxants to 12% in those patients receiving antivenom.⁷ A more recent review demonstrated pain relief in all patients receiving antivenom following symptomatic black widow envenomation.³²

ROLE IN FUNNEL-WEB SPECIES (ATRAX AND HADRONYCHE)

A rabbit IgG based funnel-web spider (*Atrax robustus* and others) antivenom is available in Australia. Since the introduction of the antivenom, no deaths have been reported.²³ Complete response following administration of antivenom was reported in 97% of envenomations in one series.²²

ROLE IN LOXOSCELES SPECIES (L. RECLUSA, L. LAETA, L. RUFESCENS, L. ARIZONICA, L. UNICOLOR)

Envenomation by the brown recluse spider *Loxosceles reclusa* is associated with low, but significant morbidity, particularly in the southeast United States. Anti-*Loxosceles* Fab blocked dermonecrosis in a rabbit model, but only if provided within 24 to 48 hours of envenomation.^{15,34} Although no commercially available antivenom exists in North America for treatment of *Loxosceles* envenomation, antivenom produced against South American *Loxosceles* spiders has cross-reactivity with North American species like *L. reclusa*.¹² The usual late presentation of patients with necrotic lesions from spider bites make antivenom use for *Loxosceles* difficult to study. National laboratories in Brazil and Argentina produce antivenoms for *L. reclusa*, *L. boneti*, and *L. rufescens*.^{5,12}

ADVERSE EFFECTS AND SAFETY ISSUES

Despite the apparent efficacy of antivenom, the decision to give horse serum for a disease with limited mortality should be considered. Death from bronchospasm and anaphylaxis is a rarely reported complication of whole IgG antivenom (Merck) administration,^{7,20,31} as is serum sickness.⁸ Serum sickness is dose-dependent and is less likely when only 1 to 2 vials are typically administered. A detailed review of one case of death following antivenom administration⁷ demonstrates that the antivenom was inappropriately prepared (not diluted) and inappropriately administered (intravenous push rather than slow infusion) to a patient with multiple drug allergies, atopy, and asthma. Resuscitation was further complicated by the development of a pneumothorax. A second death³¹ was reported in a 37 year-old man with history of asthma who received antivenom as an infusion and developed cardiac arrest as a complication of severe anaphylaxis. He died 40 hours after presentation.³¹

In Australia, antivenom to the red-back spider (*L. hasseltii*, CSL Ltd.) is made by immunizing horses for production of F(ab)₂. Horse-derived F(ab')₂ has a lower reported incidence of allergic reactions, with early allergic reactions as low as 0.5% to 0.8%. The incidence of serum sickness is reported at less than 5%.^{40,41} Analatro (under evaluation) is a similar F(ab')₂ product which would be anticipated to be a safer antivenom than the currently available Merck whole IgG product.

A review of the US National Poison Data System (NPDS) demonstrated a 3.4% rate of adverse drug reactions (ADRs) following administration of the Merck *Latrodectus* antivenom.³⁰ This is consistent with previously reported rates of ADRs following black widow antivenom administration.⁸ Directly attributing these complications to administration of antivenom is difficult as these patients received multiple therapies including opioids, benzodiazepines, and calcium salts preceding antivenom administration, and NPDS does not attribute an ADR to a specific therapy. Similarly, the nature of these ADRs is not described in NPDS. However, it is noteworthy that no deaths occurred in 374 instances of use and only five patients received antihistamines, suggesting acute hypersensitivity reactions to the Merck black widow antivenom to be uncommon and that this antivenom is generally safe. Similarly, a review of 96 assessable instances of black widow antivenom administration over a 10 year period in a single state similarly demonstrated a low rate of adverse reactions. Four (4%) patients in the series had adverse effects ascribed to antivenom administration. These reactions were generally mild and included myalgias, fatigue, generalized paresthesias, flushing, and urticarial rash. There were no cases of dyspnea, angioedema, bronchospasm, hypotension, or death.³² This low rate of severe adverse reactions and lack of death suggests that Merck black widow antivenom is a safe product when prepared and administered correctly to patients without underlying atopy, asthma, or drug allergies.

PREGNANCY AND LACTATION

Black widow envenomations during pregnancy are relatively rare. Of 12,640 patients envenomated by a blackwidow spider, 97 (3%) were pregnant. When compared with nonpregnant women, no significant differences were observed in recommended or administered treatments including the use of antivenom.⁶ There are six reported cases of *Loxosceles* envenomations in pregnant women. They were all managed with supportive therapy including analgesics, antihistamines, and short course low dose steroids. Pregnancy outcomes were favorable in all reported cases.^{2,14} Merck black widow antivenom is Pregnancy Category C. It is not known whether antivenom is excreted in human milk.

DOSING AND ADMINISTRATION

The starting dose of the Merck antivenom is one vial (2.5 mL) diluted in 50 mL of saline for intravenous administration. Although black widow spider antivenom can also be given IM, this route carries the disadvantage of slower, more erratic absorption, less control over the rate of administration, and the inability to stop the administration should an allergic reaction occur. In addition, recent studies suggest IM injection of antivenom may not yield significant serum concentrations.²⁴ For these reasons, the intramuscular route is not routinely recommended.

The initial dose of antivenom in funnel-web spider envenomation is two vials in patients with any signs or symptoms of envenomation. Patients with acute respiratory distress syndrome or decreased consciousness should receive four vials.²⁹

For severe cases, the following protocol has been suggested.²⁹ Two vials (each containing 100 mg of rabbit IgG) of antivenom are administered very slowly intravenously. The dose can be repeated in 15 minutes if no improvement occurs. The dose should be doubled for severe cases. A rapid response should occur. Administration of antivenom should be repeated until symptoms are completely reversed.¹³ *Atrax robustus* envenomations may require multiple infusions of antivenom. The recommended dosage for children is the same as for adults.

FORMULATION AND ACQUISITION

Each vial of the Merck product contains 6000 antivenom units standardized by biologic mouse assay. Because *Latrodectus* venoms are virtually identical by immunologic and electrophoretic mechanisms, antivenom created for *L. mactans* is presumed to be effective in other species of *Latrodectus* as well.²⁷

Latrodectus antivenin is supplied as a white to gray crystalline powder in vials containing not less than 6000 antivenin units with thimerosal 1:10,000 added as a preservative, along with a 2.5 vial of sterile diluent for reconstitution. The antivenin must be stored and shipped at 2 to 8°C (36–46°F), but never frozen. The reconstituted antivenin color ranges from light straw to very dark iced tea, although color has no effect on potency.^{2a}

Emergency supplies of *Latrodectus* antivenin are available for patients with symptoms due to a bite by the black widow spider within 24 hours of contacting Merck. The Antivenom Index, maintained by the Association of Zoos and Aquariums (<https://www.aza.org/antivenom-index/>) and accessible by the nation's Poison Control Centers, might also serve as a resource.

SUMMARY

- The decision to use spider antivenom must be individualized to the patient and clinical manifestations.
- Because mortality following black widow envenomation is low, antivenom is reserved for cases where symptoms are severe or do not respond to other therapies, and after a frank discussion with the patient of possible adverse effects.
- Although a large body of literature suggests that Merck black widow antivenom is safe when properly prepared and administered to patients without asthma. Adverse effects including severe anaphylaxis and death are reported.
- A new, purified F(ab)₂ black widow spider antivenom is in clinical development, but is currently unavailable.

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A35 ANTIDOTES IN DEPTH

Antivenom: Scorpion

Michael A. Darracq and Richard F. Clark

INTRODUCTION

Centruroides exilicauda (formerly known as *Centruroides sculpturatus*) is the only scorpion of medical importance in the United States. It is indigenous to the deserts of Arizona but also can be found in Texas, New Mexico, California, and Nevada.¹¹ Occasionally, envenomations occur in nonindigenous areas of the country from “stowaway” scorpions in travelers’ luggage.³²

HISTORY

Arizona poison centers receive several thousand calls annually for scorpion stings. Although the incidence of morbidity with these envenomations is significant, no deaths associated with the toxic effects of scorpion venom have been reported in the United States for almost 50 years. However, deaths are associated with anaphylactic reactions to scorpion venom.⁷ Antivenom for the *Centruroides* spp. was produced in horses in Mexico as early as the 1930s.¹¹ In 1947, antivenom was produced from rabbits and cats immunized with *C. sculpturatus* and *Centruroides gertschi*.²⁹ The Antivenom Production Laboratory at Arizona State University (APL-ASU) began producing antivenom to *C. sculpturatus* in goats in 1965. This antivenom was used for treatment of scorpion stings in Arizona until 2004, when production ceased and stockpiles expired. In June 2000, Silanes Laboratory received orphan drug status for a *Centruroides* scorpion antivenom, an equine-derived F(ab')₂ from *Centruroides limpidus*, *Centruroides noxius*, *Centruroides suffusus suffusus*, and *Centruroides meisei* (formerly known as *Centruroides elegans*) manufactured by Instituto Bioclon of Mexico, and referred to as Anascorp. In August 2011, Anascorp was approved by the US Food and Drug Administration (FDA) for the treatment of *Centruroides exilicauda* envenomations.¹⁵

PHARMACOLOGY

Antivenom for scorpions is prepared in the same manner as other antivenom products (Antidotes in Depth: A34 and A37).

Pharmacokinetics and Pharmacodynamics

In a study of 8 healthy patients (6 males and 2 females, age 17–26 years) without prior scorpion envenomation, a bolus intravenous dose of 47.5 mg of Anascorp was administered. Serial blood samples were collected over 21 days. Measured pharmacokinetic parameters (mean ± standard deviation) included: area under the curve (AUC), 706 ± 352 µh/mL; clearance, 83.5 ± 38.4 mL/h; half-life, 159 ± 57 hours; and steady state volume of distribution (Vd_{ss}), 13.6 ± 5.4 L.³³

ROLE IN CENTRUROIDES SPECIES

One vial of Anascorp antivenom contains sufficient F(ab')₂ to neutralize 150 mouse LD₅₀ of *Centruroides* venom.²⁵ Safety and efficacy are documented in both animals and humans.^{1,8,9,10} In the FDA review and subsequent approval of Anascorp, six trials were submitted for consideration. Only one study was prospective, randomized, double-blinded, and controlled and demonstrated a clear benefit in reduction of signs and symptoms of scorpion envenomation by 4 hours postadministration (8/8 vs. 1/7), reduction in quantity of sedative administered (mean midazolam dose of 0.1 mg/kg (0.0–0.2 mg/kg) versus 4.6 mg/kg (0.1–16.7 mg/kg), and absence of free serum venom concentrations at one hour after administration (mean 0.0 vs. 2.65 ng/mL).⁸

One retrospective trial using historical controls was included as representative of clinical outcomes in the absence of

antivenom administration. This trial demonstrated the need for exceedingly large dose of sedatives to treat the inability to walk and respiratory distress due to envenomation with a mean time to discharge of 12.6 hours without administration of scorpion antivenom.¹¹

One large (n = 1534), unpublished and open label study was also included for review. The majority (1204/1534) of patients were children (0.7 months–18 years) and male (52.3%). In 1396/1425 patients, the mean time to resolution of clinically important signs of envenomation following Anascorp administration was 1.42 hours (0.2–20.5 hours). Children reportedly improved slightly faster than adults (1.28 ± 0.8 hours vs. 1.91 ± 1.4 hours). Of the 1534 patients included in the study, 95% had relief of systemic signs associated with Centruroides envenomation within 4 hours of Anascorp administration.^{9,14}

Three additional open label trials (AL-02/04-adult patients, AL-02/05-pediatric patients, and AL-02/06-pediatric patients) with the use of the Instituto Bioclon of Mexico product Alacramyn (Alacramyn is the Mexican equivalent of Anascorp) were reported by the study sponsors to demonstrate 100% resolution of symptoms by 4 hours following administration of antivenom.¹⁴

ROLE IN LEIURUS SPECIES

The Leiurus quinquestriatus scorpion is indigenous to Africa, Asia, and the Middle East, including Egypt, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, and Turkey. Antivenom to L. quinquestriatus is currently made in France, Germany, Israel, Saudi Arabia, Egypt, Tunisia, and Turkey (Table A35–1).

TABLE A35–1. Worldwide Scorpion Antivenoms

<p>Androctonus species</p> <p>Algeria: Antiscorpion Serum, Institut Pasteur d'Algerie, Equine F(ab)₂,</p> <p>Egypt: Purified Polyvalent Anti-Scorpion Serum, Egyptian Organization for Biological Products and Vaccines (VACSERA), Equine F(ab)₂,</p> <p>France: ScorpiFAM, Aventis Pasteur, Equine F(ab)₂,</p> <p>Germany: Scorpion Antivenom, Twyford, Equine F(ab)₂,</p> <p>Iran: Polyvalent Scorpion Antivenom, Razi Vaccine and Serum Research Institute, Equine F(ab)₂,</p> <p>Tunisia: Scorpion Antivenom, Institut Pasteur de Tunis, Equine F(ab)₂,</p> <p>Turkey: Scorpion Antivenom, Refik Saydam Hygiene Center (RSHC), Equine F(ab)₂,</p>	<p>Heterometrus species</p> <p>India: Monovalent Scorpion Antivenom, Central Research Institute, Equine F(ab)₂,</p> <p>Leiurus species</p> <p>Egypt: Purified Polyvalent Antiscorpion Serum, Egyptian Organization for Biological Products and Vaccines (VACSERA), Equine F(ab)₂,</p> <p>France: ScorpiFAM, Aventis Pasteur, Equine F(ab)₂,</p> <p>Germany: Scorpion Antivenom, Twyford, Equine F(ab)₂,</p> <p>Israel: Anti Leiurus quinquestratus, Equine F(ab)₂,</p> <p>Saudi Arabia: Polyvalent Scorpion Antivenom, National Antivenom and Vaccine Production Center (NAVPC), Equine F(ab)₂,</p> <p>Tunisia: Scorpion Antivenom, Institut Pasteur de Tunis, Equine F(ab)₂,</p> <p>Turkey: Scorpion Antivenom, Refik Saydam Hygiene Center (RSHC), Equine F(ab)₂,</p>	<p>Scorpio maurus</p> <p>Egypt: Purified Polyvalent Anti-Scorpion Serum, Egyptian Organization for Biological Products and Vaccines (VACSERA), Equine F(ab)₂,</p> <p>France: ScorpiFAM, Aventis Pasteur, Equine F(ab)₂,</p> <p>Iran: Polyvalent Scorpion Antivenom, Razi Vaccine and Serum Research Institute, Equine F(ab)₂,</p> <p>Turkey: Scorpion Antivenom, Refik Saydam Hygiene Center (RSHC), Equine F(ab)₂,</p>
<p>Buthus species</p> <p>Algeria: Antiscorpion Serum, Institut Pasteur d'Algerie, Equine F(ab)₂,</p> <p>Egypt: Purified Polyvalent Antiscorpion Serum, Egyptian Organization for Biological Products and Vaccines (VACSERA), Equine F(ab)₂,</p> <p>France: ScorpiFAM, Aventis Pasteur, Equine F(ab)₂,</p> <p>Germany: Scorpion Antivenom, Twyford, Equine F(ab)₂,</p> <p>India: Scorpion Venom Antiserum LP, Harfline Biopharmaceutical Corporation LTD, Equine F(ab)₂,</p> <p>Morocco: Scorpion Antivenom, Equine F(ab)₂,</p> <p>Saudi Arabia: Polyvalent Scorpion Antivenom, National Antivenom and Vaccine Production Center (NAVPC), Equine F(ab)₂,</p> <p>Tunisia: Scorpion Antivenom, Institut Pasteur de Tunis, Equine F(ab)₂,</p>	<p>Mesobuthus species</p> <p>India: Monovalent Scorpion Antivenom, Central Research Institute, Equine F(ab)₂,</p> <p>Iran: Polyvalent Scorpion Antivenom, Razi Vaccine and Serum Research Institute, Equine F(ab)₂,</p> <p>Odontobuthus dorriei</p> <p>Iran: Polyvalent Scorpion Antivenom, Razi Vaccine and Serum Research Institute, Equine F(ab)₂,</p>	<p>Tityus species</p> <p>Argentina: Scorpion antivenom, Instituto Nacional de Produccion de Biologicos, Equine Fab</p> <p>Brazil: Soro Antiscorpionico, Instituto Butantan, Equine Sera</p> <p>Brazil: Soro Antiarachnidico, Instituto Butantan, Equine IgG (<i>Loxosceles</i> sp, <i>Tityus</i> sp, and <i>Phemeris</i> sp. antivenom)</p> <p>Brazil: Antiscorpion serum IVIL Instituto Vital Brazil S.A., Equine IgG</p> <p>Brazil: Antibesopionico, Fundacao Ezequiel Dias (FUNED), Equine F(ab)₂,</p>
<p>Eusecorpius carthothleus, Italian</p> <p>Turkey: Scorpion Antivenom, Refik Saydam Hygiene Center (RSHC), Equine F(ab)₂,</p>	<p>Palaemonius species</p> <p>India: Monovalent Red Scorpion Antivenom, Central Research Institute, Equine F(ab)₂,</p> <p>Parabuthus species</p> <p>South Africa: SAIMR Scorpion Antivenom, South African Vaccine Producers (Pty) Ltd. (SAMP) Equine F(ab)₂,</p>	<p>Centruroides species (<i>elegans</i>, <i>gertschi</i>, <i>limpulus</i>, <i>suffusus</i>, <i>naxosus</i>, <i>virilicauda</i>)</p> <p>Mexico: Soro Antialacran Alacramyn, Instituto Bioclon, Equine F(ab)₂,</p> <p>United States: Anascorp, Centruroides (Scorpion) Immune F(ab)₂, (Equine) Injection, Instituto Bioclon, Equine F(ab)₂,</p>

In observational studies, an intravenous infusion of 5 to 20 mL of Leiurus antivenom was needed to control venom effects, and only patients given antivenom within the first several hours demonstrated significant benefit.^{2,20} The rate of allergic reactions for the Turkish antiscorpion antivenom is reported to be 1.6% to 6.6%.²⁰ The recommended dose of the Israeli L. quinquestriatus antivenom is 5 to 15 mL for intravenous use, although several authors report lack of clinical efficacy of this particular antivenom.^{5,16,30}

L. quinquestriatus antivenom was successfully used to treat a 2 year-old boy with envenomation by Androctonus crassicauda. Symptoms resolved 2 hours after antivenom administration.²⁸

ROLE IN TITYUS SPECIES

Tityus species of scorpions are endemic to South America, particularly Brazil. An F(ab)₂ antivenom for Tityus serrulatus is available from Fundação Ezequiel Dias (FUNED), in Belo Horizonte, Brazil. The usual dose of the antivenom is 20 mL as an intravenous infusion.¹³

In a series of 18 patients with T. serrulatus envenomation treated with antivenom, vomiting and local pain decreased within 1 hour, and cardiorespiratory manifestations disappeared within 6 to 24 hours in all patients except the two presenting with acute respiratory distress syndrome.¹³ Sixteen patients recovered completely by 24 hours. The Instituto Buntantan in Brazil also produces Soro antiarachnidico and Soro antiscorpionico for treatment of Tityus spp.

Role in Androctonus Species

Scorpion antivenom in South Africa is an equine-derived antivenom available from the South African Vaccine Producers, formerly South African Institute for Medical Research (SAIMR), Johannesburg, South Africa. ScorpiFAV, produced by Aventis Pasteur, is produced for treatment of *Androctonus* spp, *B. occitanus*, and *L. quinquestriatus*.

Buthus tamulus monovalent red scorpion antivenom serum produced by Central Research Institute of India is an equine-derived lyophilized antivenom for the venom of *Mesobuthus tamulus*. The manufacturer recommends a dosage of one vial, although a dose of five vials decreased mortality significantly in one study.^{22,31}

In Pakistan, the treatment of scorpion stings was modified in 1991 to include the administration of five vials of antivenom. A retrospective case series of 950 patients treated with and without antivenom was compared to 968 cases treated after the five vial protocol was initiated. A statistically significant decrease in mortality was demonstrated. The last recorded death in Pakistan resulting from a scorpion sting occurred in 1991 in a patient who did not receive antivenom.³¹

Parabuthus spp antivenom from South African Vaccine Producers is an equine-derived antivenom to *Parabuthus* spp. In one study, antivenom was unavailable for a period of time allowing for a unique design of matched pair of patients. Patients who received antivenom had a significant decrease in hospital stay after receiving one (5 mL) vial. Pain, hypersalivation, fasciculations, tremor, and bladder distension responded best to antivenom, whereas dysphagia, ptosis, and local swelling were more resistant.⁶ More recent studies from India show equivocal results for scorpion envenomation treated with antivenom when compared to treatment with prazocin.^{4,26}

The unavailability of specific antivenoms often necessitates symptomatic treatment or use of a comparable foreign antivenom. In a study of 72 moderate scorpion stings in Para, Brazil, 33% who met criteria for antivenom administration did not receive treatment because of unavailability of the antivenom.²⁷

ADVERSE EFFECTS AND SAFETY ISSUES

Hypersensitivity reactions to Anascorp and other equine derived antivenoms may occur following administration. Patients with known equine protein allergies or previous exposure to Anascorp or other equine derived antivenoms or antitoxins may be at increased risk due to previous sensitization. No deaths were reported in clinical trials of Anascorp. Adverse effects reported from cumulative clinical trial data revealed that 2.2% of patients experienced severe adverse reactions (respiratory distress, aspiration, hypoxia, ataxia, pneumonia, and eye swelling) following Anascorp administration. However, these symptoms occurred in the setting of acute *Centruroides* envenomation, limiting the direct attribution of symptoms to antivenom administration alone. The most common adverse effects reported included vomiting (4.7%), pyrexia (4.1%), rash (2.7%), nausea (2.1%), and pruritus (2%).¹⁴ The presence of cresol as an injectable excipient may increase localized reactions and generalized myalgias following administration. No drug interaction studies have been conducted with Anascorp.

PREGNANCY AND LACTATION

Anascorp is Pregnancy Category C. Animal reproduction studies have not been conducted, and it is unknown whether Anascorp may cause fetal harm when administered to pregnant women. Reproductive capability postadministration similarly has not been assessed. Anascorp should only be administered in pregnant women if clearly needed for alleviation of symptoms and after other therapies have been utilized. It is unknown whether Anascorp is excreted in human breast milk.¹⁴

DOSING AND ADMINISTRATION

Anascorp is the only US FDA approved treatment for the clinical signs and symptoms of *Centruroides* scorpion envenomation. These include, but are not limited to, loss of motor control, roving or abnormal eye movements, slurred speech, respiratory depression, and excessive oral secretions. Package insert dosing recommendations (FDA) are three vials administered intravenously over 10 minutes after reconstitution (5 mL sterile 0.9% sodium chloride solution/vial) and dilution to a total volume of 50 mL. Additional vials may be administered every 30 to 60 minutes as needed for symptom control. The price of Anascorp may vary from hospital to hospital. In one survey of Phoenix, Arizona hospitals, the charge per vial was between \$7900 and \$15,120.³

FORMULATION AND ACQUISITION

Anascorp is supplied as a sterile lyophilized preparation in a single-use vial. When reconstituted, each vial contains not more than 24 milligrams per milliliter of protein, and not less than 150 mouse LD50 neutralizing units. Anascorp should not

be frozen, but stored at room temperature up to 25°C (77°F).¹⁴

The Antivenom Index, maintained by the Association of Zoos and Aquariums (<https://www.aza.org/antivenom-index/>) and accessible by the nation's Poison Control Centers, may serve as a resource in the event of difficulty obtaining antivenom. The World Health Organization's World Directory of Poison Centres (http://www.who.int/gho/phe/chemical_safety/poisons_centres/en/) might assist those outside of the U.S. to source more exotic antivenoms.

SUMMARY

- The indications for antivenom administration following scorpion stings remain controversial.
- The decision to use antivenom should be individualized to the patient, weighing the risk of giving an immune serum, the level of available supportive care, the risks and costs of supportive care alone, and the cost of obtaining or importing antivenom.
- Scorpion antivenom administration for some species may not improve outcome.
- The preferred route of administration of these products is intravenous. One to two vials is the recommended dose for most scorpion antivenoms; higher doses may be needed to alleviate symptoms in some cases.

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119 MARINE ENVENOMATIONS

D. Eric Brush

Human contact with venomous marine creatures is common and may result in serious harm from biological toxins or mechanical injury inflicted by the stinging apparatus. Significant morbidity results from envenomation by spiny fish, cone snails, octopi, sea snakes, and several species of jellyfish. Despite advances in basic science research regarding the biochemical nature of marine toxins and their mechanisms of action, our knowledge of the pathophysiology related to clinical syndromes in humans and the optimal therapies for human envenomation remain limited. Evidence for effective treatment is primarily derived from in vitro and in vivo animal research without the benefit of controlled human trials. However, current research in toxinology coupled with clinical observations allows the development of cogent treatment guidelines for victims of marine envenomation.

INVERTEBRATES

Cnidaria

The phylum Cnidaria (formerly Coelenterata) includes more than 9000 species, of which approximately 100 are known to injure humans. They are commonly referred to as jellyfish; however, their phylogenetic designations separate “true jellyfish” and other organisms into distinct classes (Table 119–1; Fig 119–1A). All species possess microscopic cnidae (the Greek knide means nettle), which are highly specialized organelles consisting of an encapsulated hollow barbed thread bathed in venom. Thousands of these stinging organelles, called nematocysts (or cnidoblasts), are distributed along tentacles. A trigger mechanism called a cnidocil regulates nematocyst discharge. Pressure from contact with a victim’s skin, or chemical triggers such as osmotic change, stimulates discharge of the thread and toxin from its casing. Penetration of flesh leads to intradermal venom delivery. Nematocysts of most Cnidaria are incapable of penetrating human skin, rendering them harmless. Cnidaria causing human envenomation, such as the box jellyfish, discharge threads capable of penetrating into the papillary dermis.¹³⁶

TABLE 119–1. Characteristics of Common Cnidaria

<i>Latin Name</i>	<i>Common Name</i>	<i>Habitat*</i>
Cubozoa class		
<i>Chironex fleckeri</i> [§]	Box jellyfish	Tropical Pacific Ocean, Indian Ocean, Gulf of Oman
<i>Carukia barnesi</i> [§]	Inukandji jellyfish	North Australian coast
<i>Chiropsalmus spp</i> [§]	Sea wasp or fire medusa	North Australian coast, Philippines, Japan, Indian Ocean, Gulf of Mexico, Caribbean
<i>C. quadrigatus</i>		
<i>C. quadrumanus</i>		
<i>Carybdea alata</i>	Hawaiian box jelly fish	Hawaii
<i>Carybdea rastoni</i>	Jimble	Australia
Hydrozoa class		
<i>Physalia physalis</i> [§]	Portuguese man-of-war	Eastern US Coast from Florida to North Carolina, Gulf of Mexico, Australian coastal waters (rare reports)
<i>Physalia utriculus</i>	Bluebottle	Tropical Pacific Ocean, particularly Australia
<i>Millepora albicornis</i>	Fire coral	Widespread in tropical waters, including Caribbean
Scyphozoa class		
<i>Chrysaora quinquecirrha</i>	Sea nettle	Chesapeake Bay, widely distributed in temperate and tropical waters
<i>Stomolophus meleagris</i>	Cabbage head or cannonball jelly fish	Gulf of Mexico, Caribbean
<i>Stomolophus nomurai</i> [§]		Yellow Sea between China and South Korea
<i>Cyanea capillata</i>	Lion's mane or hair jelly fish	Northwest US coast up to Arctic Sea, Norwegian and British coastlines, as well as Australia
<i>Pelagia noctiluca</i>	Mauve stinger or purple-striped jelly fish	Wide distribution in tropical zones
<i>Liruche unguiculata</i>	Thimble jelly fish	Florida, Mexico, and Caribbean
Anthozoa[§] class		
<i>Anemonia sulcata</i>	European stinging anemone	Eastern Atlantic, Mediterranean, Adriatic Sea
<i>Actinodendron plamosum</i>	Hell's fire anemone	South Pacific
<i>Actinia equina</i>	Beadlet anemone	Great Britain, Ireland

[§]Represents most common areas where stings are reported. [§]Well-documented human fatalities.



FIGURE 119-1 (A) North Atlantic Portuguese man-of-war *Physalia physalis* with multiple tentacles dangling in the water. The tentacles filled with venomous nematocysts extend several meters in length. (Used with permission of Adam Lavery. Reproduced with permission from Knoop et al., *The Atlas of Emergency Medicine*, 3e (c) 2010, McGraw-Hill Inc., New York, New York.) (B) Linear eruption from contact with an unidentified jellyfish in the South Atlantic Ocean.

(Used with permission of David Goldfarb.)

Cubozoa. Members of the class Cubozoa are not true jellyfish. Animals in the Cubomedusae order have a cube-shaped bell with four corners, each supporting between 1 and 15 tentacles. Species from this order produce the greatest morbidity and mortality of all Cnidaria. The order has two main families of toxicologic importance: Chirodropidae and Carybdeidae.

The Chirodropidae family is well known for the box jellyfish *Chironex fleckeri* (Greek cheiro means hand, Latin nex means murderer; therefore, “assassin’s hand”). When full grown, its bell measures 25 to 30 cm in diameter and 15 tentacles are attached at each “corner” of the bell. These tentacles may extend up to 3 m in length. Another member of this family is *Chiropsalmus quadrigatus*, the sea wasp. Its pale blue color makes detection in water nearly impossible.

The Carybdeidae family is most notable for *Carukia barnesi*, the Irukandji jellyfish.⁶¹ Its small size, with a bell diameter of only 2.5 cm, limits detection in open waters.

Hydrozoa. Members of the Hydrozoa class are also not true jellyfish. The order Siphonophora (Physaliidae family) includes two unusual creatures of toxicologic concern: *Physalia physalis*, the Portuguese man-of-war, and its smaller counterpart, *Physalia utriculus*, the bluebottle. They are pelagic (floating) colonial Hydrozoa, meaning they exist as a colony of multiple hydroids in a formed mass. The easily recognizable blue sail that floats above the surface of the water is filled with nitrogen and carbon monoxide. Tentacles of *P. physalis* may reach lengths exceeding 30 m and contain more than 750,000 nematocysts in each of its numerous tentacles (up to 40). *P. utriculus* has only one tentacle that measures up to 15 m.

The Milleporina order includes the sessile *Millepora alcicornis* (fire coral) that exists as a fixed colony of hydroids. It appears much like true coral and has a white to yellow-green lime carbonate exoskeleton. Small tentacles protrude through minute surface gastropores. The overall structure ranges from 10 cm to 2 m.

Scyphozoa. True jellyfish belong to the class Scyphozoa and are extremely diverse in size, shape, and color. Common varieties known to envenomate humans are *Cyanea capillata* (lion’s mane or hair jelly), *Chrysaora quinquecirrha* (sea nettle), and *Pelagia noctiluca* (mauve stinger). The mauve stinger is easily recognized; it appears pink in daylight and phosphorescent at night. Larvae of *Linuche unguiculata* cause sea bather’s eruption (SBE). The larvae are pinhead sized and are seen only when they are grouped in large numbers near the surface of the water.

Anthozoa. The Anthozoa class has a diverse membership, including true corals, soft corals, and anemones. Only the anemones are of toxicologic importance. They are common inhabitants of reefs and tide pools and attach themselves to rock or coral. Armed with modified nematocysts known as sporocysts located on their tentacles, they produce stings similar to those of organisms from other Cnidaria classes.

History and Epidemiology. Stings from Cnidaria represent the overwhelming majority of marine envenomations. In Australia, approximately 10,000 stings per year are recorded from *Physalia* spp alone.⁵⁶ Most Cnidaria stings occur during the warmer months of the year. Stings occur with greatest frequency on hotter-than-average days with low winds, particularly during times of low precipitation. “Stinger nets” are used in high-risk areas of the Australian coastline; however, one study reported that 63% of stings requiring medical attention occurred within netted waters.⁸⁸ Each stinger season, the Royal Darwin Hospital in Australia treats approximately 40 patients with stings.⁴² A prospective evaluation of stings presenting to that hospital during a 12-month period from 1999 to 2000 revealed that 70% resulted from the box jellyfish. The remaining 30% involved other Cubozoa such as *C. barnesi*.¹⁰⁹ Although this finding may indicate a predominance of box jellyfish as the cause of stings, it also suggests that stings from box jellyfish are more severe and require medical attention with greater frequency than stings from other species of Cnidaria.

Stings from *C. barnesi*, the organism originally identified as the cause of Irukandji syndrome, were initially considered unique to Australia. However, an unidentified species produced three cases of an Irukandjilike syndrome in the Florida Keys.⁶⁹ More recent reports identify an Irukandjilike syndrome north of Australian waters in the Torres Strait,¹⁰⁰ suggesting a more diverse geographical distribution and possibly more than one responsible organism.

Cases of SBE, a stinging rash evoked by contact with Cnidaria larvae, occur in clusters. Variation in intensity and frequency occurs from year to year as exemplified by a 25-year hiatus during which no cases were reported in Florida.¹⁴⁴ In 1992, more than 10,000 cases of SBE occurred in south Florida, with similar peaks in the 1940s and 1960s. Cases of SBE also are reported in Cuba, Mexico, the Caribbean, and occasionally as far north as New York.

Cnidaria common to the United States include the Portuguese man-of-war and sea nettle. Other species are widely distributed throughout the tropical and temperate waters of the globe (Table 119–1). Locations with documented Cnidaria-related deaths include the United States (Florida, North Carolina, Texas), Australia, the Indo-Pacific region (Malaysia, Langkawi Islands, Philippines, Solomon Islands, Papua New Guinea), and the coast of China.^{12,23,56,87,135} Since 1884, approximately 70 deaths in Australia are attributed to *C. fleckeri*. An estimated two to three deaths per year occur in Malaysia from an unknown species. Approximately 20 to 40 deaths are reported yearly in the Philippines from an unidentified species of the Chirodropidae family. Three deaths are well documented from *P. physalis* in the United States (Florida, North Carolina). One death from *Chiropsalmus quadrumanus* occurred along the coast of Texas. Eight fatalities in the Bohai waters of China (Yellow Sea) are reported from *Stomolophus nomurai*. Although Chirodropidae are found off the

western coast of Africa, no fatalities in that region are documented in the medical literature.

Pathophysiology. Cnidaria venoms contain a variety of components that may induce dermatonecrosis, myonecrosis, hemolysis, or cardiotoxicity, depending on the particular species. In rats, *C. fleckeri* venom evokes transient hypertension, followed by hypotension and cardiovascular collapse within minutes.¹¹⁶ Cardiac effects in animals include negative inotropy, conduction delay, ventricular tachycardia, and decreased coronary artery blood flow.⁴² However, experiments using the purest venom extracts without contamination from tentacle material demonstrate cardiovascular collapse without electrocardiographic changes.¹¹⁶ *C. fleckeri* venom also possesses dermatonecrotic and hemolytic fractions, although hemolysis is not documented in humans.⁹ Two myotoxins from *C. fleckeri* cause powerful sustained muscle contractions in isolated muscle fibers.⁴⁶ Isolated heart models using *C. fleckeri* venom suggest its mechanism of action is nonspecific enhancement of cation conductance leading to increased Na⁺ and Ca²⁺ entry into cells.¹⁰⁵ Other in vitro work confirms increased Na⁺ permeability in cardiac tissue.⁶³

C. barnesi, the Irukandji jelly, likely induces its dramatic vasopressor effects via catecholamine release. In rats, the venom produces a pressor response that is blocked by α_1 -adrenergic antagonism.¹¹⁵ The pressor response is not dose dependent; therefore, catecholamines in the venom are an unlikely cause. In vitro experiments suggest a Na⁺ channel modulator effect leading to massive catecholamine release.¹⁵⁷ No electrocardiographic abnormalities occurred in envenomated rats.

Venom from *Physalia* spp blocks neural impulses in isolated frog sciatic nerve⁸² and produces ventricular ectopy, cardiovascular collapse, hyperkalemia, and hemolysis in dogs.⁷² *Physalia* spp venom inhibits Ca²⁺ entry into the sarcoplasmic reticulum.⁸² Similar mechanisms are proposed for *Chrysaora*, *Chiropsalmus*, and *Stomolophus*. *C. quinquecirrha* venom, which contains a 150-kDa polypeptide that induces atrioventricular block¹⁹ and produces myocardial ischemia, hypertension, dysrhythmias, and nerve conduction block,^{24,25} as well as hepatic and renal necrosis.¹⁰⁴ *C. quinquecirrha*-induced hepatotoxicity is believed to be a direct toxin effect not mediated by pore formation or Ca²⁺ channel effects.⁷⁴ Equinatoxin II (EqII), found in the venom of the anemone *Actinia equina*, creates pores in cell membranes leading to hemolysis.¹ This protein belongs to a group of anemone lysins known as actinoporins that bind to cell membranes and form pores via oligimerization.⁹³

An immune-mediated response to venom may explain some sting-related symptoms. Elevated serum anti-sea nettle immunoglobulin IgM, IgG, and IgE may persist for years in patients with exaggerated reactions to stings compared with controls.²⁰ A direct correlation between titers against *Chrysaora* and *Physalia* and severity of a visible skin reaction to envenomation strongly suggests an allergic component.¹²⁶ Elevated IgG titers were demonstrated in one death from *P. physalis*.¹³⁵ Dermatonecrosis from *C. fleckeri* may involve the release of leukotrienes and other arachidonic acid derivatives as well as direct toxin-mediated cell damage.⁴³ Postenvenomation syndromes may result from an exaggerated, prolonged, aberrant T-cell response.^{26,27} Erythema nodosum following a sting from *P. physalis* lends further support to an immunologic component.⁵ SBE displays a characteristic delay in onset of symptoms and can be effectively treated with steroids, suggesting a primary immune-mediated process. This is further supported by histopathology revealing the presence of perivascular and interstitial infiltrates with lymphocytes, neutrophils, and eosinophils.¹⁵⁸

Clinical Manifestations. Most patients with stings are treated beachside and never require hospitalization. The vast majority of patients with stings who seek medical care do so because of severe pain without evidence of systemic poisoning.⁴² However, severe systemic manifestations may develop following stings from *C. fleckeri*, *C. barnesi*, *P. physalis*, and a few other Cnidaria.

Envenomation by *C. fleckeri* inflicts the most severe pain and is frequently associated with systemic toxicity. Common symptoms include immediate severe pain, followed by an erythematous whiplike linear rash with a “frosted ladder” appearance. The pain often is excruciating and may require parenteral analgesia. Systemic symptoms include nausea, vomiting, muscle spasms, headache, malaise, fever, and chills. Pain generally abates over several hours, although the rash may persist for days. In a prospective series of *C. fleckeri* stings, 58% manifested delayed hypersensitivity reactions in the form of an itchy maculopapular rash at 7 to 14 days.¹⁰⁹ Most resolved spontaneously; some were treated with antihistamines and topical corticosteroids.

Fatality is documented to occur with only 4 m of tentacle markings.¹³⁶ Death is rapid, preventing many victims from reaching medical care, or even the shore.⁸⁶ Cardiac arrest and pulmonary edema may develop in young, healthy patients without prior cardiopulmonary disease.^{78,92,156} Survival is possible with immediate cardiopulmonary resuscitation (CPR).¹⁵⁵ *C. quadumanus*, a close relative of the box jellyfish, induces symptoms that are similar to *C. fleckeri* stings, including pulmonary edema and death.¹²

Previous reports suggesting a 15% to 20% fatality rate¹²² following *C. fleckeri* envenomation likely represent a gross overestimation given the low number of documented fatalities in the context of the extraordinary number of yearly stings. A prospective study of stings from Cubozoa over one year in Australia revealed no dysrhythmias, pulmonary edema, or

death.¹⁰⁹ No patient received antivenom, and analgesia was the only pharmacotherapy implemented. Hospital admission was not required for any victim. Although most victims suffer only local severe pain, serious systemic toxicity occurs occasionally, and may include vertigo, ataxia, paralysis, delirium, syncope, respiratory distress, pulmonary edema, hypotension, and dysrhythmias. In a series of 10 reported deaths from *C. fleckeri*, all occurred in children, suggesting vulnerability due to lower body mass and thinner dermis.⁴²

Irukandji syndrome is a severe form of envenomation following Cubozoa stings from *C. barnesi*.⁷⁵ Individuals afflicted often notice a mild sting while they are in the water; however, skin findings typically are absent. Severe systemic symptoms develop within 30 minutes and mimic a catecholamine surge including tachycardia, palpitations, hyperpnea, headache, pallor, restlessness, apprehension, sweating, and a sense of impending doom. A prominent feature is severe whole-body muscle spasms that come in waves and preferentially affect the back. Spasms are described as unbearable and frequently require parenteral analgesia. Symptoms generally abate over several hours. Admission rates in patients presenting to medical care can exceed 50%.⁸⁸ Hypertension is universal and may be severe, with systolic blood pressures well over 200 mm Hg. Two fatalities are described involving severe hypertension (systolic 280/150 mm Hg and 230/90 mm Hg) resulting in intracranial hemorrhage.^{52,75} Hypotension frequently follows, requiring vasopressor support. Pulmonary edema can develop within hours. Echocardiograms consistently reveal global ventricular dysfunction.^{90,95} Restored cardiac function typically returns after several days.⁸⁹ A retrospective review of 116 cases of Irukandji presenting to Cairns Base Hospital identified elevated troponin I measurements in 22% of patients.⁷⁵ Electrocardiographic changes are described as nonspecific.

P. physalis envenomation typically induces severe pain, bullae, and skin necrosis (Fig. 119–1B). Systemic symptoms include weakness, numbness, anxiety, headache, abdominal and back spasms, lacrimation, nasal discharge, diaphoresis, vertigo, hemolysis, cyanosis, acute kidney injury, shock, and, rarely, death. Some patients experience local numbness and paralysis of the affected extremity that resolves spontaneously.⁷⁶ As with serious *C. fleckeri* stings, cardiovascular collapse and death can occur within minutes of envenomation.²³ However, fatalities can be delayed several days following envenomation and relate to complications such as myocardial infarction and aspiration pneumonitis.¹³⁵ An unusual presentation is reported of a 4 year-old child who was stung along the North Carolina coast and developed massive hemolysis requiring transfusions, followed by acute kidney failure necessitating temporary hemodialysis.⁷⁰ In contrast to *P. physalis*, *P. utriculus* stings typically are mild, although systemic toxicity occasionally develops.⁵⁸

M. alcicornis (fire coral) is a common cause of stings in southern United States and Caribbean waters. While a member of the same phylogenetic class as *P. physalis*, it produces far less significant injuries. It is a nuisance to divers who touch the coral and suffer moderate burning pain for hours. Untreated pain generally lessens within 90 minutes, with skin wheals flattening at 24 hours and resolving within one week. Hyperpigmentation may persist for up to 8 weeks.¹⁶ The feather hydroid is the most numerous of the Hydrozoa and produces only mild stings.⁹⁷

True jellyfish typically are less harmful to humans than Cubozoa or Hydrozoa. However, systemic toxicity and occasional deaths are reported from certain species such as *S. nomurai*, *C. capillata*, *C. quinquecirrha*, and *P. noctiluca*. *Stomolophus meleagris* is a common cause of stings; however, its weak venom produces only minor injury.⁴

Larvae of *Linuche unguiculata* are the primary cause of a pruritic papular eruption on the skin of sea bathers in Florida, occurring mostly in areas covered by a bathing suit as a result of larvae trapped under the garments. Cases were first noted in 1949 and dubbed SBE.¹²⁷ The larvae appear as pin-sized brown to green-brown spheres in the upper 2 inches of the water and are typically unnoticed. In a retrospective review, 50% of people reported a stinging sensation while they were in the water, and 25% reported itching upon exiting the water.¹⁵⁸ The remainder of patients developed symptoms within 11 hours. Skin lesions develop within hours of itching and appear as discrete, closely spaced papules, with pustules, vesicles, and urticaria. Most lesions occur in areas covered by the bathing suit where the larvae accumulate; however, folds of skin such as the axilla, breasts, and neck may be affected. Itching often is severe and prevents sleep. New lesions may continue to develop over 72 hours. The average duration of symptoms is just under 2 weeks, and a small percentage of patients experience a recurrence of lesions several days later. Systemic symptoms such as chills, headache, nausea, vomiting, and malaise may occur.

Following stings from sea anemones, victims may develop either immediate or delayed pain. Skin findings range from mild erythema and itching to ulceration. A review of 55 stings from *Anemonia sulcata* presenting to a hospital in Yugoslavia (Adriatic Sea) revealed that, in addition to the local skin findings, many patients suffered nausea, vomiting, muscle aches, and dizziness.⁹⁴ Larvae of the anemone *Edwardsiella lineata* also cause SBE among ocean swimmers in Long Island, New York. The hell's fire anemone *Actinodendron plumosum* is native to the South Pacific and produces significant local pain. One death occurred in the Virgin Islands following envenomation from an unknown species described as a "white anemone with blue tips." The onset of hepatic and renal failure was rapid and required transplantation, after which the patient died.⁶⁵ Nonfatal elevation of hepatic enzyme concentrations following anemone sting also is reported.¹⁷

Diagnostic Testing. Laboratory evaluation may be warranted in patients suffering systemic toxicity following Cnidaria

envenomation. Serial measurement of serum cardiac markers should be obtained from victims of Irukandji stings or others with consequential cardiovascular toxicity. Following severe stings from a variety of Cnidaria, urinalysis, hematocrit, and serum creatinine measurements should be considered to detect the presence of hemolysis and subsequent kidney injury. Chest radiography is indicated for complaints of dyspnea or abnormalities in oxygenation. Venom assays are not available, and serum antibody titers are not clinically useful.

Management. Initial interventions after Cnidaria envenomation are directed toward stabilization of cardiopulmonary abnormalities in cases of severe envenomation. Secondary measures are directed toward the prevention of further nematocyst discharge, which could intensify pain and enhance toxicity. Many topical therapies have been used for this purpose, including sea water, vinegar, a commercial solution known as Stingose, methylated spirits, ethanol, isopropyl alcohol, dilute ammonium hydroxide, urine, sodium bicarbonate, papain, shaving cream, and sand.

Vinegar is a common first-line treatment for topical application following Cnidaria stings. In vitro trials with *C. fleckeri* tentacles demonstrate complete irreversible inhibition of nematocyst discharge following a 30-second application.⁷¹ Additional study findings include massive nematocyst discharge with application of urine or ethanol, and no effect on discharge with use of sodium bicarbonate. Follow-up in vivo experiments demonstrate that vinegar is effective for other Cubozoa, including Morbakka (large Cubozoan in Australia),⁵¹ *Carybdea rastoni*,⁵⁴ and *C. barnesi*.⁵⁵ Although massive nematocyst discharge occurs when vinegar is applied to *C. capillata* tentacles in vitro, clinical exacerbation following this treatment is not reported in humans.⁵⁰ Massive discharge also occurs with *C. quinquecirrha*.⁵⁸ A smaller degree of discharge (30%) occurs with *P. physalis*,⁵⁸ whereas nematocysts of *P. utriculus* are unaffected by application of vinegar.⁷¹

Stingose is a commercially available product designed to counteract venom of insects, bees, stinging plants, and marine stingers. It is an aqueous solution of 20% aluminum sulfate and 1.1% surfactant. Its purported mechanism of action is denaturing of proteins and long-chain polysaccharides via interactions with the Al^{3+} ion, as well as osmotic removal of venom. A human volunteer trial involving stings from live tentacles of *C. fleckeri* demonstrated pain relief within 5 seconds of Stingose application.⁷³ Similar results were achieved following treatment of stings from *C. quinquecirrha*. Further investigation involved beachside evaluation of 17 *C. fleckeri* and 150 *P. utriculus* sting victims treated with Stingose immediately following injury. All victims reported rapid relief. However, placebo or alternative therapies were not used in this case series. The efficacy of treatment with vinegar, Stingose, methylated spirits, and salt water was measured in human volunteers following forearm application of *P. physalis* tentacles.¹⁴⁷ Vinegar demonstrated superior pain control compared with Stingose, whereas methylated spirits increased pain. The study assessed pain relief only and did not investigate the effects of the treatments on nematocyst discharge or systemic toxicity. A small volunteer study utilizing topical lidocaine reported successful treatment of stings via topical analgesia and reduced nematocyst discharge.¹³

In many cases the identity of the “jellyfish” causing injury is unknown. In those cases, therapy must be guided by geographic location. In the United States, where *P. physalis* and *C. quinquecirrha* are of greatest consequence, sea water should be used to aid in tentacle removal given that vinegar enhances nematocyst discharge in those species. In the Indo-Pacific region, where *C. fleckeri* and *C. barnesi* are of greatest concern, vinegar application confers greater advantage. Following a 30-second application, adherent tentacles must be carefully removed. This can be accomplished with a gloved or towel-covered hand, or with sand and gentle scraping with a credit card or other blunt, straight-edged tool.

In a nonrandomized trial, ice packs provided rapid, effective relief for patients with mild to moderate pain from Cnidaria stings in Australia.⁴⁷ Patients with severe pain were less likely to benefit from ice packs. Many Cnidaria venoms are heat labile and may be neutralized at 122°F (50°C) for 20 minutes leading some clinicians to recommend treating stings with hot water immersion (HWI). However, availability of hot water at the beach and the high temperature needed to neutralize venom limits implementation of this therapy. Some authors suggest that the use of heat is not only ineffective for venom neutralization, but that it also increases pain.¹⁸ However, recent controlled trials designed to address this controversy highlight the efficacy of HWI in lieu of cold packs for the treatment of stings from *Carybdea alata* and *Physalia* spp.^{58,91,107,142,152,161} This finding may relate more to gate control theory of pain and modulation of pain signals rather than venom destruction. HWI therapy for treatment of *C. fleckeri* stings has not been rigorously evaluated.

Pressure immobilization bandaging is a technique that applies sufficient pressure to a wound to impede lymphatic drainage and prevent the entrance of venom into systemic circulation. Its application for snakebites is commonplace outside the United States, while its role following Cnidaria stings has sparked controversy. Given the rapid onset of symptoms, the utility of a technique that impedes lymphatic drainage is unlikely to provide benefit. Although the technique would be used only after tentacle removal, some microscopic nematocysts remain adherent to the skin after visible tentacles are removed. In vitro data investigating the effect of pressure on discharged nematocysts demonstrate not only that discharged nematocysts still contain venom, but that applying pressure forces more venom down the hollow tube.¹¹² This finding is correlated clinically as patients can deteriorate following pressure immobilization bandaging.⁵⁷ Given the lack of evidence suggesting benefit, coupled with clear in vitro evidence of increased venom delivery with this technique, it should not be implemented for treatment of Cnidaria stings.

Box jellyfish antivenom is sheep-derived whole IgG raised against the “milked” venom of *C. fleckeri*. It has been

available in Australia since 1970. Combining *C. fleckeri* venom with box jellyfish antivenom prior to injection into pigs prevents all toxicity.¹⁴³ An isolated chick muscle experiment demonstrates that box jellyfish antivenom prevents the neurotoxicity and myotoxicity from *C. fleckeri* following pretreatment; however, there is no “rescue effect in this research.”¹¹³ Given that antivenom in humans is always used as a rescue therapy, the research raises concerns regarding efficacy in the clinical setting. Pretreatment of rats with box jellyfish antivenom prevented cardiovascular collapse in 40%, but did not blunt the initial hypertensive effect.¹¹⁴ In vitro data demonstrate that box jellyfish antivenom neutralizes the dermatonecrotic, hemolytic, and lethal fractions of venom from *Chiropsalmus* spp; however, the venom of *P. physalis* and *C. quinquecirrha* were not neutralized.¹⁰ Other in vitro and in vivo data demonstrate incomplete neutralization of *Chiropsalmus* spp venom.^{10,113}

There are no controlled studies in humans evaluating the efficacy of box jellyfish antivenom in the treatment of *C. fleckeri* envenomations, nor is there convincing evidence that its administration has saved human lives. Despite the frequency of hospital visits for stings from *C. fleckeri* in Australia, the use of box jellyfish antivenom is rare.⁴² Evidence for its efficacy stems from case reports suggesting that pain abates rapidly after administration.^{15,156} Although box jellyfish antivenom may improve pain control, patients still may require parenteral opioids for analgesia following antivenom administration.¹¹ Significant morbidity and mortality still occur despite antivenom use.^{41,92,136} Case reports of box jellyfish antivenom use for *C. barnesi* stings demonstrate no apparent benefit.⁴⁹

Many serious stings occur in the Northern Territory of Australia, where stinger nets are not commonly used. Distance from medical care limits the ability to obtain antivenom in a timely fashion.⁴² Although box jellyfish antivenom can be administered by paramedics via intramuscular (IM) injection,⁵⁷ poor IM absorption and incomplete venom neutralization with antivenoms, as well as delayed peak serum concentrations, limit the utility of this approach.¹²¹ The amount of antivenom required to neutralize twice the lethal dose in humans is estimated at 12 vials.⁴² The manufacturer recommends treating initially with one ampule intravenously (IV) diluted 1:10 with saline or three undiluted ampules (1.5–4 mL each) IM at three separate sites, if IV access is unavailable. Some authors who have treated multiple patients with antivenom suggest treating coma, dysrhythmia, or respiratory depression with one ampule IV, titrating up to three ampules with continuation of CPR in patients with refractory dysrhythmias until a total of six ampules have been administered.¹⁰⁹ For less serious envenomations, clinicians may consider administering one ampule if ice packs and parenteral analgesia prove ineffective.¹⁰⁹ Serious adverse events or delayed sequelae following the use of IV antivenom are uncommon, although allergic reactions are a consideration.¹³⁷

Verapamil was evaluated as a treatment for *C. fleckeri* stings based on evidence that Ca^{2+} entry into cells represents an important mechanism of toxicity. One animal model demonstrated synergy with use of verapamil in combination with box jellyfish antivenom,²⁸ whereas another showed verapamil pretreatment as well as rescue prolonged survival.²¹ This is in contrast to other models demonstrating that verapamil negates the benefits of antivenom¹¹⁴ and increases mortality.¹⁴³ Verapamil administration to animals with *C. quinquecirrha* envenomation demonstrated no benefit.¹⁰⁴ Interestingly, addition of magnesium to antivenom for treatment of *C. fleckeri* envenomation in rats prevented cardiovascular collapse in 100%, suggesting that magnesium may have a role in the treatment of stings from this species.¹¹⁴ Given that animal data are inconsistent with regard to verapamil and that hypotension may develop with severe envenomation, use of calcium channel blockers is not currently recommended for treatment of *C. fleckeri* stings.

Treatment for Irukandji syndrome should focus on analgesia and blood pressure control. Several modalities for control of severe hypertension have been suggested and include phentolamine, IV magnesium sulfate, and nitroglycerin.^{40,53} Dosing guidelines and efficacy following magnesium infusion for this indication are not established. Whereas hypotension may occur in late stages of toxicity, clinicians should also consider short-acting titratable agents such as esmolol, nitroprusside, or nicardipine.

Mollusca

The phylum Mollusca (Latin mollis meaning soft) includes the classes Cephalopoda (octopus, squid, and cuttlefish) and Gastropoda (cone snails). Cephalopod species of toxicologic concern are limited to the blue-ringed octopus *Hapalochlaena maculosa* and the greater blue-ringed octopus *Hapalochlaena lunulata*. The blue-ringed and greater blue-ringed octopi are found in the Indo-Pacific region, primarily in Australian waters (Fig. 119–2). Of the 400 species of cone snails that belong to the genus *Conus*, 18 are implicated in human envenomations.



FIGURE 119–2 The blue ringed octopus, *Hapalochlaena maculosa*. (Used with permission of Dr. Roy Caldwell, Professor of Integrative Biology, University of California, Berkeley.)

History and Epidemiology. The blue-ringed octopus normally displays a yellow-brown color, but develops iridescent blue rings when threatened. The species is not aggressive and only bites humans when handled. A 1983 review of reported octopus envenomations uncovered a total of 14 cases, all of which occurred in Australia.¹⁴⁹ There were two deaths⁶² and four serious envenomations. Other reviews suggest that up to seven deaths may have occurred prior to 1969, some outside Australia⁴⁵

Estimates of reported cone snail envenomations suggest only 15 human deaths have occurred worldwide.⁴⁸ *Conus geographicus* (fish hunting cone) is the most common species implicated, although *Conus textile* may also cause death in humans. Cone snails predominantly inhabit the Indo-Pacific, including all parts of Australia, New Guinea, Solomon Islands, and the Philippines. Two deaths from *C. geographicus* occurred in Guam.⁸⁵

Pathophysiology. The salivary gland of the blue ringed octopus secretes a toxin originally designated maculotoxin and later identified as tetrodotoxin.¹³¹ The beak of the octopus creates small punctures in human skin through which venom is introduced. Tetrodotoxin blocks Na^+ conductance in neurons, leading to paralysis. Venom also contains serotonin (5-HT), hyaluronidase, tyramine, histamine, tryptamine, octopine, taurine, acetylcholine, and dopamine.¹³⁸ Rabbits subjected to bites develop rapid flaccid paralysis without cardiotoxicity and die from asphyxia. Other animal models using venom gland extract demonstrate rapid onset of respiratory muscle paralysis and severe hypotension.⁶⁰ Death occurs despite artificial respiration and results from hypotension.

Cone snails have a hollow proboscis that contains a tooth bathed in venom. Envenomations occur when the shells are handled. The proboscis can extend the length of its shell, thereby envenomating the hand of someone touching the opposite end of the shell. Any *Conus* species contains approximately 100 peptides or conotoxins in its venom along with hyaluronidases that aid in local tissue breakdown.¹⁴⁸ Targets include voltage- and ligand-gated ion channels as well as G-protein-linked receptors (Table 119–2).^{84,110,141} Many of these peptides are used extensively in laboratory research for their ability to selectively target a variety of specific Ca^{2+} channel subtypes. Venom from *Conus imperialis* (worm hunter) contains a substantial amount of 5-HT, a component not found in any other *Conus* venom tested thus far.⁹⁹ This species also contains a vasopressinlike peptide.¹⁰⁶ The neuropeptide omega-conotoxin, isolated from *Conus magnus*, is valued for its antinociceptive properties that arise from blockade of the N-type voltage-sensitive Ca^{2+} channel in spinal cord afferents.⁹⁸ The Food and Drug Administration approved ziconotide (Prialt, Elan Pharmaceuticals) in 2004 for intrathecal (IT) infusion in patients with severe chronic pain that require IT therapy, and in whom other treatment modalities such as IT morphine are not tolerated or ineffective. Patients reported modest improvements in pain with long-term treatment.¹⁵¹ Frequent side effects such as dizziness, nausea, confusion, and memory impairment limit the broad application of this therapy.

TABLE 119–2. *Conus* Peptide Targets

Receptor Type	Peptide	Mechanism
<i>Ligand-gated ion channels</i>		
Nicotinic	α -Conotoxin	Competitive antagonism
	M1	Neuromuscular junction
	M2	Neuronal receptors
5-HT ₃	σ -Conotoxin	Noncompetitive antagonism
NMDA	Conantokins	Inhibits conductance
<i>Voltage-gated ion channels</i>		
Ca ²⁺	ω -Conotoxin	Channel blockade
Na ⁺	μ -Conotoxin	Channel blockade
	δ -Conotoxin	Delayed channel activation
K ⁺	κ -Conotoxin	Channel blockade
<i>G-protein linked</i>		
Vasopressin receptor	Conopressin-G	Receptor agonism
Neurotensin receptor	Contulakin-G	Receptor agonism

Clinical Manifestations. The blue-ringed octopus creates one or two puncture wounds with its chitinous jaws, inflicting only minor discomfort. A wheal may develop with erythema, tenderness, and pruritus. Tetrodotoxin exerts a curarelike effect characterized by paralysis without depressing mental status. Symptoms include perioral and intraoral paresthesias, diplopia, aphonia, dysphagia, ataxia, weakness, nausea, vomiting, flaccid muscle paralysis, respiratory failure, and death. Detailed case reports describe rapid onset of symptoms.^{32,149} Complete paralysis requiring intubation with findings of fixed and dilated pupils is followed within 24 to 48 hours by near-complete recovery of neuromuscular function. In one reported death, a young man placed the octopus on his shoulder. He subsequently noted a small puncture wound, developed dry mouth, dyspnea, inability to swallow, and became apneic. Asystole occurred 30 minutes after arrival at the hospital despite mechanical ventilation.⁶² Another similar bite resulted in symptom onset at 10 minutes, followed by death at 90 minutes, despite bystander CPR.¹³⁸ With less severe envenomations, cerebellar signs may arise without paralysis. Near-total paralysis with intact mentation resolving over 24 hours is described in humans.¹³⁸

Cone snail envenomation results from careless handling of the animal or rummaging through sand. Cone snails are nocturnal feeders, so they may present more of a hazard to night divers. Localized symptoms range from a slight sting to excruciating pain, tissue ischemia, cyanosis, and numbness. Systemic symptoms include weakness, diaphoresis, diplopia, blurred vision, aphonia, dysphagia, generalized muscle paralysis, respiratory failure, cardiovascular collapse, and coma. Death is rapid and occurs within 2 hours. Based on military medical records of more than 30 cases predating 1970, the mortality rate approaches 25%, with *C. geographicus* causing the most deaths.⁸⁵ Other estimates suggest that, without medical care, mortality may reach 70%.¹⁶⁰ Given the rarity of severe human envenomations from cone snails, the manner of death, whether purely from respiratory insufficiency or direct cardiovascular toxicity, remains unknown.

Diagnostic Testing. Laboratory testing following envenomation from octopi or cone snails should be directed by clinical findings. Although not a widely available assay, tetrodotoxin can be detected in the urine or serum using high-performance liquid chromatography with subsequent fluorescence detection.¹⁰⁸

Management. Primary interventions include maintenance of airway, breathing, and circulation. Some authors recommend hot water (113°–122°F, 45°–50°C,) following cone snail stings for pain relief.⁸⁵ Unlike Cnidaria envenomations, where nematocysts full of venom can persist on the skin and lead to continued venom delivery, stings from the octopus and cone snail mirror those of snakebites, where venom delivery is an immediate and finite event. Therefore, pressure immobilization bandaging may blunt toxin distribution by decreasing lymphatic spread.⁴⁸ Additional measures include local wound care and tetanus prophylaxis. Antivenom is not available for octopus or cone snail venoms.

Echinodermata, Annelida, and Porifera

The Echinodermata phylum includes sea stars, brittle stars, sea urchins, sand dollars, and sea cucumbers. Annelida are segmented worms that include the Polychaetae family of bristle worms. Sponges are classified in the Porifera phylum. One feature that all three phyla share is the passive envenomation of people who mistakenly handle or step on the animals. Most stings from these creatures are mild.

History and Epidemiology. Echinoderms, annelids, and sponges are ubiquitous ocean inhabitants. The crown-of-thorns *Acanthaster planci* is found in the warmest waters of Polynesia to the Red Sea and is a particularly venomous species because of its sharp spines that easily puncture human skin. Sea urchins inhabit all oceans of the world. Bristle worms such

as *Hermodice carunculata* typically inhabit tropical waters such as those of Florida and the Caribbean. However, some species thrive in the frigid waters of Antarctica. The fire sponge *Tedania ignis* is a brilliant yellow-orange sponge identified in large numbers off the coast of Hawaii and in the Florida Keys. Other common American sponges are *Neofibularia nolitangere* (poison-bun sponge or touch-me-not sponge) and *Microciona prolifera* (red sponge). *Neofibularia mordens* (Australian stinging sponge) is a common Southern Australian variety. In the Mediterranean, sponges are often colonized with sea anemones that may inflict severe stings.¹⁶

Pathophysiology. Sea urchins are covered in spines and pedicellariae. The pedicellariae are pincerlike appendages used for feeding, cleaning, and defense. They generally contain more venom than the spines and are more difficult to remove from wounds. Urchins laden with pedicellariae can evoke more severe stings than urchins with less pedicellariae. Venom contained within the spines consists of steroid glycosides, serotonin, hemolysin, protease, and acetylcholinelike substances. Some species harbor neurotoxins. The most venomous are species of *Diadema*, *Echinothrix*, and *Asthenosoma*. Sea stars are less noxious because they generally have short, blunt spiny projections. The crown-of-thorns is the exception with its longer, sharp spines containing toxic saponins with hemolytic and anticoagulant effects as well as histaminelike substances.¹³⁹ Sea cucumbers excrete holothurin, a sulfated triterpenoid oligoglycoside, from the anus (organs of Cuvier) as a defense. The toxin inhibits neural conduction in fish, leading to paralysis. Some sea cucumbers eat Cnidaria and subsequently secrete their venom.

Bristle worms have many parapodia that have the appearance, but not the function, of legs. Several bristles extend from each parapodium giving the family (Polychaeta) its name (poly means many, chaetae means bristles). The bristles may penetrate human skin, leading to envenomation with an unknown substance.

Sponges have an elastic skeleton with spicules of silicon dioxide or calcium carbonate. They attach to the sea floor or coral beds. Toxins include halitoxin, odadaic acid, and subcritine, the nature of which is uncertain.²² Dried sponges are nontoxic; however, on rewetting they may produce toxicity even after several years.¹³⁴

Clinical Manifestations. Most injuries from sea urchins are caused by inadvertently stepping on the spines or attempting to handle the animal. An intense burning with local tissue reaction occurs, including edema and erythema. Rarely, with multiple punctures, lightheadedness, numbness, paralysis, bronchospasm, and hypotension may reportedly occur, although this is not documented in the peer-reviewed medical literature.³ Reports of death are not well substantiated. The Pacific urchin *Tripneustes* has a neurotoxin with a predilection for cranial nerves.¹⁶ Mild elevations of hepatic enzymes are reported in one patient with foot cellulitis from an urchin sting.¹⁵⁹ Small cuts on the skin from handling starfish may allow venom to penetrate, leading to contact dermatitis. The crown-of-thorns may cause severe pain, nausea, vomiting, and muscular paralysis.⁹⁷ Cutaneous, scleral, or corneal exposure to sea cucumbers triggers contact dermatitis, intense corneal inflammation, and even blindness. Bristle worms are shrouded with bristles that can produce a reddened urticarial rash. Symptoms typically are mild and resolve over several hours to days.

Contact with the fire sponge, poison-bun sponge, or red-moss sponge causes erythema, papules, vesicles, and bullae that generally subside within 3 to 7 days. Victims may develop fever, chills, and muscle cramps. Skin desquamation occurs at 10 days to 2 months,⁴ with chronic skin changes lasting several months.²² Erythema multiforme and anaphylaxis are uncommon complications associated with *Neofibularia* spp exposure.¹⁶ Contact with sponges that are colonized with Cnidaria can lead to dermatitis with skin necrosis, referred to as sponge diver's disease.

Management. The primary objective following envenomation from sea urchins and crown-of-thorns starfish is analgesia. Submersion of the affected extremity in hot water (105°–115°F, 40.6°–46.1°C) and administration of oral analgesics often is sufficient.^{48,97} Puncture wounds require radiographic evaluation to locate potential foreign bodies. Spines frequently crumble with attempted extraction. Intraarticular spines necessitate surgical removal. Decisions regarding spines in other locations should be influenced by ease of removal, presence of infection, and persistent pain. Tetanus immune status must be addressed. Decisions regarding antibiotic prophylaxis should be based on degree of injury and patient factors such as diabetes or other comorbidities. Although most infections likely are secondary to human skin flora, marine flora such as *Mycobacterium marinum* and *Vibrio parahaemolyticus* are potential wound contaminants. Treatment of sponge exposures usually requires only removal of spicules using adhesive tape or the edge of a credit card. Antihistamines and topical corticosteroids often provide no relief from stinging sponges.²²

VERTEBRATES

Snakes

Sea snakes are members of the class Reptilia and are divided into two subfamilies: Hydrophiinae and Laticaudinae. They are close relatives of the cobra and krait. Length typically does not exceed 1 m. Their tails are flattened, and their bodies often are brightly colored. Distinction from eels is made by the presence of scales and the absence of fins and gills. All 52 species of sea snakes are venomous and at least six species are implicated in human fatalities. The most common species cited in human envenomation are *Enhydrina schistosa*, the beaked sea snake, and *Pelamis platurus*, the yellow-bellied sea

snake.

History and Epidemiology. Sea snakes are common to the tropical and temperate Indian and Pacific Oceans, but they are also found along the eastern Pacific Coast of Central and South America and the Gulf of California. In the eastern Pacific region, the yellow-bellied sea snake is the only species known. There are no sea snakes in the Atlantic Ocean. The majority of envenomations occur along the coasts of Southeast Asia, the Persian Gulf, and the Malay Archipelago (Malaysia). Snakes tend to inhabit the turbid coastlines and deeper reefs of these regions.

The true incidence of sea snake envenomation is unknown because many bites are not recorded. Worldwide the number of deaths per year may approach 150, with an overall mortality rate estimated at 3%.⁴⁸ In a review of 120 documented bites, 51.7% of victims were fishermen handling nets.¹¹⁸ The remainder of victims were wading or swimming along the coastline. In a review of 101 bites occurring from 1957 to 1964 in Northwest Malaysia, more than 50% of bites were from the beaked sea snake, including seven of the eight fatal bites in that series, bringing the mortality to 8% prior to the availability of antivenom.¹²⁰ However, 31 “dry bites” were excluded, suggesting that the overall mortality is somewhat lower. Among the 20% of patients in that series suffering “serious envenomation,” half died despite supportive care. A follow-up series of patients after the introduction of antivenom described 2 deaths out of 11 “serious envenomations,” suggesting a decreased mortality resulting from this intervention. These were all retrospective reviews of published or personally communicated cases.

Pathophysiology. All sea snakes have small front fangs. Their venom is neurotoxic, myotoxic, nephrotoxic, and hemolytic. Known components of the venom include acetylcholinesterase, hyaluronidase, leucine aminopeptidase, 5'-nucleotidase, phosphodiesterase, and phospholipase A. The neurotoxin is a highly stable 6000-to 8000-Da protein similar to that of cobra and krait venom. In mice, beaked sea snake venom is four to five times more potent than cobra venom based on a $\mu\text{g/kg}$ ratio; however, cobra venom yield is greater.³¹ Venom homology exists across many species.⁷⁷ The neurotoxin targets postsynaptic acetylcholine (ACh) receptors creating a blockade at the neuromuscular junction.¹⁴⁰ Presynaptic effects include initial enhanced ACh release and subsequent inhibition of ACh release.^{103,120,150} In vitro research confirms direct nephrotoxicity of crude venom and may partially explain the nephrotoxicity described clinically.¹³⁰ Rhabdomyolysis likely contributes to this clinical finding.

Clinical Manifestations. Sea snakes generally are docile, except when provoked, or during the mating season. Bites typically are painless or inflict minimal discomfort. Between one and four fang marks are common; however, up to 20 fang marks are possible as a result of multiple bites. The diagnosis can be obscured because victims may not associate the slight prick following the bite with later onset of ascending paralysis. Symptoms may progress within minutes, although a delay of up to 6 hours is possible. Neurotoxin-induced paralysis occurs in conjunction with muscle destruction stemming from myotoxic fractions. Painful muscular rigidity and myoglobinuria are hallmarks of sea snake myotoxicity. Myoglobinuria develops between 30 minutes and 8 hours after the bite. Other classic symptoms include ascending flaccid paralysis, dysphagia, trismus, ptosis, aphonia, nausea, vomiting, fasciculations, and ultimately respiratory insufficiency, seizures, and coma.

Diagnostic Testing. Laboratory diagnostics are directed toward identifying hemolysis, myonecrosis, hyperkalemia, and acute kidney injury. Serum electrolytes, creatinine, and creatine phosphokinase, as well as hematocrit and urinalysis, should be obtained. Elevated concentrations of hepatic enzymes may indicate severe envenomation. Serial measurement of these parameters is recommended.

Management. Prehospital management of sea snakebites mirrors treatment of terrestrial snakebites (Chap.122) and includes immobilization of the extremity and consideration of a pressure immobilization bandage to impede lymphatic drainage. Currently no data regarding the efficacy of this technique for sea snake envenomations are available. Tourniquets that impede venous or arterial flow are not recommended and may be detrimental. Airway and respiratory effort require close monitoring because paralysis can develop rapidly.

The most commonly used antivenoms for sea snakes are equine IgG Fab fragments produced using the venom of beaked sea snake (*E. schistosa*) or terrestrial tiger snake (*Notechis scutatus*) (Table 119–3). In vitro experiments demonstrate that sea snake antivenom is effective for neutralizing all species of sea snakes tested (*Praescutata viperina* in Thailand, *P. platurus* in Central America, *Laticauda semifasciata* in the Philippines, *Laticauda laticaudata* in Japan, *Hydrophis cyanocinctus*, *Lapemis hardwickii*).¹⁴⁶ Optimal neutralization occurs within the subfamily Hydrophiinae, which contains *E. schistosa*; however, effective neutralization is demonstrated within the subfamily Laticaudinae. Terrestrial tiger snake antivenom also can neutralize sea snake venom in vitro. Based on the volume of antivenom required, tiger snake antivenom was superior for neutralization of all sea snake venoms tested except that of the beaked sea snake, for which sea snake antivenom was more effective.⁷ This finding is expected because sea snake antivenom is raised against beaked sea snake venom. In contrast to volume comparisons, measurements of unit dosing demonstrate sea snake antivenom is more effective for all venoms tested. Another in vitro study comparing tiger snake and sea snake antivenom against venom *E. schistosa* demonstrated tiger snake antivenom was 10 times more effective in terms of milligram of venom neutralized per milliliter of antivenom.¹⁰² In the same study, the use of 17 different types of elapid antivenom resulted in poor neutralization of beaked sea snake venom.

TABLE 119–3. Antivenoms

Organism	Derivation	Concentration
<i>Box jellyfish</i> <i>C. fleckeri</i>	Ovine, whole IgG	20,000 Units/ampule
<i>Sea snake</i> <i>E. schistose</i> (beaked sea snake)	Equine, IgG Fab	1000 Units/ampule
<i>N. scutatus</i> (terrestrial tiger snake)	Equine, IgG Fab	3000 Units/ampule
<i>Stonefish</i> <i>S. trachynis</i>	Equine, IgG Fab	2000 Units/ampule

CSL = Commonwealth Serum Laboratories, Melbourne, Australia manufacture these antivenom.

In rescue experiments with mice using 11 sea snake venoms and 4 different antivenoms (*E. schistosa*, *E. schistosa*-*N. scutatus*, *N. scutatus*, and polyvalent sea snake *L. hardwickii*, *L. semifasciata*, *H. cyanocinctus*), tiger snake antivenom was superior to all others with respect to volume amount required to prevent death.^{2,8,64} Another finding of the study was improved efficacy with early administration of antivenom.

No controlled human trials have evaluated the efficacy of sea snake antivenom, although case reports suggest improved outcomes and more rapid recovery with its use.^{101,120} Anecdotal experience in Malaysia using sea snake antivenom suggests slow recovery from myalgias and weakness over 48 hours, compared with resolution over 2 weeks without antivenom (two cases, one control).¹¹⁹

Based on in vitro and in vivo research, selection of the optimal antivenom for treatment of sea snakebites is unclear. Both sea snake and tiger snake antivenom are effective in neutralizing a wide variety of sea snake venoms. Therefore, the most readily available antivenom should be used when needed. Commonwealth Serum Laboratories manufactures both monovalent sea snake and tiger snake antivenom for use in Australia. However, there is limited distribution to aquariums and zoos outside Australia. The manufacturer's guidelines for use of monovalent sea snake antivenom recommend administration of one ampule (1000 units) for systemic symptoms. However, because symptoms may be delayed and early administration is more likely to result in venom neutralization, any evidence of envenomation should prompt the administration of antivenom. The antivenom requires a 1:10 dilution with 0.9% sodium chloride solution followed by administered IV over 30 minutes. A 1:5 dilution can be used for small children. Skin testing is not recommended. Epinephrine and antihistamines should be readily available. No upper limit is suggested for the number of vials to administer, although larger amounts are more likely to result in serum sickness. Patients have received up to 7000 units without adverse effect directly attributable to the antivenom.¹⁰¹ One ampule (3000 units) of tiger snake antivenom can be used as an alternative if sea snake antivenom is unavailable. Other treatments should focus on wound care, tetanus prophylaxis, analgesia, and fluid administration to minimize nephrotoxicity from myoglobinuria.

Fish

Stingrays are members of the class Chondrichthyes (order Rajiformes: skates and rays). Families include Dasyatidae (whip ray or sting ray), Urolophidae (round ray), Myliobatidae (batfish or eagle ray), Gymnuridae (butterfly ray), and Potamotrygonidae (river ray, freshwater).

Spiny fish of the family Scorpaenidae include a variety of venomous creatures (Table 119–4). Fish of the genus *Pterois* are commonly called lionfish (*P. volitans* and *P. lunulata*). Stonefish are grouped under the genus *Synanceja* and include *S. trachynis* (Australian estuarine stonefish), *S. horrida* (Indian stonefish), and *S. verrucosa* (reef stonefish). They are unattractively disguised to blend in with the rocky sea bottom (Fig. 119–3). Scorpionfish have a similar appearance and belong to the genus *Scorpaena* (eg, *S. guttata*: California sculpin). Other Scorpaenidae include *Notesthes robusta* (bullrout) and *Gymnapistes marmoratus* (cobbler). The European weeverfish produce toxicity similar to members of Scorpaenidae and are classified under the family Trachinidae. This includes *Trachinus vipera* (lesser weever) and *Trachinus draco* (greater weever, aka adderpike, stingfish, seacat). These bottom dwellers are smaller and have fewer spines than Scorpaenidae and are much less ghoulish in appearance. Catfish also may envenomate humans. Although most live in freshwater, marine catfish such as *Plotosus lineatus* can inflict injury. Other venomous spiny fish include rabbitfish, stargazers, toadfish, ratfish, and even some sharks that have spines on their dorsal fins (Port Jackson shark, dogfish shark).

TABLE 119–4. Spiny Fish

<i>Latin Name</i>	<i>Common Name</i>	<i>Habitat</i>
Scorpaenidae family		
<i>Pterois</i>		
<i>P. volitans</i>	Lionfish (also zebrafish, turkeyfish, or red firefish)	Indo-Pacific region, coast of Florida to North Carolina (nonnative to US coast)
<i>P. lunulata</i>	Lionfish or butterfly cod	
<i>Synanceja</i>		
<i>S. trachynis</i>	Australian estuarine stonefish	Indo-Pacific region (Pacific and Indian Oceans)
<i>S. horrida</i>	Indian stonefish	
<i>S. verrucosa</i>	Reef stonefish	
<i>Scorpaena</i>		
<i>S. cardinalis</i>	Red rock cod, scorpionfish	Coast of Australia
<i>S. guttata</i>	California sculpin, scorpionfish	Coast of California
<i>Notesthes robusta</i>	Bullrout	Coast of Australia
<i>Gymnapistes marmoratus</i>	Cobbler	Coast of Australia
Trachinidae family		
<i>Trachinus</i>		
<i>T. vipera</i>	Lesser weeverfish	Coasts of Great Britain to Northwest Africa, throughout
<i>T. draco</i>	Greater weeverfish (also adderpike, stingfish, or seacat)	Mediterranean and Black Seas

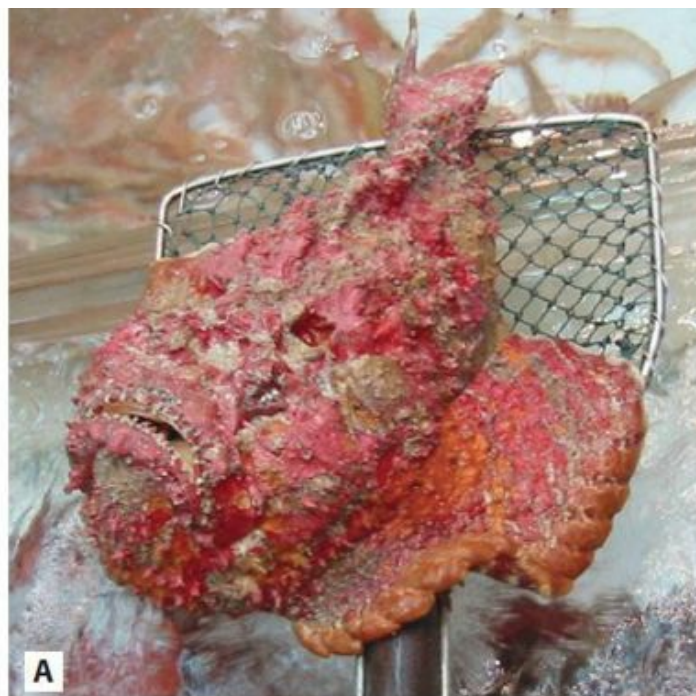


FIGURE 119-3 The stonefish, *Synanceja* spp. Note the stinging spines on the close-up. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

History and Epidemiology. There are 11 different species of stingrays in US coastal waters (seven in the Atlantic, four in the Pacific). In the southeastern United States, *Dasyatis americana* is a common inhabitant. *Urolophus halleri* is the most common species on the western coast of the United States. Some estimates suggest 1500 to 2000 stingray injuries occur yearly in the United States. Most envenomations occur when the animal is inadvertently stepped on. In one review a total of 17 fatalities resulting from trunk wounds, hemorrhage, or tetanus were identified worldwide.⁴⁸ Another review of 603 cases of stingray injuries identified two deaths resulting from intraabdominal trauma.¹²⁴

Three populations are at highest risk for spiny fish envenomation: fishermen sorting the catch from nets, waders, and aquarium enthusiasts. Only five deaths from Scorpaenidae have been reported; all resulted from stonefish and are poorly documented.^{39,48} No deaths from stonefish are reported in Australia, a country where they are commonly found in coastal waters.⁴² The incidence of weeverfish stings is unknown, but they are a common occurrence in the summertime among Italian coastal towns.^{30,133} Scorpaenidae inhabit waters throughout the tropical and temperate oceans. They exist as far north as the Gulf of Oman and Southern Japan and extend south beyond New Zealand. In the United States, Scorpaenidae stings occur in the Florida Keys, in the Gulf of Mexico, off the coast of California, and in Hawaii. Lionfish (genus *Pterois*) (Fig. 119-4) are common to home aquariums and account for most poison center calls involving spiny fish envenomation in the United States. The bullrout inhabits the eastern coast of Australia, along with the cobbler, which is found only in Australia. Weeverfish inhabit shallow temperate waters with sandy or muddy bottoms in the eastern Atlantic and Mediterranean, including the European Coast extending to the southern tip of Norway.²⁹ The marine catfish lives in the tropical Indo-Pacific waters.

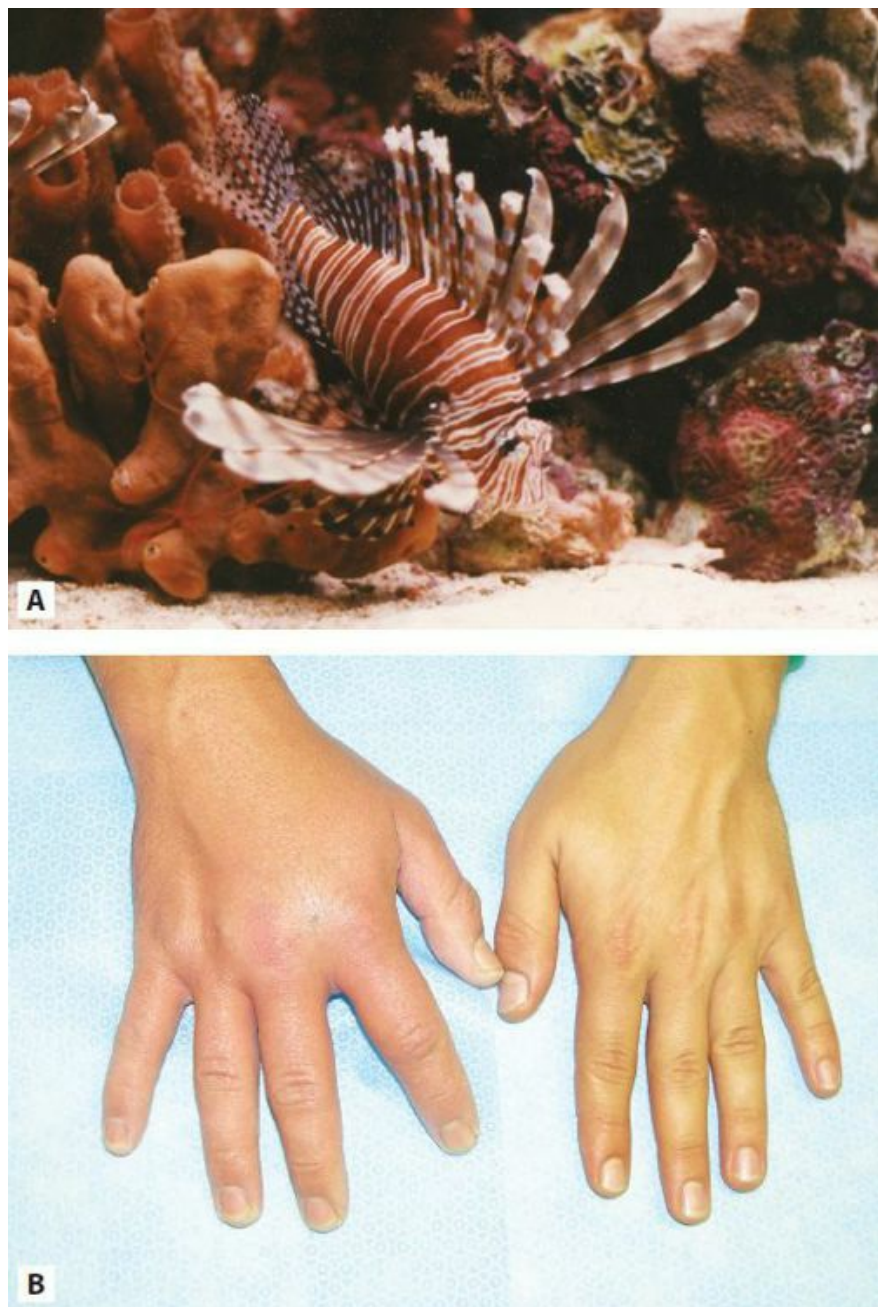


FIGURE 119-4 (A) The lionfish, *Pterois volitans*. (B) This patient's hand was envenomated by his pet lionfish while cleaning his aquarium. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Pathophysiology. Tapered, bilaterally retroserrated spines covered by an integumentary sheath emanate from the stingray tail. The ventrolateral groove contains venom glands that saturate the spine with venom and mucus. The venom contains several amino acids, serotonin, 5'-nucleotidase, and phosphodiesterase.⁴ In animal models, venom induces local vasoconstriction, bradydysrhythmias, atrioventricular nodal block, subendocardial ischemia, seizures, coma, cardiovascular collapse, and death.^{3,124} A rabbit model demonstrates initial vasodilation followed by vasoconstriction and cardiac standstill, suggesting a direct cardiac effect.¹²⁵ Wound specimens reveal necrotic muscle and neutrophilic infiltrates.⁶ Other reports show central hemorrhagic necrosis with surrounding lymphoid and eosinophilic infiltrates indicating an immune-mediated cause of delayed wound healing.⁶⁷

Scorpaenidae have 12 to 13 dorsal, 2 pelvic, and 3 anal spines that are covered with an integumentary sheath. Glands at the base contain 5 to 10 mg of venom each. Ornate pectoral fins are not venomous. Venom can remain stable for 24 to 48 hours after the fish dies.⁹⁶ Three main toxins have been isolated from various species of stonefish: stonustoxin (SNTX), verrucotoxin (VTX), and trachynilysin (TLY). SNTX, from *S. horrida*,⁶⁸ has two subunits, α and β (71,000 and 79,000 Da, respectively). It induces formation of hydrophilic pores in cell membranes.³³ Toxicity in animals includes hemolysis, local edema, vascular permeability, platelet aggregation, endothelium-dependent vasodilation, and hypotension. Decreased myocardial contractility occurs in rabbits.¹²⁸ Heating stonefish venom to 122°F (50°C) for 5 minutes prevents wound necrosis and hypotension in animal models.¹⁵³ VTX, isolated from *S. verrucosa*, shares homology with SNTX in that both block cardiac Ca^{2+} channels.⁶⁶ TLY, isolated from *S. trachynis*, is a 159-kDa protein that forms pores in cell membranes. It allows Ca^{2+} entry and causes Ca^{2+} -dependent release of ACh from nerve endings at motor end plates and increased catecholamine release.^{81,111,129} *S. trachynis* venom causes endothelium-dependent vasodilation and cardiovascular collapse

in rats, which appears to be mediated by muscarinic and adrenergic receptors.³⁴ Hemolysis is demonstrated in animals but does not occur in humans.⁸⁰ Other venoms of Scorpaenidae include hyaluronidase, proteinase, phosphodiesterase, alkaline phosphomonoesterase, arginine esterase, arginine amidinase, 5'-nucleotidase, acetylcholinesterase, and biogenic amines. Crude venom from *G. marmoratus*, *P. volitans*, and *S. trachynis* leads to increased intracellular Ca^{2+} and muscle contracture in vivo.³⁷ Toxins from other spiny fish include dracotoxin (*T. draco*), trachinine (*T. vipera*), and nocitoxin (*N. robusta*).³⁶ Effects mirror those of Scorpaenidae toxins.¹³²

Clinical Manifestations. Stepping on the body of a stingray causes a reflexive whip of the tail leading to wounds in the lower extremity. Intense pain out of proportion to the appearance of the wound is characteristic. Symptoms peak 30 to 90 minutes after injury and may persist for 48 hours. Local edema, cyanosis, erythema, and petechiae may follow rapidly and may lead to necrosis and ulceration. Systemic symptoms include weakness, nausea, vomiting, diarrhea, vertigo, headache, syncope, seizures, muscle cramps, fasciculations, hypotension, and dysrhythmias. Chest and abdominal wounds, as well as tetanus, have caused death.¹¹⁷

Stings from stonefish produce immediate, severe pain with rapid wound cyanosis and edema that may progress up the injured extremity. Pain reaches a maximum after 30 to 90 minutes and usually resolves over 6 to 12 hours, although pain may persist for days. Headache, vomiting, abdominal pain, delirium, seizures, limb paralysis, hypertension, respiratory distress, dysrhythmias, congestive heart failure, and hypotension characterize systemic toxicity.⁸³ Wound healing may require months.

A poison center case series from 1979 to 1988 identified 23 cases of *P. volitans* envenomation.¹⁴⁵ Reported symptoms included pain, swelling, nausea, numbness, joint pain, anxiety, headache, dizziness, and cellulitis. Another Poison Center series identified 51 Scorpaenidae stings (45 *P. pterois*, 6 *S. guttata*).⁷⁹ Intense pain was reported in 98%, extension of pain to the limb in 22%, swelling in 58%, and systemic signs (nausea, diaphoresis, dyspnea, chest pain, abdominal pain, weakness, hypotension, and syncope) in 13%. Thirteen percent of patients in the series developed wound infection; one patient's wound healing was delayed several weeks. Stings from weeverfish are similar to Scorpaenidae envenomation and rarely result in death.¹⁴ Injury from catfish stings is comparable to that of other stinging fish.⁴⁴

Management. Wounds inflicted by stingrays and spiny fish should be carefully examined for imbedded foreign material. Radiographs may uncover retained spines. Stingray wounds can be extensive and require surgical attention for vascular or tendonous disruption. Tetanus immune status should be addressed. Prophylactic antibiotics may decrease rates of wound infection.³⁸ In a series of 51 stings from *P. pterois* and *S. guttata*, 80% of patients had complete relief of local pain with hot water immersion.⁷⁹ Hot water produces similar relief for pain from weeverfish stings.¹²³ A review of 119 stingray envenomations demonstrates comparable efficacy with hot water immersion.³⁸ Although patients occasionally required a single dose of oral or parenteral analgesia, clinicians rarely prescribed analgesics upon discharge. In a human volunteer study in which subjects received a subcutaneous injection of stingray venom, severe pain developed immediately, and was alleviated with water heated to 122°F (50°C).¹²⁴ Pain increased with application of cold water. Local lidocaine infiltration provides an alternate modality for pain control.⁵⁹

Stonefish antivenom, an equine-derived IgG Fab fragment, is raised against the venom of *S. trachynis*. Each ampule contains 2000 units and neutralizes 20 mg venom. Between 1965 and 1981, antivenom was used in at least 267 cases.⁴² Anecdotal reports suggest it provides effective relief from pain.^{42,154} In a review of 26 documented cases in Australia where antivenom was administered IM, no acute adverse effects were identified.¹³⁷ Two of 15 patients who had follow-up visits suffered serum sickness. Rash may develop several days postinjection.¹⁵⁴ In vitro and in vivo research with the antivenom demonstrates neutralization of venom from *G. marmoratus*³⁵ and *P. volitans*³⁶; however, the application for human therapy remains untested.

The manufacturer recommends IM administration of stonefish antivenom, although IV administration may be considered. Administration is indicated for systemic toxicity or refractory pain. The number of puncture wounds guides therapy: one vial for one to two punctures, two vials for three to four punctures, and three vials for five or more punctures. Epinephrine and diphenhydramine should be readily available for treatment of anaphylactic reactions.

SUMMARY

- Fatalities from marine envenomations are rare. However, significant morbidity may result from bites and stings, including severe pain, retained foreign bodies, infection, respiratory compromise, hemodynamic instability, and a variety of other end organ toxicities.
- Special attention is required when treating envenomations inflicted by box jellyfish or sea snakes. These injuries are not uncommon and may result in serious harm or even death. Knowledge of the clinical manifestations and available antidotes may reduce morbidity.
- A thorough understanding of the mechanisms of toxicity and expected clinical course following envenomations from marine creatures will provide clinicians with the ability to manage these injuries effectively.

- Interventions should focus on patient comfort and recognition of potential complications.
- Hot water immersion (HWI) may provide adequate analgesia from a number of different species of Cnidaria, as well as stings from a variety of spiny fish.

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120 MUSHROOMS

Lewis R. Goldfrank

The diversity of mushroom species is evident in our grocery stores, our restaurant menus, and our environment. The enhanced interest in mushrooms has led to experimentation by young and old—old citizens and our newest immigrants and our young children reaching for what might become an innocuous or a serious ingestion. Rigor in analyzing the possible ingestion is indispensable for physicians treating a patient who has ingested a mushroom of concern. This chapter offers general information of the most consequential toxicologic groups of mushrooms and emphasizes clinical diagnosis over mushroom identification.

EPIDEMIOLOGY

Unintentional ingestions of mushrooms particularly in children represent a small but relatively constant percentage of consultations requested from poison centers ([Chap. 136](#)). A summary of a quarter century of American Association of Poison Control Centers (AAPCC) data reveals that mushrooms represent less than 0.25% of the reported human exposures. Combined data accumulated by the AAPCC and the Mushroom Poisoning Registry of the North American Mycological Association indicates that approximately 5 patient exposures to toxic mushrooms per 100,000 persons occur per year. Some variations result from geographic and climatic conditions and mycologic habitats.¹²¹ Although the methods of analysis of patients with mushroom exposure have changed over the past 30 years, cumulative AAPCC data consistently demonstrate the relative benignity of the vast majority of exposures. The inability of most health care providers to correctly identify the ingested mushroom and the rarity of lethal outcomes are demonstrated by the accumulated data. In 75% to 95% of cases, the exact species was unidentified¹²¹ ([Chap. 136](#)). More than 50% of exposed individuals had no symptoms. Most patients were treated at home and rarely had major toxicity. During the 30 years covered by the AAPCC data, fewer than 100 patients died of their mushroom ingestion. Of the mushrooms associated with death, most were *Amanita* spp and several were hallucinogens, *Boletus* spp, gyromitrin-containing mushrooms, while others remained unidentified. All reported deaths occurred in adults. Those containing either hallucinogens or gastrointestinal (GI) toxins were the most common reported exposures, yet they accounted for less than 10% of all mushroom exposures. All other presumed exposures represented less than 2% of the total number of identified. Because 75% to 95% of mushrooms involved in exposures are never identified, a strategy for making significant decisions with incomplete data is essential.

CLASSIFICATION AND MANAGEMENT

This chapter does not address molds, mildews, and yeasts, which in addition to mushrooms are all categorized as fungi. The unifying principle for fungi is the lack of the photosynthetic capacity to produce nutrition. Survival is achieved by the enzymatic capacity of these organisms to integrate into living materials and digest them. Molds are ubiquitous and often associated with varied adverse health effects such as rhinitis, rashes, headaches, and asthma.²¹ Trichothecenes are mold-related mycotoxins that are discussed in [Chap. 133](#) as potential biological weapons. All other molds are not associated with toxicologic emergencies concerns and are not addressed in this chapter.

Because mushroom species vary widely with regard to the xenobiotics they contain, and because identifying them with certainty is difficult, a clinical system of classification is more useful than a taxonomic system ([Table 120–1](#)). The text and tables that follow utilize the commonest species associated with a particular syndrome or xenobiotic and are not meant to be inclusive of all the exceptionally diverse mushrooms associated with many xenobiotics. In many instances the taxonomy has changed, confusing readers and investigators. For example, the text will use the current nomenclature, whereas the citations will obviously utilize prior nomenclature. In many cases, management and prognosis can be determined with a high degree of confidence from the history and the geographic origin of the mushroom, the initial signs and symptoms, the organ system or systems involved, and coexistent factors or conditions.^{31,58,75,76,104}

TABLE 120–1. Mushroom Toxicity Overview

<i>Representative Genus/Species</i>	<i>Xenobiotic</i>	<i>Time of Onset of Symptoms</i>	<i>Primary Site of Toxicity</i>	<i>Symptoms</i>	<i>Mortality</i>	<i>Specific Therapy*</i>
I <i>Amanita phalloides</i> , <i>A. tenuifolia</i> , <i>A. virosa</i> <i>Galerina autumnalis</i> , <i>G. marginata</i> , <i>G. venenata</i> <i>Lepiota josselynii</i> , <i>L. helveola</i>	Cyclopeptides Amatoxins Phallotoxins	5–24 hours	Liver	Phase I: GI toxicity— N/V/D Phase II: Quiescent Phase III: N/V/D, jaundice, ↑ AST, ↑ ALT	0%–30%	Activated charcoal Hemoperfusion/hemodialysis Penicillin G? N-Acetylcysteine Silibinin
II <i>Gyromitra ambigua</i> , <i>G. esculenta</i> , <i>G. infula</i>	Gyromitrin (metabolite: monomethylhydrazine)	5–10 hours	CNS	Seizures, abdominal pain, N/V, weakness, hepatorenal failure	Rare	Benzodiazepines, Pyridoxine 70 mg/kg IV
III <i>Clitocybe dealbata</i> , <i>Omphalotus olearius</i> , most <i>Inocybe</i> spp	Muscarine	0.5–2 hours	Autonomic nervous system	Muscarinic effects— salivation, bradycardia, lacrimation, urination, defecation, diaphoresis	Rare	Atropine—Adults: 1–2 mg Children: 0.02 mg/kg with a minimum of 0.1 mg
IV <i>Coprinopsis atramentaria</i>	Coprine (metabolite: 1-aminocyclopropanol)	0.5–2 hours	Aldehyde dehydrogenase	Disulfiramlike effect with ethanol, tachycardia, N/V	Rare	Symptomatic care
V <i>Amanita gemmata</i> , <i>A. muscaria</i> , <i>A. pantherina</i>	Ibotenic acid, muscimol	0.5–2 hours	CNS	GABAergic effects, rare delirium, hallucinations, dizziness, ataxia	Rare	Benzodiazepines during excitatory phase

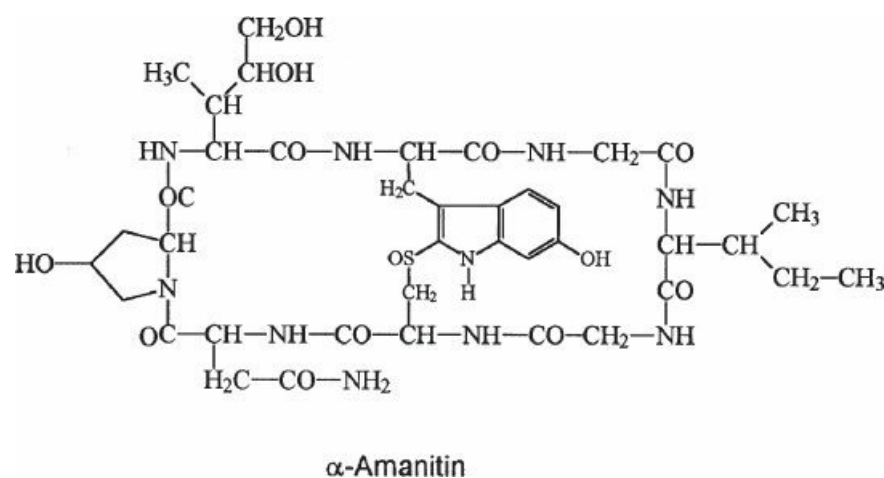
VI <i>Psilocybe cyanescens</i> , <i>P. cubensis</i> <i>Gymnopilus spectabilis</i> <i>Psathyrella loebliae</i>	Psilocybin, psilocin	0.5–1 hours	CNS	Ataxia, N/V, hyperkinesia, hallucinations, illusions	Rare	Benzodiazepines
VII <i>Clitocybe nebularis</i> <i>Chlorophyllum molybdites</i> , <i>C. esculentum</i> <i>Lactarius</i> spp, <i>Paxillus involutus</i>	Various GI irritants	0.3–3 hours	GI	Malaise, N/V/D	Rare	Symptomatic care
VIII <i>Cortinarius orellanus</i> , <i>C. rubellus</i>	Orellanine, orellanine	> 1 day–weeks	Renal	Phase I: N/V Phase II: Oliguria, kidney failure	Rare	Hemodialysis for acute kidney injury
IX <i>Amanita smithiana</i> <i>A. proxima</i>	Allenic norleucine	0.5–12 hours	Renal	Phase I: N/V Phase II: Oliguria, kidney failure	None	Hemodialysis for acute kidney injury

X	<i>Tricholoma equestre</i>	Unidentified	24–72 hours	Muscle (skeletal and cardiac)	Fatigue, nausea, muscle weakness, myalgias, ↑ CK, facial erythema, <i>disseminated intravascular coagulation</i>	25%	Sodium bicarbonate, hemodialysis for acute kidney injury
XI	<i>Clitocybe acromelalgia</i> , <i>C. amoerolens</i>	Acromelic acids	24 hours	Peripheral nervous system	Erythromelalgia paresthesias—hands and feet, dysesthesias, erythema, edema	None	Symptomatic care
XII	<i>Pleurocybella porrigens</i>	Unknown	1–31 days	CNS	Encephalopathy, convulsions, myoclonus in patients with chronic kidney failure	High (30%)	Hemodialysis
	<i>Haploporus rutilans</i>	Polyporic acid	> 12 hours	GI, CNS	N/V, abdominal pain, vertigo, ataxia, drowsiness, encephalopathy	None	Symptomatic care
XIII	<i>Pisillius involutus</i> , ? <i>Clitocybe claviceps</i> , ? <i>Boletus luridus</i>	Immune mediated response to involutin	Following repeated exposure 0.5–3 hours	Red blood cell, kidney	Hemolytic anemia, acute kidney injury	Rare	Hemodialysis
XIV	<i>Lycoperdon perlatum</i> , <i>L. pyriforme</i> , <i>L. gemmatum</i>	Spores	Hours	Pulmonary, GI	Cough, shortness of breath, fever, nausea, vomiting	None	Corticosteroids

*Supportive care (fluids, electrolytes and antiemetics) as indicated.

D = diarrhea; N = nausea; V = vomiting.

Group I: Cyclopeptide Containing Mushrooms



Worldwide most mushroom fatalities are associated with cyclopeptide-containing species.^{5,32,138} In the United States, there are two distinct ranges of the fungus *Amanita* species along the West Coast (California to British Columbia) and along the East Coast (Maryland to Maine).¹³⁶ These cyclopeptide-containing species mushrooms include a number of *Amanita* species, including *A. verna*, *A. virosa*, and *A. phalloides*; *Galerina* spp, including *G. autumnalis*, *G. marginata*, and *G. venenata*; and *Lepiota* species, including *L. helveola*, *L. josserandi*, and *L. brunneoincarnata* (Fig. 120–1).



FIGURE 12-1 Group I: Cyclopeptide containing mushrooms. (A) *Amanita phalloides* and (B) *Amanita virosa*. (Used with permission of John Plischke III.)

Early differentiation of cyclopeptide poisonings from other types of mushroom poisoning is difficult (Fig. 120-2). Patients poisoned with cyclopeptides may be ill enough to seek health care for nausea, vomiting, abdominal pain, and diarrhea, which in the absence of a rigorous detailed history often is attributed to other causes as the patient improves with supportive care. Such patients may be sent home, only to return moribund on a subsequent day. The delayed onset of more serious symptoms is typical of cyclopeptide toxicity and is a critical consideration in assessing the toxicologic potential of any exposure.

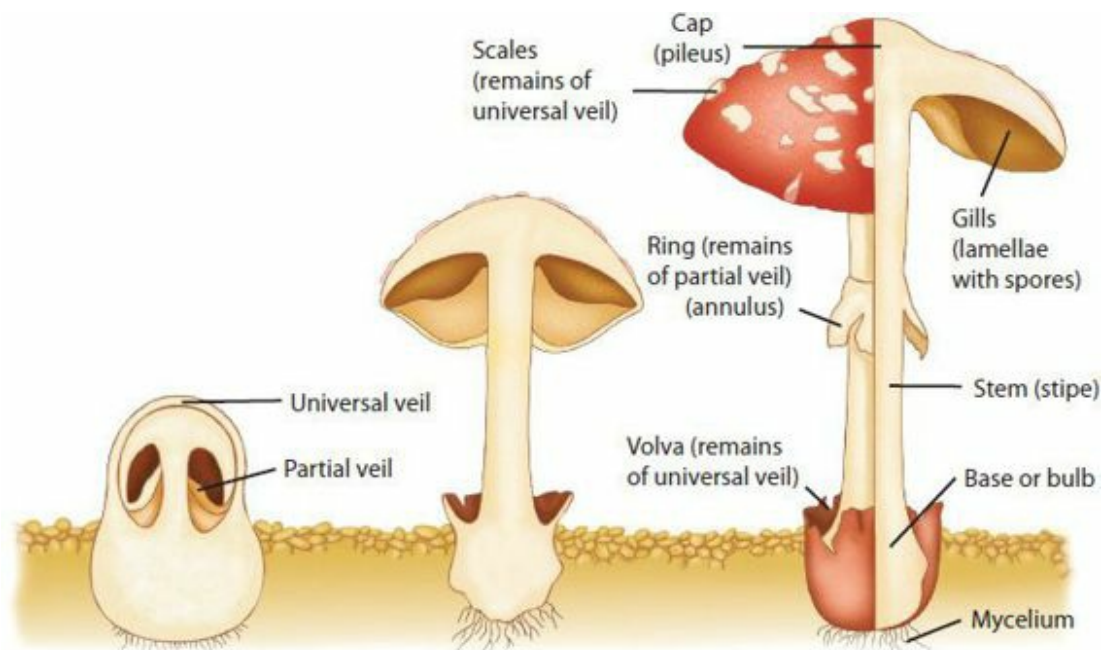


FIGURE 120-2 In the more highly specialized and evolved mushrooms, various protective tissues cover the fruit body and its constituent parts during its development. In the mushroom shown, an *Amanita* species, two veils of tissue are involved—one an outer enclosing bag, the universal veil, which ruptures as the fruit body expands to leave a volva at the base and fragments on the cap; the other an inner partial veil covering the developing gills that is pulled away as the cap opens to leave a ring on the stem. (Redrawn, with permission, from Kibby G: *Mushrooms and Toadstools, A Field Guide* : Oxford: Oxford University Press, 1979, p. 14.)

A. phalloides contains 15 to 20 cyclopeptides, each with an approximate weight of 900 Da. The amatoxins (cyclic octapeptides), phallotoxins (cyclic heptapeptides), and virotoxins (cyclic heptapeptides) are the best studied.^{37,71,131} There is no evidence for the toxicity of virotoxins in humans. Of these three chemically similar cyclopeptide molecules, phalloidin (the principal phallotoxin) appears to be a rapid-acting toxin, whereas amanitin tends to cause more delayed manifestations.¹⁰⁸ Phalloidin crosses the sinusoidal plasma membranes of hepatocytes by a carrier-mediated process. This process is shared by bile salts and can be prevented in the presence of extracellular bile salts, suggesting competitive inhibition. A sodium-independent bile salt transporting system may be responsible for phalloidin hepatic uptake, elimination, and detoxification.⁸⁵ Phalloidin interrupts actin polymerization and impairs cell membrane function, but because of its limited oral absorption it appears to have minimal toxicity, restricted mostly to GI dysfunction.

The amatoxins are the most toxic of the cyclopeptides, leading to hepatic, renal, and central nervous system (CNS) damage. These polypeptides are heat stable.³⁴ α -Amanitin is the principal amatoxin responsible for human toxicity following ingestion. Approximately 1.5 to 2.5 mg amanitin can be obtained from 1 g of dry *A. phalloides*, and as much as 3.5 mg/g can be obtained from some *Lepiota* spp.^{92,96,131} A 20-g mushroom contains well in excess of the 0.1 mg/kg amanitin considered lethal for humans.³³ α -Amanitin and β -amanitin have comparable toxicity in animal models.³⁶

The amanitins are poorly but rapidly absorbed from the GI tract.⁶³ Amatoxins show limited protein binding and are present in the plasma at low concentrations for 24 to 48 hours.⁶³ α -Amanitin hepatocellular entry appears to be facilitated by a sodium-dependent bile acid transporter. Several studies demonstrate that the sodium taurocholate cotransporter polypeptide, a member of the organic anion-transporter polypeptide OAT polypeptide family localized in the sinusoidal membranes of human hepatocytes, facilitates hepatocellular α -amanitin uptake.^{57,78} Once inside the cells the cytotoxicity amanitin results from its interference with RNA polymerase II, preventing the transcription of DNA.^{81,114} α -Amanitin may be enterohepatically recirculated. Target organs are those with the highest rate of cell turnover, including the GI tract epithelium, hepatocytes, and kidneys. Amatoxins do not appear to cross the placenta, as demonstrated by the absence of fetal toxicity in severely poisoned pregnant women.^{7,14,118}

In an intravenous radiolabeled amatoxin study in dogs, 85% of the amatoxin was recovered in the urine within the first 6 hours, whereas less than 1% was found in the blood at that time.³⁸ Amatoxins can be detected by high-performance liquid chromatography,⁶³ thin-layer chromatography, ion trap mass spectrometry,⁴² and radioimmunoassay in gastroduodenal fluid, serum, urine, stool, and liver and kidney biopsies for several days following an ingestion.^{36,37,70}

Some of the toxicokinetic analyses following unquantified ingestions demonstrate 12 to 23 μ g amatoxin excretion in the urine over 24 to 66 hours, of which 60% to 80% occurred during the first 2 hours of collection. The extreme variabilities of the type and quantity of ingested, the host, and the management make interpretations exceedingly difficult.¹²⁵ In another series, total maximal urinary α - and β -amanitin excreted over 6 to 72 hours were 3.19 and 5.21 mg, respectively. Two-thirds of the patients had total amanitin excretion greater than 1.5 mg.⁶³ Urinary amanitin excretion concentrations differ by several orders of magnitude. Whether the variation results from exposure dose, time following ingestion, or laboratory technique is unclear. Several techniques for quantitative and qualitative evaluation of urinary amanitin are under investigation.^{17,18,96,118}

Clinical. Phase I of cyclopeptide poisoning resembles severe gastroenteritis, with profuse watery diarrhea not occurring until 5 to 24 hours after ingestion. Some consider the early onset (less than 8 hours) of diarrhea as a predictive factor for hepatic failure and the need for liver transplantation.³⁴ whereas this is not supported by most other case series reviewed. It is typically considered that the onset of symptoms before 5 hours is strong support for another non-Amanita species cause for the gastrointestinal distress. Supportive fluid and electrolyte replacement leads to transient improvement during phase II, which occurs between 12 and 36 hours after ingestion.^{96,138} However, despite such supportive care, phase III, manifested by hepatic and renal toxicity and death, may ensue 2 to 6 days after ingestion.⁵ Pancreatic toxicity may rarely occur.⁴⁸ The initial hepatotoxicity begins within the second phase, but clinical hepatotoxicity (Chap. 23) with elevated concentrations of bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), hypoglycemia, jaundice, and hepatic coma are not manifest until 2 to 3 days after ingestion. Pathologic manifestations include steatosis, central zonal necrosis, and centrilobular hemorrhage, with viable hepatocytes remaining at the rims of the larger triads. Lobular architecture remains intact (Fig. 23-3).⁵

Cyclopeptide toxicity alters the hormones that regulate glucose, calcium, and thyroid homeostasis, resulting in widespread endocrine abnormalities.⁶⁸ Insulin and C-peptide concentrations are elevated at a stage of poisoning prior to hepatic and renal compromise.^{29,68} These findings are suggestive of direct toxicity to pancreatic β cells, resulting in release of preformed hormone or induction of hormone synthesis. This insulin release necessitates vigilance for hypoglycemia prior to hepatocellular damage. Serum calcitonin concentrations may be elevated, and hypocalcemia may be present. Thyroxine concentrations may be depressed and triiodothyronine concentrations undetectable, whereas thyroid-stimulating hormone concentrations may not be elevated. These thyroid-related findings were reported in a single study and merit further investigation.⁶⁸

In a series of 10 patients exposed to diverse *Lepiota* spp, 50% developed a mixed sensory and motor polyneuropathy. Most of the patients spontaneously recovered within one year, although a single patient developed progressive clinical and electromyographic deterioration.⁹⁸ These neuropathic findings have not been recognized in other case reports.

Treatment. The search for treatments has been vigorously pursued in Europe because of the persistently large number of amatoxin victims each year.⁴⁷ Survival rates in case series of variable numbers of patients poisoned by *A. phalloides* who received supportive care, fluid and electrolyte repletion, high-dose penicillin G, dexamethasone, or thioctic acid are between 70% and 100%.^{47,56,62,88,90,100,138} Many of these case series have excellent survival rates with extremely variable therapeutic interventions, limiting the capacity to determine the need for or efficacy of most of the standard conservative therapeutic regimens.

Fluid and electrolyte repletion and treatment of hepatic compromise are essential. Intravenous 0.9% sodium chloride solution and electrolytes usually are necessary because of substantial fluid loss due to vomiting and diarrhea. Dextrose repletion may be necessary because of nutritional compromise, hepatic failure, or glycogen depletion. Activated charcoal both adsorbs the amanitins and improves survival in laboratory animals.³⁶ Emesis, lavage, and catharsis are not necessary unless the patient presents within several hours after the ingestion because any substantial quantity of ingested toxin almost invariably induces emesis and catharsis. In an analysis¹¹ of the AAPCC Toxic Exposure Surveillance System (TESS) database of unintentional mushroom exposures in children from 1992 to 2005 it is suggested that a syrup of ipecac treated subgroup compared to an activated charcoal or no intervention group showed the smallest percentage of moderate or major outcomes. Activated charcoal is safe, logical, and a valuable therapeutic strategy. Although the clinical presentation often is delayed, 1 g/kg body weight of activated charcoal should be given orally every 2 to 4 hours (if the patient is not vomiting) or by continuous nasogastric infusion. Continuous nasogastric duodenal aspiration is used by multiple groups (mainly European) to remove amatoxins secreted in the bile; others use an even more difficult biliary drainage approach to disrupt the enterohepatic recirculation of the amatoxin.⁸⁴ Although there is theoretical support for early quantitative toxin removal due to substantial biliary concentration, the total quantity and actual gastroduodenal concentration remains low, offering inadequate clinical data to support gastroduodenal or biliary drainage.⁶⁴

Thioctic (α -lipoic) acid initially was reported to be beneficial in treating the amatoxin-induced liver toxicity in several different animal models, and a number of uncontrolled clinical trials in humans followed.⁵ Because of its potential effects as a coenzyme in the tricarboxylic acid cycle or as a free radical scavenger, thioctic acid was credited for the survival of 39 of 40 patients reportedly, but not definitively, poisoned by *A. phalloides*.⁷³ Hypoglycemia is a common feature of thioctic acid therapy for *Amanita* poisoning, but whether hypoglycemia results from direct toxicity of the drug or is secondary to hepatic damage is unclear. Despite the initial success, thioctic acid was not effective in various other studies and is no longer recommended.^{45,46}

Several laboratory investigations in mice and rats suggest that 1 g/kg penicillin G (1 g = 1,600,000 Units) may have a time- and dose-dependent protective effect.^{49,50} These results are limited because the amatoxins were administered intraperitoneally, resulting in the death of untreated animals 12 to 24 hours later. Additional investigations demonstrated that 1 g/kg penicillin G administered 5 hours after sublethal doses of α -amanitin decreased clinical and laboratory toxicity.⁴⁹ The mechanisms suggested include displacing α -amanitin from albumin, blocking its uptake from hepatocytes, binding circulating amatoxins, and preventing α -amanitin binding to RNA polymerase. None of these mechanisms is substantiated,³² and we no longer recommend penicillin G be used unless it is used very shortly after an ingestion as a temporizing gesture.

The active complex of milk thistle (*Silybum marianum*) is silymarin, which is a lipophilic extract composed of three isomeric flavonolignans: silibinin, silychristin, and silydianin. Silibinin represents approximately 50% of the extract, but represents about 70% to 80% of the marketed products.⁶¹ Silibinin, a mixture of Silibinin A and B, competitively inhibits the organic anion transporter (OATP1B3) that is responsible for the uptake and enterohepatic recycling of α -amanitin. Use of silibinin 50 mg/kg in dogs 5 and 24 hours following exposure to α -amanitin suppressed chemical evidence of hepatotoxicity and lethality. These same studies suggest silibinin diminishes α -amanitin enterohepatic circulation. Although silibinin is routinely available as a nonprescription supplement in most pharmacies and appears to be safe and well tolerated in patients with chronic liver disease, no reduction in mortality, improvement in histology at liver biopsy, or biochemical marker has been identified in a systematic review and meta-analysis.⁶¹ A dose of silibinin 20 to 50 mg/kg/d should be used in humans, even though it is not approved as a therapeutic for hepatic disease by the Food and Drug Administration (FDA) in the United States.^{70,129} Currently there is an amatoxin poisoning clinical trial utilizing Legalon SIL (Silibinin) at 20 mg/kg/day IV⁶⁰ (Antidotes in Depth: A36).

Because of its hepatoprotective effects, N-acetylcysteine should be given as an antidote, but no evidence for any specific benefit has been demonstrated. When fulminant hepatic failure is present, N-acetylcysteine should be administered until the patient recovers from the encephalopathy because of its presumptive benefits under these circumstances (Antidotes in Depth: A3).

In animals, cimetidine (a potent CYP2C9/2D6 inhibitor) may have a hepatoprotective effect against α -amanitin,¹⁰⁶ but it

shows no protective effect against phalloidin toxicity.¹⁰⁸ Cimetidine is proposed as a therapeutic intervention,¹⁰⁷ but no available human data support its use, and it is not currently recommended.

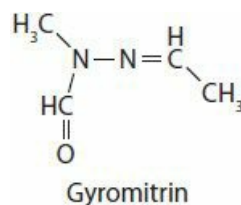
A recent randomized murine model of intraperitoneal α -amanitin poisoning comparing treatment with rescue postexposure N-acetylcysteine, benzylpenicillin, cimetidine, thiocetic acid, or silybin was unable to show any laboratory benefit with regard to hepatotoxic manifestations such as aminotransferase concentrations or histologic evidence of hepatonecrosis.¹¹⁹

Forced diuresis, hemodialysis, plasmapheresis,^{64,65} hemofiltration, and hemoperfusion⁴⁰ may be effective shortly after ingestion, but most studies offer neither clinical evidence of benefit nor supportive pharmacokinetic data for any of these therapies.^{70,95,96,110,125,128} Most studies suggest that no circulating amatoxins are present by the time the need for transplantation is evident.³⁰ “Shortly after” is not defined, although these techniques are indicated within 24 hours of a documented ingestion.⁴¹ Plasmapheresis, which is dependent on effective clearance, high plasma protein binding, and a low volume of distribution, does not remove more than 10 μ g of amatoxin. Because of the absence of prospective, controlled studies of exposure to amatoxins, in addition to the extreme variability of success with many regimens, multiple-dose activated charcoal, and supportive care remain the standard therapy. Early recognition of exposure to amanitin is an indication for hemodialysis or hemoperfusion, but most patients likely will no longer have the potential for benefit at the time they develop clinical manifestations of toxicity.⁶⁵ Future therapeutic interventions may be dependent on improved understanding of the hepatocellular bile acid transporter, which is a member of the OAT polypeptide family.^{57,74,78}

Extracorporeal albumin dialysis,³⁹ molecular adsorbent recirculating system (MARS),^{26,84,113,135} and fractionated plasma separation and adsorption system (FPSA; Prometheus system),^{35,124,126} are variant detoxification techniques used in patients with fulminant hepatic failure to remove water-soluble and albumin-bound xenobiotics while providing renal support. The typical delayed time to onset of use of MARS and other extracorporeal liver assist devices in amanitin poisoning invariably limits the potential effects of these systems not to toxin removal but to correction or stabilization of hepatic dysfunction. None of the available studies of these bridging systems are randomized or controlled. The clinical experience is solely in the care of patients with grave hepatotoxicity at a delayed stage limiting any potential for significant conclusions. These two techniques permit time for hepatic regeneration or sufficient bridging time to orthotopic liver transplantation. The criteria and timing for liver transplantation following amatoxin poisoning are far less established than for fulminant viral hepatitis, where grade III or IV hepatic encephalopathy, marked hyperbilirubinemia, and azotemia are the well-established criteria for transplantation (Chap. 23).⁹⁴ Successful transplantations were performed in individuals whose resected livers showed 0% to 30% hepatocyte viability. In these cases, the authors did not wait for progression past grade II encephalopathy or for development of azotemia or marked hyperbilirubinemia.⁹⁴ Criteria for patient selection are essential to avoid unnecessary risk while offering the potential for survival to appropriate candidates who have no functional liver. The grim prognosis associated with hepatic coma secondary to *Amanita* poisoning has led several transplant groups to consider hepatic transplantation for encephalopathic patients with prolonged international normalized ratios (INRs; greater than 6), persistent hypoglycemia, metabolic acidosis, increased concentrations of serum ammonia and AST, and hypofibrinogenemia.^{34,53,54,69,94} There are now case reports of successful liver transplantation for fulminant^{63,67,94} hepatic failure from presumed *A. ocreata*,^{69,137} *A. phalloides*, *A. virosa*,¹⁶ *Lepiota helveola*,⁸⁶ and *L. brunneoincarnata* poisoning.⁹⁸

To enhance the likelihood of success, individuals who manifest symptoms suggestive of hepatotoxic *Amanita*, *Galerina*, or *Lepiota* spp exposure should be told of the potential need for transplantation and, with their consent, be rapidly transferred to a regional liver transplantation center.^{16,34,94}

Group II: Gyromitrin Containing Mushrooms



Members of the gyromitrin group include *Gyromitra esculenta*, *Gyromitra ambigua*, and *Gyromitra infula*. *G. esculenta* enjoys a reputation of being edible in the Western United States but of being toxic in other areas. The most common error occurs in the spring, when an individual seeking the nongilled, brainlike *Morchella esculenta* (morel) finds the similar *G. esculenta* (false morel) (Fig. 120–3).



FIGURE 120–3 Group II: Gyromitrin containing mushrooms. A true morel (*Morchella* spp) on the left is compared to a false morel (*Gyromitra esculenta*) on the right. (Used with permission of John Trestrail.)

These mushrooms are found commonly in the spring under conifers and are easily recognized by their brainlike appearance. Poisonings with these mushrooms are exceptionally uncommon in the United States, representing less than 1% of all recognized events, whereas these poisonings are considered more common in Europe. Certain cooking methods may destroy the toxin, but because of the potential for toxicity, all members of this mushroom family should be avoided.

Gyromitra mushrooms contain the nonvolatile insoluble gyromitrin which on hydrolysis yields a family of N-methyl-N-formyl hydrazones, which on subsequent hydrolysis split into aldehydes and N-methyl-N-formyl hydrazine.³ Subsequent hydrolysis of N-methyl-N-formyl hydrazine yields monomethylhydrazine (Fig. 120–4). The hydrazine moiety reacts with pyridoxine, resulting in inhibition of pyridoxal phosphate-related enzymatic reactions (Figs. 58–2 and 58–3). This interference with pyridoxal phosphate disrupts the function of the inhibitory neurotransmitter γ -aminobutyric acid (GABA).⁷⁵ This decrease in GABA is thought to contribute to the diverse neurological manifestations typically associated with this ingestion.

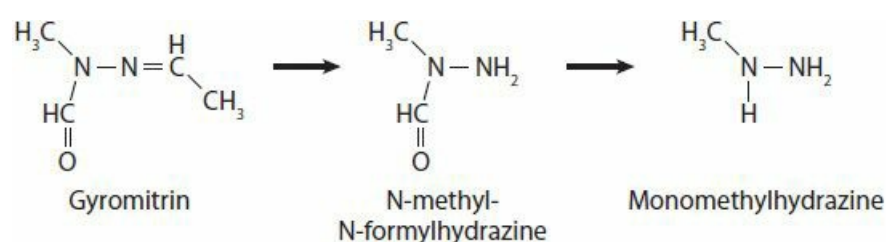


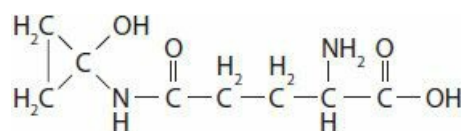
FIGURE 120–4 Gyromitra mushrooms contain gyromitrin which undergoes hydrolysis to yield a family of N-methyl-formyl hydrazines. These molecules on subsequent hydrolysis yield N-methyl-N-formyl hydrazine and monomethylhydrazine.

acetylcholine. Because muscarine lacks an ester bond, it is not hydrolysed by acetylcholinesterase.

Significant toxicity is uncommon, limiting the need for more than supportive care. Rarely, atropine (1–2 mg given IV slowly for adults or 0.02 mg/kg with a minimum of 0.1 mg IV for children) can be titrated and repeated as frequently as indicated to reverse symptomatology.

No current, clinically available, analytic techniques can identify muscarine, although high-performance liquid chromatography would be appropriate for investigative purposes.

Group IV: Coprine Containing Mushrooms



Coprine

Coprinus mushrooms, particularly *C. atramentarius*, (*Coprinopsis atramentaria*) contain the xenobiotic coprine (Fig. 120–6A). These mushrooms grow abundantly in temperate climates in grassy or woodland fields. They are known as “inky caps” because the gills that contain a peptidase autodigest into an inky liquid shortly after picking. The edible member of this group, *Coprinus comatus* (shaggy mane) (Figs. 120–6B and 6C) is nontoxic, and probably its misidentification results in collectors’ errors. Coprine, an amino acid, its primary metabolite, 1-aminocyclopropanol,^{20,83,120} or, more likely, a secondary in vivo hydrolytic metabolite, cyclopropanone hydrate, has a disulfiramlike effect (Fig. 120–7, see Chap. 79).¹³⁴ Although both of these metabolites appear to inhibit aldehyde dehydrogenase, the most stable in vivo inhibitory effect is manifested by cyclopropane hydrate.¹³⁴ Inhibition of acetaldehyde dehydrogenase results in accumulation of acetaldehyde and its accompanying adverse effects, which takes at least 0.5 to 2 hours if the patient ingests alcohol and a coprine containing mushroom concomitantly. For the subsequent 48 to 72 hours following coprine-containing mushroom ingestion if ethanol ingestion occurs toxicity may ensue. Within 0.5 to 2 hours of ethanol ingestion, an acute disulfiram effect is noted, with tachycardia, flushing, nausea, and vomiting. The simultaneous ingestion of the mushroom and alcohol does not result in immediate clinical manifestations because inhibition of aldehyde dehydrogenase occurs following coprine metabolism and the in vivo production of cyclopropane hydrate. Treatment is symptomatic with fluid repletion and antiemetics such as metoclopramide or ondansetron, although clinical manifestations usually are mild and resolve within several hours. Prophylactic use of fomepizole immediately following ingestion of ethanol and coprine-containing mushrooms has a theoretical basis, but no case reports or studies are published. This group of mushrooms rarely causes fatalities.



FIGURE 120–6 Group IV: Coprine containing mushrooms. (A) *Coprinopsis atramentaria*; (B) and (C) show *Coprinus comatus* (shaggy mane). Image (B) shows an early form which later is self digested demonstrating the gill liquefaction in image (C). (Image A Used with permission of John Plischke III, and images B and C used with permission of Lewis Nelson.)

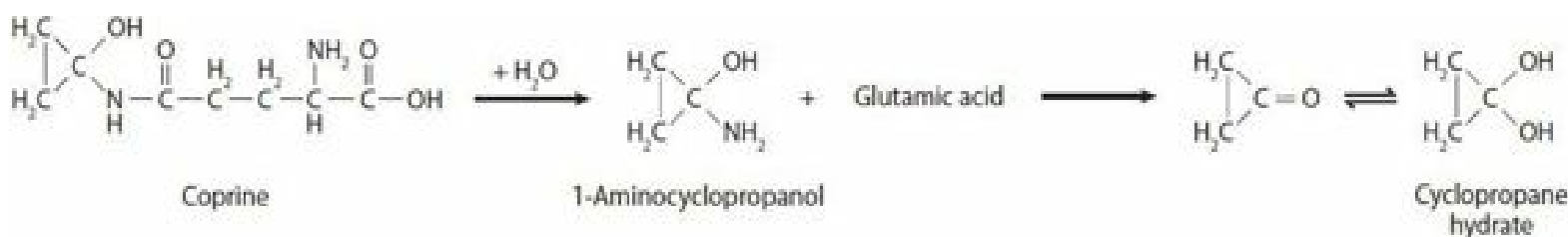
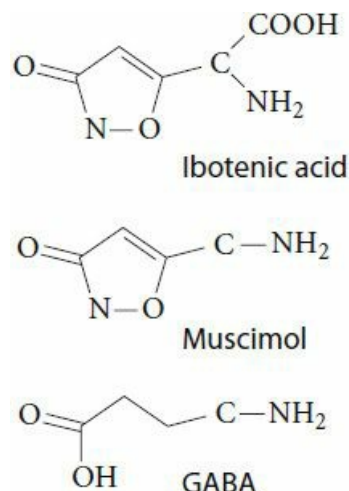


FIGURE 120–7 The *Coprinus* mushrooms contain coprine, an amino acid which is rapidly hydrolysed to 1-

aminocyclopropanol and subsequently cyclopropane hydrate. It is this last metabolite which most likely has the disulfiramlike effect.

Group V: Ibotenic Acid and Muscimol Containing Mushrooms



Most of the mushrooms in this class are primarily in the *Amanita* species, which includes *A. muscaria* (fly agaric), *A. pantherina*, and *A. gemmata* (Fig. 120–8). They exist singly and are scattered throughout the US woodlands. The brilliant red or tan cap (pileus) is that of the mushroom commonly depicted in children's books and is easily recognized in the fields during summer and fall.



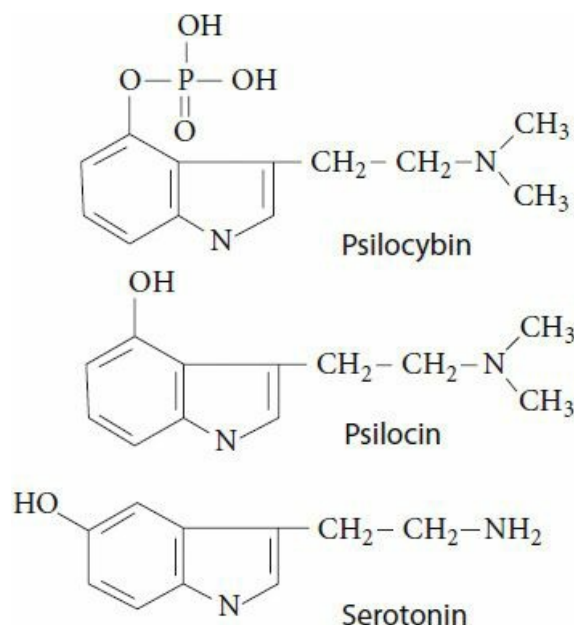
FIGURE 120–8 Group V: Muscimol containing mushrooms. This image of *Amanita muscaria* highlights different developmental forms and colors. (Used with permission of John Plischke III.)

Small variable quantities of the isoxazole derivatives ibotenic acid and muscimol are found in these mushrooms, which have been used in religious customs throughout history. Ibotenic acid is structurally similar to the stimulatory neurotransmitter glutamic acid. The stereochemistry of muscimol is very similar to that of the neurotransmitter GABA and may act as a GABA agonist.

Most patients who develop symptoms intentionally ingested large quantities of these mushrooms while seeking a hallucinatory experience. Within 0.5 to 2 hours of ingestion, these mushrooms produce the GABAergic manifestations of somnolence, dizziness, hallucinations, dysphoria, and delirium in adults, and the excitatory glutamatergic manifestations of myoclonic movements, seizures, and other neurologic findings predominate in children.⁸

Treatment is invariably supportive. Most symptoms respond solely to supportive care, although a benzodiazepine is appropriate for excitatory CNS manifestations.

Group VI: Psilocybin Containing Mushrooms



Psilocybin-containing mushrooms include *Psilocybe cyanescens*, *Psilocybe cubensis*, *Conocybe cyanopus*, *Panaeolus cyanescens*, *Gymnopilus spectabilis*, and *Psathyrella foenicis* (Fig. 120–9). These mushrooms have been used for native North and South American religious experiences for thousands of years. They grow abundantly in warm, moist areas of the United States. Drug culture magazines and Internet sources advertise mail-order kits containing *P. cubensis* spores to grow “magic mushrooms” domestically.



FIGURE 120–9 Group VI: Psilocybin containing mushrooms. Three examples of hallucinogenic mushrooms: (A) *Psilocybe cyanescens*, (B) *Psilocybe caerulipes*, and (C) *Gymnopilus spectabilis*. (Used with permission of John Plischke III.)

Toxicity from this group is common because of the popularity of hallucinogens.¹² Psilocybin is rapidly and completely hydrolyzed to psilocin in vivo. Serotonin, psilocin, and psilocybin are very similar structurally and presumably act at a similar 5-HT₂ receptor site. The effects of psilocybin as a serotonin agonist and antagonist are discussed in Chaps. 14 and 82.

The psilocybin and psilocin indoles, like those of lysergic acid diethylamide (LSD), rapidly (within one hour of ingestion) produce CNS effects, including ataxia, hyperkinesia, visual illusions, and hallucinations. Some patients manifest gastrointestinal distress, tachycardia, mydriasis, anxiety, lightheadedness, tremor, and agitation. Most manifestations are recognized within 4 hours of ingestion with a return to normalcy within 6 to 12 hours.⁵⁹ Rare cases of renal failure,^{51,97} seizures, and cardiopulmonary arrest¹² are associated with psilocybin-containing species. However, such associations should always be questioned when reported in a substance-using individual potentially simultaneously exposed to other xenobiotics.

A single patient who intravenously administered an extract of *Psilocybe* mushrooms experienced chills, weakness, dyspnea, headache, severe myalgias, vomiting associated with hyperthermia, hypoxemia, and mild methemoglobinemia.²⁷

Treatment for hallucinations usually is supportive, although a benzodiazepine may be necessary when reassurance proves inadequate.

Group VII: Gastrointestinal Toxin Containing Mushrooms

By far the largest group of mushrooms is a diverse group that contains a variety of ill-defined GI toxins. Many of the hundreds of mushrooms in this group fall into the “little brown mushroom” category. Some *Boletus* spp, *Lactarius* spp, *O.*

olearius, Rhodophyllus spp, Tricholoma spp, Chlorophyllum molybdites, and Chlorophyllum esculentum are mistaken for edible or hallucinogenic species. A frequently reported error^{4,52,123} is the confusion of the jack-o'-lantern (Omphalotus illudens) with the edible species of chanterelle (Cantharellus cibarius).

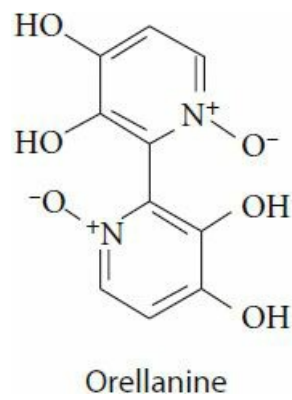
The toxins associated with this group are not identified. The malabsorption of proteins and sugars, such as trehalose, and the ingestion of a mushroom infected or partially digested by microorganisms or allergy may be responsible for symptoms. GI toxicity occurs 0.3 to 4 hours after ingestion when epigastric distress, malaise, nausea, vomiting, and diarrhea are evident. Treatment includes fluid resuscitation with control of vomiting and diarrhea. The clinical course is brief and the prognosis excellent. Those mushroom ingestions resulting in gastrointestinal toxicity more than 4 hours after ingestion are considered in Table 120–2. When symptoms seem to persist, the clinician must consider a mixed ingestion of another potentially toxic mushroom group.

TABLE 120–2. Mushroom Toxicity: Correlation between Organ System Affected, Time of Onset of Symptoms, and Mushroom Constituent Responsible

Organ System	Time of Onset		
	Early: <5 hours	Middle: 5–24 hours	Late: >24 hours
Gastrointestinal	Allenic norleucine Cepine Gastrointestinal toxins Muscarine	Allenic norleucine Amatoxin Gyromitrin	Orellanine and orellanine
Hepatic			Amatoxin
Immunologic	Involutin Spores		
Neurologic	Ibotenic acid and muscimol Psilocybin	Gyromitrin	Acromelic acid Gyromitrin Polyporic acid
Renal			Allenic norleucine Orellanine and orellanine

Rarely, clinical presentations are life threatening, with hypovolemic shock necessitating fluids and vasopressors.¹¹⁵ Resolution of symptoms usually occurs within 6 to 24 hours. The clinical courses associated with specific mushroom ingestions are variable.⁸ Death is rare.

Group VIII: Orellanine and Orellanine Containing Mushrooms



Cortinarius mushrooms, such as C. rubellus (Fig. 120–10) and C. orellanus, are commonly found throughout North American and Europe.^{19,66,109} The C. orellanus toxin orellanine is reduced by photochemical degradation to orellanine a bipyridyl molecule that is further reduced to the nontoxic orelline.^{2,91,101} The toxic compound orellanine is a hydroxylated bipyridine compound activated by its metabolism through the cytochrome P450 system. Toxicologically, these molecules are similar to paraquat and diquat and may have comparable mechanisms of action, although precise knowledge is limited (Chap. 112). Other nephrotoxins, such as cortinarines, are isolated from certain Cortinarius spp¹⁰⁷ and result in tubular damage, interstitial nephritis, and tubulointerstitial fibrosis.

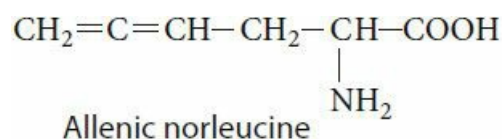


FIGURE 120–10 Group VIII Orellanine and Orellinine containing mushrooms: *Cortinarius rubellus*. (Used with permission of Astrid Holmgren, Swedish Poisons Information Centre.)

Orellanine is rapidly removed from the plasma within 48 to 72 hours and concentrated in the urine in a soluble form. It can be detected in the plasma at the time of clinical symptoms by some investigators⁹⁹ but not by other investigators.¹⁰² Thin-layer chromatography on renal biopsy material can detect orellanine long after clinical exposure.^{99,102}

Initial symptoms occur 24 to 36 hours after ingestion and include headache, chills, polydipsia, anorexia, nausea, vomiting, and flank and abdominal pain. The largest case review demonstrated that numerous patients repetitively ingested the *Cortinarius* spp prior to diagnosis.²⁸ Oliguric renal failure may develop several days to weeks after initial symptoms.¹³ The only initial laboratory abnormalities may be hematuria, leukocyturia, and proteinuria. Nephrotoxicity is characterized by interstitial nephritis with tubular damage and early fibrosis of injured tubules with relative glomerular sparing.^{19,109} Hepatotoxicity is rarely reported.¹³ Hemoperfusion, hemodialysis, and renal transplantation are used for the treatment of renal failure.^{13,28} No evidence suggests that secondary detoxification by plasmapheresis or hemoperfusion is of any benefit in preventing chronic renal failure even when initiated in the first 48 hours.^{28,70,99} The data are inadequate to define management or prognosis precisely, as many patients improve rapidly, while some require temporary intermittent hemodialysis and others require chronic therapy for persistent renal failure.¹³ No laboratory or clinical parameters predicting the individual reactions to the toxins are available. Although case reports in the literature commonly lack definitive proof of ingestion or confirmation of toxin presence, the more rapid the onset of GI and renal manifestations, the greater the risk of both acute and chronic renal failure.²⁸

Group IX: Allenic Norleucine Containing Mushrooms



Amanita smithiana poisoning is reported in the Pacific Northwest (Fig. 120–11).^{77,122,127,130} Because the mature specimen often lacks any evidence of a partial or universal veil, these mushrooms are not recognized as *Amanita* species. It appears that all of the poisoned individuals were seeking the edible pine mushroom matsutake (*Tricholoma magnivelare*), a highly desirable look-alike. The *A. smithiana*, *A. proxima*, *A. abrupta* and *A. pseudoporphyria*, and *A. abrupta* possess two amino acid toxins: allenic norleucine (amino-hexadienoic acid) and possibly 1,2-amino-4-pentynoic acid.^{23,93,139} A similar case report following the ingestion of *A. proxima* in Southern France resulted in gastrointestinal and renal manifestations.²⁵ In vitro renal epithelial tissue cultured with allenic norleucine developed necrotic morphologic changes similar to those that occur following *A. smithiana* ingestion.⁹³ In mice the extract of *A. abrupta* is hepatotoxic, which suggests that hepatotoxins and nephrotoxins are present in this species.¹³⁹

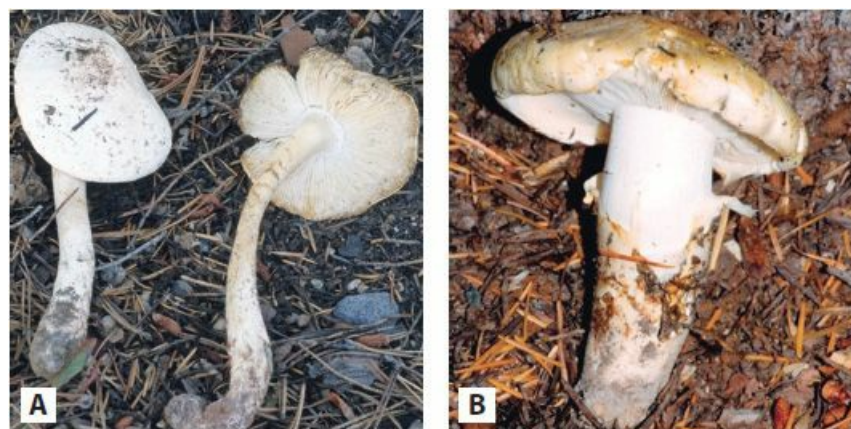


FIGURE 120-11 Group IX Allenic norleucine containing mushrooms: (A) *Amanita smithiana* compared to (B) *Tricholoma magnivelare* (matsutake, the mushroom with which it has been mistaken). (Used with permission of John Plischke III.)

Initial symptoms were noted from 0.5 to 12 hours following ingestion of either raw or cooked specimens. GI manifestations, including anorexia, nausea, vomiting, abdominal pain, and diarrhea, occurred frequently, accompanied by malaise, sweating, and dizziness. In some cases, vomiting and diarrhea persist for several days. The patients typically presented for care 3 to 6 days after ingestion, at which time they were oliguric or anuric. Acute kidney injury manifested 4 to 6 days following ingestion with marked elevation of BUN and creatinine. Lactate dehydrogenase and ALT concentrations frequently were elevated, whereas amylase, AST, alkaline phosphatase, and bilirubin were only infrequently abnormal.

Risk of toxicity was greatest in older patients and in patients with underlying renal insufficiency. Patients who required hemodialysis underwent the procedure two to three times per week for approximately one month until recovery. None of the patients in the three series died.

There is no known antidote for these nephrotoxins. Activated charcoal, although of no proven benefit, should be used in standard doses when a patient in the Northwest United States presents with early GI manifestations after mushroom ingestions. The clinician will be forced to consider the circumstances of ingestion to assess the probability of *A. smithiana* ingestion as opposed to ingestion of mushrooms containing a GI toxin.

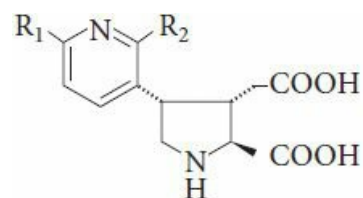
In view of the substantial morbidity associated with *A. smithiana* ingestions, historic, clinical, and/or temporal evidence of this ingestion should lead to charcoal hemoperfusion or hemodialysis as a strong consideration when the patient presents in the early phase of exposure. When a patient presents with renal compromise several days, as opposed to weeks, following mushroom ingestion and with a history of early, as opposed to delayed, GI manifestations, the clinician may be able to suggest *A. smithiana* as the etiology compared to *Cortinarius* spp exposure.

Group X: Rhabdomyolysis Associated Mushrooms

There are several reports of *Tricholoma equestre* (*Tricholoma flavovirens*) ingestions in Poland and France, where although this mushroom is considered “edible choice,” it has resulted in significant myotoxicity.^{24,89} In the first report 12 patients who ingested *T. equestre* mushrooms for 3 consecutive days developed severe rhabdomyolysis that was lethal in three cases.⁶ All patients developed fatigue, muscle weakness, and myalgias 24 to 72 hours following the last mushroom meal. The individuals also developed facial erythema, nausea without vomiting, and profuse sweating. The mean maximal creatine phosphokinase (CK) was 226,067 U/L in women and 34,786 U/L in men, with some values greater than 500,000 U/L. Electromyography revealed muscle injury with evidence of myotoxic activity. The biopsies showed myofibrillar injury and edema consistent with an acute myopathy.

Dyspnea, muscle weakness, acute myocarditis, dysrhythmias, congestive heart failure, and death ensued in three patients. Autopsy demonstrated myocardial lesions identical to those found in the peripheral muscles. Although muscle toxicity was reproduced using *T. equestre* extracts in a mouse model, the etiology of the toxicity is not defined.⁶ All the triterpenoids, sterols, indoles, and acetylenic compounds extracted from these mushrooms previously were assumed to be without toxicity. Currently all the clinical experience originates from Europe where these mushrooms are considered choice and eaten extensively; no cases are reported in the United States.

Group XI: Erythromelalgia Acromelic Acid Containing Mushrooms



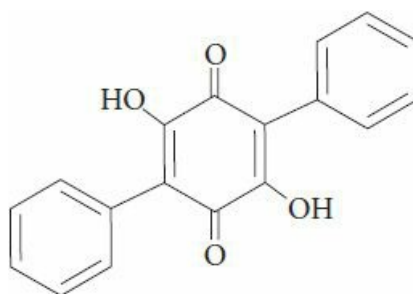
Acromelic acids D and E

D: $R_1 = \text{COOH}$; $R_2 = \text{H}$

E: $R_1 = \text{H}$; $R_2 = \text{COOH}$

A poorly defined syndrome originally recognized in Japan,⁸⁷ recently in France⁹ following the ingestion of various *Clitocybe* species (*C. acromelalga* and *C. amoenolens*), and not recognized currently in the United States. The toxic substances acromelic acids A–E have been isolated. These molecules are similar to kainic acid and are of the pyrrolidine dicarboxylic acid family, which act as ionotropic glutamate receptors. The syndrome typically occurs more than 24 hours following ingestion. Patients typically develop paraesthesias of distal extremities followed by paroxysms of severe burning dysesthesias lasting several hours. The extremities show edema and erythema. These manifestations respond variably to symptomatic and supportive care and resolve completely within several months.

Group XII: Polyporic Acid and Other Mushroom Constituents Resulting in Encephalopathy



Two groupings of toxic mushroom ingestion syndromes result in encephalopathy. In the first group, *Pleurocybella porrigens* is commonly eaten in Japanese miso soup without any adverse effects. However, their ingestion by patients with chronic renal failure resulted in delayed manifestations of encephalopathy.⁵⁵ Three-quarters (24 of 32) of the affected patients were undergoing hemodialysis at the time of the presumed poisoning. The delay from time of ingestion to the development of an altered consciousness, convulsions, myoclonus, dysarthria, dysesthesias, ataxia, respiratory failure, or death was between 1 and 31 days. No prior toxic link or known toxin in these commonly ingested mushrooms is recognized.

The second group of mushrooms associated with encephalopathy is the *Hapalopilus rutilans* reported in a German case series. More than 12 hours after ingestion an adult and two children developed nausea, vomiting, and abdominal pain; aminotransferase and creatine concentration elevations; and CNS abnormalities. Vertigo, ataxia, visual disturbances, and somnolence were reported.^{72,104} In each case the urine was a violet color, the color being noted when polyporic acid is placed in an alkaline solution. Polyporic acid, a dehydroquinone derivative (2,5-dihydroxy-3,6-diphenyl-1,4 benzoquinone), a constituent of these mushrooms, is a dehydroorotate dehydrogenase (an enzyme in the biosynthesis of pyrimidine) inhibitor that resulted in comparable clinical and biochemical manifestation when administered to rats.⁷² Symptomatic treatment is indicated with more specific therapy should hepatic or renal compromise be significant.

Group XIII: Immune Mediated Hemolytic Anemia

A small number of patients with ingestions of *Paxillus involutus*, and possibly *Clitocybe claviceps* and *Boletus luridus*, develop early onset mild GI symptoms followed by an immune-mediated hemolytic anemia, hemoglobinuria, oliguria, and renal failure. IgG antibodies to a *Paxillus* extract-containing involutin⁷⁰ were detected by a hemagglutination test in these patients.^{132,133} This syndrome occurs in Europe, typically among those who have eaten *P. involutus* numerous times in the past.

Group XIV: Lycoperdonosis

Puffball mushrooms (*Lycoperdon perlatum*, *Lycoperdon pyriforme*, or *Lycoperdon gemmatum*) are edible in the fall and can (upon decay or drying) release large numbers of spores following compression, fracture, or shaking (Fig. 120–12). Lycoperdonosis is directly related to massive exposure to spores, although many consider the syndrome an allergic bronchoalveolitis. This syndrome occurs in patients following acute inhalation of spores as an alternative or

complementary therapy for epistaxis¹¹⁷ and in adolescents for various experimental reasons.²² Massive inhalation, insufflation, and chewing of spores can lead to the development of nasopharyngitis, nausea, vomiting, and pneumonitis within hours. Over a period of several days, cough, shortness of breath, myalgias, fatigue, and fever develop. Rarely, patients require intubation because of pulmonary compromise associated with diffuse reticulonodular infiltrates.²² Lung biopsy demonstrates an inflammatory process with the presence of *Lycoperdon* spores.¹¹⁷ Patients treated with corticosteroids such as prednisone and antifungals such as amphotericin B recovered within several weeks without sequelae.

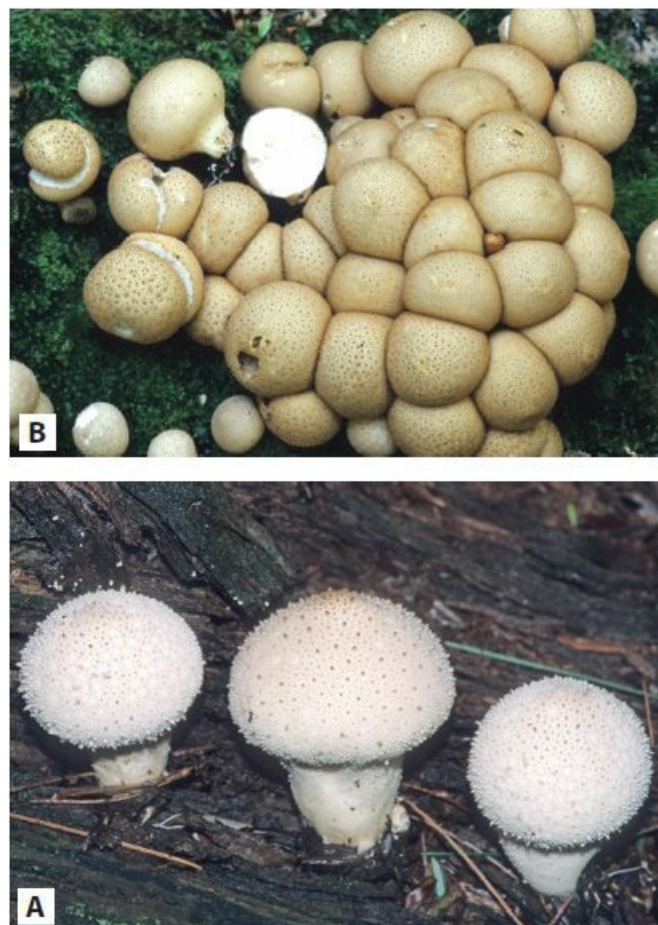


FIGURE 120–12 Puff balls: (A) *Lycoperdon pyriforme* and (B) *Lycoperdon perlatum*. (Used with permission of John Plischke III.)

MANAGEMENT

Because ingestion of certain mushrooms may lead to toxicity with substantial morbidity or mortality, patients with suspected mushroom ingestions require rigorous management. A serious effort at precise identification of the genus and species involved will make assessment, management, and follow-up easier and more logical. Beuhler and coworkers utilizing the AAPCC Toxic Exposure Surveillance System suggest that the treatment of exposures to mushrooms in children with syrup of ipecac decreases morbidity. Although this analysis suggestive of benefit in unknown exposures may be unrelated to ingestions of toxic mushrooms, the use of the syrup of ipecac is logical.¹¹ The basic regimen of adsorption should include activated charcoal if potentially toxic mushrooms are ingested or substantial enterohepatic recirculation is suspected. If nausea and vomiting persist, an antiemetic can be used to ensure that the patient can retain activated charcoal. Appropriate life support measures should be instituted as necessary. Fluids, electrolytes, and dextrose repletion, as needed, are essential.

There is a wide variability in quantity and type of xenobiotic present in mushrooms according to geography, local conditions, and individual susceptibility. The clinical course for *A. smithiana* poisoning has led us to suggest an alteration in the initial approach to patients in the northwest United States who have early onset (0.5–5 hours) of GI distress following mushroom ingestion as *A. smithiana* has a significant risk of renal failure. Prior to the recognition of this mushroom poisoning, all patients who had early onset of nausea, vomiting, diarrhea, and abdominal cramps were presumed to be poisoned by a member of the groups containing either the GI toxins or muscarine. The routine use of specific antidotes should be avoided because they usually are unnecessary.

DISPOSITION

It is important to remember that many patients with mushroom ingestions present with signs and symptoms suggestive of mixed poisonings. Whereas some ingestions produce “purer” symptom complexes than others, some ingestions, such as those of *A. muscaria*, produce GI and CNS effects, and still other ingestions, such as those of *Cortinarius* spp, have acute GI and delayed renal manifestations. Treatment or partial treatment may further confound the assessment. In addition, it is essential to remember that any acute GI disorder actually may be the manifestation of mushroom toxicity. In the spring and fall, in areas with moderate weather and humidity, it is particularly important to consider intentional or unrecognized exposure to mushroom toxins, although a logical approach to management is impossible in the absence of a precise history.

Because the clinical course of mushroom poisoning can be deceptive, all patients who manifest early gastrointestinal symptoms (less than 5 hours) and remain symptomatic for several hours despite supportive care ([Tables 120–1 and 120–2](#)) should be admitted to the hospital. In this group of patients inhabiting the Pacific Northwest, *A. smithiana* should be of particular concern. Although acute kidney injuries will likely not occur for several days necessitating careful follow-up. Patients whose delayed initial presentation (greater than or equal to 5 hours) is suggestive of amatoxin exposure should be hospitalized, as should any patient postingestion who cannot be followed safely or reliably as an outpatient. [Tables 120–1 and 120–2](#) list the characteristic times of appearance and evolution of symptoms caused by mushroom xenobiotics. Confusion may result from atypical clinical manifestations or, commonly, ingestion of several different mushrooms species, some of which may produce early symptoms and others delayed toxicity. Patients with certain types of ingestions may appear to improve initially with only supportive care. This latency period, which is characteristic of *Amanita* spp, may not be appreciated when several different species are eaten simultaneously. However, because hepatotoxicity leading to death may not appear until 2 to 3 days after ingestion (amatoxins) and nephrotoxicity may not appear for 3 to 21 days (orellanine and allenic norleucine), all patients with symptoms as do children with unknown ingestions require subsequent follow-up.

IDENTIFICATION

General

Visualizing and analyzing the gross, microscopic, or chemical characteristics of the ingested mushroom remain vital strategies that are infrequently used. When the whole mushroom or parts are unavailable, the diagnosis must be based on the clinical presentation. No rapidly available studies in EDs or clinical chemistry laboratories are available to assist with management. The development of a rapid clinical test for amatoxins,^{17,18,70} gyromitrin, orellanine, and allenic norleucine would be useful and permit early use of hemodialysis or hemoperfusion and greater vigilance with regard to use of hemodialysis. We have not yet achieved the ability to use thin-layer chromatography, high-performance liquid chromatography, gas chromatography, or gas chromatography-mass spectrometry in a clinically relevant manner. In Italy and Japan real time, polymerase chain reaction (PCR) has been developed for multiple species for experimental evaluations of cooked mushrooms and gastric aspirates. Future development of this technique might prove clinically useful.^{33,82}

Although mushroom identification is a difficult task, this section may be helpful to the clinician dealing with a suspected case of mushroom toxicity. However, it is generally best to rely on symptomatology, not mushroom appearances, to confirm a diagnosis. As a general rule, positive identification of the mushroom should be left to the mycologist or toxicologist.⁴³

The most important anatomic features of both edible and poisonous mushrooms are their pileus, stipe, lamellae or gills, and volva.

- Pileus: Broad, caplike structure from which hang the gills (lamellae), tubes, or teeth.
- Stipe: Long stalk or stem that supports the cap; the stipe is not present in some species.
- Lamellae: Platelike or gilllike structures on the undersurface of the pileus that radiate out like the spokes of a wheel. The spores are found on the lamellae. Some mushrooms have pores or toothlike structures on their pili, which contain the spores. The mode of attachment of the lamellae to the stipe is noteworthy in making an identification.
- Volva: Partial remnant of the veil found around the base of the stipe in some species.
- Veil: Membrane that may completely or partially cover the lamellae, depending on the stage of development. The “universal” veil covers the underside, the spore-bearing surface of the pileus.
- Annulus: Ringlike structure that may surround the stipe at some point below the junction, with the cap that is a remnant of the partial veil.
- Spores: Microscopic reproductive structures that are resistant to extremes in temperature and dryness, produced in the millions on the spore-bearing surface (see Lamellae). Of all the characteristics of a particular mushroom species, spores are the least variable, although many mushrooms have similar-appearing spores. A spore print is helpful in establishing an identification. A spore print viewed microscopically is comparable to a bacterial Gram stain. Spore colors range from white to black and include shades of pink, salmon, buff, brown, and purple. Spore color in general is

constant for a species.

The Unknown Mushroom

1. The most important determinant is whether the ingested mushroom is one of the deadly varieties, especially *Amanita*. Outside of the Pacific Northwest, the onset of GI symptoms within 5 hours of ingestion does not result from amatoxin poisoning. In the Pacific Northwest, symptoms may represent *A. smithiana* (allenic norleucine) poisoning ([Tables 120–1 and 120–2](#)).
2. An attempt should be made to obtain either the collected mushrooms or a detailed description of their features. Arrange for transport of the mushroom in a dry paper bag (not plastic). Ensure that the mushroom is neither moistened nor refrigerated, either of which will alter its structure. Remember that gastric contents may contain spores that may be very difficult to find, but can be crucial for analysis.
3. If the mushroom cap is available, make a spore print by placing the pileus spore-bearing surface side down on a piece of paper for at least 4 to 6 hours in a windless area. The spores that collect on the paper can be analyzed for color. White spore prints can be visualized more easily on white paper by tilting the paper and looking at it from an angle.
4. Concomitant with step 3, contact a mycologist and use the best resources available for identification. A botanical garden usually has expert mycologists on staff, or a local mycology club can locate a mycologist. A regional poison center almost always can provide this expertise or locate an expert.
5. If none of the resources in step 4 is accessible, Melzer reagent can be useful in differentiating look-alike species and defining the presence of an amatoxin. A positive reaction is indicated by the development of a dark blue color upon contact with Melzer reagent.⁷⁹ Melzer reagent is a solution of 20 mL water, 1.5 g potassium iodide, 0.5 g iodine, and 20 g chloral hydrate. Staining a sample of the spores with one drop of reagent and then viewing the sample under a microscope helps to determine whether the mushroom is a deadly *Amanita*, with bluish-black “amyloid” reacting round spores. Hospitals are not typically prepared for this type of testing which now often is only of interest to the expert mycologist and rare toxicologist.
6. An additional test used by some is the Meixner reaction. Several drops of 10N to 12N hydrochloric acid are applied to an amatoxin containing mushroom sample squeezed onto newspaper, resulting in a blue reaction.⁷⁰ The reliability of this test is doubtful, and most mycologists prefer to use the Melzer reagent. Although the Meixner test is sensitive, false-negative and false-positive tests are of concern.¹⁰

POISONING PRINCIPLES: MYTHS AND SCIENCE

Differentiating myths from science is a difficult task in any field of medicine. This effort is even more complex when discussing mushrooms. The following principles are of great value in developing a logical approach to a potential ingestion.

1. Wild mushrooms should never be eaten unless an experienced mycologist can absolutely identify the mushroom. Even experts have trouble identifying some mushrooms, yet some foragers boldly indicate that distinguishing edible from toxic mushrooms is “as easy as telling brussels sprouts from broccoli.” Remember the saying, “There are old mushroom hunters, and bold mushroom hunters; but there are no old, bold mushroom hunters.”
2. The toxicology of any species can vary, depending on geographic location. This species confusion is obvious among American immigrants stating unequivocally that “this particular mushroom” was absolutely safe and routinely eaten in the individual’s Asian or European country of origin. A 40-year epidemic in the Yunnan Highlands of China is a classic “mushroom epidemic.” Local investigators¹¹¹ have suggested epidemiologic data implicating *Troga Venenata* for the high incidence of sudden unexplained death (SUD). The work of the Chinese Field Epidemiology Training Program of the Chinese CDC suggests that two amino acids 2R-amino-4S hydroxy-5-hexynoic acid and 2R-amino-5-hexynoic acid found in these mushrooms are lethal xenobiotics in mice, which is a possible explanation for human sudden unexplained death syndrome. Although there is a high degree of suspicion and clinical correlation others have had SUD without ingestions, leading some investigators to believe that the high barium concentrations from victims and family members as well as the presence of barium in the soil, water, and other foods as well as in the previously unspiciated mushrooms (*Troga Venenata*) was causative.¹¹⁶ This discussion is typical of the evolution of understanding of the potential toxicity of a particular mushroom species or the micro-environment.
3. If toxicity is suspected, attempt to obtain samples of the mushrooms eaten, and identify them. Every ED should have a readily available resource on mushrooms, such as one of the major mycology field guides.^{1,15,79,80,103,112} In any case, identification is best made with the aid of the poison center’s consultant mycologist.
4. Mushrooms often are implicated as the cause of an illness when, in fact, infections or other diseases are responsible.

Other etiologies include the mode of preparation (the sauce or wine) or the cooking utensil.

5. There are no absolute generic approaches for evaluating the potential toxicity of a mushroom. Myths suggesting the safety or lack of safety by staining of silver, presence of insects or slugs, peeling off the mushroom cap, or the area of mushroom growth are unreliable or false. Neither odor nor taste is a good predictor of toxicity. Pure white mushrooms, little brown mushrooms, large brown mushrooms, and red-or pink-spored boletus (a mushroom without lamellae) should be considered potentially toxic.
6. Cooking may inactivate some xenobiotics but not others. In general, no wild mushroom should be eaten raw or in large quantities. Examples of toxicity associated with lack of cooking include *Armillariella mellea* (honey mushroom), which usually is well tolerated when cooked but not raw, and *Verpa bohemica* (a morellike mushroom), which is edible but causes illness if eaten in excess. Even the *Morchella esculenta*, the edible choice morel, is well recognized to cause dizziness, tremor, and ataxia when eaten raw in large quantities.¹⁰⁵
7. Associated phenomena may be responsible for or contribute to toxicity. Could insecticides have been sprayed on the mushrooms? Is it an alcohol-related response? Besides the well-known disulfiram reaction involving *C. atramentarius*, other good edibles, including the black morel (*Morchella angusticeps*) and the sulfur polypore (*Laetiporus sulfureus*), can cause adverse reactions if consumed with alcohol. The etiology of these adverse reactions is not understood.
8. “Edible” mushrooms that are allowed to deteriorate become toxic. Therefore, only young, recently matured specimens should be eaten when adequate mycologic support is available.
9. The finding that only some people who ate a mushroom species manifested characteristic toxicity should not exclude the diagnosis of mushroom poisoning. The degree of toxicity may be dose related or genetically determined, or a person may have a preexistent pathologic disposition to toxicity.
10. Mushroom allergy can manifest as an anaphylactic reaction.
11. Most poisonous mushrooms resemble edible mushrooms at some phase of their growth. For this reason, even careful examination of the ring, cap, consistency, form, and color may not reliably identify the edible species. Also, characteristic features of specific toxic mushrooms may not be present under certain conditions. Although the deadly *A. phalloides* and *A. virosa* usually have remnant patches of tissue from the universal veil that envelops the mushroom in its “button” stage, rain may wash these remnants away. Similarly, a subterranean basal cup may not be noticed if the mushroom is cut at the ground level by a novice forager (Fig. 120–1).
12. Even the new in-vogue “wild mushrooms” in the specialty markets may not be entirely safe.

SUMMARY

- It is essential to determine whether the ingested mushroom is one of the high morbidity/mortality varieties such as *Amanita*.
- The onset of GI symptoms within 5 hours of ingestion excludes exposure to an *Amanita* species except for those eaten in the Pacific Northwest where *Amanita smithiana* exists.
- Several mushroom species including *Amanita smithiana* containing allenic norleucine and *Cortinarius orellanus* containing orelline and orellanine result in renal failure more than 24 hours after ingestion.
- Silibinin, the active component of the milk thistle, may modify or occupy membrane receptor sites thereby inhibiting α -amanitin hepatocellular penetration. Silibinin is not FDA approved for therapeutic intervention, but it is available in a clinical trial (Antidotes in Depth: A36).
- The grim prognosis associated with Amanitin hepatotoxicity necessitates rapid assessment by a hepatic transplantation service, even though the clinical evolution is unpredictable and criteria for transplantation under these circumstances are not established.

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A36 ANTIDOTES IN DEPTH

Silibinin

Mary Ann Howland

INTRODUCTION

Silibinin is the active ingredient in milk thistle, *Silybum marianum*, purported to prevent and treat amatoxin induced liver failure. Legalon SIL is a purified silibinin derivative available via an FDA approved open treatment as an investigational new drug (IND) for IV administration in patients suspected of ingesting amatoxin containing mushrooms.

HISTORY

Milk thistle has been used since the 16th century for the treatment of liver disease. Legalon SIL has been used in Europe since 1984.

PHARMACOLOGY

Chemistry

Legalon SIL, silibinin-C-2',3-dihydrogen succinate disodium salt ($C_{33}H_{28}O_{16}Na_2$) is a microcrystalline water soluble powder for injection manufactured by Rottapharm/Madaus, a German pharmaceutical company.⁴ Silibinin is a mixture of cis- and trans diastereomers of silibinin A and B extracted from milk thistle fruit and then esterified with succinic anhydride to form the water soluble salt.

Related Compounds

The extract from the seeds of the plant milk thistle (*Silybum marianum*) contains 65% to 80% silymarin. Silymarin contains many flavonoids including silybin A and silybin B, with a 1:1 ratio making up silibinin.¹³ Silymarin is poorly water soluble with a low bioavailability, but has substantial enterohepatic cycling.

Mechanism of Action

Silibinin competitively inhibits the organic anion transporter (OATP1B3) that is responsible for the uptake and enterohepatic recycling of amatoxin. Early administration prevents initial uptake while later administration prevents enterohepatic recycling of the amatoxin.⁸ Other possible mechanisms of action include inhibition of hepatocyte TNF- α release, stimulation of mRNA protein synthesis, and antioxidant and antiinflammatory effects.

Pharmacokinetics and Pharmacodynamics

Legalon SIL is rapidly metabolized and eliminated from the blood. Precise details are not available.

ROLE IN AMANITA MUSHROOM EXPOSURE

There are no randomized clinical trials of Legalon SIL or silibinin in the treatment of amatoxin induced mushroom poisoning. Evidence for its use comes from observational studies in humans, a variety of animal studies with mixed results, and in vitro studies in cultured human hepatocytes.

Although in an experimental model of cultured canine hepatocytes silibinin was not able to reduce cytotoxicity, two experiments using cultured human hepatocytes demonstrated that the addition of silibinin was able to protect against lipid peroxidation and cytotoxicity, and also stimulate cell proliferation and attachment.⁵⁻⁷

One of the earliest animal studies was conducted in mice using sublethal doses of *Amanita phalloides* extract

administered intraperitoneally (IP) every 24 hours for 3 doses.² Silymarin was administered intravenously (IV) at 16 and 24 hours, with the highest dose resulting in a 58% survival compared to 11% in the control group. When the experiment was repeated using a purified α -amatoxin, time was the most important factor in predicting survival. All of the mice treated with silymarin one hour before exposure survived, while none survived when treatment was started 8 hours after exposure.² A similar study in mice treated with IP α -amatoxin followed 4 hours later with IP silibinin dosed every 4 to 6 hours for 48 hours was not able to show a benefit in reducing the increase in LFTs or a difference in the liver histopathology.¹¹

A study conducted in canines utilized an oral sublethal dose of *Amanita phalloides* extract and IV silymarin administered at 5 and 24 hours postingestion. Silymarin prevented or reduced the elevation in LFTs and the fall in clotting factors and reduced the severity of liver failure.³ A similar protocol, but this time using silibinin instead of silymarin, demonstrated similar biochemical findings and a 100% survival.¹²

A 20 year retrospective review of European and American case reports of over 2000 hospitalized patients with amatoxin induced mushroom poisoning concluded that silibinin alone, or in combination, and N-acetylcysteine show the most promise as hepatoprotective therapies.¹ The authors acknowledged the difficulty in determining efficacy of various therapies given the lack of randomized controlled trials. A more recent review included the data from the previous authors and any subsequent hospitalized patients in the interim. A multidimensional multivariate statistical analysis of the data reached a similar conclusion.⁹

A retrospective case series of *Amanita phalloides* poisoning from Australia and New South Wales included 10 patients with probable poisoning, 9 of whom were treated with silibinin since use began in 2005.¹⁰ Four of these patients died. Mistaken identity of the mushrooms, particularly in immigrants, and a large number of ingested mushrooms seemed associated with a higher mortality. There was often a time delay to administration of Legalon SIL due to stocking and acquisition issues.

ADVERSE EFFECTS AND SAFETY ISSUES

Since 1984, Legalon SIL has been administered to over 9000 patients with a good safety record.⁸ Mild flushing during intravenous infusion is commonly reported.

PREGNANCY AND LACTATION

There are no data available with regard to pregnancy and lactation. Administration should be based on a risk-to-benefit analysis.⁴

DOSING AND ADMINISTRATION

Efficacy is thought to be related to prompt administration following the diagnosis of amatoxin induced mushroom poisoning. The loading dose of Legalon SIL is 5 mg/kg IV infused over one hour. This should be followed by a maintenance dose of 20 mg/kg IV as a continuous infusion over 24 hours and continued until an elevated PT/INR returns to normal and LFTs have decreased significantly.⁴ Each 350 mg vial of Legalon SIL should be reconstituted with 35 mL of D₅NS. The dose should be further diluted in D₅W. For example, after reconstitution, four vials (the 24 hour maintenance dose for a 70 kg person) can be put in 500 mL D₅W and infused IV over 24 hours.

FORMULATION AND ACQUISITION

Each vial of lyophilized Legalon SIL contains 350 mg of silibinin. Legalon SIL can be obtained by a physician via an FDA sanctioned, open treatment IND by calling the 24 hour, toll-free hotline (866-520-4412). A stockpile is kept in the United States, allowing same day shipment.

SUMMARY

- Legalon SIL is a purified silibinin derivative for the prevention and treatment of amatoxin induced mushroom poisoning.
- Silibinin competitively inhibits the organic anion transporter (OATP1B3) that is responsible for the uptake and enterohepatic recycling of amatoxin.
- Silibinin should be administered as soon as possible following a presumed ingestion without waiting for mycologic confirmation.

- A 24 hour, toll-free hotline (866-520-4412) is available to obtain Legalon SIL.

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121 PLANTS

Lewis S. Nelson and Lewis R. Goldfrank

Five to ten percent of all human exposures reported to poison centers involve plants. Probably because plants are so accessible and attractive to youngsters, in approximately 80% of these cases the individuals are younger than 6 years of age. As indoor plants have become ever more popular, the incidence of plant exposures has increased. Data compiled by the American Association of Poison Control Centers (AAPCC) give some indication of which plants are more commonly involved ([Chap. 136](#)), but these plants typically have relatively limited toxicity. More than 80% of patients reported to the AAPCC as being exposed were asymptomatic, less than 20% had minor to moderate symptomatology, and less than 7% necessitated a health care visit. The benignity of these exposures is represented by a fatality rate of less than 0.001%. This chapter addresses the toxicologic principles associated with the most potentially dangerous plants.

HISTORY AND CLASSIFICATION OF PLANT XENOBIOTICS

Aconitine, from monkshood, exemplifies the rich history of plant toxicology. It was believed by the Greeks to be the first poison—"lycotonum"—created by the goddess Hecate from foam of the river Cerebrus. Alkaloid constituents are responsible for its toxic (and therapeutic) effects. Alkaloids represent one of several classes of organic molecules found in plants as defined by the science of pharmacognosy, which is the science of medicines derived from natural sources. The pharmacognosy approach is consistent with the literature of plant efficacy and is applied here to their toxicity ([Table 121–1](#)). Unfortunately, the science of pharmacognosy is not always straightforward, and systems of classification may vary depending on the pharmacognosist. Hence our approach borrows primarily from two groups of authors to keep the classification as consistent as possible.^{48,120} The major groups are as follows:

TABLE 121–1. Primary Toxicity of Common Important Plant Species

<i>Plant Species (Family)</i>	<i>Typical Common Names</i>	<i>Primary Toxicity</i>	<i>Xenobiotic(s)</i>	<i>Class of Xenobiotic</i>
<i>Abrys precatorius</i> (Euphorbiaceae) ^a	Prayer beans, rosary pea, Indian bean, crab's eye, Buddhist's rosary bead, prayer bead, jequinity pea	Gastrointestinal	Abrin	Protein, lectin, peptide, amino acid
<i>Aconitum napellus</i> and other <i>Aconitum</i> spp (Ranunculaceae) ^b	Monkhood and others	Cardiac, neurologic	Aconitine and related compounds	Alkaloid
<i>Aconis calamus</i> (Araliaceae)	Sweet flag, rat root, flag root, calamus	Gastrointestinal	Acarin	Phenol or phenylpropanoid
<i>Aesculus hippocastanum</i> (Hippocastanaceae)	Horse chestnut	Hematologic	Esculetide (6-β-D-glucopyranosyloxy-7-hydroxycoumarin)	Phenol or phenylpropanoid
<i>Agave lecheguilla</i> (Amaryllidaceae)	Agave	Dermatitis, photosensitivity in animals	Aglycones, smilagenin, sarsapogenin	Saponin glycoside
<i>Aloe barbadensis</i> , <i>Aloe vera</i> , others (Liliaceae/Amaryllidaceae)	Aloagave	Gastrointestinal	Barbaloin, iso-barbaloin, aloinosides	Anthraquinone glycoside
<i>Anabaena</i> and <i>Aphanizomenon</i> ^c	Blue-green algae	Neurologic	Saxitoxin equivalents	Guanidinium compound
<i>Anacardium occidentale</i> , many others (Anacardiaceae)	Cashew, many others	Contact dermatitis	Urushiol oleoresins	Terpenoid
<i>Anthoxanthum odoratum</i> (Poaceae)	Sweet vernal grass	Hematologic	Coumarin	Phenol or phenylpropanoid
<i>Areca catechu</i> (Arecaceae)	Betel nut	Cholinergic	Arecoline	Alkaloid
<i>Argemone mexicana</i> (Papaveraceae)	Mexican pricklepoppy	Gastrointestinal	Sanguinarine	Alkaloid
<i>Argyrea nervosa</i>	Hawaiian baby woodrose seeds	Neurologic	Lysergic acid amide	Alkaloid
<i>Argyrea</i> spp (Convolvulaceae)	Morning glory	Neurologic	Lysergic acid derivatives	Alkaloid
<i>Aristolochia reticulata</i> , <i>Aristolochia</i> spp (Aristolochiaceae) ^d	Texan or Red River snake root	Renal, carcinogenic	Aristolochic acid	Alkaloid relative as derivative of nothebaine
<i>Artemisia absinthium</i> (Compositaceae/ Asteraceae) ^e	Abnthe	Neurologic	Thujone	Terpenoid

<i>Asclepias</i> spp (Asclepidaceae)*	Milk weed	Cardiac	Asclepin and related cardenolides	Cardioactive steroid
<i>Astragalus</i> spp (Fabiaceae)*	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
<i>Atractylis gummifera</i> (Compositaceae)*	Thistle	Hepatic	Atractyloside, gummiferine	Glycoside
<i>Atropa belladonna</i> (Solanaceae)*	Belladonna	Anticholinergic	Belladonna alkaloids	Alkaloid
<i>Azalea</i> spp (Ericaceae)* ^a	Azalea	Cardiac, neurologic	Grayanotoxin	Terpenoid
<i>Berberis</i> spp (Ranunculaceae)	Barberry	Oxytocic, cardiovascular	Berberine	Alkaloid
<i>Blighia sapida</i> (Sapindaceae)*	Akee fruit	Metabolic, gastrointestinal, neurotoxic	Hypoglycin	Protein, lectin, peptide, amino acid
<i>Borago officinalis</i> (Boragniaceae)*	Borage	Hepatic (venoocclusive disease)	Pyrrrolizidine alkaloids	Alkaloid
<i>Brassica</i> spp ^b	Umbrella tree	Dermatitis, mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
<i>Brassica nigra</i> (Brassicaceae)	Black mustard	Dermatitis, irritant	Sinigrin	Glucosinolate (isothiocyanate glycoside)
<i>Brassica oleracea</i> var. capitata	Cabbage	Metabolic (precursor to goittrin, antithyroid compound)	Progoittrin	Isothiocyanate glycoside
<i>Cactus</i> spp ^b	Cactus	Dermatitis, mechanical	Nontoxic	None
<i>Caladium</i> spp (Araceae) ^b	Caladium	Dermatitis, mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
<i>Calotropis</i> spp (Asclepidaceae)*	Crown flower	Cardiac	Asclepin and related cardenolides	Cardioactive steroid
<i>Camellia sinensis</i> (Theaceae)	Tea, green tea	Cardiac, neurologic	Theophylline, caffeine	Alkaloid

<i>Cannabis sativa</i>	Cannabis, marijuana, Indian hemp, hashish, pot	Neurologic	Tetrahydrocannabinol	Terpenoid, resin, oleoresin
<i>Capsicum frutescens</i> , <i>Capsicum annuum</i> , <i>Capsicum</i> spp (Solanaceae) ^a	<i>Capsicum</i> , cayenne pepper	Dermatitis, irritant	Capsaicin	Phenol or phenylpropanoid
<i>Cascara sagrada</i> , <i>Rhamnus purshiana</i> , <i>Rhamnus cathartica</i> (Rhamnaceae)	Cascara, sacred bark, Chittam bark, common buckthorn	Gastrointestinal	Cascarosides, O-glycosides, emodin	Anthraquinone glycoside
<i>Cassia senna</i> , <i>Cassia angustifolia</i> (Fabaceae)	Senna	Gastrointestinal	Sennosides	Anthraquinone glycoside
<i>Catha edulis</i> (Elaeagnaceae)	Khat	Cardiac, neurologic	Cathinone	Alkaloid
<i>Catharanthus roseus</i> (formerly <i>Vinca rosea</i>) (Apocynaceae)	<i>Catharanthus</i> , vinca, madagascar periwinkle	Gastrointestinal	Vincristine	Alkaloid
<i>Caulophyllum thalictroides</i> (Berberidaceae)	Blue cohosh	Nicotinic	N-Methylocytisine and related compounds	Alkaloid
<i>Cephaelis ipecacuanha</i> , <i>Cephaelis acuminata</i> (Rubiaceae) ^a	Syrup of ipecac	Gastrointestinal, cardiac	Emetine/cephaline	Alkaloid
<i>Chlorophytum comosum</i> ^b	Spider plant	Dermatitis, contact, and allergic	Ursiol oleoresins	Terpenoid
<i>Chondrodendron</i> spp, <i>Curare</i> spp, <i>Strychnos</i> spp ^c	Tubocurare, curare	Neurologic	Tubocurarine	Alkaloid
<i>Chrysanthemum</i> spp, <i>Taraxacum officinale</i> , many other Compositaceae (Asteraceae) ^b	Chrysanthemum, dandelion, other Compositaceae	Contact dermatitis	Sesquiterpene lactones	Terpenoid
<i>Cicuta maculata</i> (Aplaceae/Umbelliferae) ^a	Water hemlock	Neurologic	Cicutoxin	Alcohol
<i>Cinchona</i> spp (Rubiaceae) ^a	Cinchona	Cardiac, cinchonism	Quinine	Alkaloid
<i>Citrus aurantium</i> (Rutaceae) ^a	Bitter orange	Cardiac, neurologic	Synephrine	Alkaloid
<i>Citrus paradisi</i> (Rutaceae)	Grapefruit	Drug interactions	Bergamottin, naringenin, or naringin	Phenol or phenylpropanoid

<i>Claviceps purpurea</i> , <i>Claviceps paspali</i> (Claviceptacea – fungus) ^a	Ergot	Cardiac, neurologic, oxytocic	Ergotamine and related compounds	Alkaloid
<i>Coffea arabica</i> (Rubiaceae)	Coffee	Cardiac, neurologic	Caffeine	Alkaloid
<i>Cola nitida</i> , <i>Cola</i> spp (Sterculiaceae)	Kola nut	Cardiac, neurologic	Caffeine	Alkaloid
<i>Colchicum autumnale</i> (Liliaceae) ^a	Autumn crocus	Multi-system	Colchicine	Alkaloid
<i>Conium maculatum</i> (Apiaceae/ Umbelliferae) ^a	Poison hemlock	Nicotinic, neurologic, respiratory, renal	Conine	Alkaloid
<i>Convallaria majalis</i> ^a	Lily of the valley	Cardiac	Convallatoxin, strophanthin (~40 others)	Cardioactive steroid
<i>Coptis</i> spp (Ranunculaceae)	Goldenthread	Oxytocic, cardiovascular	Berberine	Alkaloid
<i>Crassula</i> spp ^b	Jade plant	Gastrointestinal	Nontoxic	None
<i>Crotalaria</i> spp (Fabaceae) ^a	Rattlebox	Hepatic (venoocclusive disease)	Pyrolizidine alkaloids	Alkaloid
<i>Croton tiglium</i> and <i>Croton</i> spp (Euphorbiaceae)	Croton	Carcinogen, gastrointestinal	Croton oil	Lipid and fixed oil, also contains tropane alkaloid and diterpene
<i>Cycas circinalis</i> ^a	Queen sago, india, cycad	Neurologic	Cycasin	Glycosides
<i>Cytisus scoparius</i> (Fabaceae) ^a	Broom, Scotch broom	Nicotinic, oxytocic	Sparteine	Alkaloid
<i>Datura stramonium</i> (Solanaceae) ^a	Jimson weed, stramonium, locoweed	Anticholinergic	Belladonna alkaloids	Alkaloid
<i>Delphinium</i> spp (Ranunculaceae) ^a	Larkspur, others	Cardiac, neurologic	Methyllycaconitine	Alkaloid related compounds
<i>Dieffenbachia</i> spp (Araceae) ^b	Dieffenbachia	Dermatitis, mechanical and cytotoxic	Oxalate raphides	Carboxylic acid

<i>Digitalis lanata</i> ^a	Grecian figglove	Cardiac	Digoxin, lanatosides A–E (contains ~ 70 cardiac glycosides)	Cardioactive steroid
<i>Digitalis purpurea</i> ^a	Purple foxglove	Cardiac	Digitoxin	Cardioactive steroid
<i>Dipteryx odorata</i> , <i>Dipteryx oppositifolia</i> (Fabaceae)	Tonka beans	Hematologic	Coumarin	Phenol or phenylpropanoid
<i>Ephedra</i> spp., especially <i>sinensis</i> (Ephedraceae/Gnetaceae – Gymnosperms) ^a	Ephedra, Ma-huang	Cardiac, neurologic	Ephedrine and related compounds	Alkaloid
<i>Epipremnum aureum</i> (Araceae) ^a	Pothos	Dermatitis, mechanical, and cytotoxic	Oxalate raphides	Carboxylic acid
<i>Erythroxylum coca</i>	Coca	Neurologic, cardiac	Cocaine	Alkaloid
<i>Eucalyptus globus</i> or spp. ^a	Eucalyptus	Dermatitis, contact, and allergic	Eucalyptol	Terpenoid
<i>Euphorbia pulcherrima</i> , <i>Euphorbia</i> spp (Euphorbiaceae) ^a	Poinsettia	Dermatitis, contact, and allergic	Phorbol esters	Terpenoid
<i>Galium triflorum</i> (Rubiaceae)	Sweet-scented bedstraw	Hematologic	Coumarin	Phenol or phenylpropanoid
<i>Ginkgo biloba</i> (Ginkgoaceae)	Ginkgo	Dermatitis, contact, and allergic Hematologic Neurologic	Urushiol oleoresins Ginkgolides A–C, M 4-Methoxypyridoxine in seeds only	Terpenoid Terpenoid Alkaloid, pyridine
<i>Gloriosa superba</i> (Liliaceae) ^a	Meadow saffron	Multisystem	Colchicine	Alkaloid
<i>Glycyrrhiza glabra</i> ^a	Licorice	Metabolic, renal	Glycyrrhizin	Saponin glycoside
<i>Gossypium</i> spp	Cotton, cottonseed oil	Metabolic	Gossypol	Terpenoid
<i>Hedera pulegioides</i> (Lamiaceae) ^a	Pennyroyal	Hepatic, neurologic, oxytoxic	Pulegone	Terpenoid
<i>Hedera helix</i> (Araliaceae) ^a	Common ivy	Not absorbed	Hederacoside C, α-hederin, hederagenin	Cardioactive steroid
<i>Hedysarum alpinum</i> (Fabaceae)	Wild potato	Metabolic, neurologic	Swainsonine	Alkaloid

<i>Heliotropium</i> spp (Compositae/ Asteraceae) ^a	Ragwort	Hepatic (venoocclusive disease)	Pyrolizidine alkaloids	Alkaloid
<i>Helleborus niger</i> ^a	Black hellebore, Christmas rose	Cardiac	Hellebrin	Cardioactive steroid
<i>Hydrastis canadensis</i> (Ranunculaceae) ^a	Goldenseal	Neurologic, oxytocic, cardiovascular, respiratory	Hydrastine, berberine	Alkaloid
<i>Hyoscyamus niger</i> (Solanaaceae) ^a	Henbane, hyoscyamus	Anticholinergic	Belladonna alkaloids	Alkaloid
<i>Hypericum perforatum</i> (Clusiaceae)	St. John's wort	Dermatitis, photosensitivity, neurologic, hepatic drug interactions	Hyperforin, hypericin	Terpenoid
<i>Ilex paraguariensis</i> (Aquifoliaceae)	Maté, Yerba Maté, Paraguay tea	Cardiac, neurologic	Caffeine	Alkaloid
<i>Ilex</i> spp berries (Aquifoliaceae) ^b	Holly	Gastrointestinal	Mixture. Alkaloids, polyphenols, saponins, steroids, triterpenoids	Unidentified
<i>Illicium anisatum</i> (Illiciaceae) ^a	Japanese Star anise	Neurologic	Anasatin	Terpenoid
<i>Ipomoea tricolor</i> and other (<i>Ipomoea</i> spp (Convolvulaceae)	Morning glory	Neurologic	Lysergic acid derivatives	Alkaloid
<i>Jatropha curcas</i> (Euphorbiaceae)	Black vomit nut, physic nut, purging nut	Gastrointestinal	Curcin	Protein, lectin, peptide, amino acid
<i>Karwinskia humboldtiana</i> ^a	Buckthorn, wild cherry, tullidora, coyatillo, capulinillo, others	Neurologic, respiratory	Toxin T-514	Phenol or phenylpropanoid
<i>Laburnum anagyroides</i> (syn. <i>Cytisus laburnum</i> ; Fabaceae) ^a	Golden chain, laburnum	Nicotinic	Cytisine	Alkaloid
<i>Lantana camara</i> (Verbenaceae)	Lantana	Dermatitis, photosensitivity	Lantadene A and B, phylloerythrin	Terpenoid

<i>Lathyrus sativus</i> *	Grass pea	Neurologic, skeletal	β -N-oxalylamino-L-alanine (BOAA); β -aminopropionitrile (BAPN)	Protein, lectin, peptide, amino acid
<i>Lobelia inflata</i> (Campanulaceae)	Indian tobacco	Nicotinic	Lobeline	Alkaloid
<i>Lophophora williamsii</i>	Peyote or mescal buttons	Neurologic	Mescaline	Alkaloid
<i>Lupinus latifolius</i> and other <i>Lupinus</i> spp (Fabaceae)	Lupin	Nicotinic	Anagrine	Alkaloid
<i>Lycopersicon</i> spp (Solanaceae)*	Tomato (green)	Gastrointestinal, neurologic, anticholinergic	Tomatidine, tomatidine	Glycoalkaloid
<i>Mahonia</i> spp (Ranunculaceae)	Oregon grape	Oxytocic, cardiovascular	Berberine	Alkaloid
<i>Mandragora officinarum</i> (Solanaceae)*	European or true mandrake	Anticholinergic	Belladonna alkaloids	Alkaloid
<i>Manihot esculenta</i> (Euphorbiaceae)*	Cassava, manihot, tapioca	Metabolic, neurotoxic, motor spastic paresis and vision disturbance with chronic use	Linamarin	Cyanogenic glycoside
<i>Medicago</i> spp (Fabaceae/Legumaceae)	Sweet clover (spoiled moldy)	Hematologic	Dicumarol	Phenol or phenylpropanoid
<i>Mentha pulegium</i> (Lamiaceae)*	Pennyroyal	Hepatic, neurologic, oxytocic	Pulegone	Terpenoid
<i>Microcystis</i> and <i>Anabaena</i> spp	Blue-green algae (cyanobacteria)	Hepatotoxic, dermatitis, photosensitivity	Microcystin	Protein, lectin, peptide, amino acid
<i>Myristica fragrans</i>	Nutmeg, pericarp = mace	Neurologic (hallucinations)	Myristicin, elemicin	Terpenoid
<i>Narcissus</i> spp and other (Amaryllidaceae, Liliaceae)	Narcissus	Dermatitis, mechanical, and cytotoxic	Lycorine, homolycorin	Alkaloid
<i>Nerium oleander</i> *	Oleander	Cardiac	Oleandrin	Cardioactive steroid
<i>Nicotiana tabacum</i> and other <i>Nicotiana</i> spp (Solanaceae)*	Tobacco	Nicotinic	Nicotine	Alkaloid
<i>Oxytropis</i> spp (Fabaceae)	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
<i>Papaver somniferum</i>	Poppy	Neurologic	Morphine/other opium derivatives	Alkaloid

<i>Paullinia cupana</i> (Sapindaceae)	Guarana	Cardiac, neurologic	Caffeine	Alkaloid
<i>Pausinystalia yohimbe</i> (Rubiaceae) ^a	Yohimbe	Cardiac, cholinergic	Yohimbine	Alkaloid
<i>Philodendron</i> spp (Araceae) ^b	Philodendron	Dermatitis, mechanical, and cytotoxic	Oxalate raphides	Carboxylic acid
<i>Phoradendron</i> spp (Loranthaceae or Viscaceae)	American mistletoe	Gastrointestinal	Phoratoxin, ligatoxin	Protein, lectin, peptide, amino acid
<i>Physostigma venenosum</i> (Fabaceae) ^a	Calabar bean, ordeal bean	Cholinergic	Physostigmine	Alkaloid
<i>Phytolacca americana</i> (Phytolaccaceae) ^a	American cancer Pokeweed, poke	Gastrointestinal	Phytolaccotoxin	Protein, lectin, peptide, amino acid
<i>Pilocarpus jaborandi</i> , <i>Pilocarpus pinnatifolius</i> (Rutaceae) ^a	Pilocarpus, jaborandi	Cholinergic effects	Pilocarpine	Alkaloid
<i>Piper methysticum</i> ^a	Kava kava	Hepatic, neurologic	Kawain, methysticine yangonin, other kava lactones	Terpenoid, resin, and oleoresin
<i>Plantago</i> spp	Plantago (seed husks)	Gastrointestinal	Psyllium	Carbohydrate
<i>Podophyllum emodi</i> (Berberidaceae) ^a	Wild mandrake	Multisystem	Podophyllin (lignan)	Phenol or phenylpropanoid
<i>Podophyllum peltatum</i> (Berberidaceae) ^a	Mayapple	Multisystem	Podophyllin (lignan)	Phenol or phenylpropanoid
<i>Populus</i> spp (Salicaceae)	Poplar species	Salicylism	Salicin	Glycoside
<i>Primula obconica</i> (Primulaceae)	Primrose	Dermatitis, contact, allergic	Primin	Phenol or phenylpropanoid
<i>Prunus americana</i> , <i>Prunus</i> spp, <i>Malus</i> spp (Rosaceae) ^a	Apricot seed pits, wild cherry, peach plum, pear, almond, apple, and other seed kernels	Metabolic, acidosis, respiratory failure, coma, death	Amygdalin, emulsin	Cyanogenic glycoside

<i>Pteridium</i> spp (Polypodiaceae)	Bracken fern	Carcinogen, thiaminase	Ptaquiloside	Terpenoid
<i>Pulsatilla</i> spp (Ranunculaceae)	Pulsatilla	Dermatitis, contact	Ranunculin, protoanemonin	Glycoside
<i>Quercus</i> spp	Oak	Metabolic, livestock toxicity	Tannic acid	Phenol or phenylpropanoid
<i>Ranunculus</i> spp (Ranunculaceae)	Buttercups	Dermatitis, contact	Ranunculin, protoanemonin	Glycoside
<i>Rauwolfia serpentine</i> (Apocynaceae)	Indian snakeroot	Cardiac, neurologic	Reserpine	Alkaloid
<i>Remijna pedunculata</i> (Rubiaceae) ⁴	Cuprea bark	Cardiac, cinchonism	Quinine	Alkaloid
<i>Rhamnus frangula</i> (Rhamnaceae)	Frangula bark, alder buckthorn	Gastrointestinal	Frangulins	Anthraquinone glycoside
<i>Rheum officinale</i> , <i>Rheum</i> spp (Polygonaceae)	Rhubarb	Gastrointestinal Metabolic	Rhein anthrones Oxalic/Acid (soluble)	Anthraquinone glycoside Carboxylic acid
<i>Rheum</i> spp (Polygonaceae)	Rhubarb species	Urologic	Oxalates	Carboxylic acid
<i>Rhododendron</i> spp (Ericaceae) ⁴	Rhododendron	Cardiac, neurologic	Grayanotoxins	Terpenoid including resin and oleoresin
<i>Ricinus communis</i> (Euphorbiaceae) ²	Castor or rosary seeds, purging nuts, physic nut, tick seeds	Gastrointestinal	Ricin, curcin	Protein, lectin, peptide, amino acid
<i>Robinia pseudoacacia</i> (Fabaceae) ⁴	Black locust	Gastrointestinal	Robin (robinia lectin)	Protein, lectin, peptide, amino acid
<i>Rumex</i> spp (Polygonaceae)	Dock species	Urologic	Oxalates	Carboxylic acid
<i>Salix</i> spp (Salicaceae)	Willow species	Salicylum	Salicin	Glycosides, other
<i>Sambucus</i> spp (Caprifoliaceae)	Elderberry	Metabolic	Anthracyanins	Cyanogenic glycoside
<i>Sanguinaria canadensis</i> (Papaveraceae)	Sanguinaria, bloodroot	Gastrointestinal	Sanguinarine	Alkaloid
<i>Schefflera</i> spp (Araceae) ³	Umbrella tree	Dermatitis, mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
<i>Schlumbergera bridgesii</i> ⁴	Christmas cactus	Dermatitis, mechanical	Nontoxic	None

<i>Senecio</i> spp (Compositae/Asteraceae) ^a	Groundsel	Hepatic (venoocclusive disease)	Pyrolizidine alkaloids	Alkaloid
<i>Sida carpinifolia</i> (Malvaceae)	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
<i>Sida cordifolia</i> (Malvaceae) ^a	Bala	Cardiac, neurologic	Ephedrine and related compounds	Alkaloid
<i>Solanum americanum</i> (Solanaceae) ^a	American nightshade	Gastrointestinal, neurologic, anticholinergic	Solasodine, soladulcidine, solanine, chaconine	Glycoalkaloid
<i>Solanum dulcamara</i> (Solanaceae) ^{a,b}	Bittersweet woody nightshade	Gastrointestinal, neurologic, anticholinergic	Solanine, chaconine, belladonna alkaloids	Alkaloid
<i>Solanum nigrum</i> (Solanaceae) ^a	Black nightshade, common nightshade	Gastrointestinal, neurologic, anticholinergic	Solanine, chaconine, belladonna alkaloids	Alkaloid
<i>Solanum tuberosum</i> (Solanaceae) ^a	Potato (green), leaves	Gastrointestinal, neurologic, anticholinergic	Solanine, chaconine	Alkaloid
<i>Spathiphyllum</i> spp (Araceae) ^b	Peace lily	Dermatitis, mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
<i>Spinacia oleracea</i> (Chenopodiaceae)	Spinach, others	Urologic	Oxalates	Carboxylic acid
<i>Strychnos nux-vomica</i> , <i>Strychnos ignatia</i> (Loganiaceae) ^a	Nux vomica, Ignatia, St. Ignatius bean, vomit button	Neurologic	Strychnine, brucine	Alkaloid
<i>Swainsonia</i> spp (Fabaceae)	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
<i>Symphytum</i> spp (Boraginaceae) ^a	Comfrey	Hepatic (venoocclusive disease)	Pyrolizidine alkaloids	Alkaloid
<i>Tanacetum vulgare</i> (= <i>Chrysanthemum vulgare</i> ; Compositaceae/Asteraceae) ^a	Tansy	Neurologic	Thujone	Terpenoid
<i>Taxus baccata</i> , <i>Taxus brevifolia</i> , other <i>Taxus</i> spp (Taxaceae) ^a	English yew, Pacific yew, yew	Cardiac	Taxine	Alkaloid

<i>Theobroma cacao</i> (Sterculiaceae)	Cocoa	Cardiac, neurologic	Theobromine	Alkaloid
<i>Thevetia peruviana</i> ^a	Yellow oleander	Cardiac	Thevetin	Cardioactive steroid
<i>Toxicodendron radicans</i> , <i>Toxicodendron toxicarium</i> , <i>Toxicodendron diversilobum</i> , <i>Toxicodendron vernix</i> , <i>Toxicodendron</i> spp. many others (Anacardiaceae) ^a	Poison ivy, poison oak, poison sumac	Dermatitis, contact and allergic	Urushiol oleoresins	Terpenoid
<i>Tribulus terrestris</i> (Fabaceae)	Caltrop, puncture vine	Dermatitis, photosensitivity in animals	Steroidal saponins (aglycones, diosgenin, yamogenin)	Saponin glycoside
<i>Trifolium pratense</i> and other (Fabaceae/ Legumaceae)	Red clover	Phytoestrogen hematologic	Formononetin, Biochanin A coumarin	Phenol (isoflavone)
<i>Tussilago farfara</i> (Compositae/ Asteraceae) ^a	Coltsfoot	Hepatic (venoocclusive disease)	Pyrolizidine alkaloids	Alkaloid
<i>Urginea maritima</i> , <i>Urginea indica</i> ^a	Red, or Mediterranean squill, Indian squill, sea onion	Cardiac	Scillaren A, B	Cardioactive steroid
<i>Veratrum viride</i> , <i>Veratrum album</i> , <i>Veratrum californicum</i> (Liliaceae) ^a	False hellebore, Indian poke, California hellebore	Cardiac	Veratridine	Alkaloid
<i>Vicia faba</i> , <i>Vicia sativa</i> (Fabaceae)	Fava bean, vetch	Hematologic	Vicine, convicine	Glycoside
<i>Viscum album</i> (Loranthaceae or Viscaceae)	European mistletoe	Gastrointestinal	Viscumin	Protein, lectin, peptide, amino acid, lignan, polypeptide
<i>Wisteria floribunda</i> (Fabaceae)	Wisteria	Gastrointestinal	Cystatin	Protein, lectin, peptide, amino acid

^a Reports of life-threatening effects from plant use. ^b Plants reported commonly among calls to poison centers.

1. Alkaloids: Molecules that react as bases and contain nitrogen, usually in a heterocyclic structure. Alkaloids typically have strong pharmacologic activity that defines many major toxidromes.
2. Glycosides: Organic compounds that yield a sugar or sugar derivative (the glycone) and a nonsugar moiety (the aglycone) upon hydrolysis. The aglycone is the basis of subclassification into saponin or steroidal glycosides (including steroidal cardiac glycosides, cyanogenic glycosides, anthraquinone glycosides), and others such as atractyloside and salicin.
3. Terpenes and resins: Assemblages of five-carbon units (isoprene unit) with many types of functional groups (eg, alcohols, phenols, ketones, and esters) attached. This is the largest group of secondary metabolites; approximately 20,000 are identified. Most essential oils are mixtures of monoterpenes, and the terpene name depends on the number of isoprene assemblages. Monoterpenes have two units (C₁₀H₁₆), sesquiterpenes have three isoprene units (C₁₅), diterpenes have four isoprene units (C₂₀), and triterpenes have six (C₃₀). These molecules often play an active role in plant defense mechanisms.
4. Proteins, peptides, and lectins: Proteins consist of amino acid units with various side chains, and peptides consist of linkages among amino acids. Lectins are glycoproteins classified according to the number of protein chains linked by disulfide bonds and by binding affinity for specific carbohydrate ligands, particularly galactosamines. The toxalbumins (eg, ricin) are lectins. These components tend to be neurotoxins, hemagglutinins, or cathartics.
5. Phenols and phenylpropanoids: Phenols contain phenyl rings and have one or more hydroxyl groups attached to the ring. Phenylpropanoids consist of a phenyl ring attached to a propane side chain. These compounds are devoid of nitrogen, even though some are derived from phenylalanine and tyrosine. They constitute a major group of secondary metabolites and among plant toxins include coumarins (lactone side chains), flavonoids (built upon a flavan 2,3-dihydro-2-phenylbenzopyran nucleus, such as naringenin and rutin), lignans (two linked phenylpropanoids, such as podophyllin), lignins (complex polymers of lignans that bind cellulose for woody bark and stem), and tannins (polymers that bind to protein and can be further hydrolyzed or condensed).

Plant chemistry is complex. The simplified presentation of one xenobiotic per plant per symptom group used in [Table 121-1](#) overlooks the fact that plants contain multiple xenobiotics that work independently or in concert. Additionally, different plant families may contain similar, if not identical, xenobiotics (either from conservation of biochemical pathways inherited from a common ancestor or through convergent evolution). In some cases, xenobiotics remain unidentified and are grouped in the section Unidentified Toxins.

Dissimilar molecules from diverse pharmacognosy classes that share effects are grouped together for pragmatic purposes in the section Effects Shared Among Different Classes of Xenobiotics. They are further categorized into plant–xenobiotic interactions, sodium channel effects, antimitotic alkaloids and resins, and plant-induced dermatitis.

Our focus is on exposures to flowering plants (angiosperms) related to foraging, dietary, or occupational contact, except for some gymnosperms or algae and, rarely, medicinal contact (medicinal use as herbals is discussed in Chap. 45).⁸³ Because our understanding of plant xenobiotics is poor relative to that of pharmaceuticals, animal research is included to provide a more comprehensive foundation for comparison with human experiences that may otherwise go unrecognized without such precedent, or may likewise prove ultimately incorrect. The science of plant toxicology formally began in the United States as a response to significant poisonings of livestock. The overall quality of literature for human exposures is poor and primarily available as case reports. Many of these cases lack clear links between toxin exposure and illness, and qualitative or quantitative analyses are generally unavailable. Uncertainty is compounded by the fact that plants themselves are inherently variable, and potency and type of xenobiotic depend on the season, geography, growing environment, plant part, and methods of processing.

IDENTIFICATION OF PLANTS

Positive identification of the plant species should be attempted whenever possible, especially when the patient becomes symptomatic. Communication with an expert botanist, medical toxicologist, or poison center is highly recommended and can be facilitated by transmission of digital images or a fax.¹⁴⁸ Provisionally, simple comparison of the species in question with pictures or descriptions from a field guide of flora may help exclude the identity of the plant from among the most life threatening in Table 121–1. A plant identification can also be compared with those searched in the PLANTOX database (<http://www.accessdata.fda.gov/scripts/plantox/index.cfm>) managed by the Food and Drug Administration (FDA). To date, with some exceptions laboratory analysis is generally not timely enough to be useful except as a tool in an investigatory or forensic analysis. As the state of analytical science advances, however, it may soon be possible to confirm a diagnosis once a preliminary hypothesis based on botanical identification or symptomatology has been made.

In cases where expert identification cannot be immediately achieved, preliminary recognition of taxonomic families of poisonous plants is the simplest first step to identify or exclude poisonous plants, but it is most easily achieved when the plant is in flower or fruit. For instance, if the flower is described or looks like a flower from a tomato or potato, it probably is in the Solanaceae family. Plants of this family typically produce gastroenteric or anticholinergic findings following ingestion. It then would be appropriate to consider management with a specific antidote such as physostigmine. This approach will be less useful for xenobiotics such as pyrrolizidine alkaloids that occur in numerous different families.

APPROACH TO THE EXPOSED PATIENT AND UNDERSTANDING RISK

Identified plant species most frequently reported to poison centers are indicated in Table 121–1. In most cases, these species provide reassurance because most exposures result in benign outcomes, and only a few among these are regularly life-threatening depending on the circumstances of the exposure. Given the relatively poor understanding of toxins and in the absence of complete information about an exposure, expectant management and supportive care are the rule. Even if a plant is not marked as life threatening or commonly reported, the patient should undergo a period of observation and follow-up, given the relatively immature science of plant toxicology relative to that of pharmaceuticals.

The difficult task in human plant toxicology is the lack of adequate data to determine risk (Chap. 130). Typically, evaluations of risk are based on poison center data and usually cite the numerous calls without clinical consequence as a part of the risk equation (Chap. 136). However, poison center data are predominantly unconfirmed exposures and cases with unsubstantiated clinical manifestations (Chap. 136). These cases often represent small or nonexistent exposures, and their inclusion in the database may mask actual risks by diluting hazardous exposures with trivial or nonexistent exposures.⁶⁴ Furthermore, misidentification of the plant may occur because of either similar appearance or similar nomenclature.

In summary, basic decontamination and supportive care should be instituted as appropriate for the clinical situation and with poison center consultation. The most consequential and dangerous plant xenobiotics for humans are discussed here, and those that can produce life-threatening signs acutely are denoted in Table 121–1.

Potential symptoms listed in Table 121–1 are organized by plant name and the associated major organ system effects for quick reference as to the type of symptoms and their potential for morbidity or mortality. For instance, life-threatening symptoms such as dysrhythmias or seizures can be searched by “cardi-” or “neuro-” in the third column and compared with the plant(s) in question. The plants and xenobiotics that present life-threatening symptoms are so noted. Exposures associated with one of these plants or xenobiotics or major organ system symptoms dictate the need for possible prompt gastric emptying, decontamination, individualized therapy, and hospitalization. Nonspecific symptoms such as nausea and vomiting are listed only when they are a major cause of morbidity or mortality (toxalbumins such as ricin), but nausea and vomiting are exceptionally common in those individuals with consequential acute poisonings.

TOXIC CONSTITUENTS IN PLANTS, TAXONOMIC ASSOCIATIONS, AND SELECTED SYMPTOMS

Alkaloids

The term alkaloid refers to nitrogen-containing basic xenobiotics of natural origin. They figure prominently in the history of human–plant interaction, ranging from epidemics of poisoning caused by ergot-infected rye bread in the Middle Ages to dependency on cocaine, heroin, and nicotine in contemporary time. Numerous examples of toxic constituents of these families are given in the following discussion, which begins with a description of the major toxidromes that involves alkaloids. See also Sodium Channel Effects under Effects Shared Among Different Classes of Xenobiotics later in this chapter for descriptions of additional life-threatening alkaloids.

Anticholinergic: Belladonna Alkaloids. The belladonna alkaloids are from the family Solanaceae and the plants can be identified as members of this family by their characteristic flowers (most familiar from nightshade, potato, or tomato flowers). The belladonna alkaloids have potent antimuscarinic effects, manifested by tachycardia, hyperthermia, dry skin and mucous membranes, skin flushing, diminished bowel sounds, urinary retention, agitation, disorientation, and hallucinations (Chap. 3). Since the 1970s, the quest for recreational “highs” has surpassed unintentional ingestions as the main source of toxicity.¹⁴³ Hallucinatory effects are sought in seeds and teas, especially in late summer, when jimsonweed (*Datura stramonium*) seeds (Fig. 121–1) become available. One hundred of these seeds contain up to 6 mg atropine and related alkaloids, and an ingestion of this amount can be fatal¹⁸



FIGURE 121–1. Jimsonweed (*Datura stramonium*) initially has a showy white tubular flower which becomes a prickly fruit (pod) following maturation. Inset: The pod (inset) of Jimsonweed holds multiple small seeds containing atropine and scopolamine. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Although several anticholinergic alkaloid-containing species and even individual plants within species contain differing concentrations of several different phytochemicals, the clinical manifestations usually are similar. The onset of symptoms typically occurs 1 to 4 hours postingestion, and more rapidly if the plants are smoked or consumed as a brewed tea. The duration of effect is partly dose dependent and may last from a few hours to days.²³ The course of anticholinergic poisoning is not substantially altered by the use of physostigmine, though this may be life-saving in patients with seizures or an agitated delirium (Antidotes in Depth: A9).^{40,127} Although methods for detection of atropine and scopolamine in clinical specimens are improving, anticholinergic toxicity may be observed without detectable atropine, scopolamine, or hyoscyamine concentrations in biological fluids.

Solanine and chaconine are glycoalkaloids contained in many members of the Solanaceae family, but they are structurally and pharmacologically dissimilar to the belladonna alkaloids. The aglycone solanidine, which lacks the sugar moiety, is a steroidal alkaloid. Solanine inhibits cholinesterase in vitro, although cholinergic symptoms are not noted clinically. Nonetheless, reports of solanine-induced central nervous system (CNS) toxicity include hallucinations, delirium, and coma.¹³⁸ However, most symptomatic patients typically develop nausea, vomiting, diarrhea, and abdominal pain that begins 2 to 24 hours after ingestion, which, like CNS toxicity, may persist for several days. Although solanine is present in most of the 1700 species in the genus *Solanum*, solanine toxicity in humans is rarely encountered. The content of glycoalkaloids in tubers is usually 10 to 100 mg/kg and the maximum concentrations do not exceed 200 mg/kg. Green potatoes and the green potato plant itself are most commonly associated with symptoms, which is not surprising because the alkaloids are most concentrated in those items. The ingestion of 1 to 3 mg of glycoalkaloid per kilogram of body weight is likely to produce clinical symptoms.¹²⁵ Most reports of death come from the older literature,² and consumption of 2 to 5 g

of green components of potatoes per kilogram of body weight per day is not predicted to cause acute toxicity.¹¹³

Nicotine and Nicotineline Alkaloids: Nicotine, Anabasine, Lobeline, Sparteine, N-Methylcytisine, Cytisine, and Coniine. Nicotine toxicity (other than from inhaled sources) occurs via ingestion of leaves of *Nicotiana tabacum*, cigarettes and their remains, e-cigarette refill, organic insecticidal products, and transdermally among farm workers harvesting tobacco (green tobacco sickness)¹⁵ (Chap. 85). A topical folk remedy made from the leaf of *Nicotiana glauca* (tree tobacco) caused anabasine toxicity in an infant¹⁰⁵ The alkaloidal form of nicotine and anabasine are pale yellow oils at room temperature and readily penetrate the intact dermis. A dose of nicotine as small as 1 mg/kg of body weight can be lethal although it is more likely with doses > 4 mg/kg⁹³ Overstimulation of the nicotinic receptors by high doses of the alkaloid produces nicotinism, a toxidrome that progresses from gastrointestinal (GI) symptoms to diaphoresis, mydriasis, fasciculations, tachycardia, hypertension, hyperthermia, seizures, respiratory depression, muscle weakness, and death (Chap. 84). Wearing of protective clothing is essential for tobacco farm workers to prevent green tobacco sickness⁶

These manifestations are also produced by alkaloids other than nicotine. There are no recent reports of nicotinic toxicity from lobeline (found in all parts of *Lobelia inflata*), although its use in the 18th century resulted in morbidity and mortality.

Sparteine from broom (*Cytisus scoparius*) and N-methylcytisine from blue cohosh (*Caulophyllum thalictroides*)¹¹⁶ are examples of alkaloids that produce nicotineline effects. Laburnum or golden chain (*Cytisus laburnum*) contains cytisine, which reportedly is responsible for mass poisonings and fatalities in children and adults who eat the plants or parts thereof (even as little as 0.5 mg/kg, or a few peas).¹⁰³ Unfortunately, such reports have resulted in thousands of unnecessary hospital admissions for patients without morbidity and mortality after ingestion of this plant, demonstrating the difficulty in separating hazard from risk and in obtaining accurate dose–response information in the setting of plant exposures and human variability.

The most famous description of the end stages of nicotinic toxicity dates from approximately 2400 years ago by an observer of Socrates' fatal ingestion of a decoction of poison hemlock (*Conium maculatum*).¹¹⁷

... the person who had administered the poison went up to him and examined for some little time his feet and legs, and then squeezing his foot strongly asked whether he felt him. Socrates replied that he did not and said to us when the effect of the poison reached his heart, Socrates would depart.

Birds do not experience coniine toxicity but provide a vector for poisoning. According to the book of Exodus, quail that fed on seeds (presumably from poison hemlock) became toxic and passed the toxicity on to the Israelites who ate the fowl.¹⁶ In the 20th century, this is especially well documented in Italy, where the toxic alkaloid coniine was detected in bird meat, as well as in the blood, urine, and tissue of some individuals.¹³¹

The age of the plant seems to be directly correlated with increasing concentrations of coniine, whereas the toxin γ -coniceine occurs in greater amounts in new growth; hence, the plant remains toxic over the entire growing season. Fatal poisonings are reported on multiple continents frequently resulting from respiratory arrest. Of 17 poisoned Italian patients, all had elevated liver aminotransferases and myoglobin concentrations, and five had acute tubular necrosis.¹¹⁹ Death developed 1 to 16 days following ingestion.

Cholinergic Alkaloids: Arecoline, Physostigmine, and Pilocarpine. Betel chewing has been a habitual practice in the East since ancient times. The “quid” consists of betel nut (*Areca catechu*) and other ingredients. The effects of acute exposure to arecoline, the major alkaloid, include sweating, salivation, hyperthermia, and rarely death⁵⁵ Prolonged use is linked to dental decay and oral cancer. Physostigmine is an alkaloid derived from the Calabar bean (*Physostigma venenosum*), where it is present in concentrations of 0.15% (Antidotes in Depth: A9). Pilocarpine is derived from *Pilocarpus jaborandi* from South America. Its stimulatory effects on muscarinic receptors have proven valuable in the treatment of glaucoma. Reversal of toxicity can be achieved by atropine.

Psychotropic Alkaloids: Lysergic Acid and Mescaline. Hallucinations from the direct serotonin effects of lysergic acid alkaloids and its derivatives, and from the amphetamineline serotonin effects of the mescaline alkaloids, are reported following ingestion of morning glory seeds (*Ipomoea* spp) and peyote cactus (*Lophophora williamsii*), respectively (Chap. 82). Despite their chemical relatedness to LSD, molecules such as lysergic acid amide and lysergic acid ethylamide, found in Hawaiian baby woodrose seeds (*Argyrea nervosa*), produce findings that may appear anticholinergic¹⁷

Alkaloidal Central Nervous System Stimulants and Depressants: Ephedrine, Synephrine, Cathinone, and Opioids. The use of ephedrine-containing *Ephedra* spp in herbal dietary supplement products was banned by the FDA in 2004 because of the associated cardiovascular toxicity and deaths. Varieties of *Sida cordifolia* also contain ephedrine. Synephrine, a xenobiotic structurally related to ephedrine, occurs in bitter orange (*Citrus aurantium*), which is ingested as a plant, in foods such as marmalades, as a dietary supplement, or as a traditional medicine. Deaths and drug interactions can ensue from their use. Although illegal in the United States, another plant ingested for its CNS stimulant activity is khat (*Catha edulis*). The plant contains cathinone (α -aminopropiophenone) and cathine [(+)-norpseudoephedrine]. In addition, opioids derived from the poppy plant (*Papaver* spp) are prototypic CNS depressants and analgesics (Chap. 38).

Pyrrolizidine Alkaloids. Pyrrolizidine alkaloids are widely distributed both botanically and geographically. Approximately half of the 350 different pyrrolizidine alkaloids characterized to date are toxic when ingested. Pyrrolizidine alkaloids are found in 6000 plants and in 13 plant families, but they are most heavily represented within the Boraginaceae, Compositae, and Fabaceae families. Within these families, the genera *Heliotropium*, *Senecio*, and *Crotalaria*, respectively, are particularly notable for their content of toxic pyrrolizidine alkaloids, including the unsaturated 1-hydroxymethyl pyrrolizidine⁵⁶ The hepatic cytochrome P450 (CYP) system converts these compounds to highly reactive pyrroles in vivo. Chronic exposures stimulate the proliferation of the intima of hepatic vasculature and result in hepatic venoocclusive disease (HVOD). Poisonings occur as a result of the use of pyrrolizidine-rich plants for medicinal purposes and by contamination of food grain with seeds of pyrrolizidine-alkaloid-containing plants⁴⁴ Acute hepatocellular toxicity can occur following ingestion of 10 to 20 mg of pyrrolizidine alkaloid and is probably caused by an oxidant effect producing hepatic necrosis. An estimated 20% of patients with acute pyrrolizidine alkaloid poisoning die, 50% recover completely, and the rest develop subacute or chronic manifestations of HVOD. Pyrrolizidine alkaloids are teratogenic and are also transmitted through breast milk. Pyrrolizidine alkaloids may be present in bee pollen and have been reported in honey. Other types of plant-associated hepatic disorders are discussed in Effects Shared Among Different Classes of Xenobiotics.

Isoquinoline Alkaloids: Sanguinarine, Berberine, and Hydrastine. Adverse effects on human health due to consumption of edible mustard oil adulterated with argemone oil have been reported. Sanguinarine was detected in 26 family members who consumed a mustard oil contaminated with seeds of Mexican prickly poppy *Argemone Mexicana*¹³⁶ All patients suffered GI distress followed by peripheral edema (dropsy), skin darkening, erythema, skin lesions, perianal itching, anemia, and hepatomegaly. Ascites developed in 12%, and myocarditis and congestive heart failure occurred in approximately a third of affected individuals. Alterations in redox potentials and antioxidants in plasma may be responsible for the histopathological changes, including swollen hepatocytes and fluid accumulation in the spaces of Disse and Kupffer cell hyperplasia¹⁰ Medicinally, sanguinarine is used for dental hygiene⁹⁹ In North America, sanguinarine is found in blood root *Sanguinaria canadensis*), which, like *Argemone*, is in the Ranunculaceae family.

Berberine is structurally similar to sanguinarine and reportedly also has cardiac depressant effects. A number of medicinal plants contain berberine, including goldenseal (*Hydrastis canadensis*), Oregon grape (*Mahonia* spp), and barberry (*Berberis* spp). It causes myocardial and respiratory depression and contraction of smooth muscle vasculature and the uterus. Strychninelike movement disorders are described following ingestion of hydrastine, which makes up 4% of goldenseal.

Other Alkaloids: Emetine/Cephaline, Strychnine/Curare, and Swainsonine. Emetine and cephaline are derived from *Cephaelis ipecacuanha*, a tropical plant native to the forests of Bolivia and Brazil. They are the principal active constituents in syrup of ipecac, which produces emesis. Chronic use of syrup of ipecac, typically by patients with eating disorders or Munchausen syndrome by proxy, can lead to cardiomyopathy, smooth muscle dysfunction, myopathies, electrolyte and acid-base disturbances related to excessive vomiting, and death (Antidotes in Depth: A1). Poisoning in patients ingesting plant material is not reported.

Curare was used as an arrow poison derived from plants of the genus *Strychnos* as well as *Chondrodendron*, but the plants and their phytochemicals produce very different clinical effects. The convulsant alkaloids strychnine and brucine are found in various members of the genus *Strychnos*. Although used to produce arrow poison, the more widespread use of *Strychnos* spp in Africa was for trial by ordeal.¹¹² The seeds of *Strychnos nux-vomica* are especially rich in strychnine, which causes muscular spasms and rigidity by antagonizing glycine receptors in the spinal cord and brainstem. The plant is used as an herbal remedy for arthritis pain called “maqianzi,” which if improperly processed produces muscle spasm and weakness, including respiratory muscles (Chap. 112).

Curare is an extract of the bark of *Chondrodendron tomentosum* and certain members of the genus *Strychnos*. The physiologically active xenobiotic of curare from *Chondrodendron* is d-tubocurarine chloride, a competitive antagonist of acetylcholine at nicotinic receptors in the neuromuscular junction. Curare is the molecule from which most nondepolarizing neuromuscular blockers are derived (Chap. 68). Plant poisoning is recorded solely with its traditional use as a hunting poison.

Swainsonine has been isolated from *Swainsonia canescens*, *Astragalus lentiginos* (spotted locoweed), *Sida carpinifolia*, other species of *Swainsonia* and *Astragalus*, as well as several species in the genera *Oxytropis* and *Ipomoea*, and several fungi. After subsisting on seeds containing swainsonine for nearly 4 months, a naturalist forager manifested profound muscular weakness and died in the wilderness.⁷⁷ The compound is teratogenic and causes chronic neurologic disease called “locoism,” with weakness and failure to thrive in livestock. Swainsonine inhibits the glycosylation of glycoproteins by α -mannosidase II of the Golgi apparatus, resulting in a lysosomal storage disease. Adverse effects included hepatic, pancreatic, and respiratory manifestations, as well as lethargy and nausea.

Glycosides

Glycosides yield a sugar or sugar derivative (the glycone) and a nonsugar moiety (the aglycone) upon hydrolysis. The nonsugar or aglycone group determines the subtype of glycoside. For instance, the cardiac glycosides have saponin

(steroid) aglycone groups and are placed among the saponin glycosides.

Saponin Glycosides: Cardiac Glycosides, Glycyrrhizin, and Ilex Saponins. Poisoning by virtually all cardioactive steroidal glycosides is clinically indistinguishable from poisoning by digoxin (Chap. 64), which itself is a cardioactive steroid derived from *Digitalis lanata*. However, compared with toxicity from pharmaceutical digoxin, toxicity resulting from the cardioactive steroidal glycosides found in plants has markedly different pharmacokinetic characteristics. For example, digitoxin in *Digitalis* spp has a plasma half-life as long as 192 hours (average 168 hours).

The pharmacologic properties are true across taxonomic boundaries. Poisonings by *Digitalis* spp,^{115,137} squill (*Urginea* spp),¹⁵⁰ lily of the valley,³ oleander (*Nerium* spp),¹⁵⁶ yellow oleander (*Thevetia* spp),⁴¹ and *Cerbera manghas*⁴² are clinically similar (Fig. 121–2). The potency of these effects depends on the specific cardioactive glycoside constituents and their dose. For instance, lily of the valley is rarely associated with morbidity or mortality, whereas ingestion of only two seeds of yellow oleander by adults can produce severe symptoms, and expected outcome is grave with several more.⁴¹ Poisonings by oleander and yellow oleander occur predominantly in the Mediterranean and in the Near and Far East. These two plants are popular attractive ornamentals and commonly result in poisoning in the United States and Europe.

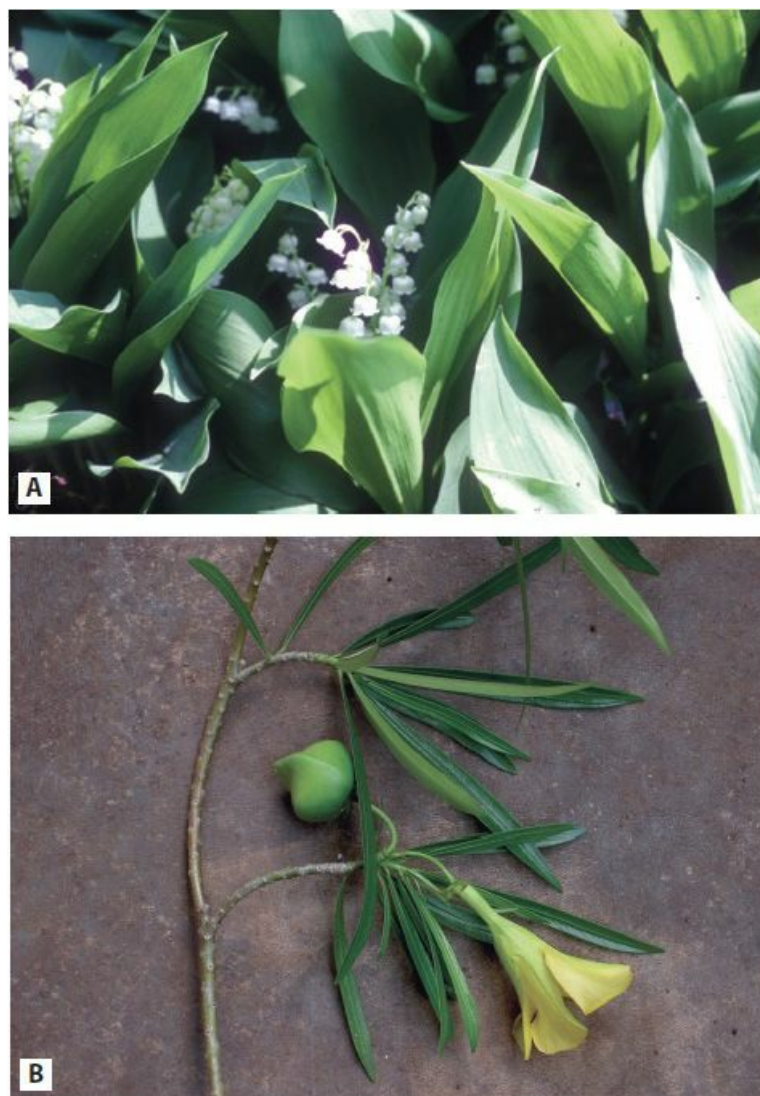


FIGURE 121–2. Saponin-glycoside containing plants: (A) Lily of the valley (*Convallaria majalis*) contains the cardioactive steroid convallatoxin. (B) Yellow oleander (*Thevetia peruviana*) contains a cardioactive steroid, thevetin. (Used with permission of Darren Roberts, M.D.)

Patients experience vomiting within several hours, followed by hyperkalemia, cardiac conduction delays, and increased automaticity (bradycardia and tachydysrhythmias). Interestingly, the cardiac manifestations may be difficult to distinguish from those produced by plants containing sodium channel blockers (section Sodium Channel Effects). Activated charcoal was beneficial in preventing death after suicide attempts with yellow oleander in Sri Lanka, and its use should not be delayed in the face of uncertain plant identity.³⁶ Antibody therapy reduces mortality threefold from yellow oleander poisoning but is too expensive for developing countries where oleander-induced mortality is highest.⁴³ In addition, various cardioactive steroids respond differently to therapeutic use of digoxin-specific antibody fragments. Use of very large doses of digoxin-specific antibody (up to 37 vials reported in one case¹¹⁸) may be necessary to capitalize on the therapeutic cross-reactivity between digoxin-specific antibody and the nondigoxin cardioactive steroids, such as oleander.¹²⁶ The potential for success should lead to use of antibody therapy without delay when available. Similarly, there is variable

cross-reactivity among the individual plant cardioactive steroids with regard to the degree to which each elevates diagnostic polyclonal digoxin assay measurements in clinical laboratories.³³ These measurements can be used only as qualitative proof of exposure but not as quantitative indicators of the exposure because the elevations can result in marked underestimation of the “functional digoxin concentrations.” Until additional technologic advances occur, any positive digoxin concentration following exposure to a plant should be assumed to be significant.

Glycyrrhizin. Glycyrrhizin is a saponin glycoside derived from *Glycyrrhiza glabra* (licorice) and other *Glycyrrhiza* spp. Glycyrrhizin inhibits 11- β -hydroxysteroid dehydrogenase, an enzyme that converts cortisol to cortisone. When large amounts of licorice root are consumed chronically, cortisol concentrations rise, resulting in pseudo-hyperaldosteronism because of its affinity for renal mineralocorticoid receptors.⁵⁰ Chronic use eventually leads to hypokalemia with muscle weakness, sodium and water retention, hypertension, and dysrhythmias.¹⁶⁵ Assessment involves evaluation of the patient’s fluid and electrolytes, and electrocardiogram. Potassium replacement is the most common necessary intervention.

Ilex Species. Holly berries from more than 300 *Ilex* spp are commonly ingested by children, especially during winter holidays. They contain a mixture of alkaloids, polyphenols, saponin glycosides, steroids, and triterpenes. Saponin glycosides appear to be responsible for GI symptoms such as nausea, vomiting, diarrhea, and abdominal cramping that result from ingestion of the berries. CNS depression was reported in a case in which a child consumed a “handful” of berries; however, this child was also treated with syrup of ipecac.¹²² The toxic quantity is undefined, but it is typically suggested that no untoward effects are to be expected for ingestions of fewer than six berries. Symptoms may be expected to be restricted to GI effects, and treatment is supportive.

Cyanogenic Glycosides: (S)-Sambunigrin, Amygdalin, Linamarin, and Cycasin. Cyanogenic glycosides yield hydrogen cyanide on complete hydrolysis. These glycosides are represented in a broad range of plant species.¹⁵³ The species that are most important to humans are cassava (*Manihot esculenta*), which contains linamarin, and *Prunus* spp, which contain amygdalin.¹² Cycad toxins are neurotoxic or pseudocyanogenic. Rare reports of cyanide poisoning associated with (S)-sambunigrin in European elderberry *Sambucus nigra*; sambunigrin) are more severe when these ingestions include leaves as well as berries.²²

Many North American species of plants contain cyanogenic compounds, including ornamental *Pyracantha*, *Passiflora*, and *Hydrangea* spp, which either do not release cyanide or are rarely consumed in quantities sufficient to result in toxicity. On the other hand, although the fleshy fruit of *Prunus* spp in the Rosaceae are nontoxic (apricots, peaches, pears, apples, and plums), the leaves, bark, and seed kernels contain amygdalin, which is metabolized to cyanide. Sufficient cyanide can be absorbed to cause acute poisoning.¹⁴⁵ Amygdalin was the active ingredient of Laetrile, an apricot pit extract promoted in the 1970s for its supposed selective toxicity to tumor cells. Its sale was restricted in the United States because it lacked efficacy and safety.^{98,100} However, patients went to other countries for Laetrile therapy, which was marketed as “vitamin B-17” and was available through alternative medicine providers. The manifestations of cyanide poisoning and treatment involving use of the cyanide antidote kit are detailed elsewhere (**Chap. 126**) (Antidotes in Depth: A39–A41).

Acute and chronic cyanide toxicity (including deaths) associated with consumption of inadequately prepared cassava (*M. esculenta*) are reported worldwide (**Chap. 126**).¹ Chronic manifestations include visual disturbances (amblyopia), upper motor neuron disease with spastic paraparesis, and hypothyroidism. These findings are associated with protein-deficient states and the use of tobacco and alcohol. The ataxic neuropathy resembles that produced by lathyrism (section Proteins, Peptides, and Lectins). A unifying hypothesis about the etiology of these two similar diseases from seemingly very different sources is that thiocyanate accumulation may lead to degeneration of the α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA)-containing neurons that are first stimulated and then destroyed in neurolathyrism.¹⁴¹

Similarly, seeds of cycads contain cycasin and neocycasin, which belong to the family of cyanogenic glycosides, as well as neurotoxins. The cyanogenic glycosides of cycads are considered pseudocyanogenic, with little potential to liberate hydrogen cyanide, but most typically produce violent vomiting 30 minutes to 7 hours after ingestion of 1 to 30 seeds.²⁶ On the island of Guam, indigenous peoples develop a devastating amyotrophic lateral sclerosis-parkinsonism dementia complex (ALS-PDC) that appears associated with ingestion of *Cycas circinalis* seeds or the flying foxes that feed extensively upon the cycads.²⁹ The implicated xenobiotic originally was believed to be an excitatory amino acid, but more recently is identified as a sterol glycoside. Research on the mechanism of this cycad-induced disease is ongoing, with the goal of understanding potential mechanisms of this disease and its links to ALS and Parkinson disease.^{19,28}

Anthraquinone Glycosides: Sennoside and Others. Anthraquinone laxatives are regulated both as nonprescription pharmaceuticals and as dietary supplements. These glycosides, such as sennoside, are metabolized in the bowel to produce derivatives that stimulate colonic motility, probably by inhibiting Na⁺K⁺–adenosine triphosphatase (ATPase) in the intestine, which also promote accumulation of water and electrolytes in the gut lumen, producing fluid and electrolyte shifts that can be life threatening.¹⁴⁴

Other Glycosides: Salicin, Atractyloside, Carboxyatractyloside, Vicine, and Convicine. Salicin is an inactive glycoside until it is hydrolyzed to produce salicylic acid (**Chap. 39**). The glycosidic bond is relatively resistant to stomach acid, and the hydrolysis must be accomplished by gut flora. The ability of individual human flora to produce the necessary enzymes

varies significantly, resulting in variable clinical effects for salicin or plant material that contains salicin. However, sufficient hydrolytic capacity for some transformation of the glycoside into salicylic acid occurs in all individuals.

Atractylis gummifera was a favorite agent for homicide during the reign of the Borgias. Atractyloside, the toxic xenobiotic primarily inhibits oxidative phosphorylation in the liver by inhibiting the ADP/ATP antiporter blocking influx of adenosine diphosphate (ADP) into hepatic mitochondria and outflow of ATP to the rest of the cell (Chap. 12). Death or severe illness as a result of liver failure or hepatorenal disease following ingestion is reported.³² *Callilepis laureola* is a South African medicinal plant that contains atractyloside and carboxyatractyloside and is reported to cause human poisonings. Cocklebur (*Xanthium strumarium*) is an herbaceous plant with worldwide distribution. The seeds contain the glycoside carboxyatractyloside. The toxic mechanism is similar to that for atractyloside, and seed ingestion has resulted in human fatalities. Nine patients presented with acute onset abdominal pain, nausea and vomiting, drowsiness, palpitations, sweating, and dyspnea after cocklebur ingestion. Several patients developed hepatocellular damage, renal compromise and myocardial injury, and three developed convulsions followed by loss of consciousness and death.¹⁵¹

Favism is a potentially fatal disorder brought about by eating fava beans or vetch seeds (*Vicia faba*, *Vicia sativa*, respectively). These seeds contain the pyrimidine glycosides vicine and convicine (divicine is the aglycone of vicine). Consumption of these compounds by individuals with an inborn error of metabolism (glucose-6-phosphate dehydrogenase deficiency) can cause acute hemolytic crisis (Chap. 22).¹³⁵

The effects of the glycosides sinigrin (from *Brassica nigra* seed and *Alliaria officinalis* {horseradish} root) and naringen (a polyphenolic glycoside from the grapefruit *Citrus paradisi*) are discussed in the sections on Plant-Induced Dermatitis and Plant–Xenobiotic Interactions, respectively.

Terpenoids and Resins: Ginkgolides, Kava Lactones, Thujone, Anisatin, Ptaquiloside/Thiaminase, and Gossypol

Ginkgolides in *Ginkgo biloba* inhibits platelet aggregation. Reports of spontaneous bleeding associated with ingestion of *Ginkgo* leaf products as an herbal medicine are perhaps explained by this property.¹²³ Another xenobiotic found only in the seed, 4-methoxypyridoxine (pyridine alkaloid), is associated with seizures.⁷⁵ A mechanism similar to isoniazid-induced seizures is plausible, suggesting treatment with pyridoxine phosphate (Chap. 58) (Antidotes in Depth: A14). The dermal effects of *Ginkgo* are discussed in the section Plant-Induced Dermatitis.

Kava lactones are a family of terpene lactones found in kava (*Piper methysticum*) that cause central and peripheral nervous system effects. Kava has enjoyed a long, ceremonial history among islanders of the South Pacific, and observers visiting Oceania have recorded its acute and chronic effects (both pleasant and unpleasant) over the centuries. Importation of kava to Australia in 1983 was a measure to assist Aborigines with alcohol abuse problems. However, the kava itself became abused, and its subsequent ban has resulted in the growth of a black market for kava. Proposed mechanisms to explain the effects of kava lactones include effects at γ -aminobutyric acid type A (GABAA) and GABAB receptors or local anesthetic effects.¹²⁹ Acute symptoms following ingestion include peripheral numbness, weakness, and sedation. Chronic use leads to kava dermopathy and weight loss. More than 70 cases of hepatotoxicity, several requiring liver transplantation, are associated with both acute and chronic effects of kava extracts on cytochrome oxygenases or other yet-to-be-defined etiologies and prompted regulatory health measures in Europe and North America.¹⁴⁸

Thujone is one of many terpenes associated with seizures. It is found in the wormwood plant (*Artemisia absinthium*), in absinthe (the liquor flavored with *A. absinthium*), and in some strains of tansy (*Tanacetum vulgare*). The α - and β -isomers of thujone are believed to act much like camphor to produce CNS depression and seizures. Invoking the structural similarity of thujone to tetrahydrocannabinol (THC), one of the terpenoids of marijuana, to explain the psychoactive effects is controversial (Chap. 77).⁹⁷

Absinthism is characterized by seizures and hallucinations, permanent cognitive impairment, and personality changes. Acute and chronic absinthism led to a worldwide ban of the alcoholic beverage absinthe, which contained thujone, in the early 1900s.¹¹⁰ Over the past several years, there has been a reexamination of the role of absinthe in the seizure disorders previously attributed to this liquor. Modern analytical procedures have been used to analyze the thujone content of vintage absinthe and modern products made using vintage recipes. Results have largely concluded that thujone content in the liquor was likely to be too low to have produced symptoms.⁷⁸ However, because the essential oil of wormwood is composed almost exclusively of thujone, it, not absinthe, is a potent cause of seizures.¹¹⁰ Wormwood oil for making homemade absinthe is currently available and is responsible for at least two reports of adverse reactions in people seeking its hallucinatory or euphoriant effects.¹⁵⁸

Anisatin is found in *Illicium* spp. This terpenoid produces seizures as a noncompetitive GABA antagonist. The Chinese star anise (*Illicium verum*) is sometimes used in teas and occasionally is confused or contaminated with other species of *Illicium*, particularly Japanese star anise *Illicium anisatum*.⁷¹ These contaminations have resulted in small epidemics of tonic-clonic seizures, particularly, but not exclusively, in infants after use of the tea to treat their infantile colic. Recently, in the United States, a case series of at least 40 individuals who had consumed teas brewed from “star anise” experienced

seizures, motor disturbances, other neurologic effects, and vomiting.⁷¹ These cases include at least 15 infants treated for infantile colic with this home remedy. This trend prompted the FDA to issue an advisory regarding the health risk from remedies sharing the common name “star anise.”

Ptaquilosides are found in the bracken fern (*Pteridium aquilinum*), a plant that is extending its range and density worldwide. In foraging animals, consumption of ptaquilosides results in acute hemorrhage secondary to profound thrombocytopenia, whereas thiaminases that are also found in the bracken fern result in cerebral disease.⁴⁷ Although no acute human poisonings are reported, these xenobiotics are transmitted through cow’s milk and are associated with increased prevalence of gastric and esophageal cancer in areas where fern is endemic and consumed by cows whose milk is not diluted.¹⁶³ Chronic toxicity through spore inhalation also produces pulmonary adenomas in animals. More recently, research defined links between alimentary cancer in humans who previously consumed bracken fern fiddleheads.

Gossypol is a sesquiterpene that is derived from cottonseed oil. It has been used experimentally as a reversible male contraceptive. The mechanism for its spermicidal effect is unclear, but the effects have been attributed to inhibition of plasminogen activation and plasmin activity in acrosomal tissue. These effects are not currently reported to produce systemic bleeding. Gossypol also inhibits 11- β -hydroxysteroid dehydrogenase, as does glycyrrhizin and may result in hypokalemia.¹⁶⁴

Proteins, Peptides, and Lectins: Ricin and Ricinlike, Pokeweed, Mistletoe, Hypoglycin, Lathyrins, and Microcystins

Lectins are glycoproteins that are classified according to their binding affinity for specific carbohydrate ligands, particularly galactosamines, and by the number of protein chains linked by disulfide bonds. Toxalbumins such as ricin and abrin are lectins that are such potent cytotoxins that they are used as biologic weapons (**Chap. 133**). Ricin, extracted from the castor bean (*Ricinus communis*; **Fig. 121–3A**), exerts its cytotoxicity by two separate mechanisms.⁹ The compound is a large molecule that consists of two polypeptide chains bound by disulfide bonds. It must enter the cell to exert its toxic effect. The B chain binds to the terminal galactose of cell surface glycolipids and glycoproteins. The bound toxin then undergoes endocytosis and is transported via endosomes to the Golgi apparatus and the endoplasmic reticulum. There the A chain is translocated to the cytosol, where it stops protein synthesis by inhibiting the 28S subunit of the 60S ribosome. In addition to the GI manifestations of vomiting, diarrhea, and dehydration, ricin can cause cardiac, hematologic, hepatic, and renal toxicity. All contribute to death in humans and animals.⁹ Despite the obvious toxicity of this compound, death probably can be prevented by early and aggressive fluid and electrolyte replacement after oral ingestion (but not injection or inhalation; **Chap. 133**). Allergic reactions to some of these lectin-bearing plants and their derivatives are noted.

Just how lethal are ingestions of the ornamental seeds? The highest concentration of xenobiotic is in the hard, brown-mottled seeds. These seeds are both tempting and available, even to children in the United States, because they are attractive enough to be used to make jewelry, and their parent plants are showy enough to have been exported for horticultural purposes outside of their native India (including to the United States). Although mastication of one seed by a child liberates enough ricin to produce death, this outcome (or even serious toxicity) is uncommon, even if the seeds are chewed, probably because GI absorption of the xenobiotic is poor and supportive care is effective.⁵ Activated charcoal should be administered promptly following ingestion.

Other ricinlike lectins are found in *Abrus precatorius* (jequirity pea, rosary pea; **Fig. 121–3B**),³⁸ *Jatropha* spp,⁸² *Trichosanthes* spp (eg. *T. kirilowii* or Chinese cucumber), *Robinia pseudoacacia* (black locust),⁷⁰ *Phoradendron* spp (American mistletoe), *Viscum album* (European mistletoe), and *Wisteria* spp (wisteria). These all produce at least one double-chain lectin that binds to galactose-containing structures in the gut or inhibits protein synthesis in a manner similar to ricin.



FIGURE 121–3. Protein, peptide, and lectin containing plants: (A) The castor bean plant. The seedpods come in bunches, two of which appear near the center of the image. Each seedpod typically contains three seeds. Inset: Castor beans (*Ricinus*

communus) which contain the toxalbumin ricin. By interfering with protein synthesis, ricin may cause multiorgan system failure when administered parenterally. However, its oral absorption is poor, and most oral poisonings cause gastroenteritis. **(B)** Rosary pea (*Abrus precatorius*) containing abrin, a toxalbumin that inhibits protein synthesis. The peas are shown strung together as a rosary. **(C)** Pokeweed (*Phytolacca americana*) has a large rootstock. The unripe berries contain phytolaccatoxin that produces gastroenteritis, but the mature, purple berries are often consumed without toxicity. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

The most commonly ingested toxic plant lectins in the United States are from pokeweed (*Phytolacca americana*; [Fig. 121–3C](#)), which is eaten as a vegetable but rarely causes toxicity or death. The mature, deep purple berries are less toxic. Pokeweed leaves are consumed after boiling without toxic effect if the water is changed between the first and second boiling (parboiling). When this detoxification technique is not followed, as in preparation of poke salad or pokeroor tea, violent GI effects can ensue 0.5 to 6 hours after ingestion. Nausea, vomiting, abdominal cramping, diarrhea, hemorrhagic gastritis, and death may occur. In addition, bradycardia and hypotension, perhaps induced by an increase in vagal tone, may be associated with nausea and vomiting.^{65,121} Phytolaccatoxin and pokeweed mitogen are found in all plant parts, but the highest concentrations are found in the plant root. Pokeweed mitogen is a single-chain protein that inhibits ribosomal RNA by removing purine groups.¹⁴ It produces a lymphocytosis 2 to 4 days after ingestion that may last for 10 days, but is without clinical consequence.

Mistletoe berries, both American and European, can produce severe gastroenteritis, especially when delivered as teas or extracts, or particularly as parenteral antineoplastic medicinal agents in Europe. As festive holiday plants they become seasonally available for children. Poison center data suggest that ingestion of three to five berries or one to five leaves of the American species may not cause toxicity, but these suggestions are based on limited evidence ([Chap. 136](#)). Despite single reports of seizure, ataxia, hepatotoxicity, and death, most authors performing such retrospective examinations conclude that mistletoe exposures are not a highly consequential risk.¹⁴²

Hypoglycin A (β -methylene cyclopropyl-L- α -aminopropionic acid) and hypoglycin B (dipeptide of hypoglycin A and glutamic acid) are found in the unripe ackee fruit and seeds of *Blighia sapida* (Euphorbiaceae). The tree is native to Africa but was imported to Jamaica in 1778 and subsequently naturalized in Central America, southern California, and Florida. The scientific name of the plant derives from Captain William Bligh, the British explorer. Epidemics of illness (Jamaican vomiting sickness) associated with consumption of the unripe ackee fruit (raw and cooked) occur in Africa but are more common in Jamaica, where ackee is the national dish.⁷⁴ The most toxic part is the yellow oily aril of the fruit,²⁷ which contains three large, shiny black seeds. Cases may also be associated with canned fruit.⁹⁶ Hypoglycin A is metabolized to methylene cyclopropyl acetic acid, which competitively inhibits the carnitine–acyl coenzyme (CoA) transferase system.¹¹ This prevents importation of long-chain fatty acids into the mitochondria, preventing their β -oxidation to precursors of gluconeogenesis. β -Oxidation and gluconeogenesis are further arrested by inhibition of various enzymes, such as glutaryl CoA dehydrogenase, which blocks the malate shunt ([Chap. 13](#)). In addition, increased concentrations of glutaric acid may inhibit glutamic acid decarboxylase, which produces GABA from glutamic acid. This not only depletes GABA but also increases concentrations of excitatory glutamate to produce seizures. Insulin concentrations remain unaffected by hypoglycin and metabolites. Carboxylic and other organic acid substrates build up in the urine and serum as a result of these metabolic disturbances. Detection of these acids can help corroborate the diagnosis.¹¹ Jamaican vomiting sickness is characterized by epigastric discomfort and the onset of vomiting starting 2 to 6 hours after ingestion. Convulsions, coma, and death can ensue, with death occurring approximately 12 hours following consumption. Laboratory findings are notable for profound hepatic aminotransferase and bilirubin abnormalities, and aciduria and acidemia without ketonemia. Cholestatic hepatitis can occur and is reported with chronic use.⁸⁰ Autopsy reveals fatty degeneration of liver, particularly microvesicular steatosis, and other organs with depletion of glycogen stores. Left untreated, patient mortality reaches 80%, with 85% of the fatal cases suffering seizures. Treatment with dextrose and fluid replacement is essential. Benzodiazepines can control seizures, but may fail if the seizures are related to depletion of GABA. L-Carnitine therapy may exert a theoretical therapeutic role similar to that noted with valproic acid toxicity ([Chap. 48](#)) (Antidotes in Depth: A8).⁸⁵

The lathyrins β -N-oxalylamino-L-alanine (BOAA) and β -aminopropionitrile (BAPN) are peptides from the grass pea (*Lathyrus sativus*) found in the seeds and leaves, respectively. BOAA produces neurolathyrism and BAPN produces osteolathyrism in individuals with a dietary dependence on this plant. Neurolathyrism is nearly indistinguishable from spastic paresis associated with consumption of improperly prepared cassava (section Cyanogenic Glycosides).^{13,30} Thiol oxidation with depletion of nicotinamide adenine dinucleotide (NADH) dehydrogenase at the level of neuronal mitochondria (ie, excitatory AMPA receptors) may be the common etiology.¹⁴¹ Epidemics have occurred in Bangladesh, Ethiopia, Israel, and India. Exposure to BOAA results in degeneration of corresponding corticospinal pathways that becomes irreversible if consumption of undetoxified grass peas is not stopped early. BOAA stimulates the AMPA class of glutamate receptors to provide constant neuronal stimulation, eventual degeneration, and hence spasticity.¹⁶² BAPN affects bone matrix and leads to bone pain and skeletal deformities that develop in adulthood. These diseases occur in areas where the plants are endemic, the food is consumed for 2 months or more, and when diets are otherwise poor in protein and possibly in zinc.⁵⁷

Microcystins are found in several cyanobacteria (blue-green algae) belonging to various species of the genera *Microcystis*, *Anabaena*, *Nodularia*, *Nostoc*, and *Oscillatoria*. They elaborate a series of peptides called microcystins and nodularins (*Nodularia spumigena*).³⁹ These compounds produce hepatotoxicity by inhibiting phosphatases and causing deterioration of the microfilament function in hepatocytes, leading to cell shrinkage and bleeding into the hepatic sinusoids. Evidence indicates that these peptides are carcinogenic to humans. Although most cases of untoward effects from blue-green algae occur in animals, the potential for harm was demonstrated by use of microcystin-contaminated water in a dialysis unit in Brazil.⁷³ Unfiltered water was identified as the risk factor for liver disease in 100 patients who attended the dialysis center (Chap. 10). Fifty of these patients died of acute liver failure following early signs of nausea, vomiting, and visual disturbances. Of concern, certain species of cyanobacteria are harvested and consumed as health foods or may be consumed secondarily in fish.⁵⁸

Phenols and Phenylpropanoids: Coumarins, Capsaicin, Karwinskia Toxins, Naringenin and Bergamottin, Asarin, Nordihydroguaiaretic Acid, Podophyllin, Psoralen, and Esculose

Phenols and phenylpropanoids represent one of the largest groups of plant secondary metabolites. Coumarins and their isomers are phenylpropanoids that are discussed in Chap. 60. Some coumarins are warfarinlike in their activity and are capable of producing a bleeding diathesis when plants containing them are consumed in sufficiently large quantities.⁶⁸ Lignans are formed when phenylpropanoid side chains react to form bisphenylpropanoid derivatives. Lignins are high-molecular-weight polymers of phenylpropanoids that bind to cellulose and provide strength to cell walls of stem and bark. Tannins are polymers that bind to proteins and divide into two groups: hydrolyzable and condensed forms.

Capsaicin is derived from *Capsicum annuum* or other species of chile or cayenne peppers. Capsaicin is a simple phenylpropanoid that causes release of the neuropeptide substance P from sensory C-type nerve fibers that act upon transient receptor potential (TRP) channels in diverse human tissues.¹⁵⁴ The immediate response to capsaicin is intense local pain and is the rationale for its use as “pepper spray.” Eventual depletion of substance P prevents local transmission of pain impulses from these receptors to the spinal cord, blocking perception of pain by the brain, explaining its use in postherpetic neuralgia.

Painful exposures to capsaicin-containing peppers are among the most common plant-related exposures presented to poison centers. They cause burning or stinging pain to the skin. If ingested in large amounts by adults or small amounts by children, they can produce nausea, vomiting, abdominal pain, and burning diarrhea. Eye exposures produce intense tearing, pain, conjunctivitis, and blepharospasm. Fatality is rare, but has occurred after inhalation and infusion.¹⁴⁰

Skin irrigation, dermal aloe gel, analgesics, and oral antacids are therapeutic agents that may be helpful as appropriate, but patients can be reassured that the effects are transitory and produce no long-term damage. Irritated eyes can be treated with irrigation and local analgesia, but generally resolve without sequelae within 24 hours.

Karwinskia toxins are found in plants commonly named buckthorn, coyotillo, tullidora, wild cherry, or capulincillo (*Karwinskia humboldtiana*). These xenobiotics are identified by their molecular weights (T-514, T-496, T-516, T-544). Toxicity has been known for more than 200 years. In 1920, an epidemic of deaths was reported after 20% of 106 Mexican soldiers died following ingestion of foraged *Karwinskia* fruits.⁹² The fruits are attractive to children. Epidemic poisonings have been reported in Central America and are possible wherever the shrub is found (in semidesert areas throughout the southwestern United States and in the Caribbean, Mexico, and Central America).⁸ Uncoupling of oxidative phosphorylation or dysfunction of peroxisome assembly and integrity is described as the mechanism of action of T-514 on Schwann cells. Each xenobiotic exhibits similar cytotoxic effects at the cellular level, but with tropism for different organs in animal models.⁹²

Within a few days of ingestion, a symmetric motor neuropathy ascends from the lower extremities to produce a bulbar paralysis that may lead to death. Deep-tendon reflexes are abolished in affected areas, but cranial nerve findings are absent. Distinction of this demyelinating motor neuropathy from Guillain-Barré syndrome, poliomyelitis, solvent, and other polyneuropathies is difficult without a history of the fruit ingestion,¹⁰⁸ but can be assisted by detection of T-514 in the blood of affected patients. The other recognized toxins are not detected in blood. Occasionally, axonal damage is observed, but demyelination is the predominant finding on biopsy. Nerve conduction studies always demonstrate loss or abolition of function in fast-conducting axons. Cerebrospinal fluid demonstrates normal protein, glucose, and cytology. Treatment is supportive, with mechanical ventilation as needed, and recovery typically is slow.

Naringin and naringenin are flavonoid, while bergamottin and 6',7'-dihydroxybergamottin are furanocoumarin phenylpropanoids derived from grapefruit that inhibit CYP3A4 in gut and liver. Grapefruit juice consumption can increase circulating concentrations of drugs reliant on CYP3A4 for metabolic elimination, including carbamazepine, felodipine, and the statins. The most plausible mechanism is inhibition of enteric CYP3A4 and P-glycoprotein.¹¹¹ These effects are maximally achieved by a single glass of grapefruit juice.⁸⁹

Comedication with St. John's wort resulted in decreased plasma concentrations of a number of xenobiotics.⁹⁰ Hyperforin is a phenylpropanoid found in St. John's wort (*Hypericum perforatum*) and is associated with plant–xenobiotic interactions through strong induction of CYP3A4 mediated drug metabolism as well as induction of P-glycoprotein. These combined mechanisms can cause subtherapeutic concentrations of xenobiotics metabolized via these pathways.

Asarin is a term sometimes used for the naturally occurring mixture of α - and β -asarones found in the root of *Asarum europaeum*, *Asarum arifolium*, and *Acorus calamus* (sweet flag). Essential oils of the plants have anthelmintic and nematocidal activity, but putative euphoric and hallucinogenic effects that motivate recreational ingestion are in contrast to confirmed reports of unpleasant GI effects.¹⁵²

Nordihydroguaiaretic acid (NDGA) is associated with hepatotoxicity after ingestion of chaparral (*Larrea tridentata*).⁶⁰ Podophyllin and psoralens are phenylpropanoids discussed in the sections Antimitotic Alkaloids and Resins, and Plant-Induced Dermatitis, respectively.

Esculose (also called esculin or aesculin) has triterpene saponin side chains and is believed to be the toxic component in horse chestnut (*Aesculus hippocastanum*). Horse chestnut extracts are used medicinally in patients with venous insufficiency. The therapeutic use of these extracts at high doses ($> 340 \mu\text{g/kg}$) is associated with renal failure or a lupuslike syndrome.⁶¹ Leaves, twigs, or horse chestnuts ingested by children or consumed as a tea by adults results in a syndrome that resembles nicotine intoxication. The syndrome consists of vomiting, diarrhea, muscle twitching, weakness, lack of coordination, dilated pupils, paralysis, and stupor. The mechanism of toxicity is not defined, but massive ingestion of horse chestnuts is suggested to be poisonous to a child.

Carboxylic Acids: Aristolochic Acids, Oxalic Acid, and Oxalate Raphides

Nitrophenanthrene carboxylic acids, collectively called aristolochic acids, are present in most members of the genus *Aristolochia*, including those used ornamentally and as traditional medicines. Consumption of these compounds can cause aristolochic acid nephropathy (AAN), a progressive renal interstitial fibrosis frequently associated with urothelial malignancies (Chap. 45).³⁷ Sources of exposure are via consumption of flour made from wheat contaminated with the seeds of *Aristolochia clematis* or other *Aristolochia* species (so called Balkan endemic nephropathy),⁶² or through use of certain traditional Asian medicines made from *Aristolochia* spp (Chinese herb nephropathy).³⁴

Oxalic acid is the strongest acid among the carboxylic acids found in living organisms. It forms poorly soluble chelates with calcium and other divalent cations. Higher plants have varying ability to accumulate these include both soluble and insoluble oxalates, and many contain crystals of calcium oxalate called raphides. Certain plant families, such as the Araceae, Chenopodiaceae, Polygonaceae, Amaranthaceae, and several of the grass families, are rich in oxalates. Human dietary sources include rhubarb, spinach, strawberries, chocolate, tea, and nuts. Human consumption of soluble oxalate-rich foods correlates with kidney stone formation.⁸⁴

The insoluble calcium oxalate raphides that are present in certain plants, usually in the Araceae family, are found in conjunction with a protein toxin that increases the painful irritation to skin or mucous membranes. This special manifestation is discussed in greater detail in the section Plant-Induced Dermatitis.

Alcohols: Cicutoxin

Cicutoxin, a diacetylenic diol, is found in *Cicuta maculata* (water hemlock), *Cicuta douglasii* (western water hemlock), and *Oenanthe crocata* (hemlock water dropwort). *O. crocata* is native to Europe where intoxications are reported and is now naturalized to the United States. Ingestion of any part of these plants constitutes the most common form of lethal plant ingestion in the United States. Hemlock has dominated plant-related fatalities among the most recent 10-year reviews of the AAPCC data and Centers for Disease Control and Prevention (CDC) plant-poisoning records (Chap. 135). In contrast to most plant exposures in humans, which tend to involve children, these ingestions usually involve adults who incorrectly identify the plant as wild parsnip, turnip, parsley, or ginseng.¹³⁴ All plant parts are poisonous at all times, but the tuber is especially toxic, and more so during the winter and early spring. Absorption of cicutoxin is rapid and occurs through the skin as well as through the gut. Although the mechanism is not fully understood, cicutoxin may noncompetitively inhibit GABA-chloride channels or block potassium channels.¹³⁴

Symptoms of mild or early poisonings consist of GI symptoms (nausea, vomiting, epigastric discomfort) and begin as early as 15 minutes after ingestion. Diaphoresis, flushing, dizziness, excessive salivation, bradycardia, hypotension, bronchial secretions with respiratory distress, and cyanosis occur and rapidly progress to violent seizures. Ingestion of as little as a 2-cm section of the sweet-tasting root of *Cicuta* can produce status epilepticus.¹³⁴ Other complications include rhabdomyolysis with renal failure and severe acidemia. Immediate gastric evacuation should be performed if practical, and benzodiazepines should be administered for seizures. No specific antidote exists; supportive and symptomatic care should be provided.

Unidentified Toxins

Consistent with the inherent complexity of plants and the relatively early stage of the science, identification of the active ingredient(s) involved in poisoning is not always possible. An epidemic of the irreversible lung disease bronchiolitis obliterans developed in Taiwan in 1994 that involved more than 200 dieters who had been eating *Sauropus androgynus* as a weight-loss vegetable. The effects were dose related (usually approximately 100 g/d) and manifested by month 7 after approximately 10 weeks of use.⁶⁹ The cases were associated with at least four deaths, in addition to pulmonary disease resulting in lung transplantation.⁸⁸ Torsade de pointes occurred in three patients, consistent with the plant's high concentration of papaverine, a toxin that produces dysrhythmias in animals. Corticosteroid and bronchodilator therapy consistently failed to improve pulmonary symptoms. A report of a later outbreak in Japan noted that the plant was consumed in an uncooked state.¹⁰⁹

Milk sickness is a historic poisoning described by pioneer farmers. It was caused by transmission of the nontoxic ketone tremetone to humans via milk of animals grazing on white snake-root plants (*Ageratina altissima*, formerly *Eupatorium rugosum*). Tremetone is transformed into an unknown, unstable toxin by hepatic microsomal enzymes.⁸¹ Toxicity is cumulative. Milk sickness can be fatal in 1 to 21 days or is associated with a slow recovery marked by weakness for months or years, relapsing sometimes to death. A delay in the development of the lactating animal's symptoms provided a lag time when xenobiotic-laden milk was taken from asymptomatic animals and thereby transmitted to humans before the problem was detected.

Breynia officinalis, the air potato or bitter yam (*Dioscorea bulbifera*) are associated with hepatotoxicity.⁸⁷ Black cohosh (*Actaea racemosa*) hepatotoxicity is suggested in case reports, but causality is not established.¹⁴⁷

Consumption of the food star fruit (*Averrhoa carambola*) and preexisting renal insufficiency are associated with development of intractable hiccups, vomiting, motor disabilities, paresthesias, confusion, seizures, and death unless patients receive supportive care and hemodialysis.¹⁴⁹ The unidentified toxin appears to be neuroexcitatory and may be oxalate.^{21,49} Charcoal hemoperfusion is reported to be successful but clearance was not determined and causality not confirmed.²⁴

EFFECTS SHARED AMONG DIFFERENT CLASSES OF XENOBIOTICS

Plant–Xenobiotic Interactions

By increasing the metabolic rate of CYP enzymes and P-glycoprotein, hyperforin in St. John's wort (*H. perforatum*) decreases concentrations of several drugs including amitriptyline, cyclosporine, digoxin, indinavir, irinotecan, warfarin, phenprocoumon, alprazolam, dextrometorphan, simvastatin, theophylline, and oral contraceptives.¹¹⁴ Bergamottins and naringenin from grapefruit reduce activity of the CYP system enzymes and increase drug concentrations. Other Citrus species also appear to increase drug concentrations.⁶⁷

Pharmacodynamic interactions may be responsible for serotonin excess or mild serotonin syndrome when St. John's wort is used concurrently with tryptophan or serotonin reuptake inhibitors.¹³² Additive effects also appear to be responsible for increased prothrombin time in patients taking *G. biloba* and various drugs that affect coagulation (eg, warfarin or aspirin) because the ginkgolides have antiplatelet activity.³⁵ Hawthorn (*Crataegus* spp), used medicinally for cardiac disorders, may produce an additive effect when taken concomitantly with digoxin, producing bradycardia. Excessive intake of broccoli provides enough vitamin K to competitively inhibit the effects of warfarin on vitamin K activation.

Sodium Channel Effects: Aconitine, Veratridine, Zygacine, Taxine, and Grayanotoxins

Several unrelated plants produce xenobiotics that affect the flow of sodium at the sodium channel. For instance, aconitine and veratrum alkaloids tend to open the channels to influx of sodium, whereas others (eg, taxine) tend to block the flow, and grayanotoxins both increase and block sodium flow.¹⁵⁵ The sodium channel opener aconitine from *Aconitum* spp or *Delphinium* spp has the most persistent toxicity and the lowest therapeutic index among the many active alkaloid ingredients of these toxic plants called aconite. Some of the related alkaloids are controlled medicinal substances in the People's Republic of China and Taiwan.²⁵ Aconite has been abused for its psychoactive "out of body" effects and for suicide and homicide. These alkaloids should be suspected in potentially poisoned patients who manifest cardiac toxicity, paresthesias, and seizures.

The mechanism of action depends on the individual alkaloid. Some compounds block and others activate sodium channels. Aconitine itself opens the voltage-dependent sodium channel at binding site 2 of the α -subunit, initially increasing cellular excitability.⁵⁵ By prolonging sodium current influx, neuronal and cardiac repolarization eventually slows. It also has calcium channel-opening effects. Those alkaloids are used in Asian prescription medicines to treat dysrhythmias and pain by reducing the excitability of the cardiac conducting system and sensory neurons, respectively.²⁵

Approximately one teaspoon (2–5 mg) of the root may cause death. The aconitine alkaloids are rapidly absorbed from the GI tract, and the calculated half-life of aconitine is 3 hours.¹⁰² CNS symptoms typically progress from paresthesias to CNS depression, respiratory muscle depression, paralysis, and seizures. Nausea, vomiting, diarrhea, and abdominal cramping occur.⁸⁶ Cardiotoxicity resembles that caused by cardioactive steroidal glycosides, and typically progresses from bradycardia with atrioventricular conduction blockade to increased ventricular automaticity resulting in diverse tachydysrhythmias. Multifocal premature ventricular contractions, bidirectional ventricular tachycardia,¹³⁹ torsade de pointes, and ventricular fibrillation may occur.⁸⁶

A history of paresthesias or muscle weakness may be useful in differentiating aconitine toxicity from that caused by cardioactive steroids. Aconite poisoning can be diagnosed by detection of the alkaloids in urine by liquid chromatography-mass spectrometry.

Management should not be delayed while awaiting testing. Empiric use of digoxin-specific antibody fragments should be administered if cardioactive steroid poisoning is strongly considered, but these antibodies are ineffective for aconitine poisoning. Antidysrhythmic success with lidocaine is limited, and amiodarone is currently the antidysrhythmic of choice.⁸⁶ Orogastric lavage, activated charcoal, and preparation for cardiac pacing, bypass, or balloon pump assist should be used as indicated, given the potential for rapid cardiovascular deterioration.

Ingestion of veratridine and other veratrum alkaloids (from *Veratrum viride* and other *Veratrum* spp) generally results from foraging errors where the root appears similar to leeks (*Allium porrum*) and above-ground parts appear similar to gentian (*Gentiana lutea*) used for teas and wines in Europe.¹³³ Typical symptoms develop within an hour of ingestion and include headache followed by nausea, vomiting, and less frequently bradycardia and diarrhea. The mechanism of action is similar to that of aconitine (sodium channel opening) but the duration of effects is shorter.¹⁵⁵ Although severe toxicity has been reported, management is supportive with fluids, atropine, and vasopressors. Deaths are rare.

Zygacine from *Zigadenus* spp (death camas) and other members of the lily family produces the same toxic effects as veratridine alkaloids (vomiting, hypotension, and bradycardia).¹⁵⁹ Symptoms begin 1 to 2 hours after ingestion and usually result from errors while foraging for onions because of the plant's look-alike bulb.¹⁰¹ Treatment options are the same as above with veratrum alkaloids.

Taxine, derived from the yew, is another alkaloid mixture of sodium channel effectors that tend to close the channel (*Taxus baccata*) (Fig. 121–4). The toxicity of *Taxus* has been known since antiquity. Toxic alkaloids are contained within the bark, leaves, and hard central seed but not in the surrounding fleshy red aril, which partly explains the low rate of toxicity in reported cases of unintentional exposure.¹⁶¹ Taxine-derived alkaloids (eg, taxine A and B, isotaxine B, paclitaxel), taxane-derived substances (eg, taxol A and B), and glycosides (eg, taxicatine) are responsible for the toxicity of *Taxus* spp. Lethal oral doses (LD_{min}) of yew leaves in humans are estimated to be 0.6 to 1.3 g/kg of body weight, or 3.0 to 6.5 mg taxines/kg of body weight.^{160,161} Suicide using leaves is reported despite the large number of leaves required.¹⁵⁷ Clinical manifestations of yew poisoning include dizziness, nausea, vomiting, diffuse abdominal pain, tachycardia (initially), and convulsions followed by bradycardia, respiratory paralysis, and death.



FIGURE 121–4. The yew (*Taxus* spp) is a common garden shrub that produces taxine, a cardiotoxin. Though the fleshy red aril is nontoxic, the hard seed it contains is toxic. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Paclitaxel (Taxol) is an alkaloid component of the relatively rare Pacific yew (*Taxus brevifolia*) that is used as an

antitumor chemotherapeutic xenobiotic because of its ability to promote the assembly of microtubules and to inhibit the tubulin disassembly process in mitotic cells. Within one hour after ingestion, toxicity progresses from nausea, abdominal pain, bradycardia, and cardiac conduction delays to wide-complex ventricular dysrhythmias, paresthesias, ataxia, and mental status changes. Four prisoners who drank an extract of yew experienced profound hypokalemia, and two died of cardiac arrest.⁵¹ Animal models indicate that bradycardia is responsive to atropine, but wide-complex tachydysrhythmias are unresponsive to sodium bicarbonate.¹²⁴

Grayanotoxins (formerly termed andromedotoxins) are a series of 18 toxic diterpenoids present in leaves of various species of *Rhododendron*, *Azalea*, *Kalmia* (Fig. 121–5), and *Leucothoe* (Ericaceae). They exert their toxic effects via sodium channels, which they open or close, depending on the toxin.¹⁵⁵ Grayanotoxin I increases membrane permeability to sodium and affected calcium channels in a manner similar to that of veratridine (and batrachotoxin).⁷² Grayanotoxins can become concentrated in honey made in areas with densely populated grayanotoxin-containing plants, mainly in the Mediterranean. Accounts of poisoning by honey date back to at least 401 bc when Xenophon's troops were incapacitated after they consumed honey made from nectar of *Rhododendron luteum*. Occasionally, grayanotoxin-containing plants or plant preparations rather than honey cause human poisonings. Bradycardia, hypotension, GI manifestations, mental status changes ("mad honey"), and seizures are described in patients or animals suffering grayanotoxin toxicity.⁶³



FIGURE 121–5. Mountain laurel (*Kalmia latifolia*), an evergreen shrub, contains the sodium channel opener grayanotoxin, which produces dysrhythmias. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Antimitotic Alkaloids and Resins: Colchicine, Vincristine, and Podophyllum

Consumption of colchicine from plant sources such as autumn crocus (*Colchicum autumnale*) produces a spectrum of effects, including nausea, vomiting, watery diarrhea, hypotension, bradycardia, electrocardiographic abnormalities, diaphoresis, alopecia, bone marrow depression, renal failure, hepatic necrosis, acute respiratory distress syndrome, convulsions, and death.¹⁴⁶

Confusion of the bulbs or leaves of this plant with those of wild onions or garlic occur as a foraging error. Unintentional consumption by children and ingestion with suicidal intent account for the other cases involving morbidity or mortality. The mechanism of toxicity is the disruption of microtubule formation in mitotic cells.⁵³

Vincristine and vinblastine are two other indole alkaloids that are used as antineoplastics and are both isolated from the Madagascar periwinkle (*Catharanthus roseus*). No reports of poisoning by these alkaloids following ingestion of the plant could be found (Chap. 37).

Podophyllum resin is the dry, alcoholic extract of the rhizomes and roots of mayapple (*Podophyllum peltatum*) (Fig. 121–6). The dry resin consists of up to 20% podophyllotoxin, α - and β -peltatin, desoxypodophyllotoxin, and dehydropodophyllotoxin. These xenobiotics are originally present in the plant as β -D-glucosides. Podophyllum resin containing podophyllin is available by prescription for topical treatment of venereal warts. Its medicinal derivative, etoposide, is used for a range of neoplastic diseases. Podophyllum is used as a popular traditional Chinese medicine. Podophyllotoxins make up 20% of the resin from the roots of mayapple (*P. peltatum*). As a group, they disrupt tubulin formation, producing multisystem organ failure. Poisonings are caused by misidentification and adulteration, possibly because the list of common names by which it is known includes mayapple, as well as mandrake, wild mandrake, American mandrake, and European mandrake.⁵⁴ Catharsis is prominent after ingestion, but onset of symptoms may be significantly

delayed. Acute, severe sensorimotor neuropathy and bone marrow suppression following transient leukocytosis can occur even after acute exposures and may be directly related to inhibition of microtubule assembly. Lethargy, confusion, encephalopathy, autonomic instability, sensory ataxia, and death are described following large exposures,¹⁰⁷ but poisoning has also occurred after “therapeutic” doses of a popular traditional Chinese medicine.¹¹⁴



FIGURE 121–6. The mayapple (*Podophyllum peltatum*) develops from an initial nodding flower that grows from the stem of this low lying ground cover plant. The whole plant contains podophyllotoxin (podophylline), though the apple is generally considered the least toxic part. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Glutamic acid has been used to prevent vincristine-induced peripheral neuropathy and would be a reasonable therapy following podophyllin ingestion.¹⁰¹

Plant-Induced Dermatitis

A large number of plants result in undesirable dermal, mucous membrane, and ocular effects, and they represent the most common adverse effects reported to US poison centers and occupational health centers. Plant-induced dermal disorders can be readily categorized into four mechanistic groups, that is, dermatitis that results from (1) mechanical injury, (2) irritant molecules that penetrate the skin, (3) allergy, or (4) photosensitivity (direct and hepatogenous) (Chap. 18).¹³⁰

There is much overlap between these categories (some plants can produce all types). Clinicians may have difficulty distinguishing between plant-induced dermatitis and skin disorders⁹⁴ or between plant-induced dermatitis and pseudophytophysitis caused by arthropods, pesticides, or wax (used in fruit and vegetable packaging). Agents that cause adverse skin reactions can also cause eye and local gastric mucosal irritation.

Dermatitis from mechanical injury often is combined with primary or allergic contact dermatitis. Stinging nettles (*Urtica dioica* and other species) have a specialized apparatus in the form of an elongated silicious cell (glandular trichome) that acts like a hypodermic syringe to deliver irritant chemicals into the skin. Contact with these stinging hairs shears off the tip of the hair, producing micromechanical injury and releasing irritant contents: acetylcholine, histamine, and 5-hydroxytryptamine.⁴ Acute motor polyneuropathy associated with cutaneous exposure to *Urtica ferox* is reported within 48 hours of walking through a patch of the nettles, with recovery occurring over several weeks.⁶⁶ The barbed trichomes (spicules) of *Mucuna pruriens* (velvet bean, cowhage) evoke a histamine-independent itch that is mediated by a cysteine protease, mucunain.⁷⁹ Workers who handpick pineapples are subject to fissuring and loss of fingerprints after proteolytic enzyme bromelain exposure following dermal abrasion by raphides.

Exposures to commonly available household plants such as dumbcane (*Dieffenbachia* spp), *Philodendron* spp, and *Narcissus* bulbs can lead to mechanical injury and painful microtrauma produced by bundles of tiny needlelike calcium oxalate crystals called raphides.¹⁰⁶ Packages of hundreds of raphides called idioblasts contain proteolytic enzymes. *Dieffenbachia* (more than 30 species) (Fig. 121–7) exposures are commonly reported household or malicious plant exposures, although such exposures are rarely serious.¹⁰⁴ When the leaves are chewed, immediate oropharyngeal pain and swelling occur.³¹ Severe oral exposures can be excruciating and progress to profuse salivation, dysphagia, and loss of speech. Soothing liquids, ice, parenteral opioids, corticosteroids, and airway protection may be indicated, but antihistamines provide little relief. The edema and pain typically begin to subside after 4 to 8 days. Ocular exposure to the sap may produce chemical conjunctivitis, corneal abrasions, and, rarely, permanent corneal opacifications.



FIGURE 121–7. This dumbcane (*Dieffenbachia* spp) plant is representative of the Arum family, which typically have variegated, waxy leaves. Many contain insoluble crystals of calcium oxalate arranged in idioblasts, which may be ejected following trauma to the leaf. (Used with permission of The New York City Poison Center Toxicology Fellowship Program.)

Similar exposures to oxalate raphide-containing household plants in the same family (*Philodendron*, *Brassaia*, *Epipremnum aureum*, *Spathiphyllum*, and *Schefflera* spp) are not as painful as those to dumbcane, presumably because the crystals are packaged differently and do not simultaneously deliver proteolytic enzymes.¹⁰⁶ One exception to their lower severity is a report of death in an 11 month-old child following complications arising from esophageal lesions induced by *philodendron*.⁹⁵

Irritant dermatitis can result from low-molecular-weight xenobiotics such as phorbol esters (from *Euphorbiaceae*) that directly penetrate the skin without antecedent mechanical injury. Similar penetrance is achieved by products of glycoside hydrolysis. For instance, hydrolysis of ranunculin gives rise to anemonin in *Ranunculaceae*, the buttercup family, and hydrolysis of sinigrin in plants in the mustard family *Brassicaceae* yields allyl isothiocyanate. Exposures to primary irritants in *Brassicaceae* and *Ranunculaceae* usually are mild. Alternatively, airborne contact dermatitis occurs in typically exposed sites such as the upper eyelids, neck, uncovered extremities, including antecubital fossae, and other skin folds (Chap. 18).⁹⁹

Phorbol esters found in spurge (*Euphorbiaceae*) are contained in milky sap that is capable of producing erythema, desquamation, and bullae. The saps of some species are more irritating than others. For instance, the manchineel tree (*Hippomane mancinella*), found in the Caribbean and Florida, once was planted on graves to deter grave robbers, and juice from the tree has been used to brand animals and to blind people. In addition to dermal and ocular injury,⁴⁶ ingestion of some spurge can induce severe GI injury. Poinsettia (*Euphorbia pulcherrima*), crown of thorns (*Euphorbia splendens*), candelabra cactus (*Euphorbia lacteal*), and pencil tree (*Euphorbia tirucalli*) are spurge found in the home as holiday or other ornamentation that rarely produce serious injury, despite reputations to the contrary. The poinsettia plant, for instance, gained a reputation of significant toxicity based on a single, inadequately documented case report from Hawaii in 1919, involving the death of a 2 year-old child.⁷ In a subsequent case, an 8 month-old child developed oral mucosal burns after chewing poinsettia.⁴⁵ Contact dermatitis, irritation of mucous membranes, and GI complaints such as nausea, vomiting, and abdominal pain are rare findings among the many reported exposures to poinsettia.

Allergic contact dermatitis results from type IV hypersensitivity response and, unlike irritant dermatitis, requires repeat exposures to the agent before symptoms manifest. The most infamous of these xenobiotics are the urushiol oleoresins derived from catechols that are found in *G. biloba* (*Ginkgoaceae*) and members of the *Proteaceae* (eg, *Macadamia integrifolia*) and the *Anacardaceae*. The latter family is notable for inclusion of poison ivy (*Toxicodendron radicans*),

poison oak (*Toxicodendron toxicarium*, *Toxicodendron diversilobum*), and poison sumac (*Toxicodendron vernix*),⁵⁹ as well as mango (*Mangifera indica*), pistachio (*Pistacia vera*), cashew (*Anacardium occidentale*), and Indian marking nut “Bhilawanol” (*Semecarpus anacardium*). Upon first exposure, urushiol resins penetrate the skin and react with proteins to form antigens to which the body forms antibodies. Upon reexposure to urushiol resins, inflammatory mediators are released, leading to urticaria, itching, swelling, and pain. In extreme cases, these reactions can progress to type I hypersensitivity. Cross-reactivity between allergens is possible, and particular vigilance is required in sensitive individuals.⁵² Prevention by removal of exposed objects that act as fomites for the oils and use of protective linaments are appropriate. Therapy includes washing with soap and water and corticosteroid creams and, for those frequently exposed, desensitization (Chap. 18).⁵⁹

Allergic contact dermatitis is the most common plant-induced occupational injury. In the United States, 33% of 462 floral shops surveyed reported that at least one employee had developed contact dermatitis.¹²⁸ Reactions are reported following exposure to tulips, *Narcissus*, Peruvian lily (*Alstroemeria* spp), and primroses (*Primula* spp). Exposure to the glycoside tuliposide A results in “tulip fingers,” the dry, painfully fissured hyperkeratosis of fingers observed in horticultural workers who chronically handle tulips.²⁰ Upon hydrolysis, this compound yields α -methylene-butylolactone, the true allergen. Cross-reactivity is possible among some of these xenobiotics. *Alstroemeria* spp, a common ornamental called Peruvian lily, contain tuliposide A and thus can cross-react with antigens in those persons already allergic to tulips, producing an allergic contact dermatitis. Primin (2-methoxy-6-n-pentyl-p-benzoquinone) from members of the Primulaceae family was responsible for the most frequently reported allergic plant dermatitis in northern Europe until workers refused to stock primroses. The “wood cutters dermatitis” of loggers occurs with development of sensitivity to compounds in liverwort (*Frullania* spp), which is cross-reactive to usnic acid in lichens and mosses found on the wood. Cross-reactivity with common weeds such as ragweed (*Ambrosia* spp) or dandelion (*Taraxacum* spp) initiate the risk of hypersensitivity from members of the Compositae family.⁷⁶ A myriad of other types of plants are involved in producing occupational dermatitides.^{106,128} Sensitivity to Compositae (daisy family) involves more than 600 sesquiterpene lactones in at least 200 of the 25,000 species in the family and is as ubiquitous as the distribution of species. Chrysanthemum allergy is a common occupational hazard in Europe.

Direct photosensitivity dermatitis is produced when compounds such as psoralens or other linear furocoumarins come into direct contact with the skin or are digested and become bloodborne to dermal capillary beds, where they interact with sunlight. These photosensitizing agents are activated by ultraviolet A radiation (320–400 nm), producing singlet oxygen and DNA adducts. In addition to severe sunburnlike symptoms (erythema, epidermal bullae), hyperpigmentation lasting for several months may result from exposure to these compounds. The mechanism by which this reaction is produced is unknown, but depletion of glutathione is postulated to indirectly stimulate melanogenesis by disinhibiting the normally suppressant tyrosinase.⁹¹ More than 200 of these xenobiotics have been identified in at least 15 plant families, including food sources, such as Apiaceae (anise, caraway, carrot, celery, chervil, dill, fennel, parsley, and parsnip), Rutaceae (grapefruit, lemon, lime, bergamot, and orange), Solanaceae (potato), and Moraceae (figs) family.

Hepatogenous photosensitivity is produced when a xenobiotic that normally is harmlessly ingested, absorbed, and hepatically excreted gains access to the peripheral circulation through failure of a liver excretion or detoxification mechanism. An example is the photosensitivity that occurs when phyloerythrin, a product of chlorophyll digestion normally eliminated in the bile, accumulates in the blood as a result of liver dysfunction. The cyanobacterium *Microcystis aeruginosa*, as well as the plants *Lantana camara*, *Tribulus terrestris*, and *Agave lechuguilla* reportedly cause this type of photosensitization in animals.

SUMMARY

- Plant exposures are among the commonest human exposures but also typically have the least morbidity and mortality.
- Plant xenobiotics can be organized by the principles of pharmacognosy.
- Some xenobiotics act directly or are metabolized to toxic principles such as tremetone, whereas others are toxic through secondary contact in animal meat or milk such as coniine, nitrates, pyrrolizidine alkaloids, and ptaquiloside.
- Some reassurance can be achieved by excluding exposure to the most life-threatening plants.

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122 NATIVE (US) VENOMOUS SNAKES AND LIZARDS

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HISTORY AND EPIDEMIOLOGY

Snakes

Over 3000 species of snakes have been identified worldwide, with nearly 800 species considered venomous. All venomous species are classified taxonomically into one of four general groups. These include the families Viperidae, Elapidae, and Colubridae, as well as the Atractaspidinae, a subfamily of the Lamprophiidae family.⁴⁹ The United States is home to nearly 30 species and subspecies of venomous snakes (Table 122–1), with many more found throughout Mexico. All belong to the Crotalinae subfamily of Viperidae or to the Elapidae family.

TABLE 122–1. Medically Important Snakes of the United States

Genus	Species	Common Name
Crotalinae		
<i>Crotalus</i>	<i>adamanteus</i>	Eastern Diamondback rattlesnake
	<i>atrox</i>	Western Diamondback rattlesnake
	<i>cerastes</i>	Sidewinder ^a
	<i>cerberus</i>	Arizona Black rattlesnake
	<i>horridus</i>	Timber rattlesnake
	<i>lepidus</i>	Rock rattlesnake ^a
	<i>mitchellii</i>	Speckled rattlesnake ^a
	<i>molossus</i>	Black-tailed rattlesnake ^a
	<i>oreganus</i>	Western rattlesnake ^a
	<i>pricei</i>	Twin-spotted rattlesnake ^a
	<i>ruber</i>	Red diamond rattlesnake ^a
	<i>scutulatus</i>	Mojave rattlesnake ^a
	<i>tigris</i>	Tiger rattlesnake
	<i>viridis</i>	Prairie rattlesnake ^a
	<i>willardi</i>	Ridgenose rattlesnake ^a
<i>Sistrurus</i>	<i>catenatus</i>	Massasauga ^a
	<i>miliarius</i>	Pygmy rattlesnake ^a
<i>Agkistrodon</i>	<i>contortrix</i>	Copperhead ^a
	<i>piscivorus</i>	Cottonmouth ^a
Elapidae		
<i>Micrurus</i>	<i>fulvius</i>	Eastern coral snake
<i>Micrurus</i>	<i>tener</i>	Texas coral snake ^a

^aSubspecies identified for this species.

Venomous snakes possess glands that are associated with specialized teeth, or fangs, which allow delivery of venom for the purpose of prey immobilization or defense. Fangs are located in the front of the mouth in most venomous species. In addition to fangs, venomous snakes have rows of small teeth that may cause additional injury during a bite.

The majority of snake species in North America are rear-fanged, non-venomous members of the Colubridae family. Bites by these species, which include corn snakes, gopher snakes, and garter snakes, are usually harmless. Colubrids do not possess venom glands, but may produce secretions from Duvernoy's glands that contain toxins similar to those found in the venom of venomous species. Although the vast majority of bites by nonvenomous colubrids do not produce symptoms, rare cases of envenomation have been documented following a bite by a nonvenomous species.⁵⁷

Venomous snakes are found throughout most of the United States. They are much more common in the southern and western states than in the northern states. Though venomous species are not endemic to Maine, Alaska, or Hawaii, bites have been reported in every state except for Hawaii. The true number of bites that occur each year is not accurately known, but an average of 5000 native venomous snakebites are reported to US poison centers annually.⁴³ Mortality is rare, with fewer than 10 deaths per year reported. Epidemiologic data on snakebites in Mexico is poor, but the number of bites and deaths is thought to be higher.²⁹

The majority of snakebites occur between April and September, with the peak number reported in July. Men comprise 75% of snakebite victims and children represent about 10% to 15% of reported cases.⁴³ Most victims are bitten on an extremity, although bites to the torso, face, and tongue also occur. Over half of reported bites occur when an individual is purposely handling a known venomous snake. Herpetologists, those who capture and keep wild snakes, and religious snake handlers are at highest risk. Occasionally people are envenomed after killing and decapitating a rattlesnake. This is likely due to persistent reflexes in the venom apparatus.

Snake handlers and collectors are at risk for multiple bites during their lifetime. There is no convincing evidence that immunity develops as a result of repeated envenomation. Victims of repeat bites may actually have a greater risk for anaphylaxis because of prior sensitization and the development of IgE antibodies to venom.

Snake enthusiasts often keep nonnative species as pets. Approximately 30 to 50 bites from a large variety of exotic venomous snakes are reported to poison centers each year.⁴⁵

Pit Vipers. The majority of native venomous snakes are members of the Crotalinae subfamily of Viperidae. These crotaline species are variably referred to as crotalids, new world vipers, or pit vipers. The term 'pit viper' describes the presence of a pitlike depression behind the nostril that contains a heat-sensing organ used to locate prey. Native pit vipers include the rattlesnakes (genera *Crotalus* and *Sistrurus*) and the cottonmouths and copperheads (genus *Agkistrodon*). These pit vipers can be distinguished from native nonvenomous species by a triangular-shaped head, vertically elliptical pupils, and easily identifiable fangs (Fig. 122-1). Crotalinae have front, mobile fangs that are paired, needlelike structures that can retract on a hingelike mechanism into the roof of the mouth. Rattlesnakes have the longest fangs, reaching 3 to 4 cm. Pit vipers may also be identified by their scales. Their undersurface has a single row of plates or scales, as opposed to the double row found on nonvenomous species. Rattlesnakes may or may not have rattles, depending on maturity. A rattling sound is often, but not always, heard before a strike. Copperheads and cottonmouths do not have rattles, but may shake their tails similarly to rattlesnakes. Cottonmouths, which are also commonly known as water moccasins, are semiaquatic and have a distinct white mouth. Copperheads are known for their reddish-brown (copper) heads and hourglass markings on their bodies (Fig. 122-2)



FIGURE 122-1. Pit vipers have a triangular shaped head, vertically elliptical pupils, and heat-sensing pits behind the nostril.



FIGURE 122–2. Copperhead (*Agkistrodon contortrix*).

The vast majority of North American snake envenomations are from bites by crotalids. Of those bites for which the type of snake is reported, about half are rattlesnake species, and the remainder copperheads and cottonmouths. Rattlesnakes are found throughout most of the United States, but encounters are most common in western and southern states. Rattlesnakes account for the greatest morbidity among the various types of pit vipers. Deaths following snakebite are almost always due to rattlesnakes, although rare deaths have been associated with copperhead bites. Copperhead bites are most often reported in the eastern and southeastern United States, although they also occur in the northeast. Cottonmouths are found mainly in the southeastern United States.⁴³

Coral Snakes. Coral snakes (genera *Micrurus* and *Micruroides*) represent the Elapidae family in North America. These brightly colored snakes typically have easily identifiable red, yellow, and black bands along the length of their bodies. In the United States, coral snakes and the similarly colored nonvenomous scarlet king snake are often confused. Coral and king snakes can be distinguished by their color patterns. Whereas coral snakes have black snouts, king snakes have red snouts. Both species have red, yellow, and black rings, but in different sequences: the red and yellow rings touch in the coral snake but are separated by black rings in king snakes (“Red on yellow kills a fellow; red on black, venom lack”) (Fig. 122–3). This general rule for identifying coral snakes does not apply to Mexican species, some of which may have different color patterns

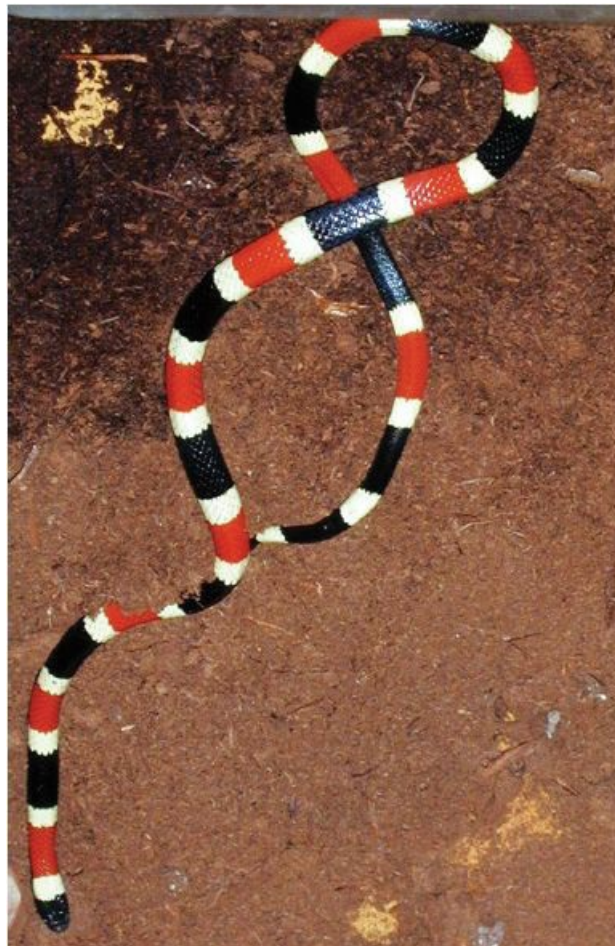


FIGURE 122–3. Coral snake with characteristic black snout and red bands bordered by yellow bands. (Used with permission of Banner Good Samaritan Medical Center Department of Medical Toxicology.)

Elapids possess front fixed fangs. The fangs of coral snakes are small, and discrete fang marks may not be obvious after envenomation. Coral snakes often latch on to a victim or “chew” for a few seconds in an attempt to deliver venom. A history of this activity may help identify a coral snakebite when the offending reptile cannot be located.

Coral snakes are responsible for approximately 2% of bites reported to US poison centers.⁴³ *Micrurus* species are found in 11 southeastern states, where up to 100 bites are reported per year. *Micrurus fulvius* (the Eastern coral snake) is responsible for the greatest morbidity and mortality, while *M. tener* (the Texas coral snake) seems to be less dangerous. The Sonoran coral snake (*Micruroides euryxanthus*) does not produce envenomation necessitating medical intervention.⁵⁶

Lizards. There are two species of lizard that are known to produce envenomation in humans. These are the Gila monster *Heloderma suspectum* (Fig. 122–4), which is native to the desert southwestern United States, and the beaded lizard *H. horridum*, which is found in Mexico. Both species are members of the Helodermatidae family. These lizards are slow moving, nocturnal, and thick bodied. Adults may reach a length of 60 cm and are generally shy, so bites are relatively rare and usually occur as a result of handling. Gila monsters are known for their forceful bites. They can hang on and “chew” for as long as 15 minutes, and they may be difficult to disengage¹⁸



FIGURE 122–4. (A) Young Gila monster (*Heloderma suspectum*). (B) Beaded lizard (*Heloderma horridum*).

The helodermatid lizards have a less effective venom delivery system than venomous snake species. The lizards possess paired venom glands that are located on either side of the anterior lower mandible. Venom ducts carry the venom from the glands to the base of grooved teeth. When a tooth produces a puncture wound, the venom travels by capillary action into the grooves and then into the wound.⁴⁰

Bites by the Gila monster and beaded lizard are extremely uncommon, even in areas where the lizards are endemic. Bites almost always occur from captive animals, whether found in the wild or kept in a zoo or personal collection. The great majority of reported cases have involved adult men.

PHARMACOLOGY

Snakes

Snake venom is a complex mixture of proteins, peptides, lipids, carbohydrates, and metal ions. Venom may contain a variety of enzymes including phospholipases A₂ (PLA₂s), metalloproteinases (SVMPs), serine proteases, acetylcholinesterases, L-amino acid oxidases, and hyaluronidases. Non-enzymatic proteins include three finger toxins (3FTXs), sarafotoxins, disintegrins, and C-type lectins among others. The content and potency of venom in any given snake may vary depending on age, diet, and geography. Thus an adult snake may have significantly different venom composition than a young snake of the same species.⁵⁴

Snakes typically produce about 100 to 200 mg dry venom in a single milking, although some may produce several hundred mg to over 1 g.⁵⁴ Many venom components are pharmacologically active and target receptors, ion channels, enzymes, or other proteins in mammals. The actions of only a fraction of snake venom components are fully understood. Identification of individual snake venom toxins, understanding of pharmacologic mechanisms, and potential medicinal uses for venom are areas of ongoing research.

Lizards. Helodermatid venom contains a complex mixture of components similar to those of snake venoms, including numerous enzymes such as hyaluronidase, phospholipase A₂, and serotonin.^{40,52} Nonenzymatic components include helospectins and helodermin, which are vasoactive peptides that activate adenylyl cyclase, and exendin-3 and exendin-4, which stimulate glucose-dependent insulin secretion. Discovery of exendins in Heloderma venom lead to development of exenatide (Byetta), a glucagon-like peptide-1 (GLP-1) receptor agonist used in the management of diabetes.^{20,52} Another important component of Heloderma venom is gilatoxin. Gilatoxin is a serine protease with kallikreinlike activity, thought to be responsible for the hypotension and angioedema that occur in some human envenomations.⁵²

PHARMACOKINETICS AND TOXICOKINETICS

Snakes

Very few pharmacokinetic studies of snake venom exist, and much remains unknown regarding absorption, distribution, and elimination of venom following a bite. When a snake bites, venom is usually deposited subcutaneously. In some cases fangs may reach muscle or even directly access vasculature. Systemic absorption of venom usually occurs via the lymphatic system. Available human and animal data suggest that venom antigens are absorbed into blood within minutes of envenomation, with peak concentrations detected within 4 hours.^{8,26,44} Venom antigen concentrations measured in the first 4 hours following a bite correlate roughly with grade of envenomation.^{2,7,26} Venom antigens are also detected in urine as early as 30 minutes after envenomation.²⁶ After administration of adequate doses of antivenom, venom antigens are no longer detected in blood; however, antigenemia may recur, and such recurrence is associated with reemergence of clinical effects.^{26,44}

The elimination half-life of snake venom appears to be long. Following subcutaneous injection of C atrox venom in a rabbit model, mean half-life was 20 hours, and venom was still detectable in blood at 96 hours.⁸

Lizards. Pharmacokinetic studies of helodermatid venom are not available. Clinical reports suggest that venom is absorbed systemically within minutes of a bite.

PATHOPHYSIOLOGY

Snakes

Pit Vipers. Crotaline venom can simultaneously damage tissue, affect blood vessels and blood, and alter transmission at the neuromuscular junction. It is difficult to attribute specific pathology or pathophysiology to any particular component of snake venom. In fact, clinical effects often occur as the result of several venom components (Table 122–2). For instance, local tissue damage results from venom metalloproteinases and hyaluronidase, which both contribute to swelling through disruption of the extracellular matrix and basement membrane surrounding microvascular endothelial cells.²⁴ As a result of reduced blood flow through damaged capillaries, they may also contribute to myonecrosis, which results primarily from the action of phospholipase A₂ enzymes (PLA₂) on muscle.²⁴ Additionally, venom metalloproteinases contribute to

dermatonecrosis, both directly and through activation of endogenous inflammatory mediators.^{24,48}

TABLE 122–2. Major Venom Components of Crotalinae Snakes

<i>General Clinical Effect</i>	<i>Responsible Venom Components</i>
Local tissue damage	Metalloproteinases Phospholipases A ₂ Hyaluronidase
Coagulation effects ^a	C-type lectinlike proteins Metalloproteinases ^b Serine proteases ^b Phospholipases A ₂
Platelet effects ^c	Disintegrins C-type lectinlike proteins Metalloproteinases Phospholipases A ₂
Neurotoxic effects	Phospholipases A ₂

^aVenom contains both pro- and anticoagulants, with anticoagulant effects predominating in North American crotaline envenomation. ^bInclude thrombinlike enzymes as well as fibrinogenolytic enzymes. ^cVenom may contain factors that inhibit, activate, or affect aggregation of platelets.

Venom effects on the hematologic system are especially complex. Numerous components act as anticoagulants, and many others act as procoagulants. Similarly, platelets may be inhibited, activated, agglutinated, aggregated, or inhibited from aggregating by various venom components. Venom components can be grouped according to certain characteristics, such as structure and enzymatic activity, but as noted above with local tissue damage, components within several groups may contribute to similar effects. For instance, anticoagulants in snake venoms are found among the C-type lectinlike proteins (CLPs), PLA₂ enzymes, serine proteases, and metalloproteinases. Conversely, components within a single group may have many different actions. Various CLPs in venom act as anticoagulants, procoagulants, or platelet modulators. PLA₂ enzymes are especially diverse, acting as anticoagulants and platelet modulators in addition to producing myotoxic and neurotoxic effects. Platelet effects result mainly from the action of disintegrins, although CLPs, PLA₂ enzymes, and other proteinases also have platelet-modulating effects.^{36,60}

Specific hematologic effects are species dependent, with no single venom containing all of the identified hemostatically active components. Of particular importance to North American rattlesnake envenomation are the thrombinlike enzymes and fibrinogenolytic enzymes. These are metalloproteinases and serine proteases that preferentially cleave fibrinopeptide A or fibrinopeptide B from fibrinogen. Unlike thrombin, they do not activate factor XIII. The end result is production of a poorly cross-linked fibrin clot that easily degrades. Multiple other venom components exist, some of which affect the vascular system and contribute to the hypotension that sometimes occurs clinically. Examples include bradykinin-potentiating peptides and vascular endothelial growth factors.^{47,60}

Snake neurotoxins act at the neuromuscular junction and do not cross the blood–brain barrier. They are classified as α -neurotoxins, which act postsynaptically, and β -neurotoxins, which act presynaptically. The Mojave rattlesnake, *C. scutulatus*, is known for its neurotoxic venom. The neurotoxin, Mojave toxin, is a PLA₂ that acts at the presynaptic terminal of the neuromuscular junction to inhibit acetylcholine release. The presence of Mojave toxin in venom appears to be geographically distributed, with Mojave rattlesnake populations in California and southeast Arizona possessing functional Mojave toxin, and central Arizona populations lacking the neurotoxin.^{22,59} Mojave toxin has also been identified in the venom of the Southern Pacific rattlesnake (*C. oreganus helleri*) found in southern California, and envenomations by this species have produced neurologic symptoms.^{10,19}

Coral Snakes. Coral snake venom contains neurotoxins that produce systemic neurotoxicity. Unlike crotaline venom, coral snake venom does not cause local tissue injury. Similar to neurotoxins present in other elapid species, α -neurotoxins bind and competitively block post synaptic acetylcholine receptors at the neuromuscular junction, leading to weakness and paralysis. Phospholipase A₂ can also cause myotoxicity, although this appears to be of less clinical importance. The LD₅₀ of *M. fulvius* venom is lower than that of *M. tener* venom, which corresponds to the more severe effects noted in humans following Eastern coral snake envenomations.⁴¹

Lizards. The pathophysiology of helodermatid venom is poorly understood. It is suggested that hyaluronidase

contributes to spreading of venom throughout tissue.⁴⁶ Gilatoxin is believed to produce hypotension and other findings such as angioedema by increasing bradykinin levels.⁵²

CLINICAL MANIFESTATIONS

Snakes

The clinical presentation of North American snake envenomation is highly variable and depends upon many factors, including the species of snake, the amount and potency of venom deposited, the location of the bite, and patient factors, such as comorbidities. It is important for the clinician to be familiar with endemic venomous snake species in order to anticipate clinical effects when presented with an envenomed patient. For bites by nonnative species, it is imperative to identify the species so that specific antivenom can be sought.

Pit Vipers. Envenomation by North American pit vipers is characterized by local swelling and cytotoxic effects. Hematologic effects are common, and there is the potential for development of systemic illness and neurotoxicity. Most patients exhibit only a subset of possible effects of envenomation. In addition, some of the signs and symptoms in a given individual, such as nausea or tachycardia, may be related to fear rather than to envenomation.

The clinical presentation following a pit viper bite can range from benign to life threatening (Table 122–3). One finding common to all victims is the presence of an identifiable disruption of skin integrity. Most commonly, one or two distinct punctures are present, though occasionally, patients exhibit multiple punctures, small lacerations, or scratches.

TABLE 122–3. Evaluation and Treatment of Crotaline Envenomation				
Extent of Envenomation	Clinical Observations	Antivenom Recommended ^a	Other Treatment	Disposition
None (“dry bite”)	Fang marks may be seen, but no local or systemic symptoms after 8–12 hours	No	Local wound care Tetanus prophylaxis	Discharge after 8–12 hours of observation
Minimal	Minor, nonprogressing, local swelling and discomfort without systemic symptoms or hematologic abnormalities	No	Local wound care Tetanus prophylaxis	Admit to monitored unit for 24-hour observation
Moderate	Progression of swelling beyond area of bite with or without local tissue destruction, hematologic abnormalities, or non–life-threatening systemic symptoms	Yes	IV fluids Cardiac monitoring Analgesics Follow laboratory parameters Tetanus prophylaxis	Admit to Intensive Care Unit
Severe	Marked progressive swelling, pain with or without local tissue destruction Systemic symptoms such as diarrhea, weakness, shock, or angioedema, and/or pronounced thrombocytopenia or coagulopathy	Yes	IV Fluids Cardiac monitoring Analgesics Follow laboratory parameters Oxygen Vasopressors as indicated Tetanus prophylaxis	Admit to Intensive Care Unit

^aSee Antidotes in Depth: A37 for dosing recommendations.

Since pit viper bites result in injection of venom only about 75% of the time, approximately 25% of bites do not result in envenomation and are considered “dry bites.” Unfortunately, it is impossible to diagnose a dry bite without an extended period of observation, since some patients may have delayed onset of symptoms for as much as 8 to 10 hours following the bite. On occasion, patients may initially present asymptomatic yet go on to develop serious illness. Even for patients who do present with symptoms, it may require a number of hours for the full extent of clinical illness to become evident. As a general rule, however, it may be assumed that envenomation from a pit viper has not occurred if no symptoms develop within 8 to 10 hours from the time of the bite.

Of the North American pit vipers, rattlesnakes are responsible for the most severe clinical presentations. Agkistrodon (cottonmouth and copperhead) bites generally tend to produce less severe local and systemic pathology than rattlesnake bites. Copperhead bites in particular rarely cause systemic symptoms, and pathology is usually limited to soft tissue

swelling without necrosis.⁵⁵ However, serious copperhead envenomations occasionally occur, and at least one death has been reported in association with this species.⁴³

Local reactions. Generally, within minutes after pit viper envenomation, the area around the puncture site becomes swollen and painful, and oozing of blood from the wound may be noted. Edema may stabilize quickly in mild envenomations, but more commonly, edema will gradually worsen over hours. In severe cases, edema may progress to involve an entire extremity within just a few hours. Swelling can worsen for days when untreated, extending proximally to involve the torso following bites to a distal extremity. Rarely, onset of appreciable swelling is delayed for as long as 10 hours. This is most often noted in lower extremity envenomations.

Ecchymosis may develop early at the wound site. Bites to the feet often exhibit a characteristic bluish tinge over the entire dorsal surface of the foot. Toes remain pink and well perfused, allowing distinction of this ecchymosis from cyanosis (Fig. 122–5). In the days to weeks following the envenomation, ecchymosis will often extend or new ecchymosis may develop proximally, even in the absence of significant venom-induced hematotoxicity.



FIGURE 122–5. Rattlesnake bite to the lower leg, with characteristic edema and bluish discoloration of the foot due to ecchymosis.

Erythema may also develop at the envenomation site and sometimes spreads proximally from the wound along lymphatic pathways. Lymphangitic streaks are occasionally noted in the absence of infection.

Hemorrhagic blisters (blebs or bullae) often form at the site of the bite after rattlesnake envenomations. This most commonly occurs after bites to digits but may occur at any bite location or even in dependent areas distant from the bite (Fig. 122–6). Blebs usually do not appear for several hours after the envenomation but can progress for several days. Tissue underlying blebs is often healthy, but extensive bleb development may signify underlying tissue necrosis (Fig. 122–7).



FIGURE 122–6. (A) Hemorrhagic bullae involving the entire digit after rattlesnake bite to the second digit. (B) Hemorrhagic bullae involving the antecubital fossa after rattlesnake bite to the hand. (Copyright © 2002, Department of Toxicology Good Samaritan Regional Medical Center.)



FIGURE 122–7. Dèbridement of hemorrhagic bullae revealed the underlying tissue to be dark and necrotic in this patient.

Myonecrosis is not a feature of most native pit viper envenomations but does sometimes occur. In rare cases fangs may

directly penetrate muscle leading to localized necrosis. With subfascial envenomation there is a risk for compartment syndrome, which could lead to necrosis. Compartment syndrome is very rare following North American snakebite and cannot be reliably diagnosed in envenomed extremities without directly measuring compartment pressures. More often than not envenomation simply mimics a compartment syndrome by producing distal paresthesias, tense soft tissue swelling, pain on passive stretch of muscles within a compartment, and muscular weakness. One study, using noninvasive vascular arterial studies and skin temperature determinations in patients with rattlesnake envenomation, demonstrated that pulsatile arterial blood flow to an envenomed extremity actually increased after envenomation, even distal to the site of envenomation.¹⁵

In addition to local myonecrosis, generalized severe rhabdomyolysis may occur in the absence of impressive muscular swelling. This finding is considered characteristic after envenomation by the Canebrake rattlesnake (*Crotalus horridus atricaudatus*), which was previously classified as a subspecies of the Timber rattlesnake (*C. horridus*). Current prevailing opinion is that they are the same species.^{12,50}

Hematologic toxicity. Venom-induced effects on the hematologic system are common following bites by North American pit vipers, in particular rattlesnakes. Coagulopathy, thrombocytopenia, or a combination of the two, may be present despite a paucity of other local or systemic effects. A decrease in platelet count, as well as decreases in fibrinogen with elevation of prothrombin time (PT), may be mild or modest initially and may either remain so or continue to worsen for several days following the envenomation. Alternatively, severe decreases in platelet counts (in the 5000–50,000/mm³ range) and fibrinogen concentrations (to near zero) with immeasurably high PTs may occur within minutes to hours of crotaline envenomation. A rise in PT generally follows a drop in fibrinogen, as concentrations of clotting factors remain normal in case reports of North American crotaline envenomation with coagulopathy.¹¹ The likelihood of thrombocytopenia or coagulopathy occurring after a given snakebite may depend on the particular species and venom populations present in the geographic area. In the desert southwest, coagulopathy occurs in approximately half and thrombocytopenia in one-third of patients presenting with envenomation.³⁹ Thrombocytopenia appears to be especially common and often severe after the bite of the Timber rattlesnake *Crotalus horridus*.³ The protein crotalocytin that is found in Timber rattlesnake venom causes platelet aggregation and is thought to be at least partially responsible for the thrombocytopenia.

Despite the high rate of hematologic effects following rattlesnake envenomations, the vast majority of patients have no clinical bleeding, even when severe laboratory abnormalities are present. Bleeding appears to be more common when platelets are very low or when both coagulopathy and thrombocytopenia are present and severe.

Systemic toxicity. Clinical findings following most pit viper bites are limited to local tissue damage or hematologic pathology, but systemic symptoms may develop. When present, systemic signs and symptoms are often mild and include nausea, metallic taste, restlessness, and nonspecific weakness. Tachycardia, vomiting, diarrhea, and confusion may also occur. These more significant systemic symptoms have been noted to precede severe systemic toxicity. In the most severe cases, patients quickly develop circulatory shock or airway edema with obstruction, which may be caused by anaphylactoid responses to venom components.

Rarely, patients bitten by crotalids may experience classic anaphylaxis from the venom itself, which may complicate evaluation or mimic a severe systemic reaction to venom. Previous sensitization to venom results in development of IgE antibodies to venom in these patients. This is thought to occur more frequently in patients who have previously experienced a snakebite, but it has also been observed in snake handlers who are thought to be sensitized to snake proteins through inhalation or skin contact. The presence of pruritus and urticaria or wheezing, uncommon with envenomation, should suggest anaphylaxis.

There are rare reports of true disseminated intravascular coagulation (DIC) with spontaneous bleeding along with significant hypotension and multiorgan system failure following rattlesnake bite. In such cases of true DIC, the patient has evidence of organ infarction and hemolysis. This has been reported after intravascular envenomation.¹⁶

Neurotoxicity. Although local tissue destruction dominates the picture of Crotalinae envenomations, neurotoxic effects may also occur. The Mojave rattlesnake (*C. scutulatus*) is best known for its neurotoxic venom. Subpopulations of the Mojave rattlesnake that possess the neurotoxic Mojave toxin may produce weakness, cranial nerve dysfunction, and respiratory paralysis in victims.²⁸ The Timber rattlesnake (*C. horridus*) is noted to commonly cause rippling fasciculations of the skin (myokymia), particularly of the facial muscles.⁴ Fasciculations are reported following envenomation by several other species of rattlesnake, including the Western Diamondback (*C. atrox*), Mojave *C. scutulatus*, and the Southern Pacific *C. o. helleri*.¹³ Fasciculations involving the shoulders, chest wall, and torso are associated with development of respiratory failure.⁵³

Coral Snakes. Coral snake fangs are small and nonmobile, and as a result, bites are less likely than pit viper bites to lead to envenomation. An estimated 40% of patients bitten by a coral snake are subsequently determined to have been envenomed, with rates for the Eastern coral snake species possibly higher.³¹ The venom of the Eastern coral snake (*Micrurus fulvius*) and Texas coral snake (*M. tener*) are more potent than that of the Sonoran coral snake (*Micruroides euryoxanthus*). In fact, there have been no reported cases of serious toxicity after the bite of the Sonoran coral snake, which is found primarily in Arizona and western New Mexico.

Coral snake fangs may not produce easily identifiable puncture wounds. In addition to the absence of a discernable

wound in some victims, coral snake envenomations are characterized by potentially serious neurotoxicity without impressive local symptoms. The effects of envenomation are characteristically delayed for a number of hours. One report described a patient who had an asymptomatic period of 13 hours followed by rapid development of paralysis severe enough to require ventilatory support.³¹ Neurologic abnormalities reported with coral snake envenomation include paresthesias, slurred speech, ptosis, diplopia, dysphagia, stridor, muscle weakness, fasciculations, and paralysis. The major cause of death is respiratory failure secondary to neuromuscular weakness. Muscle weakness may take weeks to months to resolve completely. With respiratory support, however, paralysis is completely reversible. Pulmonary aspiration is a common sequela in the subacute phase.

Lizards. The rate of envenomation following Gila monster bites is not known, but one case series reported 40% dry bites.⁴⁰ When a *Heloderma* species bites, it may release quickly or it may hang on and “chew.” Multiple reports are documented where Gila monsters were attached to the victim for up to 15 minutes, and in some cases teeth have broken off in the wound.

Pain is immediate following a bite, and local soft tissue edema may develop within minutes. Swelling may extend from the puncture site, though not as commonly or dramatically as occurs following pit viper envenomation. Helodermatid venom does not produce local tissue necrosis, but erythema at the wound site and extension of erythema to an entire extremity is well described. Lymphangitic streaking is also reported.^{18,27,46}

Nausea, vomiting, and diaphoresis may occur following helodermatid envenomation. Patients are often tachycardic and hypotension is common. There are numerous reports of upper airway angioedema developing after bites by both Gila monsters and beaded lizards. There is a single report of a young man developing a myocardial infarction after a Gila monster envenomation.³⁸

Leukocytosis is common following envenomation, with reported white blood cell counts as high as 48,000/mm³.³⁸ Unlike crotaline venom, Gila monster venom does not typically produce abnormalities in platelet counts or clotting factors, although a single report of coagulopathy exists following a Gila monster bite in the patient who also experienced a myocardial infarction.³⁸ It has been suggested that the coagulopathy occurred as a result of endothelial damage rather than direct effect of venom on the hematologic system.⁴⁶

DIAGNOSTIC TESTING

Snakes

Diagnosis of North American snake envenomation is based on a history of a snakebite and presence of clinical signs of envenomation. There are no available laboratory assays for detection of venom in a wound. Although it is possible to measure blood and urine venom antigen concentrations using enzyme-linked immunosorbent assay (ELISA), this is only available in research settings and is not useful for early diagnosis or clinical management of envenomation.

Platelet counts, fibrinogen concentrations, and prothrombin times can be useful in the diagnosis of pit viper envenomation if they are abnormal. However, normal results do not exclude envenomation since thrombocytopenia and coagulopathy do not develop in all patients with pit viper envenomation.

A validated severity score for the objective assessment of crotaline envenomation has been developed and can be useful in a research setting.¹⁷ Its purpose is to assess the clinical condition of patients with snakebite, but it is not intended as a diagnostic tool. Caution should be used when applying this scale because envenomation is a dynamic process and severity can worsen or improve with time, limiting the utility of the score obtained at any given point in time.

Lizards. The diagnosis of helodermatid envenomation is based on the history of a bite and presence of physical examination findings consistent with envenomation. There are no laboratory studies that are available to confirm or exclude the diagnosis, but a complete blood count may reveal leukocytosis.

MANAGEMENT

Snakes

When a patient with a snake envenomation presents for care, the initial objectives are to determine the presence or absence of envenomation, provide basic supportive therapy, treat the local and systemic effects of envenomation, and limit tissue loss or functional disability (Table 122–3). A combination of medical therapy (mainly supportive care and, often, antivenom) and in some cases conservative surgical treatment (mainly débridement of devitalized tissue), individualized for each patient, will provide the best results. In general, the more rapidly treatment is instituted, the shorter the period of disability.

Pit Vipers

Prehospital care. No first aid measure or specific field treatment has been proven to positively affect outcome following a crotaline envenomation. Prehospital care should generally be limited to immobilization of the affected limb,

placement of an intravenous catheter, treatment of life-threatening clinical findings, and rapid transport to a medical facility. Patients who are volume depleted, vomiting, or experiencing systemic symptoms such as diarrhea should be given an intravenous fluid bolus. Hypotension that does not quickly respond to a fluid bolus should be treated with epinephrine.

In the past, various methods have been advocated to prevent systemic absorption of venom after snakebites. All of these methods are either ineffective and delay time to definitive care, or are potentially harmful. Such useless and potentially dangerous therapies include tourniquets, incision and suction, venom extractors, electrotherapy, and cryotherapy.

Pressure immobilization bandages (PIB), which are lymphatic-restricting bandages that are applied to the bitten extremity prior to immobilization with a splint, are not recommended for use in patients with North American Crotalinae bites. A randomized, controlled study of pressure immobilization versus observation in a porcine model with intramuscular injection of *Crotalus atrox* venom showed markedly increased compartment pressures in the pressure immobilization group. All animals died in this study, but the pressure immobilization group showed a prolonged time to death as compared to the control group. With local tissue necrosis being the major morbidity associated with pit viper envenomations in humans, not death, the authors concluded that PIB application cannot be suggested as a routine field procedure.⁹ The American College of Medical Toxicology, along with five other international organizations, released a position statement recommending against use of PIB for North American Crotalinae bites.¹

Hospital care. When a patient presents to the hospital with history of crotaline snakebite, it is important to first determine whether an envenomation has occurred. While most patients do show early evidence of envenomation, absence of symptoms at presentation is not uncommon, and not all asymptomatic patients ultimately have “dry” bites. Patients who present with puncture wounds but without swelling or other evidence of envenomation must be observed for delayed onset of symptoms. Victims of a rattlesnake bite should be observed for 8 to 12 hours after the bite. If no swelling develops and laboratory studies remain normal, the bite is likely “dry,” and the patient may be discharged from medical care. A shorter, 6-hour observation period may be appropriate for copperhead bite victims prior to medical clearance.

Supportive. The initial in-hospital assessment of North American crotaline envenomation should focus on airway, breathing, and circulation. Early airway management with endotracheal intubation should be considered in all patients with evidence of angioedema or with bites to the face or tongue. All patients, regardless of presenting symptoms, should have an intravenous catheter placed in an unaffected extremity and receive a bolus of IV fluids. Patients presenting with cardiovascular collapse should receive large volumes of fluid. An epinephrine continuous infusion, starting at 0.1 µg/kg/min and titrating as needed, is the vasopressor of choice for signs of shock.

The affected extremity should be immobilized in a padded splint in near-full extension and elevated above the level of the heart to avoid dependent edema. Although there are no studies to determine the effect of limb elevation on outcome, the authors believe this to be helpful since it may decrease dependent edema, which contributes to increased pain and physical examination findings concerning for compartment syndrome. The authors maximally elevate affected upper extremities by applying stocking net around the limb and attaching the distal end to a raised IV pole.

Marking the leading edge of swelling with a pen will help to identify progression of edema. A baseline complete blood count, PT, and fibrinogen concentration should be obtained initially and repeated in 4 to 6 hours. Patients who are systemically ill should also have electrolytes, creatinine phosphokinase, creatinine, glucose, and urinalysis checked. An electrocardiogram, chest radiograph, and blood gas may also be indicated in ill patients.

A comprehensive physical examination should be done, with emphasis on vital signs, cardiorespiratory and neurologic status, neurovascular status of the affected extremity, and evaluation for evidence of bleeding. Pain should be treated with opioid analgesics as needed, and tetanus prophylaxis should be addressed. The patient should be reassessed frequently with repeat physical examinations, specifically noting any progression of swelling. This may be accomplished by taking serial circumferential measurements of the involved extremity at multiple points proximal to the wound.

Prophylactic antibiotics are not indicated as studies show extremely low (0%–3%) rates of wound infections.³⁵ There is no indication for corticosteroids or antihistamines in the routine treatment of patients with snakebites, except for treatment of anaphylaxis.

Antivenom. Patients with dry bites or with mild envenomations, such as those who present only with localized swelling that does not progress, do not meet criteria for antivenom³⁴ (Table 122–3). Patients who present with progressive swelling, thrombocytopenia, coagulopathy, neurotoxicity, or significant systemic toxicity are candidates for antivenom therapy. Antivenom given in a timely manner can reverse coagulopathy and thrombocytopenia and halt progression of local swelling. There is no evidence, however, that antivenom can prevent or reverse the development of tissue necrosis, so patients should be informed of the risk of tissue loss. This is most commonly noted with rattlesnake bites to the fingers, which occasionally lead to amputation of the digit despite appropriate treatment with antivenom.

The only currently FDA approved antivenom for North American pit viper envenomation is Crotalidae polyvalent immune Fab (CroFab, BTG). CroFab is an ovine-derived Fab fragment antivenom developed from commonly encountered North American pit vipers (*C. atrox*, *C. adamanteus*, *C. scutulatus*, *A. piscivorus*). CroFab is administered IV in an initial dose of four to six vials reconstituted in 0.9% sodium chloride solution. Patients who present with cardiovascular collapse or other life-threatening toxicity should be treated aggressively with a starting dose of 8 to 12 vials of CroFab.³⁴ The

infusion is initiated at a slow rate for several minutes, and if no signs of an anaphylactoid reaction develop, increased to complete the infusion over one hour. The patient should be reassessed after completion of the infusion for evidence of continued swelling or worsening thrombocytopenia, and, if present, an additional four-to six-vial dose is infused. This process is repeated until control of symptoms is achieved. Fibrinogen and PT may be slower to recover in response to antivenom. If these are the only findings that continue to be abnormal after antivenom, it is reasonable to repeat these studies in 4 hours to determine if redosing of antivenom is necessary. Control is generally considered cessation of progression of swelling and systemic symptoms in addition to improvement in coagulopathy and thrombocytopenia. After control has been achieved, maintenance doses of antivenom are given as two vials every 2 hours for three doses (six total additional vials after control). Although recommended in the package insert for CroFab, maintenance therapy is not routinely administered by all practitioners.⁵ For example, maintenance doses may be unnecessary in the management of copperhead envenomations. Practitioners can learn local practices and recommendations through consultation with regional poison centers. An algorithm for treatment of North American crotaline snakebite is also available online.³⁴ Antivenom therapy is discussed in detail in Antidotes in Depth: A37.

Antivenom administration in children follows the same guidelines as adults, with doses based on clinical presentation and laboratory findings rather than weight. Attention should be paid to total amount of fluid received, and if necessary, antivenom can be reconstituted in a smaller total volume of fluid. Generally, patients with severe snake envenomation have large fluid requirements, and fluid overload is not a problem.

Pregnant patients who meet criteria for treatment should also receive antivenom. Crotalidae polyvalent Fab (ovine) is currently listed as pregnancy category C, but it has been used safely during pregnancy.³² Given the relative safety of this antivenom and the potential for fetal demise after envenomation, a low threshold for treatment should be considered. Fetal and maternal monitoring should be carried out throughout the patient's care.³³

Surgery. Surgery is not routinely indicated following snakebites. An extensive review of the literature failed to identify any evidence to support the use of fasciotomy in the treatment of snakebites.¹⁴ A single case of elevated compartment pressure (55 mm Hg) after rattlesnake envenomation was managed without fasciotomy. The authors treated this patient with antivenom, as well as mannitol and hyperbaric oxygen.²³ When compartment syndrome is suspected, intracompartmental pressures should be measured. It is reasonable to attempt to treat moderately elevated compartment pressures with antivenom initially, but clinical examination and compartment pressures should be followed closely. Just as there is no strong evidence to support the use of fasciotomy, similarly there is a lack of evidence demonstrating that surgery is unnecessary when intracompartmental pressures are high. If the patient develops evidence of limb ischemia or increasing compartment pressures, fasciotomy may be indicated.

Patients with bites to the digit may present with evidence of ischemia. The finger may appear cyanotic or pale, tense, and lack sensation. The small diameter of the digit and limited ability of the skin to expand essentially creates a small compartment. In such cases it may be reasonable to perform a digital dermatomy, where a longitudinal incision is made through the skin on the medial or lateral aspect of the digit in order to decompress the neurovascular structures. Although there are no studies evaluating the efficacy of dermatomy in preventing tissue loss, the authors have seen patients with cyanotic and insensate digits regain color and sensation immediately following this procedure. Dermatomy should not be performed prophylactically in cases of digital envenomation, as most patients have good outcome without any surgical intervention.²⁵

Debridement of hemorrhagic blebs and blisters is often performed to evaluate underlying tissue and relieve discomfort. Some patients may require surgical debridement of necrotic tissue or even amputation of a digit 1 to 2 weeks after the bite. Referral to a hand surgeon is appropriate for patients with evidence of extensive tissue necrosis.

Blood Products. Immeasurably low fibrinogen concentrations, prothrombin times greater than 100 seconds, and platelet counts lower than 20,000 K/mm³ are routinely encountered after rattlesnake envenomation. Such abnormal laboratory results alone should not prompt the clinician to treat with blood products in the absence of clinically significant bleeding. The circulating crotaline venom responsible for the thrombocytopenia and coagulopathy is still present and will likely inactivate any transfused components. For this reason, the mainstay of treatment for crotaline envenomation-induced coagulopathy and thrombocytopenia is antivenom, not blood products. Correction of coagulopathy, thrombocytopenia, and bleeding can frequently be achieved with antivenom alone. Rarely, a patient will have active bleeding, and antivenom alone will not correct the platelets and fibrinogen. In such cases, fresh frozen plasma, cryoprecipitate, packed red blood cells, or platelet transfusions may be required.

In some cases, thrombocytopenia may be difficult, or impossible, to correct with even large amounts of antivenom. The Timber rattlesnake, for example, is known for producing thrombocytopenia resistant to antivenom. The initial correction of platelet counts after treatment may be transient (lasting only 12–24 hours), with thrombocytopenia sometimes persisting for days to weeks after normalization of other coagulation parameters. In the absence of bleeding, thrombocytopenia is a benign, self-limiting disorder, resolving within 2 to 3 weeks of envenomation. It may be best to closely follow patients with resistant thrombocytopenia who are not bleeding, rather than attempt further platelet transfusions or antivenom administration.³⁷

Follow-up care. Hospital stays for patients with uncomplicated pit viper envenomations are typically short, lasting approximately 1 to 2 days³⁹ Upon discharge from the hospital, patients often have residual swelling and functional disability. They may have continued progression of hemorrhagic bullae with underlying necrosis. Patients should have an out-patient follow-up evaluation to ensure wounds are healing appropriately and extremity function is returning. If joint mobility does not return to baseline as swelling resolves, the patient should be referred for physical and occupational therapy.

In a significant proportion of rattlesnake bite patients treated with Crotalidae polyvalent immune Fab antivenom, a return of swelling, coagulopathy, or thrombocytopenia may be noted after initial resolution of the effect after initial treatment with antivenom. This has been termed “recurrence” of venom effect and is attributed to the interrelated kinetics and dynamics of venom and antivenom.^{39,42} Simply stated, Fab antivenom has a clinical half-life shorter than that of venom. Administration of maintenance doses of antivenom is used in an attempt to prevent development of recurrent effects. Maintenance doses appear to be effective in preventing recurrence of local swelling in most cases, but many patients develop hematologic recurrence within 3 to 7 days of antivenom treatment despite administration of maintenance doses. Additionally, patients who never manifested thrombocytopenia or coagulopathy during their hospital presentation may later develop the effect, presumably because of initial “masking” of the effect by early antivenom administration. These recurrent or late hematologic effects have been associated with life-threatening bleeding.³⁰ No risk factors have been identified to predict which patients will develop late thrombocytopenia or coagulopathy.

The most reasonable way to address possible late hematologic effects of crotaline envenomation is careful outpatient follow-up after hospital discharge. Patients with copperhead bites may be followed as needed.^{34,39} The safest approach is to provide careful discharge instructions and consider all patients who have been treated with Crotalidae polyvalent immune Fab antivenom to be at risk for late hematologic toxicity. Patients who use antiplatelet or anticoagulant medications should be continued on these medications only after a careful risk-benefit analysis. Whenever possible the medications should be discontinued until the risk of recurrent or late hematologic toxicity passes. Patients must be warned not to undergo dental or surgical procedures for up to 3 weeks unless platelet and coagulation studies are documented to be normal immediately prior to the procedure. High-risk activities, such as contact sports, should be avoided. All patients should have platelets and coagulation studies measured 2 to 3 days, and again 5 to 7 days, after the last antivenom treatment. If values are abnormal or trending in the wrong direction, the studies should be repeated every few days until normalized. Patients should be advised to avoid surgical procedures and activities that place them at risk for injury. Opinions on when to retreat patients exhibiting late hematologic toxicity with antivenom vary. The general approach of the authors is to retreat any patient with evidence of bleeding, as well as patients with severe isolated thrombocytopenia (platelets $<25,000/\text{mm}^3$) or moderate thrombocytopenia (platelets $25,000\text{--}50,000/\text{mm}^3$) in combination with severe coagulopathy (fibrinogen $<80\text{ mg/dL}$).³⁹ Many clinicians choose to observe patients with isolated coagulopathy cautiously as outpatients rather than to retreat them with antivenom. However, if patients with isolated severe coagulopathy have other risk factors for bleeding, such as use of antiplatelet medications, retreatment with antivenom should be considered.

When the decision has been made to retreat a patient with late hematotoxicity with antivenom, an initial starting dose of two vials is recommended. Late thrombocytopenia appears to be more resistant to antivenom than early venom-induced thrombocytopenia, and it is unclear whether a different mechanism may be responsible for the late effect. It is unknown how much antivenom is needed to reverse late thrombocytopenia or at what dose a patient may be considered “resistant” to antivenom. Patients who have evidence of bleeding with severe thrombocytopenia may require platelet transfusion. Some clinicians have also given steroids to patients who have not responded to antivenom and platelet transfusions, but there is no evidence to support the efficacy of steroids in this setting.

Coral Snakes

As with North American pit viper bites, patients who are bitten by North American coral snakes should be taken to a hospital for definitive medical care as soon as possible. There are no field treatments that have been shown to affect outcome in these patients. Pressure immobilization bandages (PIB) have been shown to delay the systemic absorption of venom from Australian elapid snakes. A swine model of coral snake envenomation suggests that pressure immobilization bandaging may be effective in delaying systemic absorption of venom following coral snakebite.²¹ Patients who present for care after a PIB has been placed should have the dressing left in place until resuscitative equipment and personnel are present and, ideally, antivenom is available. The PIB should be checked to ensure it is not functioning as a tourniquet.

Patients with a history concerning for possible Eastern or Texas coral snakebite should be observed for 24 hours in a monitored unit where resuscitative measures, including endotracheal intubation, can be performed. Since neuromuscular weakness and respiratory paralysis can develop quickly, endotracheal intubation should be considered at the first sign of bulbar paralysis. Traditionally, treatment with Wyeth Antivenin (*Micrurus fulvius*) (equine origin) North American Coral Snake Antivenin (NACSA) has been recommended for all patients in whom there is strong suspicion of coral snakebite, even in the absence of signs of envenomation. This is mainly because paralysis can develop quickly and symptoms may not reverse following antivenom treatment. Approximately 10 years ago Wyeth ceased production of NACSA, creating a shortage of antivenom and prompting many clinicians to take a more conservative approach to treating patients with coral

snakebites. A recent study comparing patients who received empiric treatment with antivenom to patients who were treated when symptoms developed suggests that a conservative approach (waiting for symptoms to develop before administering antivenom) does not result in worse outcomes for patients.⁵⁸ The expiration date of current supplies of NACSA was extended to April 2014.⁵¹ Pfizer is expected to take over production of this antivenom in the near future.

If a patient is symptomatic following a coral snake envenomation, antivenom, if available, is indicated. If antivenom is unavailable, patients may be managed with supportive care alone. Mechanical ventilation may be necessary for many weeks. Acetylcholinesterase inhibitors, neostigmine and edrophonium, have been successfully used to treat patients with South American coral snakebites, but their use should be considered experimental.⁶

Sonoran coral snakes, indigenous to Arizona and California, have never been reported to cause significant toxicity, and bite victims do not require observation in the hospital or antivenom administration.

Lizards. Management of helodermatid envenomation consists of supportive care. There is no antivenom available against lizard venom. Routine wound care should be performed, and the clinician should look for the presence of teeth in the wound. There is no evidence to guide clinicians when deciding whether to administer antibiotics to patients with erythema surrounding and extending from the bite site. Most case reports describing patients with erythema also report empiric use of antibiotics. There are no reports of confirmed infections following these bites.

Patients who are symptomatic following a bite should be attached to a cardiac monitor and have an intravenous catheter placed. Although serious morbidity from lizard bites is unusual, envenomation may be life threatening. Angioedema, other evidence of respiratory compromise, or airway obstruction should prompt endotracheal intubation. Hypotension may require treatment with intravenous fluid boluses as well as vasopressors such as epinephrine. Epinephrine, corticosteroids, and antihistamines may be indicated for the treatment of anaphylactoid reactions.

SUMMARY

- Most native snake envenomations result from bites by Crotalinae species of snakes, also known as pit vipers, and commonly produce local tissue swelling and hematologic toxicity.
- A small percentage of envenomations are due to bites by coral snakes, which are known for producing neurotoxicity without local tissue effects.
- Management of patients with pit viper and coral snake envenomation should focus on aggressive supportive care and specific antivenom when indicated.
- Envenomations by Helodermatid lizards are often associated with local pain, erythema, hypotension, and angioedema.
- Clinicians are encouraged to contact a regional poison control center when a patient presents after a snake or lizard envenomation.

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A37 ANTIDOTES IN DEPTH

Antivenom: Snakes (Native [US] Venomous [Crotaline and Elapid])

Anthony F. Pizon and Anne-Michelle Ruha

INTRODUCTION

Definitive management of North American venomous snakebites is antivenom and supportive care. In the past, numerous treatments were advocated to prevent systemic absorption or to neutralize venom. These therapies included tourniquets, incision and suction, venom extractors, electrotherapy, and cryotherapy. All of these treatment modalities are either ineffective, delay time to definitive care, or harmful. The focus of treatment for the snakebite victim is a careful assessment, supportive care, evaluating for signs of envenomation, and ultimately, determining the need for antivenom.

HISTORY

Crotalidae Polyvalent Immune Fab (Ovine)

Historically, Wyeth (Marietta, PA) manufactured Antivenin Crotalidae Polyvalent (ACP) for treatment of crotaline snakebites in the United States. It was a poorly purified whole IgG product derived from horse serum with significant risk for acute and delayed allergic reactions.¹⁶ Wyeth has since stopped production of ACP, and all extant lots have expired. Many physicians still recall the use of this product, but new antivenoms have replaced ACP and have improved the approach to snakebite treatment. In October 2000, the US Food and Drug Administration (FDA) approved Crotalidae polyvalent immune Fab (FabAV), manufactured by BTG International (West Conshohocken, PA). This product is marketed as CroFab. This antivenom is derived from sheep serum and formulated specifically to treat snakebites from US Crotalinae species. It is an effective and less allergenic alternative to the previously manufactured horse serum product from Wyeth.^{16,33}

Antivenin (*Micrurus fulvius*) (Equine)

For decades, Wyeth Laboratories (Marietta, PA) manufactured Antivenin (*Micrurus fulvius*) (Equine), which is more commonly known as North American Coral Snake Antivenin (NACSA), for treatment of envenomations by the eastern coral snake (*Micrurus fulvius*) and Texas coral snake (*Micrurus tener*). Wyeth discontinued production of this antivenom. The last remaining lot (# 4030026) was labeled with an expiration date of October 31, 2008. However, the US Food and Drug Administration extended the expiration date based on stability and potency data to October 31, 2013. Additionally, lot 4030024 has a new expiration date of April 30, 2015.³⁵

PHARMACOLOGY

Crotalidae Polyvalent Immune Fab (Ovine)

Chemistry/Preparation. Crotalidae polyvalent immune Fab (FabAV) is produced by inoculating sheep with the venom of one of the following crotaline snake species: the eastern diamondback rattlesnake (*Crotalus adamanteus*), western diamondback rattlesnake (*Crotalus atrox*), cottonmouth (*Agkistrodon piscivorus*), and Mojave rattlesnake (*Crotalus scutulatus*). The species specific antivenom is then prepared by isolating the antibodies from the sheep serum and digesting the IgG antibodies with papain. The venom-specific Fab antibody fragments are then isolated by affinity purification. This refining process eliminates most of the Fc portion of the immunoglobulin and other potentially immunogenic sheep proteins. Manufacturing specifications require $\leq 1.0\%$ w/w for Fc fragments and $\leq 0.3\%$ w/w for albumin.¹⁴ All four species specific antivenoms are then combined to form the final polyvalent product. The resultant Fab antivenom is less immunogenic and more potent compared to whole IgG antivenoms used previously.^{7,12}

Mechanism of Action. FabAV is comprised of the Fab portion of IgG antibodies directed against the venom from four North American crotaline snake species. The antibodies bind and neutralize venom components. In some cases the antibodies may penetrate tissues and help redistribute the venom from its target tissue.

Pharmacokinetics. The pharmacokinetics of FabAV is poorly studied. Elimination half-life calculations were performed using only three patient samples. From these data, the half-life was estimated between 12 and 23 hours.⁸ Although a similarly prepared and sized ovine Fab product had a volume of distribution of 0.3 L/kg, a systemic clearance of 32 mL/min, and an elimination half-life of approximately 15 hours, these parameters may not apply to FabAV.³⁶

Antivenin (*Micrurus fulvius*) (Equine)

Chemistry/Preparation. NACSA is manufactured by immunizing healthy horses with venom from the eastern coral snake (*Micrurus fulvius*). The horse serum is then purified and concentrated before it is lyophilized for storage. Unlike FabAV, NACSA is a whole IgG product.

Mechanism of Action. The antibodies in this antivenin are directed against the venom of the eastern coral snake. The antibodies bind and neutralize venom components. In some cases the antibodies may penetrate tissues and help redistribute the venom from its target tissue.

Pharmacokinetics. The pharmacokinetics of NACSA are unknown and unstudied.

CLINICAL USE

Crotalidae Polyvalent Immune Fab (Ovine)

Crotalidae polyvalent immune Fab (FabAV) is specifically designed using the venoms of four North American crotalids: the eastern diamondback rattlesnake (*Crotalus adamanteus*), western diamondback rattlesnake (*Crotalus atrox*), cottonmouth (*Agkistrodon piscivorus*), and Mojave rattlesnake (*Crotalus scutulatus*). However, murine lethality studies demonstrate that FabAV has activity against the venom of six other crotaline snake species (*Crotalus viridis helleri*, *C. molossus molossus*, *C. horridus horridus*, *C. horridus atricaudatus*, *Agkistrodon contortrix contortrix*, and *Sistrurus miliaris barbouri*).⁷ In addition, numerous case reports document benefit after envenomation by many other North American crotalids.

Some case reports and anecdotal experience report venom effects resistant to FabAV. For instance, thrombocytopenia may not respond to FabAV after envenomations by the red diamond (*C. ruber ruber*) and the timber (*C. horridus horridus*) rattlesnakes.²⁷ In these cases, the thrombocytopenia often responds to initial doses of FabAV, but a subsequent decline in the platelet count is unaffected by repeat dosing of antivenom. Sometimes severe, platelet counts remain extremely low or undetectable until they rebound approximately a week after the envenomation. In rare cases, despite FabAV therapy, late spontaneous bleeding and laboratory abnormalities may occur beyond 2 weeks.²⁶ Furthermore, patients envenomated by the Southern Pacific rattlesnake (*C. viridis helleri*) may have refractory neurotoxicity unresponsive to FabAV.³¹ In general, FabAV may be used to treat envenomations for all North American pit vipers with expected overall benefit despite the occasional refractory envenomation effect in select species.²³

After an envenomation, the major indications for FabAV administration are (1) progression of swelling, (2) significant coagulopathy or thrombocytopenia, (3) neuromuscular toxicity, or (4) hemodynamic compromise. These indications are vague and allow the clinician the ability to interpret the need for antivenom under varying circumstances. If the prothrombin time is elevated, or the fibrinogen or platelet counts are decreased, antivenom should be administered. Furthermore, antivenom is indicated when patients demonstrate muscle fasciculations, weakness, or shock. Antivenom should not be given prophylactically to individuals without evidence of envenomation. Patients should not be given antivenom for limited localized tissue swelling alone when other signs of envenomation are absent. This may be interpreted as swelling localized to only the bite site or swelling that does not cross a major joint, such as a wrist, elbow, ankle, or knee ([Chap. 122](#)).²³ Nonetheless, the bedside physician should use his or her best judgment based on the severity of local swelling before providing antivenom when no other envenomation signs are present.

When indications are met, antivenom should be administered as soon as possible. Since antivenom will halt but not reverse swelling, it is anticipated that early administration would reduce pain and loss of function associated with a grossly swollen extremity, as compared to delayed administration. Animal studies report decreased mortality when antivenom is given immediately after envenomation.⁷ Similarly, the benefits of antivenom diminish with delayed treatment of even a few hours in animal models.¹² Antivenom will not reverse swelling and tissue necrosis that has already occurred, and tissue necrosis may develop despite antivenom administration. Antivenom has, at least temporarily, reversed systemic effects, coagulopathy, and platelet defects.^{4,9,10,22,33} While no studies exist comparing outcomes of envenomated patients treated with and without antivenom, it is generally agreed that antivenom reduces morbidity in patients with significant crotaline envenomation and in some situations may be a lifesaving therapy.¹⁰ The window of therapeutic efficacy in cases of delayed antivenom administration is unknown.

Antivenin (*Micrurus fulvius*) (Equine)

NACSA is the recommended treatment for envenomation by the eastern coral snake (*Micrurus fulvius*) and Texas coral snake (*Micrurus tener*). This antivenom does not treat envenomations from coral snakes found in Mexico, Central America, or South America. Furthermore, bites by the less virulent Arizona coral snake (Sonoran, *Micruroides euryoxanthus*) typically do not produce significant envenomation requiring treatment with antivenom.³⁴

In the past, prophylactic use of NACSA was recommended for all patients with an assumed or proven coral snakebite, even if asymptomatic.¹⁸ Even if there is little objective evidence to suggest envenomation several hours following a coral snakebite, systemic symptoms can develop suddenly. Therefore, antivenom was traditionally administered to prevent the development of potentially life-threatening envenomation. However, the current shortage of NACSA has prompted clinicians to take a more conservative approach and administer antivenom only after signs of envenomation develop. One study comparing patients who received empiric antivenom treatment to patients treated after symptoms arose suggested that a conservative approach was not inferior.³⁸

Indications for NACSA administration include the development of any signs or symptoms consistent with coral snake envenomation. Coral snake envenomations typically lack significant local tissue injury. Antivenom administration should follow the development of any neurologic abnormalities including, but not limited to, paresthesias, slurred speech, ptosis, diplopia, dysphagia, stridor, muscle weakness, fasciculations, and paralysis. Since anxiety is often associated with a snakebite, true signs of envenomation must be differentiated from anxiety associated with a snake encounter.

In the absence of antivenom, the mainstay of treatment consists of aggressive supportive care. In particular, respiratory failure resulting from muscle weakness may necessitate intubation and prolonged mechanical ventilation until neurological recovery occurs. Although paralysis is completely reversible, it may take weeks to months to resolve.¹⁸

ADVERSE EFFECTS AND SAFETY ISSUES

Crotalidae Polyvalent Immune Fab (Ovine)

Acute hypersensitivity reactions are the most significant safety concerns when providing antivenom products to patients. Crotalidae polyvalent immune Fab (FabAV) was specifically designed to have reduced immunogenicity. However, both acute and delayed hypersensitivity reactions are still well reported.^{5,6} Urticaria, rash, bronchospasm, pruritus, angioedema, anaphylaxis, and delayed serum sickness all are associated with use of this product.^{9,36} An early study reported acute reactions in 14.3% of patients receiving this antivenom, but more current studies suggest an incidence of 5% to 6%.^{5,10,22} Both numbers are still much lower than those reported for the poorly purified whole IgG antivenoms, but the risk of an acute allergic reaction is still a possibility.

When antivenom is administered too rapidly, nonimmunogenically mediated anaphylactoid reactions may occur as well. Anecdotally, most patients appear to tolerate 4 to 6 vials per hour without developing significant anaphylactoid reactions. If the patient requires rapid administration of antivenom because of the severity of the envenomation, H₁ histamine receptor antagonists and an epinephrine infusion should be readily available in case symptoms develop. Clinically differentiating between anaphylactoid and anaphylactic reactions may be difficult, especially when antivenom is administered rapidly. Regardless, the treatment remains the same.

For acute anaphylactic reactions (which often occur shortly following initiation of even low doses of antivenom), the antivenom should be stopped, and aggressive supportive and pharmacological therapy begun. Intravenous corticosteroids, H₁ histamine receptor antagonists, and epinephrine at 2 to 4 µg/min (0.03–0.06 µg/kg/min for children) can be initiated and then titrated to effect. After the symptoms of hypersensitivity resolve, the antivenom should be restarted only in patients at high risk for significant morbidity or mortality from snake envenomation. In such cases, the antivenom infusion is restarted at 1 to 2 mL/h, while the epinephrine infusion is continued. The antivenom infusion rate can be slowly increased as tolerated. If anaphylaxis recurs, the antivenom should be stopped and the epinephrine infusion increased until symptoms resolve. Antivenom can then be restarted while epinephrine is continued at the higher rate. With constant monitoring of patients at the bedside and careful titration of epinephrine and antivenom infusions, patients with life-threatening envenomation should be able to receive the full antivenom dose. Patients have safely received subsequent doses of antivenom after an acute life-threatening reaction.²⁴

In addition to acute allergic reactions, delayed hypersensitivity syndromes in the form of serum sickness may occur. Although most episodes of serum sickness are mild, this syndrome has not been well studied.¹⁶ Typical cases of serum sickness include urticaria, pruritus, and malaise. Arthralgias, lymphadenopathy, and fever may develop on occasion as well. In rare severe cases, glomerulonephritis, vasculitis, myocarditis and neuritis can occur. Delayed hypersensitivity reactions are poorly studied following treatment with FabAV, but are reported to occur in 16% of patients in two clinical trials.^{1,9} This number may be falsely elevated because all but one of the cases came from a single lot of antivenom that was later found to be contaminated with a high concentration of Fc antibody fragments.¹² One treatment regimen for serum sickness is to give 2 mg/kg of oral prednisone divided into two daily doses and tapered over 2 to 3 weeks. However, other

corticosteroids may be used. Oral H₁ receptor antagonists can be used for symptomatic treatment as well. The vast majority of patients can be managed as outpatients, and most respond favorably to oral antihistamines and corticosteroids.

According to the package insert, a known allergy to papaya or papain is a contraindication to the administration of FabAV only if the risks of allergy outweigh the benefits to the administration of the antivenom.⁸ Patients with known allergy to papaya or papain appear rare. However, patients who are also allergic to latex or a variety of fruits (banana, avocado, kiwi, apricot, chestnut, grape, passion fruit, and pineapple) may have crossreactivity with papain.³⁰ Caution is advised when administering FabAV to any patients with atopy, asthma, or known food allergies.

Antivenin (*Micrurus fulvius*) (Equine)

Acute and delayed hypersensitivity reactions are the most significant safety concerns when providing antivenom products to patients. However, little is published concerning adverse reactions to NACSA. The risk of acute hypersensitivity reactions with Wyeth's other equine-derived antivenom product, ACP, was between 20% and 50%, and the incidence of delayed hypersensitivity reactions increased with increasing doses.^{17,37} The exact incidence of hypersensitivity with NACSA is unknown, but approaches 100% when greater than 40 vials of ACP are administered.²⁵ Despite these concerns, severe allergic reactions to NACSA have not been reported, but this may reflect infrequent use and reporting bias.

Patients with a known horse serum allergy or who have been treated with equine derived antivenoms previously should only be treated with NACSA if there is a significant risk of severe morbidity or mortality. Patients with known horse serum allergies have tolerated equine antivenoms, but they often require more dilute doses of antivenom and pretreatment.^{15,24} Intravenous H₁ receptor antagonists, corticosteroids, and an epinephrine infusion should be started (2–4 µg/min for adults) prior to antivenom administration. The antivenom is then started at a very low rate of infusion, and if tolerated, the rate is increased. If an acute allergic reaction develops, the antivenom is immediately stopped and the epinephrine drip titrated for symptoms. Only after symptoms abate should the antivenom be restarted by carefully titrating both the antivenom and epinephrine drips. With severe allergic reactions, antivenom should only be given for life-threatening envenomations. In most cases with severe allergic symptoms, antivenom should be discontinued and followed with supportive care alone.

PREGNANCY AND LACTATION

Crotalidae Polyvalent Immune Fab (Ovine)

Pregnant patients who meet criteria for treatment should also receive antivenom. FabAV is currently listed as category C, but it has been used safely during pregnancy.¹⁹ In the pre-FabAV era, one review of 30 bites by rattlesnakes, copperheads, and cottonmouths during pregnancy reported 43% fetal demise and 10% maternal mortality.¹³ Therefore, given the relative safety of this antivenom and the potential for significant fetal compromise after envenomation, a low threshold for treatment should be considered. Fetal and maternal monitoring should be carried out throughout the patient's care.²⁰

It is unknown if FabAV is excreted in breast milk.

Antivenin (*Micrurus fulvius*) (Equine)

NACSA currently does not have a pregnancy listing. There are no reports of administration of this antivenom to a pregnant patient. Knowledge of the safety of NACSA in pregnancy is unknown. However, other antivenoms have been used safely in pregnancy, and maternal health is often considered at greater risk due to envenomation than an unknown adverse risk to the fetus as a result of antivenom.³ Considering this, and the severe morbidity associated with coral snake envenomation, pregnant patients who meet criteria for treatment should receive antivenom. It is unknown if NACSA is excreted in breast milk.

DOSING AND ADMINISTRATION

Crotalidae Polyvalent Immune Fab (Ovine)

A thorough medication history including previous treatment with antivenoms should be obtained. A history of asthma, atopy, or food allergies should be carefully considered when weighing the risks and benefits of antivenom for a particular patient. According to the manufacturer, the only contraindication is an allergy to papaya or papain. These conditions should not exclude the use of antivenom if the patient is suffering from a moderate to severe envenomation. Crotalidae polyvalent immune Fab (FabAV) is ovine derived, therefore previous reactions to equine derived antivenoms should not preclude use of this product. In cases of mild envenomation, the risk of allergic reaction to antivenom might outweigh any benefit in this patient population. Antivenom should be administered in a monitored setting where resuscitation can be performed and airway supplies can be quickly accessed. Epinephrine, corticosteroids, and antihistamines should be immediately available in the event of a hypersensitivity reaction. If the patient tolerates initial doses without ill effect, subsequent doses may be

administered in a less monitored setting, such as a medical floor or step-down unit.²³

Antivenom is packaged in vials as a lyophilized powder that must be reconstituted. Completely filling each vial with 25 mL of sterile water, rather than the 10 mL advised in the package insert, and then gently hand rolling the vials will result in dissolution times as rapid as one minute. Adding the greater volume also reduces foaming of the product.^{8,29} The reconstituted antivenom is further diluted into a 250 mL of 0.9% sodium chloride solution and administered as discussed above.

The initial recommended dose is 4 to 6 vials, which is mixed in 250 mL 0.9% sodium chloride solution and administered over one hour. Patients who present with cardiovascular collapse or life-threatening toxicity should be treated aggressively with a starting dose of 8 to 12 vials of FabAV.²³ The exact concentration of antivenom is not critical. For children, the total volume of fluid in which the antivenom is diluted can be decreased when necessary.²⁸ No dosing adjustment is required for children or small adults because the amount of venom requiring neutralization is not dependent upon the weight of the patient. On the other hand, there is no evidence to support partial doses or infusions of 1 or 2 vials in minor cases.

In order to avoid serious adverse reactions, the first dose of antivenom is administered cautiously in an escalating rate fashion. No skin testing is suggested. The first dose of antivenom (4–6 vials diluted in 250 mL 0.9% sodium chloride solution) is infused at an initial rate of 10 mL/h while the patient is observed carefully for evidence of hypersensitivity. If no adverse reactions are witnessed, then the rate is doubled every few minutes, as tolerated by the patient, with the goal of infusing the first dose over one hour. If the patient tolerates the initial dose without adverse effects, subsequent doses can be given at a rate of 250 mL/h without need for rate titration.

The total dose of antivenom required to control an envenomation may vary widely, so additional doses may be needed to halt swelling and or reverse coagulopathy or thrombocytopenia. With the introduction of FabAV, “control” was defined as arrest of local tissue manifestations and return of coagulation parameters, platelet counts, and systemic signs to normal. However, clinical experience with the product demonstrated that some patients have venom-induced coagulopathy and thrombocytopenia that is resistant to antivenom treatment.³³ Some authors advocate “control” to mean clear improvement in hematologic parameters rather than complete normalization.³³ This definition may be more realistic for the subset of patients with refractory coagulopathy and thrombocytopenia. After each dose of 4 to 6 vials, prothrombin time, fibrinogen, and platelet counts are measured, and the extent of local injury is reexamined. Multiple doses are often required to achieve control. A retrospective study reported 83% of rattlesnake bites and 98% of copperhead bites obtained control with 12 or fewer vials of FabAV.³⁹ This study emphasizes the need for multiple antivenom control doses in rattlesnake envenomations and typically only one initial dose in copperhead bites in order to gain control. If repeat dosing is necessary to control swelling, but fibrinogen, prothrombin time, and platelets remain normal, then these laboratory studies do not need to be repeated after each additional control dose.

After achieving control, maintenance doses of 2 vials every 6 hours are given, for a total of three doses. Again, the 2 vials are added to 250 mL 0.9% sodium chloride solution and administered over one hour. Because the duration of action of antivenom is less than that of venom, the maintenance doses are provided to preclude recurrence of local manifestations, thrombocytopenia, and coagulopathy. An algorithm for FabAV antivenom administration for treatment of moderate to severe crotaline envenomation is shown in [Fig. A37–1](#). Although recommended in the package insert for CroFab, maintenance therapy is not routinely administered by all practitioners.⁸ For example, maintenance doses may be unnecessary in the management of copperhead envenomations.²³ Consultation with regional poison centers can inform local practices and recommendations.

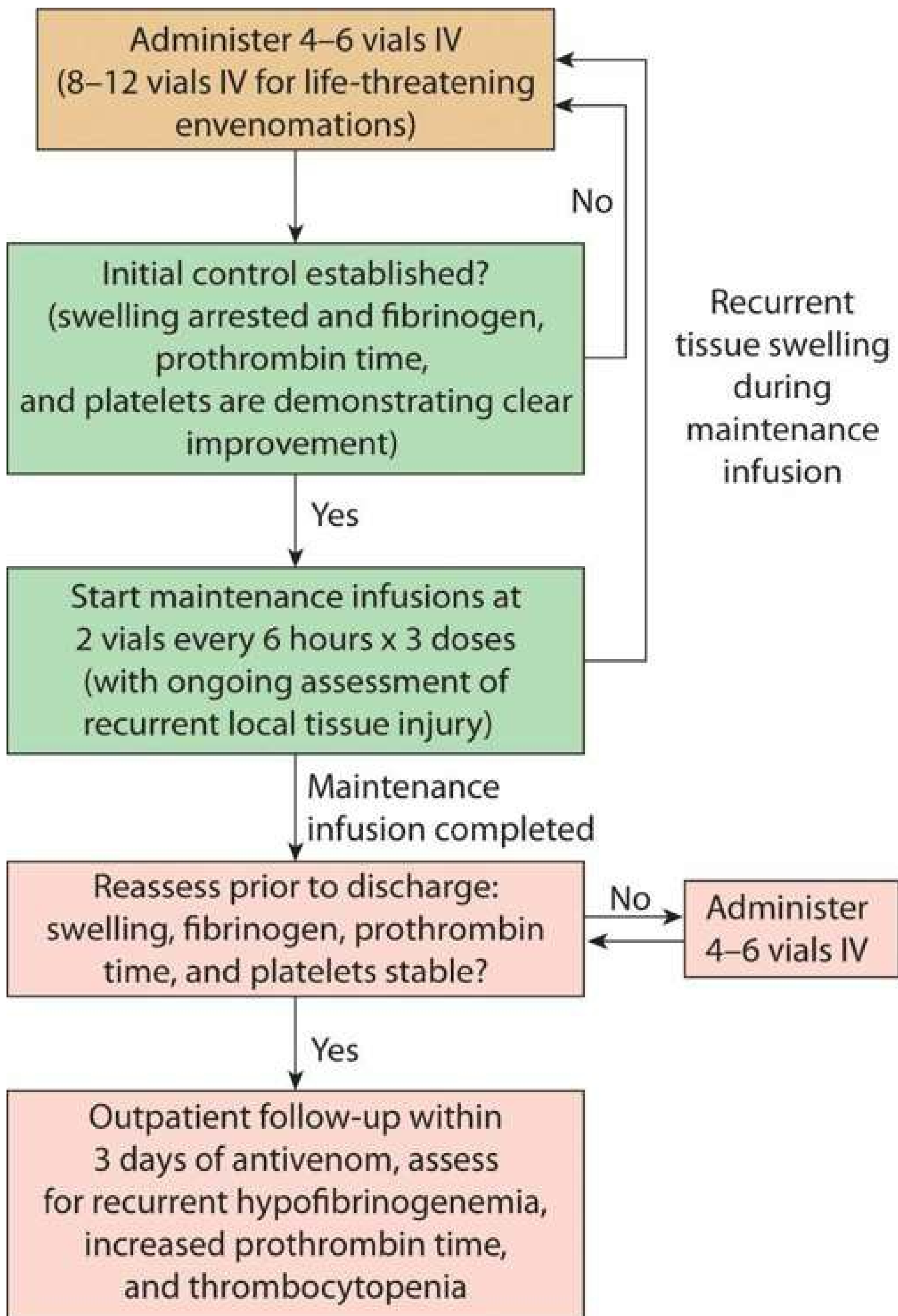


FIGURE A37–1. Algorithm for Crotalidae polyvalent immune Fab administration for treatment of moderate to severe Crotaline envenomation.

Some patients will demonstrate recurrence of swelling during their maintenance infusions. For this reason, close monitoring of extremity swelling should occur for 18 to 24 hours after apparent control has been achieved. If recurrent swelling occurs, additional control doses of 4 to 6 vials should be given until the swelling again becomes controlled. Likewise, despite successful completion of maintenance antivenom doses, patients may develop a recurrence of coagulopathy and or thrombocytopenia. Therefore, all patients should have repeat prothrombin time, fibrinogen, and platelet counts performed 2 to 3 days and again 5 to 7 days after hospital discharge to ensure late recurrent hematologic effects have not developed. One large retrospective study demonstrated new or recurrent hematologic findings in 32% of patients with rattlesnake envenomation.³² Another study suggests recurrence may be as high as 50%.² Close follow-up may be less necessary in copperhead envenomations since hematologic findings are observed less frequently.²¹

Antivenin (*Micrurus fulvius*) (Equine)

Prior to administration of NACSA, a thorough history regarding asthma, atopy, food allergies, and previous use of antivenoms should be obtained. A history of asthma or atopy should be carefully considered when weighing the risks and benefits of antivenom for a particular patient. These conditions should not preclude the use of antivenom if the patient is suffering from a moderate to severe envenomation. Antivenom should be administered in a monitored setting where resuscitation can be performed and airway supplies are immediately available. Epinephrine, corticosteroids, and antihistamines should be immediately available in the event a hypersensitivity reaction occurs.

Antivenom is packaged in vials as a lyophilized powder that must be reconstituted. Completely filling each vial with 25 mL of sterile water, rather than the 10 mL advised in the package insert, and then gently hand rolling (not shaking) the vials will result in dissolution times as rapid as one minute. Adding the greater volume also reduces foaming of the product.^{8,29} The reconstituted antivenom is then diluted into a 250 mL of 0.9% sodium chloride solution and administered as discussed above.

The initial recommended dose of NACSA is 3 to 5 vials, which is mixed in 250 mL 0.9% sodium chloride solution and administered over one hour. Additional antivenom doses may be repeated on the basis of the clinical condition. The caveats for crotaline antivenom administration (infusion rate and treatment of allergic reactions) apply to coral snake antivenom, except less antivenom is usually required for coral snakes. Up to 10 vials can be administered, although dosing recommendations are vague.

FORMULATION AND ACQUISITION

Crotalidae Polyvalent Immune Fab (Ovine)

Hospitals with native crotaline species within their region should maintain FabAV at all times.¹¹ Since rapidity of administration is the cornerstone of treatment, attempting to obtain antivenom at the time of an emergency may introduce a significant delay to treatment.

Antivenin (*Micrurus fulvius*) (Equine)

In order to obtain NASCA, contact the local poison center. Poison centers have access to the online Antivenom Index, which is useful when attempting to locate coral snake antivenom.

SUMMARY

- Definitive care of North American venomous snakebites includes antivenom and supportive care.
- If crotalid snakes are endemic to the catchment area of a hospital, Crotalidae polyvalent immune Fab should remain stocked and easily accessible at all times if cost does not make this practice prohibitive.¹¹
- In areas endemic with the eastern or Texas coral snake, supportive care may comprise the only treatment when antivenom is not easily obtained.
- Poison centers have access to the online Antivenom Index, which is useful when attempting to locate antivenom for a coral snake or a non-native snake envenomation. Local zoos may also be useful resources when attempting to locate exotic antivenom. Recommendations for these diverse antivenoms are difficult to make, but available package instructions should be followed, and preparations should be made to treat hypersensitivity reactions (Special Considerations: SC8).

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SC8 SPECIAL CONSIDERATIONS

Exotic Nonnative Snake Envenomations

Keith Boesen, Kelly A. Green Boesen, and Farshad “Mazda” Shirazi

HISTORY AND EPIDEMIOLOGY

The incidence of snakebites worldwide is difficult to ascertain, as there is no systematic reporting mechanism. This fact, when combined with the variable degree of confirmation of snakebites, makes the estimation of an accurate number extremely difficult. Attempts have been made utilizing available data from case reports in the literature, hospital records, surveys, and existing reporting systems. Current estimates place the worldwide annual incidence of snakebites as high as 5.5 million.^{11,36} Of these, roughly 50% are thought to be from venomous snakes.⁷ Estimated annual complications include 400,000 amputations³⁶ and approximately 100,000 deaths.^{11,36}

Snakes, while feared by many, are popular around the world as pets. The desire to keep venomous snakes as pets, which is typically illegal in the United States, and the implications throughout the world make the trade of exotic creatures second only to drugs and weapons on the international black market. In fact, the estimated annual worth of this trade in the United States alone is at least \$15 million.¹³

This Special Consideration will discuss the evaluation and management of patients evenomated in the United States by non-native snakes (also known as exotic snakes). From 2007 through 2011, the American Association of Poison Control Centers’ (AAPCC) National Poison Data System (NPDS) recorded 622 nonnative (“exotic”) snakebites, with 250 of these thought to be from a venomous species (Chap. 136).

This same database was reviewed from 1995 through 2004 to characterize the types of exotic snakes involved and circumstances for the envenomations. During that time period, there were 399 exotic snakebites reported, of which 350 were identified by genus and species for a total of 77 different varieties.²⁸ One US expert reported 54 consultations regarding bites from nonnative venomous snakes.¹⁹

In the AAPCC data, the most common family responsible for envenonmations was the viperidae, making up 50% of these bites. Of the Viperidae, almost half of all bites were from four different species: Godman’s Pit Viper, (Bothrops Godmanni), Gaboon viper (Bitis gabonica), Bush master (Lachesis mutus), and the Eyelash Viper (Bothrops schlegeli). The second most common family responsible for envenomations was the Elapidaes, resulting in 30% of US exotic snakebites. Sixty percent were from four different species: Indian Cobra (Naja naja naja), Monocellate Cobra (Naja naja kaouthia), Black Necked Spitting Cobra (Naja Nigricollis), and the King Cobra (Ophiophagus Hannah). The Indian Cobra was the most common snake identified during this study. Of note, there was one Atractaspidae bite (small scaled burrowing asp —Atractaspis microlepidota) and one Colubridae (Boomslang—Dispholidus typus).²⁸

TAXONOMY

The naming of snakes has evolved and the renaming currently continues at a rapid pace due to advances in DNA testing and ongoing research.^{23,24,35} There are 2700 snake species in the world,²³ of which approximately 20% of these are known to be venomous to humans.¹⁶ Venomous snakes are divided into four major families as shown in Table SC8–1.^{12,17,22–24,35}

TABLE SC8–1. Taxonomy of Snakes

Family	Subfamily	Representative Species
Elapidae	Elipinae	Cobras (<i>Naja</i> spp)
		King cobras (<i>Ophiophagus hannah</i>)
		Mambas (<i>Dendroaspis</i> spp)
		Kraits (<i>Bungarus</i> spp)
		Coral snakes (<i>Micrurus</i> spp and <i>Micruroides</i> spp)
	Hydrophiinae	Various sea snakes
	Laticaudinae	Sea kraits
Viperidae	Azemiopinae	Fea's viper is the only species (<i>Azemiops feae</i>)
	Viperinae (old or true vipers)	Russell's viper (<i>Vipera russelii</i>)
		Gaboon viper (<i>Bitis gabonica</i>)
		Saw-scaled viper (<i>Echis carinatus</i>)
		Death adders (<i>Acanthophis</i> spp)
	Crotalinae (pit vipers)	Rattlesnakes (<i>Crotalus</i> and <i>Sistrurus</i> spp)
		Copperheads (<i>Agkistrodon</i> spp)
Atractaspididae		Stiletto snakes (<i>Atractaspis</i> spp)
Colubridae		African boomslang (<i>Dispholidus typus</i>)
		Twig snake (<i>Thelotornis</i> spp)

The Elapidae family has a wide distribution in primarily tropical or arid desert settings in such continents as Asia, Australia, Africa, North America, and South America, with the sea snakes and sea kraits found in the Pacific and Indian Oceans.¹² Possibly the most well known of this family are the cobras, capable of unique characteristics such as hooding or spitting.¹² In the United States, there are three Elapidae snakes; the Eastern coral snake (*Micrurus fulvius fulvius*), the Texas coral snake (*Micrurus fulvius tenere*), and the Sonoran coral snake (*Micruroides euryxanthus*).

The Viperidae family, consisting of the three subfamilies (Azemiopinae, Viperinae, Crotalinae), exists throughout the world with a few exceptions. The majority of the snakes in this family can be divided into two main categories: old world vipers (also known as true vipers) and pit vipers.

ANTIVENOM INDEX

The Antivenom Index (AI) was created over 25 years ago as a joint effort of the Association of Zoos and Aquariums (AZA) and the AAPCC for the purpose of creating a database that would contain the location of all nonnative snake antivenoms stored throughout the zoos in the United States. For many years, this was kept in paper format at the Arizona Poison and Drug Information Center and was converted to an electronic database in 2006.

The AI can be searched by the common name or the scientific name of the venomous snake. This search will result in a list of possible snakes that match the description of the searched term. From there, a list of antivenoms active against that genus and species will be displayed, including which zoos stock them and how many vials are available. With this information, and some help from experts or the closest regional poison center, it can be determined where an adequate supply of antivenom exists and what arrangements are necessary to transport the antivenom to the health care facility where the patient in question is receiving care.

Additional information available in the AI includes package inserts for the antivenoms, many of which are translated into English, the expiration dates of the antivenoms, and additional information such as links to various recommendations on the housing, stocking, or administration of antivenoms.

Access to the AI is limited to the AZA and the AAPCC (all poison centers have access). The AZA have the ability to input updated stocking information, while the AAPCC members can view antivenom supplies. To access the AI, contact your local poison center at 1-800-222-1222. Southern Florida is unique in the storage and distribution of exotic antivenoms. The Miami-Dade Fire Rescue Venom Response Program maintains one of the largest repositories of exotic antivenoms for public use in the United States. They work with the local Poison Information Center in Miami for the clinical expertise to facilitate treatment of the envenomated patient.

VENOM TOXICITY

Exotic snake envenomations can and certainly do occur in the United States, most often during feeding or handling the snakes, cleaning the cages, or while milking the snakes for venom.^{19,34} The most common exotic envenomation between 1995 and 2004 involved male owners bitten in a private residence.²⁸ Of all bites that occurred between 1995 and 2004, 80% were the result of an Elapidae or Viperidae snake.²⁸ The venom components from these two families can be classified as neurotoxic, hemotoxic, and or myotoxic.^{5,15,34}

The venom from the Elapidae is associated with neurotoxic effects. Signs and symptoms consistent with neurotoxicity include blurred vision, paresthesias, ptosis, paralysis of facial muscles, difficulty swallowing, respiratory paralysis, and generalized flaccid paralysis.³³ The venom from the Viperidae is more commonly associated with hemotoxicity and myotoxicity, although some species also have neurotoxic effects. The hematologic signs and symptoms associated include petechiae, purpura, ecchymosis, or bleeding and changes in blood coagulation parameters, including platelets and fibrinogen, as well as prothrombin and partial thromboplastin time abnormalities. The activity of Viperidae venom on the clotting cascade occurs throughout the cascade, resulting in varying degrees of severity ([Chap. 60](#)). The signs and symptoms of myotoxins are consistent with local tissue injury and destruction, including swelling, necrosis, and blebs, and are accompanied by elevations of creatine kinase and aminotransferases with possible impairment of kidney function. While there are some classic differences in the presentation between snakes from the Elapidae and Viperidae families, it is important to note that there can also be similarities based on tremendous venom variability found from species to species and in snakes within the same species.¹⁵

CLINICAL PRESENTATION AND INITIAL MANAGEMENT

It is always important to consult with an expert to help identify the snake and determine specific signs, symptoms, and treatment options. Experts can be found within the AAPCC by calling 1-800-222-1222, or a local zoological society or serpentarium.

The clinical presentation of patients with exotic snake envenomation is extremely variable as the sequelae depend largely on the type of species involved and the same factors that influence the outcome of patients envenomated by better understood local snakes; premorbid condition of the individual, location of the bite, dose of venom delivered, and delay to health care. Local poison centers or regional experts may be familiar with species kept in area zoos as part of an emergency response system for treatment of zoo workers. People who maintain these animals as pets and subsequently are envenomated while handling become more difficult to treat. Several basic steps can be followed in initial management of these patients as outlined in [Table SC8–2](#).^{15,34}

TABLE SC8–2. General Approach to a Patient with an Exotic Snake Envenomation

Immobilize the bitten limb in a dependent position and rapidly transport the patient to a medical facility. If the eye is exposed, irrigation with water should be initiated.

Determine the time and location of bite, and mark the borders. Follow and mark the progression overtime.

Determine the species responsible for the bite. If the bite occurred at a zoo, the zoo may have a written plan for management of the specific species ready to accompany the patient (often a zoo employee) that includes the name of species, appropriate first aid, other management guidelines, and any antivenom that is available. Patients who own exotic snakes may know the identity but may use misleading or inaccurate common names. In which case, it may be necessary to contact a local herpetologist, who often can be found through the PCC, to identify the snake.

Standard resuscitation techniques are indicated for cardiovascular or respiratory failure. If there is massive extravasation or hypotension occurs, volume repletion will be necessary.

Physical examination should include signs of local envenomation (pain, swelling, bleeding, and bruising), painful and tender enlargement of lymph nodes, hypotension, spontaneous bleeding, ptosis, and myalgias. Laboratory assessment should include a complete blood count, coagulation profile, electrolytes and kidney function, creatine kinase, aminotransferase, urinalysis for blood and myoglobin, and an ECG.

Begin the process of locating, obtaining, and receiving permission to administer antivenom, even if it is unclear that foreign antivenom will be available or required.

Prepare for life threatening anaphylaxis if foreign antivenom is to be administered.

Due to uncertainties in prediction of clinical evolution and severity of symptom presentation, close monitoring in an intensive care unit is preferred for all patients with exotic envenomations. This will allow for appropriate clinical and laboratory monitoring specific to the needs of the patient. A minimum of 24 hours of hospital observation is indicated to assess delayed evolution of signs or symptoms.

Zoological and Exotic Antivenoms

Hospitals in the United States are not permitted to stock antivenoms for exotic snakes that are not produced for the US market and have not gone through the Food and Drug Administration (FDA) process for drug sale and administration. Zoos are permitted to stock antivenoms for the species of snakes locally housed for the purpose of treating an unintentional exposure. When zoological staff import antivenom from other countries, they must work with the FDA and the Centers for Biologics Evaluation and Research (CBER). The zoo facility is required to complete an Investigational New Drug (IND) Application, assign one or more local physicians who may administer the antivenom, record the name of each product and associated lot numbers, retain copies of the package insert for each product, and complete a statement that the antivenom is being imported solely for emergency use and will not be resold.³⁰ In addition, a Statement of Investigator must be prepared if any changes to the list of approved personnel for administration of the antivenom occur. When the antivenom is administered, a complete case report must be submitted to the director of CBER.

While zoos are permitted to have antivenom stocked at the facility, a recent study demonstrated that of the 106 zoos and 19 aquaria whose representatives responded, only 33 facilities stocked antivenom.³² In the 10 years prior to the study, these facilities reported a total of 39 separate incidents associated with venomous animals. It is unclear why so few facilities with potential for employee exposure do not carry the antivenom required for their local species, as it is possible that a commercially available product could prove essential. Most facilities reported some internal process to respond following an envenomation, including coordinating with the regional poison center, the local emergency medical services, and a local hospital, or have internally developed protocols.

The American College of Medical Toxicology (ACMT) recommends that a zoo or facility that houses exotic snakes have a written plan for management of an envenomation.¹ A study published in 2012 reviewed and tested the effectiveness of an emergency operation procedure.²¹ Zoo Atlanta, the Georgia Poison Center, and the Grady Health System established a procedure to manage an envenomation due to any of the 13 species of snakes housed at the zoo. All three organizations participated in the simulated drill and were evaluated on the functional aspects of coordinating patient care from the time of envenomation through stabilization. In this scenario, all personnel involved were previously alerted to the drill and had additional training as to what was to be expected. Even in this “best case” scenario that included preparation for a patient with an exotic envenomation, problems were still encountered. For instance, the protocol given to the hospital personnel lacked details about specific signs and symptoms expected, clear instructions for antivenom indication, and specific dosing and reconstitution instructions for the antivenom. There were also some general problems with personnel coordination. This study highlights the importance of having a plan in place prior to the emergency that includes the zoo facility, a regional poison center, and the treating institution.

Hospital Use of Exotic Antivenoms

Because exotic antivenoms are not readily available, it may be difficult to obtain the species specific correct antivenom in the appropriate amount. The local poison centers become a critical resources during this time. Often they can locate the closest supply and coordinate delivery. In the case of an envenomation at a zoo, the appropriate antivenom may arrive with the patient. In the case of the exotic snake owner, the poison center may help facilitate borrowing antivenom from local sources, such as zoos, known to stock the antivenom for emergency use. If there are no local sources, the poison center staff can easily access the AI to locate the closest available stock of antivenom. In one case report, it took a regional poison center 5 hours to locate and organize airborne delivery of the appropriate antivenom to the treating facility.¹³ A similar report described a 3 hour delay to administration even when the antivenom was present in the local zoo.⁹ During that delay, the patient required intubation.

Once brought to the facility, a series of steps must occur prior to the patient administration of the non FDA approved antivenom. The treating physician should contact the FDA to obtain approval to administer the antivenom as an IND under emergency use.²⁹ Contact numbers can be found at

<http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExempt>

In addition, the treating physician will need to obtain informed consent from the patient prior to administration. Since the antivenom is considered an investigational product, both the Institutional Review Board (IRB) and Drug and Formulary Committee must be notified and provide approval. Many IRBs have emergency processes to expedite such a request. If such approval cannot be obtained in a clinically relevant time, the IRB must be notified of the emergency treatment within 5 working days of the administration.^{1,21} The physician must also complete the appropriate IND paperwork (Form FDA 1571) and submit a comprehensive case report.³⁰

In addition to the legalities involved in using an investigational product, there are significant operational and logistical issues necessary to assure appropriate preparation of the product. The pharmacy department should be notified as soon as possible to allow the staff time to begin researching preparation instructions. Clinical pharmacists provide additional support for both the treating physician and drug preparation aspects in many emergency departments.²¹ The utilization of such individuals can greatly facilitate the medication preparation.

The package insert for the specific antivenom will be most helpful for the pharmacist in the preparation process. Specific instructions on diluents, storage, light or heat sensitivities, compatibility, and rate of administration are usually found in the package insert. If the specific antivenom product is known in advance, the pharmacist can begin to research these issues. Many package inserts are found in the Antivenom Index (AI) and can be obtained with the help of the regional poison center. However, not all package inserts are in English, and some must be translated or a translated copy must be located.¹⁶ Once preparation has begun, reconstitution of the antivenom can take minutes to hours to completely dissolve all the lyophilized particles. In addition to preparation, there is often a significant amount of documentation required when dispensing an IND approved drug. Having knowledge of the required procedure will expedite the administration of the antivenom.

Other Therapies

In principle, snake venoms should have some commonality, as they share the purposes of immobilizing or killing prey and beginning the digestive process, and have some common genetic linkage. In practicality, many venoms from snakes found from diverse area of the globe share constituents or antigenic characteristics.^{4,6,27,37} It may therefore be possible to use antivenoms derived against specific snakes in the treatment of envenomation from other snakes with related venoms. FDA approved coral snake antivenom was used in an experimental model of nonnative elapid envenomation.²⁶ Similarly, FDA approved crotalid antivenom demonstrated efficacy against mice treated with venom from *Crotalus durissus terrificus*, *Bothrops atrox*, and *Bitis gabonica*.^{18,25} In fact, a single case report demonstrates utilization of this principle of cross reactivity when a patient envenomated by *C. durissus terrificus* was successfully treated with US FDA approved CroFab.¹⁴ Such cross-reactivity should never be assumed based on common or taxonomic identification. The manufacturer of CroFab has listed experimental cross-reactivity with a number of species in the AI (Table SC8–3). The clinical decision to use CroFab for a patient envenomated by a non-US species of snake with known experimental cross-reactivity should be based on the severity of envenomation, the availability of species specific antivenom, and the risks associated with administration of species specific antivenom versus the risks of CroFab administration (Antidotes in Depth: A37).

TABLE SC8–3. Experimental Cross Reactivity Between CroFab and Nonnative Snakes^a

Genus	Species and Sub Species	Common Name	Natural Habitat
<i>Akistrodon</i>	<i>bilineatus bilineatus</i>	Cantil, common cantil, Mexican moccasin, tropical moccasin, Mexican cantil	Mexico and Central America
	<i>bilineatus howardgloydi</i>	Castellana	Honduras, Nicaragua, and Costa Rica
	<i>bilineatus lemosespinali</i>	Cantil, Mexican moccasin	Mexico and Central America
	<i>bilineatus russelii</i>	Cantil, common cantil, Mexican moccasin,	Mexico and Central America
	<i>bilineatus taylori</i>	Taylor's cantil, ornate cantil	Mexico
<i>Bothriechis</i>	<i>aurifer</i>	Yellow-blotched palm-pitviper, Guatemalan palm viper	Mexico and Guatemala
	<i>bicolor</i>	Guatemalan palm-pit viper, Guatemalan tree viper	Mexico, Guatemala, and Honduras
	<i>rowleyi</i>	Mexican palm pit viper	Mexico
	<i>schlegelii</i>	Eyelash viper	Central and South America
<i>Bothrops</i>	<i>asper</i>	Fer-de-lance	Mexico and South America
<i>Crotalus</i>	<i>basiliscus</i>	Mexican west coast rattlesnake, Mexican green rattler	Mexico
	<i>cerastes cerastes</i>	Sidewinder, horned rattlesnake, sidewinder rattlesnake	US and Northwestern Mexico
	<i>cerastes cerrobombus</i>	Sonoran Desert sidewinder, Sonoran sidewinder	US and Northwestern Mexico
	<i>durissus durissus</i>	South American rattlesnake, tropical rattlesnake	South America
	<i>durissus totonacae</i>	Totonacan rattlesnake	Northern Mexico
	<i>durissus tzabcan</i>	Middle American rattlesnake, Central American rattlesnake, tzabcan	Mexico and Central America
	<i>eryx eryx</i>	Baja California rattlesnake, Lower California rattlesnake	US and Northwestern Mexico
	<i>exsul (Ruber)</i>	Red diamond rattlesnake, red rattlesnake, red diamond snake	Baja California, Mexico
	<i>exsul exsul (Ruber)</i>	Red diamond rattlesnake, red rattlesnake, red diamond snake	Baja California, Mexico
	<i>intermedius gloydi</i>	Oaxacan small-headed rattlesnake	Mexico
	<i>lunomii</i>	Autlan rattlesnake	Mexico
	<i>lepidus cantaneri</i>	Rock rattlesnake	US and Mexico
	<i>lepidus klauberi</i>	Banded rock rattlesnake, green rattlesnake, green rock rattlesnake	US and Mexico
	<i>lepidus lepidus</i>	Rock rattlesnake, green rattlesnake, blue rattlesnake	US and Mexico
	<i>lepidus moalesus</i>	Durango rock rattlesnake	Mexico
	<i>lepidus morulus</i>	Rock rattlesnake	Mexico
	<i>mitchelli angelesensis</i>	Angel de la Guarda Island speckled rattlesnake	Angel de la Guarda Island in the Gulf of Mexico
	<i>mitchelli mitchelli</i>	Speckled rattlesnake, Mitchell's rattlesnake, white rattlesnake	US and Mexico
	<i>mitchelli muertensis</i>	El Muerto Island speckled rattlesnake	El Muerto Island Mexico
	<i>mitchelli pyrrhus</i>	Southwestern speckled rattlesnake, Mitchell's rattlesnake	US and Mexico
	<i>molossus estabaniensis</i>	San Esteban Island rattlesnake	San Esteban Island Mexico
	<i>molossus molossus</i>	Northern black-tailed rattlesnake, green rattler	US and Mexico
	<i>molossus nigrescens</i>	Mexican black-tailed rattlesnake	US and Mexico
	<i>molossus oaxacae</i>	Oaxacan black-tailed rattlesnake	Mexico
	<i>polystratus</i>	Mexican lance-headed rattlesnake, lance-headed rattlesnake	Mexico

<i>Ophryacus</i>	<i>undulatus</i>	Mexican horned pitviper, undulated pit viper	Mexico
<i>Porthidium</i>	<i>dunni</i>	Dunn's hognosed pitviper	Mexico
	<i>godmani</i>	Godman's montane pitviper, Godman's pit viper	Mexico and Central America
	<i>hespere</i>	Colima hognosed pitviper	Mexico
	<i>nasutum</i>	Rainforest hognosed pitviper, horned hog-nosed viper	Mexico, Central America, and South America
	<i>yucatanicum</i>	Yucatán hognosed pitviper	Mexico
<i>Sistrurus</i>	<i>novus</i>	Mexican pigmy rattlesnake, Mexican pygmy rattlesnake	Mexico

*"Cross reactivity" defined here as experimental evidence supplied by the manufacturer to the Antivenom Index. While clinical evidence of benefit is lacking, use of Crofab can be considered in these envenomations based on a risk-to-benefit analysis when species specific antivenom is lacking, delayed, or contraindicated (due to allergy), and the envenomation is a risk to life or limb.

The venom of many neurotoxic snakes interferes with neuromuscular transmission similar to neuromuscular blockers used in clinical medicine (Chap. 69). Neostigmine and other cholinesterase inhibitors increase the LD₅₀ of animals treated with *Naja haje haje* venom.¹⁰ Additionally, case reports and case series suggest a benefit of neostigmine with or without atropine in humans suffering neurotoxic snake envenomation.^{3,8,20,31} In these reports, patients typically received 0.5 to 1 mg of neostigmine IV immediately following pretreatment with 0.5 to 0.6 mg of atropine IV. In some cases, this is repeated

every 10 to 30 minutes based on response. Unfortunately, this benefit is not universal² and may be dependent on a number of factors, including differences in the mechanism of neuromuscular blockade between snake species. However, since the complications of atropine and neostigmine at these doses are small and there is a suggestion that they may reverse neuromuscular blockade, administration may be indicated if antivenom is unavailable or delayed. Further guidance can be found in Chap. 69 and in Table 69–5.

It is important to remember that there is a wide variation in the standards for preparation of antivenoms around the world. While many products are highly purified antibody fragments, some continue to use whole immunoglobulins that maintain the risk for anaphylaxis. Prior to antivenom administration, preparations must be made to treat life-threatening anaphylaxis. The appropriate level of nursing care and monitoring should be available, IV access should be secured, typical drugs (epinephrine, corticosteroids, antihistamines) and airway management tools should be present at the bedside.

SUMMARY

- Many venomous snakes are available in homes and zoos far from their native habitats.
- It is essential to develop sophisticated systems of care in collaboration with poison centers and zoos assuring preparedness for worker or hobbyist injury.
- The use of internationally prepared antivenom may be life-saving and hazardous. The risks can be limited by understanding the risks and benefits of available internationally prepared antivenoms.
- The Antivenom Index, available to poison centers and the AZA, provides invaluable information about matching an antivenom to a particular snake, location of antivenoms, package inserts, and often English translations of foreign package inserts.
- The use of antivenoms not FDA approved must follow the rules for an IND.
- FDA approved antivenoms may have cross reactivity against some nonnative snakes.

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M. OCCUPATIONAL AND ENVIRONMENTAL TOXINS

CASE STUDY 11

History A rapid response team (RRT) was called to the endoscopy suite because a patient developed shortness of breath and decreased oxygen saturation. On arrival, the responders found a 55 year-old man with the following vital signs: blood pressure, 166/112 mm Hg; pulse, 142 beats/min; respiratory rate, 40 breaths/min; oxygen saturation, 87% on 4 liters/minute of oxygen via nasal cannula. The man had a history of Barrett's esophagus and obstructive sleep apnea (OSA) and had to undergo periodic upper gastrointestinal endoscopy as a screening procedure for cancer.

The gastroenterologist who called the RRT reported that the patient had no complaints during the pre-procedural time out and that the following vital signs had been recorded: blood pressure, 142/88 mm Hg; pulse, 88 beats/min; respiratory rate, 16 breaths/min; tympanic temperature, 97.6°F (36°C); and oxygen saturation, 99% on room air. Just prior to administration of conscious sedation, the patient became uncomfortable and complained of shortness of breath. Within a few minutes his vital signs deteriorated and he became cyanotic.

Immediate Assessment and Management The patient was immediately given high flow oxygen via a 100% nonrebreather mask, and although his respiratory rate and pulse improved somewhat, his oxygen saturation remained between 86% and 88%. Physical examination was notable for an ill appearing man who could only speak in short sentences. Although he denied chest pain, review of systems was positive for headache and nausea. His skin and nailbeds were cyanotic, his chest was clear, and his heart was regular and tachycardic without extra sounds. The patency of his intravenous line was confirmed, and an electrocardiogram was obtained and showed sinus tachycardia without ST segment or T wave changes suggestive of ischemia or infarction. When he failed to respond to supplemental oxygen, he was moved to the emergency department (ED).

On arrival to the ED, the following vital signs were obtained: blood pressure, 152/104 mm Hg; pulse, 122 beats/min; respiratory rate, 32 breaths/min; tympanic temperature, 97.8°F (36.5°C); oxygen saturation, 88% on 100% oxygen; and end tidal CO₂, 28 mm Hg.

What Is the Differential Diagnosis? This patient presented with hypertension, tachycardia, tachypnea, cyanosis, and decreased oxygen saturation. The most common causes for these findings are cardiac and pulmonary disease. Hypoxia and cyanosis in a normal environment (breathing a normal FiO₂) can result from a shunt, ventilation-perfusion mismatch, diffusion abnormalities, or pump failure (Chaps. 17 and 29). The absence of underlying heart disease, unremarkable electrocardiogram, pulse and blood pressure that is adequate for tissue perfusion, and clear chest examination essentially excludes these disorders, although laboratory and radiologic confirmation should be obtained (see following sections). When cardiac and pulmonary disorders are excluded, dyshemoglobinemias should be considered, specifically methemoglobinemia and sulfhemoglobinemia (Chap. 127).

What Immediate Diagnostic and Therapeutic Interventions Are Indicated? The patient was maintained on 100% oxygen, and bilevel positive airway pressure (BiPAP) was started while preparations were made for endotracheal intubation. Reasonable initial testing would include a chest radiograph, bedside echocardiogram, and an arterial blood gas (ABG) analysis. In many sections of this book the relationship between a venous blood gas (VBG) and an ABG are discussed (Chap. 29). While under most clinical circumstances a VBG is adequate, when evaluating a patient with decreased oxygen saturation an ABG is preferred, as the VBG will nearly always demonstrate desaturation as oxygen is extracted across the tissue capillary bed.

A chest radiograph showed no cardiac or pulmonary disease, and an ABG was obtained. The resident commented that while she was certain that the blood was obtained from an artery, it looked dark as if it were venous blood. The results demonstrated the following: pH, 7.32; PCO₂, 33 mm Hg; PO₂, 426 mm Hg; with an oxygen saturation of 100%. The results were interpreted as a primary metabolic acidosis with respiratory compensation (respiratory alkalosis). This corresponded to a serum bicarbonate concentration of approximately 16 mEq/L (Chap. 19) and reinforced the clinical impression that the patient was significantly ill.

What Rapid Clinical and Laboratory Analyses Can Confirm the Diagnosis? The combination of cyanosis with a low oxygen saturation by pulse oximetry, failure to respond to supplemental oxygen, dark colored blood, and a normal or high PO₂ on the ABG is essentially diagnostic of methemoglobinemia or sulfhemoglobinemia (Chaps. 29 and 127). When methemoglobinemia is suspected, the color of the blood is related to the methemoglobin level (Fig. CS11-1). While confirmation can and should be obtained via cooximetry analysis of either venous or arterial blood, the clinical information above is sufficient to initiate treatment if cooximetry is either unavailable or delayed.

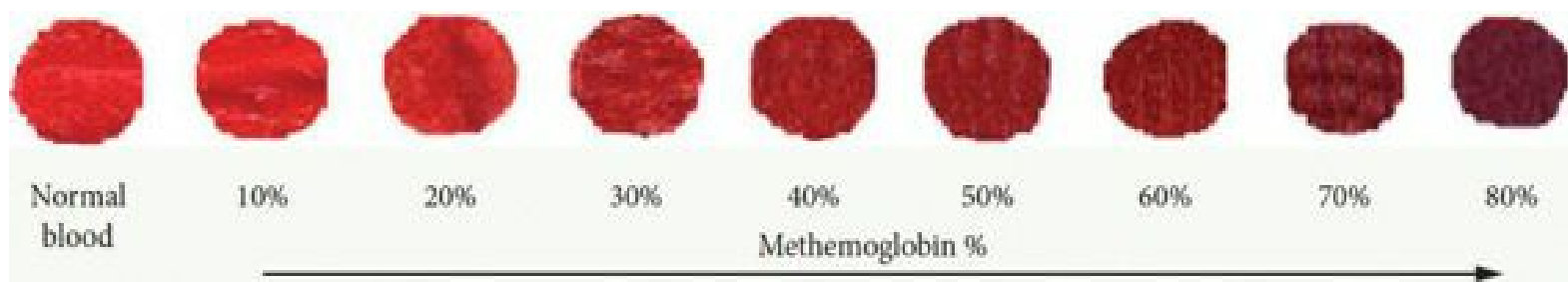


FIGURE CS11-1. The relationship between methemoglobin level and blood color. This figure demonstrates the relationship between methemoglobin level and the color of blood. If anticoagulated blood is placed on a white background, the methemoglobin level can be estimated accurately by comparison with the scale. It is important to note that while normal anticoagulated venous blood will oxygenate spontaneously (become more red over time) if exposed to room air, methemoglobin is incapable of extracting oxygen from air and will remain dark over time. (Reproduced with permission from: Shihana F, Dissanayake DM, Buckley NA, Dawson AH: A simple quantitative bedside test to determine methemoglobin. *Ann Emerg Med.* 2010;55:184–189. Copyright Elsevier.)

Further Diagnosis and Treatment Venous blood sent for cooximetry revealed: total hemoglobin, 14.6 gm/dL; oxyhemoglobin, 52%; deoxyhemoglobin, 6%; and methemoglobin, 43%. The patient was given 100 mg of methylene blue by slow intravenous administration (Antidotes in Depth: A42). Within about 5 minutes of starting the infusion, his oxygen saturation by pulse oximetry dropped to 64% without a change in his vital signs. Over the next 15 minutes his oxygen saturation gradually increased to 99%, and his respiratory rate, heart rate, and blood pressure normalized. His shortness of breath resolved. A repeat methemoglobin level taken 30 minutes after the end of the methylene blue administration was 3%. The patient remained well.

Further discussion with the gastroenterologist revealed that there were concerns over the patient's history of OSA and the potential complications of procedural sedation, so extensive use of topical anesthesia was attempted prior to the procedure. The medical administration record demonstrated that the local anesthetic chosen contained benzocaine (the most common cause of acquired methemoglobinemia in hospitalized patients), although the exact dose delivered was not documented. Since the generation of methemoglobin following benzocaine administration is dose dependent and occurs more slowly (peak effect is delayed several minutes) than the rate of anesthesia (peak anesthesia in 15–30 seconds), it is easy to conceptualize how a patient can be given an overdose of benzocaine when the appropriate time for maximal anesthesia is not taken before administering a repeat dose. Both the patient and physician were educated on the risks of topical anesthetics, and anesthesia was consulted to assist with airway management and sedation during his rescheduled endoscopy. Two weeks later he returned for his procedure, which was successfully accomplished following combined therapy with topical lidocaine and ketamine for procedural sedation. While he may have been able to tolerate an appropriate dose of benzocaine, it was decided to try an alternative approach.

123 INDUSTRIAL POISONING: INFORMATION AND CONTROL

Peter H. Wald

Many important problems are associated with the diagnosis and treatment of occupational and environmentally caused diseases, including (1) the ability to correctly establish the diagnosis, (2) the ability to correctly treat the condition, and (3) the ability to correctly act on any public health issues related to the exposure. The following discussion instructs clinicians on how to assemble adequate information to achieve the appropriate diagnosis and treatment.

TAKING AN OCCUPATIONAL HISTORY

Because time spent at work is a large percentage of many people's day, the occupational health history should be a routine part of any medical history. This is especially true of patients who present to health care with potential xenobiotic exposures. The history should include several brief survey questions. Positive responses then lead to a more detailed occupational and environmental history, which is composed of three elements: present work, past work, and nonoccupational exposures.

The Brief Occupational Survey

The following three questions should be incorporated into the occupational survey:

Exactly what kind of work do you do?

Are you exposed to any physical (radiation, noise, extremes of temperature or pressure), chemical (liquids, fumes, vapors, dusts, or mists), or biologic hazards at work ([Table 123–1](#))?

TABLE 123–1. Hazard Classes, Hazard Types, and Several Common Examples Found in the Workplace

<i>Hazard Class</i>	<i>Hazard Type</i>	<i>Examples</i>
Physical hazards	Human–machine interfaces	Repetitive motion Lifting Vibration Mechanical trauma, electric shock
	Physical environment	Temperature Pressure Long or rotating shifts
	Energy	Ionizing radiation: x-ray, ultraviolet Nonionizing radiation: infrared, microwave, magnetic fields Lasers Noise
Chemical hazards	Solvents	Aliphatics, aromatics, alcohols, ketones, ethers, aldehydes, acetates, peroxides, halogenated compounds
	Metals	Lead, mercury, cadmium
	Gases	Combustion products, irritants, simple and chemical asphyxiants, oxygen-deficient environments
	Dusts	Organic (wood) and inorganic (asbestos or silica), nano-materials
	Pesticides	Organic chlorine, organic phosphorus, carbamate
	Epoxy resins and polymer systems	Toluene diisocyanate, phthalates
Biologic hazards	Bacteria	<i>Bacillus anthracis</i> , <i>Legionella pneumophila</i> , <i>Borrelia burgdorferi</i>
	Viruses	Hepatitis, HIV, Hantavirus
	Mycobacteria	<i>Mycobacterium tuberculosis</i>
	Rickettsia and <i>Chlamydia</i>	<i>Chlamydia psittaci</i> , <i>Coxiella burnetii</i>
	Fungi	<i>Histoplasma capsulatum</i> , <i>Coccidioides immitis</i>
	Parasites	<i>Echinococcus</i> spp, <i>Plasmodium</i> spp
	Envenomations	Arthropod, marine, snake
	Allergens	Enzymes, animals, dusts, insects, latex, plant pollen dusts

Are your symptoms related in any way to starting or being away from work? For example, do the symptoms start when you arrive at work at the beginning of the day or week or when you work at a specific location or during a specific process at work?

Present Work

Collected data on a person's present job reveal what his or her present exposures may be, which can help formulate the differential diagnosis for the employee's complaints. These data can be systematically collected by focusing on four areas: specifics of the job, hazardous exposures, health effects, monitoring, and control measures (Table 123–2).

TABLE 123–2. Components of an Occupational Health History

Current work history
 Specifics of the job
 Employer's name

Type of industry

Duration of employment

Employment location, hours, and shift changes

Description of work process

Unusual activities of the job that are occasional (eg, maintenance)

Adjacent work processes

Hazardous exposures (Table 123-1)

Possible health effects

Suspicious health problems

Temporality of symptoms

Specific distribution of symptoms (rash, paresthesias)

Affected coworkers

Presence or absence of known risk factors (smoking, alcohol)

Workplace sampling and monitoring

Individual or area air monitoring

Surface sampling Biologic monitoring

Medical surveillance records

Exposure controls

Administrative controls

Process engineering controls

Enclosure

Shielding

Ventilation

Electrical and mechanically controlled interlocks

Personal protective equipment

Respirators

Protective clothing

Earplugs, glasses, gloves, face shields, head and foot protection

Work history (prior)

Review current work history for all past employment

Nonoccupational exposures

Secondary employment

Hobbies

Outdoor activities

Residential exposures

Community contamination

Habits: tobacco, alcohol, other xenobiotics

Specifics of the Job. It is not sufficient simply to inquire what the patient does for a living. Similar to health care professionals, workers in other industries have their own jargon. When asked for a job title, a patient may respond with a title that has meaning only in his or her trade. Even if the job title is recognizable, it may not provide any useful information and, in fact, may be misleading. A secretary working in a small plastics manufacturing plant may have occupational exposures that are quite different from a secretary who works for a law firm.

The important specific information requested should include the name of the employer, type of industry, duration and location of employment, hours and shift changes, process description (including unusual occasional activities), and adjacent processes. The employer may be able to provide information about materials used at the plant. However, clinicians should always obtain the patient's permission before calling the employer. A patient may be fired or otherwise discriminated against (despite legal protections) for suggesting that health problems are work related.

It is important to learn precisely what happens in the patient's immediate work environment because nearby work processes may contribute other exposures. If possible, the patient should be asked for a diagram of the work area. The patient also should be questioned about job process changes. A previously safe job may have been changed to a potentially dangerous job without a change in the patient's job title.

The patient should describe exactly what he or she does on any given day and for how long. Unusual and nonroutine tasks, such as those performed during overtime, maintenance, or in an emergency, should also be described. The primary job may not involve xenobiotics, but the patient may nevertheless perform tasks that entail unprotected exposure to a toxic xenobiotic.

Hazardous Exposures. The names or types of all xenobiotic to which the patient may be exposed are important in determining potential adverse effects and any relationship to the patient's complaints. It is important to elicit any recent changes in suppliers of these products because even a slight change in the formulation of a xenobiotic may cause adverse effects in an individual who previously had no problems working with that xenobiotic. This information may be obtained from the material safety data sheet (MSDS), an important but not universally reliable source of information. In addition to adverse health effects, the MSDS contains information on chemical reactivity, safety precautions, and other data. As an initial step, the MSDS should be requested and reviewed; however, information provided on health effects should be confirmed using other resources. Four major concerns result from relying solely on the MSDS: (1) some MSDS forms are excellent, but others are incomplete and inadequate; (2) components of a product that are regarded as "trade secrets" do not have to be revealed; (3) components that have important health effects (eg, solvent or solid carriers of the "active ingredients") often may be grouped together under "inert ingredients" without being specifically named; and (4) process intermediates or unintended byproducts of a manufacturing process may not be identified. However, if a xenobiotic is believed to be related to a health effect, manufacturers are required to release to a physician all information, including trade secrets and inert components.

Exposures to physical and biologic xenobiotics can be elicited during the review of job processes. Most patients know what they are, or have been, exposed to, even if they do not know the exact name of the xenobiotics or its medical effects.

Health Effects. Significant occupational exposures usually cause medical effects, although some do so only after a substantial latency period. Key areas of inquiry include suspicious health problems, temporality of symptoms, and affected coworkers. These data, combined with workplace monitoring and sampling data, may help in determining whether the patient is experiencing a work-related illness ([Table 123–3](#)). Patients may suspect that their illness or complaint is work related, especially when symptoms occur at the workplace and improve or disappear over the weekend or during a vacation. Specific distribution of findings, such as a rash in a bilateral glove pattern, is supportive of an occupational cause. Coworkers with similar complaints (not necessarily of the same severity) should raise suspicion that a workplace exposure is responsible for a particular symptom complex. Diseases such as lung cancer or hepatitis, which occur in the absence of known risk factors such as smoking and alcohol, must be epidemiologically investigated

TABLE 123–3. Evidence Supporting Work-Relatedness of Occupational Disease

Known or documented exposure to a causative xenobiotic
Symptoms consistent with suspected workplace exposure
Suggestive or diagnostic physical signs
Similar problems in coworkers or workers in related occupations
Temporal relationship of complaints related to work
Confirmatory environmental or biologic monitoring data
Scientific biologic plausibility
Absence of a nonoccupational etiology
Resistance to maximum medical treatment because employee continues to be exposed at work

Workplace Sampling, Monitoring, and Control. Control of workplace hazards begins with an industrial hygiene monitoring program. Employers are required to give results of both area and individual sampling to employees. A medical surveillance program that includes periodic spirometry and respiratory questionnaires usually indicates that the patient works with a potential respiratory toxin. A medical surveillance program that includes biologic monitoring for a specific xenobiotic may also provide an immediate clue to what may be causing the patient's complaints. Finally, if the patient knows exactly what he or she is working with, the physician can usually quickly determine whether any of the xenobiotics are compatible with the patient's complaints. Many companies do not perform routine industrial hygiene monitoring or medical surveillance. Individuals who become sick or ill at work are often sent to local emergency departments. In such situations, emergency physicians may need to perform the type of time-consuming, detailed occupational history outlined here or be able to consult or refer immediately to appropriate physicians or clinics.

Portions of [Table 123–2](#) and the following section on Evaluation and Control of Workplace Hazards detail the types of controls typically used in workplaces. It is important to determine whether the workplace uses any of the following control measures; engineering controls, work practice protocols, administrative controls, or personal protective equipment. The existence of control measures usually indicates that the employer recognizes and has attempted to deal with a hazardous exposure.

Past Work

It is important not to limit the occupational history to the patient's current workplace and job. Many occupational diseases have long latency periods between xenobiotic exposure and initial development of clinical symptoms. In addition, patients may have been exposed to xenobiotics at work that make them more sensitive to other environmental xenobiotics. For example, someone who developed asthma secondary to a previous workplace exposure may have asthma attacks upon exposure to simple irritants in the current workplace. When taking an in-depth occupational history, issues that may be relevant to the current work history as well as for each previous job should be explored.

Nonoccupational Exposures

Workers may be exposed to toxic xenobiotics in the course of pursuing secondary employment, hobbies, or outdoor activities in contaminated or industrial areas. Residential exposures, such as those from gas and wood stoves, chemically treated furniture and fabrics, and pest control, may be relevant. It is important to ask patients about these potential exposures before focusing entirely on exposures in their primary place of employment. This obviously includes relevant issues from the social history, such as tobacco, alcohol, and both licit and illicit drug use.

EVALUATION AND CONTROL OF WORKPLACE HAZARDS

Initial Workplace Evaluation

The Occupational Safety and Health Act (OSHA) places legal responsibility for providing a safe and healthy workplace on the employer. The rationale for this placement of responsibility is that the employer is in the best position to make any modifications necessary to prevent additional work-related illness and injury. The physician may wish to initiate a dialogue with a patient's employer to promote preventive action but should do so only with the patient's informed consent. The initial treating physician may also refer the patient to an occupational medicine specialist, who is specifically trained to manage work-related exposures and diseases and initiate prevention programs.

Because the initial contact may influence subsequent events, it is important for the health care provider to identify an individual with an appropriate administrative role, such as someone in the company's medical department, the patient's supervisor, the plant's safety officer, or the shop manager. If management is willing to examine the hazardous conditions, a plant walk-through inspection can provide unique insight and information usually unavailable in an office setting. A walk-through by an occupational medicine specialist makes it easier to understand the work environment, identify safety and

health hazards, assess control measures, and recognize opportunities for prevention. It also facilitates a good working relationship with key personnel in management and labor. The physician, who cares for a number of patients who work in the plant or who provides health services to the workers through the company or labor union, may wish to be involved in the walk-through. Assistance with plant inspections can be obtained from occupational health specialists, such as occupational physicians or industrial hygienists.

Industrial Hygiene Sampling and Monitoring

Equipment is available to measure airborne concentrations of toxic xenobiotics, noise levels, radiation levels, temperature, and humidity. Employees can be fitted with pumps and other devices to measure individual exposure concentrations at the breathing zone, where, depending on what controls are used, concentrations may vary from those in the general work area. These results then can be compared with OSHA standards and other available standards to help determine the extent of the hazard and to formulate a control plan. OSHA requires that employers monitor the concentrations of only a few specific hazards, including arsenic, asbestos, benzene, cadmium, chromium, cotton dust, ethylene oxide, formaldehyde, lead, noise, and vinyl chloride. A complete listing of all xenobiotics is available in the OSHA standard 29 CFR 1910 Part Z—Toxic and Hazardous Substances (http://www.osha.gov/pls/oshaweb/owastand.display_standard_group?p_toc_level=1&p_part_number=1910). In addition, monitoring is required for certain operations such as hazardous waste operations or entering a confined space that may have an oxygen-deficient atmosphere. Ongoing sampling of the remaining estimated 60,000 xenobiotics used in the workplace is not required. Where industrial hygiene sampling is performed, OSHA's medical access standard gives any exposed worker or his or her representative the right to review and copy all sampling data.

Control of Workplace Exposures

Control of exposures in the workplace has traditionally relied on a hierarchy of methods to protect workers. The preferred solution is complete elimination of the exposure by substitution. When substitution is not possible, the next preferred method consists of shielding for workers to reduce their exposure. The least favored method is personal protective equipment, which requires a positive action from the worker.

Engineering Controls. Health and safety professionals prefer, and OSHA regulations require when feasible, the use of engineering controls to reduce worker exposure to hazardous xenobiotics. These controls intercept hazards at their source or in the workplace atmosphere before they reach the worker. Engineering controls include redesign or modification of process or equipment to reduce hazardous emissions; isolation of a process through enclosure; automation of an operation; and installation of exhaust systems that remove hazardous dusts, fumes, and vapors. Local exhaust systems, such as hoods, are preferable to general dilution ventilation because the former removes contaminants closer to their source and at relatively high rates.

Engineering controls have several advantages over control measures focused on the worker. Properly installed and maintained engineering controls are reliable and consistent, and their effectiveness does not depend on human supervision or interaction. They can simultaneously limit exposure through several routes, such as inhalation and skin absorption. In addition, engineering controls do not place a burden on the worker or interfere with worker comfort or safety.

Work Practices. Work practices are procedures that the worker can follow to limit exposure to hazardous xenobiotics. Examples are the use of high-powered vacuum cleaners instead of compressed air cleaning and pouring techniques that direct hazardous xenobiotics away from the worker. Although not as effective as engineering controls, work practice can be a useful component of an overall hazard control program.

Administrative Controls. Administrative controls reduce the duration of exposure for any individual worker or reduce the total number of workers exposed to a hazardous xenobiotic. Examples are rotating workers into and out of hazardous areas so that no single worker is exposed full time and scheduling procedures likely to generate high concentrations of xenobiotics, such as cleaning or maintenance activities, during nights or weekends. Administrative controls sometimes have the side effect of exposing more workers, albeit at lower doses that are hoped do not cause health effects.

Personal Protective Equipment. Personal protective equipment, such as respirators, earplugs, gloves, and hard hats, is the least effective but most commonly used control method. Personal protective equipment may be the only viable protection strategy when other controls are not practical but can also be used as an additional layer of protection in the presence of engineering controls. Some employers may favor personal protective equipment over the institution of more costly engineering and administrative controls.

Respirators and other forms of personal protective equipment often are hot, uncomfortable, and awkward to wear and may make it difficult for workers to breathe, speak, or hear, depending on the equipment involved. Consequently, workers often remove or refuse to wear the protection. Respirators place extra stress on the heart and the lungs. Both respirators and earplugs limit conversation and therefore present a safety hazard in themselves.

Because personal protective equipment does not stop a hazard from entering the environment, the worker is entirely vulnerable to exposure if the equipment fails. In addition, generally only one route of exposure is protected. For example,

the commonly used half-mask respirator still leaves the skin and eyes exposed.

Choosing the right piece of personal protective equipment can be difficult and may depend on the nature and extent of the hazard. For example, each type of respirator is rated for the amount of protection it provides; as expected, the cost of a respirator increases with its protection factor. Use of the wrong type of respirator can leave the worker insufficiently protected.

Half-mask respirator cartridges are available in various colors that are coded to the xenobiotic filtered out of the breathing environment. If the wrong cartridge is used, the worker is essentially unprotected from the hazardous contaminant. To be effective, a respirator must be meticulously fit to the individual worker. Failure to achieve a proper seal negates the respirator's usefulness. High cheekbones, dentures, scars, perspiration, talking, head movements, and facial hair can prevent a proper seal. These factors often are ignored or overlooked by an employer who adopts a "one-size-fits-all" policy.

Even if each employee is provided the proper respirator, the respiratory protection program may not be effective. OSHA requires that employers institute a program of proper fit testing, cleaning, maintenance, and storage of respirators, which can be at least as costly as the institution of engineering controls.

In some instances, use of personal protective equipment may be unavoidable. An employer may need to control a hazardous exposure through a combination of measures, such as engineering controls and personal protective equipment. Ideally, the employer is using personal protective equipment as a control of last resort and in strict compliance with OSHA standards.

Worker Education and Training. Regardless of the control measures used, workers and supervisors must be educated in the recognition and control of workplace hazards and the prevention of work-related illness and injury. The OSHA Hazard Communication Standard requires that employers train workers in ways to detect the presence or release of hazardous xenobiotics, their physical and health hazards, methods of protection against the hazards, and proper emergency procedures, as well as how to read the labeling system and how to read and use an MSDS.

With the passage of federal, state, and local right-to-know laws, many consulting companies now offer hazard communication training. These programs are of uneven quality. Those that tend to focus on acute hazards, ignore chronic effects, and that emphasize personal protective equipment over other control measures may not be effective in training workers to recognize and control hazardous xenobiotics.

Medical Monitoring. Together with industrial hygiene monitoring, exposure control, and worker education, a medical monitoring program can form the foundation of an effective occupational disease prevention regimen. However, medical monitoring is fraught with technical and ethical pitfalls. Medical monitoring encompasses both medical screening and medical surveillance.

Medical screening refers to the cross-sectional testing of a population of workers for evidence of excessive exposure or early stages of disease that may or may not be related to work and that may or may not influence the ability to tolerate or perform work.

Preemployment and preplacement physical examinations are another type of medical screening that are often favored by employers. The Americans with Disabilities Act (ADA) and the newer ADA Amendment Act of 2008 (ADAAA) regulate the timing, scope, content, and use of these examinations and the information gathered. Comprehensive resources for information on the ADA are available at <http://www.adata.org>. The ADA prohibits "preemployment" medical examinations and inquiries. After a job offer has been made, "preplacement" examinations and inquiries can be conducted to determine whether an applicant can perform a job safely and effectively. The physician evaluates the individual's medical history, current symptoms, and physical laboratory findings to determine whether he or she currently has the physical or mental abilities necessary to perform the essential functions of the job, and whether the individual can do so without posing a "direct threat" to the health or safety of him- or herself or others. This threat must be more than theoretical and cannot be based on some future time; the threat must be concrete and relatively immediate.

Few tests and few conditions are good predictors of either the ability to perform a task or increased susceptibility to a particular exposure. Many workers and their advocates view preplacement examinations as a way for employers to choose the "fittest" worker and to avoid their legally mandated obligation to provide a safe and healthy workplace for all workers. This is not true for most employers. Physicians asked by an employer to perform preplacement examinations should be sure that each component of the examination relates to the actual job the individual is being hired to perform and the actual risks he or she will encounter on the job. Both the law and sound occupational medical practice dictate that the employer's attention and efforts be directed toward redesign of the job and its hazards so that it is safe and healthy for all workers to perform.

Medical surveillance refers to the ongoing evaluation, by means of periodic examinations, of high-risk individuals or potentially exposed workers to detect early pathophysiologic changes indicative of significant exposure. OSHA requires little in the way of medical surveillance, although several OSHA standards require employers to institute medical surveillance programs, for example, for workers exposed to asbestos, arsenic, cadmium, chromium, vinyl chloride, lead, and ethylene oxide. Depending on the potential exposure, medical surveillance may include a history and physical examination, chest radiography, pulmonary function tests, blood and urine tests, and other laboratory evaluations.

A medical surveillance program may also include biologic monitoring, the purpose of which is not to identify the occurrence of disease but to measure the uptake or presence of a particular xenobiotic or its metabolites in body fluids or organs. Ideally, this occurs before any pathophysiologic damage occurs. Consequently, biologic monitoring is potentially a primary preventive measure. For example, several volatile organic compounds, such as benzene and toluene, if inhaled or absorbed through the skin, produce metabolites that can be measured in urine.

Biologic monitoring can have some advantages over air monitoring because biologic monitoring measures the actual absorption of a xenobiotic by the body as opposed to ambient concentrations in the workplace. The amount of a chemical absorbed may not be closely correlated to ambient xenobiotics for several reasons, including differences in individual work habits, use and effectiveness of personal protective equipment, dermal absorption of xenobiotics unrelated to their concentration in the air, and nonoccupational exposures.

Biologic monitoring, however, has several significant limitations. For most xenobiotics, there are no standards of “normal” or “safe” concentrations against which results can be compared. The timing of specimen collection is critical because different xenobiotics have different biologic half-lives. The storage and handling of specimens and interpretation of results are vulnerable to error. Nevertheless, if carefully designed and implemented, biologic monitoring can be a useful complement to a comprehensive industrial hygiene program.

With the exception of biologic monitoring, medical monitoring programs identify disease processes already underway and therefore are, at best, a form of secondary prevention. If workers are identified as having higher than acceptable exposures, they should be removed from exposure with continuing pay while their concentrations decline, and while the employer investigates any potential breakdown in the workplace controls. To be an effective preventive measure, these programs must be coordinated with environmental monitoring programs that identify the nature, source, and extent of workplace hazards; implementation of engineering controls and other measures that control hazards as close as possible to the source; and worker education programs that, at a minimum, inform workers of exposures, their effects, and proper control measures.

Both medical monitoring programs and preplacement examinations raise issues of doctor–patient confidentiality. Employee medical records should be available only to the corporate medical or first aid department and not to the personnel office and general management. Unless required by statute, employers should never be told the results of history, physical, or diagnostic examinations unless the patient gives his or her written consent. The examining physician need only inform the employer that an individual is or is not capable of performing a particular job with or without specified restrictions. The physician should not disclose diagnostic information about medical conditions.

INFORMATION RESOURCES

Health care professionals require information on industrial toxins in a number of situations, ranging from caring for an acutely ill patient in an emergency department, when information must be obtained quickly, to caring for a patient with chronic symptoms that may reflect an occupational disease. However, the use of information resources depends on the proper identification of the xenobiotic in question. If the xenobiotic, its generic name, and ingredients are not known, the research process becomes more difficult.

The practitioner should take a logical approach to seeking information about industrial xenobiotics. First, the xenobiotic must be identified by its generic name. This can be done by reviewing the MSDS or by contacting poison centers (PCs), the employer, manufacturer, unions, or government agencies. MSDSs also are available by searching online. A good starting point to find MSDSs on the Internet is <http://www.ilpi.com/MSDS/index.html>, but typing “MSDS” into any online search engine yields a number of sites offering data sheets.

Poison Centers

Regional PCs can provide assistance even when the exact chemical name is unknown because information on xenobiotics and their management may be cross-referenced by trade name and manufacturer. Moreover, Specialists in Poison Information can usually suggest additional resources. Most PCs have computerized listings of poisons that are updated regularly. The best-known system is POISINDEX (Truven Health Analytics, Ann Arbor, MI). Subscribers to this system receive quarterly updates of an alphabetically organized listing of approximately 500,000 industrial and nonindustrial xenobiotics. The system includes trade names, the components, and the concentrations, when available, of each xenobiotic listed. These elements are then cross-referenced to management protocols. The name of the manufacturer is also listed.

Employers and Manufacturers

Many state and federal laws require manufacturers to generate, retain, and disclose information that may help physicians care for persons with work-related health problems. Scientific information, exposure data, information on health effects, and collected medical data are included in the types of information that must be retained.

The Chemical Transportation Emergency Center (CHEMTREC; 800-424-9300; <http://www.chemtrec.com>), sponsored

by the Chemical Manufacturers Association, has as its primary responsibility providing information to health care practitioners responding to hazardous spills. However, it also provides information on commercial products found in patients’ workplaces. Employers are required to furnish this information to employees in the form of MSDSs.

Worker’s Compensation Insurance Carriers

Smaller companies often lack internal health and safety staffs. Worker’s compensation or company risk insurance carriers may have valuable information about exposures and controls in the workplace. As a service to their clients, carriers often do walk-throughs and hazards evaluations for clients that lack these resources and suggest appropriate engineering controls. Health care professionals can contact the carrier directly to see what additional information is available.

Regulatory Agencies

OSHA requires chemical manufacturers to create an MSDS for each chemical they produce, and employers who use chemicals must retain the MSDSs in the workplace. Required information includes xenobiotic and common names; physical, safety, and health hazard data; exposure limits; precautions for safe handling and use; generally applicable control measures; and emergency and first aid procedures. The OSHA Hazardous Communication Standard requires individual employers to provide employees with information on the xenobiotics used in their workplaces. With the patient’s permission, a call to the plant manager, foreperson, or safety officer may be all that is necessary to determine the name of the xenobiotic in question. Employers may be able to provide information on exposure concentrations in the patient’s work environment. In addition, company medical departments (where they exist) may have results of medical testing done on the patient.

There is an important point to reiterate about MSDSs: health care providers should not rely on these sheets as the sole source of information. The MSDSs are created by the chemical manufacturers as they generate scientific and health data during the course of seeking approval from the Environmental Protection Agency (EPA) to manufacture xenobiotics, and they are not a complete product evaluation. In addition, Section 8(c) of the Toxic Substances Control Act (TSCA) requires chemical manufacturers to report records of significant adverse reactions to human health or the environment. When contacting chemical manufacturers, physicians should ask to speak with a toxicologist, chemist, or someone in the products information department.

Unions

Labor unions can be excellent sources of information on xenobiotic exposures. At the local level, union officers, health and safety committee members, and shop stewards may be able to provide MSDSs, exposure data, medical and epidemiologic information, and reports of incidents or cases of interest in a particular plant. The health and safety department of the American Federation of Labor and Congress of Industrial Organizations (AFL-CIO), (<http://www.aflcio.org/Issues/Job-Safety>) in Washington, DC, can provide information on occupational health and safety activities and advice on which member unions may be of specific help. At the international level, unions often have well-trained health and safety professionals who may provide or suggest sources of helpful information (<http://www.ilo.org/global/topics/safety-and-health-at-work/lang—de/index.htm>). In addition, some cities and states (<http://www.nycosh.org/>) have a coalition of occupational safety and health groups that may provide information about other known exposed or affected workers.

Government Agencies

A myriad of agencies have some regulatory authority over manufacturing and services industries. These agencies and their important regulatory authority are listed in [Table 123–4](#).

TABLE 123–4. Government Agencies and Their Important Regulatory Authority of the Workplace—A Timeline

Regulation	Agency	Authority
Occupational Safety and Health Act (OSHA, 1970)	Department of Labor	<p>Congress passed OSHA and created the Occupational Safety and Health Administration to ensure worker and workplace safety. The goal was to make sure employers provide their workers a place of employment free from recognized hazards to safety and health, such as exposure to toxic xenobiotics, excessive noise levels, mechanical dangers, heat or cold stress, and unsanitary conditions.</p> <p>To establish standards for workplace health and safety, the Act also created the National Institute for Occupational Safety and Health (NIOSH) as the research institution for the Occupational Safety and Health Administration. Part 1910.1200 of OSHA established the Hazardous Communication Standard (HazCom). The purpose of this section is to ensure that the hazards of all xenobiotics produced or imported are evaluated and that information concerning their hazards is transmitted to employers and employees. This transmittal of information is to be accomplished by means of comprehensive hazard communication programs, which are to include container labeling and other forms of warning, material safety data sheets, and employee training.</p>
Resource Conservation and Recovery Act (RCRA, 1976)	Environmental Protection Agency (EPA)	<p>RCRA (pronounced "rick-rah") gave the EPA the authority to control hazardous waste from "cradle to grave." This includes the generation, transportation, treatment, storage, and disposal of hazardous waste. RCRA also set forth a framework for the management of nonhazardous wastes. The 1986 amendments to RCRA enabled the EPA to address environmental problems that could result from underground tanks storing petroleum and other hazardous xenobiotics. RCRA focuses only on active and future facilities and does not address abandoned or historic sites (see CERCLA).</p> <p>HSWA (pronounced "hiss-wa"), the Federal Hazardous and Solid Waste Amendments, are the 1984 amendments to RCRA that required the phasing out of land disposal of hazardous waste. Some of the other mandates of this strict law include increased enforcement authority for the EPA, more stringent hazardous waste management standards, and a comprehensive underground storage tank program.</p>
Toxic Substances Control Act (TSCA, 1976)	EPA	<p>TSCA was enacted by Congress to give the EPA the ability to track the 75,000 industrial xenobiotics currently produced or imported into the United States. The EPA repeatedly screens these xenobiotics and can require reporting or testing of those that may pose an environmental or human health hazard. The EPA can ban the manufacture and import of xenobiotics that pose an unreasonable risk.</p> <p>Reporting requirements include (1) premanufacturing notification for new xenobiotics, (2) allegation of significant adverse reactions, (3) reporting of health and safety studies, and (4) notification of suspicion of substantial risk to health.</p>
Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, 1980)	EPA	<p>CERCLA, commonly known as the Superfund Act, was enacted by Congress on December 11, 1980. This law created a tax on the chemical and petroleum industries and provided broad federal authority to respond directly to releases or threatened releases of hazardous xenobiotics that may endanger public health or the environment. Over 5 years, \$1.6 billion was collected, and the tax went to a trust fund for cleaning up abandoned or uncontrolled hazardous waste sites. CERCLA (1) established prohibitions and requirements concerning closed and abandoned hazardous waste sites, (2) provided for liability of persons responsible for releases of hazardous waste at these sites, and (3) established a trust fund to provide for cleanup when no responsible party could be identified.</p> <p>The law authorizes two types of response actions: (1) short-term removals, in which actions may be taken to address releases or threatened releases requiring prompt response, and (2) long-term remedial response actions that permanently and significantly reduce the dangers associated with releases or threats of releases of hazardous xenobiotics that are serious but not immediately life threatening. These actions can be conducted only at sites listed on the EPA's National Priorities List (NPL).</p>
Superfund Amendments and Reauthorization Act (SARA, 1986)	EPA	<p>SARA reflected the EPA's experience in administering the complex Superfund program during its first 6 years and made several important changes and additions to the program. SARA (1) stressed the importance of permanent remedies and innovative treatment technologies in cleaning up hazardous waste sites, (2) required Superfund actions to consider the standards and requirements found in other state and federal environmental laws and regulations, (3) provided new enforcement authorities and settlement tools, (4) increased state involvement in every phase of the Superfund, (5) increased the focus on human health problems posed by hazardous waste sites, (6) encouraged greater citizen participation in making decisions on how sites should be cleaned up, and (7) increased the size of the trust fund to \$8.5 billion. SARA also required the EPA to revise the Hazard Ranking System (HRS) to ensure that it accurately assessed the relative degree of risk to human health and the environment posed by uncontrolled hazardous waste sites that may be placed on the NPL. Emergency Planning and Community Right-to-Know Act (EPCRA), also known as Title III of SARA, was enacted by Congress as the national legislation on community safety. This law was designated to help local communities protect public health, safety, and the environment from xenobiotic hazards. The law requires manufacturers to report the amount of toxic xenobiotics released each year (Toxic Release Inventory [TRI]).</p> <p>To implement EPCRA, Congress required each state to appoint a State Emergency Response Commission (SERC). The SERCs were required to divide their states into Emergency Planning Districts and to name a Local Emergency Planning Committee (LEPC) for each district.</p>
Americans with Disabilities Act (ADA, 1990) and the ADA Amendments Act of 2008 (ADAAA)	Department of Labor	<p>The ADA was enacted by Congress to establish clear and comprehensive prohibition of discrimination on the basis of disability. The act specifically covers discrimination in the areas of (1) employment, (2) public services, (3) public accommodations and services operated by private entities, and (4) telecommunications. The ADAAA reaffirms Congress' initial intent of the 1990 law to (1) broadly define "disability," (2) use the definition of "handicapped individual" under the Rehabilitation Act of 1973 and (3) state that mitigating measures (eg, insulin for diabetes) shall not be a factor when determining whether an impairment substantially limits a major life activity. The final regulations for the Act were published in the Federal Register in March 2011. http://www.eeoc.gov/laws/regulations/adaaa_fact_sheet.cfm.</p>

OSHA of the U.S. Department of Labor (<http://www.osha.gov>) is responsible for setting and enforcing workplace health and safety standards. It is empowered to investigate occupational health and safety complaints and can inspect work sites and levy fines for violations of its standards. In approximately half of the 50 states, the OSHA program is implemented by a state agency. Individual workers, their representatives (unions), or their physicians can file a complaint with the state or federal OSHA program and request an inspection. OSHA regulations protect workers from discrimination and punishment by their employer, who may be angered by their filing a complaint.

Some state OSHA agencies have separate enforcement and consultation arms. Thus, companies can request assistance from the occupational health specialists in the consultation branch without fear of reprisal from the enforcement branch. Health care workers should be familiar with the functions of their state agency and workers' rights under the law.

The National Institute for Occupational Safety and Health (NIOSH) of the U.S. Department of Health and Human Services is part of the Centers for Disease Control and Prevention (<http://www.cdc.gov/niosh>). NIOSH is not a regulatory agency and is responsible for researching the causes of occupational disease and injury and methods for their prevention and control, evaluating workplace conditions, recommending exposure limits to OSHA for standard setting, and training occupational health and safety professionals. It is empowered to conduct onsite evaluations of health hazards in response to requests from employee representatives or employers. After conducting these evaluations, NIOSH investigators immediately contact OSHA, the employees, and the employer if they find that the workers are in imminent danger.

As part of the process of recommending exposure standards to OSHA, NIOSH develops comprehensive documents that critically evaluate all available scientific data on particular xenobiotics. These “criteria documents” review the chemical’s properties, production methods, uses, and workers at risk as well as studies of exposure effects in humans and animals. Methods of screening, surveillance, and control are presented. The agency periodically issues technical reports and special occupational hazard reviews of specific occupations. In conjunction with OSHA, NIOSH develops and disseminates health hazard alerts to inform employers, employees, and health care professionals of serious health effects of particular xenobiotics.

The EPA (<http://www.epa.gov>) is charged with protecting the nation’s land, air, and water. The agency administers a number of laws designed to preserve the public health and environment, one of which is the Toxic Substances Control Act (TSCA). This act authorizes the EPA to collect information on xenobiotic risks from manufacturers and processors and to review information on new xenobiotics and new uses of xenobiotics before they are manufactured. Unless designated a trade secret, this information is subject to disclosure and therefore is available. The TSCA assistance office may be most useful when resource materials and government documents contain no information about the xenobiotics or processes in question.

The National Toxicology Program (NTP; <http://ntp.niehs.nih.gov/>) is a federal program established in 1978 to develop scientific information on exposure to xenobiotics.

The Agency for Toxic Substances and Disease Registry (ATSDR; <http://www.atsdr.cdc.gov>) was created by Congress in the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERLA; also known as Superfund Act) to implement the health-related sections of laws that protect the public from hazardous wastes and environmental spills of hazardous substances. In 1986, the Superfund Amendments and Reauthorization Act (SARA) made amendments to the initial enabling legislation of 1980 and broadened the ATSDR’s responsibilities in the areas of health assessment, toxicologic databases, information dissemination, and medical education. One of its offices, the Division of Health Assessment and Consultation, provides emergency response for toxic and environmental disasters, consults in public health emergencies, assesses hazardous waste sites, provides technical assistance to agencies and organizations, and estimates health risks to humans from exposure to hazardous xenobiotics. The program areas in which ATSDR operates include health assessments, toxicologic profiles, emergency response, and exposure and disease registries.

Online Databases

Printed material often is adequate for determining the adverse health effects of xenobiotic exposures, but some resources may be unavailable to physicians, and textbook publications usually lag 2 years or more behind new information. As a result, current findings and reports may be missed if the practitioner relies solely on printed material. The National Library of Medicine (<http://www.nlm.nih.gov>) now sponsors Internet searching of both Medline (PubMed: <http://www.ncbi.nlm.nih.gov/pubmed>) and a number of databases in the Toxicology Data Network (TOXNET: <http://www.toxnet.nlm.nih.gov>) that are very useful for finding information about industrial xenobiotics. Additional databases are available for searching on the OSHA, NIOSH, EPA, and ATSDR web sites.

Obligations of the Health Care Provider to the Individual Patient, Coworkers, Employer, Government, and Community

Occupational diseases and injuries are, in principle, preventable. Physicians who diagnose a work-related disease or injury have an opportunity and an ethical obligation to participate in the identification and control of workplace hazards and the prevention of further occupational illness and injury. Physicians can choose from a range of possible follow-up measures, the goals of which are to prevent recurrence or worsening of the disease or injury in the patient and to prevent the development of disease or injury in other potentially exposed workers. Some of these activities may necessitate contact with occupational medicine physicians, toxicologists, industrial hygienists, lawyers, journalists, government officials, management personnel, and union officials.

Obligations to the Patient

Inform the Patient That the Illness May Be Work Related. When the workplace is determined to be a factor in the etiology or aggravation of the patient’s illness, this fact and its implications should be discussed with the patient. It should never be assumed that the patient is fully aware of the health risks associated with any workplace exposure. The worker

should be provided information regarding the nature of workplace hazards, their health risks, preventive measures, and recommendations regarding continued exposure.

Suggest How the Patient Can Reduce the Exposure. In some cases, the patient can take steps to reduce exposure. Adjustments in work habits that may be helpful include using a respirator or other personal protective equipment provided by the employer; using workplace shower and dressing rooms to avoid carrying xenobiotics from the workplace to the home; and avoiding ingestion of workplace xenobiotics by careful hand washing before eating or smoking and by taking lunch, coffee, and smoking breaks away from the work station. Obviously, these recommendations assume that the employer provides the appropriate equipment and facilities, which is not always the case. The most effective hazard control measures require significant commitment by, and cooperation from, the employer.

Suggest That the Patient Remove Him-or Herself from the Exposure. The employer may be willing to transfer the patient to a location away from the offending hazard. This may result in a reduction in pay, seniority, or other benefits, which may be compensable under workers' compensation. The employment provisions of the ADA require employers to make "reasonable accommodations" for both work-and non-work-related disabilities. Nevertheless, the employer may not be able to accommodate the patient. The patient should be counseled carefully, and other options should be explored.

Advise the Patient to Notify the Employer. Patients who are experiencing a work-related illness may be entitled to workers' compensation benefits, Social Security disability, or other government-sponsored benefit programs. In addition, they may have a valid claim against the manufacturer of a xenobiotic, a defective product, or another third party. The degree of disability necessary to bring a successful claim varies.

After a patient is informed that he or she has a work-related illness, strict time limits are set in motion, and failure to meet them can preclude the patient from successfully filing a claim or receiving needed benefits. The patient should be advised to provide written notice immediately to his or her employer of a work-related illness (supported by a physician's letter) and to seek advice about statutes of limitations and other requirements. This information is generally available from the State Workers' Compensation Board and is usually required to be provided to the employee by the employer. If a union is available at the workplace, it may be able to advise and assist the patient.

Obligations to Coworkers A patient with a work-related illness should be advised to inform his or her coworkers about the condition. If the patient belongs to a union, he or she should inform the union representative. If there is no union, the patient may contact OSHA or discuss the situation with the employer.

If the patient is a union member and agrees, the physician can contact the union, which may assist in hazard investigation, identify and warn other workers potentially affected by the hazard, and pressure the employer to take corrective action if it is unwilling to do so. The union can help the patient obtain any available benefits. The patient may be able to identify appropriate contacts, such as shop stewards, members of the union's health and safety or workers' compensation committees, an occupational health specialist employed by the union at the local or national level, or an official of the union local.

Committees on Occupational Safety and Health (COSH); coalitions of labor, health, and legal professionals; and community and environmental activists working to prevent job-related illness and injury may be able to help with the diagnosis and follow-up of occupational diseases. These groups provide education and technical assistance nationwide on a range of topics, including the health effects of specific hazards, control measures, how to use government agencies, and the legal rights of disabled workers.

Obligations to Notify the Government

States may have laws that require direct physician reporting of occupational disease. If management is uncooperative despite notification of a hazardous situation, OSHA should be contacted, with the patient's consent. In addition to the federal agencies specifically empowered to protect worker health and safety, physicians may contact the state or local health department, which may initiate action or refer the problem to one of the federal agencies. Many states also require physicians to report any occupational injury or illness to the workers' compensation carrier.

Obligation to Notify the Employer

When treating a patient with an occupational injury or illness, health care providers often are required to report to government agencies, health departments, or insurance carriers. As part of that reporting process, the employer should also be notified. When there is imminent danger to coworkers or the public health, the employer should be contacted to correct the exposure situation.

Obligation to Inform Colleagues and the Public

On occasion, an individual primary care physician or specialist is the first person to suspect a link between a workplace exposure and a serious health problem. This is likely to recur in the future, especially if the physician practices in a small town or industrial area or provides health care to worker groups through a company or union. Armed with an increased index of suspicion and the occupational history, the physician may be able to alert workers and companies and prevent the

occurrence of a major health problem. Even if the physician chooses not to be involved in subsequent investigation or research, it is important that information about suspected problems and hazards be made available to workers and employers in similar industrial settings, government agencies, health care professionals, and perhaps the public at large. Case reports discussed in the medical literature, at medical meetings, or through the media can be helpful in this regard.

SUMMARY

- Industrial, workplace, and environmental exposures represent a different kind of challenge to primary care and emergency physicians.
- Patients often present as a diagnostic dilemma or with common symptoms that do not respond to the usual medical treatment. The challenge for nonoccupational health professionals is to correctly establish and treat the condition.
- The basic approach to all patients emphasizes additional questions integrated into the medical history and access to printed and electronic information resources.
- Exposures to occupational and environmental xenobiotics have public health implications.
- Physicians who make the diagnosis of an occupationally or environmentally related disease have an obligation to prevent further injury.

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124 SIMPLE ASPHYXIANTS AND PULMONARY IRRITANTS

Lewis S. Nelson and Oladapo A. Odujebe

The respiratory system is responsible for gas exchange, elimination of certain xenobiotics, insensible water loss, temperature regulation, and minor metabolic processes. The principle function of the respiratory system is gas exchange, which occurs in the greater than 300 million alveoli that make up approximately 90% of the human lung volume. The average resting adult inhales about 8 L/min of air (a tidal volume of about 500 mL) and averages 16 breaths/min, and this volume can be increased exponentially by increasing the respiratory rate and tidal volume as occurs during exertion. In a 24-hour period, an average adult human at rest will have been exposed to 11,500 L of air. There are a number of protective systems within the respiratory system to prevent exposure to xenobiotics, but these systems can be overwhelmed. The principles of respiratory system function are covered extensively in [Chap. 29](#).

The respiratory tract performs several important physiologic functions. Its most important role involves the transfer of oxygen to hemoglobin across the pulmonary endothelium. This transfer facilitates oxygen distribution throughout the body to permit effective cellular respiration. Diverse xenobiotics may act at unique points in this distribution pathway to limit or impair tissue oxygenation. For example, whereas opioids and neuromuscular blockers may induce hypoventilation, carbon monoxide and methemoglobin inducers prevent loading and unloading of oxygen onto and off of hemoglobin. Certain xenobiotics prevent adequate oxygenation of hemoglobin at the level of pulmonary gas exchange. Two mechanistically distinct groups of xenobiotics are capable of interfering with gas exchange: simple asphyxiants and pulmonary irritants. Impairment of transpulmonary oxygen diffusion, regardless of the etiology, reduces the oxygen content of the blood and may result in tissue hypoxia.

HISTORY AND EPIDEMIOLOGY

Unlike most xenobiotic exposures, simple asphyxiant and pulmonary irritant poisonings frequently occur on a mass scale because of the nature of the inhalational route. For example, the large-scale emission of carbon dioxide from Lake Nyos, a carbonated volcanic crater lake in Cameroon, West Africa, resulted in nearly 2000 human deaths and many more livestock deaths ([Chap. 2](#)).¹⁷ In this disaster, simple asphyxiation was likely because medical evaluation of both survivors and fatalities demonstrated neither signs of cutaneous or pulmonary irritation nor toxicologic abnormalities.²⁰⁶ The widespread use of compressed liquefied gases, which expands several hundredfold on depressurization or warming, account for a substantial number of workplace injuries.^{128,188}

Irritant gases similarly may result in mass casualties. For this reason, chlorine and phosgene were used in battle during World War I, resulting in thousands of Allied deaths ([Chap. 132](#)).⁸⁷ Atmospheric sulfur dioxide and oxides of nitrogen are the primary components of photochemical smog. During the London Fog incident in 1952, 4000 deaths occurred primarily from respiratory causes.¹⁷⁶ Similar smog incidents have occurred across the globe. Relatedly, the diverse irritants found in fire smoke are a major cause of death after smoke inhalation.¹⁸⁵

Unexpected release of other irritant inhalants may lead to large-scale poisoning. In 1984, an inadvertent release of methylisocyanate in Bhopal, India, resulted in immediate and persistent respiratory symptoms in approximately 200,000 local inhabitants, with approximately 2500 deaths.^{18,57}

Isolated exposures to individuals occur as well, often in workplaces, and more frequently in contained spaces (eg, indoors). Additionally, the use of simple asphyxiation as a painless and relatively undetectable method for committing suicide and, paradoxically, for euphoric experiences, can be found in books, on the Internet, and in the medical literature.^{71,79,81,167}

SIMPLE ASPHYXIANTS

Simple asphyxiants work primarily by displacing oxygen from ambient air, unlike chemical asphyxiants, which cause cellular hypoxia and are discussed in [Chaps. 125, 126, and 127](#). Virtually every gas, excluding oxygen, is capable of acting

as a simple asphyxiant.

Pathophysiology

Simple asphyxiants displace oxygen from ambient air, thereby reducing the fraction of inspired oxygen (FiO_2) in air to below 21%, and result in a decrease in the partial pressure of oxygen. The partial pressure is a measure of the contribution of oxygen to the total inspired air and is based on both FiO_2 and barometric pressure. For example, because the ambient pressure at sea level (less water vapor, 47 mm Hg) is 713 mm Hg and the percentage of oxygen is 21%, the partial pressure of oxygen in the lungs is 150 mm Hg. However, this relationship is not applicable at other barometric pressures. For example, at the summit of a mountain, the reduced barometric pressure results in a decrease in the partial pressure of oxygen despite a near-normal FiO_2 . The barometric pressure decreases in a linear fashion with altitude (above sea level) and increases with descent below sea level. This reduced partial pressure may be insufficient to allow adequate oxygen saturation, and supplemental oxygen becomes necessary. As barometric pressure decreases, exposure to simple asphyxiant gases may further reduce the oxygen partial pressure to life-threatening levels. Conversely, underwater divers reduce their FiO_2 to below 21% by adding simple asphyxiant gases, such as helium, to their breathing mixture to avoid oxygen toxicity, yet they still maintain adequate oxygenation. This is because the elevated barometric pressure increases the partial pressure of oxygen to normal amounts despite the addition of an asphyxiant gas. However, systemically poisonous gases that enter the breathing mixture would have a magnified effect, given their increased partial pressure at depth.

Conceptually, simple asphyxiants have no pharmacologic activity. For this reason, exceedingly high ambient concentrations of these gases are necessary to produce asphyxia. Asphyxiation typically occurs in confined spaces or with rapid release of concentrated simple asphyxiants.

Clinical Manifestations

A patient exposed to any simple asphyxiant gas will develop characteristic clinical findings of hypoxia, or lack of oxygen at the cellular level (Table 124–1). These clinical findings are directly related to the reduction in the partial pressure of oxygen in ambient air, which leads to hypoxemia, or low oxygen content of the blood.¹²⁸ Cardiovascular and central nervous system (CNS) complications of simple asphyxiants predominate because these organs have the greatest oxygen requirements. As hypoxemia becomes severe, multisystem organ failure and death from tissue hypoxia may occur.⁵³ Postmortem findings are generally minimal, hampering the cause of death determination without historical evidence or advanced laboratory testing.¹²

TABLE 124–1. Clinical Findings Associated with Reduction of Inspired Oxygen

FiO_2^a	Signs and Symptoms
21	None
16–12	Tachypnea, hyperpnea, (resultant hypocapnia), tachycardia, reduced attention and alertness, euphoria, headache, mild incoordination
14–10	Altered judgment, incoordination, muscular fatigue, cyanosis
10–6	Nausea, vomiting, lethargy, air hunger, severe incoordination, coma
<6	Gasping respiration, seizure, coma, death

^aAt sea level, barometric pressure; appropriate adjustments must be made for altitude and depth exposures.

FiO_2 = fraction of inspired oxygen.

During simple asphyxiation, carbon dioxide exchange is not impaired, and hypercapnia does not occur. Because dyspnea develops more rapidly from hypercapnia than hypoxemia, the breathlessness associated with physical or simple chemical asphyxiation does not develop until severe hypoxemia intervenes.^{96,116} In these circumstances, victims may succumb to hypoxemia without ever developing the expected warning symptoms. In the case of carbon dioxide inhalation, hypercapnia may occur very rapidly, which itself may produce acute cognitive impairment.

Specific Xenobiotics

Noble Gases: Helium, Neon, Argon, and Xenon. Noble gases, which are stored almost exclusively in the compressed form, have numerous industrial and medical roles. Argon is predominantly used as a shielding gas during welding

operations, and it is also used in processing titanium and growing crystals. Neon is used in the manufacture of decorative lighting. Xenon, in its radioactive gaseous form, has diagnostic medical applications in ventilation-perfusion scans. Xenon is also used in lighting, solar simulators, digital projectors, and plasma display cells (along with neon). Helium has the lowest molecular weight and is the smallest member of the noble gas family of elements. Because of its lower lipid solubility, helium is used by divers to replace nitrogen to prevent nitrogen narcosis at depth (see Nitrogen). Even at diving gas mixtures of 50% helium, divers suffer no adverse effects as long as a normal partial pressure of oxygen is maintained by the mixture at depth. At depth, the quantity (molar quantity, not volume) of air inspired per breath is several-fold greater than at sea level. The lower density of helium than nitrogen results in a lower viscosity, with a marked decrease in flow resistance. This property of helium is the basis for its use in patients with increased airway resistance (Heliox mixture), such as those with asthma.

Helium is also used in magnetic resonance imaging scanners to keep the coils super cooled. During emergency shutdown of a superconducting electromagnet, an operation known as “quenching,” the liquid helium is rapidly boiled from the device and vented into the scanner room. This may displace oxygen from the environment and cause asphyxia.⁹⁰ Helium is also used in lung imaging studies and pulmonary function testing. Similarly, helium’s low viscosity has led to its use as an inflation gas for intraaortic balloons, for which rapid inflation and deflation are critical.

All noble gases, when compressed, form cryogenic liquids, which expand rapidly to their gas phase on decompression. Liberation of these gases in closed spaces may result in either asphyxiation or freezing injuries, or both.⁹⁰ Xenon, unlike the other noble gases, has unique anesthetic properties because of its high lipid solubility and inhibition of N-methyl-D-aspartic acid (NMDA) receptors.⁹⁰ The other noble gases have no known direct toxicity.

Short-Chain Aliphatic Hydrocarbon Gases: Methane, Ethane, Propane, and Butane. The short-chain aliphatic hydrocarbon gases are primarily used in the compressed form as fuel.

Methane (CH_4) has no known direct toxicity. Animals can breathe a mixture of 80% methane and 20% oxygen without manifesting hypoxic symptoms because their FiO_2 , and thus their oxygen content, essentially is normal. Methane, also known as “natural gas” and “swamp gas,” may be present in high ambient concentrations in bogs of decaying organic matter. In addition, compressed natural gas is now used as an alternative fuel for automotive use. Methane exposure is an occupational hazard for miners who historically carried canaries into their workplace as an “early warning” sign for the presence of toxic gases and/or oxygen deficiency. Theoretically, the higher metabolic and respiratory rates of small animals (and children) make them more rapidly susceptible to gas exposures. Methane is also an explosive risk.

Methane is odorless and undetectable without sophisticated equipment.³⁶ For this reason, natural gas is intentionally adulterated with a small concentration of ethyl mercaptan, a stenching agent, which is responsible for the well recognized sulfur odor of natural gas. Cooking with natural gas may cause respiratory symptoms and pulmonary dysfunction.⁹⁹ However, methane itself is unlikely to be the cause, because its combustion is generally complete and ambient concentrations are negligible. It is likely that exposure to nitrogen dioxide (NO_2), one of the products of combustion of methane in air (70% nitrogen), is the explanation for these symptoms.

Ethane (C_2H_6) is an odorless gas that is a component of natural gas and is used as a refrigerant. It has characteristics similar to methane and is occasionally implicated as a simple asphyxiant. Propane (C_3H_8) is widely used in its compressed, liquefied form both as an industrial and domestic fuel, and as an industrial solvent. Butane (C_4H_{10}) is a common fuel and solvent. Deliberate butane inhalation from cigarette lighters or air fresheners for recreational purposes predominantly in adolescents is associated with cardiovascular dysfunction and cerebral damage (**Chap. 84**).^{63,183}

Carbon Dioxide (CO_2). Although not a simple asphyxiant gas by definition because it produces physiologic effects, carbon dioxide closely resembles simple asphyxiants from a toxicologic viewpoint. Carbon dioxide gas has many practical industrial uses, such as production of carbonation in soft drinks and use as a shielding gas during welding. It is used in laboratories as a painless form of animal euthanasia and as a means of large-scale euthanasia of diseased livestock.¹⁵⁶ Carbon dioxide is widely used to extinguish fires because of its ability to safely displace oxygen from the local environment.⁷⁸ Dry ice, the frozen form of carbon dioxide, is an extremely cold substance (-141.3°F $\{-78.5^\circ\text{C}\}$) that undergoes conversion from solid to gas without liquefaction, a process known as sublimation. Poisoning may occur when dry ice is allowed to sublimate in a closed space.³⁹ such as the cabin of a car or in a cold storage room at 39.2°F (4°C).^{78,61} Furthermore, inadvertent connection of respirable gas hoses to carbon dioxide and other nonrespirable sources has occurred in both industrial^{96,189} and medical¹⁰⁰ settings, with resultant worker and patient fatalities. This occurrence is uncommon because of the mandated use of engineering controls to prevent the incorrect connection of hose and source terminals.

Pharmacology and pathophysiology. Carbon dioxide, an end product of normal human metabolism, dissolves in the plasma and is in equilibrium with carbonic acid (H_2CO_3). The pH at the central chemoreceptors, reflective of the dissolved carbon dioxide (PCO_2), is responsible for our respiratory drive, and PCO_2 is tightly controlled by the CNS through regulation of breathing.¹¹⁶ For this reason, exogenous carbon dioxide, combined with oxygen, was at one time used

medically as a respiratory stimulant in neonates. Under normal conditions, ambient air contains approximately 0.03% CO₂. When ambient concentrations increase, uptake of carbon dioxide occurs, which further stimulates respiration,¹⁵³ increasing the uptake of ambient carbon dioxide. Accordingly, closed anesthesia systems use scrubbers containing sodium hydroxide (NaOH) to chemically eliminate exhaled carbon dioxide. Failure of the scrubber system results in increasing depth of anesthesia from hypercapnia-induced hyperventilation.

Clinical manifestations. Carbon dioxide produces both acute and subacute poisoning syndromes. The latter occurs during hypoventilation when a patient fails to eliminate endogenous carbon dioxide, develops hypercapnia, and typically presents with gradual somnolence. This occurrence may be linked to respiratory failure, as in the case of emphysema or opioid poisoning, or it may be iatrogenic, as occurs during permissive hypercapnia.¹³⁸ Alternatively, intense carbon dioxide exposure may produce rapid and lethal poisoning. However, unlike other simple asphyxiants, experimental models of acute carbon dioxide poisoning in which a normal FiO₂ is maintained demonstrate that central nervous and respiratory system manifestations occur within seconds^{89,98} This finding suggests that CO₂ is not solely a simple asphyxiant, but also possesses a potential for systemic effects

Nitrogen (N₂) Gas. Although nitrogen, like carbon dioxide, may produce clinical effects independently of hypoxemia, most poisonings are characterized by the manifestations of simple asphyxiants. Nitrogen gas is used as a carrier gas for chromatography, as a fertilizer, as a cryogenic gas for surgery, and extensively in manufacturing. Poisoning by nitrogen gas is uncommon, but may occur after rapid evaporation of the liquid^{103,104}

Pharmacology and pathophysiology. Nitrogen is a colorless, odorless, and tasteless gas that makes up 78% by volume of air. Under standard conditions, it is an inert diatomic gas that has no direct physiologic toxicity.

Clinical manifestations. Inadvertent connection of air-line respirator hoses to nitrogen and other inert gas sources results in acute asphyxiation, with unconsciousness occurring in approximately 12 seconds^{96,128,188} and death shortly thereafter. More indolent inhalational poisoning by nitrogen is characterized by impairment of intellectual function and judgment, giddiness, and euphoria, which is qualitatively similar to ethanol intoxication¹³¹ More severely poisoned patients may manifest lethargy or coma⁷⁰ Systemic absorption is not rapid, however, and prolonged, high-level exposure is required for poisoning. Nitrogen poisoning, also known as nitrogen narcosis, occurs in underwater divers while they are breathing air that contains 70% nitrogen. It has been called rapture of the deep (l'ivresse des grandes profondeurs) and has led to many deaths in the subaquatic environment. The underlying mechanism of nitrogen narcosis is unknown⁵² but the simple structure and relatively high lipophilicity of nitrogen suggest a mechanism similar to that of the anesthetic gases⁷⁰ To avoid nitrogen narcosis, a less lipid-soluble inert gas such as helium is generally substituted for nitrogen. Substitution with oxygen, although intuitively logical, is inappropriate because of the risk of oxygen toxicity (see Oxygen).

Dermal exposure to liquid nitrogen produces frostbite because of liquid nitrogen's extremely cold temperature.¹⁶⁰ Ingestion of liquid nitrogen similarly produces a freezing injury of the gastrointestinal (GI) tract.^{108,208} Rarely, bubbles introduced through the skin embolize through the vascular system and impair organ blood flow.⁶²

Treatment

Treatment of all individuals poisoned by simple asphyxiants begins with immediate removal of the persons from exposure and provision of ventilatory assistance. Provision of supplemental oxygen is preferable, but room air usually suffices. Hyperbaric oxygen therapy has shown no benefit in the majority of cases. Restoration of oxygenation through spontaneous or mechanical ventilation occurs after only several breaths. Support of vital functions is the mainstay of therapy, but is generally unnecessary after a brief exposure.

PULMONARY IRRITANTS

The irritant gases are a heterogeneous group of chemicals that produce toxic effects via a final common pathway: destruction of the integrity of the mucosal barrier of the respiratory tract (Table 124–2).

TABLE 124–2. Characteristics of Common Respiratory Irritants

<i>Gas</i>	<i>Source or Exposure</i>	<i>Solubility (g%)^a</i>	<i>Detection Threshold (ppm)</i>	<i>Regulatory Standard (ppm)^b</i>	<i>IDLH^c (ppm)</i>	<i>STEL (ppm)</i>
Ammonia	Fertilizer, refrigeration, synthetic fiber synthesis	90	5	50	300	35
Cadmium oxide fumes	Welding	I	Odorless	0.005 mg/m ³	9 mg/m ³ (as Cd)	NA
Carbon dioxide	Exhaust, dry ice sublimation	0.2	Odorless	5000	40,000	30,000
Chloramine	Bleach plus ammonia	M	NA	NR	NR	NR
Chlorine	Water disinfection, pulp, and paper industry	0.7	0.3	0.5	10	1
Copper oxide fumes	Welding	I	NA	0.1 mg/m ³	100 mg/m ³ (as Cu)	NA
Ethylene oxide	Sterilant	M	500	1	800	5
Formaldehyde	Chemical disinfection	M	0.8	0.016	20	2
Hydrogen chloride	Chemical	67	1–5	5	50	5
Hydrogen fluoride	Glass etching, semiconductor industry	M	0.042	3 (as F)	30 (as F)	6
Hydrogen sulfide	Petroleum industry, sewers, manure pits	0.4	0.025		100	50
Mercury vapor	Electrical equipment, thermometers, catalyst, dental fillings, metal extraction, heating or vacuuming elemental mercury	I	Odorless	0.1 mg/m ³	10 mg/m ³	0.05

Methane	Natural heating gas, swamp gas	3.3	Odorless	NR	NR	NR
Methyl bromide	Fumigant	2	20	20	250	NA
Nickel carbonyl	Nickel purification, nickel coating, catalyst	0.05	1–3	0.001	2 (as Ni)	0.1
Nitrogen		0.017	Odorless	NR	NR	NR
Nitrogen dioxide	Chemical synthesis, combustion emission	P	0.12	3	20	5
Nitrous oxide	Anesthetic gas, whipping cream dispensers (abuse), racing fuel additive	0.07	2	25	100	NA
Ozone	Disinfectant, produced by high-voltage electrical equipment	0.001	0.05	0.1	5	0.1
Phosgene	Chemical synthesis, combustion of chlorinated compounds	P	0.5	0.1	2	0.1
Phosphine	Fumigant, semiconductor industry	P	2	0.3	50	1
Propane	Liquefied propane gas	0.007	Odorless	1000	2100	NR
Sulfur dioxide	Environmental exhaust	23	1	2	100	5
Zinc chloride fumes	Artificial smoke (no longer in use)	432	NA	1 mg/m ³	50 mg/m ³	2 mg/m ³
Zinc oxide	Welding	0.16	Odorless	5 mg/m ³	500 mg/m ³	10 mg/m ³

1g/L = grams of gas per 100 mL water, if applicable. * Standards are either Threshold Limit Value–Time Weighted Average (TLV–TWA) set by the American Conference of Governmental Industrial Hygienists (ACGIH) or permissible exposure limits (PELs) set by the Occupational Safety and Health Administration (OSHA). † Immediately dangerous to life and health (IDLH; National Institute for Occupational Safety and Health (NIOSH), revised 1995. (Documentation for each IDLH is available at <http://www.cdc.gov/niosh/idlh/idlhintr.html>.)

I = floating; I = insoluble; M = miscible; NA = not available; NR = no regulatory standard; P = poor; STEL = short-term exposure limit, 15 minute average not to be exceeded.

Pathophysiology

In the lung, irritant chemicals damage both the more prevalent type I pneumocytes and the surfactant-producing type II pneumocytes.¹¹¹ Neutrophil influx, recruited in response to macrophage-derived inflammatory cytokines such as tumor necrosis factor (TNF)- α , releases toxic mediators that disrupt the integrity of the capillary endothelial cells.^{121,158} This host defense response results in accumulation of cellular debris and plasma exudate in the alveolar sacs, producing the characteristic clinical findings of the acute respiratory distress syndrome (ARDS). The specific mechanisms by which the irritant gases damage the pulmonary endothelial and epithelial cells vary. Many irritant gases require dissolution in lung water to liberate their ultimate toxicant, which often is an acid, as occurs when hydrogen chloride gas produces hydrochloric acid. The exact mechanism by which acids damage cells and induce an inflammatory response remains uncertain. Oxidation of intracellular proteins may result in rapid cytoskeletal shortening, creating spaces between endothelial cells and allowing fluid movement into the alveolar spaces.¹⁹⁴ Other gases, such as oxygen and ozone, induce pulmonary damage solely through free radical-mediated oxidative stress on the cellular membranes. Nitrogen dioxide (NO₂) and chlorine are characteristic of a group of gases that produce both acid and free radical oxidants. Furthermore, other respirable xenobiotics, such as metals, injure the respiratory tract through oxidant stress and other mechanisms. Because the precise toxicologic and pathophysiologic effects vary widely depending on the physicochemical properties of the xenobiotic, these mechanisms are covered more completely in the following specific discussions.

By virtue of its use as a war agent, phosgene has received more investigation than the other irritant gases. Although the specific mechanisms of toxicity of the other irritants remain poorly defined, they likely cause injury through a similar process. The acids liberated upon dissolution in the mucosal water react with functional groups on epithelial and endothelial cell membranes and, via cellular messengers, result in a complex inflammatory response.^{170,145} Phosgene stimulates the synthesis of lipoxygenase-derived leukotrienes and other cytokines such as TNF- α .¹⁷⁰ Leukotrienes are important chemotactic factors for neutrophils, which accumulate, liberate oxidants, and produce ARDS.⁹⁷ ARDS can be prevented in rabbits by tomelukast, a leukotriene receptor antagonist,⁸⁵ and by methylprednisolone, which blocks leukotriene synthesis; both of which are beneficial postexposure.⁸⁵ Ibuprofen, an inhibitor of the arachidonic acid cascade, and xenobiotics capable of reducing neutrophil influx, such as colchicine and cyclophosphamide, reduce lung injury and

mortality in mice when they are administered shortly after phosgene exposure.^{77,172} Intratracheal dibutyryl cyclic adenosine monophosphate (DBcAMP), a cAMP analog, and other cAMP amplifiers, such as terbutaline or aminophylline, inhibit the release of leukotrienes and reduce toxicity.^{102,173} When administered 45 minutes after exposure to phosgene-poisoned rabbits, intratracheal N-acetylcysteine (NAC) decreases the formation of leukotrienes by an undefined means and limits the development of ARDS.¹⁷⁴ Presumably, administration via nebulization would prove similarly effective. Intravenous administration of NAC to patients with mild to moderate ARDS, none of whom had phosgene-induced pulmonary damage, improved systemic oxygenation and reduced their need for ventilatory support.¹⁹⁰ However, progression to respiratory failure was not altered.

Free radicals are highly reactive molecular derivatives, typically from oxygen or nitrogen which bind to and destroy tissue near their site of generation. Through initiation of a lipid peroxidative cascade, free radicals destroy lipid membranes and inhibit energy production through the electron transport chain (Chap. 12). Products of lipid peroxidation and cellular damage initiate neutrophilic influx, presumably in an immunologic attempt to combat a pathogen. Ironically, free radicals generated by the invading inflammatory cells contribute to pulmonary damage. Fortunately, the lung has both enzymatic (eg, superoxide dismutase, glutathione peroxidase, catalase) and nonenzymatic (eg, glutathione, ascorbate) antioxidant systems, which detoxify virtually all free radicals present in the lung.¹⁵⁴ However, the oxidant burden imposed by oxidant gases can preempt these detoxifying systems and produce cellular damage. For example, nebulization of manganese superoxide dismutase into the airway one hour after smoke inhalation, a form of oxidant lung injury, did not improve lung edema or pulmonary gas exchange.¹¹⁹ However, the observed benefit of NAC may also be related to improved hemodynamic function (Antidotes in Depth: A3).⁹¹

Clinical Manifestations

Regardless of the mechanism by which the mucosa is damaged, the clinical presentations of patients exposed to irritant gases are similar. Those exposed to gases that result in irritation within seconds generally develop mucosal injury limited to the upper respiratory tract. The rapid onset of symptoms is usually a sufficient signal to the patient to escape the exposure. Patients may present with nasal or oropharyngeal pain in addition to drooling, mucosal edema, cough, or stridor.¹⁹³ Conjunctival irritation or chemosis, as well as skin irritation, is often noted because concomitant ocular and cutaneous exposure to the gases usually is unavoidable. Gases that are less rapidly irritating may not provide an adequate signal of their presence and may not prompt expeditious escape by the exposed individual. In this case, prolonged breathing allows entry of the toxic gas farther into the bronchopulmonary system, where delayed toxic effects may subsequently be noted. Tracheobronchitis, bronchiolitis, bronchospasm, and ARDS are typical inflammatory responses of the airway and represent the spectrum of acute lower respiratory tract injury.

Experimental models assessing the water solubility of a gas to predict the location of its associated lesions have largely agreed with the clinical data.¹⁰⁵ However, exceptions to this relationship of a gas and its expected toxicity are common. For example, in situations in which escape from ongoing exposure is prevented, patients may develop lower respiratory tract injury after prolonged exposure to acutely irritating gases. Alternatively, rapid onset of upper respiratory irritation may be noted in patients after exposure to concentrated gases that are generally associated with delayed symptomatology. Exposure to exceedingly high concentrations of any irritant gas may produce hypoxemia analogous to that resulting from exposure to a simple asphyxiant gas.

The most characteristic and serious clinical manifestation of irritant gas exposure is ARDS.^{13,20,162,163} ARDS consists of the clinical, radiographic, and physiologic abnormalities caused by pulmonary inflammation and alveolar filling that must be both acute in onset and not attributable solely to pulmonary capillary hypertension as occurs in patients with congestive heart failure.^{13,20,162,163} ARDS is a nonspecific syndrome resulting from diverse physiologic insults such as sepsis or trauma. Patients with ARDS may present with dyspnea, chest tightness, chest pain, cough, frothy sputum, wheezing or crackles, and arterial hypoxemia. Typical radiographic abnormalities include bilateral pulmonary infiltrates with an alveolar filling pattern and a normal cardiac silhouette that differentiate this syndrome from congestive heart failure.

In 2012, the diagnostic criteria for ARDS was updated as a consensus guideline known as the Berlin Definition.^{9,10} The draft definition proposed three mutually exclusive strata of ARDS based on the degree of hypoxemia (Table 124–3). Some essential changes of the new definition include: acute was defined as one week or less; the term acute lung injury (ALI) was discontinued; measuring the PaO₂/FiO₂ ratio now requires a specific amount of positive end-expiratory pressure (PEEP); chest radiograph criteria have been clarified to improve interrater reliability; the pulmonary capillary wedge pressure (PCWP) criterion was removed; and additional clarity was added to improve the ability to exclude cardiac causes of bilateral infiltrates.

TABLE 124–3. The Berlin Definition of Acute Respiratory Distress Syndrome^{9,10}

Characteristic	Definition
Timing	Within one week of a known clinical insult, or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation/hypoxemia	
Mild	$200 < \text{PaO}_2/\text{FiO}_2 \leq 300$ with PEEP or CPAP ≥ 5 cm H ₂ O
Moderate	$100 < \text{PaO}_2/\text{FiO}_2 \leq 200$ with PEEP ≥ 5 cm H ₂ O
Severe	$\text{PaO}_2/\text{FiO}_2 \leq 100$ with PEEP ≥ 5 cm H ₂ O

Specific Xenobiotics

Acid-or Base-Forming Gases Highly Water-Soluble Xenobiotics

Ammonia (NH₃). Ammonia is a common industrial and household chemical used in the synthesis of plastics and explosives, and as a fertilizer, a refrigerant, and a cleaner. The odor is characteristic and may be an effective warning signal of exposure and stimulus to avoid further exposure. Dissolution of NH₃ in water to form the base ammonium hydroxide (NH₄OH) rapidly produces severe upper airway irritation. Patients with exposures to highly concentrated NH₃ or exposures for prolonged periods may develop tracheobronchial or pulmonary inflammation. Experimental inhalation of nebulized high-dose ammonia causes ARDS within 2 minutes of exposure¹⁷⁹ Ultrastructural study of the lungs from two individuals dying acutely of ammonia inhalation revealed marked swelling and edema of type I pneumocytes consistent with ARDS³⁵ Chronic inhalation of low concentrations of NH₃ or repetitive exposure to high concentrations of ammonia may cause pulmonary fibrosis³¹

Chloramines. This series of chlorinated nitrogenous compounds (Fig. 124–1) includes monochloramine (NH₂Cl), dichloramine (NHCl₂), and trichloramine (NCl₃). The chloramines are most commonly generated by the admixture of ammonia with sodium hypochlorite (NaOCl) bleach, often in an effort to potentiate their individual cleaning powers⁷² Interestingly, the addition of bleach to septic systems may result in liberation of the chloramines after the reaction of bleach with urinary nitrogenous compounds¹²⁹ On dissolution of the chloramines in the epithelial lining fluid, hypochlorous acid (HOCl), ammonia, and oxygen radicals are generated, all of which act as irritants. Although less water soluble than ammonia, the chloramines typically promptly result in symptoms. Because these initial symptoms are often mild, however, they may not prompt immediate escape, resulting in prolonged or recurrent exposure with pulmonary and ocular symptoms predominating⁴¹ Exposure to trichloramine occurs at indoor swimming pools⁴³ and is responsible for inducing permeability changes in the pulmonary epithelium, the consequences of which are not yet understood³⁸

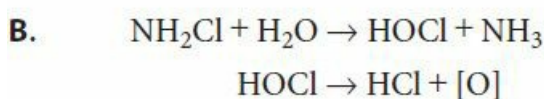


FIGURE 124–1. Chloramine chemistry. (A) Sodium hypochlorite (bleach) plus ammonia form monochloramine and dichloramine. (B) Chloramine dissolves in water to liberate hypochlorous acid; hydrochloric acid; ammonia; and nascent oxygen [O], an oxidant.

Hydrogen chloride (HCl). The largest and most important use of hydrogen chloride gas is in the production of hydrochloric acid. Dissolution of hydrogen chloride gas in lung water after inhalation similarly produces hydrochloric acid^{34,152} Pyrolysis of polyvinyl chloride (PVC), a plastic commonly used in pipe fabrication, generates HCl and is an occupational hazard for firefighters¹⁴¹ By adsorbing to respirable carbonaceous particles generated in the fire, HCl may be deposited in the alveoli and produce pulmonary toxicity.

Hydrogen fluoride (HF). Hydrogen fluoride and its aqueous form, hydrofluoric acid, are used in the gasoline, glassware, building renovation, and semiconductor industries. Hydrogen fluoride gas dissolves in epithelial lining fluid to

form the weak acid hydrofluoric acid. The intact HF molecule is the predominant form in solution, and few free hydronium ions (H_3O^+) are liberated. Low-dose inhalational exposures may result in irritant symptoms^{200,212} and large exposures may cause bronchial and pulmonary parenchymal destruction^{30,200}. Death after inhalation may result from ARDS, but usually is related to systemic fluoride poisoning independent of the route of exposure because of the resultant calcium binding and subsequent hypocalcemia and hyperkalemia^{26,59} (Chap. 107).

Sulfur dioxide and sulfuric acid (SO_2 and H_2SO_4). Sulfur dioxide has multiple industrial applications and is a byproduct found in the smelting and oil refinery industries. It may also be generated by the inadvertent mixing of chemicals, such as an acid with sodium bisulfite (NaHSO_3). Sulfur dioxide is highly water soluble and has a characteristic pungent odor that provides warning of its presence at concentrations well below those that are irritating. In the presence of catalytic metals (Fe, Mn), environmental sulfur dioxide is readily converted to sulfurous acid (H_2SO_3) within water droplets. Sulfurous acid is a major environmental concern and the cause of “acid rain.” Exposure to atmospheric sulfur dioxide results in a roughly dose-related bronchospasm, which is most pronounced and difficult to treat in patients with asthma. Inhalation of sulfurous acid or dissolution of sulfur dioxide in epithelial lining fluid produces typical pathologic and clinical findings associated with ARDS¹⁵⁹. In addition to the effect of acid generation upon dissolution, sulfur dioxide may cause oxidative damage to the lungs¹²⁷. Large acute exposure to either xenobiotic produces the expected acute irritant response of both the upper and lower respiratory tracts⁴⁴ and pulmonary dysfunction (see Asthma and Reactive Airways Dysfunction Syndrome) may persist for several years¹⁴⁹.

Intermediate Water-Soluble Xenobiotics

Chlorine (Cl_2). Chlorine gas is a valuable oxidizing agent with various industrial uses, and occupational exposure is common. Chlorine gas was used as a chemical warfare agent by both the French and the Germans in World War I (Chap. 132). Although chlorine gas is not generally available for use in the home, domestic exposure to chlorine gas is common. The admixture of an acid to bleach liberates chlorine gas (Fig. 124–2)^{80,135}. Because the anionic component of the acid is not involved in the reaction, combining hypochlorite with virtually any acid, such as phosphoric, hydrochloric, or sulfuric acid, may result in the release of chlorine gas. As such, inappropriate mixing of cleaning products is the cause of most nonoccupational exposures¹³⁵. Rarely, patients have intentionally generated chlorine gas in this manner for purportedly “pleasurable” purposes¹⁵⁵. Concentrated chlorine gas may be generated when aging swimming pool chlorination tablets, such as calcium hypochlorite [$\text{Ca}(\text{OCl}_2)$] or trichloro-s-triazinetriene (TST), decompose^{118,213} or are inadvertently introduced to a swimming pool while swimmers are present^{15,205}. Inadvertent mixture of $\text{Ca}(\text{OCl}_2)$ and TST results in excessive chlorine gas generation and may also be explosive¹¹⁸. Acute chlorine toxicity may occur when there is a failure of the system when compressed chlorine gas is used for direct chlorination of public swimming pools^{15,204} or for drinking water systems. Occasional mass poisoning may occur during scientific, industrial, or transportation incidents^{42,198}.

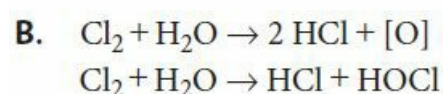


FIGURE 124–2. Chlorine chemistry. (A) Formation of chlorine gas from the acidification of hypochlorous acid. (B) Dissolution of chlorine in mucosal water to generate both hydrochloric and hypochlorous acids (HCl and HOCl) and oxidants [O].

Mass exposure has also been reported when a chlorine storage tank was being recycled, and it ruptured.⁴⁰ The odor threshold for chlorine is low, but distinguishing toxic from permissible air concentrations may be difficult until toxicity is manifest. The intermediate solubility characteristics of chlorine result in only mild initial symptoms after moderate exposure and permit a substantial time delay, typically several hours, before clinical symptoms develop. Chlorine dissolution in lung water generates HCl and hypochlorous (HOCl) acids. Hypochlorous acid rapidly decomposes into HCl and nascent oxygen (O). The unpaired nascent oxygen atom produces additional pulmonary damage by initiating a free radical oxidative cascade. Although the majority of life-threatening chlorine poisonings occur after acute, large exposures, patients with chronic, low-concentration exposure or recurrent, moderate concentration poisonings may manifest increased bronchial responsiveness.^{5,69,76}

Hydrogen sulfide (H_2S). Hydrogen sulfide exposures occur most frequently in the waste management, petroleum, and natural gas industries⁹² although poisoning occurs in asphalt, synthetic rubber, and nylon industry workers as well. It is also rarely seen in hospital workers using acid cleaners to unclog drains clogged with plaster of Paris sludge¹⁴⁸. Hydrogen sulfide is present in natural sources such as volcanic emission, in caves, and in sulfur springs. It is a decay product of organic material found in sewers or manure pits. Hydrogen sulfide, hydrogen fluoride, and phosphine are differentiated

from the other irritant gases by their ability to produce significant systemic toxicity. Hydrogen sulfide inhibits mitochondrial respiration in a fashion similar to that of cyanide (Chap. 126^{64,157}

H₂S has the distinctive odor of “rotten eggs,” which, although helpful in diagnosis, is not specific. Despite a sensitive odor threshold of several parts per billion,¹⁵⁷ rapid olfactory fatigue ensues, providing a misperception that the exposure and its attendant risk have diminished. At low and moderate concentrations (≤ 500 ppm), upper respiratory tract mucosal irritation occurs and is the principal toxicity.¹⁹² The rapidity of death in patients exposed to high H₂S concentrations makes it likely that either simple asphyxiation or cytochrome oxidase inhibition is causal in most cases.

Phosgene (carbonyl chloride {COCl₂}). During World War I, phosgene was an important weapon of mass destruction that produced countless deaths (Chap. 132). Currently, phosgene is used in the synthesis of various organic compounds, such as isocyanates, and it occasionally produces poisoning. It is a byproduct of heating or combustion of various chlorinated organic compounds¹⁸¹

Exposure to phosgene initially may produce limited manifestations, but may result in acute mucosal irritation after intense exposure. In fact, the pleasant odor of fresh hay, rather than prompting escape, ironically may promote deep and prolonged breathing of the toxic gas. The most consequential clinical effect related to phosgene exposure is delayed ARDS.^{27,169} Because of the accumulation of a significant alveolar burden of phosgene, symptoms generally are severe after they occur. The delay in onset may take up to 24 hours, so prolonged observation of patients thought to be phosgene-poisoned is warranted. The mechanism of phosgene toxicity is dependent on the dissolution of the gas into the fluid of the epithelial lining with resultant liberation of hydrochloric acid and reactive oxygen species (ROS).¹⁶⁹

Oxidant Gases. Rather than acidic or alkaline metabolites, free radicals mediate the pulmonary toxicity of certain irritant gases. Many of the chemicals discussed participate in both acid–base and oxidant types of injury. However, the clinical distinction between acid-or alkali-forming agents and oxidant gases is difficult but ultimately may prove therapeutically relevant.

Oxygen (O₂). Oxygen toxicity is uncommon in the workplace but, ironically, is common in hospitalized patients. Although O₂ may produce CNS and retinal toxicity, pulmonary damage is more common.¹⁸⁰ Several clinical studies indicate that humans can tolerate 100% O₂ at sea level for up to 48 hours without significant acute pulmonary damage.^{37,56} Under hyperbaric conditions (2.0 atmospheres absolute), such as during compressed-air diving or while inside a pressurized hyperbaric chamber, oxygen toxicity may develop within 3 to 6 hours.⁴⁷ ARDS occurs in approximately 5% of patients administered hyperbaric oxygen for therapeutic purposes.¹⁸⁰ Delayed pulmonary fibrosis, presumably from healing of subclinical injury, may develop in patients breathing lower concentrations of O₂ at sea level for shorter periods.

Although it appears paradoxical that O₂, an essential molecule, may be deleterious at elevated concentrations, it is not. In mitochondria, O₂ plays a critical role as the ultimate acceptor for electrons completing the electron transport chain. It is this same potent oxidizing activity that allows O₂ to remove electrons from other compounds generating the reactive oxygen intermediates.¹⁶⁴

Generation of ROS, including superoxide (O₂^{•−}), hydroxyl radical (OH[•]), hydrogen peroxide (HOOH), singlet oxygen (O[•]), and nitric oxide (NO), produces cellular necrosis, increases pulmonary capillary permeability, and induces apoptosis.^{142,164} NO, produced by inducible NO synthase (iNOS) in the setting of oxidative stress, is directly cytotoxic or may combine with superoxide anions to form the more reactive oxidant peroxynitrite (ONOO[−]).⁹³ Experimental prevention of these effects by administration of either parenteral NAC,^{165,207} a chemical antioxidant, or superoxide dismutase, an enzymatic antioxidant,^{37,199} suggests that the mechanism of toxicity relates to the oxidant, or electrophilic, effects of these ROS (Chap. 12). Although several other therapies have shown promise in preventing oxygen-mediated toxicity, none has yet proven to be valuable for patients who already manifest pulmonary toxicity. Current techniques for preventing pulmonary oxygen toxicity emphasize reduction of the inspired oxygen concentration by use of PEEP ventilation, although this approach failed to prove beneficial in at least one clinical trial.¹⁴ The potential role of liquid ventilation of the lung with perfluorocarbons to prevent or treat pulmonary oxygen toxicity remains under investigation.¹⁴

Oxides of nitrogen (NO_x). Oxides of nitrogen are a series of variably oxidized nitrogenous compounds.⁷³ The most important substances included in this series are the stable free radicals nitrogen dioxide (NO₂) and nitric oxide (NO), as well as nitrogen tetroxide (dinitrogen tetroxide [N₂O₄]), nitrogen trioxide (N₂O₃), and nitrous oxide (N₂O). The oxides of nitrogen are of limited value in industrial operations, although they may be generated during welding and brazing. NO₂, in addition to hydrogen cyanide, is produced in the pyrolysis of nitrocellulose, which is a substantial component of radiographic film. For example, a fire in the radiology department of the Cleveland Clinic in 1929 resulted in 125 casualties, with virtually all deaths resulting from cyanide or NO₂ gas poisoning.⁸² NO₂ toxicity may occur when propane-driven ice-cleaning machines are used in indoor ice skating rinks with poor ventilation, thereby allowing accumulation of the generated NO₂.¹¹⁴ Military exposure to high NO₂ concentrations may occur during closed-space fires, such as in

submarines¹²⁰ NO₂ also causes silo filler's disease, in which the toxic gas generated during decomposition of silage accumulates within the silo shortly after grain storage, eliminating rodents that feast on the grains^{60,215} In the absence of ventilation, high concentrations of NO₂ may accumulate in the silo such that an individual entering the silo is rapidly asphyxiated from the depletion of oxygen⁸³ Additionally, substantial quantities of NO₂ remaining after incomplete ventilation may produce the delayed-onset pulmonary toxicity characteristic of silo filler's disease. Chronic indoor exposure to NO₂, generated during cooking⁹⁹ or outdoor exposure to photochemical smog, of which the oxides of nitrogen are a component, may predispose individuals to the development or exacerbation of chronic lung diseases.

The various oxides of nitrogen may directly oxidize respiratory tract cellular membranes, but more typically generate reactive nitrogen intermediates, or radicals, such as ONOO⁻, which subsequently damage the pulmonary epithelial cells.¹⁴⁶ In addition to generating oxidant cascades, dissolution in respiratory tract water generates nitric acid (HNO₃) and NO, which produce injury consistent with other inhaled acids. In fact, inhalation of HNO₃ produces the same clinical and pathologic syndrome.⁸⁶ Antioxidants afford significant protection to human endothelial cells exposed to NO₂, indicating an important role of free radicals in the toxicology of these xenobiotics.²⁰¹

NO, an endogenous compound important as a neurotransmitter and vasorelaxant, is used clinically as exogenous inhalational therapy for pulmonary hypertension and ARDS.¹⁹⁵ In patients with ARDS not resulting from sepsis (although not specifically from inhalational injury), low concentrations of inhaled NO (5 ppm) did not improve the clinical outcome.¹⁹⁵ However, one patient with NO₂ pulmonary toxicity improved clinically after NO therapy, so further consideration is warranted.¹¹² Furthermore, its use in premature infants with respiratory distress syndrome is well accepted.¹⁶⁸ NO is less soluble in the fluid lining the epithelial surfaces than are the other oxides of nitrogen and produces irritant effects after large exposures.^{88,211} Its pulmonary oxidative toxicity, the manifestations of which are typical of the oxidant gases, is substantially enhanced by conversion to reactive nitrogen intermediates such as ONOO⁻.¹⁹ This radical selectively interacts with tyrosine to produce nitrotyrosine, which may subsequently serve as a marker for oxidant damage.⁸⁸ NO may be absorbed from the lung and is rapidly bound by hemoglobin to form nitrosylhemoglobin and methemoglobin.

Ozone (O₃). Ozone is abundant in the stratospheric region found between 5 and 31 miles above the planet. Ozone is formed by the action of ultraviolet light on oxygen molecules, thus reducing the amount of solar ultraviolet irradiation reaching earth. The ozone concentration in passenger aircrafts may at times be above regulatory limits¹⁸² although a specific relationship with the development of clinical effects in airline crew members is elusive.¹³⁶ Ozone is another important component of photochemical smog and, as such, contributes to chronic lung disease.^{32,202} It is produced in significant quantities by welding and high-voltage electrical equipment and in more moderate doses by photocopying machines and laser printers. Because of its high electronegativity (only fluorine is higher), ozone is one of the most potent oxidizing agents available. For this reason, it is used as a bleach, particularly as an alternative to chlorine in water purification and sewage treatment.

The pulmonary toxicity associated with ozone primarily results from its high reactivity toward unsaturated fatty acids and amino acids with sulfhydryl functional groups.^{21,101} Ozonation and free radical damage to the lipid component of the membrane initiate an inflammatory cascade, with resultant influx of inflammatory cells.^{22,158} Reactive nitrogen species are also implicated, as NO synthase knockout mice are relatively protected from ozone-induced inflammation and tissue injury.⁶⁷ Increased permeability of the pulmonary epithelium results in alveolar filling from the transudation of proteins and fluids characteristic of ARDS. Antioxidant agents (eg, vitamin E) that react preferentially with free radicals before membrane damage occurs prevent or limit the pulmonary toxicity of ozone.

Miscellaneous Pulmonary Irritants

Methylisocyanate. Methylisocyanate (MIC; Fig. 124–3) is one of a series of compounds sharing a similar isocyanate (N=C=O) moiety. Toluene diisocyanate (TDI) and diphenyl-methane diisocyanate (MDI) are important chemicals in the polymer industry. In those exposed to MIC in Bhopal, ARDS was evident both clinically and radiographically.¹³⁰ MIC is a significantly more potent respiratory irritant than the other regularly used isocyanate derivatives such as TDI.⁶ Cyanide poisoning does not occur, and empiric antidotal therapy is not indicated

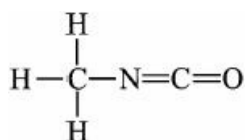


FIGURE 124–3. Methylisocyanate.

Riot control agents: capsaicin, chlorobenzylidenemalononitrile, and chloroacetophenone. Historically, riot control

agents (Fig. 132–5), commonly called Mace, consisted primarily of chloroacetophenone (CN) or chlorobenzylidenemalononitrile (CS)²⁴. Both are white solids that are dispersed as aerosols. The dispersion is generally accomplished through mixture with a pyrotechnic agent such as a grenade or with a volatile organic solvent in a personal protection canister. Because the delivery systems of these agents are of limited sophistication and are subject to prevailing environmental conditions, dosing is unpredictable, and unintended self-poisoning is common²⁴. After low-concentration exposure, ocular discomfort and lacrimation alone are expected, accounting for the common appellation tear gas. The effects are transient, and complete recovery within 30 minutes is typical, although long-lasting pulmonary effects may occur (see Asthma and Reactive Airways Dysfunction Syndrome¹⁶¹). Closed-space or close-range exposure, as well as physical exertion during exposure, may produce significant ocular toxicity, dermal burns, laryngospasm, ARDS¹⁹⁶ or death²⁴. Because of their high potential for severe toxicity, CN and CS were replaced for civilian use by oleoresin capsicum (OC), also known as pepper spray or pepper mace. Although capsaicin, its active component, is considerably less toxic, it is occasionally responsible for pneumonitis²³ and death¹⁸⁶.

Capsaicin interacts with the vanilloid receptor-1 (VR1), which was recently renamed the transient receptor potential vanilloid-1 (TRPV1).¹⁹¹ Stimulation of this receptor invokes the release of substance P, a neuropeptide involved with transmission of pain impulses. Substance P also induces neurogenic inflammation, which, in the lung, results in ARDS and bronchoconstriction (see Asthma and Reactive Airways Dysfunction Syndrome).¹⁹¹ The severe pulmonary toxicity of CS and CN likely is related to their ability to alkylate tissues in a manner similar to nitrogen mustard.⁴⁸

Metal pneumonitis. Acute inhalational exposures to certain metal compounds produce clinical effects identical to those of the chemical irritants. For example, zinc chloride (ZnCl₂) fume is used as artificial smoke because of the dense white character of the fume, and an aqueous solution is still used as a soldering flux. Exposure to zinc chloride fumes for just a few minutes is associated with ARDS and death^{66,94,95} (Chap. 103). Cadmium oxide (CdO) is generated during the burning of cadmium metal in an oxygen-containing environment, as occurs during smelting or welding (Chap. 91). The refining of nickel using carbon monoxide (Mond process) produces nickel carbonyl [Ni(CO)₄], a volatile pulmonary oxidant¹⁷⁵ (Chap. 99). Inhalation of volatilized elemental mercury¹³⁴ which occurs during the vacuuming of mercury spills or home extracting of precious metals, may be toxic. Although at sufficient concentrations, many of these metal exposures produce warning symptoms, severe toxicity may occur even in the absence of warning symptoms. The mechanism of toxicity may relate to overwhelming oxidant stress with a pronounced inflammatory response as measured by serum cytokines (eg, TNF-α) concentrations.⁹⁵ Experimental findings suggest a role for inactivation of natural antioxidant systems.²¹⁴ Patients with metal-induced pneumonitis present with chest tightness, cough, fever, and signs consistent with ARDS. Metal pneumonitis is distinguishable from other causes of ARDS only by history or, retrospectively, by elevated serum or urine metal concentrations.⁸ In particular, metal pneumonitis should be differentiated from the more common and substantially less consequential metal fume fever, discussed later in this chapter. In addition to standard supportive measures, patients with acute metal-induced pneumonitis should be hospitalized and receive corticosteroids.⁹⁵ Chelation therapy has no documented benefit for treatment of patients with ARDS, but should be used based on conventional indications.

MANAGEMENT

Standard and Supportive Measures

Management of patients with acute respiratory tract injury begins with meticulous support of airway patency by limiting bronchial and pulmonary secretions and maintaining oxygenation. Although various theoretical and experimental treatment modalities have been proposed, supportive care remains the mainstay of therapy. Supplemental oxygen, bronchodilators, and airway suctioning should be used if clinically indicated. Nitrovasodilators, diuretics, and morphine have little role in the management of patients with ARDS, although low-dose morphine may prove beneficial as an anxiolytic.^{3,150} Corticosteroid therapy, designed to reduce the inflammatory host defense response, frequently improves surrogate markers of pulmonary damage,^{123,124} such as oxygenation status, but generally offers little outcome enhancement in patients with ARDS.^{4,147} Clinical data on the efficacy of corticosteroids used in human beings exposed to pulmonary irritants is limited and inconclusive. There might be some benefit in the first 14 days after an exposure, but methylprednisolone was associated with increased mortality at 60 and 180 days (when steroids were continued after the first 14 days). A recent article reviewed animal studies published from 1966 to January 2010 and did not find a benefit in animal studies, especially after severe exposures.⁵⁴ Importantly, most studies of ARDS involve predominantly septic or traumatized patients, with few patients suffering from inhalational poisoning. Because the inflammatory response initiated by bacterial endotoxin differs from that caused by irritant gases, the applicability of these studies to the treatment of poisoned individuals is limited. There is an interesting report of simultaneous, presumably equivalent chlorine exposure in two sisters, with improved outcome in the sister who received steroid treatment.⁴⁵ Most available research evaluates parenterally administered corticosteroids, although animal models demonstrate a beneficial effect of nebulized beclomethasone^{84,54} and nebulized budesonide^{209,54} after acute chlorine poisoning. Nebulized budesonide compared to

intravenous betamethasone had similar effects.⁵⁴ However, a human pretreatment model of inhaled budesonide fails to document a substantive alteration of the effects of ozone inhalation.¹³⁷ Ketoconazole, an antifungal agent with antiinflammatory effects,¹ and nonsteroidal antiinflammatory agents, such as ibuprofen,¹⁷¹ variably improve experimental lung function or mortality in patients with ARDS of various nontoxicologic etiologies and have little current role in the therapeutic armamentarium. Furthermore, most of the aforementioned studies assess acute outcome and not long-term effects in survivors. Because corticosteroids experimentally reduce the late fibroproliferative phase during lung recovery, they ultimately may prove beneficial. Overall, there is little reason to suspect any specific benefit of corticosteroids and other antiinflammatory drugs in most poisoned patients. However, because most studies demonstrate some benefit and little identifiable risk, corticosteroid use appropriately remains routine and based largely on local practices.

The clinical similarities among patients with irritant gas exposure and other etiologies of ARDS suggest that similar management principles should be applied. Prone positioning during ventilation,^{7,74} PEEP,⁶⁸ and inverse-ratio ventilation are successful in enhancing the oxygenation of patients with ARDS of various causes but are not necessarily successful in improving outcome. Lower tidal volume mechanical ventilation using 6 mL/kg and plateau pressures 30 cm H₂O attenuated the inflammatory response¹⁴³ and resulted in lower mortality and less need for mechanical ventilation than traditional volume ventilation with 12 mL/kg.^{2,132} Although not specifically evaluated in any of these studies, there are sound theoretical reasons to believe that all of these modalities should improve oxygenation in poisoned patients as well. Although it is always important to reduce the inspired concentration of oxygen to below 50% as rapidly as possible, patients poisoned by irritant gases may be even more susceptible to oxygen toxicity as a result of depletion of endogenous antioxidant barriers.¹⁷⁸

Neutralization Therapy

A therapy unique to several of the acid- or base-forming irritant gases is chemical neutralization. Although contraindicated in acid or alkali ingestion, the large surface area of the lung and the relatively small amount of xenobiotic present allow dissipation of the heat and gas generated during neutralization. Case studies suggest that nebulized 2% sodium bicarbonate may be beneficial in patients poisoned by acid-forming irritant gases.²⁰⁴ The vast majority of these cases involve chlorine gas exposure, and most patients received other symptomatic therapies as well.²⁸ Although there appears to be no specific benefit for patients exposed to chloramine, nebulized bicarbonate therapy appears to be safe.¹⁴⁴ A prospective evaluation of patients poisoned with chloramine and chlorine gas did not show any clinically significant difference between the group getting nebulized sodium bicarbonate and the control group, although there was a small but statistical improvement in forced expiratory volume in one second (FEV₁) at 120 and 240 minutes in the group that received nebulized sodium bicarbonate.¹¹ Any sodium bicarbonate solution used should be sufficiently diluted to prevent irritation. Typically, 1 mL of 7.5% or 8.4% sodium bicarbonate solution is added to 3 mL sterile water (resulting in an approximately 2% solution for nebulization).

Whether nebulized sodium bicarbonate therapy alters the natural course of irritant-induced pulmonary damage remains uncertain. The fact that many irritants produce concomitant oxidant injury suggests that it may not. Nebulized 4% sodium bicarbonate administered to chlorine-poisoned sheep improved oxygenation, but failed to decrease mortality rates.⁴⁶ Therefore, patients receiving nebulized bicarbonate therapy require observation beyond the time of symptom resolution. Because administration of neutralizing acids for alkaline irritants, such as ammonia, has not been attempted, their use cannot be recommended at this time (Antidote in Depth: A5).

Antioxidants

Antioxidants include reducing agents such as ascorbic acid, NAC,¹⁰⁶ free radical scavengers such as vitamin E, and enzymes such as superoxide dismutase. Studies in humans have noted both increased¹⁶⁶ and decreased²⁹ endogenous antioxidant concentrations in bronchoalveolar lavage fluid in patients with ARDS. Although the concept of treating pulmonary oxidant stress with antioxidants or free radical scavengers is intriguing, most currently available evidence suggests that these xenobiotics offer negligible benefit.^{133,140} The rapid onset of the self-perpetuating destructive effects initiated by redox reactions may hinder any postexposure therapy. This interpretation is supported by pretreatment models in which antioxidants are effective at preventing or at least limiting the pathologic effects. Use of these and other newer therapies targeted against inflammatory mediators or the oxidative cascade are in the earliest investigative stages.

Xenobiotic-Directed Therapy

Patients with inhalational exposure to hydrogen fluoride should undergo frequent electrocardiographic evaluations and correction of serum electrolytes. Administration of nebulized 2.5% calcium gluconate, prepared as 1.5 mL 10% calcium gluconate plus 4.5 mL 0.9% sodium chloride solution or sterile water, should be considered to limit systemic fluoride absorption.^{107,113,200} By binding fluoride ion locally, nebulized calcium may prevent fluoride-induced cellular and systemic

toxicity. Systemic calcium salts should be administered as needed to correct hypocalcemia ([Chap. 107](#) and Antidotes in Depth: A29).

Current therapy for inhalation of capsaicin, or of any tear gas, is primarily supportive. Extracorporeal membrane oxygenation has been used in children to maintain oxygenation in the presence of severe pulmonary toxicity resulting from capsaicin exposure.²³ Although no antidotes currently are available, the newly developing insight into the receptor mechanism of capsaicin suggests that a receptor active agent may hold future promise.

Advanced Pharmacologic Therapy

Perfluorocarbon Partial Liquid Ventilation. Partial liquid ventilation involves the intrapulmonary administration of perfluorocarbons, which are inert liquids with low surface tension and excellent oxygen-carrying capacity. Studies in patients with nonchemically induced ARDS suggest that exfoliated tissue, and presumably persistent xenobiotic, may be effectively lavaged from the bronchopulmonary tree with this method.⁵¹ Perfluorocarbons improve oxygenation and may have an antiinflammatory effect, as demonstrated by reduced oxidant lung injury after liquid ventilation in animals.⁵⁰ Although it may prove to be a highly useful therapy in the future, the limited availability, high cost, and lack of demonstrated efficacy of this therapy make it suitable only for academic and research settings.⁵¹

Exogenous Surfactant

Several other developments may prove useful in the general management of patients with ARDS. Surfactant replacement therapy initially received attention as a treatment for patients with ARDS because of its beneficial effects in infant respiratory distress syndrome. Although several experimental and clinical studies suggested the safety and efficacy of surfactant therapy in patients with ARDS, large randomized, controlled clinical trials fail to show a benefit on survival.¹⁸⁴ Patients who received surfactant had a greater improvement in gas exchange during the 24-hour treatment period than patients who received standard therapy alone, suggesting the potential benefit of a longer treatment course.¹⁸⁴ But because most studies involved patients with sepsis-related ARDS, the inability to show a beneficial effect may not adequately reflect the potential of surfactant in irritant gas-induced ARDS.¹⁵¹ Many oxidant gases inactivate endogenous surfactant, although the specific effects on exogenous surfactant are not well understood.¹⁵¹

Nebulized Epinephrine. There are early studies being performed in animal models to evaluate the efficacy of nebulized epinephrine to attenuate the acute injury to lung tissue caused by smoke inhalation. A study in sheep suggests that nebulized epinephrine (4 mg) attenuates pulmonary dysfunction and decreases pulmonary hyperemia without systemic effects like hyperglycemia and elevated plasma catecholamines.¹¹⁰

OTHER INHALED PULMONARY XENOBIOTICS

A particulate, or dust, is a solid dispersed in a gas. Dust is a substantial source of occupational particulate exposure and is an important cause of acute pulmonary toxic syndromes. A respirable particulate must have an appropriately small size (generally <10 microns) and aerodynamic properties to enter the terminal respiratory tree. Nonrespirable particulates, also called nuisance dusts, are trapped by the upper airways and are not generally thought to cause pulmonary damage. In distinction from the irritant gases, there is no unifying toxic mechanism among the respirable particulates. Many of the particulate diseases, such as asbestos exposure and its sequelae, are chronic in nature; only the acute or subacute syndromes are discussed here.

Inorganic Dust Exposure

Silicosis is a range of pulmonary diseases associated with inhalation of crystalline silica (SiO_2), or quartz. It typically occurs in workers involved in occupations in which rock or granite is pulverized, including mining, quarry work, and sandblasting. Although typically a chronic disease, intense subacute exposure may produce acute silicosis in a few weeks and death within 2 years. The mechanism of toxicity probably relates to the relentless inflammatory response generated by the pulmonary macrophages.¹³⁹ These cells engulf the indigestible particles and are destroyed, releasing their lytic enzymes and oxidative products locally within the pulmonary parenchyma. Patients present with dyspnea, cor pulmonale, restrictive lung findings, and classic radiographic findings. Treatment is limited and includes steroids and supportive care.

Silica combined with other minerals is referred to as silicates, the most important of which include asbestos and talc. Talc, or magnesium silicate [$(\text{Mg}_3\text{Si}_4)\text{O}_{10}(\text{OH})_2$], is widely used in industry, but its use in the home has been curtailed over the past two decades because of cases of severe pulmonary injury.¹¹⁷ Much of the toxicity of talc is related to free silica or asbestos contamination. Improvement after acute massive exposure may be accompanied by progressive pulmonary fibrosis.

Organic Dusts

Inhalation of dusts from cotton or similar natural fibers, usually during the refinement of cotton fibers (byssinosis), produces chest tightness, dyspnea, and fever that typically begin within 3 to 4 hours of exposure. Similar reactions may occur after inhalation of hay, silage, grain, hemp, or compost dust. Symptoms often resolve during the workweek but return after a weekend hiatus. Byssinosis is probably caused by an endotoxin present on the cotton and is not immunologic in nature.²¹⁰ “Grain fever” is caused by a respirable compound associated with grain dust, as occurs during harvesting, milling, and transporting.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is the final common pathway for many different organic dust exposures.¹⁸⁷ The name attached to the individual syndrome typically identifies the associated occupation or substrate. For example, bagassosis is the term associated with sugar cane (bagasse), and farmer’s lung is the term associated with moldy hay, although both conditions are caused by thermophilic *Actinomyces* spp. When associated with puffball mushroom spores (*Lycoperdon* spp), the syndrome is called lycoperdonosis ([Chap. 120](#)); when caused by bird droppings, it is called bird fancier’s lung. The implicated allergen is capable of depositing in the pulmonary parenchyma and eliciting a cell-mediated (type IV) immunologic response. Clinical findings include fever, chills, and dyspnea beginning 4 to 8 hours after exposure. The chest radiograph usually is normal, but may reveal diffuse or discrete infiltrates. Progressive disease is associated with a honeycombing pattern on the radiograph and a restrictive lung disease pattern on formal pulmonary function testing. Treatment includes corticosteroids and avoidance of the antigen.

Metal Fume Fever and Polymer Fume Fever

Metal fume fever is a recurrent influenzalike syndrome that develops several hours after exposure to metal oxide fumes generated during welding, galvanizing, or smelting. Although most symptoms of metal fume fever are similar to those expected with irritant gas exposures (dyspnea, cough, chest pain), the presence of fever, typically 100.4°F to 102.2°F (38°C–39°C), distinguishes the syndromes.²⁵ In addition, patients may experience headache, metallic taste, myalgias, and chills. Direct pulmonary toxicity probably does not occur, and patients with metal fume fever generally have normal chest radiographs. Interestingly, acute tolerance develops, so repeat daily exposures produce progressively milder symptoms. However, the tolerance disappears rapidly, and after a short work hiatus such as a weekend, the original intensity resumes, thus accounting for the designation “Monday morning fever.” Many metal oxides are capable of eliciting this syndrome, but it is noted most frequently in patients who have welded galvanized steel, which contains zinc. Metal fume fever also occurs commonly after the high-temperature welding of copper-containing compounds, thus accounting for the historical appellation “brass foundry workers’ ague.” There is a strong association between welding-related metal fume fever and welding-related respiratory symptoms suggestive of occupational asthma.⁶⁵ Serum and urine metal concentrations typically are not elevated after the acute event, although they may be chronically elevated from daily occupational exposure. The etiology of metal fume fever is debated, but the syndrome has features suggestive of both an immunologic and a toxic etiology.²⁵ Antigen release with immunologic response appears to be responsible for the induction of symptoms. On subsequent exposure, proinflammatory cytokines, such as TNF- α , and various interleukins can be detected in bronchoalveolar lavage fluid.¹⁰⁹ However, because symptoms may occur with the first exposure to fumes, a direct toxic effect on the respiratory mucosa presumably exists.¹²² Exposure to certain metal fumes, such as cadmium oxide or other zinc compounds, may produce direct toxic effects on the pulmonary parenchyma.¹²²

The management of patients with metal fume fever is supportive and includes analgesics and antipyretics. There is no specific antidote, and chelation therapy should not be instituted unless otherwise indicated; patients with ARDS probably have metal toxicity (eg, cadmium pneumonitis). The natural course of metal fume fever involves spontaneous resolution within 48 hours. Persistent symptoms are rare and should prompt investigation for metal toxicity.

A remarkably similar syndrome occurs subsequent to inhaling pyrolysis products of fluorinated polymers (eg, Teflon), which is aptly termed polymer fume fever.¹⁷⁷ Patients develop self-limited viral illness-type symptoms several hours after exposure to the fumes. As with metal fumes, very large exposures to polymer fumes may result in direct pulmonary toxicity. Supportive care is the therapy of choice.

Asthma and Reactive Airways Dysfunction Syndrome

Asthma, or reversible airways disease, is a clinical syndrome that includes intermittent episodes of dyspnea, cough, chest pain or tightness, wheezes on auscultation, and measurable variations in expiratory airflow. Episodes typically are triggered by a xenobiotic or physical stimulus and resolve over several hours with appropriate therapy. The underlying process is immunologic in most cases, with allergen-triggered release of inflammatory mediators causing bronchiolar smooth muscle contraction and subsequent inflammation. Because asthma affects 5% to 10% of the world’s population and the triggers often are nonspecific, it is not surprising that work-aggravated asthma is extremely common. The patients are

previously sensitized, and the initial irritant exposure causes bronchospasm or similar symptoms. Thus, work-aggravated asthma is discovered early in the worker's employment, and a more appropriate workplace or occupation can be pursued.

Occupational asthma, or asthma occasioned by a workplace exposure to a sensitizing xenobiotic, accounts for perhaps 10% to 17% of all newly diagnosed asthma in adults.^{115,197} Casual exposure to one of the 250 or more known sensitizers (Table 124-4) is usually associated with a latency period of weeks or months of exposure before symptom onset. After symptoms begin, however, they recur consistently after reexposure to the inciting trigger agent. Occupational asthma with latency may be IgE dependent, in which case it is identical to allergic asthma, or is IgE independent.²⁰³ The IgE-dependent form is most commonly associated with high-molecular-weight compounds (>5000 Da) or with certain haptenic low-molecular-weight agents (eg, acetic anhydride). The low-molecular-weight agents (eg, nickel, isocyanates) more typically cause IgE-independent disease, which manifests as the delayed reaction pattern of cell-mediated, or type IV, hypersensitivity. Because contact with a trigger may be difficult to avoid in either case, reassignment or an outright occupational change may be required. Treatment for exacerbations is comparable to standard asthma therapy and includes bronchodilators and corticosteroids.

TABLE 124-4. Common Xenobiotic Sensitizers Producing Occupational Asthma

<i>Molecular Weight</i>	<i>Example</i>	<i>Primary Risk Occupations</i>
High		
Proteins	Crab shell protein	Seafood processors
Low		
Acrylate	—	Adhesives, plastics
Glutaraldehyde	—	Health care workers
Isocyanates	Toluene diisocyanate	Polyurethane foam, automobile painters
Metals	Nickel sulfate	Nickel platers
Trimellitic anhydride	—	Chemical workers
Wood dust	Western red cedar (<i>Thuja plicata</i>)	Foresters, carpenters

Acute exposure to irritant gas may result in the development of a persistent asthmalike syndrome also termed reactive airways dysfunction syndrome (RADS), irritant-induced asthma, or occupational asthma without latency. Virtually every irritative xenobiotic is reported to cause this syndrome, and those not yet described probably are simply unrecognized. Although asthma typically is associated with massive inhalational exposure, as occurred after the World Trade Center collapse,¹⁶ occasional patients are susceptible to low-level exposure.³³ RADS is often compared to occupational asthma because both disorders are chemically induced and most frequently occur after chemical exposure in the workplace.⁴⁹ However, in comparison with those who develop occupational asthma, patients who develop RADS have a lower incidence of atopy and are exposed to agents not typically considered to be immunologically sensitizing.³³ In addition, the airflow improvement with β_2 -adrenergic agonist therapy is significantly better in patients with occupational asthma.⁷⁵ Bronchial biopsy performed in patients with RADS generally reveals a chronic inflammatory response.⁷⁵ RADS may have a neurogenic etiology,¹²⁵ as opposed to an immunologic origin as in patients with occupational asthma, which may differentiate these clinically similar diseases on a mechanistic basis. Neurogenic inflammation results from increased vascular permeability, presumably secondary to release of substance P from unmyelinated sensory neurons (C fibers).⁵⁸ Neurogenic inflammation is inhibited by substance P depletors, such as capsaicin, and enhanced by substances that inhibit neutral endopeptidase, the enzyme responsible for degradation of substance P.¹²⁶ The role of corticosteroids is undefined, but animal models suggest an antiinflammatory benefit, and they are widely used.⁵⁵ Recovery may take months, with the delay related to either ongoing low-level exposures to endopeptidase inhibitors or persistent irritation of impaired tissue by environmental irritants such as pollution.

SUMMARY

- Although the spectrum of xenobiotics capable of causing pulmonary toxicity is large, the pathologic changes are rather limited.
- Gases that have little or no irritant potential or systemic toxicity cause simple asphyxiation, in which the ambient atmosphere has a diminished oxygen concentration.

- Parenchymal irritation occurs after exposure to acid forming or free radical generating gases and may progress to severe toxicity manifesting as ARDS.
- RADS is described in patients after exposure to virtually all of the irritant gases.
- Treatment of all such exposures centers on symptomatic and supportive care.

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125 CARBON MONOXIDE

Christian Tomaszewski

Carbon Monoxide (CO)	
MW	= 28.01 Da
Gas density	= 0.968 (air = 1.0)
Blood carboxyhemoglobin level	
Nonsmokers	= 1%–2%
Smokers	= 5%–10%
Action level	> 10%
TLV–TWA	= 50 ppm

HISTORY AND EPIDEMIOLOGY

Carbon monoxide (CO) is formed during the incomplete combustion of virtually any carbon-containing compound. Because it is an odorless, colorless, and tasteless gas, it is remarkably difficult to detect in the environment even when present at high ambient concentrations and is a leading cause of poisoning morbidity and mortality in the United States. Based on US national death certificate data, there were 439 annual deaths from unintentional non-fire exposure to CO from 1999 to 2004.^{25,123} The groups with the highest risk were male gender and elderly age, possibly because of occupational exposure and inability to discern CO symptoms, respectively. CO related mortality remained essentially unchanged in 2002 despite increased CO detector use.^{22,24,26} More than half of these cases (64%) occurred in homes with faulty furnaces, usually in the fall or winter months. Many clusters are associated with power failures during catastrophic weather, such as ice storms, blizzards, and hurricanes.^{22,23} With improved data collection, the CDC WONDER database reported 1944 deaths in the United States in 2010 due to the toxic effects of CO.²⁷

Just as important as mortality, are the greater number of survivors from CO poisoning. Despite increased awareness for CO poisoning, in 2004 to 2006, there were still an average of 20,636 nonfatal, unintentional, non-fire-related CO exposures treated annually in the United States.²⁶ More than 40% of cases occurred in the winter, with almost 75% occurring in residences. However, exclusion of intentional and fire related cases severely underestimates the extent of the problem. Based on firsthand hospital data, a minimum of 50,000 CO cases present to US Emergency Departments (EDs) each year, up to half resulting in hospitalization.^{80,91} More recent data using probable and suspected cases suggests that there were over 230,000 ED visits in 2007 alone that were unintentional and related to non-fire CO poisoning.⁹²

The bigger problem with CO poisoning may be the associated morbidity that survivors risk even after acute treatment. The most serious complication is persistent or delayed neurologic or neurocognitive sequelae, which occurs in up to 50% of patients with symptomatic acute poisonings.^{68,144,196} There is still no highly reliable method of predicting who will have a poor outcome, requiring the threshold for HBO therapy for CO poisoning and follow-up be particularly low.

Potential sources of CO abound in our society, often resulting in unintentional poisoning²⁶ (Table 125–1). Although CO is found naturally in the body as a byproduct of hemoglobin degradation by heme oxygenase found in the liver and spleen,⁴⁰ it is readily available for inhalation from the incomplete combustion of virtually any carbonaceous fuel. Alternatively, absorption—dermal, ingestion, or inhalation—of methylene chloride may result in CO toxicity after hepatic metabolism¹²⁸ (Chap. 108). Despite catalytic converters and other emission controls, more than 50% of unintentional CO deaths are still caused by motor vehicle exhaust.^{39,123} Occupants of motor vehicles are not the only victims of exhaust gases; CO poisoning is also reported in occupants of the beds of pickup trucks and on boats.^{21,79} Workers can become symptomatic from use of propane powered equipment indoors such as ice skating rink resurfacers²⁰ and forklifts.⁵⁵ For optimal performance, propane-powered forklifts are typically adjusted to produce no less than 10,000 ppm of CO in exhaust, but in fact average more than 30,000 ppm.⁵⁶ In an enclosed warehouse with poor ventilation, even with proper emission control, CO levels could exceed safe recommendations within an hour.

TABLE 125–1. Sources of Carbon Monoxide Implicated in Poisonings

Anesthetic absorbents
Banked blood
Boats
Camp stoves and lanterns
Charcoal grills
Coffee roasting
Formic acid (with strong acid)
Gasoline powered equipment (eg, generators, power washers)
Ice resurfacing machines
Methylene bromide
Methylene chloride
Natural gas combustion furnaces (water heaters, ranges and ovens)
Propane powered forklifts
Underground mine explosions
Wood pellet storage

In the past 10 years, non-vehicular sources of CO have increasingly accounted for the majority of unintentional poisonings.¹²³ Predominantly, these have involved the burning of charcoal, wood, or natural gas for heating and cooking.⁷⁶ Natural gas (methane or propane) burning furnaces for heating are often implicated, especially when the flue is blocked.^{83,84} Gas kitchen stoves are also an important source of CO in indigent populations with marginal heating systems.⁸⁴ In fact, the use of gas stoves for supplemental heat is predictive of CO poisoning in patients who present to the ED with headache and dizziness. During ice storms, blizzards, hurricanes, and other natural disasters, the indoor use of gasoline powered generators¹⁸⁹ and charcoal burning grills, the latter particularly in immigrant populations, has resulted in epidemic CO poisoning outbreaks.^{22,23,202}

Fires are another important source of CO exposure, contributing substantially to the approximate 5613 smoke inhalation deaths each year.³⁹ CO is considered to be the most common hazard to smoke inhalation victims.^{61,155} These cases are further compounded by the high incidence of hydrogen cyanide poisoning ([Chap. 126](#)).⁷¹

TOXICOKINETICS

CO is readily absorbed after inhalation. The Coburn-Forster-Kane (CFK) model allows the prediction of COHb levels based on exposure history.⁴¹ This model has been simplified to allow estimation of the equilibrium based on the ambient concentration of CO in ppm: $\text{COHb (\%)} = 100/[1 + (643/\text{ppm CO})]$.¹⁸¹ This assumes that the individual weighs 70 kg and is not anemic. With exponential uptake, it may take more than 4 hours for equilibrium to be attained. Therefore, within minutes of high CO exposures, the arterial COHb level may actually overshoot predicted estimates before equilibration.^{8,13} Endogenous production of CO is not factored in because its contribution to COHb is only 2%.

After it has been absorbed, CO is carried in the blood, primarily bound to hemoglobin. The Haldane ratio states that hemoglobin has approximately a 200 to 250 times greater affinity for CO than for oxygen. Therefore, CO is primarily confined to the blood compartment, but eventually up to 15% of total CO body content is taken up by tissue, primarily bound to myoglobin.⁴¹ Therefore, the dissolved CO level in the plasma may better reflect the ultimate potential for poisoning because it is available for diffusion into all tissue compartments, including the muscle and brain.¹⁰⁷

Elimination of CO, like absorption, from the blood can be modeled mathematically using the CFK model. The equation predicts a half-life of 252 minutes. In actual volunteer studies, means of 249 and 320 minutes breathing room air are reported.¹⁴¹ With 100% oxygen, these half-lives can be reduced significantly to means ranging 47 to 80 minutes in studies of volunteers who attain COHb levels of 10% to 12%.^{141,163} Patients poisoned with CO showed actual mean half-lives ranging from 74 to 131 minutes when treated with 100% oxygen.^{196,197}

Methylene chloride, a paint stripper, is another source of CO. It is readily absorbed through the skin or by ingestion or inhalation and is metabolized in the liver to CO.¹⁵⁸ Reaching peak COHb levels may take 8 hours or longer and may range from 10% to 50%.^{106,147} Because of ongoing production of CO, the apparent COHb half-life is prolonged to 13 hours in these patients.¹⁴⁵ COHb levels after methylene chloride exposure appear to be proportional to the concentration and duration of exposure.¹⁴⁵

PATHOPHYSIOLOGY

The most obvious deleterious effect of CO is binding to hemoglobin, rendering it incapable of delivering oxygen to the cells. Therefore, despite adequate partial pressures of oxygen in blood (PO_2), there is decreased arterial oxygen content. Further insult occurs because CO causes a leftward shift of the oxyhemoglobin dissociation curve, thus decreasing the offloading of oxygen from hemoglobin to tissue¹⁵⁰ (Fig. 22–2). This may result in part from a decrease in erythrocyte 2,3-bisphosphoglycerate (2,3-BPG) concentration. The net effect of all these processes is the decreased ability of oxygen to be delivered to tissue.

CO toxicity cannot be attributed solely to COHb-mediated hypoxia. Neither clinical effects nor the phenomena of delayed neurologic deficits can be completely predicted by the extent of binding between hemoglobin and CO.^{75,177} Furthermore, such a model fails to explain why even minimal levels of COHb (4%–5%) may result in cognitive impairment. An early study showed that dogs breathing 13% CO died within 1 hour and had COHb levels of 54% to 90%. However, exchange transfusion of this same blood into healthy dogs to reach similar COHb levels caused no untoward effects.⁶² Hemorrhaging the dogs to comparable degrees of anemia also produced no adverse effects. The appropriate conclusion was that inherent to CO toxicity is its delivery to target organs such as the brain and heart and that although COHb is easily measured; it rarely has a significant contribution to clinical toxicity. For CO to reach tissue, it had to be dissolved in the plasma rather than bound to hemoglobin.^{66,67}

CO interferes with cellular respiration by binding to mitochondrial cytochrome oxidase. Initial studies show that this binding is especially exaggerated under conditions of hypoxia and hypotension. In vitro rat models demonstrate that this oxidative stress causes mitochondrial damage with protein oxidation and lipid peroxidation, particularly in the hippocampus and corpus striatum.¹⁶⁴ In vivo models reveal that CO poisoning causes cell loss in the frontal cortex, which is associated with decrements in learning and memory.¹⁴² Although no comparable brain studies exist in humans, the peripheral lymphocytes and monocytes of CO-poisoned patients show cytochrome oxidase inhibition accompanied by increased lipid peroxidation.^{59,118} In a small clinical series of CO-poisoned patients, normalization of this cytochrome activity lagged behind and seemed to agree better with symptom severity than COHb levels.¹¹⁹

Inactivation of cytochrome oxidase may be only an initial part of the cascade of inflammatory events that results in ischemic reperfusion injury to the brain after CO poisoning (Fig. A38–1). During recovery from the initial poisoning, white blood cells are attracted to and adhere to the damaged brain microvasculature.^{169,170,171} This attraction may be partly attributable to endothelial changes from initial cytochrome oxidase dysfunction, mediated primarily through the free radical nitric oxide (NO).^{169,175} CO displaces NO from platelets that in turn form peroxynitrites, which are even stronger inactivators of cytochrome oxidase.¹⁷⁵ Multiple animal studies demonstrate that NO is ultimately responsible for much of the endothelial damage from CO and that NO synthase inhibitors can prevent toxicity.^{174,175} The NO formation promotes platelet–neutrophil aggregates that in turn lead to neutrophil adhesion to the brain microvasculature.¹⁷⁰ Myelin peroxidase activation in the area may further promote neutrophil adhesion with degranulation and release of proteases that convert xanthine dehydrogenase to xanthine oxidase, an enzyme that promotes formation of oxygen free radicals.¹⁶⁸ The end result of this process is delayed lipid peroxidation of the neurons, and the extent of destruction may be correlated with decrements in learning in rodents.¹⁶⁸ Rats depleted of xanthine oxidase through a tungsten modified diet show no changes in myelin basic protein and cognitive function after CO poisoning.⁸²

Simultaneously, with all this perivascular oxidative stress in the brain, there is activation of excitatory amino acids, which ultimately may be responsible for the subsequent neuronal cell loss.¹⁷⁵ In fact, in rat brains, glutamate concentrations increase after CO poisoning. Glutamate is an excitatory amino acid that can bind at N-methyl-D-aspartate (NMDA) receptors and cause intracellular calcium release, resulting in delayed neuronal cell death (Chap. 14). Blockade of NMDA receptors may prevent the neuronal death and learning deficits that accompany serious CO poisoning in mice.⁹³ Increases in the glutamate concentrations in rat brain in the first hour after severe CO poisoning are followed by a later increase in hydroxyl radicals.¹⁴² Ultimately, at 1 to 3 weeks, the animals show histologic evidence of both neuronal necrosis and apoptosis in the frontal cortex, globus pallidus, and cerebellum that are accompanied by deficits in learning and memory.

CO neuronal cell death may be caused by apoptosis, which has been confirmed in various models. In bovine pulmonary artery cells, CO exposure is accompanied by activation of caspase-1, a protease implicated in delayed cell death.¹⁷³ Confirmatory evidence was provided in the same study because both caspase-1 and NO synthase inhibitors blocked apoptosis. The end result of all these cellular processes is brain injury, particularly in the basal ganglia and hippocampus.¹⁹² In some studies this is accompanied by learning impairment.¹⁴² Thus, animal models correlate well with what ultimately occurs in victims of serious CO poisoning, namely, persistent or delayed deficits in learning and memory associated with structural changes in the brain.

Myoglobin, another heme protein, binds CO with an affinity about 60 times greater than it binds oxygen.⁴² About 10% to 15% of the total body store of CO is extravascular, primarily binding to myoglobin.^{13,41} A dog model demonstrates that this binding is enhanced under hypoxic conditions.⁴² This binding may partially explain the myocardial impairment that occurs in both animal studies and low-level exposures in patients with ischemic heart disease. The combination of COHb formation, which decreases oxygen-carrying capacity, and reduced myoglobin in the heart, which decreases oxygen

extraction, may explain the preterminal dysrhythmias that occur in animals.

Several studies suggest that CO effects on the cardiovascular system are necessary for ischemic reperfusion injury of the brain. Hypotension is an essential component and results from a combination of myocardial depression and vasodilation. CO, perhaps because of its similarity to NO, activates guanylate cyclase, which in turn relaxes vascular smooth muscle. Also, CO may further displace NO from platelets, resulting in additional vasodilation.¹⁷⁴ These factors contribute to the hypotension that occurs in animal experiments with exposure to high concentrations of CO.⁶² Such an episode of hypotension may present clinically as syncope, and this finding portends a worse clinical outcome.³⁴ In rhesus monkeys, cerebral white matter lesions correlate better with decreases in blood pressure than with COHb level.⁶⁵ Lipid peroxidation of the brain in rats develops an hour after a CO exposure that has produced syncope and hypotension.¹⁶⁷ This delay is comparable to the time that is necessary to produce mitochondrial destruction from oxidative stress in rats exposed to CO. In a feline model, central nervous system (CNS) damage from CO can be reproduced only when hypoxia is accompanied by an interval of ischemia, confirming the ischemic-reperfusion model.¹³²

Endogenous CO behaves like NO, binding to guanylate cyclase and thereby increasing cGMP concentrations.⁹⁴ Although low endogenous concentrations are physiologic, excessive concentrations of CO from exogenous sources may be problematic because CO persists much longer than NO. CO appears to be a neuronal messenger by virtue of the fact that as a gas, it can diffuse and signal adjacent cells.¹¹²

CLINICAL MANIFESTATIONS

Acute Exposure

The earliest symptoms associated with CO poisoning are often nonspecific and readily confused with other illnesses, typically a viral syndrome¹⁹³ (Table 125–2). The initial symptom reported by volunteers within 4 hours of exposure to 200 ppm CO (producing COHb levels of 15%–20%) is headache; shorter exposures at 500 ppm also produce nausea.¹⁶⁰ The incidence of CO poisoning in symptomatic patients presenting to EDs in the winter with an influenzalike illness ranges from 3% to 24% in some series.^{51,84} The typical presenting complaints include headache, dizziness, and nausea, and the most frequent exposures occur during the winter, explaining why influenza is the most common misdiagnosis.⁵¹ The most common symptom, headache, is usually described as dull, frontal, and continuous. CO poisoning is also frequently misdiagnosed as food poisoning, gastroenteritis, and even colic in infants. Similar to adults, children tend to develop nonspecific symptoms, complicating diagnosis.

TABLE 125–2. Clinical Manifestations of CO Poisoning

Ataxia	Myocardial ischemia
Cardiac dysrhythmias	Nausea
Chest pain	Syncope
Confusion	Tachypnea
Dizziness	Visual blurring
Dyspnea	Vomiting
Headache	Weakness

Continued exposure to CO may lead to symptoms attributable to oxygen deficiency in the heart. Low-level exposures, leading to COHb levels of 2% to 4%, in volunteers with stable angina results in decreased exercise tolerance as well as signs and symptoms of myocardial ischemia.² At higher levels (COHb 6%), there is a greater frequency of premature ventricular contractions during exercise. Myocardial infarction and dysrhythmias are described in victims of CO poisoning, and acute mortality from CO is usually a result of ventricular dysrhythmias.^{1,2} Prolonged exposure to CO or high COHb levels are associated with temporary myocardial stunning, lasting usually less than 24 hours and reflected by a decrease in left ventricular ejection fraction (LVEF).⁹⁵ This stunning is reflected by a decrease in LVEF and is correlated with increased β -type natriuretic peptide. Troponin may also be elevated in the absence of any coronary artery disease or even ECG or ECHO changes.^{28,46} These patients have an increased propensity for cardiac mortality, with almost one-third dying within 8 years after serious CO poisoning.⁸⁵

The CNS is the organ system that is most sensitive to CO poisoning. Acutely, otherwise healthy patients may manifest headache, dizziness, and ataxia at COHb levels as low as 15% to 20%; with higher levels or longer exposures causing syncope, seizures, or coma.¹⁹³ Patients may present with focal neurologic symptoms suggestive of a cerebrovascular accident. The electroencephalogram (EEG) may show diffuse frontal slow-wave activity. Within a day of exposures that result in coma, computed tomography (CT) and magnetic resonance imaging (MRI) can show decreased density in the

central white matter and globus pallidus (Fig. 125–1).¹⁰⁸ Autopsies show involvement of other areas, including the cerebral cortex, hippocampus, cerebellum, and substantia nigra.¹⁰⁴



FIGURE 125–1. Computed tomography of the brain showing bilateral lesions of the globus pallidus (arrows) in a patient with poor recovery from severe carbon monoxide poisoning. (Used with permission of The New York City Poison Center Fellowship in Medical Toxicology.)

Metabolic changes may reflect CO's toxic effects better than any particular COHb level. Patients with mild CO poisoning may develop respiratory alkalosis in an attempt to compensate for the reduction in oxygen-carrying capacity and delivery. More substantial exposures result in metabolic acidosis with lactate production that accompanies tissue hypoxia.¹⁵⁷ Even in the absence of hypotension, lactate was an independent predictor of worse mental status and inpatient complications.¹²² The importance of metabolic acidosis was highlighted in a retrospective series of 48 CO-poisoned patients, in which hydrogen ion concentration was a better predictor of poor recovery during initial hospitalization than was COHb level.¹⁸⁶

Although the brain and heart are the most sensitive, other organs may also manifest the effects of CO poisoning. One-fifth to one-third of patients with severe CO poisoning—those who required endotracheal intubation—develop pulmonary edema.⁶⁹ This can be due to cardiac depression directly from CO and ARDS from associated smoke inhalation.^{71,95,155} This does not appear to be a direct effect of CO on lung tissue because sheep with prolonged exposure to CO, resulting in COHb levels greater than 50%, showed no anatomic or physiologic changes in lung function.¹⁵⁴ Although myonecrosis and even compartment syndromes occur, patients rarely develop acute kidney injury (AKI). Retinal hemorrhages may develop with exposures greater than 12 hours.⁹⁶ Cherry-red skin coloration occurs only after excessive exposure (2%–3% of cases referred to one hyperbaric center) and may represent a combination of CO-induced vasodilation, concomitant tissue ischemia, and failure to extract oxygen from arterial blood.¹⁴⁸ Another classic but uncommon phenomenon is the development of cutaneous bullae after severe exposures. These bullae are thought to be caused by a combination of pressure necrosis and possibly direct CO effects in the epidermis.

NEUROCOGNITIVE SEQUELAE

The persistent or delayed effects of CO poisoning are varied and include dementia, amnestic syndromes, psychosis, parkinsonism, paralysis, chorea, cortical blindness, apraxia and agnosia, peripheral neuropathy, and incontinence.¹⁰⁵ If not diagnosed at initial poisoning, neurologic deterioration can be delayed and preceded by a lucid period of 2 to 40 days after the initial poisoning.³⁴ In patients admitted to an intensive care unit for severe CO poisoning and treated with 100% oxygen, 14% of survivors had permanent neurologic impairment.¹⁰⁰ In a Korean series of 2360 CO-poisoned patients, 3% continued to show memory failure or parkinsonian features one year after exposure.³⁴ Another series of 63 seriously

poisoned patients showed memory impairment in 43% and deterioration of personality in 33% at 3-year follow-up.¹⁵⁷ Children also develop behavioral and educational difficulties after severe poisoning.¹⁰³ However, patients older than 30 years of age appear to be more susceptible to the development of delayed sequelae.^{34,198} Most cases of delayed neurocognitive sequelae are associated with loss of consciousness in the acute phase of toxicity.³⁴

Neurocognitive sequelae probably involve lesions of the cerebral white matter.⁶³ Weeks after exposure, autopsies show necrosis of the white matter, globus pallidus, cerebellum, and hippocampus. MRI studies confirm the damage to the white matter and hippocampus.^{58,108,193} Animal studies show that having a markedly elevated COHb level alone cannot cause similar white matter lesions but that there must also be an episode of hypotension.^{65,132} The fact that the areas permanently damaged in serious CO poisoning cases are the areas with the poorest vascular supply in the brain is consistent with these findings.

CHRONIC EXPOSURE

Often, patients complain of persistent headaches and cognitive problems after long-term exposure to low concentrations of CO. Unfortunately, to date, there have been no controlled studies demonstrating that in the absence of a severe acute poisoning episode, this type of exposure results in any long-term sequelae. Warehouse workers who are chronically exposed to CO from propane combustion have intermittent problems with headache, nausea, and lightheadedness.⁵⁵ Fortunately, unless there has been an episode of severe poisoning with acute deterioration, most workers go on to have resolution of their symptoms.⁵⁶ One series of chronic CO poisoning demonstrates a high incidence of headache and memory complaints along with motor slowing and memory problems on neuropsychologic testing.¹²⁵ Although many of the objective deficits improved with elimination of the exposure and HBO treatment, many continued to have posttraumatic stress and conversion disorders. Although it is unclear that chronic exposure to low concentrations of CO can cause permanent damage, health care providers still should be vigilant for symptomatic individuals to prevent continued or catastrophic outcomes.

DIAGNOSTIC TESTING

The most useful diagnostic test obtainable in a suspected CO poisoning is a COHb level. Normal levels of COHb range from 0% to 5%. Levels at the high end of this range occur in neonates and patients with hemolytic anemia because CO is a natural byproduct of the breakdown of protoporphyrin to bilirubin.³³ Of note, in blood samples from neonates, falsely high COHb levels up to 8% can occur due to interference of fetal hemoglobin with spectroscopy.¹⁹¹ COHb levels average 6% in one-pack-per-day smokers but may range as high as 10%.¹⁵⁹ Although high COHb levels confirm exposure to CO, particular levels are not necessarily predictive of symptoms or outcome.^{75,140}

The usual method for measuring COHb is with a cooximeter, a device that spectrophotometrically reads the percentage of total hemoglobin saturated with CO. Traditionally, arterial blood was used for this determination; however, venous blood levels are accurate as there is little CO extraction from hemoglobin across the capillary bed.¹⁸⁵ Refrigerated heparinized samples yield accurate COHb levels for months and at room temperature for 28 days, making retrospective clinical and postmortem evaluations reliable.^{73,102}

Bedside tests using ammonia or sodium hydroxide are unable to differentiate reliably various levels of COHb versus control subjects.¹³⁴ Because of the similarities in extinction coefficients, COHb is misinterpreted as oxyhemoglobin on most types of pulse oximetry (Chap. 29).⁷ Thus, the pulse oximetry reading is usually normal in the setting of even severe CO poisoning.⁷² Some newer pulse oximeters, called pulse cooximeters, have the ability to measure COHb noninvasively.⁵ A study in 10 healthy volunteers who inhaled CO at 500 ppm until they reached a peak COHb level of 15% found good agreement between pulse cooximetry and cooximetry.⁶ Early models of a commercial bedside pulse cooximeter showed very poor agreement, mischaracterizing half the patients with levels over 15% as lower.¹⁸⁵ Subsequently, another large cohort of ED patients, using a later model of the same device, found that it measured COHb well, with a bias of 3% and precision of 3.3%.¹⁴⁹ Because it tends to overestimate COHb, the authors recommend a normal upper limit of 6.6% as triggering intervention. Because the pulse cooximeter is noninvasive, it may be useful in screening ED patients for occult CO poisoning who present with nonspecific symptoms.³¹ In addition, it may be used in the field for screening fire victims, patients with potential CO exposure, and rescuers.

Breath-sampling methods may be used for screening patients.^{43,45,53} A cutoff of 53 ppm in patients breathing air and 43 ppm in those breathing oxygen has an approximate reliability of approximately 80% in predicting COHb levels above 10%.⁵⁷ Breath sampling for CO has been advocated as a quick screening device for detecting recent exposure to CO in ED patients.

Some clinical laboratories measure CO directly in blood samples rather than COHb. This technique involves assaying

CO directly with infrared spectrophotometry after it is extracted from the blood sample with a manometer. Based on calculations rather than true experimental data, the assumption has been made that for a patient with a normal hemoglobin, a CO level of 1 mmol/L corresponds to an 11% COHb concentration. A simpler method to measure serum CO content is to add a known solution of hemoglobin followed by sodium dithionite to form COHb. The resulting COHb is measured spectrophotometrically with the assumption that 1 mole of hemoglobin binds 4 moles of CO. Interestingly, in one study, serum CO ranged from 0.14 to 0.6 mg/L but was the same in smokers (average, 4.6% COHb) and nonsmokers (average, 1% COHb).²⁰⁰ At this time, further research is required to determine the clinical importance of serum CO content.

Additional laboratory tests may be useful in severe poisoning cases. An arterial or venous blood gas analysis will confirm the presence of metabolic acidosis, and a measurement of serum lactate concentration can be performed simultaneously. Metabolic acidosis with elevated lactate concentration may serve as a more reliable index of severity than a measurement of the COHb concentration.¹⁵⁷ Unfortunately, arterial pH does not correlate well with either initial neurologic examination or the COHb level, making it a poor criterion for deciding the need for HBO treatment.¹²⁴ Specificity of lactate may also be low in smoke inhalation victims, where it may indicate concomitant cyanide poisoning (Chap. 126).

Cardiac monitoring and a 12-lead electrocardiography (ECG) are essential to identify ischemia or dysrhythmias in symptomatic patients with preexisting coronary artery disease or severe exposure. Mild elevations of creatine phosphokinase are common (ranging 20–1315 IU/L in one series of 65 cases), usually because of rhabdomyolysis rather than cardiac sources.¹⁵³ However, because CO may cause myocardial infarction in the presence of normal coronaries,⁹⁵ it is not surprising to see nonspecific increases in troponin concentrations, which may reflect diffuse cardiac myonecrosis rather than focal coronary artery disease.²⁹ Congestive heart failure or hypotension can be evaluated with a β -type natriuretic peptide or echocardiography (or both), looking for evidence of myocardial stunning.⁹⁵ Because of the potential for increased cardiovascular mortality,⁸⁵ patients with ECG changes or elevated cardiac enzymes may benefit from further cardiac testing, a stress test, or angiography.

The problem with using COHb levels to base treatment is that there is a wide variation in clinical manifestations across patients with identical COHb levels. Furthermore, particular COHb levels are not predictive of symptoms or final outcome.^{114,131,157} In a large prospective study of CO poisoning, COHb levels did not correlate with loss of consciousness and were not predictive of delayed neurologic sequelae.¹⁴⁴ Admission COHb levels are inaccurate predictors of peak levels, and the use of nomograms to extrapolate to earlier levels has not been validated. Their credibility is also suspect because of the great variability in COHb half-lives and differences in treatment with oxygen.

Because of the inherent unreliability of COHb levels in predicting outcome, researchers are searching for other surrogate markers. Rats have early increases in glutathione released from erythrocytes, a potential marker for CO oxidative stress that could ultimately lead to brain injury.¹⁷⁶ Another promising marker is serum S100B, a structural protein in astroglia that is released from the brain after hypoxic stress. A series of 38 consecutive patients poisoned with CO showed that those who presented with normal neurologic findings and no loss of consciousness had normal S100B concentrations.¹⁵ Patients who presented with loss of consciousness and neurologic deficits all had elevated concentrations. CO-poisoned rats treated with HBO did not develop elevated S100B concentrations unlike those treated with ambient oxygen therapy.¹⁴ Although markers used for cerebral injury, specifically S100B and neuron-specific enolase, do rise after CO poisoning, they have not been shown to be predictive of final outcome.^{17,146} Levels at the target organ, the brain, show that S100B in the cerebrospinal fluid predicted extreme neurological sequelae, that is, persistent vegetative state, only.⁹⁰ A recent pilot study concluded that almost 100 different plasma proteins—cytokines, chemokines, and other biomarkers—increase after CO poisoning in patients; their significance awaits more definitive studies.¹⁷²

NEUROPSYCHOLOGIC TESTING

The extent of neurologic insult from CO can be assessed with a variety of tests. The most basic is documentation of the normal neurologic examination with a quick mini mental status examination. A more sensitive indicator of the acute effects of CO on cortical function is a detailed neuropsychologic test battery developed specifically for CO patients.¹¹⁷ The advantages of such testing, which usually takes about 30 minutes, are that it can reliably distinguish 79% of the time between CO-poisoned patients and control subjects, and it shows improvement with appropriate HBO treatment.¹¹⁷ Unfortunately, such testing shows a sensitivity of only 77% and specificity of 80% for CO poisoning. There may be practice effects as well if repeated testing is performed. Another study suggested that the degree of impairment CO patients had on a test of short-term rote and context-aided verbal memory correlated well with the number of HBO treatments needed.¹¹⁵ The biggest problem with such neuropsychiatric testing is that it is unclear if deficits in the test during the acute CO poisoning phase are at all predictive of the development of neurologic sequelae and therefore the necessity of HBO treatment.

NEUROIMAGING

Acute changes on CT scans of the brain occur within 12 hours of CO exposure that resulted in loss of consciousness.^{108,120} Symmetric low-density areas in the region of the globus pallidus, putamen, and caudate nuclei are frequently noted.⁸⁸ Changes in the globus pallidus and subcortical white matter early within the first day after poisoning are associated with poor outcomes¹³⁶ (Fig. 125–1). Alternatively, in one series of 18 patients, a negative CT within a week of admission was associated with favorable outcome.¹⁸² The use of contrast may enhance early isodense changes not visible on initial CT scan²⁰⁶ but is not routinely performed.

MRI appears to be superior in detecting basal ganglia lesions after CO poisoning.¹⁰⁸ One study found a much higher incidence of periventricular white matter changes on MRIs done within the first day after exposure. However, such changes had no correlation with COHb level or cognitive sequelae.¹³⁶ These periventricular changes are more common and probably more sensitive than globus pallidus lesions. Globus pallidus lesions were present on MRI in only one patient (1.4%) in a prospective study of CO-poisoned patients, half of whom had loss of consciousness.⁸⁸ Diffusion-weighted MRI may have more promise in detecting changes in subcortical white matter within hours of serious CO poisoning.¹⁶⁵ Regardless, neuroimaging usually does not influence patient management and can be reserved for patients who show poor response or have an equivocal diagnosis.

The most promising area of neuroimaging after CO poisoning is in assessing regional cerebral perfusion.^{37,135} Single-photon emission CT (SPECT) gauges regional blood flow noninvasively using an iodine or technetium tracer. In one series of 13 patients with delayed neurologic sequelae, all cases showed patchy hypoperfusion throughout the cerebral cortex within 11 days of poisoning.³⁵ These changes in perfusion may occur as early as one day after poisoning and primarily involve watershed regions such as the temporoparietooccipital area.⁴⁹ Perfusion defects on SPECT scanning appear to be associated with neuropsychological impairment months after serious CO poisoning.⁵⁸ Unfortunately, because of the scant availability of the procedure and the lack of comprehensive studies, SPECT scanning is not the definitive tool at this time for determining prognosis or need for HBO. In addition, when imaging patients 1 to 2 years post poisoning, it appears that T2 weighted imaging on MRI is more sensitive than SPECT scanning.³²

Positron emission tomography (PET) can also be used to evaluate regional blood flow as well as oxygen metabolism in the brain after CO exposure. In one series of severely CO-poisoned patients, PET examination after HBO treatment showed increased oxygen extraction and decreased blood flow in the frontal and temporal cortices.⁴⁷ Of note, patients with permanent deficits persisted in showing these abnormalities on PET scanning. One delayed PET study demonstrated that increases in dopamine D₂ receptor binding in the caudate and putamen after CO poisoning were improved with bromocriptine, at which time neuropsychiatric symptoms resolved.²⁰⁵ Although PET scanning cannot be used to predict outcome, abnormalities that persist on the scan may be indicative of patients with permanent neurologic sequelae.

To complement perfusion studies, EEG mapping has also been performed on CO-poisoned patients. Although initial studies demonstrate that many patients have regional EEG abnormalities after poisoning, it is unknown if these are predictive of persistent or delayed neurologic problems. EEG mapping may be discrepant relative to SPECT scanning because EEG preferentially demonstrates subcortical lesions.

MANAGEMENT

The mainstay of treatment is initial attention to the airway. One hundred percent oxygen should be provided as soon as possible by either non-rebreather face mask or endotracheal tube. Although concerns have been raised regarding toxicity from excess oxygen, patients poisoned with CO can still have cellular hypoxia in spite of normal oxygen saturation.^{12,72} It is important to remember that a non-rebreathing mask only delivers 70% to 90% oxygen; a positive pressure mask or an endotracheal tube is necessary to achieve higher oxygen concentrations. The immediate effect of oxygen is to enhance the dissociation of COHb.¹⁵⁰ In volunteers, the half-life of COHb is reduced from a mean of 5 hours (range, 2–7 hours) when breathing room air (21% oxygen) to approximately one hour (range, 36–137 minutes) when breathing 100% oxygen at normal atmospheric pressure.¹⁴¹ Actual poisonings show a range in half-lives of 36 to 137 minutes (mean, 85 minutes) when breathing 100% oxygen; the longer elimination half-lives appear to be most often associated with long, low-level exposures.^{126,197} With oxygenation and intensive care treatment, hospital mortality rates for serious exposures range from 1% to 30%. The duration of treatment is unclear, with a valid end point being the resolution of symptoms, usually accompanied by a COHb below 5%.

Cardiac monitoring and intravenous (IV) access are necessary in any patient with systemic toxicity from CO poisoning. Hypotension can initially be treated with IV fluids; inotropes may also be necessary to treat myocardial depression. An evaluation for cardiac ischemia, including ECG and cardiac markers, should be considered in symptomatic patients at risk. Standard advanced cardiac life support protocols can be followed for the treatment of patients with life-threatening dysrhythmias. Patients with a depressed mental status should have a rapid blood glucose checked. Animal studies of CO

poisoning suggest that hypoglycemia can be deleterious.¹³⁸ Correction of any acidemia with bicarbonate is controversial and may result in further cellular injury secondary to a left shift of the oxyhemoglobin dissociation curve, so it is not recommended unless the acidemia is profound and persistent.

HYPERBARIC OXYGEN

HBO therapy appears to be the treatment of choice for patients with significant CO exposures.¹⁷⁸ But the most obvious effect, may not be the most important. One hundred percent oxygen at ambient pressure reduces the half-life of COHb from about 320 minutes to 85 minutes; at 2.5 atmospheres absolute (ATA), it is reduced to 20 minutes.^{141,197} Actual CO-poisoned victims treated with HBO have half-lives ranging from 4 to 86 minutes.¹²⁶ HBO also increases the amount of dissolved oxygen by about 10 times, which is sufficient alone to supply metabolic needs in the absence of hemoglobin (Chap. 29).¹⁰ This is rarely an important clinical issue because most patients have already been stabilized and have appreciably decreased COHb with ambient oxygen alone before arrangements can be made for an HBO treatment.

Therefore, HBO is more than just a modality to clear COHb more quickly than ambient oxygen (Antidotes in Depth: A38). More importantly, in rats after loss of consciousness from CO exposure, hyperbaric, but not normobaric, oxygen therapy prevents brain lipid peroxidation.¹⁶⁶ HBO appears to prevent ischemic reperfusion injury by a variety of mechanisms. First, in animal models, HBO accelerates regeneration of inactivated cytochrome oxidase, which may be the initiating site for CO neuronal damage.¹² Unlike 100% oxygen at room pressure, in clinical trials, HBO was much more effective at restoring mitochondrial function within peripheral white blood cells in CO poisoned patients.⁵⁹ Second, HBO also prevents β -integrin mediated neutrophil adhesion to brain microvascular endothelium, a process essential for amplification of CNS damage from CO.¹⁷⁸ This may explain why HBO, but not 100% oxygen at atmospheric pressure, prevented delayed deficits in a learning and memory maze model.¹⁷⁰

Clinical studies of the effectiveness of HBO in preventing neurologic damage from CO are not as convincing as basic science studies would suggest. In uncontrolled human clinical series, the incidence of persistent neuropsychiatric symptoms, including memory impairment, ranged from 12% to 43% in patients treated with 100% oxygen and was as low as 0% to 4% in patients treated with HBO.^{69,114,127,131}

More recently, several controlled clinical trials have evaluated the efficacy of HBO in CO poisoning (Table 125–3). The first randomized study of CO poisoning included more than 300 patients and failed to show a benefit from HBO in patients who had no initial loss of consciousness.¹⁴⁴ Unfortunately, seriously ill patients were not randomized to surface pressure oxygen; they received either one or three treatments of HBO. Flaws in the study included significant delays to treatment and the use of suboptimal pressure of 2.0 ATA. A smaller (n = 60) controlled study avoided some of these flaws and showed that HBO decreased delayed neurologic sequelae at 3 to 4 weeks from 23% to 0% in CO-poisoned patients who presented without loss of consciousness.¹⁸⁰ However, patients with syncope, a marker of serious poisoning, were excluded. A very small study (n = 26) of patients presenting with Glasgow Coma Scores (GCS) above 12 after CO poisoning included almost half with loss of consciousness.⁵² Randomization to HBO versus 100% normobaric oxygen resulted in decreased EEG abnormalities and less reduction in blood flow reactivity to acetazolamide at 3 weeks. Unfortunately, all of these studies failed to definitively study all CO-poisoned patients, including those with syncope or coma.

TABLE 125–3. Unfavorable Cognitive Outcome at 4 to 6 Weeks After Exposure to Carbon Monoxide in Randomized Clinical Trials of Hyperbaric Oxygen

Study	Design	Max HBO Pressure	Time to Treatment	Syncope (%)	Suicide (%)	Treatment	Control	Odds Ratio (95% CI)
Mathieu ¹⁴⁰	HBO 90 minutes vs. 12 hour NBO	2.5 ATA	<12 hours	N/A	N/A	69/299	73/276	0.83(0.57–1.22)
Raphael ¹⁴¹	HBO 2 hours vs. 6 hour NBO	2.0 ATA	Mean, 7.1 hours	0	N/A	51/159	50/148	0.93(0.57–1.49)
Thom ¹⁴²	HBO 2 hours vs. 100% NBO until asymptomatic	2.8 ATA	Mean, 2.0 hours	0	N/A	0/30	7/30	0.05(0.00–0.95)
Scheinkestel ¹⁵²	HBO 1 hour vs. NBO 100 minutes	2.8 ATA	Mean, 7.1 hours	53%	69%	30/48	25/40	1.00(0.42–2.38)
Weaver ¹⁴³	HBO 2 hours (x3) vs. NBO 2 hours (x1)	3.0 ATA	Mean, 5.6 hours	53%	31%	19/76	35/76	0.39(0.20–0.78)
Annan ⁴	HBO 2 hours vs. NBO 6 hours	2.0 ATA	< 6 hours	97%	0%	33/93	29/86	1.08 (0.58–2.00)

Data from Buckley N, Juurlink D, Ibister G, et al: Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev*. 2011;CD002041 and Tomaszewski C. The case for the use of hyperbaric oxygen in carbon monoxide poisoning. In: Penney DG, ed. *Carbon Monoxide Poisoning*. New York: CRC Press; 2008:375–390.

ATA = atmospheres absolute; CI = confidence interval; HBO = hyperbaric oxygen; N/A = not applicable; NBO = normobaric oxygen.

The first randomized trial to directly address the issue of HBO efficacy in seriously CO-poisoned patients evaluated 191 CO-poisoned patients referred for HBO treatment.¹⁵² Patients were randomized to a minimum of three daily treatments of HBO (2.8 ATA for 60 minutes) or 100% oxygen at 1.0 ATA for 3 days. Although the HBO group had a higher incidence of persistent neurologic sequelae at one month, there was no significant difference between the two groups; more than two-thirds of each group had persistent problems. This study, although the largest controlled, randomized study to date, suffered from several flaws. Fewer than half of the patients had follow-up at one month. Disproportionate numbers of suicide cases (about two-thirds) and drug toxicity (44%), with accompanying neuropsychologic defects, could have confounded any beneficial effect from HBO. Finally, HBO treatment was delayed for 6 hours, making it much less likely to be effective.^{69,144}

A more recent randomized, double-blind, placebo-controlled study identified a beneficial effect of HBO in CO-poisoned patients.¹⁹⁶ Most of these patients were ill, with a mean initial COHb level of 25% and a 50% incidence of loss of consciousness. Patients were all treated within a 24-hour window after exposure, but the success of the study might be partially attributable to the rapid mean time to treatment of less than 2 hours. Patients received HBO three times at intervals of 6 to 12 hours, each at 2.0 ATA, except for the first hour of the first treatment, which was at 3.0 ATA. Control patients received sham treatments in the HBO chamber with 100% oxygen at 1.0 ATA. At 6 weeks, the HBO group had a 24% incidence of cognitive sequelae versus 46% in the control group. Based on these data, the number of patients needed to treat to prevent one case of cognitive impairment is only five. Critics of this study point out that the neuropsychiatric tests were not significantly different between the groups except for digit span and trail making, and there was no difference in activities of daily living. However, untreated patients had increased self-reported memory problems at 6 weeks (28% vs. 51%), and the beneficial effect on cognitive sequelae lasted well into 12 months.

A more recent study of 179 patients with transient loss of consciousness after CO poisoning showed no benefit from a single HBO treatment.⁴ Neurological recovery at one month was approximately 60% regardless of HBO or normobaric oxygen. However, the study was done only at 2.0 ATA, which is below the customary initial dose for CO in positive studies. In addition, over 20% of patients were lost to follow-up.

Based on the strong animal and basic science experience, the positive human studies mentioned above, and few adverse effects, it is not surprising that the Underwater and Hyperbaric Medical Society (UHMS) recommends HBO for all CO patients with signs of serious toxicity.¹⁹⁵ With the low risk of this procedure,^{151,156} almost 1500 patients are treated with HBO for CO poisoning in the United States each year.⁷² Therefore, HBO has become the standard of care for serious CO poisoning, even though there is substantial disagreement in the interpretation of the existing evidence.^{83,109,201}

Indications for Hyperbaric Oxygen Therapy. Although specific indications for HBO after acute CO poisoning are listed (Table 125–4), they have not been prospectively evaluated. The patients most likely to benefit are those most at risk for persistent or delayed neurologic sequelae, such as those presenting in coma or with a history of syncope.¹⁹⁸ These may be clinical markers for the episode of hypotension that are necessary for causing neuronal damage from CO-induced ischemic–reperfusion injury in animal models^{65,133} However, syncope is neither particularly sensitive nor specific marker for cognitive sequelae. Patients with long exposures, or “soaking” periods, typically longer than 6 hours, are also at greater risk for neurologic sequelae.¹¹ The presence of a significant metabolic acidosis may be a surrogate marker.^{157,186} Patients

who present with decreased level of consciousness, a GCS <9 in one series, had an odds ratio of 7.0 for development of neurological sequelae¹⁴⁰ Some authors advocate ongoing myocardial ischemia as an indication for HBO; however, in our experience, these patients usually already meet neurologic criteria for treatment, such as loss of consciousness or ongoing mental status changes. Isolated cardiac ischemia, more importantly, deserves immediate proven myocardial salvaging therapy rather than delayed treatment with an unproven therapy such as HBO

TABLE 125–4. Suggested Indications for Hyperbaric Oxygen^a

Syncope (loss of consciousness)
Coma
Seizure
Altered mental status (GCS<15) or confusion
Carboxyhemoglobin >25%
Abnormal cerebellar function
Age = 36 years
Prolonged CO exposure (=24 hours)
Fetal distress in pregnancy

^aPatients with these risk factors for cognitive sequelae have the highest potential to benefit from HBO treatment. GCS = Glasgow Coma Score.

Some authors advocate treating all patients with COHb levels of 40% or greater with HBO. Many HBO centers arbitrarily use a more conservative level of 25% as an indication for HBO.⁷⁸ More important than actual level are patient history and examination. Further analysis of data from the most recent controlled trial demonstrates that in patients not treated with HBO, there were no reliable factors (COHb level, loss of consciousness, or base excess) for predicting who progressed to cognitive sequelae.¹⁹⁸ This recent multivariate analysis showed that of all factors (loss of consciousness, age, exposure time, and COHb levels) only age of 36 years or older and CO exposure duration of 24 hours or longer predicted cognitive dysfunction at 6 week follow-up. More problematic is the incidence of cognitive sequelae in patients without those risk factors: 32% in those younger than age 36 years and 36% in those with less than 24 hours of exposure. In conclusion, it appears that there are no reliable predictors for screening out patients who will do well and not develop cognitive sequelae, and therefore can avoid HBO treatment with mild CO poisoning.

Multiple studies have looked for serum markers after acute CO poisoning that would predict neurological sequelae. COHb, although confirming exposure, does not correlate with future outcome, let alone acute symptoms.^{75,198} Multiple serum markers, including cytokines, do increase after CO poisoning, but their predictive accuracy is unclear.¹⁷² Although impaired mitochondrial cytochrome function and elevated lipid peroxidation are seen in peripheral lymphocytes and monocytes after clinical CO poisoning, they only confirm CO exposure and are too nonspecific to use as predictors of neurological sequelae.⁵⁹

Therefore, at this time, it is prudent to refer for HBO treatment those patients with the most serious neurologic symptoms, regardless of their COHb level. Such symptoms include coma, seizures, focal neurologic deficits, altered mental status (GCS <15), and although controversial, loss of consciousness. Patients who have had cardiac arrest from CO poisoning and had the return of spontaneous circulation may be poor candidates for HBO therapy because all these cases have been fatal.⁸¹ In fact, such deaths from CO poisoning are no contraindication to organ donation.

Excluding patients from HBO with milder symptoms after CO poisoning may be problematic because even they are susceptible to neurocognitive sequelae. One series of 55 patients with mild poisoning as defined by absence of loss of consciousness and maximum measured COHb level less than 15% found that even one-third of these individuals had neurocognitive sequelae up to 12 months after exposure.³⁰ This was no different than that occurring in the severely poisoned group, although the milder group had a much longer duration of exposure as well as a greater delay to COHb level drawn. Brain imaging studies have confirmed that mild exposures, marked by no LOC and COHb levels lower than 15%, may result in visible changes.^{58,143} Taken to its logical but impractical conclusion, because even apparently mild cases of CO poisoning may have poor neurocognitive outcomes, HBO treatment of every CO-exposed patient, regardless of severity, could be justified.

It is still unclear if mild neurologic symptoms, such as confusion, headache, dizziness, visual blurring, or abnormal mental status testing on initial presentation after CO poisoning, are prognostic for cognitive sequelae, which would necessitate HBO treatment. These symptoms simply represent CO poisoning, which, at COHb levels approaching 10% in volunteers, may cause temporary impairment of learning and memory.³ In one prospective clinical trial of CO poisoning, the incidence of cerebellar dysfunction portended a higher incidence of cognitive sequelae (odds ratio, 5.7 {95% confidence interval, 1.7–19.3}).¹⁹⁶ Therefore, difficulty with finger-to-nose, heel-to-shin, rapid alternating hand movements, or even ataxia, should be considered indications for HBO. Patients with other mild neurologic findings, such as

headache, warrant at least several hours of oxygen by non-rebreather facemask until symptoms resolve. If symptoms do not resolve, HBO may be considered; however, any delay in HBO may decrease its efficacy.

A more promising method to discern patients who may respond to HBO may be the genotype, apolipoprotein E, specifically the isoform $\mu 4$.⁸⁹ This particular polymorphism allele is present in up to one-quarter of the population, and it is associated with worse neurologic outcome from trauma and stroke. In the presence of CO poisoning, it is associated with lack of response to HBO for preventing neurocognitive sequelae. Further studies may support not treating patients with this particular allele, focusing on those with the potential for response to HBO therapy.

Because of the confusion in determining which CO poisoned patients really need HBO treatment, several professional societies have developed evidence-based guidelines. As alluded to previously, the American College of Emergency Physicians has noted that no clinical variable can be used to predict patients at risk of cognitive sequelae and therefore most likely to benefit from HBO.²⁰¹ Similarly, the Cochrane Collaboration review on the use of HBO in CO poisoning concluded that because of so much conflicting data, there is insufficient evidence to support HBO for CO poisoning at this time.¹⁶ The collective odds ratio for protective effect at 4 to 6 weeks with HBO versus normobaric oxygen was 0.78 [95% CI 0.54–1.12] based on a collective experience of 1361 patients in six studies. The most recent guideline from the UHMS states that CO-poisoned patients should be referred for HBO if they have serious poisoning, such as unconsciousness, whether it is transient or persistent; age 36 years or older; or CO exposure duration of 24 hours or longer, even if intermittent.¹⁹⁵ This is all consistent with the prior studies discussed earlier. The UHMS guidelines also state that many physicians treat when neuropsychologic testing is abnormal or COHb levels are greater than 25% to 30%.

Some authors recommend selective use of HBO because of cost and difficulties in transport if the primary facility lacks a chamber. However, complications that may make such transfers and treatment unsafe are rare.¹⁵⁶ At the present time, we routinely recommend HBO for selected patients poisoned by CO based on the indications in [Table 125-4](#). Fortunately, even without HBO, anywhere from one-third to three-quarters of cases with persistent cognitive sequelae resolve over the subsequent year.^{34,196}

Delayed Administration of Hyperbaric Oxygen. The optimal timing and number of HBO treatments for CO poisoning is unclear. Patients treated later than 6 hours after exposure tend to have worse outcomes in terms of delayed sequelae (30% vs. 19%) and mortality (30% vs. 14%).⁶⁹ This may explain the failure of one of the first randomized trials on HBO in CO, which had a mean time to treatment of over 6 hours after poisoning.¹⁵² Meanwhile, HBO treatments delivered within 6 hours after poisoning in patients with loss of consciousness after CO seem to almost completely prevent neurologic sequelae.²⁰⁷ However, patients may benefit if they are treated even later. In the most recent randomized clinical trial showing beneficial effects of HBO, although all patients were treated within 24 hours of exposure, 38% of patients were treated later than 6 hours after exposure. Therefore, it is not unreasonable to consider HBO, contingent on transport limitations, within 24 hours of presentation for symptomatic acute poisoning.

One case series suggests beneficial effects for HBO used up to 21 days after exposure, even after patients have developed neuropsychologic sequelae.¹²⁷ The problem with studies showing HBO benefits days after an acute poisoning or after chronic poisoning is that these cases are all anecdotal and lack control subjects. In fact, delayed neurocognitive sequelae frequently resolve within 2 months in patients with mild CO poisoning,¹⁸⁰ and in those with serious CO poisoning who survive to HBO treatment, one-third resolve within one year.¹⁹⁶ It is possible that these delayed or chronic cases may simply represent the placebo effect of HBO.

Repeat Treatment with Hyperbaric Oxygen. A randomized clinical trial demonstrated that three HBO treatments within the first 24 hours improved cognitive outcome.¹⁹⁶ Unfortunately, there was no group treated with only one or two HBO sessions in that study. Regardless, multiple treatments are advocated for patients who have persistent symptoms, particularly coma, and do not clear after their first HBO session. In a pilot study, one hyperbaric oxygen treatment was enough to promote almost total mitochondrial cytochrome activity, as measured in peripheral lymphocytes, after CO poisoning.⁵⁹ In a nonrandomized retrospective study, CO-poisoned patients who received a second HBO treatment had a reduction in delayed neurologic sequelae from 55% to 18% compared with control subjects who had only one treatment.⁶⁸

It is not clear that more HBO treatments are better. A large recent study showed that in seriously poisoned CO patients, two hyperbaric treatments resulted in a worse outcome than one treatment, with complete recovery 47% versus 68% respectively.⁴ There were serious flaws in that study, including lack of formal neuropsychological testing and the use of only 2.0 ATA of pressure, well below the 3.0 ATA used initially in favorable studies. With the lack of prospective studies comparing single versus multiple courses of HBO therapy, multiple treatments cannot be recommended routine at this time. The most recent clinical guidelines from the UHMS state that the optimal number of HBO treatments for CO poisoning is unknown and that one should consider reserving multiple treatments for patients who fail to fully recover after one treatment.¹⁹⁵

TREATMENT OF PREGNANT PATIENTS

The management of CO exposure in the pregnant patient is difficult because of the potential adverse effects of both CO and HBO. A literature review of all CO exposures during pregnancy revealed a high incidence of fetal CNS damage and stillbirth after severe maternal poisonings.¹⁸⁸ A series of three severely symptomatic patients who did not receive HBO had adverse fetal outcomes: two stillbirths and one case of cerebral palsy.⁹⁹ There have even been cases of limb malformations, cranial deformities, and a variety of mental disabilities in children poisoned in utero.^{18,110,111} A recent epidemiological study in Guatemala showed that CO exposure from wood smoke during the third trimester was inversely associated with neuropsychological performance at ages 6 to 7 years when corrected for socioeconomic confounders.⁵⁰

Traditionally, it was thought that fetal hemoglobin had a high affinity for CO. Pregnant ewe studies show a delayed but substantive increase in COHb levels in fetuses, exceeding the level and duration of those in the mothers.¹¹¹ Thus, it appeared that fetuses are a sink for CO and could be poisoned at levels lower than mothers. However, such data may not apply to humans because in vitro work shows that as opposed to sheep, human fetal hemoglobin actually has less affinity for CO than maternal hemoglobin, at a ratio of 0.8. Under conditions of low oxygenation and high 2,3-BPG, as in serious CO poisoning, the affinity of human fetal hemoglobin starts to approach that of maternal.¹⁹⁹ The more important issue with maternal CO exposure is the precipitous decrease in fetal arterial oxygen content that occurs within minutes at CO concentrations of 3000 ppm.⁶⁴ Therefore, the ensuing hypoxia of the fetus, rather than increase in fetal COHb, may be of more concern.

Maternal COHb levels do not accurately reflect fetal hemoglobin or tissue levels.⁴⁴ In primate studies, a single CO exposure insufficient to cause clinical disease in the mother led to intrauterine hypoxia, fetal brain injury, and increased rate of fetal death.^{64,65} In humans, there are a few cases of fetal demise with maternal levels of COHb less than 10%.¹⁸ However, in that series, some mothers were treated with oxygen before obtaining their COHb levels. Another issue with some of these data is that often the mother has been chronically “soaked” with CO, making levels difficult to interpret. Rodent studies show that chronic low level CO exposure in pregnant mothers may result in permanent cognitive deficits in the subsequent progeny.⁴⁸

Because maternal COHb does not necessarily predict fetal demise, clinicians must direct their attention to maternal symptoms of CO toxicity. Multiple case series demonstrate that pregnant women who present with normal mental status and no loss of consciousness after CO poisoning have excellent outcomes in terms of normal deliveries.^{18,99} These infants have no subsequent delay in attaining their developmental milestones. Therefore, it appears that mothers who appear well after acute CO poisoning will have good outcomes with respect to their pregnancies.

The bigger dilemma for clinicians is the approach to treatment of seriously symptomatic CO-poisoned pregnant patients. All patients should receive 100% oxygen by facemask, at least until the mother is asymptomatic. However, CO absorption and elimination are slower in the fetal circulation than in the maternal circulation.¹¹¹ A mathematical model predicts that elimination of CO from fetuses takes 3.5 times longer than maternal CO elimination.⁸⁶ However, based on the fact that some of these data are based on sheep fetal hemoglobin kinetics, the optimum time for treatment of the mother cannot be recommended at this time.

For exposed pregnant women with a loss of consciousness or high COHb levels, HBO might be considered. Unfortunately, pregnant patients were excluded from all prospective trials documenting efficacy of HBO. However, treatment of pregnant patients with HBO is not without theoretical risk. Animal studies show conflicting results on the effects of HBO on fetal development. Some studies have shown that HBO causes developmental abnormalities in the central nervous, cardiovascular, and pulmonary systems of rodent fetuses. This is in marked contrast to the extensive Russian experience, in which hundreds of pregnant women were treated with HBO, apparently without significant perinatal complications and with improvement in fetal and maternal status for their underlying conditions of toxemia, anemia, and diabetes.¹²¹ Cases in the United States have been published in which HBO used for mild CO poisoning resulted in infants who were normal at birth. However, less than optimal outcomes have occurred in cases of sicker patients in which the mother has had loss of consciousness or presented comatose.⁵⁴ Thus, it appears that HBO should be safe and have the same efficacy for pregnant patients as in nonpregnant patients. However, its effect in preventing adverse fetal outcomes is unclear.

There currently is no scientific validation for an absolute level at which to provide HBO therapy for a pregnant patient with CO exposure. Arbitrarily, COHb levels greater than 20% are recommended as an indication in a pregnant patient regardless of symptoms. Pregnant patients should not be treated any differently if they meet criteria for HBO that have already been mentioned (Table 125–4). Additional criteria include any signs of fetal distress, such as abnormal fetal heart rate.

TREATMENT OF CHILDREN

It has been suggested that children are more sensitive to the effects of CO because of their increased respiratory and metabolic rate.³³ Epidemiologic studies suggest that children can become symptomatic at COHb levels less than 10%,

which is lower than commonly expected in adults.⁹⁸ The other problem is that these patients may have unusual presentations. Although most children manifest nausea, headache, or lethargy, an isolated seizure or vomiting may be the only manifestation of CO toxicity in an infant or child.

While obtaining COHb levels in infants, clinicians must be aware of two confounding factors. First, many cooximeters give falsely elevated COHb levels in proportion to the amount of fetal hemoglobin present.¹⁹⁰ Second, CO is produced during breakdown of protoporphyrin to bilirubin. Therefore, infants normally have higher levels of COHb, which are even higher in the presence of kernicterus. Some neonates not exposed to CO can have COHb cooximetry readings approaching 8%.¹⁹¹ Thus, before it is assumed that an elevated COHb level implies CO poisoning in an infant, the contribution of jaundice and fetal hemoglobin must be considered in the final analysis.

Although children may be more susceptible to acute toxicity with CO, their long-term outcomes appear to be more favorable than adults. In a series of 2360 serious CO cases, all incidences of delayed neurologic sequelae were in adults older than age 30 years.³⁴ Pediatric series of CO poisoning demonstrated an incidence of delayed neurologic sequelae of 10% to 20% of children after severe CO poisoning.³³ This low incidence, in patients treated only with 100% oxygen at 1.0 ATA, has been used as an argument to avoid HBO. However, there still is a real risk of such sequelae, and HBO has been used successfully to prevent it.²⁰⁴ Children do well with HBO treatment, with mortality mainly related to concomitant smoke inhalation if present.³⁶ If the use of surface-pressure oxygen is selected to treat a child, it is comforting to know that the COHb half-life is approximately 44 minutes, faster elimination than that seen in adults.⁹⁸ Often, children exposed to CO in similar circumstances, but appear well, are treated simultaneously with the sick parent, especially if a multiplace chamber is available.

NOVEL NEUROPROTECTIVE TREATMENTS

A variety of neuroprotective agents have been tested in animal models. They are targeted primarily at preventing the delayed neurologic sequelae associated with serious CO poisoning. One of the simplest treatments tested is insulin. Hyperglycemia exacerbates neuronal injury from stroke as well as in arrest situations. In CO poisoning of rodents, it is associated with worse neurologic outcome.¹³⁸ However, insulin, independent of its glucose-lowering effect, may be the protective agent after ischemia. In rodent studies, improved neurologic outcome, as measured by locomotor activity, occurs after those with CO poisoning treated with insulin. In light of these findings, it is reasonable to aggressively treat documented hyperglycemia with insulin in patients with serious CO poisoning.

Many neuroprotective agents involve blockage of excitatory amino acids that are implicated in neuronal cell death after CO poisoning. Pretreatment of mice with dizocilpine (MK-801), which blocks the action of glutamate at N-methyl-D-aspartate receptors, ameliorates learning, memory, and hippocampal deficits with CO poisoning.⁹³ Ketamine, another glutamate antagonist, decreases the mortality rate of rats poisoned with CO after carotid ligation.¹³⁹ Treatment of mice with various glutamate antagonists prevents learning and memory deficits in a model of CO poisoning.⁶² Blockage earlier in the immunologic cascade, with a neuronal NO synthase inhibitor also prevented NMDA receptor activation, thus protecting mice from learning deficits after CO poisoning.¹⁷⁵ One exciting approach is the use of antioxidants, such as dimethyl sulfoxide and disulfiram, that prevent learning and memory deficits when given after CO poisoning in mice.⁶² Use of these or related therapeutics, although promising, awaits further animal testing because of potential adverse effects.

Other modalities have been tested in preventing neuronal damage from CO without much success. Hypothermia, rather than being beneficial, actually increases mortality in animals.¹⁶² Allopurinol which prevents formation of free radicals through xanthine oxidase inhibits lipid peroxidation in CO poisoning when given prior to exposure.¹⁶⁸ This strategy has not been promising because of the necessity for pretreatment.

PREVENTION

Early diagnosis prevents much of the morbidity and mortality associated with CO poisoning, especially in unintentional exposures. The increased quality of home CO-detecting devices allows personal intervention in the prevention of exposure.¹⁰¹ If a patient presents complaining that his or her CO alarm sounded, it is important to realize that the threshold limit for the alarm is set roughly to approximate a COHb level of 10% at worst. Therefore, manufacturers must have their alarms activate within 189 minutes at 70 ppm CO, 50 minutes at 150 ppm, and 15 minutes at 400 ppm (Underwriters Laboratories, UL2034). Alarms are not to activate for prolonged exposures below 30 ppm to prevent epidemic alarms during winter thermal inversions in large cities.⁹ Government ordinances for obligatory CO alarms could potentially prevent many poisonings, particularly during winter storms.^{22,70} Although most serious CO poisonings are associated with the absence of CO alarms, a recent series of such patients showed that even with alarms, patients become seriously poisoned.³⁸

Routine laboratory screening of ED patients during the winter is not very efficacious in diagnosing unsuspected CO

poisoning; the yield is less than 1% when patients are tested in whom the diagnosis of CO exposure was already excluded by history. Instead, selecting patients with CO-related complaints, such as headache, dizziness, or nausea, increases the yield to 5% to 11%.^{53,161} During the winter, risk factors such as gas heating or symptomatic cohabitants in patients with influenzalike symptoms such as headache, dizziness, or nausea, particularly in the absence of fever, is the most useful method for deciding when to obtain COHb levels for potential patient.

The issue of symptomatic cohabitants is especially important from a preventive standpoint. Alerting other cohabitants to this danger and effecting evacuation may prevent needless morbidity and mortality. This is especially critical for multifamily domicile, like hotels, that have resulted in dramatic collective exposures and even deaths.¹⁹⁴ Most communities have multiple resources for onsite evaluation. Usually the local fire department or utility company can either check home appliances or measure ambient CO concentrations with portable monitoring equipment. Current workplace standard for ambient CO exposures is 35 ppm averaged over 8 hours with a ceiling limit of 200 ppm (measured over a 15-minute period).¹²⁹ Just a 4-hour exposure to 100 ppm of CO may result in COHb level greater than 10% with symptoms.

SUMMARY

- Unintentional exposures to CO are easily missed or misdiagnosed. Patients with a suspected influenzalike illness should be screened for potential home sources of CO, and symptomatic cohabitants should be alerted.
- CO exposure should also be considered in patients with unexplained coma, acidosis, or signs of cardiac ischemia, especially if attempted suicide is suspected.
- Fire victims, in addition to airway complications and potential cyanide toxicity, may succumb to CO toxicity.
- The mainstay of treatment in CO poisoning is good supportive care with early oxygenation to increase the elimination of COHb.
- Because of the overwhelming clinical successes with HBO and its limited risks, early use of this treatment modality in severe exposures is encouraged.
- Discussion with a regional poison center or hyperbaric facility will help in identifying patients who are most likely to benefit from such treatment.

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A38 ANTIDOTES IN DEPTH

Hyperbaric Oxygen

Stephen R. Thom

INTRODUCTION

Hyperbaric oxygen (HBO) is used therapeutically in poisoning by carbon monoxide (alone or if complicated by cyanide poisoning), methylene chloride, hydrogen sulfide, and carbon tetrachloride. It is also a recognized therapy for air or gas embolism, such as may arise from ingestion of hydrogen peroxide, and for anemia, a functional form of which arises from oxidants that induce methemoglobinemia.

HISTORY

Hyperbaric medicine became established as a clinical discipline in the later half of the 20th century with a focus on treatment of decompression sickness. Utilization of hyperbaric chambers has expanded in the past 60 years with improved understanding of basic mechanisms of action. The first case reports of HBO for documented CO poisoning appeared in 1960,¹⁹² and the consistent application of HBO in CO poisoning began in many centers at that time.¹⁹⁰ The first report presenting statistical evidence of the superiority of HBO compared to normobaric oxygen in CO poisoning, as well as a description of the “late syndrome,” was published in 1969.⁷⁴

PHARMACOLOGY

Chemistry and Preparation

In hyperbaric oxygen (HBO) therapy the patient breathes 100% O₂ while exposed to increased atmospheric pressure. Treatments are performed in either a monoplace (single patient) or a multiplace (typically 2–14 patients) chamber. Pressures applied while patients are in the chamber usually are 2 to 3 atmospheres absolute (ATA), where sea level air pressure equals 1 ATA. Treatments generally last for 1.5 to 8 hours, depending on the indication, and may be performed one to three times daily. Monoplace chambers usually are compressed with pure oxygen. Multiplace chambers are pressurized with air, and patients breathe pure oxygen through a tight fitting face mask, a head tent, or endotracheal tube as clinically indicated.

Mechanisms of Action

Therapeutic mechanisms of action for HBO are based on elevation of both hydrostatic pressure and the partial pressure of oxygen. Elevation of the hydrostatic pressure reduces the volume of a gas according to Boyle’s law (within a closed system, absolute pressure and volume of a given mass of a confined gas are inversely proportional, if the temperature remains unchanged). This action has direct relevance to pathologic conditions in which gas bubbles are present in the body, such as arterial gas embolism, decompression sickness, and ingestion of concentrated solutions of hydrogen peroxide (H₂O₂). During treatment, the arterial oxygen tension typically exceeds 1500 mm Hg and achieves tissue oxygen tensions of 200 to 400 mm Hg—over fivefold higher than when breathing air.²⁰³ While one is breathing air under normal environmental conditions, hemoglobin is saturated with oxygen on passage through the pulmonary microvasculature, and the primary effect of HBO is to increase the dissolved oxygen content of plasma. In addition, HBO affects neutrophil adhesion to blood vessels and restores mitochondrial, neutrophil, and immunologic disturbances caused by CO poisoning.

Pharmacokinetics

Oxygen inhaled at hyperbaric pressure is rapidly absorbed. Application of each additional atmosphere of pressure while breathing 100% oxygen increases the dissolved oxygen concentration in the plasma by 2.2 mL O₂/dL (vol%) (Chap. 29). In five human subjects performing breath holds during compression to 20 m, oxygen consumption also significantly increased,

which was attributed to increased cardiac output.¹²⁵ Animal models of focal ischemia suggest that hyperbaric oxygen rapidly distributes to target organs to improve penumbral oxygenation.¹⁹⁹ HBO increases tissue oxygen concentration and wound oxygen delivery in humans.¹⁷² Regarding pharmaceutical interactions, hyperbaric hyperoxia does not appear to produce appreciable alterations in the pharmacokinetics of pentobarbital, salicylate, or theophylline in canine models^{111–113} or gentamicin in healthy human volunteers.¹⁴²

Pharmacodynamics

There are transient benefits from HBO for reducing bubble volume in disorders such as air embolism and also oxygenating tissues in conditions where hemoglobin-based O₂ delivery is impaired. These rather straightforward mechanisms form the basis for using HBO for patients with massive ingestions of hydrogen peroxide (H₂O₂) associated with intravascular gas embolism and for life-threatening poisonings from cyanide (CN), hydrogen sulfide (H₂S), and exposure to oxidizers causing methemoglobin. HBO is also used for carbon tetrachloride (CCl₄) poisoning, where acute application of oxygen and pressure may inhibit the cytochrome P450 oxidase system responsible for producing hepatotoxic free radicals.^{30,136} HBO also has well described vasoconstriction effects,^{38,197,216} compared to dynamic CO-associated effects on cerebral vasodilation.¹²²

Recent years have shown that benefits persisting beyond the short period when a patient is in a hyperbaric chamber are related to production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).^{206,207} Reactive species can have positive and negative effects that depend on the concentration of reactant generated and its intracellular localization. Hence, with regard to HBO as with any drug, the precise dose may define the risks and benefits of therapy. Because exposure to hyperoxia in typical clinical HBO protocols is rather brief, most studies show that antioxidant defenses are adequate to avoid tissue injuries.^{52,53,173,220}

There are at least three separate therapeutic mechanisms supporting the use of O₂ when treating carbon monoxide (CO) poisoning. Administration of supplemental O₂ is a historical cornerstone for treatment based on reducing body burden of carboxyhemoglobin (COHb). Elevated COHb can result in tissue hypoxia, and exogenous O₂ both hastens dissociation of CO from hemoglobin and provides enhanced tissue oxygenation directly through the increased PO₂. HBO causes COHb dissociation to occur at a rate greater than that achievable by breathing 100% O₂ at sea level pressure.¹⁵⁸ Additionally, HBO accelerates restoration of mitochondrial oxidative processes.²⁸ Among the earliest events observed in both an animal model and in humans suffering CO poisoning is platelet-neutrophil interactions that mediate intravascular neutrophil activation. These changes precipitate neutrophil adherence to blood vessel walls that initiate vascular changes and a cascade of events leading to neurological dysfunction (Fig. A38–1).^{96,208,213} Immunological responses to altered myelin basic protein (MBP) cause neurological dysfunction in animals, and presence of MBP in cerebrospinal fluid of CO poisoned patients is suggested as a predictive marker for onset and persistence of CO-mediated encephalopathy.^{17–19,94,95,102}

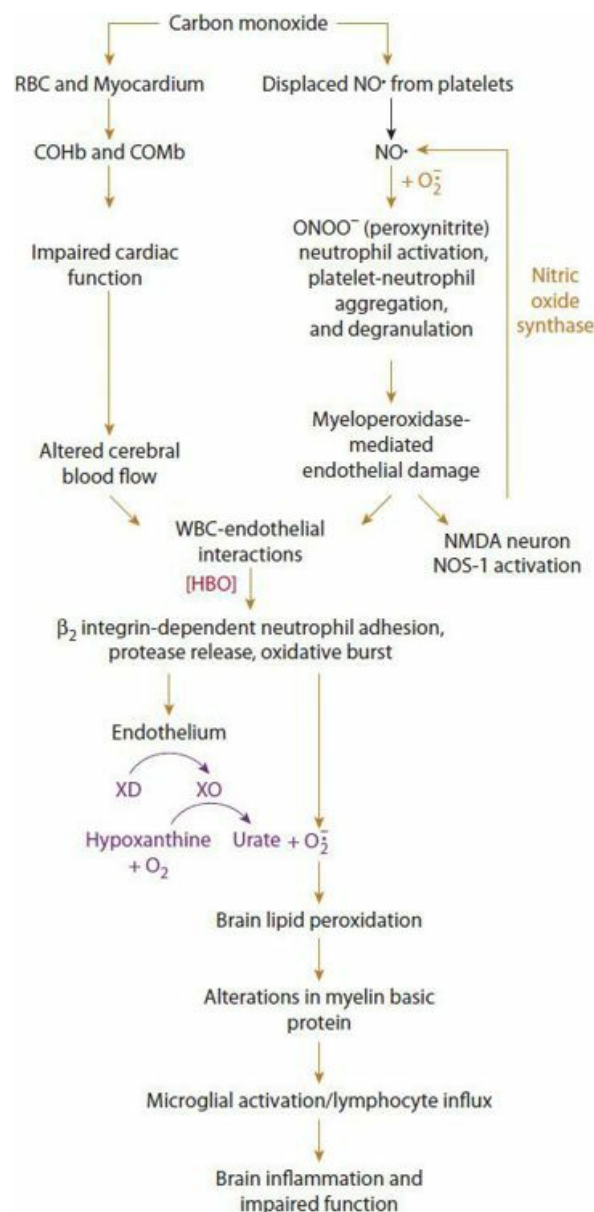


FIGURE A38–1. The final common pathway demonstrating concurrent events leading to vascular injury with CO poisoning and the sequence of events leading to neurological injuries. • = peroxynitrite, NO • = nitric oxide, O₂ • = superoxide radical, COHb = carboxyhemoglobin, COMb = carboxymyoglobin, NMDA = N-methyl-D-aspartate neurons, NOS-1 = neuronal nitric oxide synthase, NO₂ = nitrite (major oxidation product of NO•), WBC = leukocytes, XD = xanthine dehydrogenase, XO = xanthine oxidase.

Animals poisoned with CO then treated with HBO have more rapid improvement in cardiovascular status,⁵⁸ lower mortality,¹⁶¹ and lower incidence of neurological sequelae.^{84,205} Benefits are likely based on improved oxygenation and mitochondrial function as well as inhibition of neutrophil adhesion. Exposure to 2.8 to 3.0 ATA O₂ for 45 minutes temporarily inhibits neutrophil adherence to endothelium mediated by the activation-dependent β₂-integrins on the neutrophil membrane in both rodents and humans.^{41,101,114,204,214} The ability of HBO to inhibit function of neutrophil β₂-integrin adhesion molecules in animal models forms the basis for amelioration of encephalopathy resulting from CO poisoning and decompression sickness, smoke-induced lung injury, as well as reperfusion injuries of brain, heart, lung, liver, and skeletal muscle.^{8,105,135,200,201,204,217,221,226,240–242} HBO inhibits neutrophil β₂ integrin expression but not its expression on other circulating leukocytes due to RNS generation by type-2 nitric oxide synthase and myeloperoxidase present in neutrophil-specific α-granules. That is, it is the presence of both enzymes within the same granules that is required to generate the requisite RNS to impair neutrophil adherence. The reaction leads to excessive S-nitrosylation of cytoskeletal β actin, which in turn impedes the function of β₂ integrins.²¹⁰ This leads to modifications in cytoskeletal regulation of a number of proteins.^{211,212} It is important to comment that HBO does not reduce neutrophil viability, and functions such as degranulation and oxidative burst in response to chemoattractants remain intact.^{204,211,214} This contrasts with alternative interventions such as monoclonal antibodies which can inhibit β₂ integrins and ameliorate ischemia-reperfusion injuries but cause profound immunocompromise.^{144,145}

ROLE IN CARBON MONOXIDE POISONING

Survivors of CO poisoning are faced with potential impairments to cardiac and neurological functions. CO poisoning can cause acute cardiac compromise, and survivors exhibit an increased risk for cardiovascular related death in the subsequent 10 years.^{88,175} Some patients exhibit acute abnormalities wherein they have impaired consciousness and or focal neurological findings from the time of initial presentation and never recover.^{3,47,50,69} Other patients seemingly recover from acute poisoning but then manifest neurological or neuropsychiatric abnormalities from 2 days to about 5 weeks after poisoning.^{42,55,73,92,131,139,143,152,166,183,186,215,235} Events occurring after a clear or “lucid” interval are termed “subacute or delayed” neurological sequelae. These terms have gained popularity and may have some clinical utility, but animal studies suggest neuropathology is more of a continuum. That is, various pathways of injury occur in close proximity, and in some cases they occur concomitantly.^{68,97,140,153,208,209,213}

Since 1960, HBO has been used with increasing frequency for severe CO poisoning because clinical recovery appeared to improve beyond that expected with ambient pressure oxygen therapy. Support for HBO use comes from this experience.^{73,74,93,115,138,152,155,171} The clinical efficacy of HBO for acute CO poisoning has been assessed in six prospective, randomized trials published in peer-reviewed journals. Only one clinical trial satisfies all items deemed to be necessary for the highest quality of randomized controlled trials.²³⁵ This double-blinded, placebo-controlled clinical trial involved 152 patients, who received treatment with either three sessions of HBO therapy or normobaric O₂ with sham pressurization to maintain blinding. The group treated with HBO had a lower incidence of cognitive sequelae than the group treated with NBO after adjustment for pre-treatment cerebellar dysfunction and stratification (odds ratio 0.45, 95% confidence interval 0.22–0.92, $p = 0.03$).

The only other blinded, prospective, randomized trial was published in 1999, and it involved 191 patients of different severity treated with either daily HBO (2.8 ATA for 60 minutes) with intervening high flow oxygen for 3 or 6 days versus high flow normobaric oxygen for 3 or 6 days.¹⁷⁸ Additional HBO treatments (up to six daily) were performed in patients without adequate neurological recovery. The primary outcome measure for this trial was testing performed at completion of treatment (3–6 days) and not from long term follow-up. This study had a high rate of adverse neurological outcomes in all patients, regardless of treatment assignment. Neurological sequelae were reported in 74% of HBO treated patients and in 68% of controls. No other clinical trial has described this magnitude of neurological dysfunction. The high incidence may be related to the assessment tool which could not discern true neurological impairments from poor test taking related to depression.¹⁷⁹ Suicide attempts with CO represented 69% of cases in this trial. Moreover, 54% of subjects were lost to follow-up. Outcomes at one month were not reported, but were stated to show no difference. Multiple statistical comparisons were reported without apparent planning or the requisite statistical correction. Both treatment arms received continuous supplemental mask O₂ for 3 days between their hyperbaric treatments (both true HBO and “sham”), resulting in greater overall O₂ doses than conventional therapy. Multiple flaws in the design and execution of this study are discussed in the literature, so it is impossible to draw meaningful conclusions from the data.^{80,148} Despite these issues, conclusions from this trial have been accepted in systematic reviews.^{29,238}

Other randomized trials of HBO for CO poisoning were not blinded. The first prospective clinical trial involving HBO therapy did not demonstrate therapeutic benefits.¹⁶⁶ This study was criticized because the authors used a low oxygen partial pressure (2 ATA) versus the more usual protocols with 2.5 to 3 ATA, an unvalidated questionnaire to assess neurological function, and because nearly half of the patients received hyperbaric treatments more than 6 hours after they were identified.²⁷ This 1989 study protocol was used again in a more recent trial with no modifications despite the criticisms voiced over a decade earlier. Not surprisingly, the outcome was virtually the same. If study results are expressed on an intention-to-treat basis, patients with transient loss of consciousness had an incidence of neurological sequelae based on the self-assessment questionnaire of 48%, and those treated with HBO had an incidence of 51%. Patients with initial coma who were treated once with HBO had an incidence of sequelae of 47%; patients who were treated with two HBO treatments had an incidence of sequelae of 60% (not significantly different from any of the other groups).⁶

HBO was found effective in several other prospective investigations. In a trial involving mildly to moderately poisoned patients, 23% of patients (7/30) treated with ambient pressure oxygen developed neurologic sequelae, whereas no patients (0/30; $p < 0.05$) who were treated with HBO (2.8 ATA) developed sequelae.²¹⁵ In another prospective, randomized trial, 26 patients were hospitalized within 2 hours of discovery and were equally divided between two treatment groups: ambient pressure oxygen or 2.5 ATA O₂.⁵⁵ Three weeks later, patients treated with HBO had significantly fewer abnormalities on electroencephalogram, and single-photon emission computed tomography (SPECT) scans showed that cerebral vessels had nearly normal reactivity to carbon dioxide, in contrast to diminished reactivity in patients treated with ambient pressure oxygen.

In conclusion, efficacy of HBO for acute CO poisoning is supported in animal trials, and studies provide a mechanistic basis for treatment. In this era of evidence-based medicine a great deal of emphasis has been placed on systematic reviews, which have stressed the need for new studies because of the range in quality of published clinical trials.^{29,238} Practice recommendations are published based on existing studies with the best design that most closely address the actual practical

handling of patients.⁸³ HBO should at least be considered in all cases of serious acute CO poisoning and normobaric 100% oxygen continued until the time of HBO administration. CO poisoned patients who receive three HBO treatments within 24 hours following presentation manifest approximately one half the rate of cognitive sequelae at 6 weeks, 6 months, and 12 months following treatment as those treated with only normobaric oxygen. Risk factors for long term cognitive impairment in patients not treated with hyperbaric oxygen include age >36 years, exposure >24 hours, loss of consciousness, and COHb >25%. Recommendations for children can pose special challenges, but in clinical series there appear to be no marked differences in clinical manifestations compared to those reported in adults.^{62,82,108,162} Pregnancy poses another special situation in that CO readily crosses the placenta and may cause fetal distress and fetal death. HBO has been administered safely to pregnant women, but there are no prospective studies of efficacy, so standard adult guidelines for treatment are often utilized.

Another study has shown that HBO is only beneficial in reducing neurological sequelae among patients who do not possess the apolipoprotein ε4 allele.⁸⁹ Because genotype is typically unknown, this report does not alter existing treatment guidelines, but it may become important for future research. Although the basic mechanisms are unknown, it is well established that the apolipoprotein genotype can have profound effects on risk for a variety of neuropathological events.^{1,64,141,176} Whether apolipoprotein ε4 modifies the primary pathophysiological insults of CO or the mechanisms of HBO are currently unknown. As of yet, no objective method is available for staging the severity of CO poisoning, although preliminary reports suggest plasma markers may be used in the future.²⁰⁹ Psychometric screening tests have not proved reliable because abnormalities during the initial screening do not correlate with development of delayed sequelae.²¹⁵

ROLE IN METHYLENE CHLORIDE POISONING

Methylene chloride (CH_2Cl_2) is an organic solvent used commercially in aerosol sprays, as a solvent in plastics manufacturing, in photographic film production, in food processing as a degreaser, and as a paint stripper (eg, for bathtub refinishing).³⁹ It is readily absorbed through the skin or by inhalation. Immediate effects of methylene chloride are attributable to the direct depressant actions of this solvent on the CNS and resulting hypoxia. There are two metabolic pathways involved in its metabolism: an oxidative one mediated by cytochrome P450s, mainly CYP2E1 that may involve a metabolic-switch or two-active site process, and another pathway mediated by glutathione (GSH) that involves mainly glutathione S-transferases (GST).^{59,195} The P450 pathways generate formyl chloride and CO, with a secondary conjugation of formyl chloride to GSH. The separate GSH/GST pathway involves conjugation of methylene chloride, primarily by metabolism through GST-theta, to generate CO_2 as well as DNA adducts. These GSH/GST conjugation pathway DNA adducts play a role in late-onset carcinogenesis.^{228,229} Acute methylene chloride toxicity can have many of the same manifestations as CO poisoning.¹⁹¹ Production of CO is slow, and peak COHb levels of 10% to 50% may not be reached for 8 hours or more.^{37,40,60,103,116,131,132,185,195} Effects that are present after one hour or more, particularly if the COHb level is elevated, may be partially caused by CO toxicity. Anecdotal reports of HBO treatment for methylene chloride poisoning report both success and failure, which may reflect an additional component due to solvent toxicity.^{35,109,170,174} HBO treatment recommendations, using a standard three treatment protocol, follow those in patients meeting the aforementioned considerations in CO poisoning. Additional treatments in the setting of ongoing CO production or persistent symptoms may be required.¹¹⁷ Prolonged normobaric 100% oxygen therapy may be used in patients with HBO contraindications.^{90,167}

ROLE IN COMBINED CARBON MONOXIDE AND CYANIDE POISONING

CO and CN poisonings can occur concomitantly from smoke inhalation.^{4,5,12-15,21,44,49,128,130,146,184,188,231,236} Experimental evidence suggests that they can produce synergistic toxicity.^{10,149,156,158} Animal studies demonstrate that ambient pressure 100% O_2 can protect against CN toxicity¹⁸¹ and also can enhance CN metabolism to thiocyanate when thiosulfate is used concomitantly.²³ HBO may have either direct effects on reducing CN toxicity^{48,98,99,120,202} or augment other antidotes.^{33,121,181,233} However, animal studies have not uniformly found that HBO improved outcome,²³² and clinical experience regarding CN treatment with HBO is sparse.^{3,72,180} A series of symptomatic smoke inhalation victims with elevated concentrations of both CO and CN who received HBO and treatment for CN involving sodium nitrite and sodium thiosulfate, four of five patients survived without apparent neurologic damage.⁸⁶ Clinical case reports where HBO was used along with standard antidote treatment (sodium nitrite plus sodium thiosulfate) for isolated CN poisonings are equivocal regarding benefit.^{72,126,180,218} One case showed dramatic improvement,²¹⁸ but another showed none.¹²⁶ Methemoglobin formation with the standard antidote treatment involving nitrite is not thought to generate concerning high methemoglobin concentrations, but in the setting of concomitant COHb the additional reduction of oxygen carrying capacity may pose.^{107,78} Hence, there is a special advantage for hydroxycobalamin use in combined poisonings. Further research in this area is necessary. Because CN is among the most lethal poisons and toxicity is rapid, standard antidotal therapy for isolated CN poisoning is of primary importance. Hyperbaric oxygen should be considered in any case of dual (CO and CN)

poisoning and in CN poisoning when vital signs and mental status do not improve with antidote treatment. Possible use of HBO therapy may change as data on alternative antidotes such as hydroxycobalamin are investigated. Some evidence suggests each offers supportive effects on brain metabolism.^{120,121}

ROLE IN HYDROGEN SULFIDE POISONING

Hydrogen sulfide (H_2S) binds to cytochrome a-a_3 . This is similar to CN, although it is more readily dissociated by O_2 .¹⁹⁶ Clinical manifestations of toxicity are also similar to those with CO and CN.¹⁹⁶ Management of patients with serious H_2S poisoning principally involves oxygenation and cardiovascular support, as well as consideration of antidotal therapy with sodium nitrite to induce methemoglobinemia.^{66,76,79,154} HBO may be more effective than sodium nitrite in preventing mortality in animals.²² Several clinical reports indicate that HBO, sometimes in conjunction with supplemental oxygen and blood pressure support, appears to be beneficial.^{7,16,32,77,123,191,237} Relatively late treatment with HBO (eg, over 10 hours after poisoning) is reported to be beneficial in some²²⁵ but not all cases.^{2,193} No definitive data regarding use of HBO for H_2S poisoning are available, but HBO should be considered in cases where altered mental status or unstable vital signs persist after standard resuscitation measures.

ROLE IN OXIDANT-INDUCED METHEMOGLOBINEMIA

Oxidation of ferrous (2^+) heme to the ferric (3^+) form renders hemoglobin nonfunctional, and the presence of oxidized hemoglobin varieties causes a left shift of the oxyhemoglobin dissociation curve.¹⁹⁸ Hence, the manifestations of toxicity from acquired methemoglobinemia are usually more severe than those produced by a corresponding degree of anemia. In healthy people, when the fraction of methemoglobin is 10% to 20% (~ 1.5 g/dL) patients may appear cyanotic, but otherwise asymptomatic. With approximately 30% methemoglobin, there may be vague, nonspecific symptoms such as headache, fatigue, dyspnea, tachycardia, and dizziness. Unconsciousness is common at levels above 50% and death at 70%. There are numerous anecdotal accounts of clinical improvement with HBO in patients suffering from life-threatening methemoglobinemia.^{54,70,71,75,100,119,124,177,230} Ongoing exposure to any oxidants and the potential need for methylene blue to treat methemoglobinemia (Antidotes in Depth: A42) should also be addressed.

ROLE IN CARBON TETRACHLORIDE POISONING

Carbon tetrachloride (CCl_4) induced hepatotoxicity may be diminished by HBO. Mortality was decreased in a number of animal studies,^{20,31,147,168} and there are several case reports of patients surviving potentially lethal ingestions with HBO therapy.^{118,194,219,243} Because there are no proven antidotes for CCl_4 poisoning, HBO should be used for patients with large CCl_4 exposures. However, there may be a delicate balance between oxidative processes that are therapeutic and those that mediate hepatotoxicity.²⁴ Therefore, when HBO is being considered, it should be instituted before the onset of liver function abnormalities. More recently, N-Acetylcysteine (NAC) is effective in limiting liver damage in animals and appears of clinical benefit in humans with massive ingestions.^{133,137,222,239} Additive benefit from concomitant use of NAC and HBO was shown in an animal model demonstrating a diminution of toxicity in L-arginine induced pancreatitis, but there is no experience with CCl_4 poisoning.¹⁵⁷

ROLE IN HYDROGEN PEROXIDE INGESTION

Ingestion of concentrated hydrogen peroxide (H_2O_2) solutions (eg, 35%) can result in venous and arterial gas embolism due to liberation of large volumes of O_2 . Exposure to household concentrations of H_2O_2 (3%) has resulted in symptomatic portal venous air embolism on rare occasion.¹³⁴ At standard temperature and pressure, ingestion of 1 mL of household 3% H_2O_2 liberates approximately 10 mL oxygen gas; by comparison, each milliliter of 35% hydrogen peroxide yields 115 mL of oxygen gas.¹⁵⁰ Symptoms vary with the affected organ. Seizures, alterations in mental status, and strokelike manifestations occur with CNS involvement from arterial emboli and nausea, vomiting, hematemesis, and abdominal pain with gastrointestinal and hepatic venous involvement, acute obstruction of the portal vein, portal venous hypertension, and bowel edema.^{43,91,127,160,182} HBO has been a successful intervention for portal venous gas and in some cases of impaired consciousness and or focal neurological findings.^{9,63,134,150,160,169,224} HBO reduces the volume of offending gas and improves solubility of gas into tissues and plasma.¹⁶⁰ A history of inadvertent ingestion of concentrated H_2O_2 , significant signs or symptoms, or radiologic evidence of gas embolism should prompt patient placement in a Trendelenburg, left lateral decubitus position, administration of 100% oxygen and sufficient fluids to sustain perfusion, and consideration for

immediate transportation to the nearest hyperbaric facility. HBO to treat gas embolism has demonstrated benefit even if delayed beyond 20 hours.⁵⁶

ADVERSE EFFECTS AND SAFETY ISSUES

Many HBO facilities have equipment and treatment protocols and abilities analogous to those found in an intensive care unit.^{104,227,234} The possible capabilities will vary and interventions with HBO should never be undertaken if standard patient support cannot also be achieved. The inherent toxicity of O₂ and potential for injury resulting from elevations of ambient pressure must be addressed whenever HBO is used therapeutically. Preexisting conditions that require evaluation for possible management before initiation of HBO include claustrophobia, sinus congestion, and patients with scarred or noncompliant structures in the middle ear, such as otosclerosis.¹⁰⁶ Middle ear barotrauma is the most common adverse effect of HBO treatment,³⁷ and it occurs in 1.2% to 7% of patients.^{46,164,220} When autoinsufflation fails, puncturing the ear drum or tympanostomy tube placement will resolve the problem. Pneumothorax is a rarely reported complication.²⁵ Toxicity resulting from O₂ can be manifested by injuries to the CNS, lungs, and eyes. CNS O₂ toxicity manifests as a generalized seizure and occurs at an incidence of approximately 1-4/10,000 patient treatments.^{51,85,164} Pulmonary oxygen toxicity typically does not arise when standard treatment protocols are followed.^{45,61,87,165} Progressive myopia may occur in patients undergoing prolonged daily therapy, but typically reverses within 6 weeks after treatments are terminated.¹²⁹ Nuclear cataracts can form with excessive treatments, exceeding a total of 150 to 200 hours, and they may rarely develop with standard treatment protocols.^{67,159} Absent on-site hyperbaric capability, the risks of interfacility transportation (clinical decompensation, vehicle crashes, etc) also will factor into decision making.

PREGNANCY AND LACTATION

HBO in pregnant patients presents the additional risks of fetal CNS, ocular, pulmonary, and cardiac toxicity.¹¹ In CO poisoning, these must be weighed against the potentially devastating fetal outcomes such as spontaneous abortion, intrauterine fetal demise, anatomic malformations, CNS injury, respiratory distress, and neonatal jaundice, which may occur even in only mildly symptomatic CO poisoned mothers.^{36,110} For these reasons, carboxyhemoglobin thresholds (eg, 15%–20%) for HBO therapy are often set lower for the pregnant patients than for other adults in HBO treatment algorithms. Normal fetal outcomes have followed HBO, even in the setting of severe maternal toxicity, whereas significant adverse fetal outcomes have followed normobaric oxygen therapy.¹¹⁰ A summary of over 700 Russian patients treated with HBO for various hypoxemic states did not find any detrimental HBO effects.²²³ HBO was used safely in a prospective study of 44 pregnant women poisoned by CO.⁵⁷ Multiple other case reports document successful maternal and fetal outcomes in CO poisoned pregnant patients.^{26,65,187} HBO has also been employed successfully in patients with obstetrical procedures complicated by gas embolism.¹⁵¹ Treatment decisions will ultimately be made on an individual case basis after weighing potential risks and benefits. There are no data regarding HBO effects on lactation.

DOSING AND ADMINISTRATION

Rodent and human studies demonstrate that exposure to 2.8 to 3.0 ATA O₂ for 45 minutes is required to temporarily inhibit neutrophil adherence to endothelium mediated by the activation-dependent β_2 -integrins on the neutrophil membrane.^{41,101,114,204,214} Clinical trials employing HBO at only 2 ATAs have been unable to demonstrate a benefit of HBO.^{6,166} Multiple trials using HBO (2.5 ATA or above) have demonstrated efficacy.^{55,139,215,235} One trial using HBO (2.8 ATA) was unable to demonstrate benefit, subject to the previously discussed limitations.¹⁷⁸ If undertaken, HBO therapy (2.5–3.0 ATA, weighted toward the latter) should be provided as early as possible, as a mortality benefit is demonstrated if HBO is administered within 6 hours.⁷⁴ Clinical trials have initiated therapy within 24 hours of the end of carbon monoxide exposure.²³⁵ The use of more than one treatment is supported by retrospective and prospective analysis,^{73,235} although clinical practice is highly variable in this regard.^{34,81}

FORMULATION AND ACQUISITION

HBO therapy is provided in monoplace or multiplace chambers, which are considered class II medical devices. For sites not possessing HBO capacity, various online organizational and professional directories may assist in locating hyperbaric facilities in the absence of preexisting HBO transfer protocols.

SUMMARY

- Mechanisms of action and efficacy of HBO are complex and remain an area of active investigation. Research findings are provocative because they highlight the fact that traditional assessments of mechanisms for toxicity of some xenobiotics are incomplete.
- While the efficacy of HBO for acute CO poisoning is supported in animal trials, questions persist on many issues, including patient selection, optimal dose, and session frequency.
- HBO merits consideration in serious acute CO poisoning, particularly in those cases with end organ manifestations, recognizing highly varied clinical practice scenarios and preferences.
- Further investigation is required to discern those cases where clear benefit arises with HBO treatment and to define the constraints that may limit its efficacious use.
- Anecdotal evidence supports HBO therapy in hydrogen sulfide and carbon tetrachloride poisoning, in oxidant induced methemoglobinemia, and in hydrogen peroxide ingestion.

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126 CYANIDE AND HYDROGEN SULFIDE

Christopher P. Holstege and Mark A. Kirk

Cyanide	
MW	= 26.02 Da
Whole blood	< 1 µg/mL
	< 38.5 µmol/L
Concentrations	
Airborne	
Immediately fatal	= 270 ppm
Life threatening	= 110 ppm >30 minutes
Hydrogen Sulfide	
MW	= 34.08 Da
Airborne	
Odor threshold	= 0.01–0.3 ppm
Olfactory paralysis	= 100–150 ppm
Immediately fatal	= 1000 ppm

CYANIDE POISONING

History and Epidemiology

Cyanide exposure is associated with smoke inhalation, laboratory mishaps, industrial incidents, suicide attempts, and criminal activity.^{39,113} Cyanide is a chemical group that consists of one atom of carbon bound to one atom of nitrogen by three molecular bonds ($C\equiv N$). Inorganic cyanides (also known as cyanide salts) contain cyanide in the anion form (CN^-) and are used in numerous industries, such as metallurgy, photographic developing, plastic manufacturing, fumigation, and mining. Common cyanide salts include sodium cyanide ($NaCN$) and potassium cyanide (KCN). Sodium salts react readily with water to form hydrogen cyanide. Organic compounds that have a cyano group bonded to an alkyl residue are called nitriles. For example, methyl cyanide is also known as acetonitrile (CH_3CN). Hydrogen cyanide (HCN) is a colorless gas at standard temperature and pressure with a reported bitter odor. Cyanogen gas, a dimer of cyanide, reacts with water and breaks down into the cyanide anion. Cyanogen chloride ($CNCl$) is a colorless gas that is easily condensed; it is a listed agent by the Chemical Weapons Convention.

Many plants, such as the *Manihot* spp, *Linum* spp, *Lotus* spp, *Prunus* spp, *Sorghum* spp, and *Phaseolus* spp contain cyanogenic glycosides.¹¹¹ The *Prunus* species consisting of apricots, bitter almond, cherry, and peaches have pitted fruits containing the glucoside amygdalin. When ingested, amygdalin is biotransformed by intestinal β -d-glucosidase to glucose, aldehyde, and cyanide (Fig. 126–1). Laetrile, which contains amygdalin, was inappropriately suggested to have antineoplastic properties despite a lack of evidence to support such claims.⁸³ When laetrile was administered by intravenous infusion, amygdalin bypassed the necessary enzymes in the gastrointestinal tract to liberate cyanide and did not cause toxicity. However, ingested laetrile can cause cyanide poisoning. Despite data demonstrating its lack of utility in the treatment of cancer, it still is available via the Internet.

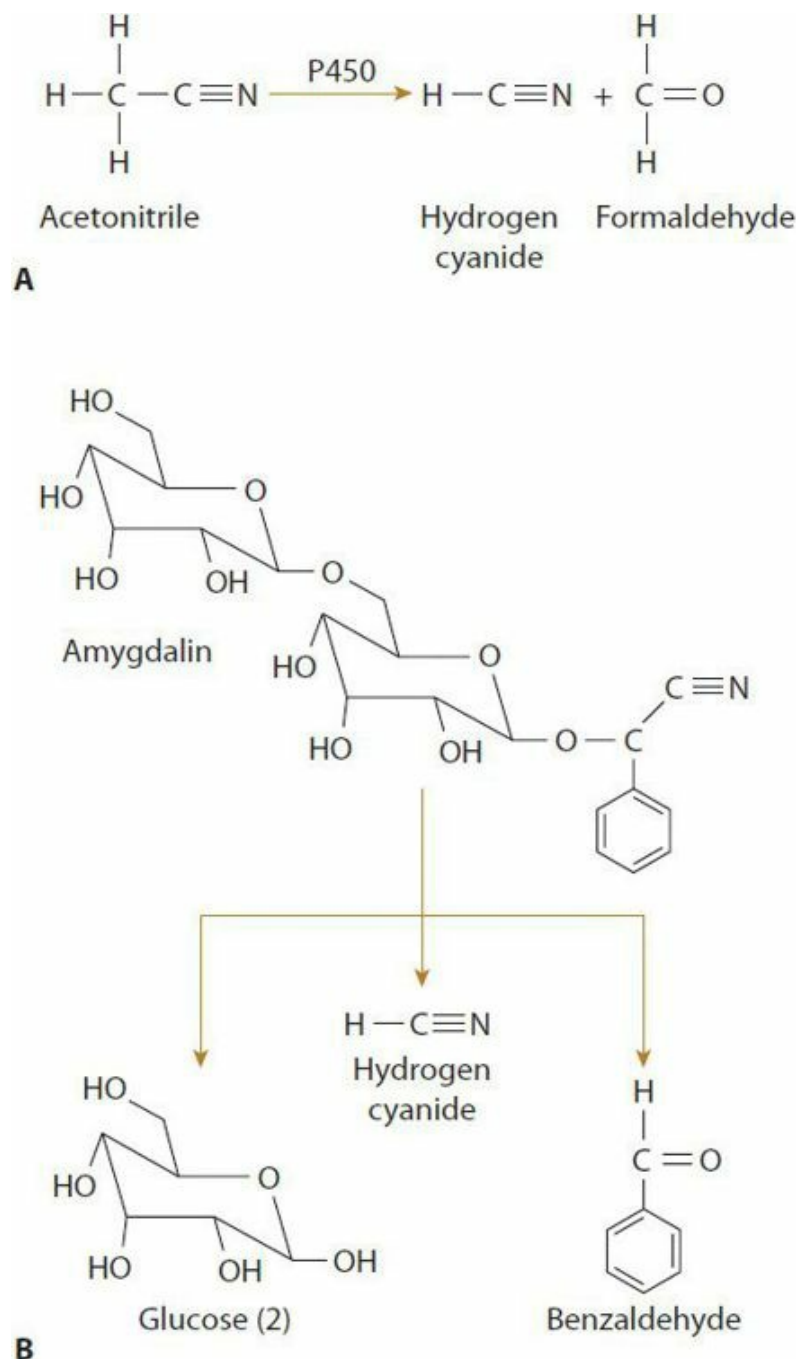


FIGURE 126–1. Biotransformation of cyanogens (**A**) acetonitrile and (**B**) amygdalin to cyanide.

Cassava (*Manihot esculenta*) root is a major source of food for millions of people in the tropics. It is a hardy plant that can remain in the ground for up to 2 years and needs relatively little water to survive. Because the shelf life of a cassava root is short once it is removed from the stem, cassava root must be processed and sent to market as soon as it is harvested. However, proper processing must occur to assure the food's safety. Processed cassava is called Gari. Linamarin (2-hydroxy-4-oxo-4-phenylbutanenitrile-β-D-glycoside) is the major cyanogenic glycoside in cassava roots. It is hydrolyzed to hydrogen cyanide and acetone in two steps during the processing of cassava roots.¹²⁴ Soaking peeled cassava in water for a single day releases approximately 45% of the cyanogens, whereas soaking for 5 days causes 90% loss. If processing is inefficient, linamarin and cyanohydrin, the immediate product of hydrolysis of linamarin, remain in the food.⁹² Consumed linamarin is hydrolyzed to cyanohydrin by β-glucosidases of the microorganisms in the intestines. Cyanohydrin present in the food and formed from linamarin then dissociates spontaneously to cyanide in the alkaline pH of the small intestines.

Iatrogenic cyanide poisoning may occur during use of nitroprusside for the management of hypertension. Each nitroprusside molecule contains five cyanide molecules, which are slowly released in vivo. If endogenous sulfate stores are depleted, as in the malnourished or postoperative patient, cyanide may accumulate even with therapeutic nitroprusside infusion rates (2–10 μg/kg/min).

In 1782, the Swedish chemist Carl Wilhelm Scheele first isolated hydrogen cyanide. He reportedly died from the adverse health effects of cyanide poisoning in 1786. Napoleon III was the first to employ hydrogen cyanide in chemical warfare, and it was subsequently used on World War I battlefields. During World War II, hydrocyanic acid pellets (brand name Zyklon B) caused more than one million deaths in Nazi gas chambers at Auschwitz, Buchenwald, and Majdanek. In 1978, KCN was used in a mass suicide led by Jim Jones of the People's Temple in Guyana, resulting in 913 deaths. Other notorious suicide cases include Wallace Carothers, Herman Goring, Heinrich Himmler, and Ramon Sampedro. In 1982,

seven deaths resulted from consumption of cyanide-tainted acetaminophen in Chicago that subsequently lead to the requirement of tamper-resistant pharmaceutical packaging. Numerous copycat murders subsequently have occurred using cyanide-tainted capsules, with the last high-profile case occurring in 2010 involving an Ohio emergency medicine physician who murdered his wife with a cyanide-laden calcium capsule.¹⁴ Cyanide has also been used for illicit euthanasia.²⁰

Cyanide poisoning accounted for 1148 exposures reported to the American Association of Poison Control Centers from 2007 to 2011 (Chap. 136).²⁴ One study of poison center data found that 8.3% of intentional overdose cases died and another 9% developed cardiac arrest but survived; 74% did not receive an antidote, most likely due to the failure of the initial treatment team to recognize the poisoning.¹³ The majority of reported cyanide exposures are unintentional. These events frequently involve chemists or technicians working in laboratories where cyanide salts are common reagents.¹⁹ The potential for cyanide poisoning also exists following smoke inhalation, especially following the combustion of materials such as wool, silk, synthetic rubber, and polyurethane.^{8,30,108} Ingestion of cyanogenic chemicals (ie, acetonitrile, acrylonitrile, and propionitrile) is another source of cyanide poisoning.¹¹⁵ Acetonitrile (C_2H_3N) and acrylonitrile (C_3H_3N) are themselves nontoxic, but biotransformation via cytochrome P450 liberates cyanide (Fig. 126–1).¹²⁶

Pharmacology

The dose of cyanide required to produce toxicity is dependent on the form of cyanide, the duration of exposure, and the route of exposure. However, cyanide is an extremely potent toxin with even small exposures leading to life-threatening symptoms. For example, an adult oral lethal dose of KCN is approximately 200 mg. An airborne concentration of 270 ppm ($\mu\text{g/mL}$) of hydrogen cyanide (HCN) may be immediately fatal, and exposures >110 ppm for more than 30 minutes are generally considered life threatening. The current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for both hydrogen cyanide and cyanogen is 10 ppm as an 8-hour time-weighted average (TWA) concentration. The Immediately Dangerous to Life or Health (IDLH) value for hydrogen cyanide is 50 ppm.

Acute toxicity occurs through a variety of routes, including inhalation, ingestion, dermal, and parenteral. Hydrogen cyanide readily crosses membranes because it has a low molecular weight (27 Da) and is nonionized. After absorption and dissolution in blood, cyanide exists in equilibrium as the cyanide anion (CN^-) and undissociated HCN. Hydrogen cyanide is a weak acid with a pK_a of 9.21. Therefore, at physiologic pH 7.4 it exists primarily as HCN. Rapid diffusion across alveolar membranes followed by direct distribution to target organs accounts for the rapid lethality associated with HCN inhalation.

Toxicokinetics

Cyanide is eliminated from the body by multiple pathways. The major route for detoxification of cyanide is the enzymatic conversion to thiocyanate. Two sulfurtransferase enzymes, rhodanese (thiosulfate-cyanide sulfurtransferase) and β -mercaptopyruvate-cyanide sulfurtransferase, catalyze this reaction. The primary pathway for metabolism is rhodanese, which is widely distributed throughout the body and has the highest concentration in the liver. This enzyme catalyzes the transfer of a sulfane sulfur from a sulfur donor, such as thiosulfate to cyanide to form thiocyanate. In acute poisoning, the limiting factor in cyanide detoxification by rhodanese is the availability of adequate quantities of sulfur donors. The endogenous stores of sulfur are rapidly depleted, and cyanide metabolism slows. Hence, the efficacy of sodium thiosulfate as an antidote stems from its normalization of the metabolic inactivation of cyanide. The sulfation of cyanide is essentially irreversible, and the sulfation product thiocyanate has relatively little inherent toxicity. Thiocyanate is eliminated in urine. A number of minor pathways of metabolism ($<15\%$ of total) account for cyanide elimination, including conversion to 2-aminothiazoline-4-carboxylic acid, incorporation into the 1-carbon metabolic pool, or in combination with hydroxycobalamin to form cyanocobalamin.

Limited human data regarding the cyanide elimination half-life are available. Elimination appears to follow first-order kinetics,⁷³ although it varies widely in reports (range 1.2–66 hours).^{8,51,73} Disparity in values may result from the number of samples used to perform calculations and the effects of antidotal treatment. The volume of distribution of the cyanide anion varies according to species and investigator, with 0.075 L/kg reported in humans.³⁴

Pathophysiology

Cyanide is an inhibitor of multiple enzymes, including succinic acid dehydrogenase, superoxide dismutase, carbonic anhydrase, and cytochrome oxidase.^{80,87} Cytochrome oxidase is an iron containing metalloenzyme essential for oxidative phosphorylation and, hence, aerobic energy production. It functions in the electron transport chain within mitochondria, converting catabolic products of glucose into adenosine triphosphate (ATP). Cyanide induces cellular hypoxia by inhibiting cytochrome oxidase at the cytochrome a_3 portion of the electron transport chain (Fig. 126–2).^{95,128} Hydrogen ions that normally would have combined with oxygen at the terminal end of the chain are no longer incorporated. Thus, despite

sufficient oxygen supply, oxygen cannot be utilized, and ATP molecules are no longer formed.⁷⁸ Unincorporated hydrogen ions accumulate, contributing to acidemia.

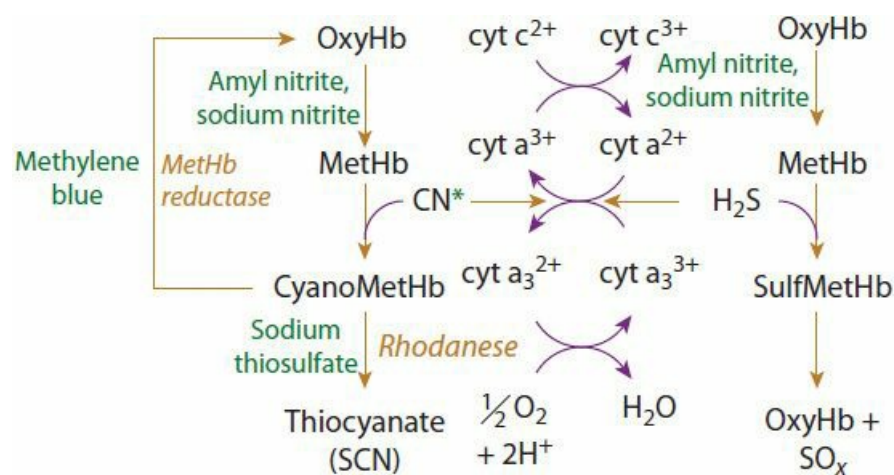


FIGURE 126–2. Pathway of cyanide and hydrogen sulfide toxicity and detoxification.

Hyperlactemia occurs following cyanide poisoning because of failure of aerobic energy metabolism. During aerobic conditions, when the electron transport chain is functional, lactate is converted to pyruvate by mitochondrial lactate dehydrogenase. In this process, lactate donates hydrogen moieties that reduce nicotinamide adenine dinucleotide (NAD^+) to NADH. Pyruvate then enters the tricarboxylic acid cycle, with resulting ATP formation. When cytochrome a_3 within the electron transport chain is inhibited by cyanide, there is a relative paucity of NAD^+ and predominance of NADH, favoring the reverse reaction, in which pyruvate is converted to lactate.

Cyanide is also a potent neurotoxin. Cyanide exhibits a particular affinity for regions of the brain with high metabolic activity. Central nervous system (CNS) injury occurs via several mechanisms, including impaired oxygen utilization, oxidant stress, and enhanced release of excitatory neurotransmitters. Cranial imaging of survivors of cyanide poisoning reveals that injury occurs in the most oxygen-sensitive areas of the brains, such as the basal ganglia, cerebellum, and sensorimotor cortex.

Cyanide enhances N-methyl-D-aspartate (NMDA) receptor activity and directly activates the NMDA receptor, which increases release of glutamate and inhibits voltage-dependent magnesium blockade of the NMDA receptor. This NMDA receptor stimulation results in Ca^{2+} entry into the cytosol of neurons. Cyanide also activates voltage-sensitive calcium channels⁶⁴ and mobilizes Ca^{2+} from intracellular stores.^{81,98} As a result, cytosolic Ca^{2+} rises and activates a series of biochemical reactions that lead to the generation of reactive oxygen species and nitrous oxide.^{70,84,106} These reactive oxygen species initiate peroxidation of cellular lipids, which, together with cyanide-induced inhibition of the respiratory chain, adversely affect mitochondrial function, initiating cytochrome c release and execution of apoptosis, necrosis, and subsequent neurodegeneration.^{6,64,97,107} Experimental studies demonstrate that NMDA inhibitors such as dextrorphan and dizocilpine, antioxidants, and cyclooxygenase inhibitors all protect neurons against cyanide-induced damage.^{61,77,125}

Sulfurtransferase metabolism via rhodanese is crucial for detoxification. However, the aforementioned cyanide-induced metabolic derangement may decrease enzyme detoxification. Decreased ATP and reactive oxygen species and increased cytosolic Ca^{2+} stimulate protein kinase C activity, which in turn inactivates rhodanese.³

Clinical Manifestations

Acute Exposure to Cyanide. The amount, duration of exposure, route of exposure, and premorbid condition of the individual influence the time to onset and severity of illness. A critical combination of these factors overwhelms endogenous detoxification pathways, allowing cyanide to diffusely affect cellular function within the body. No reliable pathognomonic symptom or toxic syndrome is associated with acute cyanide poisoning.⁴⁷ The initial clinical effects of acute cyanide poisoning may be nonspecific, generalized, and nondiagnostic, thereby making the correct diagnosis difficult to obtain. Clinical manifestations reflect rapid dysfunction of oxygen-sensitive organs, with central nervous and cardiovascular findings predominating. The time to onset of symptoms typically is seconds with inhalation of gaseous HCN or intravenous injection of a water soluble cyanide salt and several minutes following ingestion of an inorganic cyanide salt. The clinical effects of cyanogenic chemicals often are delayed, and the time course varies among individuals (ranging from 3–24 hours), depending on their rate of biotransformation.¹¹⁵ Clinically apparent cyanide toxicity may occur within hours to days of initiating nitroprusside infusion, although concurrent administration of thiosulfate or hydroxocobalamin may prevent toxicity (Chap. 63).¹⁰⁴

CNS signs and symptoms are typical of progressive hypoxia and include headache, anxiety, agitation, confusion,

lethargy, nonreactive dilated pupils seizures, and coma. A centrally mediated tachypnea occurs initially, followed by bradypnea and apnea.

Cardiovascular responses to cyanide are complex. Studies of isolated heart preparations and intact animal models show that the principal cardiac insult is slowing of rate and loss of contractile force.⁷ Several reflex mechanisms, including catecholamine release and central vasomotor activity, may modulate myocardial performance and vascular response in patients with cyanide poisoning.⁷¹ In laboratory investigations, a brief period of increased inotropy caused by reflex compensatory mechanisms occurs before myocardial depression. Clinically, an initial period of tachycardia and hypertension may occur, followed by hypotension with reflex tachycardia, but the terminal event is consistently bradycardia and hypotension. Ventricular dysrhythmias do not appear to be an important factor.

Pulmonary edema may be found at necropsy.⁴⁷ Inhalation of HCN may be associated with mild corrosive injury to the respiratory tract mucosa.

Gastrointestinal toxicity may occur following ingestion of inorganic cyanide and cyanogens and includes abdominal pain, nausea, and vomiting. These symptoms are caused by hemorrhagic gastritis, which is frequently identified on necropsy, and are thought to be secondary to the corrosive nature of cyanide salts. However, if death occurs rapidly, this gastritis may not be seen at autopsy because development of inflammation occurs over time.⁴⁷ Following ingestion, a smell of bitter almonds should not be relied upon to be emitted from the gastrointestinal system as health care providers in nearly all case reports published do not mention this finding.⁶³

Cutaneous manifestations may vary. Traditionally, a cherry-red skin color is described as a result of increased venous hemoglobin oxygen saturation, which results from decreased utilization of oxygen at the tissue level. This phenomenon may be more evident on fundoscopic examination, where veins and arteries may appear similar in color. Despite the inference in the name, cyanide does not directly cause cyanosis. The occurrence of cyanosis is commonly reported in published case reports and is likely due to cardiovascular collapse and subsequent poor perfusion.¹²²

Delayed Clinical Manifestations of Acute Exposure. Survivors of serious, acute poisoning may develop delayed neurologic sequelae. Parkinsonian symptoms, including dystonia, dysarthria, rigidity, and bradykinesia, are most common. Symptoms typically develop over weeks to months, but subtle findings can be present within a few days. Head computerized tomography and magnetic resonance imaging consistently reveal basal ganglia damage to the globus pallidus, putamen, and hippocampus, with radiologic changes appearing several weeks after onset of symptoms. Whether delayed manifestations result from direct cellular injury or secondary hypoxia is unclear. Extrapyrarnidal manifestations may progress or resolve. Response to pharmacotherapy with antiparkinsonian agents is generally disappointing

Chronic Exposure to Cyanide. Chronic exposure to cyanide may result in insidious syndromes, including tobacco amblyopia, tropical ataxic neuropathy, and Leber hereditary optic neuropathy. Tobacco amblyopia is a progressive loss of visual function that occurs almost exclusively in men who smoke cigarettes. Affected smokers have lower serum cyanocobalamin and thiocyanate concentrations than unaffected smoking counterparts, suggesting a reduced ability to detoxify cyanide. Cessation of smoking and administration of hydroxocobalamin often reverses symptoms. Tropical ataxic neuropathy is a demyelinating disease associated with improperly processed cassava consumption.^{91,112} Neurologic manifestations include Parkinson disease, spastic paraparesis, sensory ataxia, optic atrophy, and sensorineural hearing loss.¹²² Concomitant dermatitis and glossitis suggest an association of high dietary cassava with low vitamin B₁₂ intake. Elevated thiocyanate concentrations in affected individuals further implicate cyanide as the etiology. Removal of dietary cassava and institution of vitamin B₁₂ therapy alleviates symptoms. Leber hereditary optic atrophy, a condition of subacute visual failure affecting men, is thought to be caused by rhodanese deficiency⁴²

Chronic exposure to cyanide is associated with thyroid disorders.¹ Thiocyanate is a competitive inhibitor of iodide entry into the thyroid, thereby causing the formation of goiters and the development of hypothyroidism. Chronic exposure to cyanide in animals is associated with hydropic degeneration in hepatocytes and epithelial cells of the renal proximal tubules; however, these morphologic lesions are not linked to functional alternations.¹¹¹

Diagnostic Testing

Because of nonspecific symptoms and delay in laboratory cyanide confirmation, the clinician must rely on historical circumstances and some initial findings to raise suspicion of cyanide poisoning and institute therapy (Table 126–1).

TABLE 126–1. Cyanide Poisoning: Emergency Management Guidelines

When to suspect cyanide

Sudden collapse of laboratory or industrial worker

Fire victim with coma or academia

Suicide with unexplained coma or academia

Ingestion of artificial nail remover

Ingestion of seeds or pits from Prunus species

Patient with altered mental status, acidemia, and tachyphylaxis to nitroprusside

Supportive care

Control airway, ventilate, and give 100% oxygen

Crystalloids and vasopressors for hypotension

Administer sodium bicarbonate; titrate according to ABG and serum HCO_3^-

Antidotes

1) Hydroxocobalamin

Initial adult dose: 5 g IV over 15 minutes; pediatric dose 70 mg/kg up to 5 g

or

2) Cyanide Antidote Kit

Amyl nitrite pearls are included in the kit for prehospital use. For hospital management, sodium nitrite is the preferred methemoglobin inducer and is given in lieu of the pearls.

Give sodium nitrite (NaNO_2) as a 3% solution over 2–4 minutes IV: Adult dose: 10 mL (300 mg)

Caution: Monitor blood pressure frequently, and treat hypotension by slowing infusion rate and giving crystalloids and vasopressors. Obtain methemoglobin level 30 minutes after dose, and consider possible excessive methemoglobin formation if patient deteriorates during therapy. Withhold nitrites if COHb is suspected to be present.

Give sodium thiosulfate (NaS_2O_3) as a 25% solution IV:

Adult dose: 50 mL (12.5 g)

Pediatric dose: 1.65 mL/kg up to 50 mL

Decontamination

Protect health care provider from contamination

Cutaneous: Carefully remove all clothing and flush the skin

Ingestion: Oro- or nasogastric lavage and instill 1 g/kg activated charcoal

Laboratory

Arterial blood gas

Electrolytes and glucose

Blood lactate

Whole-blood cyanide concentration (for later confirmation only)

Laboratory findings suggestive of cyanide poisoning reflect the known metabolic abnormalities, which include metabolic acidosis, elevated lactate concentration, and increased anion gap. Elevated venous oxygen saturation results from reduced tissue extraction.⁶⁵ A venous oxygen saturation >90% from superior vena cava or pulmonary artery blood indicates decreased oxygen utilization. This finding is not specific for cyanide and could represent cellular poisoning from other

agents such as carbon monoxide, clenbuterol, hydrogen sulfide, and sodium azide, or medical conditions such as sepsis high-output cardiac syndromes and left to right intracardiac shunts.

Hyperlactatemia is found in numerous critical illnesses and typically is a nonspecific finding. However, a significant association exists between blood cyanide and serum lactate concentrations.^{9,10} ABG analysis of whole blood may provide additional information. Arterial pH correlates inversely with cyanide concentration.¹⁰ The finding of a narrow arterial–venous oxygen difference also may suggest cyanide toxicity.

Cyanide results in nonspecific electrocardiographic (ECG) findings.⁴⁰ Rhythm disturbances such as sinus tachycardia, bradydysrhythmias, atrial fibrillation, ventricular tachycardia, and ventricular fibrillation are all reported, as are elevation or depression of the ST segment, shortened ST segments, and fusion of the T wave into the QRS complex.

Blood cyanide concentration determination can confirm toxicity, but this determination is not available in a sufficiently rapid manner to affect initial treatment. Whole blood or serum can be analyzed, with most reports utilizing whole blood for cyanide detection. In mammals, including primates, whole-blood concentrations are twice serum concentrations as a result of cyanide sequestration in red blood cells. Background whole-blood concentrations in nonsmokers range between 0.02 and 0.5 µg/mL.^{52,59} Higher blood concentrations suggest toxicity. Coma and respiratory depression are associated with whole blood concentrations >2.5 µg/mL and death with concentrations >3 µg/mL. Detecting urinary cyanide is difficult, and urinary thiocyanate is a more readily detectable and useful marker of cyanide exposure. Serum thiocyanate concentrations are of little value in assessing patients with acute poisoning because of little correlation with symptoms but are useful in confirming exposure.

A semiquantitative assay that uses calorimetric paper test strips may immediately detect cyanide. Cyantesmo test strips currently are used by water treatment facilities to detect cyanide. An investigation of the utility of these strips in clinical practice found that the test strips incrementally increased to a deep blue color over a progressively longer portion of the test strip with increasing concentrations of cyanide in the blood.¹⁰² These strips accurately and rapidly detected, in a semiquantifiable manner, CN concentrations >1 µg/mL.

Management

Because cyanide poisoning is rare, it is easy to overlook the diagnosis unless there is an obvious history of exposure. Thus, the most critical step in treatment is considering the diagnosis in high-risk situations (Table 126–1) and initiating empiric therapy with 100% oxygen and either hydroxycobalamin or the cyanide antidote kit. The initial care (Table 126–1) of the cyanide-poisoned patient begins by directing attention to airway patency, ventilatory support, and oxygenation. Acidemia should be treated with adequate ventilation and sodium bicarbonate administration.

Intravenous access should be rapidly obtained and blood samples sent for renal function, glucose, and electrolyte determinations. A whole-blood cyanide concentration can be obtained for later confirmation of exposure. ABG analysis and serum lactate concentration will help assess acid–base status. Initiation of crystalloid and infusion of vasopressor for hypotension are warranted.

First responders should exercise extreme caution when entering potentially hazardous areas such as chemical plants and laboratories where a previously healthy person is “found down.” Exposure to cyanide may occur by multiple routes, including ingestion, inhalation, dermal, and parenteral. For patients with inhalation exposure, removal from the area of exposure is critical. Further decontamination is generally unnecessary. Decontamination of the cyanide-poisoned patient occurs concurrently with initial resuscitation. The health care provider should always be protected from potential dermal contamination by using personal protective devices such as water-impervious gowns, gloves, and eyewear. For patients with cutaneous exposure, remove their clothing, brush any powder off the skin, and flush the skin with water. Particular attention should be given to open wounds because CN[−] or HCN is readily absorbed through abraded skin.

Instillation of activated charcoal often is considered ineffective because of low binding of cyanide (1 g activated charcoal only adsorbs 35 mg cyanide). However, a potentially lethal oral dose of cyanide (ie, a few hundred milligrams) is within the adsorptive capacity of a typical 1 g/kg dose of activated charcoal. Prophylactic activated charcoal administration improved survival in animals given an LD₁₀₀ dose of KCN.⁷⁴ Based on the potential benefits and minimal risks, activated charcoal may be considered in the patient with an intact protected airway.

Although either hydroxocobalamin or the cyanide antidote kit can be administered as soon as cyanide poisoning is suspected, hydroxocobalamin is preferred. Hydroxocobalamin is a metalloprotein with a central cobalt atom that complexes cyanide, forming cyanocobalamin (vitamin B₁₂). Cyanocobalamin is eliminated in the urine or releases the cyanide moiety at a rate sufficient to allow detoxification by rhodanese. One molecule of hydroxocobalamin binds one molecule of cyanide, yielding a molecular weight binding ratio of 50:1. The US-approved adult starting dose is 5 g administered by intravenous infusion over 15 minutes. Depending upon the severity of the poisoning and the clinical response, a second dose of 5 g may be administered by intravenous infusion for a total dose of 10 g. Hydroxocobalamin has few adverse effects, which include allergic reaction and a transient reddish discoloration of the skin, mucous membranes, and urine.^{25,21,53} No hemodynamic adverse effects other than a potential mild transient rise of blood pressure are

observed^{16,105} (Antidotes in Depth: A41).

The cyanide antidote kit contains amyl nitrite, sodium nitrite, and sodium thiosulfate. Both thiosulfate and nitrite individually have antidotal efficacy when given alone in animal models of cyanide poisoning, but they have even greater benefit when they are given in combination.⁸⁰ Thiosulfate donates the sulfur atoms necessary for rhodanese-mediated cyanide biotransformation to thiocyanate. The mechanism of nitrite is less clear. Traditional rationale relies on the ability of nitrite to generate methemoglobin. Because cyanide has a higher affinity for methemoglobin than for cytochrome a_3 , cytochrome oxidase function is restored. However, improved hepatic blood flow and nitric oxide formation are alternate explanations (Antidotes in Depth: A39 and A40). Amyl nitrite is contained within glass pearls that are crushed and intermittently inhaled or intermittently introduced into the ventilator system to initiate methemoglobin formation. The amyl nitrite pearls are reserved for cases where intravenous access is delayed or not possible. Intravenous sodium nitrite is preferred and is supplied as a 10-mL volume of 3% solution (300 mg). Adverse effects of nitrites include excessive methemoglobin formation and, because of potent vasodilation, hypotension and tachycardia. Avoiding rapid infusion, monitoring blood pressure, and adhering to dosing guidelines will limit adverse effects. Because of the potential for excessive methemoglobinemia during nitrite treatment, pediatric dosing guidelines are available (Table 126–2). Sodium thiosulfate is the second component of the cyanide antidote kit. It is supplied as 50 mL of 25% solution (12.5 g). It is a substrate for the reaction catalyzed by rhodanese that is essentially irreversible, converting a highly toxic entity to a relatively harmless compound. However, thiocyanate does have its own toxicity in the presence of kidney failure, including abdominal pain, vomiting, rash, and CNS dysfunction. Thiosulfate itself is not associated with significant adverse reactions. The pediatric dose of thiosulfate is adjusted for weight.

TABLE 126–2. Cyanide Management: Pediatric Sodium Nitrite Guidelines^a

Hemoglobin (g)	NaNO ₂ (mg/kg)	3% NaNO ₂ solution (mL/kg)
7.0	5.8	0.19
8.0	6.6	0.22
9.0	7.5	0.25
10.0	8.3	0.27
11.0	9.1	0.30
12.0	10.0	0.33
13.0	10.8	0.36
14.0	11.6	0.39

^aPediatric thiosulfate dose: 1.65 mL/kg of 25% solution up to 50 mL.

Adapted, with permission, from Berlin CM: The treatment of cyanide poisoning in children. *Pediatrics*. 1970;46:793–796.

In Europe, 4-dimethylaminophenol (4-DMAP), rather than sodium nitrite, is the methemoglobin-inducer of choice.⁵⁴ It generates methemoglobin more rapidly than sodium nitrite, with peak methemoglobin concentrations at 5 minutes after 4-DMAP rather than 30 minutes after sodium nitrite. The dose of 4-DMAP is 3 mg/kg and is coadministered with thiosulfate. As with sodium nitrite, its major adverse effect is excessive methemoglobin formation and potential for hypotension. Cobalt in the form of dicobalt edetate has been used as a cyanide chelator, but its usefulness is limited by serious adverse effects such as hypotension, cardiac dysrhythmias, decreased cerebral blood flow, and angioedema.^{22,86} The cobalamin precursor cobinamide has been used both prophylactically and therapeutically to treat experimental cyanide toxicity, and when given at high enough doses, it has rescued animals from cyanide-induced apnea and coma.²³ Cobalamin has been used in France to treat human cyanide exposure, either alone or combined with sodium thiosulfate. Cobinamide is an investigational treatment that has a much greater affinity for cyanide ion than cobalamin.²⁹ Hyperbaric oxygen has been considered in the past, but recent evidence suggests no benefit in cyanide poisoning.⁷⁶

In animal models, the antioxidant vitamins A, C, and E diminish the extent of tissue damage caused by subacute cyanide intoxication.⁸⁹ This is especially important in the tropics, where the majority of dietary staples are cyanophoric crops such as cassava.

Patients who do not survive cyanide poisoning are suitable organ donors. Heart, liver, kidney, pancreas, cornea, skin, and bone have been successfully transplanted following cyanide poisoning.⁴¹

HYDROGEN SULFIDE POISONING

History and Epidemiology

Hydrogen sulfide (H_2S) exposures are often dramatic and can be fatal. The American Association of Poison Control Centers' National Poison Data System reported 5383 exposures from 2007 through 2011 (Chap. 136). Only 1534 of these exposures required evaluation at a health care facility, 457 reported moderate or major effects, and 36 deaths occurred.²⁴ Over a 10 year period from 1983 to 1992, 5563 exposures and 29 deaths attributed to hydrogen sulfide were reported in the National Poison Data System.¹¹⁰ Most often, serious consequences of hydrogen sulfide exposures occur through workplace exposures, but they can also occur in environmental disasters and most recently in suicides.

Bacterial decomposition of proteins generates hydrogen sulfide, and the gas is produced in many industrial activities. Decay of the sulfur-containing products such as fish, sewage, and manure produce hydrogen sulfide. Industrial sources include pulp paper mills, heavy-water production, the leather industry, roofing asphalt tanks, vulcanizing of rubber, viscose rayon production, and coke manufacturing from coal.³¹ It is a major industrial hazard in oil and gas production, particularly in sour gas fields (natural gas containing sulfur).

Between 1990 and 1999, hydrogen sulfide poisoning was associated with the deaths of 18% of US construction workers killed by toxic inhalation.³⁵ Many died while working in confined spaces such as sewers or sewer manholes. Agricultural workers operating near livestock manure storage tanks are at greatest risk of harm from an inhalation exposure.^{12,55} Poisoned workers are “knocked down,” prompting coworkers to attempt a rescue. Numerous case reports describe multiple victims because the would-be rescuers often themselves become victims when they attempt a rescue in an environment having high concentrations of hydrogen sulfide.^{12,35,55} Studies report that up to 25% of fatalities involve rescuers.^{35,44,58}

OSHA and a variety of occupational organizations such as the American Industrial Hygiene Association, the National Institute of Occupational Safety and Health, the American Shipbuilding Association, and the US Chemical Safety Board recognize the serious dangers of hydrogen sulfide exposures in the workplace and continue to promote safety alerts and educational programs.⁹³

Natural sources of hydrogen sulfide are volcanoes, caves, sulfur springs, and underground deposits of natural gas.^{31,101} Hydrogen sulfide is also implicated in several environmental disasters. In 1950, 22 people died and 320 were hospitalized in Poza Rica, Mexico, when a local natural gas facility inadvertently released hydrogen sulfide into the air.⁸² Hydrogen sulfide claimed nine lives when a sour gas well failed, releasing a cloud of the poisonous gas into the Denver City, Texas community in 1975.⁸⁵ In 2003, a gas drilling incident in southwest China released natural gas and a cloud of hydrogen sulfide into a populated area, killing more than 200 people, injuring 9000, and necessitating the evacuation of more than 40,000.¹²⁹

Recently, a large number of suicides called “chemical suicides” or “detergent suicides” have been attributed to mixing common household chemicals such as pesticides or fungicides and toilet bowl cleaners to create hydrogen sulfide gas.^{116,119} This practice is of concern because the recipes are easily found on Internet sites, precursor chemicals are readily accessible from the cleaning section of many local stores, first responders are at risk of harmful toxic effects from exposure, and the toxic gas can inadvertently expose groups of people in nearby buildings. In Japan, it is reported that more than 500 people killed themselves in the first half of 2008 by this means.¹³⁰ Information resources on the Internet are implicated for the widespread practice and prompted police to request purging the suicide recipes from Internet sites.⁵⁶ In the United States, chemical suicides from hydrogen sulfide are likely underreported but rose from 2 in 2008 to 19 in 2010.¹⁰⁰ In as many as 80% of incidents, first responders report exposures following attempted rescue of victims.¹⁰⁰ Suicide victims using this method to harm themselves inadvertently cause injuries and evacuations because of the toxic gas permeating buildings. One incident in Japan caused 90 people to become ill from the toxic gas as it permeated an apartment building, and another resulted in 350 people evacuating a building.¹¹⁹

Pharmacology and Toxicokinetics

Hydrogen sulfide is a colorless gas, more dense than air, with an irritating odor of “rotten eggs.” It is highly lipid soluble, a property that allows easy penetration of biologic membranes. Systemic absorption usually occurs through inhalation, and it is rapidly distributed to tissues.¹⁰¹

The tissues most sensitive to hydrogen sulfide are those with high oxygen demand. The systemic toxicity of hydrogen sulfide results from its potent inhibition of cytochrome oxidase, thereby interrupting oxidative phosphorylation.³¹ Hydrogen sulfide binds to the ferric (Fe^{3+}) moiety of cytochrome a_3 oxidase complex with a higher affinity than does cyanide. The resulting inhibition of oxidative phosphorylation produces cellular hypoxia and anaerobic metabolism.^{31,131}

Cytochrome oxidase inhibition is not the sole mechanism of toxicity. Other enzymes are inhibited by hydrogen sulfide and may contribute to its toxic effects.¹⁰¹ Besides producing cellular hypoxia, hydrogen sulfide alters brain neurotransmitter release and transmission through potassium channel-mediated hyperpolarization of neurons, potentiate NMDA receptors,

and other neuronal inhibitory mechanisms.^{90,101} A proposed mechanism of death is poisoning of the brainstem respiratory center through selective uptake by lipophilic white matter in this region.¹²⁷ The olfactory nerve is a specific target of great interest. Not only does the toxic gas cause olfactory nerve paralysis, but it is thought to be a portal of entry into the central nervous system because of its direct contact with the brain.¹³¹ It is also cytotoxic through formation of reactive sulfur and oxygen species. It may also react with iron to fuel the Fenton reaction causing free radical injury¹¹⁷ (Chaps. 12 and 13).

In addition to systemic effects, hydrogen sulfide reacts with the moisture on the surface of mucous membranes to produce intense irritation and corrosive injury. The eyes and nasal and respiratory mucous membranes are the tissues most susceptible to direct injury.^{75,131} Despite skin irritation, it has little dermal absorption.

Along with nitric oxide and carbon monoxide, researchers recently recognized hydrogen sulfide as a signaling molecule of the cardiovascular, inflammatory, and nervous systems, and therefore, they proposed to add hydrogen sulfide as the “third endogenous gaseous transmitter.” In 2005, a report in *Science* demonstrated mice inhaling a low dose of hydrogen sulfide, which decreased their metabolic demands and caused them to enter a “suspended animationlike state.”¹⁸ This report propelled researchers into studies probing the biosynthesis, metabolism, and physiological responses of hydrogen sulfide in hopes of developing future beneficial therapies to combat the adverse consequences of ischemia/reperfusion injury.^{37,90} The research results reveal fascinating and sometimes puzzling and contradictory results. Administering hydrogen sulfide to rodents appears to switch off metabolic demands and protect some species from ischemic insults. On the contrary, large animal models have yet to show global protection but support local, organ-specific protective effects. In total, these studies reveal hydrogen sulfide to have complex interactions that are variable among organ systems and species while clearly demonstrating a dose-dependent effect with higher exposures producing the well-known toxic effects. Besides its ability to attenuate metabolic demands during ischemia, hydrogen sulfide influences many signaling pathways and has vasodilating, neuromodulating, antiinflammatory, antiapoptotic, and antioxidant effects. Using hydrogen sulfide as a therapy requires additional investigation, but several hydrogen sulfide donating drugs are already in clinical trials.⁷⁹ Researchers’ enthusiastic pursuit of a better understanding of hydrogen sulfide with an intent to create innovative therapies will likely also benefit our understanding of its mechanisms of toxicity and potentially lead to new treatments for toxic exposures.

Inhaled hydrogen sulfide enters the systemic circulation where it dissociates into hydrosulfide ions (HS^-), sulfide (S^{2-}), and sulfate (SO_4^{2-}). Once dissociated, hydrosulfide ions interact with metalloproteins, disulfide containing enzymes, and thio dimethyl S transferase.³² Hydrogen sulfide and dissociation products are then rapidly metabolized by oxidation, methylation, and binding to metalloproteins. The major pathway of detoxification is enzymatic and nonenzymatic oxidation of sulfides and sulfur to thiosulfate and polysulfides.^{131,90} Other pathways, such as methylation to dimethyl sulfide and conversion to sulfite or sulfate by oxidized glutathione, also may play a role in detoxification and elimination.^{31,131} Sulhemoglobin is not found in significant concentrations in the blood of animals or fatally poisoned humans.^{90,96}

Clinical Manifestations

Acute Manifestations. Hydrogen sulfide poisoning should be suspected whenever a person is found unconscious in an enclosed space, especially if the odor of rotten eggs is noted. The primary target organs of hydrogen sulfide poisoning are those of the CNS and respiratory system. The clinical findings reported in two large series are listed in Table 126–3^{4,26}

TABLE 126–3. Hydrogen Sulfide Poisoning

When to suspect hydrogen sulfide poisoning

- Rapid loss of consciousness (“knocked down”)
- Rotten eggs odor
- Rescue from enclosed space, such as sewer or manure pit
- Multiple victims with sudden death syndrome
- Collapse of a previously healthy worker at work site

Clinical Manifestations

System	Signs and Symptoms
Cardiovascular	Chest pain, bradycardia, sudden cardiac arrest
Central nervous	Headache, weakness, syncope, convulsions, rapid onset of coma
Gastrointestinal	Nausea, vomiting
Ophthalmic	Conjunctivitis
Pulmonary	Dyspnea, cyanosis, crackles, apnea
Metabolic	Metabolic acidosis

Hydrogen sulfide poisoning has a distinct dose response, and the intensity of exposure likely accounts for the diverse clinical findings in the reports. The odor threshold is between 0.01 and 0.3 ppm, and a strong intense odor is noted at 20 to 30 ppm. Mild mucous membrane irritation occurs at 20 to 100 ppm. Olfactory nerve paralysis occurs at 100 to 150 ppm rapidly extinguishing the ability to perceive the gas odor at higher concentrations. Prolonged exposure can occur when the extinction of odor recognition is misinterpreted as dissipation of the gas. Strong irritation of the upper respiratory tract and eyes and ARDS occur at 150 to 300 ppm. At >500 ppm, hydrogen sulfide produces systemic effects. Rapid unconsciousness and cardiopulmonary arrest occur at concentrations >700 ppm. At 1000 ppm, breathing may cease after one to two breaths.^{11,49,101}

Hydrogen sulfide reacts with the moisture on the surface of mucous membranes to produce intense irritation and corrosive injury. Mucous membrane irritation of the eye produces keratoconjunctivitis. If exposure persists, damage to the epithelial cells produces reversible corneal ulcerations (“gas eye”) and, rarely, irreversible corneal scarring.^{75,123} The irritant effects on the respiratory tract include rhinitis, bronchitis, and ARDS.^{4,26,131}

Neurologic manifestations are common and may be severe. Hydrogen sulfide’s rapid and deadly onset of clinical effects have been termed the “slaughterhouse sledgehammer” effect. In one case series, 75% of 221 patients with acute hydrogen sulfide exposure lost consciousness at the time of exposure.²⁶ If the patient is rapidly removed from the exposure, recovery may be prompt and complete. Hypoxia from respiratory compromise can cause secondary neurologic effects.^{11,31,131,50} Neurologic outcome can be quite variable, ranging from no neurologic impairment to permanent sequelae. Delayed neuropsychiatric sequelae may occur after acute exposures.²⁷ Most evidence suggests that the early rapid CNS effects are direct neurotoxic effects of hydrogen sulfide, whereas the permanent neurologic sequelae result from hypoxia secondary to respiratory insufficiency.^{11,131} Reported neuropsychiatric changes include memory failure (amnesic syndrome), lack of insight, disorientation, delirium, and dementia.^{31,131} Neurosensory abnormalities include transient hearing impairment, vision loss, and anosmia. Motor symptoms are likely caused by injury to the basal ganglia and result in ataxia, position/intention tremor, and muscle rigidity.¹²⁰ Common neuropathologic findings observed on neuroimaging and at autopsy are subcortical white matter demyelination and globus pallidus degeneration.²⁷

Acute exposures also affect other organ systems. Myocardial hypoxia or direct toxic effects of hydrogen sulfide on cardiac tissue may cause cardiac dysrhythmias, myocardial ischemia, or myocardial infarction.⁴⁸ Because unresponsiveness is rapid, trauma from falls should not be overlooked.^{4,45} In a report, 7% of patients experiencing a “knockdown” had associated traumatic injuries.⁴

Chronic Manifestations. Most data about chronic low-level exposures to hydrogen sulfide come from oil and gas industry workers. Mucous membrane irritation seems to be the most prominent problem in patients with low-concentration exposures. Workers report nasal, pharyngeal, and eye irritation, fatigue, headache, dizziness, and poor memory with low-concentration, chronic exposures. The chronic irritating effects of hydrogen sulfide were thought to be the cause of reduced lung volumes observed in sewer workers.¹⁰³ Volunteer studies have not demonstrated significant cardiovascular effects after long term exposure to concentrations less than 10 ppm.¹⁷ The liver, kidneys, and endocrine system are unaffected. No studies demonstrate increased incidences of cancer with low-level exposures.³¹

Rapid loss of consciousness from hydrogen sulfide exposure was a well-known and, amazingly, accepted part of the workplace in the gas and oil industry for many years.⁶⁰ Some workers experienced repeated “knockdowns,” and these workers reported an increased incidence of respiratory diseases and cognitive deficits. Single or repeated high-

concentration exposures resulting in unconsciousness can cause serious cognitive dysfunction. The acute effects of rapid loss of consciousness are most likely due to hydrogen sulfide neurotoxicity. Although a clear association exists between knock-down and chronic neurologic sequelae, many of the case reports are complicated by associated apnea or hypoxemia from respiratory failure, asphyxia or exposure to other xenobiotics in a confined space, head injury from a fall, or near drowning in liquid manure or sludge.¹³¹ The association of neurotoxic sequelae are less clear with protracted low-concentration exposures. Case series suggest that low-concentration exposures can cause subtle changes that can be measured by only the most sensitive neuropsychiatric tests.⁷²

Epidemiologic data regarding the effects of low-concentration environmental exposures to hydrogen sulfide are clouded in populations exposed to complex mixtures of pollutants. Other malodorous sulfur compounds (eg, methyl mercaptan and methyl sulfide) are generated as byproducts of pulp mills. Study populations exposed to this complex mixture of pollutants demonstrate a dose-related increase in nasal symptoms, cough, nausea, and vomiting.³¹

These changes are nonspecific, and many of the cases have a poorly documented exposure assessment. Currently, the association of protracted and low-concentration hydrogen sulfide exposure with chronic neurological sequelae remains controversial and needs further study.^{50,131}

The strong odor of low concentrations of hydrogen sulfide can magnify irritant effects by triggering a strong psychological response.¹³¹ The odor of hydrogen sulfide at low levels has been the alleged source of mass psychogenic illness cases.⁴⁶ Clinical, epidemiologic, and toxicologic analyses suggested that 943 cases of illness in Jerusalem were caused by the odor of low concentrations of hydrogen sulfide gas. The most frequent associated symptoms are headaches; faintness; dizziness; nausea; chest tightness; dyspnea and tachypnea; eye, nose, and throat irritation; weakness; and extremity numbness. Low concentration exposure to hydrogen sulfide may produce nonspecific signs and symptoms that could closely mimic psychogenic illness. Attempting to identify true toxicity from a powerful emotional reaction can be extremely difficult.⁴⁶ Therefore, symptomatic patients must be assessed for toxicity even when mass psychogenic illness is suspected.

Diagnostic Testing

In hydrogen sulfide poisoning, diagnostic testing is of limited value for clinical decision making following acute exposures, confirmation of acute exposures, occupational monitoring, and forensic analysis following fatal accidents.

Clinicians must base management decisions on history, clinical presentation, and diagnostic tests that infer the presence of hydrogen sulfide because no method is available to rapidly and directly measure the gas or its metabolites. Circumstances surrounding the patient's illness often provide the best evidence for hydrogen sulfide poisoning (Table 126–3). At the bedside, the smell of rotten eggs on clothing or emanating from the blood, exhaled air, or gastric secretions suggests hydrogen sulfide exposure. In addition, darkening of silver jewelry is a clue to exposure. Paper impregnated with lead acetate changes color when exposed to hydrogen sulfide and is used to detect its presence in the patient's exhaled air but is not rapidly available.³¹

Specific tests for confirming hydrogen sulfide exposure are not readily available in clinical laboratories. Therefore, directly measuring the gas in atmospheric air samples by monitoring devices provides stronger evidence of hydrogen sulfide as the causative agent. Epidemiologic data show hydrogen sulfide as one of the most common causes of death and injury from toxic inhalation in confined spaces, especially manholes and sewers.³⁶ Recognizing confined spaces as extremely hazardous environments, OSHA published the Confined Space Entry Standard to protect workers.² It mandates training, rescue procedures, and atmospheric testing before entry, including measuring for the presence of hydrogen sulfide. Because of OSHA's regulations, most emergency response teams are equipped to investigate toxic environments from hazardous materials incidents using a "four-gas detection unit" that measures hydrogen sulfide by electrochemical sensors along with measurements for atmospheric oxygen concentration and the presence of explosive gases and carbon monoxide.¹²¹ In general, the clinician must interpret environmental detection results with caution. Toxic gases may dissipate prior to atmospheric air sample collection, leading to negative results, or interfering gases can trigger false positive readings on detection devices.⁵⁷ A positive reading on a field device does not equate to confirmation of that specific gas. Clinical decision making should consider correlation with other circumstantial and clinical data and not rely solely on detection results.

In acute poisoning, readily available diagnostic tests that are biomarkers of hydrogen sulfide poisoning may be useful but are nonspecific. ABG analysis demonstrating metabolic acidosis with an associated elevated serum lactate concentration is expected, and oxygen saturation should be normal unless ARDS is present. Hydrogen sulfide, like cyanide, decreases oxygen consumption and is reflected as an elevated mixed venous oxygen measurement. Because sulfhemoglobin typically is not generated in patients with hydrogen sulfide poisoning, an oxygen saturation gap is not expected.^{90,96}

After serious injury from hydrogen sulfide, diagnostic testing for neurologic structure and function may show abnormalities for weeks or months. Brain MRI and head CT studies demonstrate structural changes, such as globus pallidus degeneration and subcortical white matter demyelination. Neuropsychological testing after serious hydrogen sulfide poisoning demonstrates specific abnormalities in cortical functions, such as concentration, attention, verbal abstraction, and

short-term retention. Single-photon emission computed tomography (SPECT)/PET brain scans define neurotoxin-induced lesions that correlate well with clinical neuropsychological testing.²⁸

No clinically available biological markers or direct measurements of hydrogen sulfide and its metabolites exists, therefore, confirming poisoning is challenging for clinicians, researchers, and forensic specialists.⁹⁰ Whole blood sulfide concentrations >0.05 mg/L are considered abnormal. Reliable measurements are ensured only if the concentration is obtained within 2 hours after the exposure and analyzed immediately.¹⁰¹

In acute exposures, blood and urine thiosulfate concentrations may be reflective of exposure.⁶⁹ Urinary thiosulfate excretion may be useful to monitor chronic low-concentration exposure in the workplace. However, one study could not demonstrate a correlation between the degree of exposure and change in urine thiosulfate from baseline measurements.³⁸ Another study analyzed the value of blood and urine thiosulfate from data collected in case series of fatal and nonfatal hydrogen sulfide victims.^{66,68} Because thiosulfate was detected in the urine but sulfide and thiosulfate were not detected in the blood of nonfatal exposures, this report concluded that thiosulfate in urine is the only indicator to prove hydrogen sulfide poisoning in nonfatal cases.

Sulfide concentrations obtained in postmortem investigations may be useful, but their use requires rapid sample collection because sulfide concentrations rise with tissue decomposition.¹⁰¹ In addition to blood sulfide concentrations, sulfide and thiosulfate concentrations are at their highest in lung and brain.⁶⁷ If death is rapid, urinary thiosulfate concentrations may be nondetectable despite blood sulfide and thiosulfate concentrations 10-fold or greater than normal concentrations.⁶⁷ At autopsy, a greenish discoloration of the gray matter, viscera, and bronchial secretions may be noted.^{67,88}

Management

The initial treatment (Table 126–4) is immediate removal of the victim from the contaminated area into a fresh air environment. High-flow oxygen should be administered as soon as possible. Optimal supportive care has the greatest influence on the patient’s outcome. Because death from inhalation of hydrogen sulfide is rapid, limited human cases reaching the hospital for treatment are reported in the literature. Most patients experience significant delays before receiving treatment. Therefore, specific treatments and antidotal therapies do not show definitive improvement in patient outcome.

TABLE 126–4. Hydrogen Sulfide Poisoning: Emergency Management

Supportive care

Prehospital

Attempt rescue only if using appropriate respiratory protection

Move victim to fresh air

Administer 100% oxygen

During extrication, consider traumatic injuries from falls

Apply ACLS protocols as indicated

Emergency department

Maximize ventilation and oxygenation

Consider PEEP for ARDS

Treat metabolic acidosis based on arterial pH and serum bicarbonate analysis

Administer crystalloid and vasopressors for hypotension

Antidote

Give sodium nitrite (3% NaNO₂) IV over 2–4 minutes

Adult dose: 10 mL (300 mg)

Pediatric dose: See [Table 126–2](#); if hemoglobin unknown, presume 7 g Hb for dosing

Caution:

Monitor blood pressure frequently

Obtain methemoglobin level 30 minutes after dose

The proposed toxic mechanisms, animal studies, and human case reports suggest that oxygen therapy is beneficial for hydrogen sulfide poisoning.^{31,33,99,131} Proposed mechanisms for the beneficial effects of oxygen are competitive reactivation of oxidative phosphorylation by inhibiting hydrogen sulfide–cytochrome binding, enhanced detoxification by catalyzing oxidation of sulfides and sulfur, and improved oxygenation in the presence of ARDS. Recent studies demonstrate hydrogen sulfide’s binding to cytochrome oxidase is readily reversible in the presence of oxygen.³³ Other studies show an inverse relationship between tissue concentrations of hydrogen sulfide and oxygen.⁹⁰ Increased oxygen concentrations enhance the consumption of hydrogen sulfide through metabolic pathways, while oxygen deprivation results in the accumulation of hydrogen sulfide in tissue.⁹⁰ All patients suspected of hydrogen sulfide poisoning should receive supplemental oxygen. In case reports, poisoned patients receiving HBO had favorable clinical outcomes.^{5,62,109} However, no clinical data is available to suggest HBO is superior to normobaric oxygen for acute poisoning or preventing delayed neurological sequelae.

The similarities in the toxic mechanism between hydrogen sulfide and cyanide created an interest in the use of nitrite-induced methemoglobin as an antidote. Methemoglobin protects animals from toxicity of hydrogen sulfide poisoning in both pretreatment and postexposure treatment models. Nitrite-generated methemoglobin acts as a scavenger of sulfide. The affinity of hydrogen sulfide for methemoglobin is greater than that for cytochrome oxidase. When hydrogen sulfide binds to methemoglobin, it forms sulfmethemoglobin.¹⁵ Because hydrogen sulfide poisoning is rare, no studies have evaluated the clinical outcomes of patients treated with sodium nitrite. Animal studies suggest that nitrite must be given within minutes of exposure to ensure effectiveness.¹⁵ However, several human case reports showed rapid return of normal sensorium when nitrites were administered soon after exposure.^{62,94,114} Patients with suspected hydrogen sulfide poisoning who have altered mental status, coma, hypotension, or dysrhythmias should receive sodium nitrite by slow infusion at the same dose given for cyanide poisoning. Sodium thiosulfate is of no benefit in the treatment of hydrogen sulfide. In addition, only a single in vivo mouse model and a single case report with a fatal outcome is published to suggest a beneficial effect of hydroxocobalamin as an antidote for hydrogen sulfide poisoning.^{43,118} Additional research is warranted to determine its usefulness for hydrogen sulfide poisoning.

Treatment of patients with hydrogen sulfide poisoning requires optimal supportive care. Treatments and antidotes beyond supportive care are not of proven clinical benefit. Because hydrogen sulfide toxicity is severe and research studies suggest potential benefits of nitrite therapy, it should be considered for seriously ill patients exposed to hydrogen sulfide. This therapy should be initiated after optimum supportive care has been ensured.

Only a few inhalation risks are similar to hydrogen sulfide in their ability to rapidly “knock-down” victims. Some examples include low-oxygen environments in an enclosed space, hydrogen cyanide, volatile nerve agents, and carbon monoxide. The etiology may be unclear early in the patient’s emergency care and require clinicians to make treatment decisions without confirmatory evidence of poisoning. Clinicians faced with victims of “knock-down” syndrome should search for clues, such as victims’ activities (eg, working at a manure pit), reports of chemicals detected at the scene by first responders, or suggestive clinical signs. The critical decision is whether to administer specific antidotes empirically. Vapor exposure to volatile nerve agents would likely result in miosis and require antidotes such as atropine, pralidoxime, and benzodiazapines. Which cyanide antidotes to administer in a “knock-down” situation, if any, is most difficult. The basic aims are to gather as many facts and suggestive clues as possible, weigh the risk benefits for treatment or not, and treat early in the course. All this while meticulous attention to optimal supportive care is required.

SUMMARY

- Both cyanide and hydrogen sulfide are high risk xenobiotics.
- There are particular metabolic risks and concerns with regard to exposure to both xenobiotics because they bind specifically to the ferric moiety of the cytochrome a_3 oxidase complex.
- Odor recognition is unreliable and is not a definitive approach to diagnosis.
- The laboratory evaluation usually is not timely for diagnostic purposes.
- Decontamination, removal from the site of exposure, and oxygen are essential.

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A39 ANTIDOTES IN DEPTH

Sodium and Amyl Nitrite

Mary Ann Howland

INTRODUCTION

Sodium nitrite is an effective cyanide antidote when administered in a timely fashion and followed by sodium thiosulfate, which acts in synergy. The utility of amyl nitrite, a volatile drug available in ampules that can be broken and administered by inhalation while sodium nitrite is being prepared to administer intravenously, is questioned.¹³ Although the exact mechanism of action of the nitrites is unclear, the production of methemoglobin is both therapeutic in cyanide poisoning and potentially life-threatening if nitrites are administered to a patient with impaired oxygen carrying capacity, from elevated concentrations of carboxyhemoglobin, methemoglobin, or sulfhemoglobin from any cause. In the latter cases, hydroxocobalamin and or sodium thiosulfate can still be administered intravenously without causing harm.

HISTORY

Expanding on earlier work that demonstrated the limited role of methylene blue and the efficacy of sodium nitrite in cyanide poisoned dogs, inhaled amyl nitrite prevented the development of cyanide-induced seizures and muscular rigidity.⁴ Amyl nitrite administered by inhalation protected dogs from up to four minimum lethal doses of sodium cyanide (a total of 24 mg/kg subcutaneously). In the regimen used, therapy was started within 5 to 7 minutes of exposure and was continued for several hours. The frequency of inhalation was based on clinical response. These experimental results led to the use of inhaled amyl nitrite for patients poisoned by cyanide. The same authors discovered that intravenous (IV) use of sodium thiosulfate alone protected against three minimum lethal doses of cyanide in dogs and that the combination of sodium thiosulfate with either inhaled amyl nitrite or IV sodium nitrite protected against 10 to 18 minimum lethal doses, respectively.^{3,5}

PHARMACOLOGY

Chemistry

The chemical formula for sodium nitrite is NaNO_2 and for amyl nitrite is $\text{C}_5\text{H}_{11}\text{NO}_2$. Sodium nitrite has a molecular weight of 69 Da and amyl nitrite has a molecular weight of 117 Da. Amyl nitrite is volatile even at low temperatures and is highly flammable.

Cyanide quickly and reversibly binds to the ferric iron in cytochrome oxidase, inhibiting effective energy production throughout the body. The ferric iron in methemoglobin preferentially combines with cyanide, producing cyanomethemoglobin. This drives the reaction toward cyanomethemoglobin and liberates cyanide from cytochrome oxidase. Stroma-free methemoglobin is effective against four minimum lethal doses of cyanide in rats.²⁰ Nitrites oxidize the iron in hemoglobin to produce methemoglobin. Because nitrites are accepted antidotes for cyanide poisoning, for many years methemoglobin formation was assumed to be their sole antidotal mechanism of action.^{14,24} Other, faster methemoglobin inducers, such as 4-dimethylaniline and hydroxylamine, also are effective as cyanide antidotes.^{14,22} The production of methemoglobin by nitrite is slow, but when methylene blue is administered to prevent methemoglobin formation, nitrite remains an effective antidote.^{14,24} Reasoning that nitrite-induced vasodilation might be part of the mechanism of action, investigators considered the antidotal actions of other vasodilators. The α -adrenergic antagonists and ganglionic blockers only demonstrate antidotal activity when administered with sodium thiosulfate.²⁴ It is possible that the benefits of nitrites given shortly after cyanide result from reversal of cyanide-induced circulatory effects rather than reversal of the effects of cyanide on cytochrome oxidase.²¹ Experimental evidence in organ damage induced by hypoxia or hypotension suggests that the benefits of nitrite may be related to its conversion to nitric oxide, a potent vasodilator. The conversion to nitric oxide appears to occur only in tissues or blood with the lowest oxygen concentrations.^{6,15}

PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetics of sodium nitrite are not established. Most studies were directed at measuring methemoglobin levels rather than nitrite concentrations.²²

Sodium nitrite administered intramuscularly to dogs is not effective as a cyanide antidote unless atropine is given as pretreatment.²³ Most likely the rapid reversal of cyanide-induced bradycardia by atropine allows sufficiently rapid absorption of sodium nitrite, which then can be effective.²³ In one study, 300 mg IV sodium nitrite produced peak methemoglobin levels of 10% to 18% in healthy adults, and values of 7% when 4 mg/kg was administered.^{3,17} Inhalation of crushed amyl nitrite ampules in human volunteers produces insignificant amounts of methemoglobin and causes headache, fatigue, dizziness, and hypotension.¹²

The package insert states that approximately 40% of sodium nitrite is renally eliminated unchanged, while the remainder is metabolized to ammonia and other related molecules.¹⁷

ROLE IN CYANIDE TOXICITY

Maximal benefits of sodium nitrite are realized experimentally when sodium nitrite is given prophylactically, but benefits are still evident even when sodium nitrite is administered following cyanide poisoning. Sodium nitrite is clearly effective soon after administration, even when methemoglobin levels are low. Thus a target methemoglobin concentration should not be used to determine the correct dose of sodium nitrite, although care must be taken to avoid excessive methemoglobinemia.¹¹ Administration of sodium nitrite should always be followed by sodium thiosulfate. Sodium thiosulfate donates a sulfur, which, with the help of rhodanese (cyanide sulfur transferase) and mercaptopyruvate sulfurtransferase, carries sulfane sulfur to bind to cyanide, producing thiocyanate. Thiocyanate is a much less toxic substance than cyanide and is renally eliminated.⁴

As early as 1952, the literature reported 16 cyanide-poisoned patients who survived following administration of nitrites and sodium thiosulfate.³ Even patients who were unconscious or apneic survived when given timely cardiopulmonary resuscitation and antidotal therapy.³ Case reports attest to the ability of amyl nitrite, sodium nitrite, and sodium thiosulfate to reverse the effects of cyanide if they are administered in a timely fashion.^{8,25} A 34 year-old man who ingested 1 g potassium cyanide became comatose within 45 minutes. One hour after ingestion, he arrived in the emergency department, became apneic, and was intubated. His blood pressure was 134/84 mm Hg and pulse 84 beats/min with fixed and dilated pupils. At 1 hour 15 minutes, he was given 300 mg sodium nitrite intravenously over 20 minutes, followed by 12.5 g sodium thiosulfate. Seizure activity that began just prior to sodium nitrite infusion resolved rapidly, and by the time the sodium thiosulfate was infused, his pupils were reactive and spontaneous respirations had returned.⁸

In another case, a 4 year-old boy ingested twelve 50 mg tablets of laetrile (amygdalin), became unresponsive, and developed seizures within 90 minutes.¹⁰ Upon arrival at a second hospital, the patient required intubation, had no blood pressure, and had dilated minimally responsive pupils. Arterial blood gas analysis revealed: pH, 6.85; PCO₂, 15 mm Hg; PO₂, 169 mm Hg on 100% oxygen with an anion gap of 26 mEq/L. His vital signs improved with intermittent inhalation of amyl nitrite pearls. Six hours after ingestion (and 1 hour 45 minutes after amyl nitrite administration), sodium nitrite and sodium thiosulfate obtained from another hospital were administered. Within 30 minutes of completion of 5 mL (0.33 mL/kg) 3% sodium nitrite solution by IV infusion, spontaneous respirations returned, and his blood pressure and pulse normalized. Over the next 3 hours, his mental status and acid-base status improved. Fifteen hours after ingestion, he was alert, oriented, and extubated. Elevated whole blood cyanide concentrations verified the ingestion.

A study in swine evaluated the effect of hydroxocobalamin plus sodium thiosulfate versus sodium nitrite and sodium thiosulfate in a model utilizing a continuous infusion of cyanide. There was no difference between the groups in metabolic acidosis with elevated lactate concentrations at times 20 and 40 minutes or in cardiac output and pulse rate at 40 minutes, or in mortality. The mean arterial pressure was higher in the hydroxocobalamin plus sodium thiosulfate group, beginning at 5 minutes and lasting for the entire 40 minute monitoring period.¹

ADVERSE EFFECTS AND SAFETY ISSUES

Amyl nitrite and sodium nitrite may work in part by inducing methemoglobinemia, but excessive methemoglobinemia is potentially lethal. Therefore, nitrite dosages must be carefully calculated to avoid excessive methemoglobinemia, especially in cases where other coexisting conditions, such as carboxyhemoglobin, sulfhemoglobin, and anemia, might compromise hemoglobin oxygen saturation.^{9,16} Children are particularly at risk for medication errors because of dosage miscalculations. A reported death from methemoglobinemia was caused by the administration of an adult dose of sodium nitrite to a 17 month-old child suspected of ingesting a toxic amount of cyanide.²

Nitrites are potent vasodilators, resulting in transient hypotension. Other common adverse effects include headache,

tachycardia, palpitations, dysrhythmia, blurred vision, nausea, and vomiting.^{3,17}

PREGNANCY AND LACTATION

The nitrites are FDA Pregnancy Category C. There are no adequate studies in pregnant women, and nitrites should only be used in pregnant women when the potential benefit exceeds the potential risk. Sodium nitrite has caused fetal death in humans as well as animals.¹⁷ The fetus is particularly sensitive to methemoglobinemia with the potential for prenatal hypoxia. High concentrations of nitrites in maternal drinking water have led to teratogenic effects.

Hydroxocobalamin is also FDA Pregnancy Category C; however, even with the limited data available it may have a lesser risk than nitrite use for a pregnant woman.⁷

It is not known whether nitrites are excreted in breast milk, but the risk is likely to exceed the benefit.

DOSING AND ADMINISTRATION

Adults

Sodium nitrite 300 mg (10 mL of 3% solution) should be injected intravenously at a rate of 2.5 to 5 mL/min. The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear.^{17,18}

Amyl nitrite can be used prior to IV administration of sodium nitrite, but only as a temporizing measure until IV sodium nitrite can be administered. Time is better spent administering IV sodium nitrite. Break one amyl nitrite ampule, and hold it in front of the patient's mouth for 15 seconds on and 15 seconds off.^{7,18} Inhalation of amyl nitrite should be discontinued prior to sodium nitrite administration. The health care provider should be extremely careful not to inhale the amyl nitrite to prevent lightheadedness and syncope. Immediately following the completion of the sodium nitrite infusion, 50 mL of 25% solution (12.5 g) sodium thiosulfate should be infused intravenously. The same needle and vein can be used, and the dose of the thiosulfate can be repeated at half the initial dose whenever manifestations of cyanide toxicity.¹⁸

In situations where additional methemoglobin formation would be harmful, as in patients with carbon monoxide poisoning, it may be safer to withhold the nitrite and only administer the IV hydroxocobalamin with or without sodium thiosulfate. Sodium thiosulfate can be administered through a separate IV line following the hydroxocobalamin. The initial dose of hydroxocobalamin in adults is 5 g IV over 15 minutes with a second dose administered if warranted.⁷

Children

Intravenously inject 0.2 mL/kg (6 to 8 mL/m² BSA) or 6 mg/kg of 3% sodium nitrite solution, at a rate of 2.5 to 5 mL/min, not to exceed 10 mL or 300 mg.^{17,18} Based on an in vitro calculation, this dose would be safe for a child with a hemoglobin of 7 g/dL in the absence of other factors that could compromise hemoglobin oxygen saturation, such as carboxyhemoglobin or sulphemoglobin.² The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear (Table 126-2).¹⁸

The dose of sodium thiosulfate in children is 1 mL/kg using a 25% solution (250 mg/kg or approximately 30–40 mL/m² of BSA) not to exceed 50 mL (12.5 g) total dose immediately following administration of sodium nitrite.^{17,19} The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear. The same needle and vein can be used.

Amyl nitrite inhalation can be used in children at the same dose and with the same precautions as mentioned above for adults.

In situations where additional formation of methemoglobin would be harmful, as in patients with smoke inhalation from a fire in which other toxic gases may coexist, the nitrite can be withheld and hydroxocobalamin administered with or without sodium thiosulfate. In children, a dose of 70 mg/kg of hydroxocobalamin up to the adult dose has been employed.⁷

Care must be taken not to administer the hydroxocobalamin and sodium thiosulfate through the same IV line since a physical incompatibility occurs, inactivating the hydroxocobalamin.

FORMULATION AND ACQUISITION

Sodium nitrite is available in ampules containing 300 mg in 10 mL (3% concentration) water for injection (USP).¹⁸ It contains no additives or preservatives. It is also available in a kit known as Nithiodote, containing one vial of sodium nitrite (300 mg in 10 mL water for injection) with one vial of sodium thiosulfate (12.5 g in 50 mL water for injection), with boric acid or sodium hydroxide added to adjust the pH.¹⁷

SUMMARY

- Sodium nitrite is an effective cyanide antidote when administered in a timely fashion and followed by sodium thiosulfate for a synergistic effect.
- The production of methemoglobin is both therapeutic in cyanide poisoning and potentially life threatening if nitrites are administered to a patient with impaired oxygen carrying capacity from elevated levels of carboxyhemoglobin, sulfhemoglobin, or methemoglobin from any cause.
- In situations where additional methemoglobin formation would be harmful, as in patients with carbon monoxide poisoning, it may be safer to withhold the nitrite and administer IV hydroxocobalamin with or without sodium thiosulfate.

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A40 ANTIDOTES IN DEPTH

Sodium Thiosulfate

Mary Ann Howland

INTRODUCTION

Sodium thiosulfate is a safe and effective antidote that detoxifies cyanide by donating a sulfur moiety to form thiocyanate. Thiocyanate is much less toxic than cyanide and is renally eliminated. Sodium thiosulfate works synergistically with nitrites and is probably at least additive to hydroxocobalamin in the detoxification of cyanide. Because sodium thiosulfate does not compromise hemoglobin oxygen saturation, it can be used without nitrites in circumstances where the formation of methemoglobin would be detrimental, as in patients who have elevated levels of carboxyhemoglobin or preexistent methemoglobinemia from smoke inhalation, drug exposure, or congenital dyshemoglobinemias when hydroxocobalamin is unavailable. Based on the mechanism of action of sodium thiosulfate, particularly when used alone, it is unlikely to be as effective as hydroxocobalamin, or work as quickly. A recent study in a swine cyanide model could not show a benefit of sodium thiosulfate as sole therapy or show an added benefit to that offered by hydroxocobalamin.³ Sodium thiosulfate is used prophylactically with nitroprusside to prevent cyanide toxicity. Sodium thiosulfate is also used to treat calcific uremic arteriolopathy (calciophylaxis) theoretically by increasing the solubility of calcium deposits, inducing vasodilation, and acting as a free radical scavenger.^{6,24,28,32}

HISTORY

In 1933, Chen and colleagues⁸ noted that preexposure treatment with intravenous (IV) sodium thiosulfate protected dogs against three minimum lethal doses of sodium cyanide, and even more remarkable were the synergistic effects obtained by combining sodium thiosulfate with either inhaled amyl nitrite or IV sodium nitrite, which protected the dogs against 10 to 18 minimum lethal doses of cyanide.^{7,8}

PHARMACOLOGY

Chemistry

The chemical formula of sodium thiosulfate is $\text{Na}_2\text{S}_2\text{O}_3$. The molecular weight of sodium thiosulfate is 248 Da. It forms a pentahydrate that is highly water soluble.

Mechanism of Action

The sulfur provided by sodium thiosulfate binds to cyanide with the help of rhodanese (cyanide sulfur transferase) and mercaptopyruvate sulfur transferase.^{8,36,38} Sulfane sulfur (a divalent sulfur bound to one other sulfur) is the only sulfur that reacts with cyanide to produce thiocyanate, which is minimally toxic and renally eliminated. In several animal models, sodium thiosulfate protects against several minimum lethal doses of cyanide.^{16,20} The addition of rhodanese increases the efficacy of sodium thiosulfate, but the use of rhodanese is impractical in the clinical setting.^{20,37} The cationic site on rhodanese is crucial to cleaving the sulfur–sulfur bond of thiosulfate and forming a sulfur–rhodanese complex that readily reacts with cyanide.³⁸

Rhodanese is probably not solely responsible for sulfur–sulfur bond cleavage, as rhodanese is largely a mitochondrial enzyme found in the liver and skeletal muscle, and sodium thiosulfate is a divalent ion that poorly crosses membranes.^{12,20,25,36,38} It is also suggested that both mercaptopyruvate sulfurtransferase and rhodanese are involved in the formation of sulfane sulfur in the liver from sodium thiosulfate, and that serum albumin then carries the sulfane sulfur from the liver to other organs. When cyanide is present, albumin delivers this sulfur to cyanide, forming thiocyanate.^{17,36–38}

Pharmacokinetics and Pharmacodynamics

Animal Studies. Sodium thiosulfate is a large divalent anion. Canine studies suggest that sodium thiosulfate rapidly distributes into the extracellular space and then slowly into the cell, perhaps with a carrier facilitating entry into the mitochondria.^{15,25} When administered prior to cyanide, thiosulfate converted more than 50% of the cyanide to thiocyanate within 3 minutes and increased the endogenous conversion rate more than 30 times.³⁵ A canine model employing continuous intravenous (IV) infusion of cyanide to induce a respiratory arrest, demonstrated that the IV administration of 500 mg/kg of sodium thiosulfate decreased the serum cyanide concentration and restored respiration within 3 minutes.¹⁰ Thiosulfate is filtered and secreted in the kidney. At low serum concentrations, thiosulfate is largely reabsorbed, whereas at high serum concentrations filtration and secretion predominate.^{14,25}

Human Studies. A volunteer study examined the pharmacokinetics of sodium thiosulfate and the fate of thiosulfate.^{16,25} After injection of 150 mg/kg, the volume of distribution (Vd) was 0.15 L/kg, the distribution half-life was 23 minutes, and the elimination half-life was 3 hours. The peak serum thiosulfate concentration rose 100 fold. Approximately 50% of the drug was eliminated in 18 hours, most of that within the first 3 hours. Baseline thiosulfate concentrations were higher in starved patients and children, presumably because of their higher protein metabolism to thiosulfate.¹⁶ Normally, the kidney actively reabsorbs thiosulfate, but this study found that with exogenous administration, thiosulfate clearance equaled creatinine clearance.¹⁶

The study of thiosulfate as a cisplatin neutralizer demonstrated a half-life of 80 minutes, and that renal clearance accounted for only 30% of the total clearance.³¹ Oral sodium thiosulfate is poorly absorbed and acts as a laxative.²⁵

A pharmacokinetic study was conducted in healthy volunteers as well as hemodialysis (HD) patients both on and off of HD.¹³ Eight grams of sodium thiosulfate was diluted in 50 mL of 0.9% NaCl and infused over 8 minutes. The use of a population pharmacokinetic model revealed a small Vd (0.226 L/kg), a nonrenal clearance similar to the renal clearance accounting for about 50% of the elimination in both healthy volunteers and HD patients. Total body clearance in the HD patients undergoing HD was double that of the same patients not receiving HD. A one compartment distribution model was assumed due to the absence of rebound concentrations after HD ended. Oral bioavailability was only about 8% and was calculated after 5 g of the IV solution was diluted in 100 mL of water and ingested rapidly.

ROLE IN CYANIDE TOXICITY

In 1952, 16 cyanide-poisoned patients survived following the administration of nitrites and sodium thiosulfate.⁷ Even patients who were unconscious or apneic survived following expeditious cardiopulmonary resuscitation and antidotal therapy.⁷ A more recent study in swine evaluated the effect of hydroxocobalamin with sodium thiosulfate versus sodium nitrite and sodium thiosulfate in a model utilizing a continuous infusion of cyanide. There was no difference between the groups with a metabolic acidosis with an elevated lactate concentration at times 20 and 40 minutes or in cardiac output and pulse rate at 40 minutes, or in mortality. The mean arterial pressure was higher in the hydroxocobalamin with sodium thiosulfate group, beginning at 5 minutes and lasting for the entire 40 minute monitoring period.⁴ A second study in swine done by the same group could not show a benefit to sodium thiosulfate as sole therapy or show an added benefit to hydroxocobalamin in a model following intravenous cyanide exposure.³ All 12 swine in the sodium thiosulfate group died compared to only 1/12 in the hydroxocobalamin group.

Case reports attest to the ability of sodium nitrite and sodium thiosulfate to reverse the effects of cyanide following timely administration.^{9,23,25}

In the few reported cases of cyanide ingestion treated solely with sodium thiosulfate, all patients had favorable outcomes.²⁵ However, prior to sodium thiosulfate administration, we advocate the use of sodium nitrite, or preferably hydroxocobalamin. As noted, nitrites would be relatively contraindicated for patients who have elevated carboxyhemoglobin or methemoglobin concentrations from smoke inhalation.

ROLE IN NITROPRUSSIDE-INDUCED CYANIDE TOXICITY

Canine experiments reveal that when the nitroprusside infusion rate is greater than 0.5 mg/kg/h, cyanide concentrations in the blood begin to rise. Coadministration of sodium thiosulfate with sodium nitroprusside (which contains five cyanide ions) in a 5:1 molar ratio prevents the rise in cyanide concentration.²⁵ The usual dosage of sodium nitroprusside is 3 µg/kg/min (range 0.25–10 µg/kg/min).²¹ Each mole of nitroprusside has a molecular weight of 298 Da, including the sodium dehydrate. A 70 kg person administered 3 µg/kg/min would receive 12.6 mg/h (0.042 mmol/h) of nitroprusside. This would require 52.4 mg (0.211 mmol) of sodium thiosulfate per hour to detoxify the five cyanide ions liberated from nitroprusside. Prolonged infusion or doses in excess of the detoxifying capability of the body may lead to thiocyanate or cyanide toxicity. Some authors recommend adding 0.5 g sodium thiosulfate to each 50 mg of nitroprusside.²² Although this

dose of sodium thiosulfate usually is sufficient to prevent cyanide toxicity from nitroprusside, thiocyanate may accumulate, especially in patients with renal insufficiency. Although thiocyanate is relatively nontoxic compared to cyanide, it may produce dose-dependent tinnitus, miosis, hyperreflexia, and hypothyroidism, especially at serum concentrations greater than 60 µg/mL.²¹ Thiocyanate is hemodialyzable. Nitroprusside-induced cyanide toxicity should be treated by stopping the nitroprusside and administering standard doses of hydroxocobalamin with or without sodium thiosulfate.

ROLE IN CALCIFIC UREMIC ARTERIOLOPATHY (CALCIPHYLAXIS)

Sodium thiosulfate decreases calcification of the medial layer of arteries leading to subcutaneous nodules that typically progress to necrotic skin ulcers as a manifestation of this rare vascular disease associated with chronic kidney failure patients.^{1,2,6,24} The dose of sodium thiosulfate is usually 5 to 25 g IV in adults during or after hemodialysis.^{24,27,32} Thiosulfate may increase the water solubility of calcium leading to enhanced excretion of calcium thiosulfate, induce vasodilation, and act as a free radical scavenger.^{27,28,32} In a uremic rat model, sodium thiosulfate was able to prevent vascular calcifications but also induced a metabolic acidosis and reduced bone strength.²⁹ A patient being treated for calcific uremic arteriolopathy developed a severe anion gap metabolic acidosis following each repeated dose of sodium thiosulfate.³⁰

ADVERSE EFFECTS AND SAFETY ISSUES

The toxicity of sodium thiosulfate is low. The LD₅₀ for animals is approximately 3 to 4 g/kg, with death attributed to metabolic acidosis, elevated sodium concentration, and decreased blood pressure and PO₂.²⁰ Sodium thiosulfate is hyperosmolar, delivering a significant sodium load resulting in an osmotic diuretic effect.²⁵ Administering the infusion over 10 to 30 minutes limits some of these adverse effects.²⁵ Adverse effects associated with therapeutic doses include hypotension, nausea, and vomiting.

PREGNANCY AND LACTATION

Sodium thiosulfate is FDA pregnancy Category C. No reports of congenital anomalies in infants born to women exposed to sodium thiosulfate during pregnancy are described.²⁶ Teratogenic effects were not observed in hamster offspring treated with doses of sodium thiosulfate comparable to those that would be used for cyanide toxicity. Sodium thiosulfate should be used in pregnant woman when the potential benefit clearly outweighs any potential risk. It is not known whether sodium thiosulfate is excreted in breast milk.

DOSING AND ADMINISTRATION

Cyanide Toxicity

Adults. In a patient with presumed cyanide poisoning, the adult dose of sodium thiosulfate is 12.5 g (50 mL of 25% solution) administered intravenously either as a bolus injection or infused over 10 to 30 minutes, depending on the severity of the exposure.²⁶ The dose of sodium thiosulfate can be repeated at half the initial dose if manifestations of cyanide toxicity reappear.²⁶

In situations where the formation of methemoglobin by a nitrite would not be harmful, intravenously inject 300 mg of sodium nitrite (10 mL of 3% solution) at a rate of 2.5 to 5 mL/min prior to administration of sodium thiosulfate. The same needle and injection site can be used. The dose of sodium nitrite can be repeated at half the initial dose if manifestations of cyanide toxicity reappear.^{26,33}

Amyl nitrite can be used prior to IV administration of sodium nitrite, but only as a temporizing measure until IV sodium nitrite can be administered. Time is better spent administering IV sodium nitrite.¹⁸ Break one amyl nitrite ampule, and hold it in front of the patient's mouth for 15 seconds on and 15 seconds off. Inhalation of amyl nitrite should be discontinued prior to administration of sodium nitrite. The health care provider must not inhale the amyl nitrite.

In situations where the additional formation of methemoglobin would be harmful, as in patients in whom carboxyhemoglobin or methemoglobin may be present from smoke inhalation, or dyshemoglobinemias or drug-induced methemoglobinemia, the nitrites can be withheld and hydroxocobalamin administered with or without sodium thiosulfate. The initial dose of hydroxocobalamin in adults is 5 g IV over 15 minutes with a second dose administered if warranted.¹¹ Care must be taken not to administer the hydroxocobalamin and sodium thiosulfate through the same IV line since a physical incompatibility occurs, inactivating the hydroxocobalamin.

Children. The dose of sodium thiosulfate in children is 1 mL/kg using a 25% solution (250 mg/kg or approximately 30–

40 mL/m² of BSA) not to exceed 50 mL (12.5 g) total dose immediately following administration of sodium nitrite.^{26,34} The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear.

In situations where the formation of methemoglobin by a nitrite would not be harmful, intravenously inject 3% sodium nitrite solution at 0.2 mL/kg (6–8 mL/m² or 6 mg/kg) at a rate of 2.5 to 5 mL/min not to exceed 10 mL or 300 mg, prior to administration of sodium thiosulfate. The same needle and vein can be used. Based on an in vitro calculation, this dose would be safe for a child with a hemoglobin of 7 g/dL in the absence of other factors that could compromise hemoglobin oxygen saturation, such as carboxyhemoglobin, methemoglobin, or sulfhemoglobinemia.⁵ The dose of sodium nitrite can be repeated at half the initial dose if manifestations of cyanide toxicity reappear or at 2 hours after the first dose as prophylaxis.

Amyl nitrite inhalation can be used in children at the same dose and with the same precautions as mentioned above for adults.

In children, a dose of 70 mg/kg of hydroxocobalamin up to the adult dose has been employed.¹¹ Sodium thiosulfate is often used following hydroxocobalamin to provide an added benefit, although the extent of this added benefit has been questioned.³ Care must be taken not to administer the hydroxocobalamin and sodium thiosulfate through the same IV line since a physical incompatibility occurs, inactivating the hydroxocobalamin.

FORMULATION AND ACQUISITION

Sodium thiosulfate is available in 50-mL vials containing 12.5 g in water for injection (USP), with boric acid or sodium hydroxide added to adjust the pH.³⁴ It is available in a kit known as Nithiodote, containing one vial of sodium nitrite (300 mg in 10 mL water for injection) with one vial of sodium thiosulfate (12.5 g in 50 mL water for injection), with boric acid or sodium hydroxide added to adjust the pH.²⁶

SUMMARY

- Sodium thiosulfate detoxifies cyanide by forming thiocyanate.
- The action of sodium thiosulfate is slower in onset than hydroxocobalamin or the nitrites.
- Thiocyanate is significantly less toxic than cyanide and is renally eliminated.
- Prophylactic administration of sodium thiosulfate along with sodium nitroprusside reduces cyanide toxicity by converting liberated cyanide to thiocyanate.
- Sodium thiosulfate is synergistic with nitrites.
- Sodium thiosulfate may be used following hydroxocobalamin, but animal data do not demonstrate an added benefit.

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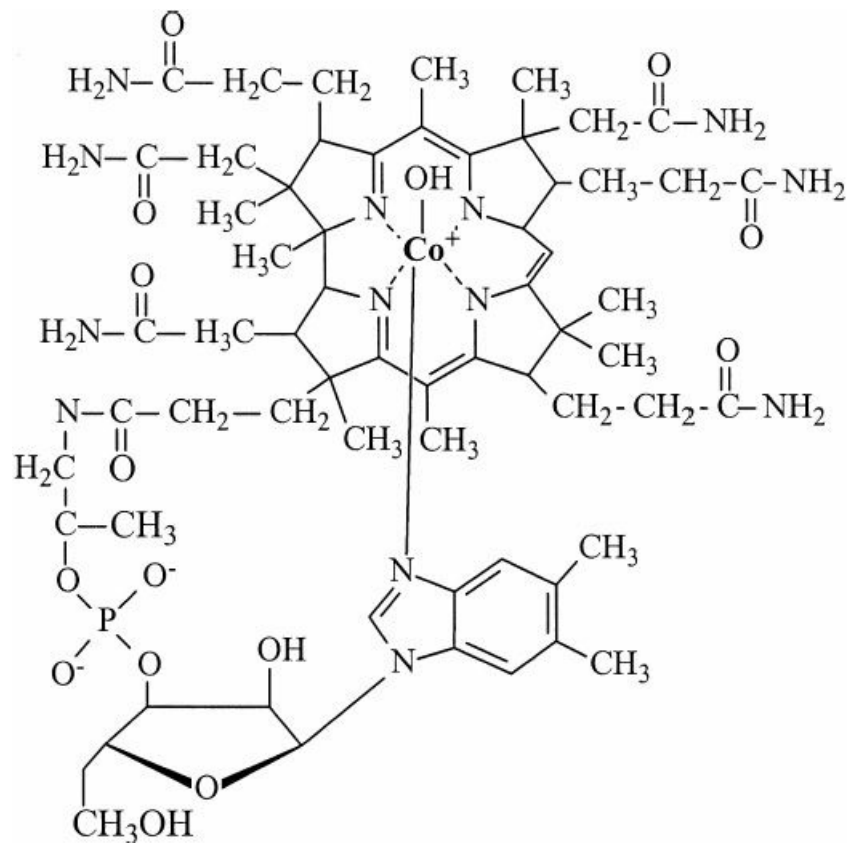
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A41 ANTIDOTES IN DEPTH

Hydroxocobalamin

Mary Ann Howland



INTRODUCTION

Cyanocobalamin, vitamin B₁₂, is formed when hydroxocobalamin combines with cyanide, quickly dropping cyanide concentrations and improving hemodynamics. Nitrites and sodium thiosulfate have traditionally been used to treat patients with cyanide toxicity. Nitrites have the disadvantage of producing methemoglobin, which is dangerous in a patient with coexistent elevated carboxyhemoglobin concentrations, such as would be found in fire victims suspected of having cyanide toxicity. Based on the mechanism of action of sodium thiosulfate, particularly when used alone, it is unlikely to be as effective as hydroxocobalamin, or work as quickly. A recent study in swine did not show a benefit to sodium thiosulfate as sole therapy or show an added benefit to hydroxocobalamin in a model of intravenous cyanide toxicity.⁷

HISTORY

The antidotal actions of cobalt as a chelator of cyanide were recognized as early as 1894.^{15,47} Hydroxocobalamin has been used as a cyanide antidote in France for many years, first as a sole agent and then in combination with sodium thiosulfate.²⁵ Hydroxocobalamin was finally approved by the Food and Drug Administration (FDA) in December 2006 and is available under the trade name Cyanokit.^{14,16}

In experimental models, hydroxocobalamin was successful in protecting against several minimum lethal doses of cyanide when an equimolar ratio of hydroxocobalamin to cyanide was used.^{1,10,36,43}

PHARMACOLOGY

Chemistry

The molecule is porphyrinlike in structure and has a cobalt ion at its core. The only difference between cyanocobalamin (vitamin B₁₂) and hydroxocobalamin (vitamin B_{12a}) is the replacement of the CN group with an OH group at the active site in the latter.^{31,38}

Mechanism of Action

The cobalt ion in hydroxocobalamin combines with cyanide to form the nontoxic cyanocobalamin.^{35,36} One mole of hydroxocobalamin binds 1 mole of CN. Given the molecular weights of each, 52 g of hydroxocobalamin are needed to bind 1 g of cyanide.²⁵ An ex vivo study using human skin fibroblasts demonstrated that hydroxocobalamin penetrates intracellularly to form cyanocobalamin.² In the setting of cyanide poisoning, hydroxocobalamin removes cyanide from the mitochondrial electron transport chain, allowing oxidative metabolism to proceed. Hydroxocobalamin also binds nitric oxide, a vasodilator, causing vasoconstriction both in the presence and in the absence of cyanide. This same property potentially contributes to its beneficial effects by increasing systolic and diastolic blood pressure and improving the hemodynamic status of cyanide poisoned patients.^{10,21} Other cobalt chelators, such as dicobalt ethylenediaminetetraacetic acid (EDTA), have been used both experimentally and clinically in other countries, but their therapeutic index is narrow, especially in the absence of cyanide. Additionally, idiosyncratic adverse effects make these compounds less advantageous.^{35,47} In France, hydroxocobalamin is used with sodium thiosulfate as it is thought to have an additive effect in the treatment of cyanide.^{41,44}

Pharmacokinetics and Pharmacodynamics

Under an FDA Investigational New Drug permit, the first pharmacokinetic study of intravenous (IV) hydroxocobalamin was performed in the United States and published in 1993.^{16,17} Adult volunteers who were heavy smokers were given 5 g hydroxocobalamin (5%) intravenously. The first four patients received the dose undiluted over 20 minutes.¹⁷ Then they received 12.5 g (50 mL of 25% solution) of sodium thiosulfate intravenously infused over 20 minutes. The next 11 patients received the same dose of hydroxocobalamin but diluted with 100 mL water for injection (USP) and infused over 30 minutes. The serum and urine sampling of hydroxocobalamin differed in the two patient groups, yielding somewhat different half-lives (4 vs. 1.27 hours). The α distribution half-life was 0.52 hours in the group 1 patients. Peak hydroxocobalamin concentrations averaged 813 $\mu\text{g/mL}$ (604 $\mu\text{mol/L}$), and volume of distribution (Vd) averaged 0.38 L/kg. A mean of 62% of the dose was recovered in the urine in 24 hours. Whole-blood cyanide concentrations significantly decreased in all subjects following hydroxocobalamin. A problem with this study was the short collection time for serum hydroxocobalamin concentrations of only 6 hours, making the pharmacokinetic analysis imprecise.^{27,28}

A pharmacokinetic study in France²⁵ was conducted in adult victims of smoke inhalation given hydroxocobalamin, 5 g (5%) by IV infusion over 30 minutes, starting within 30 minutes of patient removal from the fire.^{27,28} The α distribution half-life of hydroxocobalamin was 1.86 hours, elimination half-life was 26.2 hours based on sampling up to 6 days, and the Vd was 0.45 L/kg. The peak serum cyanocobalamin concentration was 287 $\mu\text{g/mL}$ (212 $\mu\text{mol/L}$). In the one patient who was subsequently determined not exposed to cyanide, the hydroxocobalamin elimination half-life was 13.6 hours and Vd was 0.23 L/kg. Renal clearance of hydroxocobalamin was 37% in the cyanide-exposed patients compared with 62% in the unexposed patient.

In another study in France in which 12 fire victims were suspected of having cyanide poisoning, the patients received IV hydroxocobalamin 5 g in 100 mL sterile water (USP) over 30 minutes.³⁰ Pretreatment and posttreatment cyanide concentrations and cyanocobalamin concentrations were analyzed. In patients with cyanide concentrations less than 1.04 $\mu\text{g/mL}$ (< 40 $\mu\text{mol/L}$), a linear relationship existed between the blood cyanide concentration and the formation of cyanocobalamin. In the three patients with blood cyanide concentration greater than 1.04 $\mu\text{g/mL}$ (> 40 $\mu\text{mol/L}$), the formation of cyanocobalamin reached a plateau, implying that all the hydroxocobalamin was consumed. When the patient with a blood cyanide concentration greater than 1.04 $\mu\text{g/mL}$ (> 40 $\mu\text{mol/L}$) received a second 5 g dose of hydroxocobalamin, the cyanocobalamin concentration subsequently rose.^{3,30}

The protein binding and tissue distribution of cyanide, hydroxocobalamin, and cyanocobalamin likely are different.²⁹ In addition, hydroxocobalamin probably causes redistribution of cyanide from the intracellular to the intravascular space.²⁹

ROLE IN CYANIDE TOXICITY

Animals

The ability of hydroxocobalamin to bind cyanide and produce beneficial effects on mortality and hemodynamics has been

demonstrated in many animal species, including rabbits, swine, dogs, and baboons.²⁶ A recent study in swine evaluated the effect of hydroxocobalamin plus sodium thiosulfate versus sodium nitrite and sodium thiosulfate in a model utilizing a continuous infusion of cyanide. There was no difference between the groups with regard to metabolic acidosis with an elevated lactate concentration at times 20 and 40 minutes, cardiac output and pulse rate at 40 minutes, or mortality. The mean arterial pressure was higher in the hydroxocobalamin plus sodium thiosulfate group, beginning at 5 minutes and lasting for the entire 40 minute monitoring period.⁸ A second cyanide study in swine done by the same group could not show a benefit to sodium thiosulfate as sole therapy or show an added benefit of sodium thiosulfate to hydroxocobalamin.⁷

Humans

Many case reports and studies in France document the efficacy of hydroxocobalamin combined with sodium thiosulfate for treatment of cyanide toxicity.^{6,11,20,24} An observational case series reviewed 69 adult smoke inhalation victims suspected of cyanide poisoning who were treated either at the scene of the fire or in the intensive care unit (ICU).¹⁰ They received a median dose of 5 g of hydroxocobalamin, up to a maximum of 15 g, infused as a 5% solution in sterile water for injection over 15 to 30 minutes. Cardiopulmonary arrest occurred in 15 patients, with a mean blood cyanide concentration of 123 $\mu\text{mol/L}$ ($100 \mu\text{mol/L} = 2.7 \mu\text{g/mL}$, which is a fatal concentration if untreated) and a mean carboxyhemoglobin of 30%. Two of these patients survived with normal neurologic function. Of 42 patients with confirmed cyanide concentrations greater than 39 $\mu\text{mol/L}$ ($1 \mu\text{g/mL}$, which is potentially fatal), 28 (67%) survived. The contribution to toxicity of carboxyhemoglobin is difficult to determine in this study. Of the 69 patients in this study, 57 also received hyperbaric oxygen, complicating the interpretation of the outcome.¹⁰

An 8 year retrospective analysis of the use of hydroxocobalamin in the prehospital setting concluded that the risk-to-benefit ratio favors its use in smoke inhalation victims suspected of cyanide poisoning.¹⁸ Of 72 patients in whom survival status could be determined, 30 (42%) survived. Cyanide blood concentrations were not measured in these patients. Although 21 of the 38 patients found in cardiac arrest had hemodynamic improvement, survival was dismal with only two patients ultimately surviving. The neurologic function of those two patients was not described.

Hydroxocobalamin also prevented the rise in cyanide concentration following nitroprusside infusion compared with patients who only received nitroprusside.¹² When nitroprusside is administered, the use of concomitant hydroxocobalamin prevents cyanide accumulation and toxicity in both animal models and in humans.^{11,12,48} Sodium thiosulfate also prevents nitroprusside induced cyanide toxicity (Antidotes in Depth: A40). There are currently no studies comparing the nitrite plus sodium thiosulfate regimen with hydroxocobalamin in patients with cyanide poisoning.⁴¹ There are no studies comparing hydroxocobalamin with or without sodium thiosulfate to sodium thiosulfate alone in smoke inhalation victims presumed to be cyanide toxic.

The kidneys, heart, and liver of a patient who was declared brain dead after third degree burns and smoke inhalation following a fire, were successfully transplanted into four patients.¹⁹ The victim received 10 g of hydroxocobalamin. Whole-blood cyanide concentrations were later confirmed to be significantly elevated.

ADVERSE EFFECTS AND SAFETY ISSUES

Hydroxocobalamin has a wide therapeutic index.^{10,18,46} Large doses have been administered to animals with no adverse effects.^{35,40,42} The LD_{50} (median lethal dose in 50% of test subjects) in mice is 2 g/kg.

Red discoloration of mucous membranes, serum, and urine may occur and last from 12 hours to many days after therapy.^{10,14,18} Patients should be warned to avoid direct sun exposure while their skin remains red for fear of a photosensitivity reaction.¹⁴ Allergic reactions including anaphylaxis and angioedema are reported, but serious allergic reactions are rare.^{5,6,11,38} Prior chronic exposure to hydroxocobalamin or cyanocobalamin for treatment of vitamin B₁₂ deficiency is associated rarely with development of anaphylaxis.²⁵ A study in 102 healthy volunteers demonstrated that chromaturia is universal, and as the dose increases from 2.5 to 10 g, the incidence of erythema, rash (predominantly acneiform), headache, injection site reaction, nausea, pruritus, chest discomfort, and dysphagia increases.⁴⁶ The dermatologic manifestations are quite variable, both rapid and delayed onset with protracted courses may occur. Of 102 volunteers randomized to receive hydroxocobalamin, 24 experienced a clinically significant rise in diastolic blood pressures, up to 124 mm Hg. However, only three of them also had clinically significant elevations in systolic blood pressure. These elevations in blood pressure resolved within 4 hours of the end of the infusion. Urinary oxalate crystals were reported in patients receiving hydroxocobalamin whether or not the patient is exposed to cyanide.¹⁴

Colorimetric assays are most likely to be adversely affected because both hydroxocobalamin and cyanocobalamin have an intensely red color. Many clinical chemistry laboratory tests can be artificially increased, decreased, or unpredictable.^{9,14} Hematology tests including hemoglobin, MCH, MCHC, and basophils are artificially increased.¹⁴ Coagulation tests are unpredictable. Urinalysis tests are usually artificially increased, but pH can also be artificially low

with low doses of hydroxocobalamin.¹⁴ An in vitro study found statistically significant alterations in serum concentrations of aspartate aminotransferase (AST), total bilirubin, creatinine, magnesium, and iron after hydroxocobalamin administration.¹³ Although an in vitro study demonstrated a considerable false increase in carboxyhemoglobin concentrations following hydroxocobalamin administration when measured by cooximetry, other authors suggest that the interference is minimal and results in slight overestimates depending on the instrument and the concentration of hydroxocobalamin.^{4,22,32} Inconsequential increases of 1% to 5.7% in the carboxyhemoglobin level were reported in another study.²² However, more worrisome is the report of two instances where the carboxyhemoglobin levels were falsely low by a factor of 4 to 14 times.³⁴

Because of the inaccuracies in laboratory determinations, blood should be drawn before the administration of hydroxocobalamin whenever possible. This is particularly important in fire victims when carboxyhemoglobin concentrations may be necessary for management decisions.

PREGNANCY AND LACTATION

Hydroxocobalamin is FDA pregnancy category C. Animal studies are insufficient and there are no controlled trials in pregnant women. Hydroxocobalamin should be used in pregnant women when the potential benefit outweighs the potential risk to the fetus. A pregnant woman in her fourth week of gestation was inadvertently administered 5 g of hydroxocobalamin during a volunteer study. She went on to deliver a normal healthy baby at term.¹⁴

DOSING AND ADMINISTRATION

Cyanide Toxicity

The initial dose of hydroxocobalamin in adults is 5 g. Each vial is reconstituted with 200 mL of 0.9% sodium chloride and administered intravenously over 15 minutes. If 0.9% sodium chloride is unavailable, lactated ringers solution or D₅W may be used. Each vial should be inverted or rocked (not shaken) for 60 seconds prior to administration. The reconstituted solution should be dark red and free of particulate matter and should be used within 6 hours of reconstitution.¹⁴ A second dose of 5 g can be repeated as clinically necessary and infused over 15 minutes to 2 hours depending on patient status.¹⁴

In children, a dose of 70 mg/kg of hydroxocobalamin up to the adult dose is recommended.¹⁴

Sodium thiosulfate can be administered in addition to hydroxocobalamin, but the administration of the hydroxocobalamin should take precedence. The sodium thiosulfate is expected to be additive and has been used extensively in conjunction with hydroxocobalamin.^{23,24,33} Care must be taken not to administer the hydroxocobalamin and sodium thiosulfate simultaneously through the same IV line since this may inactivate the hydroxocobalamin.²⁹ The adult dose of sodium thiosulfate is 12.5 g (50 mL of 25% solution) and should be administered intravenously as either a bolus injection or infused over 10 to 30 minutes, depending on the severity of the situation. The dose of sodium thiosulfate in children is 1 mL/kg using a 25% solution (250 mg/kg or approximately 30–40 mL/m² of BSA) not to exceed 50 mL (12.5 g) total dose. The dose can be repeated at half the initial dose if manifestations of cyanide toxicity reappear.^{39,45}

Nitroprusside Induced Cyanide Toxicity

Nitroprusside induced cyanide toxicity should be treated like cyanide toxicity from any other cause: stop the nitroprusside dosage and administer hydroxocobalamin with or without sodium thiosulfate according to the doses and precautions listed. The dose of hydroxocobalamin to prevent cyanide toxicity from the IV infusion of nitroprusside is not precisely known, but a dose of hydroxocobalamin of 25 mg/h in one study was sufficient to decrease the red cell and serum cyanide concentrations and to prevent the development of a metabolic acidosis while the nitroprusside continued to be administered.⁴⁸ These authors recommend possibly continuing the hydroxocobalamin for 10 hours after the discontinuation of the nitroprusside. Hydroxocobalamin could also be used as rescue therapy in the typical dosage, as could sodium thiosulfate (Antidotes in Depth: A40).

FORMULATION AND ACQUISITION

Each Cyanokit contains one 250 mL glass vial containing 5 g of lyophilized dark red, hydroxocobalamin crystalline powder for injection.¹⁴ The kit also contains one sterile transfer spike, one sterile IV infusion set, one quick reference guide, and one package insert, but no diluent.

SUMMARY

- Hydroxocobalamin is effective for cyanide toxicity generated from all routes of exposure. Intravenous hydroxocobalamin is safe in the setting of a fire when carboxyhemoglobin is also expected to be present.
- Hydroxocobalamin affects all laboratory tests that are colorimetric, producing falsely elevated or lowered results. Of particular importance may be the significantly falsely diminished assay for carboxyhemoglobin.
- Hydroxocobalamin causes a red discoloration of the skin and mucous membranes that may last hours to days.

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127 METHEMOGLOBIN INDUCERS

Dennis P. Price

HISTORY AND EPIDEMIOLOGY

Methemoglobinemia is a disorder of the red blood cell. Exposure to various xenobiotics can adversely affect the red cell membrane, intracellular metabolism, and, as is the case with methemoglobinemia, interfere with hemoglobin function. Methemoglobin occurs when the iron atom in hemoglobin loses one electron to an oxidant, and the ferrous (Fe^{2+}) or oxidized state of iron is transformed into the ferric (Fe^{3+}) state. Although methemoglobin is always present at low concentrations in the body, methemoglobinemia is defined herein as an abnormal elevation of the methemoglobin level above 1%. The ubiquity of oxidants, both in the environment and in the hospital, has increased the number of cases of reported methemoglobinemia.

Methemoglobin was first described by Felix Hoppe-Seyler in 1864.³⁵ Subsequently, in 1891, a case of transient drug induced methemoglobinemia was described.⁷³ In the late 1930s, methemoglobinemia was recognized as a predictable adverse effect of sulfanilamide use, and methylene blue was recommended for treatment of the ensuing cyanosis.^{46,108} Some authors even recommended concurrent use of methylene blue when sulfanilamides were used.¹⁰⁸ Methylene blue was used prophylactically during general surgery to treat an individual with congenital methemoglobinemia.⁷ In 1948, an enzyme identified as coenzyme 1 was reported in six patients in two families who had idiopathic methemoglobinemia. The defect in coenzyme 1 (NADH methemoglobin reductase) caused cyanosis in the absence of cardiopulmonary disease and responded to ascorbic acid.³⁷

Methemoglobinemia may be hereditary or acquired. The hereditary types are rare, with only several hundred cases reported.^{47,103} Although the frequency with which xenobiotic-induced methemoglobinemia occurs is unknown, the American Association of Poison Control Centers' annual data over the past 5 years has shown approximately 100 yearly uses of methylene blue as an antidote. These data substantially underestimate the incidence of this poisoning because poison centers are not notified in most cases (Chap. 136).

Methemoglobinemia is relatively common and generally produces no clinical findings. Cooximetry data collected at two teaching hospitals noted a significant number of elevated methemoglobin levels.⁴ Of a total of 5248 cooximetry tests over 28 months on 1267 patients, 660 tests revealed methemoglobin levels above 1.5% in 414 patients (some patients had more than one test). Thus, 12.5% of all tests and 19.1% of all patients who had cooximetry performed had an abnormal methemoglobin level. A total of 138 patients with peak methemoglobin levels greater than 2% were identified. The mean peak methemoglobin level was 8.4% (range, 2.1%–60.1%), and the ages of the patients ranged from 4 days to 86 years.⁴

Benzocaine spray accounted for the most seriously poisoned patients ($n = 5$), with a mean peak methemoglobin level of 43.8% (range, 19.1%–60.1%).⁴ Dapsone accounted for the largest number of cases ($n = 58$), with a mean peak of 7.6% (range, 2.1%–34.1%). Of those patients who had elevated methemoglobin levels, 8% had symptomatic methemoglobinemia, approximately one-third received methylene blue. One fatality and three near-fatalities were directly attributed to methemoglobinemia. These data likely represent an underestimation of the true number of cases of methemoglobinemia at these institutions because cooximetry was performed only on physician orders for suspected dysmethemoglobinemia, and 25% of cases with levels above 2% were found incidentally when cooximetry was performed in the catheterization laboratory to provide data on oxyhemoglobin and deoxyhemoglobin. In addition, not all patients taking dapsone were tested.⁴ Extrapolating these data throughout the country would suggest underreporting and substantial underrecognition of this entity with its potential danger.

Another study screened a small sample of infants younger than 3 months of age who presented to the emergency department with dehydration due to diarrhea. A small number of patients had elevated levels of methemoglobin.³¹ Furthermore, the incidence of induced methemoglobinemia in the workplace is poorly documented. A number of reports document several hundred such cases of methemoglobinemia and several more workplace exposures.^{15,62,88} Underreporting and underrecognition occur because of the limited symptoms associated with low levels of methemoglobin in most cases. Acute pesticide poisoning leading to methemoglobinemia is common in many parts of the world. In Sri Lanka, a large, multicenter study followed 431 patients with intentional propanil ingestions and found a 10.7% mortality rate in those with methemoglobinemia.⁹² Copper sulfate is another commonly found substance used industrially and as a pesticide that causes

both methemoglobinemia and hemolysis.^{34,76,101}

HEMOGLOBIN PHYSIOLOGY

Hemoglobin consists of four polypeptide chains noncovalently attracted to each other. Each of these subunits carries one heme molecule deeply within the structure. The polypeptide chain protects the iron moiety of the heme molecule from inappropriate oxidation (Fig. 127–1).

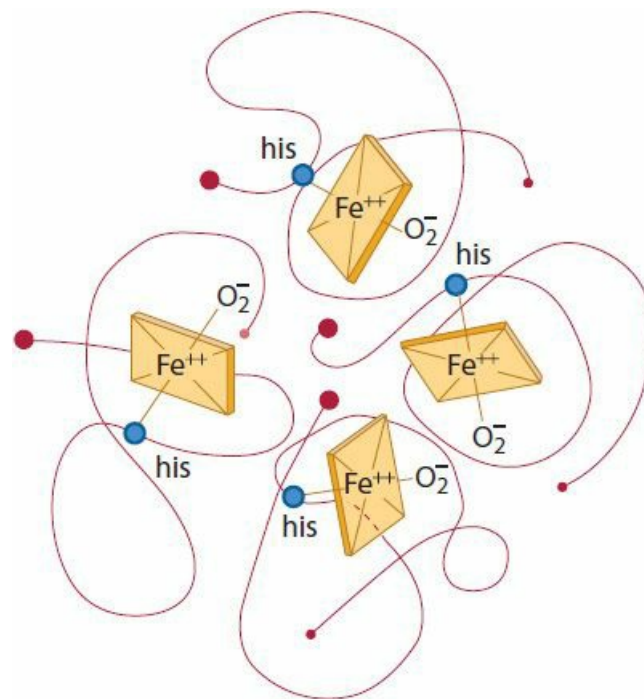


FIGURE 127–1. Hemoglobin molecule symbolically represented with its heme center surrounded by the globin portion of the molecule. his = histidine.

The iron is held in position by six coordination bonds. Four of these bonds are between iron and the nitrogen atoms of the protoporphyrin ring with the fifth and sixth bond sites lying above and below the protoporphyrin plane. The fifth site is occupied by histidine of the polypeptide chain. A variety of hemoglobin mutations are attributable to changes in the amino acid sequence of the polypeptide chain, as with hemoglobin M diseases. This influences this protective “pocket,” allowing easier iron oxidation (Fig. 127–2), or hemoglobin autooxidation. The sixth coordination site is where most of the activity within hemoglobin occurs. Oxygen transport occurs here, and this site is involved with the formation of methemoglobin or carboxyhemoglobin (Fig. 127–3). It is at this site that an electron is lost to oxidant xenobiotics, transforming iron from its ferrous (Fe^{2+}) to its ferric (Fe^{3+}) state.

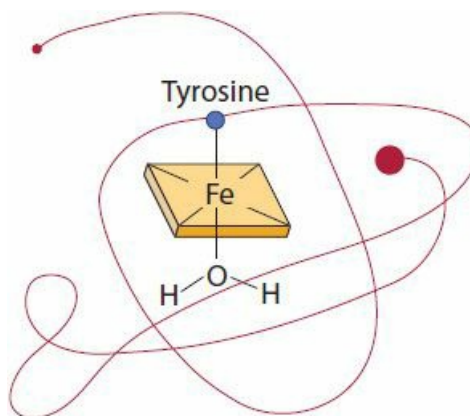


FIGURE 127–2. Hemoglobin M occurs when histidine is replaced by tyrosin in the amino acid sequence of the polypeptide chain. Hemoglobin M is more easily autooxidized (as shown) to methemoglobin.

FIGURE 127–4. Role of glycolysis in the Embden-Meyerhof pathway and the role of methylene blue in the reduction of methemoglobin using NADPH generated by the hexose monophosphate shunt. Hb (Fe^{3+}) is methemoglobin.

Oxidized iron can be reduced nonenzymatically using either ascorbic acid or reduced glutathione as electron donors, but this method is slow and quantitatively less important under normal circumstances.

Within the red cell is another enzyme system for reducing oxidized iron that is dependent on the NADPH generated in the hexose monophosphate shunt pathway (Fig. 127–4). Although it is generally accepted that this NADPH-dependent system reduces only a small percentage of methemoglobin under normal circumstances, it may play a more prominent role in maintaining oxidant balance in the cell.⁶¹ Patients with an isolated deficiency of NADPH methemoglobin reductase do not exhibit methemoglobinemia under normal circumstances,⁹⁶ perhaps because of the prominence of other cellular protective mechanisms.

However, when the NADPH methemoglobin reductase system is provided with an exogenous electron carrier, such as methylene blue, this system is accelerated and may assist in the reduction of oxidized hemoglobin (Antidotes in Depth: A42).

XENOBIOTIC INDUCED METHEMOGLOBINEMIA

Nitrates and nitrites are powerful oxidizing agents that are two of the most common methemoglobin-forming compounds. Sources of nitrates and nitrites include well water, food, industrial compounds, and pharmaceuticals. Nitrogen-based fertilizers and nitrogenous waste from animal and human sources may contaminate shallow rural wells. Community-based water serves the majority of Americans; however, there are 37 million private wells in the United States. These wells are not tested regularly and may be more shallow than necessary to prevent contamination from fertilizers.^{5,20} The contamination of drinking water occurs mainly with nitrates because nitrites are easily oxidized to the highly soluble nitrates in the environment. Furthermore, foods such as cauliflower, carrots, spinach, and broccoli have high nitrate content, as do preservatives in meat products such as hot dogs and sausage.⁶

The reactions of nitrates that occur both in vivo and in vitro are complex and poorly understood. Ingested nitrates are reduced to nitrites by bacteria in the gastrointestinal (GI) tract (especially in infants) and then can be absorbed, ultimately leading to methemoglobin production. However, this conversion is not essential because nitrates themselves can oxidize hemoglobin.^{32,45,102} Some question whether well water consumption alone can cause serious methemoglobinemia in the absence of comorbid disease.²⁸

In the past, nitrate-contaminated well water was associated with infant fatalities because of methemoglobinemia.^{63,71} A number of reports from the midwestern United States demonstrated the problems of poorly constructed shallow wells that permit contamination by surface waters containing chemicals, pesticides, fertilizers, and microorganisms.⁷⁴ In several South Dakota studies, 20% to 50% of wells contained both coliform bacteria and water that exceeded the Environmental Protection Agency standards for permissible quantities of nitrogen as nitrates (10 ppm or 10 mg/L).⁵⁴ In New York, 419 wells from rural farms demonstrated elevated concentrations of nitrogen compounds, and 15.7% were found to have well water nitrate concentrations higher than 10 mg/L.³⁶ In Texas, wells that were studied longitudinally have shown increasing nitrate contamination.²⁰ Governmental programs, such as the Private Well Initiative, are aiming to improve drinking water quality throughout the country.⁵

Nitroglycerin (glyceryl trinitrate) and organic nitrates are more effectively absorbed through mucous membranes and intact skin than from the GI tract. Their onset of action is more rapid, and the total effect is much greater, when mucous membrane or cutaneous absorption occurs.^{22,50,85} Aromatic amino and nitro compounds indirectly produce methemoglobin.⁵⁷ These xenobiotics do not form methemoglobin in vitro; therefore, they are assumed to do so by in vivo metabolic chemical conversion to some active intermediates.^{15,59}

Elevated methemoglobin and carboxyhemoglobin levels are found in victims of fires and automobile exhaust fume poisoning.^{12,50,56,67} Heat-induced hemoglobin denaturation in burn patients and the inhalation of oxides of nitrogen from combustion are suggested to be causative factors for methemoglobin formation.

Topical anesthetics are widely used to facilitate multiple procedures and are implicated in the most serious of toxic methemoglobin cases.^{1,43} These xenobiotics continue to be a problem despite numerous case studies and recommendations by authors and manufacturers about safe use standards.^{23,40,53} Cetacaine spray (14% benzocaine, 2% tetracaine, 2% butylaminobenzoate) and 20% benzocaine sprays commonly produce methemoglobinemia. The dosing recommendations are difficult to comprehend (eg, 0.5-second spray repeat once) and are often ignored. One study showed that the dose is dependent on the residual volume in the canister and the physical orientation of the canister as the spray is being applied.⁶⁰

A review of 52 months of data from the US Food and Drug Administration (FDA) Adverse Event Reporting System demonstrated 132 cases of benzocaine-induced methemoglobinemia. Benzocaine spray was implicated in 107 severe adverse events and two deaths. In 123 cases, the product was a spray. In 69 cases in which the dose was specified, 37

patients received a single spray.⁷⁵

This FDA effort is exclusively based on self-reporting and probably greatly underestimates the extent of the problem.⁴¹ The FDA itself has estimated that approximately 10% of serious events are reported and that some studies show 1% or less serious event reporting.⁷⁵

In one institution, the incidence of benzocaine-induced methemoglobinemia occurring during transesophageal echocardiograms was determined in 28,478 patients over a 90-month period. The incidence was low at 0.067% (1 case per 1499 patients), with sepsis, anemia, and hospitalization suggested as predisposing factors.⁵⁵ During a 32-month period at another institution, an incidence of 0.115% (5 of 4336) of benzocaine-induced methemoglobinemia was observed.⁸¹ There were no cases of methemoglobinemia in a study of 154 patients receiving lidocaine for bronchoscopy at doses as high as 15 mg/kg. Lidocaine is a much weaker oxidant than benzocaine and is a reasonable substitute in susceptible individuals and has been recommended by some authors.⁵³

Nitric oxide (NO) delivered by inhalation is used to treat persistent pulmonary hypertension of newborns and other cardiopulmonary diseases associated with pulmonary hypertension because it is a potent vasodilator.⁹³ Despite being a potent oxidant, if NO is used in doses of less than 40 ppm, most patients will maintain methemoglobin levels below 4%.^{48,107} Some cases of serious toxicity have occurred because of intentional and unintentional overdoses.

Dapsone is implicated as a cause of methemoglobinemia and is used in patients with AIDS.⁸⁴ Cases of prolonged methemoglobinemia from dapsone ingestion are related to the long half-life of dapsone and the slow conversion to its methemoglobin-forming hydroxylamine metabolites.²⁵ Patients receiving dapsone should be carefully monitored for methemoglobinemia.¹¹⁰ The bladder analgesic phenazopyridine is a commonly reported cause of methemoglobinemia.^{21,30,36,77} For this reason, its use should be limited to short periods of time and at the lowest dose to improve symptoms. This approach is particularly pertinent in the presence of kidney failure. Predispositions for methemoglobinemia are listed in [Tables 127–1 and 127–2](#).

TABLE 127–1. Factors That May Predispose an Individual to Methemoglobinemia

Acidosis ^{84,96}	Diarrhea ^{37,77}
Advanced age ⁷²	Hospitalization ^{47,72}
Age < 36 months ^{21,69,95}	Kidney failure ³³
Anemia ⁴⁷	Malnutrition
Concomitant oxidant use ^{3,58,73}	Sepsis ^{47,57,72,74}

TABLE 127–2. Causes of Methemoglobinemia

Hereditary

- Hemoglobin M
- Cytochrome b₅ reductase deficiency (homozygote and heterozygote)

Acquired

- Medications
 - Amyl nitrite
 - Benzocaine
 - Dapsone
 - Lidocaine
 - Nitric oxide
 - Nitroglycerin
 - Nitroprusside
 - Phenazopyridine

Prilocaine

Quinones (chloroquine, primaquine)

Sulfonamides (sulfanilamide, sulfathiazide, sulfapyridine, sulfamethoxazole)

Other Xenobiotics

Aniline dye derivatives (shoe dyes, marking inks)

Chlorobenzene

Fires (heat-induced denaturation)

Organic nitrites (eg, Isobutyl nitrite, butyl nitrite)

Naphthalene

Nitrates (eg, well water)

Nitrites (eg, foods)

Nitrophenol

Nitrogen oxide gases (seen in arc welders)

Silver nitrate

Trinitrotoluene

Pediatric

Reduced NADH methemoglobin reductase activity in infants (< 4 months)

Associated with low birth weight, prematurity, dehydration, acidosis, diarrhea, and hyperchloremia

Underlying illness,^{31,55,65,81,83} the treatment with xenobiotics for these illnesses,^{3,18,59,66,74,82} and the diagnostics and therapeutic modalities^{48,73} in patient care all predispose patients to methemoglobinemia. For many individuals, methemoglobin is not caused by one oxidant stressor, but rather by a series of stressors that makes methemoglobinemia clinically apparent and potentially predictable.

METHEMOGLOBINEMIA AND HEMOLYSIS

The enzyme defect responsible for most instances of oxidant-induced hemolysis is G-6-PD deficiency. Reviews of hemolysis addressed the confusion regarding the relationship between hemolysis and methemoglobinemia.^{10,11,33}

Both hemolysis and methemoglobinemia are caused by oxidant stress, and hemolysis may occur after episodes of methemoglobinemia.^{11,84} Certain protective mechanisms involving NADPH and reduced glutathione nonspecifically reduce the oxidant burden and prevent the development of both disorders. Another source of confusion concerning hemolysis and methemoglobinemia is that reduced glutathione is required to protect against both toxic manifestations. Erythrocytes can withstand hemolytic oxidant damage as long as they can maintain adequate concentrations of reduced glutathione, the principal cellular antioxidant. Glutathione is maintained in its reduced form by using NADPH as its reducing agent. Cells with reduced capacity to produce NADPH (ie, erythrocytes of patients with G-6-PD deficiency or cells with depleted reduced glutathione or NADPH) are thus susceptible to hemolysis. In the presence of methemoglobinemia, reduced glutathione plays a minor role as a reducing agent, but NADPH is necessary for successful antidotal therapy with methylene blue. This codependence on the reducing power of NADPH links the two disorders. Competition for NADPH by oxidized glutathione and exogenously administered methylene blue is postulated to be the cause of methylene blue-induced hemolysis (ie, competitive inhibition of glutathione reduction). Methylene blue itself is an oxidant, but in an assessment of the hemolytic potency of varied drugs, methylene blue in doses of 390 to 780 mg proved to be only a moderate hemolytic agent.⁵⁸ The clinical importance of this phenomenon is uncertain. It may be easier to consider hemolysis and methemoglobin formation as subclasses of disorders of oxidant stress. They should be considered separate clinical entities sharing limited characteristics.

However, oxidative damage to erythrocytes occurs at different locations in the two disorders. Hemolysis occurs when oxidants damage the hemoglobin chain acting directly as electron acceptors or through the formation of hydrogen peroxide or other oxidizing free radicals. This results in oxidants forming irreversible bonds with sulfhydryl group of hemoglobin cause denaturation and precipitation of the globin protein to form Heinz bodies within the erythrocyte (Fig. 127–5). Cells with large numbers of Heinz bodies are removed by the reticuloendothelial system, producing hemolysis. Alternatively, a limited number of oxidants can destroy the erythrocyte membrane directly, causing non-Heinz body hemolysis. Methemoglobinemia does not necessarily progress to hemolysis, even if untreated.

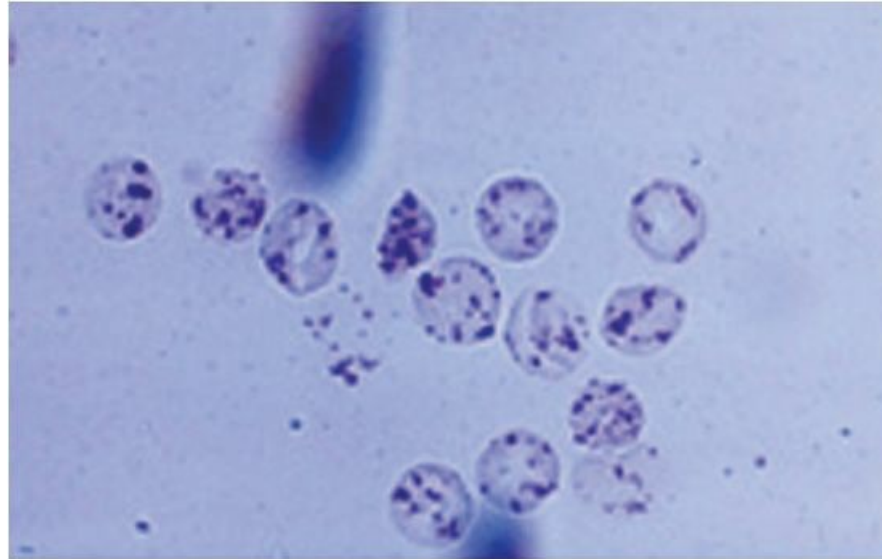


FIGURE 127–5. Heinz bodies are particles of denatured hemoglobin, usually attached to the inner surface of the red cell membrane. Xenobiotics that result in the oxidative denaturation of hemoglobin in normal (eg, phenylhydrazine) or glucose-6-phosphate dehydrogenase deficient (primaquine) individuals and unstable hemoglobin mutants are prone to develop these bodies. The Heinz bodies can be identified when blood is mixed with a supravital stain, notably crystal violet. The Heinz bodies appear as purple inclusions. (Reproduced with permission from Lichtman MA, Shafer MS, Felgar RE, Wang N. Lichtman’s Atlas of Hematology, 1st ed. New York: McGraw-Hill, Inc; 2007.)

Numerous cases describe the occurrence of hemolysis after methemoglobinemia. The combined occurrence is reported with dapsone,^{25,53} phenazopyridine,^{21,30,38,77} amyl nitrite,¹⁷ copper sulfate,³⁴ and aniline.^{54,57} These instances of combined syndromes may represent the incidental toxicity of an oxidizing agent at both locations or may represent the depletion of all cellular defenses against oxidants. Currently, it is not possible to predict when hemolysis will occur after methemoglobinemia with any degree of certainty.

CLINICAL MANIFESTATIONS

The clinical manifestations of methemoglobinemia are related to impaired oxygen-carrying capacity and delivery to the tissue. The clinical manifestations of acquired methemoglobinemia are usually more severe than those produced by a corresponding degree of anemia. This discordance occurs because methemoglobin not only decreases the available oxygen-carrying capacity but also increases the affinity of the unaltered hemoglobin for oxygen. This shifts the oxygen hemoglobin dissociation curve to the left, which further impairs oxygen delivery²⁴ (Chap. 29). This effect is attributed to the formation of heme compounds intermediate between normal reduced hemoglobin (all four iron atoms are ferrous) and methemoglobin, in which one or more of the iron moieties are in the ferric state.²⁴ The degree to which this high oxygen affinity hemoglobin reduces oxygen delivery to the tissue from arterial blood is unclear but is clinically significant.¹⁹

Because the symptoms associated with methemoglobinemia are related to impaired oxygen delivery to the tissues, concurrent diseases such as anemia, congestive heart failure, chronic obstructive pulmonary disease, and pneumonia may greatly increase the clinical effects of methemoglobinemia (Fig. 127–6). Predictions of symptoms and recommendations for therapy are based on methemoglobin percentage in previously healthy individuals with normal total hemoglobin concentrations.

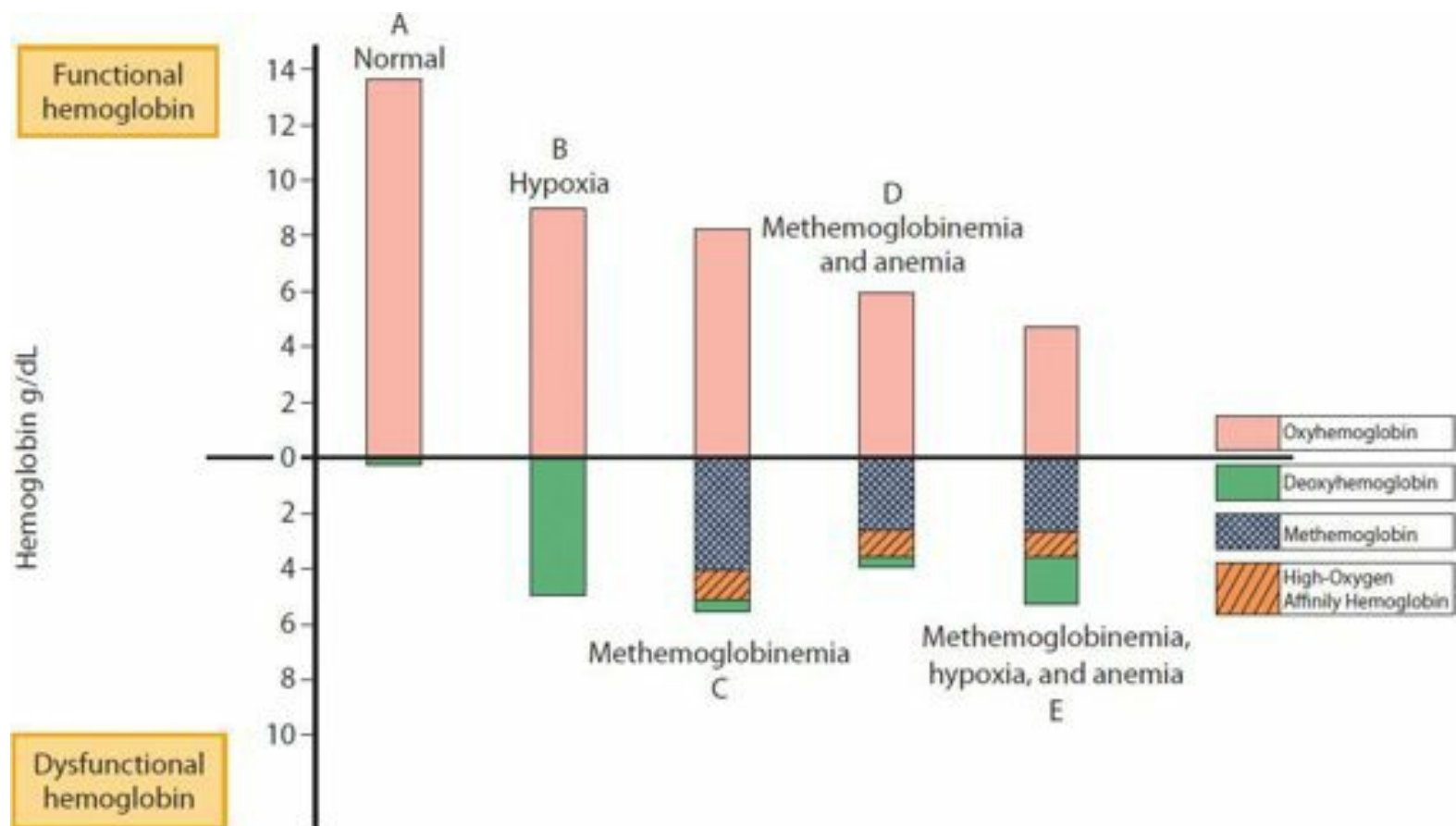


FIGURE 127-6. Clinical manifestations of methemoglobinemia depend on the level of methemoglobin and on host factors such as preexisting disease, anemia, and hypoxemia. Five examples of arterial blood gas and cooximeter analyses are presented. (A) Blood gas from a normal individual with 14 g/dL of hemoglobin. Almost all hemoglobin is saturated with oxygen. (B) Blood gas from a patient with cardiopulmonary disease producing cyanosis in which only 9 g/dL of hemoglobin is capable of oxygen transport. (C) Methemoglobin level of 28% in an otherwise normal individual will reduce hemoglobin available for oxygen transport to less than 9 g/dL (~ 4 g/dL of methemoglobin and 1.3 g/dL of high oxygen affinity hemoglobin because of the left shift of the oxyhemoglobin dissociation curve). (D) Same degree of methemoglobin as in C but in a patient with a hemoglobin of 10 g/dL. Only 6 g/dL of hemoglobin would be capable of oxygen transport. (E) Methemoglobinemia and anemia to the same degree as D but in a hypoxic patient.

Cyanosis is a consistent physical finding in patients with substantial methemoglobinemia and is caused by the deeply pigmented color of methemoglobin. Cyanosis typically occurs when just 1.5 g/dL of methemoglobin is present. This represents only 10% conversion of hemoglobin to methemoglobin if the baseline hemoglobin is 15 g/dL. By contrast, 5 g/dL of deoxyhemoglobin (which represents 33% of the total hemoglobin concentration) is needed to produce the same degree of cyanosis from hypoxia (Table 127-3).

TABLE 127-3. Signs and Symptoms Typically Associated with Methemoglobin Levels in Healthy Patients with Normal Hemoglobin Concentrations

<i>Methemoglobin Level (%)</i>	<i>Signs and Symptoms</i>
1–3 (normal)	None
3–15	Possibly none Pulse oximeter reads low SaO ₂ Slate gray cutaneous coloration
15–20	Chocolate brown blood Cyanosis
20–50	Dizziness, syncope Dyspnea Exercise intolerance Fatigue Headache Weakness
50–70	Central nervous system depression Coma Dysrhythmias Metabolic acidosis Seizures Tachypnea
> 70	Death Grave hypoxic symptoms

The cyanosis associated with methemoglobinemia is both peripheral and central. Patients often appear in less distress or less ill than patients with the same degree of cyanosis secondary to cardiopulmonary causes.

The symptoms of methemoglobinemia are determined not only by the absolute percent of methemoglobin but also by its rates of formation and elimination. A percentage of methemoglobin that may be clinically benign when caused by hereditary defects or maintained chronically likely will produce more severe signs when acutely acquired. Healthy subjects lack the compensatory mechanisms that develop over a lifetime in individuals with hereditary compromise, such as erythrocytosis and increased 2,3-bisphosphoglyceric acid.

DIAGNOSTIC TESTING

For an individual in whom methemoglobinemia is suspected, a source for the oxidant stress should be sought. Arterial blood gas sampling may reveal blood with a characteristic chocolate brown color. However, in patients who are clinically stable and not in need of an arterial puncture, a venous blood gas will be accurate in demonstrating the methemoglobin level. The arterial PO₂ should be normal, reflecting the adequacy of pulmonary function to deliver dissolved oxygen to the blood. However, arterial PO₂ does not directly measure the hemoglobin oxygen saturation (SaO₂) or oxygen content of the blood. When the partial pressure of oxygen is known and oxyhemoglobin and deoxyhemoglobin are the only species of hemoglobin, oxygen saturation can be calculated accurately from the arterial blood gas. If, however, other hemoglobins are present, such as methemoglobin, sulfhemoglobin, or carboxyhemoglobin, then the fractional saturation of the different hemoglobin species must be determined by cooximetry in the laboratory.

The cooximeter is a spectrophotometer that identifies the absorptive characteristics of several hemoglobin species at different wavelengths. Because oxyhemoglobin, deoxyhemoglobin, methemoglobin, and carboxyhemoglobin all have different absorptions at the different measuring points of the cooximeter, their proportions and concentrations can be determined. Some newer cooximeters have an expanded spectrum at which they read and are also able to read fetal hemoglobin and sulfhemoglobin.¹¹³

The pulse oximeter applied to a patient's finger at the bedside was developed to estimate oxygen saturation trends in critically ill patients. The device takes advantage of the unique absorptive characteristics of oxyhemoglobin and deoxyhemoglobin and the different concentrations of these two hemoglobin species during different phases of the pulse. Each manufacturer has calibrated its oximeter using volunteers breathing progressively increasing hypoxic gas mixtures in the absence of a dysmethemoglobinemia.^{88,100,106} In other words, the oxygen saturation values displayed on the pulse oximeter are derived independently by each manufacturer, which develops a formula using their own hardware and sensor. The manufacturer then compares this value with a set of validation data derived from their own experimental population.

Most pulse oximeters in use today use two different wavelengths to determine O₂ saturation and the manufacturers do not provide validation data for situations where any dyshemoglobin is present. These manufacturers disclaim accuracy under such circumstances. Similar to cooximetry, the dual-wavelength pulse oximeter reads absorbance of light at wavelengths of 660 and 940 nm, which are selected to efficiently separate oxyhemoglobin and deoxyhemoglobin. However, methemoglobin absorption at these wavelengths is greater than that of either oxyhemoglobin or deoxyhemoglobin.^{8,71} Therefore, when methemoglobin is present, the readings become inaccurate. The degree of inaccuracy is unique for each brand of instrument and may be influenced by signal quality, skin temperature, refractive error induced by blood cells, and other factors (eg, finger thickness and perfusion).⁹⁰ Hemoglobin variants—of which thousands exist—have been shown to interfere with pulse oximetry accuracy as well.¹⁰⁵

In the dog model, the pulse oximeter oxygen saturation (SpO₂) values decrease with increasing methemoglobin levels. This decrease in SpO₂ is not exactly proportional to the percentage of methemoglobin. However, the pulse oximeter overestimates the level of actual oxygen saturation. For example, in a case in which the methemoglobin level measured in the blood using a cooximeter was 20%, the pulse oximeter indicated an SpO₂ of 90%.^{9,104} However, as the methemoglobin concentration approached 30%, the pulse oximeter saturation values decreased to about 85% and then leveled off, regardless of how much higher the methemoglobin level became.^{9,104}

From our experience and that of others,^{42,89} in humans, much lower levels of oxygen saturation (SpO₂) than 85% can be displayed by pulse oximetry when methemoglobin levels increase above 30%.⁵² These differences result from variations in the way different model pulse oximeters deal with methemoglobin interference.^{88,89} Therefore, health care professionals must understand how the particular pulse oximeter measures oxygen saturation when methemoglobin levels are elevated and recognize that cooximetry determination is needed when methemoglobinemia is suspected.

Although the pulse oximeter reading in patients with methemoglobinemia may not be as accurate as desired, it may be helpful when it is compared with that of the arterial blood gas: if there is a difference between the measured oxyhemoglobin saturation of the pulse oximeter (SaO₂) and the calculated oxyhemoglobin saturation of the arterial blood gas (SpO₂), then a “saturation gap” exists. The calculated SaO₂ of the blood gas will be greater than the measured SpO₂ if methemoglobin is present (Table 127–4).

TABLE 127–4. Hemoglobin Oxygenation Analysis

Measuring Device	Source	What Is Measured	How Data Are Expressed	Benefits	Pitfalls	Insight
Blood gas analyzer	Blood	Partial pressure of dissolved oxygen in whole blood	PO ₂	Also gives information about pH and PCO ₂	Calculates SaO ₂ from the partial pressure of oxygen in blood; inaccurate if forms of Hb other than OxyHb and DeoxyHb are present	An abnormal Hb form may exist if gap exists between ABG and pulse oximeter
Cooximeter	Blood	Directly measures absorptive characteristics of oxyhemoglobin, deoxyhemoglobin, methemoglobin, and carboxyhemoglobin at different wavelength bands in whole blood	SaO ₂ , %MethHb, %CoHb, %OxyHb, %DeoxyHb	Directly measures hemoglobin species	Provides data on hemoglobin only; most instruments will not measure sulfhemoglobin, HbM, and some other forms of Hb	Most accurate method of determining the oxygen content of blood
Pulse oximeter	Monitor sensor on patient	Absorptive characteristics of oxyhemoglobin in pulsatile blood assuming the presence of only OxyHb and DeoxyHb in vivo	SpO ₂	Moment-to-moment bedside data	Inaccurate data if interfering substances are present (methemoglobin, sulfhemoglobin, carboxyhemoglobin, methylene blue)	Maximum depression, 75%–85% regardless of how much methemoglobin is present

ABG = arterial blood gas; Hb = hemoglobin; HbM = hemoglobin M; SaO₂ = hemoglobin oxygen saturation; SpO₂ = pulse oximeter oxygen saturation.

Several manufacturers have developed pulse oximeters that read multiple wavelengths to identify other hemoglobin species such as methemoglobin, carboxyhemoglobin, and total hemoglobin concentration.^{26,27,98,112} Validation studies using human volunteers with these new pulse oximeters suggest that the accuracy for detecting methemoglobin is acceptable.^{26,27} Volunteers breathing room air given sodium nitrite at 75% of the cyanide kit recommended dose developed methemoglobinemia that was detected by the multiwavelength device. There was spuriously low SpO₂ recorded.^{26,27} However, this may not be an issue if it alerts the clinician to a potential problem. Certainly, in a situation where xenobiotics known to produce methemoglobinemia are being used such as in the endoscopy or bronchoscopy suite to determine changes from baseline in methemoglobin.

Methemoglobin produces a color change that can be observed when a drop of blood is placed on absorbant white paper. In one study when various concentrations of methemoglobin from 10% to 100% were produced in vitro and a drop of each concentration placed on a white background a color chart was developed that could reliably be used to predict methemoglobin concentrations.⁹⁹ In situations where laboratory evaluation is limited this may be useful.

MANAGEMENT

For most patients with mild methemoglobinemia of approximately 10%, no therapy is necessary other than withdrawal of the offending xenobiotic because reduction of the methemoglobin will occur by normal reversion mechanisms (NADH methemoglobin reductase). However, in some patients, even small elevations of methemoglobin should be considered problematic because they suggest the individual is at a point where further oxidant stress may cause methemoglobin levels to increase. An individual receiving dapsone with a small elevation of methemoglobin level may be more susceptible to clinically significant methemoglobinemia if challenged with a benzocaine-containing anesthetic or an increase in dapsone dose. In the clinical setting, continued absorption, prolonged half-life, and toxic intermediate metabolites may prolong methemoglobinemia. Patients should be examined carefully for signs of physiologic stress related to decreased oxygen delivery to the tissue (Fig. 127–7). Obviously, changes in mental status or ischemic chest pain necessitate immediate treatment, but subtle changes in behavior or inattentiveness may be signs of global hypoxia and should be treated. Patients with abnormal vital signs tachycardia and tachypnea or an elevated lactate concentration thought to be caused by tissue hypoxia or the functional anemia of methemoglobinemia should be treated aggressively. A mildly elevated methemoglobin level alone generally is not an adequate indication of need for therapy but as levels reach 30% to 40% almost all patients should be treated.

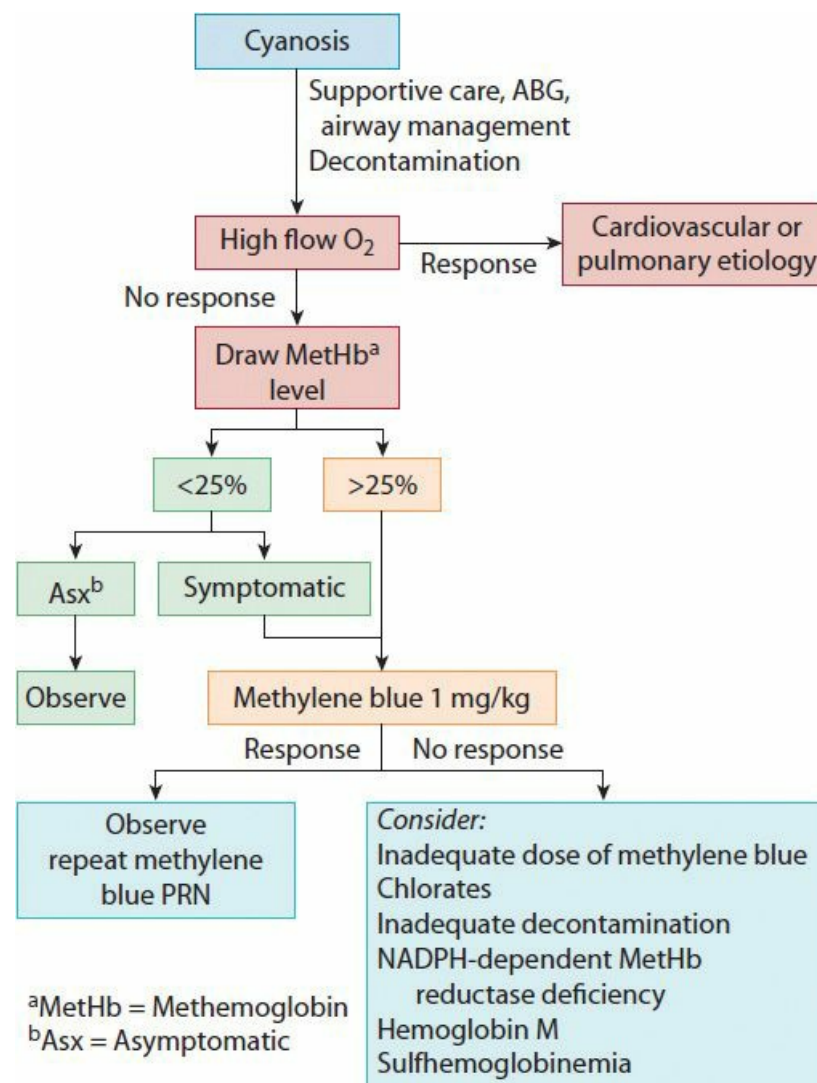


FIGURE 127–7. Toxicologic assessment of a cyanotic patient.

The most widely accepted treatment of methemoglobinemia is administration of 1 to 2 mg/kg body weight of methylene blue infused intravenously (IV) over 5 minutes. This is 0.1 to 0.2 mL/kg of 1% solution. The use of a slow 5-minute infusion helps prevent painful local responses from rapid infusion. A painful reaction can be minimized by flushing the IV rapidly with a bolus of at least 15 to 30 mL of fluid following the infusion. Clinical improvement should be noted within minutes of methylene blue administration. If cyanosis has not disappeared within one hour of the infusion, then a second

dose should be given and other factors considered (Fig. 127–7). Methylene blue causes a transient decrease in the pulse oximetry reading because its blue color has excellent absorbance at 660 nm.^{62,68}

The use of methylene blue in patients with G-6-PD deficiency is controversial. Deficiency of this enzyme is an estimated 200 million people worldwide. Its incidence in the United States is highest among African Americans (11%),¹⁰ among whom the disease has different degrees of severity. For this reason, G-6-PD–deficient patients were once excluded from most treatment protocols because methylene blue is a mild oxidant and case reports have suggested the toxicity of methylene blue. However, because of the lack of immediate availability of G-6-PD testing, most patients who need treatment receive methylene blue therapy before their G-6-PD status is known. Although many patients with G-6-PD deficiency undoubtedly have been treated unknowingly, few case reports of toxicity have been described.

Even the authors of the review most frequently cited as a rationale for withholding methylene blue treatment were unsure whether the methylene blue given to their G-6-PD–deficient patient produced hemolysis⁹⁴; the dose of methylene blue given to the patient was small, and the patient had taken other xenobiotics capable of producing hemolysis. Patients with G-6-PD deficiency have variable activity of the enzyme and manifest different degrees of disease in response to oxidant stress. For all of these reasons, the judicious use of methylene blue is warranted in most patients with G-6-PD deficiency and symptomatic methemoglobinemia.

If methylene blue treatment fails to significantly reverse methemoglobinemia, a number of possibilities should be considered. The cause of the oxidant stress may not have been identified and adequately removed, allowing for continuing oxidation. In such situations, decontamination of the gut and skin cleansing must be assured. Additional doses of methylene blue are also indicated. Patients who have sulfhemoglobinemia, or are deficient in NADPH methemoglobin reductase, may not improve after methylene blue therapy (Antidotes in Depth: A42).

Theoretically, exchange transfusion or hyperbaric oxygen (HBO) may be beneficial when methylene blue is ineffective. Both interventions are time consuming and costly, but HBO allows the dissolved oxygen time to protect the patient while endogenous methemoglobin reduction occurs. Ascorbic acid is not indicated in the management of acquired methemoglobinemia if methylene blue is unavailable because the rate at which ascorbic acid reduces methemoglobin is considerably slower than the rate of normal intrinsic mechanisms.¹⁴ Methylene blue has no therapeutic benefit in the presence of sulfhemoglobinemia.⁸⁶

Treatment with dapsone deserves special consideration because of its tendency to produce prolonged methemoglobinemia. N-hydroxylation of dapsone to its hydroxylamine metabolite by a cytochrome P450–mediated reaction is partly responsible for methemoglobin formation in both therapeutic and overdose situations. Both the parent compound and its metabolites are oxidants with long half-lives. Cimetidine is a competitive inhibitor in the cytochrome P450 metabolic pathway and reduces methemoglobin concentrations during therapeutic dosing because less dapsone will be metabolized by the route.⁹¹ In situations of overdose, cimetidine may exert some protective effects and should be used with methylene blue. When dapsone is therapeutically indicated but low levels of methemoglobin are found, cimetidine should be considered as a method for reducing oxidant stress.

SULFHEMOGLOBIN

Sulfhemoglobin is a variant of hemoglobin in which a sulfur atom is incorporated into the heme molecule but is not attached to iron. The exact location of the sulfur atom in the porphyrin ring is unclear. Sulfhemoglobin is a darker pigment than methemoglobin, producing cyanosis when only 0.5 g/dL of blood is affected. The cyanosis produced is similar to that produced by methemoglobinemia. Sulfhemoglobin also reduces the oxygen saturation determined by the pulse oximeter^{2,80} and is characterized in the laboratory by its spectrophotometric appearance and its lack of reaction when cyanide is added to the mixture. Cyanide does not react with sulfhemoglobin but does react with methemoglobin, forming cyanomethemoglobin, which has no adsorption at the spectrums tested. By contrast, the methemoglobin absorption peak will no longer be present after the addition of cyanide. Using conventional cooximetry, sulfhemoglobin is misidentified as methemoglobin. However, the addition of cyanide to the blood sample eliminates the methemoglobin peak (through conversion to cyanomethemoglobin) but not the methemoglobin peak caused by sulfhemoglobin. This technique is not routinely done in the clinical laboratory, and the diagnosis often is made based on the patient's failure to improve with methylene blue.^{2,64,70,80} In the laboratory, isoelectric focusing techniques further define sulfhemoglobin.

Sulfhemoglobin is an extremely stable compound that is eliminated only when red blood cells are removed naturally from circulation. Although the oxygen-carrying capacity of hemoglobin is reduced by sulfhemoglobinemia, unlike methemoglobinemia there is a decreased affinity for oxygen in the remaining “unaltered” hemoglobin. The oxyhemoglobin dissociation curve is shifted to the right. This makes oxygen more available to the tissues. This phenomenon reduces the clinical effect of sulfhemoglobin in the tissues.

Sulfhemoglobin can be produced experimentally in vitro by the action of hydrogen sulfide on hemoglobin and was produced in dogs fed elemental sulfur.⁸⁶ A number of xenobiotics induce sulfhemoglobin in humans, including acetanilid, phenacetin, nitrates, trinitrotoluene, and sulfur compounds. Most of the xenobiotics that produce methemoglobinemia are

reported in various degrees to produce sulfhemoglobinemia. Sulfhemoglobinemia is also recognized in individuals with chronic constipation and in those who abuse laxatives.⁸⁶

Sulfhemoglobinemia usually requires no therapy other than withdrawal of the offending xenobiotic. It appears that patients come to the attention of clinicians earlier because sulfhemoglobinemia produces more cyanosis than does methemoglobinemia. There is no antidote for sulfhemoglobinemia because it results from an irreversible chemical bond that occurs within the hemoglobin molecule. Exchange transfusion would lower the sulfhemoglobin concentration, but this approach usually is unnecessary.

SUMMARY

- Methemoglobinemia is defined as an abnormal level of methemoglobin above 1%.
- Methemoglobinemia is clinically identified by cyanosis without cardiovascular causes, a normal PO₂ on blood gas analysis, chocolate colored blood, and elevated methemoglobin level on cooximetry.
- Symptoms are usually milder than the appearance of the cyanosis would suggest and can be as minimal as mild fatigue and exertional dyspnea to seizures and central nervous system depression depending on degree and coexisting disease.
- Indications for methylene blue therapy include symptoms of cardiovascular or respiratory distress, any central nervous system symptoms or findings, and metabolic acidosis. Patients with levels above 30% methemoglobin should be considered as candidates for therapy.
- Patients with low methemoglobin levels should be considered to be under oxidant stress and at risk for more serious methemoglobinemia if oxidant stressors persist or increase in their environment.
- Methemoglobinemia should be considered to be a disease state sometimes caused by an acute, overwhelming oxidant protective mechanism of the host by an oxidant or more commonly and, importantly, as a final clinical manifestation of multiple oxidant stressors.
- Multiwavelength pulse oximeters are becoming more accurate and should be used routinely to monitor patients undergoing procedures where oxidants, such as benzocaine and lidocaine, are being used.

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A42 ANTIDOTES IN DEPTH

Methylene Blue

Mary Ann Howland

INTRODUCTION

Methylene blue is an extremely effective antidote for acquired methemoglobinemia. Methylene blue has other actions, including the inhibition of nitric oxide synthase and guanylyl cyclase, and the inhibition of the generation of oxygen free radicals. These actions may explain the beneficial effects of methylene blue in the treatment of refractory hypotension, hepatopulmonary syndrome, treatment of priapism, modulation of streptozocin-induced insulin deficiency, prevention and treatment of ifosfamide-induced encephalopathy, in the treatment of sepsis, and the reduction of the development of postsurgical peritoneal adhesions.^{15,16,21,25,34,44,52,59}

HISTORY

Methylene blue was initially recommended as an intestinal and urinary antiseptic and subsequently recognized as a weak antimalarial.²⁰ In 1933, Williams and Challis successfully used methylene blue for treatment of aniline-induced methemoglobinemia.⁶⁴

PHARMACOLOGY

Chemistry

Methylene blue is tetramethylthionine chloride,²⁰ a basic thiazine dye with a molecular weight of 319 Da. It is deep blue in the oxidized state and colorless when reduced to leucomethylene blue.

Mechanisms of Action

Methylene blue is an oxidizing agent, which, in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and NADPH methemoglobin reductase, is reduced to leucomethylene blue (Fig. 127–4). Leucomethylene blue then becomes available to reduce methemoglobin to hemoglobin.^{9,20,60} Reduction of methemoglobin via this NADPH pathway is limited under normal circumstances. However, in the presence of methylene blue, the role of the NADPH pathway is dramatically increased and becomes the most efficient means of methemoglobin reduction.

Recently, attention has focused on the ability of methylene blue to reverse refractory hypotension due to many causes including drug overdose, vasoplegia, and sepsis. Methylene blue inhibits nitric oxide synthase and guanylyl cyclase in vascular smooth muscle. This reduces the amount and effect of nitric oxide. Systemic vascular resistance and cardiac output increase, and the sensitivity of adrenergic receptors to sympathomimetics is enhanced.^{12,14,36,27,38,63}

Pharmacokinetics

The pharmacokinetics of methylene blue were studied in animals and human volunteers following intravenous (IV) and oral administration of 100 mg.^{9–11,45} Methylene blue exhibits complex pharmacokinetics consistent with extensive distribution into deep compartments, followed by a slower terminal elimination, with a half-life of 5.25 hours. Peak concentrations after oral administration were reached in 1 to 2 hours, but were only approximately 80 to 90 nmol/L, as opposed to 8000 to 9000 nmol/L following IV administration. The substantial differences in whole blood concentrations achieved by these routes of administration can be attributed to extensive first-pass organ distribution into the intestinal wall and liver, following oral administration.³⁵ Total urinary excretion at 24 hours accounts for 28.6% of the drug following IV administration, compared with 18.5% after oral administration. In both instances, one third was in the leucomethylene blue form.

Pharmacodynamics

The onset of action of methylene blue for the reversal of methemoglobin is often within minutes. Maximum effects usually occur by 30 minutes.²³

ROLE IN XENOBIOTIC-INDUCED METHEMOGLOBINEMIA

Methylene blue is indicated in patients with symptomatic methemoglobinemia. This usually occurs at methemoglobin levels greater than 20%, but may occur at lower levels in anemic patients or those with cardiovascular, pulmonary, or central nervous system compromise.

Historically, sulfanilamide induced methemoglobinemia was reversed by methylene blue in IV doses of 1 to 2 mg/kg or oral doses of 65 to 130 mg, given every 4 hours.^{22,61} With these regimens, a very rapid fall in methemoglobin was accompanied by disappearance of cyanosis. Subsequent investigations confirmed the effectiveness and safety of IV doses of 1 to 2 mg/kg in reversing the methemoglobinemia produced by sulfanilamide,⁶¹ aniline dye,¹³ silver nitrate, benzocaine, nitrites, phenazopyridine, and other xenobiotics.^{55,58}

The risk-to-benefit ratio of using methylene blue in a patient for methemoglobinemia must always be weighed as with any other drug. In this case, the benefit of using methylene blue for a patient with significant methemoglobinemia will almost always outweigh the risk of possibly precipitating serotonin toxicity in a patient taking an SSRI (refer to Adverse Events).

Methylene blue is ineffective in the treatment of sulfhemoglobinemia ([Chap. 127](#)).

ROLE IN HYPOTENSION

Hypotension refractory to vasopressors occurs in the setting of sepsis, vasoplegia, and drug ingestion. Methylene blue has successfully reversed the low systemic vascular resistance in a few case studies and case reports.^{12,14,27,28,32,35,36,38,47,63}

ADVERSE EFFECTS AND SAFETY ISSUES

Reports of the paradoxical induction of methemoglobinemia by methylene blue suggest an equilibrium between the direct oxidization of hemoglobin to methemoglobin by methylene blue and its ability (through the NADPH and NADPH methemoglobin reductase pathway, and leukomethylene blue production) to reduce methemoglobin to hemoglobin.^{4,5} Methylene blue does not produce methemoglobin at doses of 1 to 2 mg/kg. The equilibrium seems to favor the reducing properties of methylene blue, unless excessively large doses of methylene blue are administered,^{3,19,62} or the NADPH methemoglobin reductase system is abnormal. This equilibrium constant may vary substantially, as 20 mg/kg IV in dogs and 65 mg/kg intraperitoneally in rats failed to produce methemoglobinemia.⁵⁴ In early studies, 50 to 100 mL of a 1% concentration (500–1000 mg) of methylene blue was used intravenously in volunteers³⁹ as well as in the treatment of patients with aniline dye induced methemoglobinemia.⁶⁴ In these studies, methemoglobin levels, measured when symptoms were most pronounced, were approximately 1.0 g/dL (0.4%–8.3% of total hemoglobin), and unlikely to be solely responsible for the adverse effects demonstrated. Other consequential adverse effects included shortness of breath, tachypnea, chest discomfort, a burning sensation of the mouth and stomach, initial bluish tinged skin and mucous membranes, paresthesias, restlessness, apprehension, tremors, nausea and vomiting, dysuria, and excitation. Urine and vomitus may appear blue in color. These limited studies led to the recommendation to avoid doses higher than 7 mg/kg.

In high doses, methylene blue can induce acute hemolytic anemia independent of the presence of methemoglobinemia.^{19,33} In dose–response studies in glucose-6-phosphate dehydrogenase (G6PD) deficient homozygous African American men, daily doses of 390 to 780 mg (5.5–11 mg/kg) of methylene blue produced hemolysis,³¹ which was comparable with the results following exposure to 15 mg of primaquine base.³¹ Because of the sensitivity of neonates (hemoglobin F and diminished NADH reductase) to these risks, the smallest effective dose of methylene blue should be used.^{24,30} Because any oxidizing agent can independently induce a Heinz body hemolytic anemia, the specific contribution of methylene blue often is difficult to elucidate.³⁰

Since methylene blue is a dye it will alter pulse oximeter readings.⁷ Large doses may interfere with the ability to detect a clinical decrease in cyanosis; therefore, repeat cooximeter measurements and arterial blood gas analysis should be used in conjunction with clinical findings to evaluate improvement.

Intraamniotic injection of methylene blue may result in a number of adverse effects, including infants born with blue skin (with resultant inaccurate pulse oximetry readings),⁴³ methemoglobinemia, hemolysis, phototoxic skin reactions,⁴⁶ or intestinal obstruction.^{7,8,29,33,37,42,49,57} One infant exposed in utero at 5.5 weeks was normal at birth.²⁹ An excessive dose of enterally administered methylene blue that subsequently leaked into the peritoneum of a premature neonate most likely was

responsible for a hemolytic anemia appearing 3 days later.¹

Methylene blue leads to a bluish-green discoloration of the urine, and can potentially cause dysuria.⁴⁸ IV methylene blue is irritating and exceedingly painful. It may cause local tissue damage even in the absence of extravasation.⁴⁹ Subcutaneous and intrathecal administrations are contraindicated.⁴⁹

Two recent reviews reveal an association between an encephalopathy and the use of methylene blue for localization of parathyroid tumors in women on serotonin reuptake inhibitors.^{41,56} Five out of 132 patients in the first review developed one or more of the following: confusion, expressive aphasia, lethargy, and vertigo, which lasted from 2 to 3 days. The second review detailed seven patients with signs and symptoms consistent with serotonin toxicity. It should be noted that these patients usually received 3 to 5 mg/kg of methylene blue as a continuous infusion over 1 hour. A subsequent in vitro study documented the ability of methylene blue to competitively bind to monoamine oxidase A, raising the possibility that methylene blue might interact with serotonergic xenobiotics by acting as a monoamine oxidase inhibitor.⁵⁰ Two recent reviews also conclude that methylene blue has the potential to interact with drugs that elevate serotonin to cause serotonin excess and toxicity.^{18,40}

High doses of methylene blue (7 mg/kg) have the potential to decrease splanchnic blood flow in the setting of septic shock.²⁸

One author suggests that methylene blue directly inactivates lactic acid giving a potentially false impression of improved perfusion.¹⁴ However, this finding needs to be confirmed.

Use in Patients with Glucose-6-Phosphate Dehydrogenase Deficiency

Methylene blue is frequently hypothesized to be ineffective in reversing methemoglobinemia in patients with G6PD deficiency⁴¹ because G6PD is essential for generation of NADPH (Chap. 23). Without NADPH, methylene blue cannot reduce methemoglobin. However, G6PD deficiency is an X-linked hereditary deficiency with more than 400 variants. The red cells containing the more common G6PD A⁻ variant found in 11% of African Americans retain 10% residual activity, mostly in younger erythrocytes and reticulocytes. By contrast, the enzyme is barely detectable in those of Mediterranean descent who have inherited the defect. Therefore, it is impossible to predict before the use of methylene blue which persons will or will not respond, and to what extent. Currently, it appears that most individuals have adequate G6PD and express deficiency states in relative terms. This variable expression of their deficiency allows an effective response to most oxidant stresses. In addition, in theory, normal cells might convert methylene blue to leukomethylene blue, which might diffuse into G6PD deficient cells and effectively reduce methemoglobin to hemoglobin.²

Before assuming that G6PD deficiency is responsible for a continued elevation of methemoglobin levels despite administration of methylene blue, ongoing xenobiotic absorption and or continued methemoglobin production must be excluded. On the other hand, when therapeutic doses of methylene blue fail to have an impact on the methemoglobin concentration, the possibility of G6PD deficiency should be considered, and further doses of methylene blue should not be administered because of the risk of methylene blue induced hemolysis. In these cases, exchange transfusion and hyperbaric oxygen are potential alternatives for treating methemoglobinemia (Chap. 127).

PREGNANCY AND LACTATION

Methylene blue is a category X drug in pregnancy. IV methylene blue has led to fetal abnormalities, including atresia of the ileum and jejunum, ileal occlusions, hemolytic anemia, hyperbilirubinemia, and methemoglobinemia when used via intraamniotic injection. Human data suggest developmental toxicity when used in the second and third trimesters.⁶

There are no data available on lactation, but it is not likely to present a danger to the nursing infant.⁶

DOSING AND ADMINISTRATION

In most cases, a dose of 1 to 2 mg/kg given IV over 5 minutes, followed immediately by a fluid flush of 15 to 30 mL to minimize local pain, is both effective and relatively safe. In neonates, 0.3 to 1 mg/kg doses often are effective.^{17,26} The onset of action is rapid, and maximal effects usually occur within 30 minutes.

Repetitive dosing of methylene blue may be required in conjunction with efforts to decontaminate the gastrointestinal tract when there is continued absorption or slow elimination of the xenobiotic producing the methemoglobinemia, such as with dapsone.

Intraosseous administration of 0.3 mL of 1% solution (1 mg/kg) of methylene blue over 3 to 5 minutes into the anterior tibia of a 6 week-old infant was well tolerated.^{24,43} The dose of methylene blue for refractory hypotension is not established. Doses of 1 to 3 mg/kg increase systemic vascular resistance and mean arterial pressure and improve tissue oxygenation.²⁴ Although doses of 7 mg/kg may produce further increases in mean arterial pressure, this result is at the

expense of decreasing splanchnic blood flow.²⁸

FORMULATION AND ACQUISITION

Methylene blue is available in 10 mL vials of a 1% solution for injection, containing 10 mg/mL.

SUMMARY

- Methylene blue is an effective reducing agent for patients with acquired methemoglobinemia.
- When used in the proper dose, the onset of action for methylene blue is rapid and its adverse reactions are limited.
- Repeat doses often are required when methemoglobin-producing drugs with a long duration of effect, such as dapsone, are ingested.

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128 SMOKE INHALATION

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HISTORY AND EPIDEMIOLOGY

Smoke is generated as the result of thermal degradation of a material; it is a complex mixture of heated air, suspended solid and liquid particles (aerosols), gases, fumes, and vapors. Particulates and aerosols typically make these thermal degradation products visible to the naked eye, resulting in the black, acrid substance so often thought of as “smoke”; however, thermal decomposition also results in generation of gaseous substances that are invisible to the naked eye. The ever-growing variety of materials used in our environment contributes to the broad spectrum of products present in typical smoke.²⁶ The chemical composition of the parent materials, oxygen availability, and temperature at the time of decomposition determines the combustion products found in smoke (Table 128–1).^{99,112} As a result of these variabilities, specific thermal degradation products resulting from a fire are difficult to predict; in fact, even the composition of smoke is quite variable within the same fire environment.¹¹²

TABLE 128–1. Common Materials and Their Thermal Degradation Products

<i>Products</i>	<i>Thermal Degradation Products</i>
Wool	Ammonia, carbon monoxide, chlorine, cyanide, hydrogen chloride, phosgene
Silk	Ammonia, cyanide, hydrogen sulfide, sulfur dioxide
Nylon	Ammonia, cyanide
Wood, cotton, paper	Acetaldehyde, acetic acid, acrolein, carbon monoxide, formic acid, formaldehyde, methane
Petroleum products	Acetic acid, acrolein, carbon monoxide, formic acid
Polystyrene	Styrene
Acrylic	Acrolein, carbon monoxide, hydrogen chloride
Plastics	Aldehydes, ammonia, chlorine, cyanide, hydrogen chloride, nitrogen oxides, phosgene,
Polyvinyl chloride	Carbon monoxide, chlorine, hydrogen chloride, phosgene
Polyurethane	Cyanide, isocyanates
Melamine resins	Ammonia, cyanide
Rubber	Hydrogen sulfide, sulfur dioxide
Sulfur containing material	Sulfur dioxide
Nitrogen containing material	Cyanide, isocyanates, oxides of nitrogen
Fluorinated resins	Hydrogen fluoride
Fire retardant materials	Hydrogen bromide, hydrogen chloride

Smoke inhalation is a complex medical syndrome involving diverse toxicologic injuries, making care of smoke-injured patients very challenging. In fact, smoke inhalation—not burns—is the leading cause of death from fires. However, cutaneous burns found concurrently with smoke inhalation complicate airway management and fluid resuscitation, and

increase the risk of infection. Consequently, burn victims with smoke inhalation injury have higher morbidity and mortality than those with burns alone.^{36,138}

Disastrous fires are a frequent reminder of the role of inhalation injury in fire deaths. Throughout the United States, a fire department responds to a fire every 23 seconds.⁶⁷ In 2011, the National Fire Protection Agency reported 1,389,500 fire incidents in the United States, with 3005 fire deaths and 17,500 fire injuries.⁶⁷ On average, a civilian fire death occurred every 208 minutes and a civilian injury from a structural fire occurs every 30 minutes.

Compared with other industrialized countries, the United States has one of the highest rates of fire-related deaths in the world.⁴ An estimated 50% to 80% of these deaths result from smoke inhalation rather than dermal burns or trauma.^{13,58,99,158} More than 30% of patients hospitalized in burn units develop complications of concomitant pulmonary injury, and 75% of these patients die.^{61,139} Data from the World Health Organization demonstrate that indoor smoke from heating and cooking fuel is one of the four most common causes of death and disease in developing countries, resulting in an estimated 3.5 million deaths worldwide in 2010.^{12,79}

Fire injuries may result from an array of inhaled toxic xenobiotics and/or thermal burns. Before 1942, toxic inhalation was not considered in the etiology of morbidity and mortality of structural fire victims. However, in that year, a fire at the Coconut Grove Night Club in Boston resulted in a number of fatalities in which victims had no cutaneous burns. This led to the observation that toxic gases are generated in typical structure fires and may result in significant pathology.¹¹¹ From 1955 to 1972, death from smoke inhalation injury increased threefold and was attributed to abundant use of newer synthetic materials for building and furnishings.¹³ Despite improved firefighting resources, mass casualties from smoke inhalation continue. A fire in a crowded Rhode Island nightclub on February 20, 2003, killed 100 people and injured more than 200 people, with the majority suffering from smoke inhalation.³² On December 31, 2004, a fire at a nightclub in Argentina killed 175 people and injured more than 700. Most of the victims died of smoke inhalation.³ On November 24, 2012, a fire swept through the lower floors of a Bangladesh garment factory, killing 112 and trapping many others on the top floors until rescuers arrived. Hundreds of those trapped above the blaze sustained inhalation injuries.¹⁴⁷ More recently, at least 230 people died in a nightclub fire in Brazil when a fire ignited above the concert stage. Smoke inhalation resulted in many of the deaths and forced many others to seek medical treatment.¹³² In 2010, a total of 29 catastrophic fires claimed 175 lives in the United States.⁴ Interestingly, in 2011, explosions caused an unusually high number of catastrophic fires in the United States.⁴ These statistics highlight the complexity of fire victims with the potential for victims to have any combination of inhalation injury, burns, and trauma.

PATHOPHYSIOLOGY

Toxic combustion products are classified into three categories: simple asphyxiants, irritant toxins, and chemical asphyxiants (Table 128–2). Simple asphyxiants, such as carbon dioxide, exert their toxicity by displacing oxygen, resulting in an oxygen-deprived environment.⁴⁶ To further complicate this issue, combustion consumes oxygen, further reducing the available oxygen in the environment (Chap. 124).⁴⁶

TABLE 128–2. Toxic Thermal Degradation Products

<i>Asphyxiants</i>	<i>Irritants</i>
Simple	High water solubility (upper airway injury)
Carbon dioxide	Ammonia
Chemical	Hydrogen chloride
Carbon monoxide	Sulfur dioxide
Hydrogen cyanide	Intermediate water solubility
Hydrogen sulfide	(upper and lower respiratory tract injury)
Oxides of nitrogen (methemoglobinemia)	Chlorine
	Isocyanates
	Low water solubility
	(pulmonary parenchymal injury)
	Oxides of nitrogen
	Phosgene

Irritant gases are chemically reactive compounds that exert a local effect on the respiratory tract, primarily through the production of acids, alkalis, or reactive oxygen species (ROS; Chap. 124). Ammonia is generated when wool, silk, nylon,

or synthetic resins are burned. It reacts with mucosal moisture to produce ammonium hydroxide.⁷⁸ Sulfur dioxide, an oxidation product of sulfur-containing material, is found in more than 50% of air samples from fires.²¹ Sulfurous acid forms when sulfur dioxide reacts with the water of the respiratory mucosa. Hydrogen chloride, chlorine, and phosgene are formed from the thermal degradation of polyvinyl chloride, a plastic widely used in home and office furnishings, floor coverings, and electrical insulation.^{14,15} In the presence of mucosal water, these combustion products generate hydrogen chloride and ROS.³⁴ Phosgene, which is also formed, typically reacts slowly, producing delayed alveolar injury.¹⁶ Isocyanates, generated from combustion of foam furniture padding, cause intense irritation of the upper and lower respiratory tracts.¹¹⁷ High concentrations of the irritant acrolein are measured in air samples from fire environments and in the blood of fire victims.¹⁴⁵ Acrolein penetrates cell membranes easily because it is lipid soluble and injures cells by denaturing cellular proteins.⁴⁷

Thermal degradation of organic material produces finely divided carbonaceous particulate matter (soot) suspended in hot air and gases. These particles are not just composed of carbon; organic acids, aldehydes, heavy metals, and reactive chemicals such as sulfur dioxide, hydrogen chloride, chlorine, and phosgene are adsorbed to their surface.^{72,121} Soot adheres to the mucosa of the airways, allowing adsorbed irritant xenobiotics to react with the mucosal surface moisture and often enhancing and prolonging exposure to irritants in a fire environment. The deposition of these particles in the respiratory tract depends on their size, with particles of 1 to 3 μm reaching the alveoli.⁹² Irritant gases can also “piggyback” on aerosol droplets and alter the site of gas deposition.⁵⁹ Experimental animals demonstrate markedly decreased lung injury when exposed to toxic gases from smoke that was filtered to remove particulates.⁷²

For irritant gases, the degree of water solubility is the most important chemical characteristic in determining the timing and anatomic location of respiratory tract injury. Highly water-soluble xenobiotics primarily injure the upper airway by rapidly combining with mucosal water, leaving little of the parent compound to travel further down the airway. These xenobiotics quickly damage mucosal cells, which subsequently release mediators of inflammation or ROS.^{19,80,94,121} This produces early irritation, providing a warning that the environment is unsafe and prompting escape. After more than a trivial exposure, the intense inflammatory response increases microvascular permeability and allows movement of fluid from the intravascular space into the tissues of the upper airway.⁹ The loosely attached underlying tissue of the supraglottic larynx may become markedly edematous, causing upper airway obstruction within minutes to hours.⁶⁵ The obstruction may progress to the point of complete upper airway occlusion.¹²⁸ Xenobiotics with low water solubility react with the upper respiratory mucosa more slowly and do not elicit the irritation or aversion stimulus that prompts an escape response. These xenobiotics more typically reach the distal lung parenchyma, where they react slowly to create delayed toxic effects. Xenobiotics with intermediate water solubility, such as chlorine, are more likely to result in damage to both the upper and lower respiratory tracts. Other factors, such as concentration of the inhaled xenobiotic, duration of exposure, particle size, respiratory rate, absence of protective reflexes, and preexisting disease influence the region of respiratory tract injury. For example, as the concentration of a highly water-soluble irritant gas increases more chemical is presented to the lower airway, possibly leading to damage of the lower respiratory tract. In addition, patients with loss of consciousness may increase their exposure secondary to their loss of protective reflexes.

Damage to the tracheobronchial tree is mediated by many of the same mechanisms as those of the pharynx and hypopharynx: inhaled particulates and toxic gases result in deposition of corrosives and oxidants. Direct thermal injury is less likely to occur as a result of the efficient cooling ability of the upper airways.⁹⁴ Direct injury to the tracheobronchial tree and an intense inflammatory response, evoked in part by airway nociceptive sensory neurons, leads to an increase in airway resistance from mucosal edema, bronchoconstriction, and accumulation of intraluminal debris and airway secretions.^{9,68,84,142} Increased tracheobronchial vascular permeability contributes to interstitial edema of the airways and increased airway resistance. Bronchoconstriction and subsequent wheezing are caused by a reflex response to toxic mucosal injury and a response to mediators of inflammation.^{55,143} Damaged cells release chemotactic factors that stimulate production of an exudate rich in protein, including fibrin and inflammatory cells.^{39,149} This injury eventually results in sloughing of the mucosa, which combines with inflammatory cells and exudate to create casts in the airways.³⁹ Casts can block both the small and large airways, increasing airway resistance and mechanically preventing passage of oxygen to the alveoli.³⁰

Irritant xenobiotics that reach the alveoli injure the lung parenchyma.¹⁰³ Corrosives, proteolytic enzymes, reactive free radicals, and mediators of inflammation all contribute to acute respiratory distress syndrome (ARDS).^{74,116,143,156} Pathophysiologic changes of ARDS decrease lung compliance, bacterial defenses, and lead to ventilation-perfusion mismatch with intrapulmonary shunting, increased extravascular lung water, and microvascular permeability.^{25,143,149,152} Lung compliance is further decreased by atelectasis when xenobiotics inactivate pulmonary surfactant.^{103,113} In animal studies, patchy atelectasis rapidly occurs after smoke inhalation.¹⁰³ In addition, ventilation-perfusion mismatch occurs when pulmonary blood flow is diverted by hypoxia and vasoactive mediators of inflammation.^{82,104} Xenobiotics cause additional injury by impairing mucociliary clearance, altering alveolar macrophage function, and impairing phagocytosis of bacteria, all of which predispose to pulmonary infections and sepsis.^{10,43,60,127} The combination of the delayed toxic effects

of some inhaled xenobiotics and the slowly developing inflammatory response may explain the limited initial manifestations of parenchymal injury during the first 24 hours after smoke exposure.

Nitric oxide plays a significant role in the pathogenesis of smoke inhalation induced lung injury.^{41,89,150} Combined smoke inhalation and burn injury results in an upregulation of inducible nitric oxide synthase (iNOS) mRNA synthesis in animal models and subsequently results in increased activity of iNOS.^{40,42,89,136} Increased concentrations of nitric oxide may result in myocardial contractile dysfunction with subsequent hypotension.¹³⁶ It also increases vascular permeability with resultant edema.⁸⁹ One possible mechanism is the formation of the highly reactive peroxynitrite (ONOO⁻) radical from the combination of nitric oxide and ROS, which may lead to alveolar capillary membrane damage and subsequent ARDS.^{40,89} Inhibition of iNOS reduced lung injury in combined smoke inhalation and burn injury in an ovine model.⁴¹

Chemical asphyxiants exert their toxic effects at extrapulmonary sites. Incomplete combustion of organic materials generates carbon monoxide, which is considered the most common serious acute hazard to victims of smoke inhalation injury ([Chap. 125](#)).^{1,145} Carbon monoxide (CO) prevents oxygen from binding to hemoglobin, creating a functional anemia. It also hinders the release of oxygen at the tissues, shifting the oxyhemoglobin dissociation curve to the left. In addition, CO binds myoglobin in cardiac and skeletal muscle and cytochrome oxidase in all tissues.^{23,66} The combination of these features impairs oxygen utilization by the myocardium and contributes to myocardial dysfunction. Other mechanisms of toxicity include induction of oxidative stress and lipid peroxidation ([Chap. 125](#)).¹⁴⁰

Cyanide is produced from combustion of organic nitrogen-containing products such as plastics, melamine resins, polyurethanes, wool, silk, nylon, nitrocellulose, polyacrylonitriles, synthetic nitrile rubber, and paper.¹¹² Many common building materials such as insulations and laminates are comprised of these cyanide-producing substances. High concentrations of cyanide are measured in air samples from fires, and elevated blood cyanide concentrations occur in both survivors as well as those who die in fires.⁴⁵ Cyanide has at least an additive, if not synergistic, effect with carbon monoxide in smoke inhalation toxicity ([Chaps. 125 and 126](#)).^{91,106,120} Combustion of nitrogen-containing materials also generates oxides of nitrogen, which are irritants and can induce the formation of methemoglobin ([Chap. 127](#)).

Depending on the fuel, other combustion products are aerosolized and act by local irritation or systemic toxicity. Metal oxides, hydrocarbons, hydrogen fluoride, and hydrogen bromide may contribute to toxicity. In addition, antimony, bromine, cadmium, chromium, cobalt, gold, iron, lead, and zinc often are recovered from air samples taken during fires and from soot removed from the surface of the trachea and bronchi of fire victims.^{11,33} Fires at industrial sites, clandestine drug laboratories, transportation incidents, and natural disasters, such as erupting volcanoes, produce additional unique toxic inhalants.

CLINICAL MANIFESTATIONS

The primary clinical problem in smoke inhalation victims is respiratory compromise; therefore, clinical evaluation should specifically address this issue. Patients may complain of mucous membrane, ocular, and pharyngeal irritation. Changes in voice may occur and speech may progressively worsen as the airway becomes increasingly edematous. Cough, chest tightness, and complaints of dyspnea are common. The patient may develop stridor and acute respiratory arrest. Patients may have difficulty managing their airway secretions, with expectoration of copious quantities of soot containing sputum.

On examination the patient may have burns to the face or singed hairs of the head, face, or nasal passages. The oropharynx and nares may be erythematous, coated with soot, or have progressive edema. Visualization of the vocal cords by laryngoscopy is sometimes difficult secondary to soot accumulation, secretions, or edema. Conjunctival injection, corneal ulcerations, marked lacrimation, and blepharospasm may be noted on ophthalmic examination.

Auscultation of the chest may reveal rhonchi, crackles, and wheezing suggestive of ARDS.⁵³ Bronchospasm may occur, particularly in patients with underlying reactive airway disease. Breath sounds, including wheezing, may become virtually inaudible in patients with severe bronchospasm. ARDS is a common complication and is defined as acute onset diffuse alveolar filling with hypoxemia not otherwise explained by congestive heart failure or fluid overload.¹⁴⁸ ARDS is classified as mild, moderate, or severe based on the degree of impairment as determined by the PO₂ to FiO₂ ratio ([Chap. 29](#)).¹⁴⁸

Tachycardia and tachypnea may be pronounced. Hypotension may occur, with faint or absent peripheral pulses.¹³⁶ Victims may develop altered mental status, including agitation, confusion, or coma. This is most often attributable to hypoxia from either pulmonary compromise or cellular hypoxia, but the altered consciousness may also be due to trauma, drug, or alcohol intoxication, or a combination thereof.

DIAGNOSTIC TESTING

Diagnostic studies should focus on assessing for airway and pulmonary injury as well as the ability of the patient to oxygenate and ventilate. An arterial blood gas (ABG) analysis with cooximetry and chest radiography (CXR) should be

obtained initially in all patients with smoke inhalation. Health care professionals should consider obtaining a rapid lactate concentration in all seriously ill patients to aid in evaluation of possible cyanide toxicity.

ABG analysis assesses both pulmonary function (gas exchange) and blood pH. The presence of metabolic acidosis may be an early clue to tissue hypoxia or cyanide poisoning. Serial measurements of arterial oxygenation and ventilation are helpful in identifying progressive hypoxemia or ventilatory failure. The accuracy of oxygen saturation measurement depends on the method used. Measurement of oxygen saturation by transcutaneous pulse oximetry is unreliable in patients with smoke inhalation because it overestimates oxygen saturation in the presence of carboxyhemoglobin.^{6,18,146} Similarly, oxygen saturation calculated from standard ABG analysis may be unreliable in the setting of an elevated blood carbon monoxide concentration. In the setting of smoke inhalation, oxygen saturation is most accurately determined by cooximetry which will directly measure oxygenated and deoxygenated hemoglobin.

Cooximetry also measures carboxyhemoglobin and methemoglobin concentrations and should be obtained for all victims of smoke inhalation.^{24,157} When using blood sampling, either arterial or venous samples can accurately measure carboxyhemoglobin concentrations.⁸³ Noninvasive bedside pulse cooximetry is a rapid and acceptably sensitive screening tool for the detection of carbon monoxide; its use is becoming more prevalent in clinical practice¹³⁰ (Chap. 29). Unfortunately, the carboxyhemoglobin concentration alone is a poor predictor of the severity of smoke inhalation because a low or nondetectable concentration does not exclude the possibility of developing inhalation injury.^{87,137} Rarely methemoglobin levels are elevated in fire victims. Because methemoglobin can further reduce oxygen-carrying capacity and contribute to morbidity, methemoglobin levels should also be included in the initial laboratory evaluation.^{62,133}

Blood cyanide analysis is of little clinical utility because results of analysis are not typically available for hours or days, and therapy should never await laboratory confirmation of the presence of cyanide. Accurate measurement depends on acquiring the sample soon after exposure as cyanide is rapidly eliminated from the blood.^{8,70} Blood pH and lactate are more useful tools in acutely assessing for cyanide exposure. A plasma lactate concentration greater than 10 $\mu\text{mol/L}$ in the setting of smoke inhalation suggests cyanide poisoning and supports empiric antidotal treatment of critically ill patients, particularly in the absence of an elevated carboxyhemoglobin level or shock.⁸

CXR should be obtained early in the assessment of a patient with smoke inhalation but is an insensitive indicator of pulmonary injury.^{118,153} In one series of patients admitted to the intensive care unit (ICU) with smoke inhalation, no significant differences in the duration of either ventilation or duration in the ICU stay were observed between those who exhibited abnormal findings on the first CXR examination and those without abnormalities.⁵³ The most frequent abnormal findings on initial CXR are diffuse alveolar and interstitial changes, found in up to 34% of patients.⁵³ Serial CXR after a baseline study are generally more helpful in detecting evolving pulmonary injury after smoke inhalation (Fig. 128–1).⁵⁵ Subtle findings within 24 hours of exposure include perivascular haziness, peribronchial cuffing, bronchial wall thickening, and subglottic edema.^{75,139} Widespread airway disease usually occurs more than 24 hours after inhalation injury and may represent ARDS, aspiration, infection, or volume overload.¹³⁹ Computed tomography (CT) of the lungs appears to be a more sensitive modality than plain radiography for detecting early pulmonary injury after smoke inhalation.^{71,115,125} However, no data are currently available to support improved patient outcomes when using this radiographic modality.

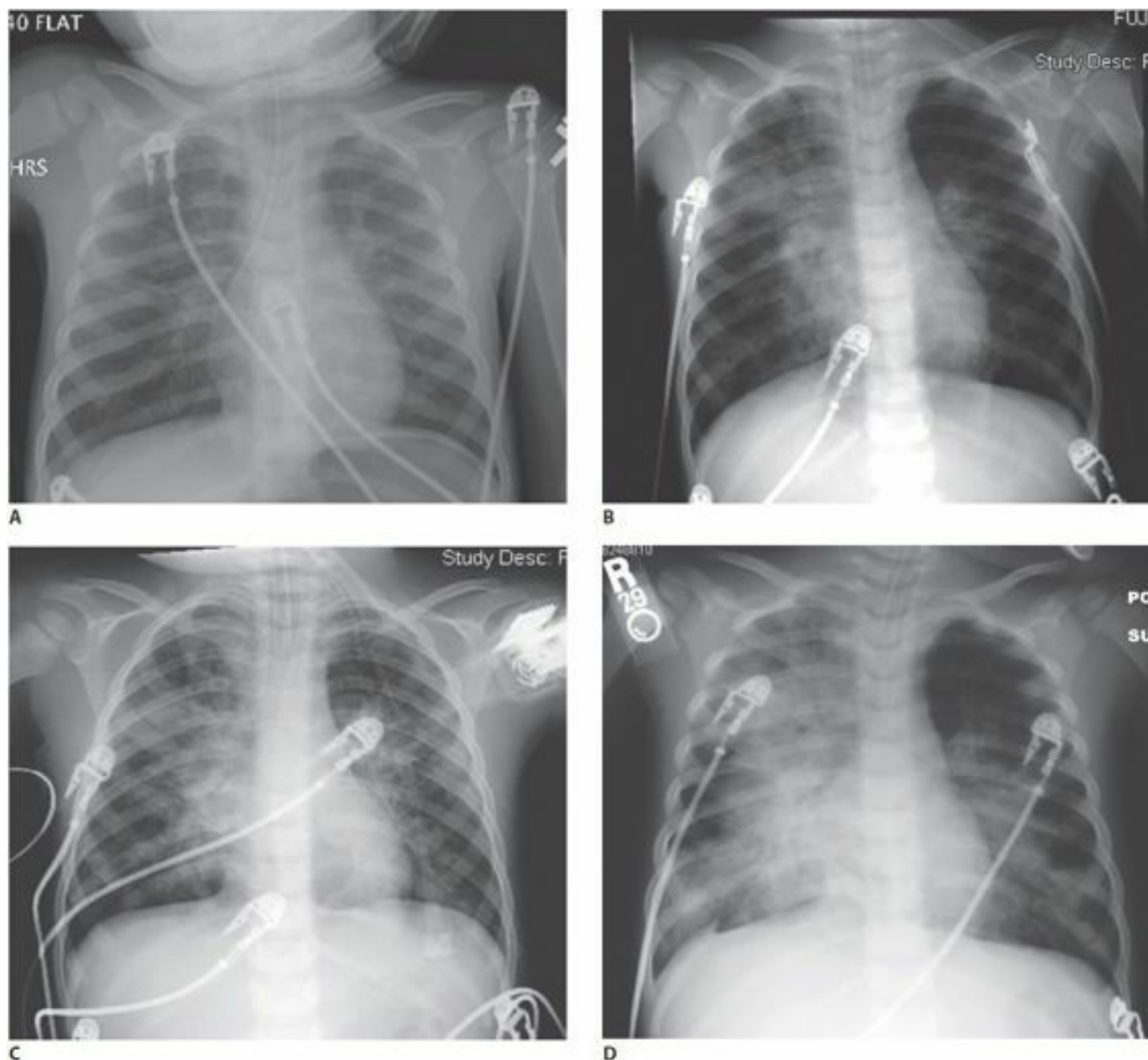


FIGURE 128–1. (A) Initial chest radiograph of a 3 year-old boy involved in a structural fire (approximately 60 minutes after the event). (B) Chest radiograph approximately 3 hours after exposure demonstrating the appearance of right upper lobe and perihilar infiltrates. (C) Evolution of chest radiograph findings approximately 17 hours after initial exposure demonstrating evolution of the right upper and perihilar infiltrates. (D) Approximately 60 hours after exposure demonstrating diffuse alveolar and interstitial infiltrates representative of inhalation induced acute respiratory distress syndrome. (Used with permission of The University of Virginia Medical Toxicology Fellowship Program.)

In intubated patients, diagnostic bronchoscopy may be useful in detecting those at risk for developing significant inhalational injury.¹³¹ Bronchoscopy allows for direct visualization and potential grading of the injury.^{2,95} While early bronchoscopy has yet to show an improvement in outcome, as therapeutic modalities designed to limit pulmonary damage continue to evolve, early predictors of inhalational injury, such as CT scanning and/or early bronchoscopy, may become more useful in identifying those patients who may benefit from such therapies.^{2,95,110}

MANAGEMENT

From oxygen acquisition to cellular utilization, the final common pathophysiologic effect from smoke injury is hypoxia. Basic critical care strategies that optimize oxygen delivery and utilization are of primary importance in treatment. Once removed from the source of exposure and placed on oxygen, the primary problems that the clinician must treat are the effects of thermal injury and irritant gases on the airway, and systemic effects of cellular asphyxiants. High-flow oxygen, preferably humidified, should accompany initial resuscitation in symptomatic patients. In hypotensive patients insert two large-bore intravenous (IV) lines and provide aggressive fluid resuscitation to optimize perfusion and aid in oxygen delivery.

Critical airway compromise may be present upon initial hospital presentation or may develop in the ensuing hours.^{54,128} A major pitfall in the management of smoke inhalation is failing to appreciate the possibility of rapid deterioration. History and physical findings help to determine significant thermal injury or smoke exposure and the potential for clinical deterioration. The clinical effects of smoke exposure and their appropriate treatment are described in [Fig. 128–2](#). Early airway intervention must always be considered as a seemingly patent airway may develop progressive obstruction that can make subsequent intubation difficult or impossible. For signs of current or impending airway compromise, upper airway patency must be rapidly established. When obvious oropharyngeal burns are observed, upper airway injury almost certainly is present. Singed hairs of the head, face, or nasal passages and soot in the oropharynx or nares may signify potential for airway edema.

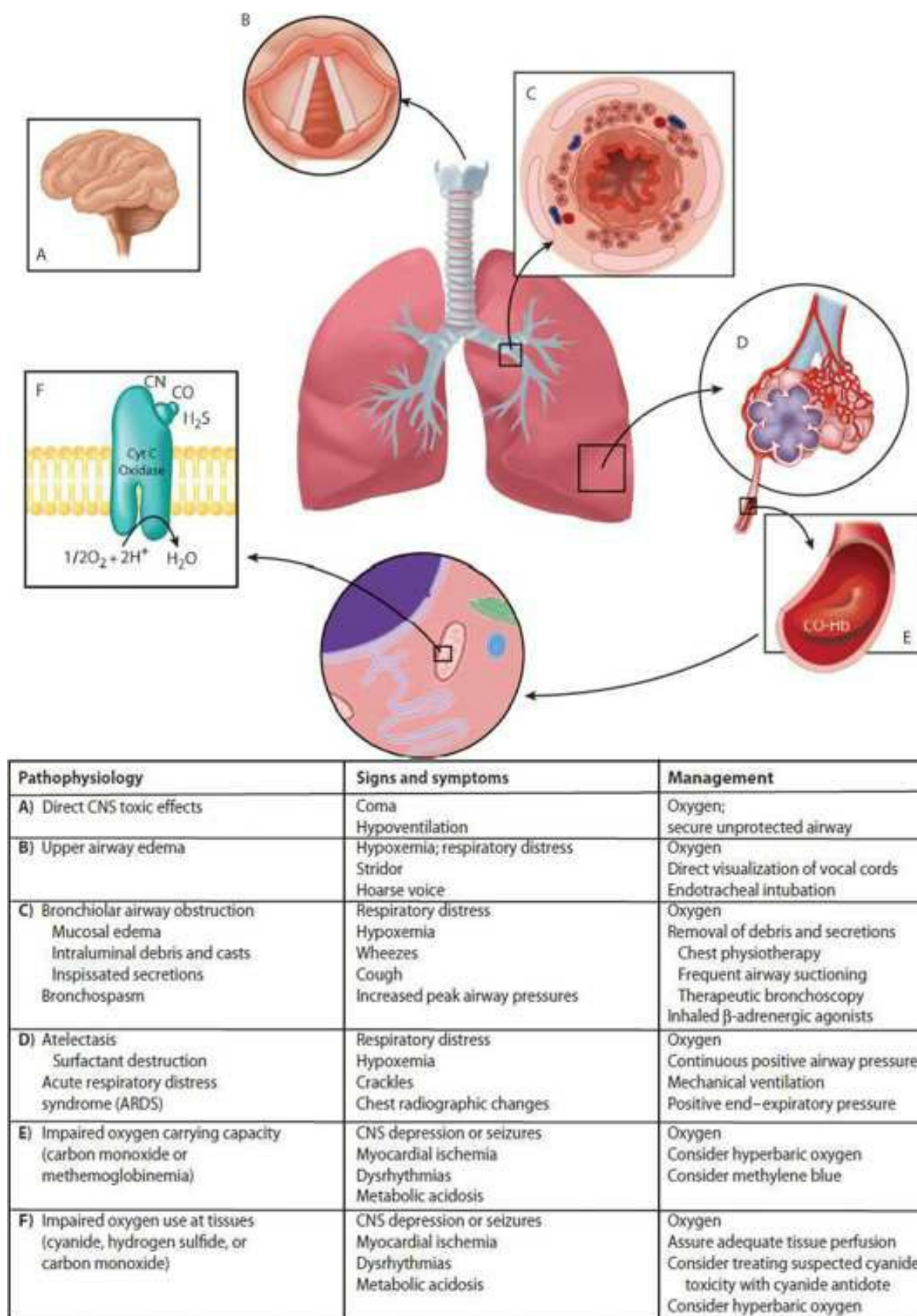


FIGURE 128–2. The final common pathway from all pathophysiologic changes that occur in smoke inhalation is hypoxia. All treatments should be focused on improving oxygen delivery and oxygen utilization.

Even if overt injuries are not visualized, distal injury may be present and underestimated.⁵⁴ Direct evaluation of the upper airway, preferably with fiberoptic endoscopy, is essential for assessing patients at high risk for inhalation airway injury.^{54,55,65} When evidence of upper airway injury exists, early endotracheal intubation should be performed under controlled circumstances, preferably with preparations for advanced or surgical airway interventions in the event that orotracheal intubation cannot be easily established. Other indications for early intubation include coma, stridor, and full-

thickness circumferential neck burns.^{7,54,55,128} Edema of injured tissue, including that of the airway, is worsened with massive fluid resuscitation in burned patients; therefore, health care professionals should also consider early intubation for patients with any amount of inhalation injury and concomitant dermal burns undergoing aggressive fluid management.^{54,55,98,128}

Pathophysiologic changes in the lung may result in progressive hypoxia over hours to days. Basic treatment of progressive respiratory failure includes continuous positive airway pressure, mechanical ventilation using lung protective strategies, positive end-expiratory pressure (PEEP), and vigorous clearing of pulmonary secretions.¹⁰¹ Decreased lung compliance is common secondary to cast formation, tissue damage, and atelectasis.^{90,101} Recommendations for limiting barotrauma in mechanically ventilated patients include using a low tidal volume (6–8 mL/kg), PEEP, and allowing permissive hypercapnia as necessary.^{81,90,100} Fraction of inspired oxygen (FiO₂) should be weaned to below 0.4 as rapidly as tolerated to limit oxygen toxicity.⁹⁰ Frequent airway suctioning, chest physiotherapy, and therapeutic bronchoscopy can clear inspissated secretions, plugs, and casts.^{30,90,97} As xenobiotics and soot can coat the airway in smoke inhalation victims, early bronchoscopy with bronchoalveolar lavage would intuitively be logical in an attempt to decontaminate the airway, similar to irrigation for dermal exposure. However, there are no data available regarding this modality in the care of smoke inhalation. High-frequency percussive ventilation (HFPV) may be considered as an alternative to conventional forms of ventilation in patients with inhalational injury. Several studies have investigated the use of HFPV in ventilated patients with inhalational injury. Although limited, some evidence suggests that HFPV may decrease peak pulmonary pressures, limit barotrauma, decrease the incidence of pneumonia, and improve mortality.^{22,28,50,90,124} A number of studies have examined experimental therapies such as percutaneous arteriovenous carbon dioxide removal, perfluorocarbons, inhaled nitric oxide, extracorporeal membrane oxygenation, instillation of natural surfactant into the lung, and deferoxamine–hetastarch complex for improving inhalation injury; however, none of these modalities have been definitively shown to improve outcome.^{29,35,57,73,96,105,108,109,122}

Inhaled β_2 -adrenergic agonists are considered first-line therapy for acute reversible bronchoconstriction resulting from asthma or chronic obstructive pulmonary disease and can be used to improve oxygenation and ventilation in victims of smoke inhalation. Pathophysiologic changes induced by irritant toxins in smoke are similar to those found in asthma, suggesting that β_2 -adrenergic agonists would also improve airflow obstruction in smoke inhalation.^{69,86} β_2 -adrenergic agonists also possess antiinflammatory properties, partially through interaction with β -adrenergic receptors on immune cells.^{85,151} β_2 -adrenergic agonists may also enhance resolution of alveolar edema by modulating the flow of sodium and potassium across cell membranes.^{85,151} Limited data in an ovine model suggest that nebulized albuterol may improve pulmonary function after smoke inhalation and burn injury.¹¹⁴ Although human data on the efficacy of β_2 -adrenergic agonists in smoke inhalation injury are lacking, their role is well established in conditions with reversible bronchoconstriction; animal studies lend support for their use and the potential benefits greatly outweigh the risks.^{114,151}

Corticosteroids have been used for smoke inhalation in an attempt to limit inflammation and improve outcome. One argument for their use is for the treatment of lung injury induced by oxides of nitrogen. Pulmonary sequelae, including bronchiolitis obliterans, are known to occur after significant exposure to oxides of nitrogen, which may be a prominent composition of smoke.^{64,76} Although data regarding efficacy are limited, corticosteroids are often used in treatment of nitrogen oxide exposure in relation to industrial exposure and silo filler's disease to prevent bronchiolitis obliterans.^{64,134} The mixed xenobiotic exposure from smoke inhalation appears to further complicate the outcome. One early rat study showed a trend toward reduced mortality in animals given supraphysiologic doses (25–100 mg/kg) of methylprednisolone; however, other tested corticosteroids (hydrocortisone, dexamethasone, cortisone) failed to demonstrate similar improvement. Consequently, this study failed to effectively prove that corticosteroids reduce mortality after rat exposure to white pine smoke.³⁸ Human studies have also failed to show an improvement in clinical outcome and may trend toward worsening outcome.^{20,77,102,129} Thus, the available literature does not support the use of corticosteroids for treatment of patients with smoke inhalation.

A significant amount of pulmonary injury after smoke inhalation is attributable to free radical damage. Smoke inhalation decreases systemic concentrations of the antioxidant vitamin E in sheep models and treatment with nebulized vitamin E (α - and γ -tocopherol) attenuates smoke inhalation induced pulmonary injury in animal models.^{51,93,144,155} Similarly, both nebulized heparin and N-acetylcysteine (NAC) are used by some centers to limit pulmonary damage.⁸⁸ Heparin is a glycosaminoglycan with anticoagulant and antiinflammatory properties occasionally used both topically and intravenously in burn treatment. In an ovine model of combined cutaneous burn and smoke inhalation, nebulized heparin combined with recombinant human antithrombin reduced airway obstruction and improved gas exchange.³⁹ The mechanism is likely attributable to decreased airway inflammation and decreased fibrin deposition and, consequently, decreased cast formation in the airway.³⁹ Nebulized heparin combined with NAC appeared to attenuate lung injury in two small studies; however, other studies have failed to show benefit.^{37,63,88} Human data are currently limited regarding each of these modalities with little current evidence that each treatment improves outcomes. The initial treatment strategy for carbon monoxide poisoning

focuses on optimizing oxygen delivery with supplemental oxygen administration.

Oxygen can be administered by a high-flow tight-fitting mask, endotracheal tube, or hyperbaric oxygen therapy (HBO). HBO can achieve very high arterial oxygen concentrations enhancing oxygen delivery to tissues and accelerating elimination of carbon monoxide from blood and tissues.^{56,119} HBO is recommended as a modality for treatment in certain situations involving carbon monoxide exposure; however, smoke inhalation injury is much more complex than poisoning with carbon monoxide alone (eg, a furnace leak).⁵² In victims of smoke inhalation, other clinical requirements, such as maintaining a secure airway and the need for additional resuscitative measures to treat ARDS, cardiovascular instability and metabolic derangements go beyond providing supplemental oxygen to treat CO poisoning. Optimal timing of HBO administration is often during the same period when intensive resuscitative efforts and focused ventilator management are required and could limit attention to these important therapies. In addition, it is known that pulmonary toxicity may result from elevated partial pressures of oxygen.¹³⁵ Very little information is available to predict the effect of hyperoxygenation on pulmonary toxicity following smoke inhalation.^{141,154} Therefore, the decision to treat a smoke inhalation patient with HBO should take into account risks and other clinical requirements when determining the appropriate therapy¹⁷ (Chap. 125 and Antidotes in Depth: A37).

Cyanide is a common product of combustion, with toxic concentrations often measured in fire victims. Because no diagnostic test is readily available in the field or in the emergency department, cyanide poisoning should be suspected in seriously ill patients with smoke inhalation, particularly in the presence of metabolic acidosis with an elevated lactate concentration.^{44,126} Serum lactate concentrations at the time of hospital admission correlate closely with blood cyanide concentrations, with serum lactate concentrations of 10 $\mu\text{mol/L}$ reported to be a sensitive indicator of cyanide toxicity.⁸ Baud demonstrated that carboxyhemoglobin levels of more than 10% also correlate with elevated cyanide concentrations. Additional clinical markers of potential cyanide poisoning include alteration of the central nervous system and cardiac function, although other factors of smoke inhalation injury can have similar effects. Specific treatment of cyanide toxicity should be implemented while other life support measures, including 100% oxygen therapy, are instituted.^{8,91,107} Treatment options include supportive care with or without empiric administration of a cyanide antidote. Systematic reviews of the human evidence regarding various cyanide antidotes conclude that it is possible to survive even cardiorespiratory arrest due to cyanide poisoning if given an appropriate antidote.^{48,123} In one review, 50% of cyanide poisoned victims (the majority due to smoke inhalation) had transient return of spontaneous circulation and 12% survived to hospital discharge; outcomes of treatment with hydroxocobalamin, thiosulfate, or a combination of sodium nitrite, amyl nitrite, and sodium thiosulfate were indistinguishable.^{48,123} The reviews found the onset of action of sodium thiosulfate slower when compared to hydroxocobalamin as the only clinically significant difference.^{48,123} Because definitive evidence of superiority is lacking, hydroxocobalamin (with or without sodium thiosulfate as an adjunct) or sodium thiosulfate alone are the antidotes of choice and should be considered for administration to smoke inhalation victims suspected of cyanide poisoning and exhibiting neurological impairment, cardiorespiratory collapse, or metabolic acidosis with elevated lactate¹²³ (Chap. 126, Antidotes in Depth: A38 and A40).

Cyanide antidotes are intended as an adjunct to basic critical care strategies that optimize oxygen delivery and utilization. Therefore, the amyl nitrite and sodium nitrite components of the classic cyanide antidote kit should be avoided in victims of smoke inhalation. Amyl nitrite and sodium nitrite produce methemoglobinemia, which binds cyanide to form cyanmethemoglobin (Chap. 126 and Antidotes in Depth: A38). Unfortunately, methemoglobin is a dysfunctional type of hemoglobin that poorly utilizes oxygen, impairing delivery to the tissues.³¹ Impairing oxygen-carrying capacity and oxygen delivery to tissues with nitrite-induced methemoglobinemia is a valid concern in the presence of tissue hypoxia from carboxyhemoglobinemia, lung injury, or other factors. Furthermore, rapid infusion of sodium nitrite may cause hypotension secondary to vasodilation.⁴⁹

Victims of fires may have respiratory compromise and other pathology not directly related to smoke inhalation, but rather from trauma or other underlying medical problems. Trauma from falls or explosions must be suspected and treatment started simultaneously with treatment of burns and inhalation injury. Comatose patients should be considered to have other causes for their status and should receive naloxone, thiamine, and hypertonic dextrose as indicated. Inhaled xenobiotics, such as carbon monoxide, may directly cause altered mental status, but drug and ethanol intoxication contribute significantly to fire fatalities and injuries. Blood ethanol concentrations correlate with elevated concentrations of carbon monoxide and cyanide, implying that intoxication impairs escape and prolongs toxic smoke exposure.^{5,11,99} Intracranial pathology should be considered and CT scans obtained as indicated.

Xenobiotics may injure the skin or mucous membranes in addition to the respiratory mucosa.²⁷ The duration of contact of a xenobiotic with tissue is an important factor in determining the extent of chemical injury to the skin and eyes. Rapid removal of soot from the skin or eyes may prevent continued injury. The eyes should be evaluated for corneal burns caused by thermal or irritant chemical injury. Patients with signs of ophthalmic irritation should have their eyes irrigated, and dermal decontamination should be considered to prevent burns from toxin-laden soot adherent to the skin.

SUMMARY

- Smoke inhalation contributes significantly to the morbidity and mortality of fire victims.
- Smoke inhalation is a complex syndrome involving diverse toxicologic injury. A spectrum of damage may occur, ranging from rapid upper airway occlusion to delayed ARDS.
- The end result of toxicity is tissue hypoxia.
- Goals of treatment should focus on maximizing oxygen delivery while avoiding unnecessary therapies that may hinder oxygenation.
- Early airway management should be implemented for patients with airway compromise. High-flow oxygen will help reverse tissue hypoxia, and fluid resuscitation should be instituted to improve cardiovascular status.
- Definitive antidotes are available in select cases and should be utilized when appropriate to help stabilize the patient.

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129 NANOTOXICOLOGY

Silas W. Smith

HISTORY

Nanotechnology has been serendipitously employed by humanity for hundreds of years. Artistically, gold-ruby glass (cranberry glass), present in the Roman Lycurgus cup and later in many church stained glass windows, owes its striking red color and optical properties to gold nanoparticles created when a gold precursor is added to molten silicate glass.¹²² Cosmetically, to blacken hair, the Greco-Roman practice of mixing of lead oxide and slaked lime with water created lead sulfite nanocrystals (5 nm), which accumulated in the hair cuticle and cortex.³⁷¹ Martiallly, seventeenth century Damascus steel sword blades owed their high-quality mechanical properties to carbon nanotubes (CNTs) and cementite (Fe_3C) nanowires found within their structure.²⁸⁹ Medicinally, specially prepared, “Swarna bhasma,” nanosized colloidal gold, has been employed as an antirheumatic, anti-asthmatic, and anti-diabetic in Indian Ayurvedic practice for centuries.³⁷

Langmuir’s detailed experimental work establishing the existence of monatomic films garnered him the Nobel Prize in 1932.¹⁷² In 1959, the physicist Richard Feynman proposed the theoretical framework for “manipulating and controlling things” all the way down to the atomic level.⁸⁹ Norio Taniguchi is generally credited with coining the term “nanotechnology”—“the processing of separation, consolidation and deformation of materials by one atom or one molecule”—in 1974.³⁴⁰ The invention of the scanning tunneling microscope in 1981 enabled the visualization of individual atoms and allowed the direct physical manipulation of atomic surfaces.¹⁵² In 1985, Kroto and colleagues reported on a novel, minute crystalline allotropic form of carbon, conceptualized some 15 years previously.^{57,166,258} These soccer ball-shaped carbon-60 structures were named “buckminsterfullerenes” after Buckminster Fuller. The discovery of CNTs followed in 1991.¹³⁴

Health and safety of nanotoxicology came to fore during the first consumer recall of a purported nano-based invention.³⁸⁴ In 2006, the bathroom cleaning product “Magic-Nano” was released in Germany. Within days, more than 110 cases of illness were reported, and several patients were hospitalized with severe respiratory complaints, including acute lung injury. No further episodes of illness occurred after product recall only 3 days after introduction.¹⁴⁷ Although it was ultimately determined that “Magic-Nano” contained no nanoparticles, the incident raised many questions about nanotechnology development, regulation, and health risks.^{21,22} More than 1600 consumer products now incorporate nanotechnology, with multiple products reaching the market weekly.³⁴⁶

PHYSIOCHEMICAL PRINCIPLES

Nanotechnology is defined as the “control and restructuring of matter at the nanoscale, in the size range of approximately 1 to 100 nanometers, in order to create materials, devices, and systems with fundamentally new properties and functions due to their small structure.”²⁸¹ The American Society for Testing and Materials (ASTM) International defines an ultrafine particle as a particle ranging in size from approximately 0.001 (1 nm; 10 Å) to 0.1 μm (100 nm; 1000 Å) and a nanoparticle as an ultrafine particle with lengths in two or three dimensions greater than 0.001 μm (1 nm; 10 Å) and smaller than about 0.1 μm (100 nm; 1000 Å).⁸

For spherical nanoparticles, as particle diameter decreases, the percentage of molecules on the surface of the nanoparticle increases relative to the total number of molecules. This percentage increases quite steeply below 100 nm.¹⁶³ This provides a large area (high surface to volume ratio) for chemical reactions to occur and for contact and interaction with biologic systems. Furthermore, as particles reach sizes below 100 nm, quantum mechanical principles become manifest, and, thus, acoustic, diffusion, electrical, magnetic, mechanical, optical, and solubility properties may emerge, which differ from those seen at larger as well as smaller (atomic) scales. Nanoparticles may exist as aggregations (individual particles held together by strong forces) and agglomerations (held together by weak forces such as van der Waals forces, electrostatic, and surface tension). The extent of aggregations and agglomerations, particle dispersal, and electrical charge varies, depending on the primary particle constituents and on solvents or media.³³ This imparts additional properties to identical substances even at the nanoparticle level. Whereas C_{60} fullerenes are intensely hydrophobic and essentially insoluble in water, colloidal C_{60} clusters remain mono-dispersed in water as long as electrostatic repulsions are

not disrupted by salts.³³ Single elemental materials can also be engineered with complex architecture (eg, gold and platinum nanostars) to alter catalytic activity.²⁰⁰

Nanoparticles may be derived “naturally,” such as those originating from volcanic explosions, fires, ocean spray, sand storms, soil and sediment weathering, and biomineralization processes.³⁶¹ “Incidental” nanosized particles are generated as byproducts of processes such as combustion, cooking, or welding, or even simply rubbing bulk solids of C_{60} between fingertips or glass slides.⁶³ “Engineered” nanomaterials are intentionally created for research purposes or for manufacture for end-use applications. Nanomaterials and nanoparticles include a vast array of structures, such as coatings, composite nanodevices, dendrimers, fullerenes, graphenes, liposomes, nanocrystals, nanogels, nanofibers (nanotubes and nanorods), nanoshells, nanospheres, nanowires, polymeric micelles, quantum dots (QDs) and quantum rods, and supermagnetic particles (Fig. 129–1). They are composed of materials as diverse as their applications, including carbon, lipids, metals and metal oxides (eg, cadmium, cerium, copper, germanium, gold, iron, silver, selenium, zinc, zirconium), nucleic acids, polymers, proteins, and combinations thereof.

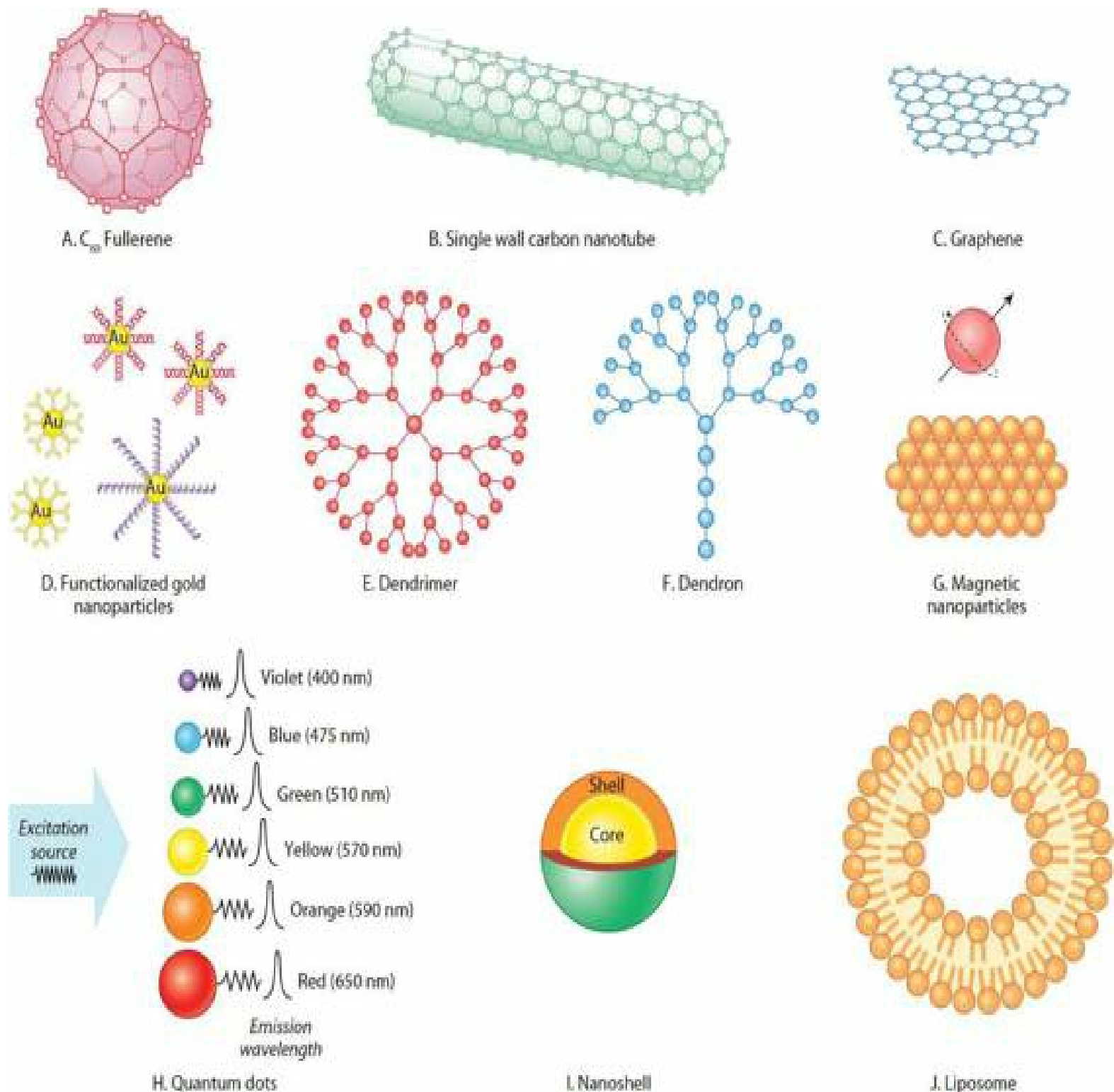


FIGURE 129–1. Nanoparticles (not to scale). (A) C_{60} is a prototypical fullerene, or carbon cage, which may enclose additional atoms, ions, or molecular clusters. Fullerols (fullerenols) employ polyhydroxylation at their surface to improve water solubility. (B) Carbon nanotubes (CNTs) are single-walled (SWCNTs) or multiple-walled (MWCNTs) cylinders,

which are capped at each end and can bundle together into longer and wider agglomerates. (C) Graphene consists of a single layer of carbon atoms (ie, a sheet) in a hexagonal lattice. (D) Gold nanoparticles and other nanosized noble metals (eg, silver, copper, platinum) have unusual catalytic, optical, electronic, and (photo)thermal properties and can be conjugated to dyes, antibodies, peptides, and oligonucleotides. (E) Dendrimers are branched polymers consisting of a central core, an internal branching region, and surface terminal groups; drugs, genes, and imaging agents can be loaded into the inner protected cavities. (F) Dendrons are wedge-shaped sections of dendrimers with an accessible reactive group. (G) Magnetic nanoparticles include superparamagnetic iron oxide (SPIO) nanoparticles (Fe_2O_3 , Fe_3O_4), pure metals (Fe and Co), and alloys (CoPt_3 and FePt). They are usually surrounded by a shell to minimize agglomeration and chemical reactivity. Magnetism-engineered iron oxide (MEIO) nanoparticles can be doped with cobalt, manganese, and nickel to create unique magnetism properties. (H) Quantum dots (QDs) and QRods (rod-shaped QDs) are semiconductor nanocrystals capable of size-dependent fluorescence with a “tunable” emission spectrum in the 400-nm to 2- μm range. Analogous but chemically inert Cornell dots (CU or C dots) contain covalently bound fluorescent dyes in a sol–gel-derived silica matrix. (I) Nanoshells contain a dielectric silica core surrounded by thin metal gold shell. (J) Liposomes are globular vesicles with hydrophobic and hydrophilic zones composed of phospholipids, sphingolipids, and ceramides or other esters or polymers ranging in size from 25 nm to the micron range. Nanoparticles can be further derivatized, chemically modified, or bioengineered with a variety of detection, imaging, or targeting molecules.

CURRENT AND PROJECTED APPLICATIONS

Nanotechnologies are currently or anticipated to be incorporated into an ever-widening range of disciplines and industries. These include agriculture; automobile components; chemical and materials science (alloys, catalysts, ceramics, coatings, and thin films), defense, electronics, energy capture and storage, environmental sensing and remediation, food processing, fuel additives, house-cleaning products, paints, flame-retardants, varnishes, and sealants, pharmaceuticals, textiles, and water purification.²⁸¹ Specific human and biomedical applications include biomaterials, cosmetic and external products, diagnostics, drug and gene delivery systems, imaging, immune and transplantation sciences, and oncology therapy.³⁰⁶ Biomaterial products include creation of scaffolds for in vivo or ex vivo growth to support tissue healing, engineering, and regenerative medicine; coatings to minimize immunogenicity, inhibit specific tissues or cell types, and allow macromolecular repair; and implant engineering in prosthetics to control fibrous tissue formation and biointegration, and implant performance.^{93,336,344,345} Nanotechnology is radically advancing imaging capability for specific organs, tumors, sentinel lymph nodes, and vasculature. Molecular imaging now permits differentiation of cellular subcompartments, uptake mechanisms, cell architecture, intracellular trafficking, and single proteins and receptors.^{14,108,167} Sunscreens, cosmetics, and conditioners have embraced a range of nanotechnologies. Nanoformulations of TiO_2 and ZnO , which the FDA has permitted in sunscreens since 1999, provide both aesthetic appeal (sunscreen with transparency, lower viscosity, and improved skin blending) and clinical benefit (more efficient UV filtration).^{244,384} Wound care is incorporating dressings containing nanocrystalline silver and other delivery systems in order to improve wound healing through inflammation suppression, upregulation of micronutrients, and antibacterial actions.^{232,349,376} Nanotechnology is advancing medical diagnostic capability, detection thresholds, and pathogen sensing, with tagged nanoparticles currently employed in commercial genotyping tests and other assays.³³³ Nanoengineering holds the promise of improved pharmacokinetics, solubility, delivery, and targeting of pharmaceuticals, proteins, and genes in a cell-, tissue-, tumor-, or organ-specific manner. New formulations, magnetic drug targeting, thermal ablation, and delivery to incredibly diverse difficult-to-access spaces (eg, intracellular pathogens, tumors, and the central nervous system) are being investigated or brought to market.^{23,154,313,319,377} Table 129–1 presents selected commercial nanotechnology-based diagnostics, imaging compounds, and therapeutics.

TABLE 129–1. Selected Commercial Nanotechnology-Based Diagnostics and Therapeutics

<i>Xenobiotic</i>	<i>Proprietary Name</i>	<i>Route</i>	<i>Class or Indication</i>	<i>Nanotechnology Platform</i>
Aminosilane/iron oxide	NanoTherm (EU)	IV	Magnetic tumor thermotherapy	SPIO nanoparticle (aminosilane-coated)
Amphotericin	Abelcet, Amphotec, Ambisome	IV	Antifungal	Liposomal
Aprepitant	Emend	PO	Antiemetic	Nanocrystal
Certolizumab pegol (TNF antagonist)	Cimzia	SQ	Immunosuppressant	Polymer-protein conjugate
Cytarabine	Depocyt	IV	Chemotherapeutic	Liposomal
Daunorubicin	DaunoXome	IV	Chemotherapeutic	Liposomal
Dendoleukin diltiox	Ontak	IV	Chemotherapeutic	Diphtheria toxin-antibody-functionalized nanoparticle
Dominant-negative construct of human cyclin-G1 gene	Rexin-G ⁺ (Philippines)	IV	Chemotherapeutic	Targeted (collagen binding domain) nanoparticle
Doxorubicin	Doxil, Caelyx, Myocet	IV	Chemotherapeutic	Liposomal
Estradiol	Estrasorb	TD	Menopausal symptom	Micellar nanoparticle
Estradiol	Elestrin	TD	Menopausal symptom	Calcium phosphate nanoparticles
Fenofibrate	Tricor, Triglide	PO	Antilipidemic	Nanocrystal
Ferucarbotran	Resovist (EU)	IV	MRI contrast agent	SPIO nanoparticle (carboxydextran-coated)
Ferumoxide	Feridex, Endorem	IV	MRI contrast agent	SPIO nanoparticle (dextran-coated)
Ferumoxil	GastroMARK, Lumirem	IV	MRI contrast agent	SPIO nanoparticle (siloxane-coated)
Glatiramer acetate (L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine)	Copaxone	SQ	Autoimmune disease mitigation (multiple sclerosis)	Polymeric substances
Gold	Verigene	NA	Molecular diagnostics	Oligonucleotide- or antibody-functionalized nanoparticle

Peginesatide (erythropoietin receptor agonist)	Omontys ^d	IV, SQ	Polycythemic	Polymer protein conjugate
Peginterferon alfa-2b	PegIntron	SQ	Antiviral (hepatitis C)	Polymer protein conjugate
Peginterferon alfa-2b	Pegasys	SQ	Antiviral (hepatitis B/C)	Polymer protein conjugate
Pegloticase	Krystexa	IV	Antihyperuricemic	Polymer protein conjugate
Pegvisomant (PEG-human growth hormone analog)	Somavert	SQ	Acromegaly	Polymer protein conjugate
Propofol	Diprivan	IV	Anesthetic	Liposome
Sevelamer HCl (crosslinked with epichlorohydrin)	Renagel	PO	Phosphate reduction	Polymeric crosslinked resin
Silver	Acticoat	Topical	Wound healing	Nanoparticle
Sirolimus	Rapamune	PO	Immunosuppressant	Nanocrystal
Titanium dioxide	Numerous	Topical	Ultraviolet-protectant	Nanoparticle
Vincristin	Marqibo	IV	Chemotherapeutic	Liposomal
Verteporfin	Visudyne	IV	Aged-related macular degeneration	Liposomal

^aUS FDA Orphan Drug Approval but not Marketing Approval. ^bSouth Korean marketing approval. ^cUS FDA IND approval. ^dVoluntary marketing withdrawal.

EU = European Union; G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony stimulating factor; IND = investigational new drug; IM = intramuscular; IV = intravenous; I/O = intravitreal; MRI = magnetic resonance imaging; NA = not applicable; PEG = polyethylene glycol; PO = oral; SCID = severe combined immunodeficiency disease; SPIO = superparamagnetic iron oxide; SQ = subcutaneous; TD = transdermal; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor; NA = not available. No endorsement is implied.

EXPOSURE AND DISTRIBUTION

Nanoparticle exposure is anticipated through a variety of mechanisms (Fig. 129–2). Exposure might occur through environmental discharge into air, water, or soil during the primary manufacturing process; disposition of industrial or research waste; or engine combustion. Sanding, machining, wearing and weathering, or disposing of nanomaterial-containing products could also liberate nanoparticles. Exposure might also occur during biologic elimination from a primary target or due to implant or device wear.

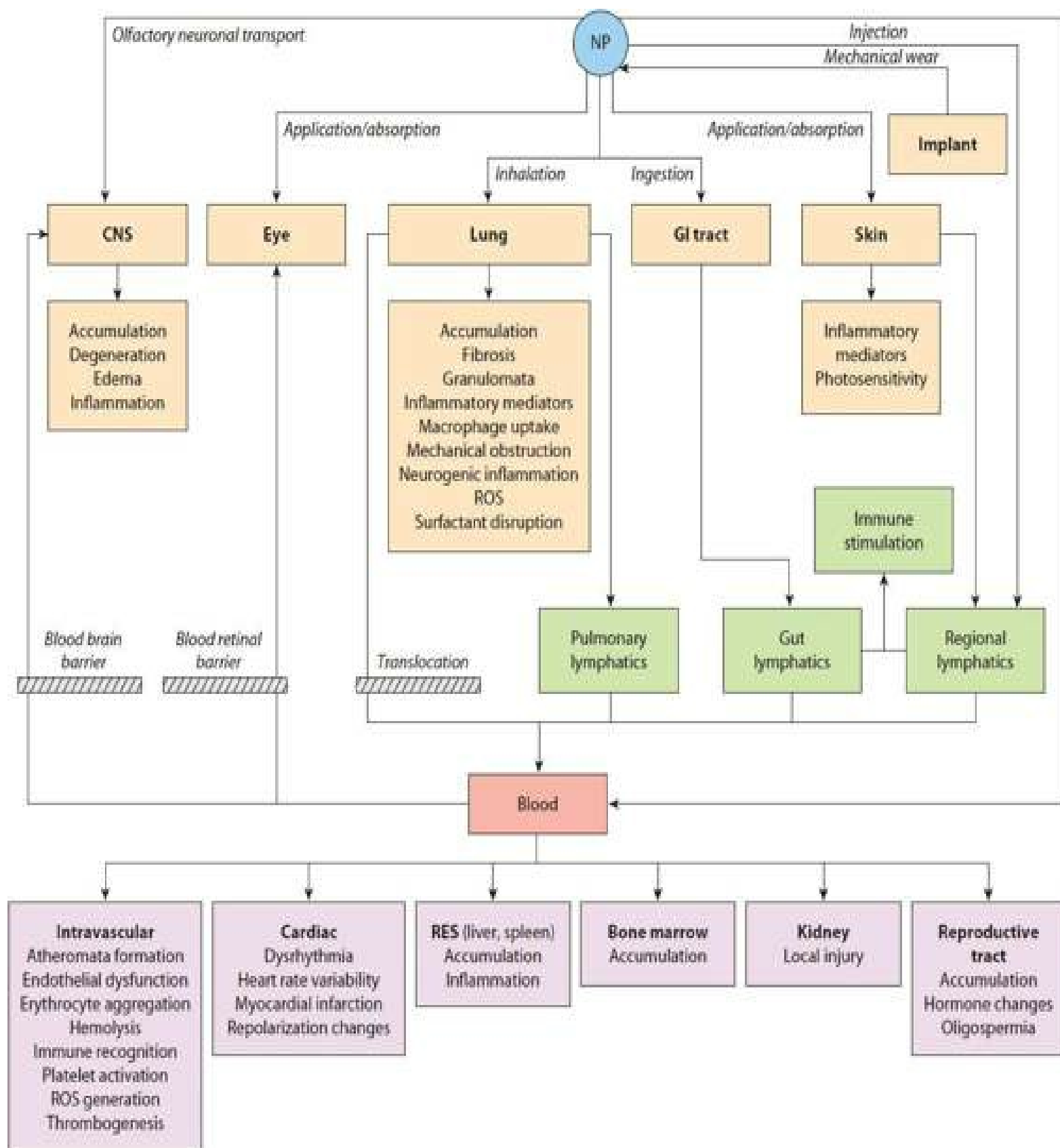


FIGURE 129–2. Potential mechanisms of nanoparticle exposure, distribution, and systemic toxicity. Accumulation may not be limited to the organ systems depicted. NP = nanoparticle; RES = reticuloendothelial system; ROS = reactive oxygen species.

Dermal Exposure

Podoconiosis (endemic non-filarial, geochemical elephantiasis) is presumed to occur from absorption of various colloid-sized elemental particles in irritant clays (eg, aluminum, silicon, magnesium, iron), which undergo macrophage phagocytosis, induce collagenization of afferent lymphatics, and obliterate them.⁶¹ Thus, transdermal exposure to and disease from certain nanoparticles is assumed established. Nanocompositions in paints and coatings, clothing, transdermal drug delivery devices, topical ultraviolet protection products, or proprietary cosmetics are of concern. Nanoparticles can be taken up by human epidermal keratinocytes and/or cause DNA damage; at issue is whether epidermal penetration to affect such damage actually occurs.^{244,300,305} Reviews summarizing TiO₂ and ZnO nanoparticles concluded that dermal

penetration for those substances was unlikely beyond the stratum corneum.^{244,245} However, TiO₂ and ZnO nanoparticles (in currently available sunscreens) can reside in the stratum corneum and follicular sink.³⁵⁹ Solvents or diseased (eg, psoriatic), injured, or mechanically stressed skin might allow increased dermal penetration.³⁵⁹ In experiments simulating heavy industrial solvent exposure, toluene, cyclohexane, or chloroform could transport C₆₀ fullerenes across the stratum corneum into viable epidermis.³⁹⁰ Epidermal and dermal penetration of a phenylalanine-based fullerene amino acid-derivatized peptide occurred via passive diffusion and was enhanced with skin flexion.²⁹⁶ Oil-water emulsion base products containing diclofenac sodium released nanoparticles capable of reaching human epidermis.³⁰⁸ Neutral, anionic, or cationic coated commercially available QDs applied to porcine skin at workday exposure doses could reach the epidermis and dermis.²⁹⁹ Silver nanoparticles cause focal, microscopic inflammation and edema and localize on the surface and in the upper stratum corneum layers when applied topically for 14 days in pigs.³⁰⁵ Near-infrared QDs intradermally injected in pigs could be followed to sentinel lymph nodes 1 cm below the skin.¹⁵⁷ Intradermally injected CdSe core-CdS capped-PEG nanoparticles remained in the skin and drained via lymphatic ducts to regional lymph nodes, and then accumulated in the liver, kidney, spleen, and hepatic lymph nodes.¹¹²

Inhalational Exposure

Nanoparticle aerosols may be generated in manufacturing or research environments. Anthropomorphic ultrafine products are encountered in welding, soldering, cooking fumes, and pollution. As the iron to carbon (soot) ratio increases in diesel combustion, the number and size of self-nucleated metallic nanoparticles and larger agglomeration of metallic and carbon particles increase.¹⁷⁴ Carbon fullerenes can be detected in flaming soot following combustion of various hydrocarbon fuels.³²¹ Combustion-derived nanoparticles carry soluble organic compounds, polycyclic aromatic hydrocarbons, and oxidized transition metals on their surface.²¹⁶ Secondary nanoparticles can form in the atmosphere via gas-to-particle conversions following nucleation and coagulation or condensation.²⁸ Intermediate particles (> 80 nm and < 200 nm) may remain suspended in air for days to weeks.³⁵⁸

Deposition of inhaled particles is determined by various factors including diffusion and inertial impaction. In rat nasal passages, computational fluid dynamics (CFD) models predicted that 3 nm particles deposited mostly in the anterior nose and larger 30 nm particles distributed throughout the nasal passages.⁹⁷ At deeper levels, gravity contributes to greater particle deposition of fine particles in the central airways instead of the lung periphery.⁶⁰ However, particles of less than 2500 nm reach the alveoli, transported from the airway duct by convective bulk flow combined with particle motion from sedimentation and diffusion.¹²⁷ Alveolar deposition models indicate a saddle-shaped, volume- and rate-sensitive curve, a minimum particle deposition at 50 microns and peak deposition at 30 nm and 4000 nm.⁵³ Consistent with theory, total deposition fraction of ultrafine aerosols in healthy human volunteers increased by as median particle diameter decreased from 100 nm to 40 nm, as tidal volume increased, and as respiratory flow rate decreased (longer respiratory and retention time).¹³⁹ Deep breathing similarly increased deposition of inhaled 100-cm³ aerosol boluses of ^{99m}Tc–radiolabeled carbon ultrafine particles. In shallow breathing, particles deposit with a greater proportion asymmetrically in the left lung, for unclear reasons.²¹⁹ While large particles or those with a high aspect ratio (ie, high length to width ratio) would not be expected to achieve deep lung penetration, “aerodynamic diameter” (D_{ae})—defined as the diameter of a sphere of unit density (1 g/cm³) with the same terminal settling velocity as the particle itself—actually determines respirability.⁷³ As D_{ae} is proportional to the fiber diameter and not to its length, “paradoxical respirability” of high aspect ratio nanoparticles can occur.⁷³

Clearance may be affected by mucociliary movement and augmented by macrophages at the alveolar level. Macrophages may either move particles toward ciliated epithelium, uptake and store particles, or contribute to transepithelial movement, whereby particles may deposit in the basement membrane or enter the lymphatics or bloodstream.^{163,199,249} Translocation demonstrates size- and species-dependence. Iridium particles (2–4 nm) crossed the air-blood barrier to reach secondary target organs to a greater extent than carbon (5–10 nm) particles, and translocation and accumulation was greater with 20 nm iridium aggregates than with 80 nm aggregates.¹⁶⁴ Soluble compounds are generally rapidly absorbed. Nanoparticles may evade effective clearance. Several studies have indicated that 15 to 80 nm particles are inefficiently taken up by macrophages (~ 20%), but are retained in epithelial cells or interstitium.²⁴⁹ Prolonged particle pulmonary persistence was seen in one human ultrafine particle inhalation study, accounting for translocation and urinary elimination.²²⁴ In an animal study, at 60 days, 81% of multiple-walled CNTs (MWCNTs) and 36% of ground CNTs administered intratracheally (0.5 mg/rat) could be recovered.²²⁶ In contrast to small particles which transit the visceral pleura, reach the pleural space, and drain into the lymphatic system through chest wall pores (3–8 μm), long nanotubes may travel and embed in the subpleural wall and within subpleural macrophages.^{74,298}

Oral Exposure

Multiple nanoparticulate systems are under evaluation for their ability to enhance solubility, permeability, bioadhesion, bioavailability, and efficacy of poorly absorbed drugs, proteins, and vaccines.^{66,269,394} Unintentional oral exposure is expected to be uncommon. Aerosol deposition in the upper aerodigestive tract could provide matter for subsequent swallowing. Nanoparticles can enter bacteria and living cells, providing a mechanism for food-chain bioaccumulation.²⁵ Nanoparticles can cross either para-cellularly (between cells) or transcellularly. Transcellular uptake is thought primarily to occur at associated lymphoid tissue, but may also occur at villi. In general, nanoparticle uptake is enhanced by smaller size and absence of charge.^{49,126} Hydrophobicity studies show mixed results (depending on altered permeation through various layers).¹⁷⁶ Similar to skin, inflamed or infected intestinal mucosa can increase permeability and alter experimental results.¹⁷¹

Single-walled CNTs (SWCNTs) ingested by *Drosophila* larvae at concentrations as low as 16 ppm traverse the gut wall, enter the dorsal vessel, and can embed in the central nervous system.¹⁷⁹ Mice exposed to ZnO powder (20 and 120 nm) at 1 to 5 g/kg showed pathological damage in stomach, liver, heart and spleen, with slightly different patterns of effect.³⁷² Orally administered TiO₂ large particles (475 nm) associated with gut associated lymphoid tissue (GALT) are translocated to systemic organs such as the liver and the spleen (6.5%).¹³⁸ Macrophages in human GALT frequently contain multiple microparticles: the food additive TiO₂ (100–200 nm), aluminosilicates (kaolinite illite, mica, smectite, or vermiculite) (< 100–400 nm), and mixed aluminum-free environmental silicates (100–700 nm in length).²⁷⁹ These correlated with chronic latent granulomatous inflammation in susceptible individuals. Water-soluble fullerenes had very poor oral absorption in one rat study. Trace amounts that did cross the gastrointestinal barrier demonstrated prolonged retention and the ability to reach brain tissue.³⁹¹ Four and 10 nm diameter colloidal gold particle uptake occurred by persorption through single enterocytes at villi in the proximal ileum, distal ileum, and in Peyer's patch regions of the small intestine.¹²⁶ Gold nanoparticles (15 nm) similarly penetrated rat intestine in a separate in vitro experiment.³²⁸ Rats fed silver nanoparticles (~ 60 nm) showed dose-dependent accumulation in kidneys, liver, brain, lungs, and blood; female rats showed more accumulation of silver nanoparticles in all kidney regions.¹⁵⁸

Internal Deposition and Degradation

Additional understanding of human-particle interactions proceeds from experience with early colloidal treatments for rheumatoid arthritis, surgical procedures, and implanted devices. Decades ago, it was demonstrated in human and animal models that gold particles of less than 20 nm could spread beyond injected joints to lymph nodes, liver, spleen, and kidneys, to induce cellular uptake, mitochondrial damage, and degenerative renal tubular lesions.^{332,397} Metallic fragments from surgical diathermy instruments can deposit in urinary tract tissues to induce granulomatous inflammation.¹²⁴ Joint replacements and spinal implants can produce particulate wear debris. Dense and loose connective tissue, giant cells, and macrophages, and phagocytosed iron and chromium particulate debris have been found surrounding stainless steel spinal implants removed due to late operative site pain.³¹⁴ In hip implants, periprosthetic tissue may contain cobalt, chromium, and bone cement wear particles.^{39,111} Local particle accumulation leads to a repetitive cycle of macrophage phagocytosis, cell degeneration and death, release of intracellular enzymes and ingested metallic debris, and tissue necrosis.³⁰⁴ Submicron mechanical wear particles (including polyethylene, titanium, alloys of titanium-aluminum-vanadium, cobalt-chromium-molybdenum, stainless-steel cobalt-chromium-nickel-tungsten, barium sulfate, zirconium oxide, corrosion products of cobalt-chromium, and stainless-steel) from patients wearing failed orthopedic replacements disseminated to lymph nodes, liver, and spleen.³⁶⁵ Lymph nodes demonstrated both granulomatous and fibrotic reactions and particle-laden macrophages; elevated serum metal concentrations and granulomatous lesions in the liver and spleen were occasionally found. Rare and severe deterioration can produce massive metallosis and systemic metal toxicity.²⁵³

Circulation, Retention, and Elimination

As indicated in the previous sections, circulatory access may occur through intravenous administration of nanoparticle pharmaceuticals, pulmonary translocation, intestinal absorption, dermal penetration, or draining lymphatics (Fig. 129–2). In human volunteers, inhaled ^{99m}Tc-labeled ultrafine carbon particles (< 100 nm) reached the blood within one minute, peaked between 10 to 20 minutes, and persisted for up to 60 minutes.²⁴¹ Both hepatic accumulation and urinary excretion occurred. Gold nanomers (30 nm) can be recovered rapidly in blood platelets of the alveolar capillaries after rat intratracheal injection.¹⁹ Aerosolized gold nanoparticles accumulated in more than 20 rat organs and tissues, particularly the lungs, esophagus, kidneys, aorta, spleen, and heart.⁴⁰²

Tight junctions (< 2 nm) between endothelial cells preclude most nanoparticles from exiting the systemic circulation. However, organ-specific endothelial characteristics (hepatic fenestrations and splenic discontinuity), transcytosis, or leak-inducing disease conditions (inflammation and cancer) may allow exit of large particles. Reticuloendothelial system (RES) and renal clearance are specific to individual particle and coating.^{161,180} Shielding nanoparticles with neutral compounds or those providing steric repulsion or hindrance is thought to impair opsonization with subsequent RES clearance.²⁵⁹ Neutral

charge may also improve renal elimination of certain dendrimers.² Size differences of as little as 2 μm may shift elimination from renal to hepatic.¹⁵⁹

DETECTION AND DOSE QUANTIFICATION

Previous sampling of generated aerosols generally focused on the average chemical composition and the mass of all deposited particles, with the exception of asbestos, for which the number of fibers with a specific shape and composition is important.²¹¹ Production of engineered nanoparticles frequently results in a distribution of sizes. Dose assessment is complicated by the multiple differences among nanoparticles and ongoing investigation as to the most appropriate metric to measure: bulk amount (total particulate mass), particle burden (number of particles of a certain size), size distribution, total surface area, surface functional groups, delivered or deposited dose (per cell or other biological unit), internalized dose, or an alternative metric. Measurement approaches include various devices to assess particle mass directly (filter collection with analysis, size-selective static sampling, tapered element oscillating microbalance) or indirectly (via various impactor technologies), direct number assessments (via electron microscopy, optical or condensation particle counters, differential mobility analyzing systems, and scanning mobility particle sizers), and surface area.^{85,101,192,211,236,237} The chosen method is critical, as mass concentration measurements can demonstrate significant variation compared to particle number counts in industrial settings.^{85,274}

TOXICITY

Overview

Certain organisms intentionally synthesize nanoparticles (eg, selenium-respiring bacteria, magnetotactic bacteria, gold nanoparticles in alfalfa).^{98,175,255} The diverse nature of the substances, compositions, structures, and physical properties involved in nanotechnology limits generalization regarding possible human effects. Representative of the knowledge gap, the US Hazardous Substances Data Bank identifies only few nanosubstances, namely, carbon black, carbon nanotubes, fullerenes, octinoxate, cerium oxide, iron, platinum, samarium oxide, silver, selenium, titanium oxide, and zinc oxide nanoparticles. Multiple reviews have attempted to address the diverse issues surrounding nanoparticle toxicity, and various schemes have been proposed to categorize nanoparticles.^{10,82,118,192,199,248,264,323} One older review reported 428 studies documenting adverse events of 965 unique nanoparticles.¹¹⁸ Reviews of a single “class” of nanoparticles have documented both adverse and neutral effects. Inference of systemic biological effects in humans is hindered by the *in vitro* nature of many experiments. Differences in experimental methodology, cell line, substance concentration, particle size and geometry, exposure parameters (route, duration, and frequency), duration of observation, and end points or surrogate markers have hindered comparisons. Data on the long-term effects are lacking. Cell-line specific, organ-specific, and species-specific toxicities remain to be fully characterized.

To address these deficiencies, methodologies are being developed to assess nanotechnology risk in a systematic fashion. Classifying nanoparticles based on the results of multi-dose-range biological assay profiles (ATP content, reducing equivalents, caspase-mediated apoptosis, and mitochondrial membrane potential) in multiple cell lines has been advocated.³²⁰ Other techniques to evaluate toxicity and biologic reactivity of nanoparticles have been reviewed and include cellular proliferation, necrosis, and apoptosis assays; reactive oxygen species (ROS) generation and oxidative stress; activation of proinflammatory signaling or other messenger molecules; genotoxicity and gene expression analysis; and *in vivo* exposure route, short and long term effects, tissue localization, biodistribution, and clearance studies.^{207,326,334} Studies and models of quantitative structure-activity relationships (QSAR) may take on more importance to profile toxicity as the number of compounds proliferates.^{286,381}

Despite the many unknowns, antecedent work within the discipline of particle toxicology has provided extensive epidemiologic and experimental evidence associating airborne pollution particulate matter (PM) with human mortality, cardiovascular, pulmonary, neurologic, and reproductive injury, altered neurocardiac function (decrease heart rate variability and repolarization), and malignancy.^{36,67,71,153,268,272,297,366,403} The strength of the association depends on the particle size, type, and the outcome of interest. Similarly, ultrafine particles in home-generated cooking fumes have received attention for their possible role in pulmonary disease, inflammation, and genotoxicity.^{217,326,327,369,386}

Genetic or unique susceptibilities to nanoparticles are not well categorized. Preexisting acute or chronic disease (pulmonary disease, cardiac disease, malignancy, infection) or individual genetic variations (resistance to oxidative stress, immune composition, surface or serum proteins) may modify nanoparticle toxicity. For example, following identical ultrafine particle aerosol exposure, patients with chronic obstructive pulmonary disease (COPD) received an increased “dose” (deposition factor and/or rate) compared to normal individuals.³⁸ Retention of ultrafine particles was similarly higher in patients with COPD than healthy nonsmokers.²²⁴ Patients with preexisting cardiovascular disease or older age show increased susceptibility to concentrated ambient air pollution particles.⁶⁷

Although the following sections generally report “positive” studies in order to highlight nanotoxicity principles, it is important to acknowledge that many other studies have also produced negative results, and some have challenged the concept of “nano-specific” toxicity.⁷³ Toxicities identified experimentally must be coupled with an understanding of physicochemical properties (which impact organism and environmental transport) and exposure assessments in order to appropriately characterize risks.

Dose

Depending on the nanosubstance, “dose” (particle number or bulk amount) may or may not play a role. Appropriate dose-response curves (linear, supralinear, biphasic, or threshold) for different toxic effects have not yet been described for most particles.²⁴⁹ For example, anti-HER2 antibody-tagged silica-gold nanoshells showed no inherent in vitro toxicity to breast adenocarcinoma cells over a range of concentrations and exposure durations.¹⁸⁹ CdSe/ZnS QDs encapsulated in phospholipid block-copolymer micelles injected into *Xenopus* blastospheres were “nontoxic” until doses of 5×10^9 nanocrystals/cell produced “abnormalities.”⁷⁶ CdSe/ZnS QDs at higher doses (20 nM/L) increased apoptotic cell death and cytokine release.²²⁹ The principal toxic mechanism changed from intracellular oxidative stress to cadmium ion release as QD concentration increased in another study.¹⁸² Dose-dependent cytotoxicity was seen in human keratinocytes as SWCNT concentration increased from 0.11 to 10 $\mu\text{g/mL}$.²⁰⁴ Dose- and time-dependent effects were apparent in human peripheral blood lymphocytes exposed to oxidized or pristine MWCNTs.³⁰ Nano-SiO₂ caused cytotoxicity and induced the apoptotic pathway in dose- and time-dependent manners.³⁹⁸ In zebrafish embryos, silver nanoparticles induced dose-dependent embryotoxicity and multiple developmental abnormalities.¹⁷⁸ Silver nanowires show dose-dependent cytotoxicity from 1.9 to 1900 $\mu\text{g/mL}$ in human laryngeal epithelial and cervical carcinoma cells.¹ Carbon black and fullerene (C₆₀) manufactured nanoparticles were genotoxic in vitro and in vivo in a dose-dependent manner.³⁵³

Size and Surface Area

Despite a comparable exposure on a mass-for-mass basis, nanoparticle toxicity may diverge significantly from bulk material. This may occur due to several factors including increased surface area, chemical reactivity, or ionization; altered absorption profiles; altered cellular interactions; or access to “protected” intracellular spaces. Cobalt-ferrite particles (6 nm) were more cytotoxic and genotoxic than 10 or 120 μm particles.⁵⁵ Cytotoxicity of amorphous silica particles increased 33-fold as particle size decreased from 104 nm to 14 nm.²³⁵ Elemental carbon particles (5–10 nm) induced significantly more inflammatory mediators than larger carbon black particles (14 or 51 nm).¹⁶ CoCr nanoparticles generate more superoxide and hydroxyl free radicals and more DNA damage than CoCr microparticles, possibly due to faster dissolving or corrosion within the cell.²⁶² TiO₂ nanotubes (diameter 15–30 nm) permitted the best cellular adhesion, migration, viability, and differentiation compared to larger 50 nm nanotubes.²⁶⁶ CdTe QDs of approximately 2, 4, and 6 nm had over a six-fold difference in inhibition of human hepatoma cell growth.⁴⁰⁵ CdTe QDs (2.1 nm) can rapidly enter the nucleus of human macrophages and gold nanoparticles (1 nm) can penetrate cell and nuclear membranes.^{231,356} CdTe QDs (2.2 nm) were more cytotoxic than equally charged, larger QDs (5.2 nm).¹⁹³ Nano-tungsten carbide-metallic cobalt particles (~80 nm) generated more hydroxyl radicals, induced greater oxidative stress, and caused faster cell growth/proliferation than fine (4 μm) particles.⁶⁸

Composition

Toxicity may be primarily related to that of the bulk material. Elemental carbon particles (90 nm) were found to be significantly more toxic than diesel exhaust particles of comparable size (120 nm).³²⁰ Redox-active transition metals may pose a particular hazard.⁷³ Gold, chrysotile asbestos, Al₂O₃, Fe₂O₃, ZrO₂, and TiO₂ nanoparticles differed in cytotoxicity in murine lung macrophage cells.³³⁰ QD core materials (cadmium, lead, selenium) can be toxic at relatively low concentrations to the plasma membrane, mitochondrion, and nucleus.^{52,120,194} Degradation of coated nanoparticles in the acidic and oxidative conditions of endosomes and lysosomes may result in exposure to inherently toxic core materials or ions. Derivatization or degradation may mitigate or exacerbate toxicity. Functionalization with quaternary amines prevented silica mesoporous nanomaterial-induced cellular injury.³⁴² Conversely, compared to “pristine” SWCNTs, acid-functionalized SWCNTs blocked cell cycling of murine lung epithelium cells, and produced a more pronounced inflammatory response in mouse lungs in vivo.³⁰⁹ Similarly, oxidized MWCNT were significantly more toxic to human T cells than their “pristine” counterparts or carbon black.³⁰ Decay of certain water-soluble fullerenes produces daughter compounds with increased toxicity in vivo.²⁰

Contaminants

Contaminants may introduce or mitigate toxicity. “Doping” intentionally introduces impurities in order to modify the behavior of materials (eg, electrical properties of semiconductors). Similarly, doping can change the electronic, optical, and magnetic properties of nanocrystals.²⁴⁶ Nitrogen doping of MWCNTs improved biocompatibility and reduced lethality in mice exposed via multiple routes.⁴³ Nitrogen-doped MWCNTs also proved more biocompatible in *E. histolytica*.⁸¹

The manufacturing process may unintentionally instill contamination—atomic or molecular impurities in the nanomaterial structure itself, residual reagents or catalysts, or manufacturing byproducts. Even “purified” SWCNTs retain significant percentages of cobalt, molybdenum, iron, nickel, yttrium, and zinc.^{170,203} Consequentially, non-purified, iron-rich SWCNTs (26 wt.% of iron) generated hydroxyl radicals and lipid hydroperoxides and depleted GSH more than “purified” SWCNTs (0.23 wt.% of iron).¹⁴⁴ Purified fullerenes generate significantly less biological oxidative damage and adverse mitochondrial effects than unrefined fullerenes.^{17,285} Residual contaminants and impurities of substances used in surface modification of QDs are cytotoxic and genotoxic in vitro.¹³⁰ Washing off unbound cetyltrimethylammonium bromide eliminated near total lethality of gold nanoparticles modified with this compound.⁵⁶ Single walled carbon nanohorns, prepared from pure graphite without a metal catalyst, showed no skin irritation, eye irritation, or perioral toxicity.²¹⁸

Coating and Surfactant Materials

Coating materials may shield toxicity of core compounds or possess inherent toxicity. They can mediate biocompatibility, duration of circulation, and organ- or cell-specific uptake. For example, various densities of electrostatic poly(glutamic acid)-based peptide coatings altered delivery of cationic polymer-plasmid DNA nanoparticles to liver, spleen, and bone marrow.¹²¹ QDs coated with carboxylic acids, amines, or PEG increased uptake by human epidermal keratinocytes in that order, with carboxylic acid-coated QDs demonstrating cytotoxicity 24 hours earlier.³⁰⁰ Nanoparticle cores of 2-diethylamino ethyl methacrylate polymerized with poly(ethylene glycol) dimethacrylate were significantly more toxic to dendritic cells than cores surrounded by a 2-aminoethyl methacrylate shell.¹³² Upon inhalation, SiO₂-coated rutile TiO₂ nanoparticles but not uncoated rutile or anatase or nanosized SiO₂ induced pulmonary neutrophilia and inflammatory markers.²⁹⁵

Conversely, covalent materials may reduce toxicity. Carboxylic acid grafting of cobalt-ferrite nanoparticles reduced toxicity by reducing leaching of Co²⁺ into solution.⁵⁵ Gelatin coating reduced (but did not eliminate) cytotoxicity of CdTe QDs in human acute monocytic leukemia cells.⁴⁰ PEG substituted CdSe core/CdS shell QDs were less cytotoxic extracellularly than “bare” QDs.⁴⁵ However, some benign coatings can be rendered cytotoxic by air exposure or photodecomposition.⁶⁵

Nanoparticles tend to aggregate due to attractive forces (van der Waals), and become progressively difficult to re-disperse as size decreases.²⁸⁰ SWCNTs agglomerations induced significantly more adverse effects than identical, well-dispersed SWCNTs.³⁷⁹ As CNTs are intensely hydrophobic, solvents or surfactant materials are used to disperse them and avoid clumping, although these materials themselves may be cytotoxic.³⁷⁹ Exposure to protein rich biological fluids may change the tendency to agglomerate, and therefore produce size-dependent effects. Using surfactants to disperse nanoparticles (eg, SWCNTs) can decrease protein adherence, and therefore alter biological effect or fate.^{78,103}

Geometry and Architecture

Nanoparticle geometry may modulate toxicity and biological interactions. Previous observations suggested that toxicity might vary with the type of crystalline structure of a given material. For example, asbestos particle shape affects genotoxicity, and inflammatory and mutagenic properties vary by silica type (crystalline or amorphous).³¹¹ Identical concentrations of various aluminosilicate zeolite crystals (erionite, mordenite, and synthetic zeolite Y) of 0.1 to 10 micron size produced variant cytotoxicity and hydroxyl radical generation in rat lung macrophages.⁸⁶ Material surface defects are important for ROS generation: amorphous TiO₂ crystals were found to generate significantly more ROS than anatase, mixed anatase/rutile, or rutile crystals.¹⁴⁰ In a separate analysis, nano-TiO₂ (anatase) generates more biological oxidative damage than nano-TiO₂ (rutile),¹⁷ and generally anatase nano-TiO₂ is more photocatalytic than the rutile form.³⁵⁹

High aspect ratio is thought to contribute to nanoparticle pulmonary toxicity, including penetration of the alveolar wall and visceral pleural.^{73,215} SWCNT produced pulmonary granulomata and inflammation, whereas nanoparticle carbon black did not.^{17,203,325} “Long” (825 nm) CNTs, which were less easily enveloped by macrophages than their 220-nm counterparts, increased the degree of inflammatory response in rats.³⁰⁷ Asbestoslike pathology was also seen for “long” MWCNT (nanometer diameter, 15+ μ m length) in mice.²⁷⁶ In mice, single wall nanohorns showed significantly less toxicity than SWCNTs.¹⁹⁷ Nanofibers and graphene nanoplates with high aspect ratios but low aerodynamic diameter can persist to frustrate macrophage engulfment and contribute to toxicity.³¹² However, gold nanorods had significantly less cellular uptake than comparable spherical structures.⁵⁰ This geometry dependence was reversed upon PEGylation.²⁰² Attachment by

HepG2 cells to micelles with PEG copolymer films varied depending on whether PEG polymer was in a “brush” (anchored at one end) or “mushroom” (anchored at both ends) conformation.¹³² Compared to control wafers of the same composition, Fe-Co-Ni nanowires hindered macrophage growth and development.³ Dendritic clusters consisting of aggregated 60 nm nickel nanoparticles produced higher embryonic toxicity than spherical 30-, 60-, and 100-nm particles of the same material.¹³⁶

Additionally, nanoparticles may adsorb varying layers of surrounding biological proteins or lipids, altering effective size, shape, and density. Curvature and size of the nanoparticle may affect the extent of this “corona” and influence interactions with bound proteins such as albumin, apolipoprotein, and complement which may effect cells entry or receptor interactions.^{196,310} Bioassociation may also change nanomaterial properties. ZnO nanoparticles changed particle size, distribution, and charge in the cell culture media.³⁷⁵ SWCNTs adsorbed with serum proteins (primarily albumin) had an antiinflammatory effect, which was lost when surfactant-treated SWCNTs precluded adsorption.⁷⁸ The same authors found, in contrast, prevention of protein adsorption to amorphous silica particles reduced toxicity.

Charge

Surface charge (zeta potential, ζ P) may significantly alter the physical characteristics of nanoparticles, biological interactions, or effects. Neutral SWCNTs aggregate in aqueous solution; introducing a strong negative charge induces dispersal.³⁰⁹ Negatively charged nanoparticles permeated model pig skin, which excluded positively charged and neutral particles.¹⁶⁰ Increasing surface charge density alters protein absorption; a positive charge promotes electrostatic association with negatively charged serum proteins.^{102,121} Charged nanoparticles are recognized as important inducers of complement activation.⁶⁹ Strongly charged particles can also mediate direct membrane damage (hole formation) in the lipid bilayer.^{128,129} Positively charged polystyrene nanospheres induced oxidative stress, those with neutral charge did not.³⁸⁹ Toxic effects of strongly negatively charged acid-functionalized SWCNTs were abrogated by pretreatment with neutrality-inducing L-lysine.³⁰⁹ Positive charge mediates actin-dependent amorphous silica nanoparticle movement along filopodia and microvillilike structures.²⁵⁷ Mouse peritoneal macrophages and human hematopoietic monocytic cells show charge-dependent endocytosis—the higher the negative or positive surface charge of albumin particles, the greater the uptake.²⁹⁴ An overlap of the conduction band energy (E_c) level of metal oxide nanoparticles with the cellular redox potential (−4.12 to −4.84 eV)—which signifies the permissibility of electron transfers in biological environments—correlated with induction of oxygen radicals, oxidative stress, and inflammation.⁴⁰⁴ Also, within lysosomes, positively charged nanoparticles are capable of acting as “proton sponges,” enhancing cytoplasmic delivery and inducing cell death signaling.³¹⁷

pH

pH might be expected to effect toxicity by altering charge, solubility, protective or functional groups, bioavailability, and other mechanisms. pH alters the zeta potential of both microemulsion (3–5 nm) and hydrothermal (8–10 nm) cerium oxide nanoparticles, which in turn alters protein adsorption and cellular uptake.²⁶⁷ The significant toxicological difference in mice between 23.5 nm and 17 μ m copper particles was judged secondary to stomach retention, with persistent depletion of H^+ ions leading to systemic metabolic alkalosis and generation of ionic copper.²¹⁴ CdSe core QDs exposed to low-pH simulated gastric fluid decreased cell viability in vitro, possibly due to degradation of the ZnS shell and increased solubility of cadmium from shell-free particles.³⁷³ Acidic intracellular organelle localization raises degradation and damage concerns; the inflammatory potential of 15 metal/metal oxide nanoparticle correlated with acidic conditions, hypothesized to be related to elimination of the corona in lysosomes to expose a charged surface.⁵¹ Targeted drug delivery employs intentional engineering of pH-responsive nanoparticles. In the acidic environment of the endosome or lysosome (~ pH 4.5), core-shell particles can swell by almost 3 times, disrupting these structures and allowing cytosolic entry.¹³² Alternatively, at altered pH, certain functional groups can be cleaved, resulting in altered charge and improved QDs delivery.²²¹

Cellular Toxicity

At the cellular level, nanoparticle toxicity has been attributed to multiple mechanisms (Fig. 129–3). Oxidative stress, membrane and cytoskeleton structural alterations, cytoplasmic and nuclear protein interactions, energy failure, phototoxicity, and genotoxicity have all been described. Nanoparticles may stress cell types differently. This may be due to engineered properties (associated targeting molecules), properties of nanomaterials themselves (size-dependent reticuloendothelial system deposition), or biological processes of target cells (eg, phagocytosis ability, resistance to oxidative stress, cytoskeletal architecture, cell division propensity). Tests in immortalized cell lines may not reflect in vivo findings due to inherent differences in genomic stability or specifically selected traits.

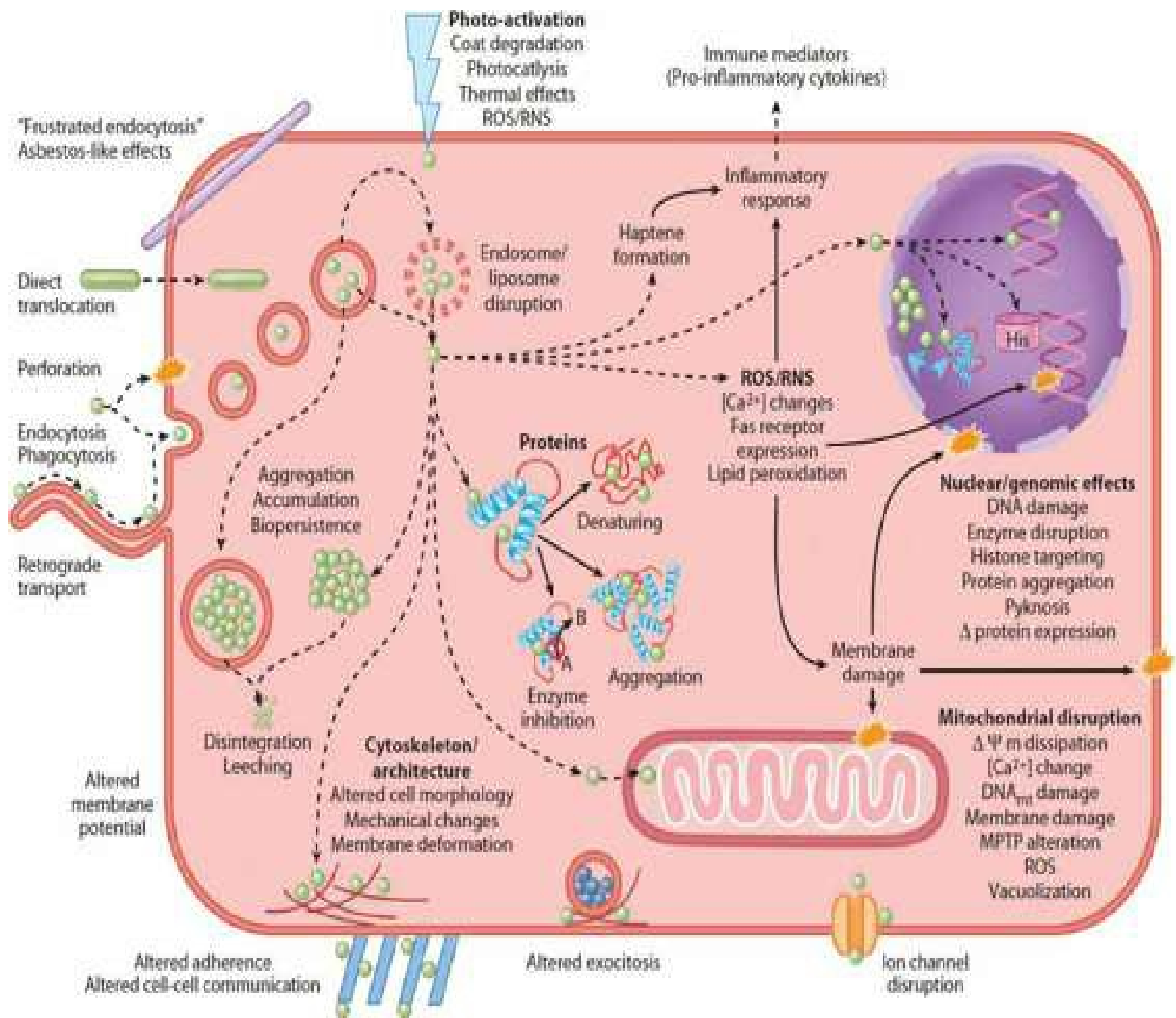


FIGURE 129-3. Potential mechanisms of nanoparticle cellular toxicity. $\Delta\psi_m$ = mitochondrial membrane potential, DNA_{mt} = mitochondrial DNA; His = histone; MPTP = mitochondrial permeability transition pore; RNS = reactive nitrogen species; ROS = reactive oxygen species.

Uptake. Unintended cellular uptake may contribute to toxicity. Depending on the particle architecture, several mechanisms have been described, including phagocytosis/endocytosis (clathrin-mediated scavenger receptor-mediated, mannose receptor-mediated, Fcγ receptor-mediated, complement receptor-mediated), potocytosis (caveolin dependent), (macro)pinocytosis, and direct cytoplasmic entry^{70,99,239,265,322,348,362} Various types of ammonium-, acetamido-, fluorescein isocyanate-, and methotrexate/fluorescein isocyanate-functionalized SWCNTs and MWCNTs were internalized by a wide range of cell lineages (mammalian, fungal, yeast, and bacterial), some of which lack phagocytic and endocytic capacity, and under conditions which block energy dependent pathways¹⁶² Dextran-coated supermagnetic iron oxide (SPIO) nanoparticles are taken up by human monocyte-macrophages and concentrated into lysosomes in a nonsaturable manner²²⁸ Nonendocytic uptake (eg, 78-nm fluorescent polystyrene microspheres and 25-nm gold particles) provides nonmembranebound nanoparticles direct access to intracellular proteins, organelles, and DNA¹⁰⁰

Engineered nanoparticles, which are capable of endocytosis, would be expected to translocate to distant sites within the body.⁸²

Oxidative Stress. Oxidative stress with subsequent lipid peroxidation, DNA damage, and apoptotic or necrotic pathway induction is a significant concern. Biologic oxidative damage as assessed by the ferric reducing ability of human serum revealed a diverse capacity for oxidative potential among nanoparticles.¹⁷ Metal oxide nanocompounds (eg, Co_3O_4 , Cr_2O_3 , Ni_2O_3 , Mn_2O_3 , and CoO) capable of electron transfers effectively produce oxygen radicals and oxidative stress.⁴⁰⁴ Research findings are complicated by differences in generation of reactive oxygen species (ROS) under abiotic conditions

versus intracellularly.³⁸⁹ Biological mediums may also alter ROS generation.⁹² In neuroblastoma cells CdTe QDs induced lipid peroxidation and Fas cell death receptor upregulation, which could be mitigated by capping QDs with N-acetylcysteine.⁵² Adult zebrafish raised in solutions containing silver nanoparticles demonstrated oxidative injury, apoptosis, and cellular stress response (eg, GSH and p53 induction).⁵⁴ Fullerenes have shown more conflicting results. Depending on experimental conditions and purity, they may either induce $O_2^{\bullet -}$ and OH^{\bullet} or possess antioxidant (and antiperoxidation) activity.^{104,392} SWCNTs and tungsten carbide-cobalt nanoparticles generate ROS and activate pathways leading involved in cytotoxicity and neoplastic transformation.^{68,204}

Organelle and Substructure Damage. Nanoparticles may compromise diverse subcellular components. Mitochondrial reduction capacity (eg, MTT assay) is one of the standard in vitro methods to assess nanoparticle toxicity. Nanoparticles' mitochondrial toxicity includes alterations in mitochondrial calcium levels, dissipation of the mitochondrial membrane potential, lipid membrane destruction, and localization within the mitochondria.^{52,194,260,389} Small gold nanoparticles (3 nm) can access the voltage-dependent anion channel (porin) to cross the mitochondrial membrane.³⁰¹ Induction of the mitochondrial base excision repair pathway enzymes suggests that MWCNTs can induce mitochondrial DNA damage.⁴⁰⁶ Polyamidoamine (PAMAM) dendrimers (45 nm) can down-regulate mitochondrial DNA-encoded genes involved in the maintenance of mitochondrial membrane potential and caused the release of cytochrome C, triggering apoptosis.¹⁷⁷

QDs (2.1 nm) have been visualized to localize rapidly (< 30 minutes) and preferentially in the nucleus of human macrophages, mediated by endosomal transport along microtubular tracks.²³¹ Co_3O_4 nanoparticles (45 nm) readily enter cells and their nucleus in vitro.²⁶³ SWCNTs can accumulate in the cell nucleus by crossing the lipid bilayer.²⁷⁷ Genotoxic consequences of this migration are described later.

Nanoparticles may cause disruption and compromise integrity of biological membranes by such means as hole formation in the lipid bilayer.^{128,129} Alteration in cellular adherence, migration, and actin cytoskeleton or microtubule function and structure have been described following exposure to SWCNTs, gold/citrate, TiO_2 , and SPIO nanoparticles.^{95,106,113,145,270} Calcium-mediated cytoskeletal function (as evidenced by cell stiffening) was altered by ultrafine carbon particles (12 nm, 90 nm) but not by diesel exhaust or urban dust particles.²²³ Functional processes may be impaired in the absence of the loss of viability. SiO_2 , TiO_2 , Ag, and Au, alone or functionalized with either positive or negative side chains, altered exocytosis and decreased secretion of chemical messenger molecules.^{191,209} Other protein functions may also be altered by nanoparticles. Copper nanoparticle clusters selectively induced unfolding and precipitation of hemoglobin A0 and E, whereas almost none occurred with hemoglobin A2.²⁴ Nanoparticulate anatase TiO_2 (5 nm) can directly bind lactate dehydrogenase and induced protein unfolding.⁷⁵ C_{60} fullerene noncompetitively inhibits glutathione peroxidase in a substrate-specific manner.¹³⁷ While relatively high concentrations were required (250 μM), the C_{60} fullerene derivative, dendrofullerene, selectively inhibited P450 metabolism of progesterone.⁹¹ Modification of protein structures by reactive nanoparticles might also serve as a mechanism for haptene formation and immunoreactivity.

Gene Expression and Genotoxicity. Overwhelming nanoparticle toxicity can induce a cascade of expression of genes involved in either apoptotic or necrotic pathways. Nanoparticles can also upregulate stress-and inflammation-related genes as well as alter expression of genes involved in the cytoskeleton, trafficking, protein degradation, metabolism, growth and division, and detoxification. As a consequence of direct nuclear entry, nanoparticles can aggregate within the nucleus, bind directly to DNA or chaperone proteins, or induce nuclear membrane damage. Gold clusters (1.4 nm) present in growth media can access and directly associate with the major grooves of DNA to induce complete cell death in multiple carcinoma cell lines at concentrations at which cisplatin is only 10% effective.^{260,356,382} Nanosilver materials similarly bind with E coli genomic DNA.³⁹⁶ Some QDs can target histones.²³¹ Other nanoparticles (eg, SiO_2) can cause clustering of critical enzymes such as topoisomerase I and sequestration of nuclear proteins (histones, splicing factor SC35, nucleolar protein fibrillarin, promyelocytic leukemia body protein PML, and p80 coilin), altering subnuclear architecture.⁴⁸ DNA damage also occurs through induction of ROS.²²²

Nanoparticle damage may be addressed by base repair and other restorative mechanisms or may be so severe that DNA strand breaks, genome duplication or deletion, chromosomal instability, aneuploidy, malignant transformation, and proliferation occur in vitro and in vivo.^{133,355,406} Poorly tumorigenic or benign cells can acquire aggressive metastatic capacity when exposed to TiO_2 nanoparticles.²⁵⁴ Alternatively, premature senescence was recently described using a C_{60} carboxylated adduct. Such an ability could be protective as a tumor suppression mechanism or compromise organ systems function.⁹⁶

Photothermal Toxicity. Nanoparticles containing photo-reactive dyes or intrinsic photothermal properties are useful for imaging and attractive for targeted chemotherapy. The approved liposomal verteporfin (benzoporphyrin derivative monoacid ring A) generates 1O_2 following activation by low-intensity nonthermal laser light (689 nm). This is believed to induce cell death and prevent the loss of visual acuity in patients with subfoveal choroidal neovascularisation.¹⁵¹ Similarly, dextran-iron oxide nanoparticles linked to a photosensitizer which generates singlet oxygen caused complete cell death

when exposed to specific light wavelengths²¹³ Nonmetal graphene QDs irradiated with blue light (470 nm) generated reactive oxygen species, including singlet oxygen, and killed human glioma cells by causing oxidative stress mechanism²⁰⁶ C₆₀(OH)_{22–26}, a water-soluble C₆₀ derivative under investigation as an antitumor, antibiotic, and drug delivery compound, was only mildly cytotoxic in the dark, but was significantly phototoxic to human lens epithelial cells via both type 1 (free radical) and type 2 (singlet oxygen) mechanisms under visible light³⁸⁰ The concern is that ambient electromagnetic radiation could excite nontherapeutic nanoparticles to generate either ROS or thermal injury. Photolytic conditions have rendered coatings unstable, exposing toxic core metal components¹²⁰ Irradiation of TiO₂, which can act as a photocatalyst, yields both oxidation and reduction reactions⁹⁴ Gold/citrate nanoparticles (13 nm) were capable of easily crossing human dermal fibroblast membranes and absorbing UV radiation²⁷⁰ C₆₀ fullerenes can generate ROS in the presence of visible light under physiologic conditions³⁹³ The ROS extent depended upon C₆₀ aggregation and associated stabilizing molecules in the aqueous phase¹⁷⁶

A host of miscellaneous cellular effects are still being characterized. Alterations in cellular resting membrane potential and ion channel functioning by metallic and carbon-based nanoparticles are a particular concern in neuronal tissue.^{18,185} Silver nanoparticles caused conformational changes of neuronal voltage-activated sodium currents and produced a hyperpolarizing shift and delayed recovery from inactivation.¹⁸⁶ QDs can provoke intracellular lipid droplet formation due to accumulation of newly synthesized lipids and down-regulation of the β -oxidation of fatty acids.²⁸⁴ SPIOs can generate intracellular gas vesicles.²⁰¹

Organ Systems Toxicity

Central Nervous System. A significant concern is the ability of nanoparticles to access “protected” spaces, such as the brain, the eye, and the reproductive tract. While targeted CNS drug delivery and imaging using engineered nanoparticles via intranasal or intravenous administration shows promise^{88,150} unintended access is worrisome

Seventy years ago, intranasal inoculation of small viral (nano)particles (the poliomyelitis virus, 25–30 nm) were shown to produce extensive polio invasion of the olfactory bulbs and lesions extending in a continuous series to the brain stem and beyond.^{26,27,131,354} Other small viruses (vesicular stomatitis, herpes simplex, and rabies virus) also access retrograde transport from the olfactory bulb to reach deeper brain structures.²⁹⁰ Anthropomorphic and engineered nanoparticles also may utilize this mechanism, with variable efficacy. Nanogold particles injected into rabbit olfactory areas demonstrated a direct connection between the olfactory bulb and the CSF.⁵⁸ Intranasal instillation of SiO₂-nanoparticles in rats led to wide distribution, striatal deposition, and a reduction in dopamine activity.³⁸⁵ In inhalation-exposed rats, ultrafine elemental ¹³C particles translocated into axons of the olfactory nerve.²⁵⁰ Rats exposed to aerosolized gold nanoparticles (20 nm) experienced particle distribution to the olfactory bulb and entorhinal cortex.⁴⁰² Rats exposed to poorly soluble manganese oxide ultrafine particles (30 nm) showed olfactory bulb uptake and CNS delivery to the striatum, frontal cortex, and cerebellum.⁷⁹ Other animal models demonstrated that cadmium, cobalt, manganese, mercury, nickel, and zinc reach the olfactory bulb when applied intranasally, and neuronal connections carry cobalt, manganese and zinc into deeper brain structures.^{35,123,271,352} Children and dogs exposed to pollution show prefrontal white matter hyper-intense lesions, associated with significant cognitive deficits in children. Ultrafine particulate matter deposition, vascular pathology, and neuroinflammation were evident in the dogs.⁴¹ Chronic respiratory tract inflammation might further diminish nasal respiratory and olfactory barriers and contribute to brain inflammation.²⁷³

Circulating nanoparticles may reach the brain. The blood–brain barrier (BBB) might be infiltrated via low density lipoprotein (LDL)–receptor mediated transcytosis of nanoparticles with nonspecific apolipoprotein adherence, endocytic processes, paracellular aqueous diffusion, or transcellular lipophilic diffusion.^{88,316} Intravenously administered water-soluble fullerene and intra-abdominally injected nano-TiO₂ (5 nm, anatase) migrate to brain in experimental models.^{88,391} Nanoparticle entry can produce CNS inflammatory changes, inflammatory gene expression, demyelination, oxidative stress, lipid peroxidation, NO generation, and altered mitochondrial energy production.^{42,79,188,198,318} Cyclooxygenase-2, interleukin-1 β , and CD14 upregulation in the olfactory bulb, frontal cortex, substantia nigrae, and vagus nerves and disruption of the BBB associated with particulate matter deposition were reported in patients exposed to high chronic pollution levels.⁴² Similarly, intravenous and intraperitoneal administration in rats of engineered silver, copper, and aluminum nanoparticles disrupted the ventral brain and proximal frontal cortex BBB to produce brain edema.³¹⁸

Nanoparticles can contribute to secondary excitatory neurotoxicity. Intranasal delivery of carbon black (14 nm) increased olfactory bulb excitatory glutamate levels.³⁵¹ Similarly, nano-Ag increased spontaneous excitatory postsynaptic currents and network activity.¹⁸⁷ Given the number of CNS and systemic human amyloidoses, a concerning finding was that polymer nanoparticles, quantum dots, carbon nanotubes, and cerium nanoparticles all greatly enhanced the rate of β_2 -microglobulin amyloid fibrillation by decreasing lag time for nucleation.¹⁸⁴ Chronic dietary exposure to TiO₂ nanoparticles

in juvenile rainbow trout led to brain accumulation and 50% inhibition of Na⁺-K⁺-ATPase activity, which did not recover following removal from exposure.²⁸⁸

Pulmonary System. The lungs are expected to be the major portal of entry for anthropomorphic nanoparticles and engineered nanoparticles in manufacturing or research settings. Concerns include nanoparticle accumulation and persistent, acute and chronic inflammation, and surfactant disruption. In the bronchial airways, 24 hour retention depends on size fraction, which is negligible for particles greater than 6 µm but increases to 80% at 30 nm.¹⁶⁵ In vitro studies show a variety of effects depending on the particle and experimental model. Canine and human alveolar macrophages uptake of elemental carbon particles (5–10 nm) induced lipid mediators AA, PGE₂, LTB₄, and 8-isoprostane in a dose-dependent fashion.¹⁶ SWCNTs activated alveolar macrophages, SWCNTs and C₆₀ fullerenes disrupted plasma membranes, and SWCNT and MWCNTs effected antigen processing, presentation, and activation of T lymphocytes.¹¹⁶ In rat alveolar type 2 and epithelial cells as well as in human bronchial epithelial cells nanoparticulate carbon black particles (14 nm) induced dose-dependent proliferation via EGF-R and β1-integrin membrane receptors, phosphoinositide 3-kinases, and the protein kinase B (Akt) signaling cascade.³⁶³ Cerium oxide nanoparticles can be taken up by human fibroblasts.¹⁸³ However, 3 hour exposures to aerosols of this fuel additive, while increasing catalase activity and minimally decreasing glutathione, did not alter cell viability, ATP content, TNF-α production, glutathione peroxidase activity, or superoxide dismutase activity in rat lung slices.⁸⁷ Combustion-derived nanoparticles of organic compounds (1–3 nm) were mutagenic in Ames tests.³¹⁵ Positive evidence for carcinogenicity of inhaled nanoparticles has been summarized.²⁹³

All types of carbon nanotubes and nanofibers are considered a respiratory hazard by the National Institute for Occupational Safety and Health (NIOSH).²³⁸ Carbon nanotubes can produce a variety of adverse effects in animal models: upper airway mechanical blockage, occlusive airway granulomas, macrophage uptake and inter-macrophage carbon bridges, abnormal macrophage mitoses, type I pulmonary epithelial cell damage, lymphocytic proliferation, multifocal granulomas, aggregation in alveolar spaces and interstitium, increased inflammatory and oxidative stress biomarkers, fibrinogenic reactions, alveolar wall thickening, bronchiolar epithelial cell hypertrophy, and peribronchial inflammation.^{143,170,203,226,238,324,374} At high doses, mice exposed to MWNTs orally, intraperitoneally, or via nasal installation showed essentially no tissue response, whereas intratracheal administration showed dose-dependent pulmonary tissue invasion, inflammation and granuloma formation, and death.⁴³ Mice aspirating 40 µg of SWCNT and acid-functionalized SWCNTs had significantly higher BAL cell counts, PMNs, and cytokines (IL-6, TNF-α, and MIP2).³⁰⁹ Also of concern are MWCNT retention, persistent inflammation, and asbestoslike effects suggested by in vitro and in vivo experiments.^{275,298,330} A systematic review of 54 animal studies indicated that carbon nanotubes and nanofibers caused adverse pulmonary effects including inflammation (44 of 54 studies), granulomas (27 of 54), and pulmonary fibrosis (25 of 54), which were similar to other fibrogenic materials such as silica, asbestos, and ultrafine carbon black.²³⁸ Mice receiving both a known initiator chemical plus inhalation exposure to MWCNT were significantly more likely to develop tumors (90% incidence) and have more tumors than mice receiving the initiator chemical alone, suggesting that MWCNT can increase the risk of cancer in mice exposed to a known carcinogen.²³⁸

While rats exposed to C₆₀ fullerenes nanoparticles (55 nm) for 10 days did not have visible of microscopic pathological lesions, particle burden and BAL protein concentrations were elevated.¹¹ Intratracheally delivered single wall nanohorns generated no inflammatory response, although nanohorns accumulated and persisted.²¹⁸ Intratracheal instillation of ultrafine (< 200 nm) particles from combusted coal induced a higher degree of neutrophil inflammation and cytokine levels than did the fine or coarse particles.¹⁰⁹ Rats intratracheally instilled with ultrafine carbon black or TiO₂ demonstrated neutrophil recruitment, type 2 epithelial cell damage, cytotoxicity, impaired macrophage phagocytic ability, and enhanced macrophage sensitivity to chemotactins.²⁹¹ A summary of nanosized TiO₂ particle effects concluded that the crystalline form has the greatest impact on pulmonary responses, whereas particle surface area, alumina or amorphous silica coating, and shape have lesser influences on toxicity.¹⁹⁹ Nasal instillation resulted in neutrophil recruitment. Alveolar macrophages took up inhaled elemental silver nanoparticles, and deposition in the alveolar wall was noted.³³⁹ While particles were rapidly cleared from lungs, there was evidence of circulatory spread. Longer-term studies showed significant silver lung persistence, chronic macrophage accumulation and alveolar inflammation, and systemic distribution.³³⁷ The severe toxicity of air-generated polytetrafluorethylene (PTFE fumes) can be reduced by aging, filtering, and preexposure, suggesting nanoparticle upregulation of pulmonary inflammatory cytokines and antioxidants.¹⁴²

Pulmonary surfactant provides low surface tension and can identify and bind targets for phagocytosis. Independent of cellular effects, in vitro lung models suggest that nanoparticle deposition may cause pulmonary surfactant dysfunction during the breathing cycle.¹⁴⁸ The collectins (phagocytosis enhancers), human surfactant protein-A and -D, bind double wall carbon nanotubes in a calcium-dependent manner.³⁰³ Diesel exhaust particulate matter can be solubilized and dispersed in the major component of pulmonary surfactant (dipalmitoyl phosphatidyl choline) and induce genotoxicity in multiple different assays in bacteria and mammals.^{303,370}

A report of uncontrolled workplace exposure to polyacrylic ester nanoparticles and other materials causing retained

intracellular nanoparticles, pulmonary inflammation, pulmonary fibrosis, and pleural foreign-body granulomata was criticized for lack of causality and differential diagnosis.^{32,329} Similarly, a report of submesothelial deposition of carbon nanoparticles after toner exposure has been criticized for lack of plausibility and causality.^{347,378}

Cardiovascular and Hematological Systems. Ultrafine particles can alter human cardiac function (decreasing heart rate variability and repolarization^{67,119,350,367,403} Heart rate variability provides a measure of cardiac autonomic control; a decrease predicts mortality in subjects with prior myocardial infarction³⁵⁰ Significant pulmonary inflammation is not a prerequisite, although autonomic reflexes from pulmonary nerve endings may mediate these effects¹⁰⁵ Jugular vein or femoral artery administration of silver, copper, and aluminum nanoparticles immediately but transiently slows heart rate³¹⁸ Engineered nanoparticles made of flame soot (Printex 90), spark discharge generated soot, anatase TiO₂, and SiO₂ induced catecholamine-mediated dose dependent increases in heart rate and dysrhythmias in Langendorff heart model systems³³¹ Human wood smoke exposure increases levels of serum amyloid A (a cardiovascular risk factor) and factor VIII in plasma¹⁵ Inhaled TiO₂ nanoparticles impair rat coronary arteriole endothelium-dependent vasoreactivity and relaxation, likely due to microvascular ROS¹⁷³

Intravascularly, nanoparticle characteristics and concentration determine leukocyte and immune stimulation (detailed in a later section), erythrocyte effects, thrombogenesis, endothelial dysfunction, and atherogenesis. Dendrimers can adversely alter human erythrocyte morphology, induce clustering, and provoke significant hemolysis.^{72,77} Dendrimer generation, concentration, charge, exposure duration, and material type determine the extent to which this occurs. Intravenously provided diesel exhaust particles aggregate within erythrocytes, decreasing counts.²⁴³ Polycationic (but not neutral or anionic) water-soluble fullerene C₆₀ derivatives, surfactant stabilized poly (lactic coglycolic) acid (PLGA) nanoparticles, and polystyrene nanoparticles all induce significant hemolysis.^{29,155,210} Chitosan/pDNA and uncoated polymer nanoparticles both induce significant hemoagglutination.^{121,190}

Engineered and combustion-derived carbon nanoparticles (MWCNTs, SWCNTs, and mixed carbon nanoparticles) stimulated human platelet aggregation, activation of GPIIb/IIIa, and accelerated the rate of vascular thrombosis in rat carotid arteries.²⁸⁷ The effect on platelet aggregation was aspirin-resistant but was reduced by low affinity (P2Y₁₂) ADP receptor antagonism. Multiple metal nanoparticles (iron, copper, gold, cadmium sulfide) also induced dose-dependent platelet aggregation through the P2Y₁₂ ADP receptor; an effect was blocked by clopidogrel.⁶² Epidemiologic studies support an association between exposure to particulate matter of less than 10 microns and increased risk of deep venous thrombosis.⁹ Diesel exhaust particles (20–50 nm) and positively charged polystyrene nanoparticles cause rapid activation of circulating blood platelets and microcirculatory thrombi.^{240,242} Healthy volunteers exposed to concentrated ambient air particles increase fibrinogen levels.¹⁰⁷

Compared to larger particles, ultrafine particles produce larger atherosclerotic lesions, decrease the antiinflammatory effect of HDL, and induce oxidative stress in susceptible animal models.⁶ At doses which produced no significant pulmonary inflammatory changes, rats exposed to nano-TiO₂ aerosols display systemic impaired endothelium-dependent arteriolar dilation, outright constriction, and decreases in NO bioavailability by increasing local reactive oxidative and nitrosative species.²⁴⁷

Immune System. Nanoparticle interaction with the immune system is complex: depending on biophysiochemical properties, nanoparticles can stimulate, silence, or elude immune responses⁴⁰⁷ Most concerning is induction of chronic inflammation. Work in murine macrophage cells lines demonstrated that MWCNTs produced a cytotoxic response nearly identical to asbestos³³⁰ Commercially and academically available MWCNTs induced asbestoslike, length-dependent pathology in mice^{275,360} MWCNTs can reach the subpleura in mice after a single inhalation exposure to produce mononuclear cell aggregates and subpleural fibrosis²⁹⁸ On the other hand, immune suppression may also occur. Fullerene suppression of mast cell-mediated hypersensitivity reactions appears to proceed from endocytosis, endoplasmic reticulum accumulation, intracellular persistence, and the inhibition of calcium and ROS generation⁶⁴

Particle-specific interactions may yield cellular accumulation, antigen mediated-immune stimulation, inflammatory mediator release, or fibrous or granulomata formation. Mouse granulocyte-macrophage colony formation is now a standard testing methodology for assessing nanoparticle toxicity.⁷ Macrophages exposed to Fe-Co-Ni nanowires in vitro increased production of IFN- γ , IL-1 α , IL-4, and IL-10.³ Ultrafine carbon caused macrophages to release²²⁵ lipid mediators arachidonic acid, PGE₂, LTB₄, and 8-isoprostane.¹⁶ Subcutaneously implanted “hat-stacked” carbon nanofibers in rats generated fibrous connective tissue formation and macrophage recruitment and ingestion without inflammatory response (necrosis, degeneration, or neutrophil infiltration).⁴⁰⁰ Intratracheal exposure to nano-sized nickel and cobalt particles induced rat blood neutrophils to release reactive oxygen species and reactive nitrogen species.²²⁰ Human volunteer exposures to concentrated ambient particles (< 200 nm) increased inflammatory blood mediators.¹¹⁰ IV administration of ultrafine diesel exhaust particles promoted monocyte and granulocyte proliferation.²⁴³ Other cell lines can also be induced to release inflammatory mediators. SWCNTs induced human epidermal cells exposed to release interleukin-8. MWCNT

introduced in human neonatal epidermal keratinocytes increased IL-8 and IL-1 β release.³⁸²

Direct immune stimulation can also occur. Fullerenes can induce an IgG response capable of cross-reaction with other fullerenes.^{31,46} The degree of induced opsonization by various IgG and complement molecules is thought to explain part of the differences seen in blood clearance and tissue distribution of nanoparticles.²⁵⁹ Upon readministration, PEGylated liposomes have accelerated blood clearance due to IgM binding; this is inhibited by chemotherapeutics which inhibit B-cell proliferation.¹³⁵ In the absence of direct immune stimulation, carbon nanotubes can boost immune response as adjuvants.²⁶¹ Indeed, pharmaceutical nanoparticles show promises for eliciting polyclonal and monoclonal antibodies to nonimmunogenic haptens as diverse as herbicides, antibiotics, and vitamins.²⁰⁵

Liposome- and polymer-based therapeutic nanomedicines have been compromised by non-IgE mediated hypersensitivity reactions due to complement system activation which releases C3a and C5a anaphylatoxins.⁵ The drug solubilizer Cremophor E-L (polyethoxylated castor oil) forms micelles (8–25 nm) at concentrations above 60 μ g/mL and causes its occasionally severe immune reactions presumable due to complement activation. Carbon nanotubes can activate human complement via both classical and alternative pathways; C1 q binds directly to carbon nanotubes.³⁰² Surface density of coating materials can also alter complement consumption.⁴ Certain dendrimers may also strongly activate the complement system.²²⁶ MnFe₂O₄ magnetic nanoparticles (10-nm diameter) induce severe inflammatory reactions in mice.¹⁶⁹ Microcrystalline silica particles induced a strong Th1 response, whereas carbon black particles and polystyrene particles induced a mixed Th1:Th2 response.³⁶⁸ PLGA-based nanoparticles did not induce complement consumption, indicating that this action is nanoparticle specific.⁴⁴

Ocular System. The ocular system is of particular interest due to its immunological privilege and physiologic characteristics. Therapeutically, nanosuspensions show promise for extended release and decreased drug clearance from the cornea and diminished systemic drug exposure.^{114,283} In vitro studies have shown adverse effects. Silver nanoparticle block the proliferation and migration and inhibit cell survival of bovine retinal endothelial cells.¹⁴⁶ Water-soluble fullerene derivatives are phototoxic to human lens epithelial cells under visible light.³⁸⁰ Conversely graphene oxide nanosheets, even when intravitreally injected, did not demonstrate significant effects.³⁹⁵ Cerium oxide nanoparticles appear to offer a protective effect, scavenging reactive oxygen intermediates in rat retina cell culture.⁴⁷ In vivo confocal neuroimaging conclusively demonstrated negatively charged nanoparticle-rhodamine formulations injected into rat jugular vein crossed the blood-retinal barrier within 40 minutes.²⁸² Intravenously administered gold nanoparticles (20 nm) can bypass the blood-retinal barrier to distribute in all retinal layers within 24 hours.¹⁵⁶

Reproduction and Development. Reproductive effects of nanoparticles are incompletely characterized. One review concluded that nanoparticles can breach the blood-testis barrier and locate in the testes.²¹² Subsequent studies using inhaled fluorescent magnetic nanoparticles (50 nm) and injected gold nanoparticles confirmed testicular distribution and persistence.^{12,168} Chronic intratracheal administration of carbon black (14 and 56 nm) showed similar partial vacuolation of the seminiferous tubules and decreased daily sperm production.⁴⁰¹ Silver nanoparticles caused dose-dependent mitochondrial impairment and cytotoxicity in spermatogonia in vitro; aluminum nanoparticles caused apoptosis.³⁴ Gold nanoparticles can penetrate human sperm cells, resulting in fragmentation and dysmotility.³⁸³ Environmental exposure to relevant concentrations of ZnO, TiO₂, SiO₂ nanoparticles produced reproductive toxicity in nematodes, which was correlated with ROS production and attenuated with antioxidants (ascorbate and N-acetylcysteine).³⁸⁷

Female reproductive effects are less well described. Oral ZnO nanoparticles achieved lactation and placenta transport and resulted in increased post-implantation loss rate, decreased live births, and zinc accumulation in offspring liver and kidney.¹⁴¹ In perfused human placenta models, PEGylated gold nanoparticles (10–30 nm) were retained mainly in the trophoblastic cell layer and internalized by trophoblastic cells and did not cross in detectable amounts into the fetal circulation over 6 hours of evaluation.²³⁰ Aquatic studies have illustrated detrimental reproductive and developmental effects. *Daphnia magna* were unable to reproduce again after exposure during pregnancy to sub-lethal concentrations of water stable fullerenes. Less than 10% of daughter daphnids matured following maternal exposure.³⁴¹ Following exposure to silver nanoparticles (0.1 or 0.5 mg/L for 3 days), nematode offspring decreased by 70%; oxidative stress was the presumed toxicological mechanism.²⁹² In the animal model of organogenesis, medaka (rice fish) eggs easily took up 39.4-nm fluorescent particles and concentrated them in the yolk area and gallbladder during embryonic development.¹⁴⁹ Adults demonstrated diffuse uptake into reproductive organs as well as the brain, liver, intestine, gills, and kidney. Medaka fertilized eggs exposed to silver nanoparticles produced a variety of malformations including systemic edema, hemostasis, and vertebral, finfold, optic, and cardiac abnormalities over the range of concentrations tested (100–1000 μ g/L).³⁸⁸ Altered hormone levels and offspring sex ratios seen in some experimental models of nanoparticle exposure suggest endocrine disruption.^{195,233}

Bioaccumulation and Persistence. Nanoparticles might accumulate in cells, tissues, or organs to achieve threshold toxicities at a later time than initial exposure. At the cellular level, nanocrystals can be passed to daughter cells upon

mammalian cell division^{117,208} Retained fluorescing QDs have been used experimentally to trace *Xenopus* cells from embryo to tadpole stage⁷⁶ As with different fine particles (fiberglass, rock wool, slag wool, asbestos), their biopersistent potential seems to underlie toxic effects¹²⁵ This knowledge drives the concern regarding preliminary studies demonstrating MWCNT persistence, inflammatory induction, and asbestoslike pathology^{225,275,298,338} Compared to sodium selenite, nano-selenium particles displayed hepatic hyperaccumulation and persistence in fish models, with associated oxidative stress and toxicity¹⁸¹ Similarly, uptake, bioconcentration, and alimentary toxicity of TiO₂ nanoparticles were demonstrated in crustaceans⁵⁹ Their transmission and bioaccumulation (by a factor of over 100% in certain species) up the food chain was also apparent³⁹⁹ Nanocrystalline C₆₀ had a greater propensity to accumulate in *D. magna* fetuses due to their higher lipid fraction (including the egg sac yolk) and correlated with higher mortality³⁴¹ Even short-term oral exposure may lead to reticuloendothelial accumulation in some animal models³⁴³

While desirable for chemotherapeutic applications, prolonged periods of persistence could allow leaching and toxicity of initially protected materials.³⁷⁷ Bone marrow deposition of nanoparticles²⁷⁸ could allow for ongoing systemic exposure. Persistence in other compartments could also permit more extensive distribution (eg, translocation from lung tissue). Dextran-coated ultrasmall SPIO particles currently used in clinical trials are retained by human monocyte-macrophages for days.^{227,228} QDs persisted at least 4 months in mice, while those conjugated to bovine serum albumin or coated with mercaptoundecanoic acid underwent negligible elimination in rats.^{13,90} Due to intrinsic resistance to lysosomal degradation, inorganic or metal nanoparticles can have extremely low rates of excretion, resulting in long-term accumulation.³⁷⁷

ADMINISTRATIVE, REGULATORY, AND RESEARCH ISSUE

The 21st Century Nanotechnology Research and Development Act guides US nanotechnology policy.³⁶⁴ Elements include federal interagency coordination, establishment of national strategic plans for nanotechnology, and triennial review by the National Research Council; establishment of a public database for funded environmental, health, and safety (ENS), educational and societal dimensions, and nanomanufacturing projects; fiscal support for a Nanotechnology Coordination Office; mandates for research in environmental, health, and safety; development of nomenclature and engineered nanoscale standard reference materials standards; development of standards for detection, measurement, monitoring, sampling, and testing of engineered nanoscale materials for environmental, health, and safety impacts; and nanotechnology education. The National Nanotechnology Initiative (NNI) is composed of 15 federal agencies with administrative, funding, liaison, regulatory, and research roles, including the Department of Defense, National Science Foundation, Department of Education, National Institutes of Health, NIOSH, FDA, National Institute of Standards and Technology (NIST), Environmental Protection Agency (EPA), US Department of Agriculture, and others. In its congressionally mandated role to review federal nanotechnology research and development, the National Nanotechnology Advisory Panel provides ongoing recommendations for development of infrastructure, standards and metrics, and EHS risk analysis concurrent with applications research.²⁸¹ International regulatory frameworks continue to evolve.²⁵²

The detailed NNI strategy for EHS research recommends incorporation of many factors in conducting a nanotechnology risk assessment, including nanomaterials synthesis and use, nanomaterial lifecycle stages (from raw materials through disposal or recycling), transport, transformation, secondary contaminants, abiotic effects, environmental concentrations, exposure of environmental and biologic systems, internal dose, biologic response, and systemic environmental effects.^{335,359–361} Identified immediate priority needs included the development of nanomaterial detection methods, certified reference materials, standardized physiochemical assessments, and measurement tools, understanding generalizable toxicologic characteristics of nanomaterials in biologic systems, identification of environmental, occupational, and other population exposures and health surveillance, and evaluation of risk management approaches to nanomaterials.³³⁵

Standards

NIST is the coordinating agency for instrumentation, metrology, and analytical methods in the United States. Given the broad cross-disciplinary impact of nanomaterials, international standards are urgently required for nomenclature and terminology, measurements and metrics, reference nanoparticles, toxicity testing, and occupational guidelines. Where available, selected national and international standards relating to these areas are provided in [Table 129–2](#).

TABLE 129–2. Selected Nanotechnology Standards

Nomenclature and Terminology	
ASTM E2456 - 06(2012)	Standard terminology Relating to Nanotechnology
ISO/TS 27687:2008	Nanotechnologies – Terminology and Definitions for Nano-Objects – Nanoparticle, Nanofibre and Nanoplate
ISO/TR 11360:2010	Nanotechnologies, Methodology for the classification and categorization of nanomaterials
ISO/TS 80004-1:2010	Nanotechnologies – Vocabulary – Part 1: Core terms
ISO/TS 80004-4:2011	Nanotechnologies – Vocabulary – Part 4: Nanostructured materials
ISO/TS 80004-5:2011	Nanotechnologies – Vocabulary – Part 5: Nano/bio interface
ISO/TS 80004-7:2011	Nanotechnologies – Vocabulary – Part 7: Diagnostics and therapeutics for health care
Measurements and Metrics	
ASTM E2578 - 07(2012)	Standard Practice for Calculation of Mean Sizes/Diameters and Standard Deviations of Particle Size Distributions
ASTM E2490 - 09	Standard Guide for Measurement of Particle Size Distribution of Nanomaterials in Suspension by Photon Correlation Spectroscopy (PCS)
ASTM E2834 - 12	Standard Guide for Measurement of Particle Size Distribution of Nanomaterials in Suspension by Nanoparticle Tracking Analysis (NTA)
ASTM E2859 - 11	Standard Guide for Size Measurement of Nanoparticles Using Atomic Force Microscopy
ASTM E2865 - 12	Standard Guide for Measurement of Electrophoretic Mobility and Zeta Potential of Nanosized Biological Materials
Toxicity Testing and Risk Assessment	
ASTM E2524 - 08	Standard Test Method for Analysis of Hemolytic Properties of Nanoparticles
ASTM E2525 - 08	Standard Test Method for Evaluation of the Effect of Nanoparticulate Materials on the Formation of Mouse Granulocyte-Macrophage Colonies
ASTM E2526 - 08	Standard Test Method for Evaluation of Cytotoxicity of Nanoparticulate Materials in Porcine Kidney Cells and Human Hepatocarcinoma Cells
ISO 10808:2010	Nanotechnologies – Characterization of nanoparticles in inhalation exposure chambers for inhalation toxicity testing
ISO 29701:2010	Nanotechnologies – Endotoxin test on nanomaterial samples for in vitro systems – Limulus amoebocyte lysate (LAL) test
ISO/TR 13121:2011	Nanotechnologies – Nanomaterial risk evaluation
ISO/TR 13014:2012	Nanotechnologies – Guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment
Occupational Health and Safety	
ASTM E2535 - 07	Standard Guide for Handling Unbound Engineered Nanoscale Particles in Occupational Settings
ISO/TR 27628:2007	Workplace atmospheres – Ultrafine, nanoparticle and nano-structured aerosols – Inhalation exposure characterization and assessment
ISO/TS 12901-1:2012	Nanotechnologies – Occupational risk management applied to engineered nanomaterials – Part 1: Principles and approaches
ISO/TR 13329:2012	Nanomaterials – Preparation of material safety data sheet (MSDS)

ASTM = ASTM International, ISO = International Organization for Standardization. No endorsement is implied.

Food, Drug, and Device Safety. The FDA regulates food and color additives, drugs, biologics, devices, blood products, and cosmetics to ensure that they are “safe” and unadulterated. The FDA does not regulate “nanotechnology,” and has forgone even adopting a regulatory definition¹¹⁵ Rather, marketing authorization occurs on a product-by-product basis, with further variation for different product classes. While the FDA can require manufacturers to provide necessary information (eg, chemistry, manufacturing, active ingredients, pharmacological and toxicological results, and particle size) to support decisions regarding premarket approval, in evaluating the sponsor “claims,” the FDA may be unaware that nanotechnology is being used, particularly if no nano-related claims are supplied. In general, the FDA has treated nanomaterial ingredients no differently than bulk material ingredients or products. Guidance in draft form only has been provided for nanotechnology and nanomaterials issues in industry, cosmetics, food substances, and dietary supplements. Several countries have excluded engineered nanoparticles from food labeled “organic.”³⁵⁸

Occupational Health and Safety. NIOSH leads federal agencies in conducting research and providing guidance on the occupational safety and health implications and applications of nanotechnology²³⁸ NIOSH has released multiple reports to guide commercial and research entities, including “Approaches to Safe Nanotechnology,”²³⁶ “Filling the Knowledge Gaps for Safe Nanotechnology in the Workplace.”²³⁸ and “General Safe Practices for Working with Engineered Nanomaterials in Research Laboratories.”²³⁷ These identify potential health concerns (nanoparticle dose, deposition, reactivity, toxicity, translocation, and tumorigenicity) and safety issues (fire, explosion, oxidation, and catalytic potential). Recommendations included epidemiology, surveillance, and background nanoaerosol measurements, personnel exposure sampling and assessment, engineering controls with verification, implementation of risk management programs, and use of filters, respirators, and other proper personal protective equipment when necessary²³⁶ To address specific risks associated with carbon nanotubes and nanofibers, the Occupational Safety and Health Administration (OSHA) recommends that worker exposure not exceed 1.0 µg/m³ elemental carbon as an 8 hour time-weighted average (TWA), based on the NIOSH-proposed occupational recommended exposure limit (REL)²⁵¹ OSHA recommends that worker exposure to TiO₂ nanoscale

particles not exceed the NIOSH REL of 0.3 mg/m³, an order of magnitude less than the NIOSH REL of 2.4 mg/m³ for fine TiO₂ particles (> 100 nm²⁵¹). The REL for soluble silver compounds and silver metal dust is 0.01 mg/m³, an order of magnitude less than the threshold limit value (TLV) for metallic silver (0.1 mg/m³) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH). The general federal statute limiting “particulates not otherwise regulated” (PNOR) (also known as “inert or nuisance dusts”) to a respirable fraction of 15 million particles per cubic foot of air (5 mg/m³) would also apply include nanoparticles, although this is suggested to provide inadequate protection^{80,325}. NIOSH anticipates that properly fit, NIOSH-certified respirators in conjunction with respiratory control programs will protect workers from most inhaled nanoparticles^{236,238}. Other occupational professional guidance can be found in national and international guidelines and reviews^{234,256}.

Environmental Protection. The EPA is the coordinating federal agency for human nanomaterials environmental research. Nanomaterial applications for environmental remediation and water purification are particularly attractive, but require weighing against unintended consequences (eg, nanopollution³⁵⁸). Regulation of nanomaterials and the effects of nanotechnology may also come under the EPA’s broad authorities under the Clean Air Act (CAA), Pollution Prevention Act (PPA), Clean Water Act (CWA), Safe Drinking Water Act (SDWA), Federal Insecticides and Rodenticides Act (FIFRA), Comprehensive Environmental Response Compensation and Liability Act (CERCLA), National Environmental Policy Act (NEPA), Resource Conservation and Recovery Act (RCRA), and Toxic Substances Control Act (TSCA³⁵⁸). For example, the EPA determined that (nano) silver ion-generating washing machines marketed with bactericidal claims were subject to registration requirements under FIFRA, and extended the requirement to copper- and zinc-emitting devices and ion generators in swimming pools⁸³. Under FIFRA, it has fined corporations for making unsubstantiated antimicrobial claims with nano-coating technology³⁵⁷. Under TSCA, new nanomaterials such as carbon nanotubes have been regarded as “chemical substances” and subject to review.⁸⁴

The rapid evolution of the discipline will mandate constant updating and assessment of available knowledge. A selected list of organizational resources is provided in [Table 129–3](#).

TABLE 129–3. Selected Nanotechnology Organizational Resources

Organization	Web Site
Center for Biological and Environmental Nanotechnology (CBEN)	http://cben.rice.edu/
Center for Nanotechnology and Nanotoxicology	http://www.hsph.harvard.edu/nano/mission/nanocenter/
Center for Nanotechnology in Society at Arizona State University (CNS-ASU)	http://cn.asu.edu/
European Commission, Nanotechnology Homepage	http://ec.europa.eu/nanotechnology/index_en.html
German Federal Institute for Occupational Safety and Health (BIAuA), Nanotechnology	http://www.biaua.de/en/Topics-from-A-to-Z/Hazardous-Substances/Nanotechnology/Nanotechnology.html
International Association of Nanotechnology (IANT)	http://www.ianano.org/
International Council on Nanotechnology (ICON)	http://icon.rice.edu/
Nano/Bio Interface Center	http://www.nanotech.upenn.edu/
Nanoscale Science and Engineering Center (NSEC)	http://www.nsec.wisc.edu/
National Cancer Institute (NCI), Alliance for Nanotechnology in Cancer	http://nano.cancer.gov/
Nanotechnology Center for Learning and Teaching (NCLT)	http://www.ncit.ac/
National Institutes of Health (NIH), Nanotechnology at NIH	http://www.nih.gov/science/nanotechnology/index.htm
National Nanotechnology Infrastructure Network (NNIN)	http://www.nnin.org/
National Science Foundation (NSF) National Nanotechnology Initiative	http://www.nsf.gov/crsprgm/nano/
Organization for Economic Co-operation and Development (OECD), Work on Nanotechnology	http://www.oecd.org/sti/nano
Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars	http://www.nanotechproject.org/
Safenano (UK Institute of Occupational Medicine)	http://www.safenano.org/
US Department of Agriculture, National Institute of Food and Agriculture	http://www.cseers.usda.gov/nanotechnology.cfm
US Department of Commerce, National Technical Information Service, Nanotechnology	http://www.ntis.gov/nanotech/nano.asp
US Environmental Protection Agency (EPA), Nanotechnology & Nanomaterials Research	http://www.epa.gov/nanoscience/
US EPA, Nanotechnology under the Toxic Substances Control Act (TSCA)	http://www.epa.gov/ogpt/nano/
US Food and Drug Administration (FDA), Nanotechnology	http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm
US National Institute for Occupational Safety and Health (NIOSH), Workplace Safety & Health Topics Nanotechnology Page	http://www.niosh.gov/niosh/topics/nanotech/
US National Institute of Standards and Technology (NIST), Nanotechnology Portal	http://www.nist.gov/nanotechnology-portal.cfm
US National Nanotechnology Initiative (NNI)	http://www.nano.gov/
US National Science Foundation (NSF) National Nanotechnology Initiative	http://www.nsf.gov/crsprgm/nano/
US National Toxicology Program (NTP), Nanotechnology Safety Initiative	http://ntp.ehponline.org/?objectId=7E6B19D0-BD85-42F8-FAE73D113D4F542A

Many of these websites are searchable for nano-related developments, policy, research, and toxicology. Web sites retrieved August 1, 2013. No endorsement is implied.

SUMMARY

- Nanotechnology and nanotoxicology represent ever expanding disciplines.
- The special physiochemical properties of nanoparticles can yield nonintuitive biologic effects, which complicate toxicological assessments.
- Nanoparticle profiles are incomplete. While surrogate markers of toxicity are suggestive, human risk remains incompletely characterized.
- Appropriate research methodologies, in vitro and in vivo models, risk assessment, and workplace and environmental standards await further exploration and consensus.

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N. DISASTER PREPAREDNESS

130 RISK ASSESSMENT AND RISK COMMUNICATION

Charles A. McKay

All health care professionals confront questions involving risk on a daily basis. In the area of toxicology, these questions may take many forms. An anxious parent with questions about a child's potentially toxic exposure, an urgent consultation for a critically ill patient in the emergency department or intensive care unit, a request to interpret a laboratory test, media requests for information about environmental public health issues, a response to a hazard-materials situation, and biopreparedness education all involve directed communication of information and recommendations. Toxicologists and Certified Specialists in Poison Information (CSPIs) must establish rapport and provide information, instructions, and when appropriate, reassurance, typically by telephone or in short face-to-face interactions. For CSPIs, attribution of the patient's complaints to one or more potential exposures and ascertaining the true reason or concern behind a call are also difficult given the limited information and time and lack of visual clues that are usually available during a clinical evaluation. All of these situations require a knowledgeable, compassionate, and well-reasoned response.

This chapter focuses on two particular components of this response: risk assessment and risk communication. These principles apply equally to individual calls to poison control centers, interactions with the public and medical professionals in educational outreaches, occupational and environmental exposure evaluations, and supportive roles with other public health agencies in bioterrorism preparedness, environmental public health tracking programs, and research.

RISK ASSESSMENT

In the context of this text, risk assessment is the process of determining the likelihood of toxicity for an individual or group after a perceived exposure to some substance, generally referred to as a xenobiotic. It involves determining the nature and extent of the exposure (ie, xenobiotic, dose, duration, route) and its specific clinical effects, defining an exposure pathway, and assessing the likelihood of effects from a given situation. A published body of knowledge can be applied to some components of risk characterization or assessment. An overview and a number of tools can be accessed through the Web sites of the US Environmental Protection Agency (EPA) and the Agency for Toxic Substance and Disease Registry (ATSDR) of the Centers for Disease Control and Prevention (CDC).^{1,9} However, any given risk assessment is often based on incomplete information. This may include such features as uncertainty regarding the exposure xenobiotic or mixture, whether there has been an actual exposure or just proximity to the xenobiotic (completion of an exposure pathway), lack of the exact dose, or unpredictable features such as host factors (underlying medical conditions or genetic polymorphisms) that could modify the response to a potential exposure. Unfortunately, those conducting a risk assessment are affected by their own biases and assumptions in the interpretation of their results, as are the people to whom a risk assessment is communicated. The emotional response to being "poisoned" makes evaluation and attribution even more difficult.

A good example of the practical difficulties involved in a risk assessment is evident from a published description of mass psychogenic illness.¹⁸ In this incident, many individuals at a school complained of odor-triggered symptoms that spread in a so-called "line of sight" transmission with no evident dose-response pattern. Extensive testing identified the possibility of potential sources of exposure, such as dry floor drain traps. However, no actual release was documented, nor was a scenario that would present significant harm identified. Yet symptoms recurred when people returned to the school. This is considered an example of psychogenic illness. The extent of investigation of these events can be profound, highlighting the difficulty in appropriately applying potentially unlimited laboratory technology to a situation. In addition, our ability to assess a "no-risk" situation is limited, as can be noted in the letters to the editor of the journal in which the article was published criticizing the methods or conclusions in this event and "subsequent and comparable" outbreaks.^{4,16,23}

The response of individuals to uncertainty correlates with their affinity for one component of the negative data paradigm—"the absence of evidence of harm" versus "evidence of absence of harm." Both of these positions should have at their core the continued evaluation of evidence as it becomes available, with subsequent refinement of a resulting risk assessment. Unfortunately, these potentially converging points on a spectrum of knowledge and research have been polarized in debate and policy as two opposing principles: the Kehoe Principle and the Precautionary Principle. The Kehoe Principle is best summarized as "prove something is harmful before excluding a product with known benefits because of concern about potential, unproven future adverse effects." A common example of the use of this principle is the

continued marketing of a xenobiotic after another member of the class has been removed because of safety issues. More intense scrutiny may be indicated, but a class-wide medication recall without evidence of some level of harm by an individual therapeutic drug is very rare. This principle has been misused in the past to minimize known risks attributable to environmental lead pollution to delay removal of lead additives from gasoline.²⁶ Critics of the Kehoe Principle have suggested that waiting for evidence of harm from a substance results in costly or irreparable damage.

The alternative position of the Precautionary Principle is often summarized as “where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason to postpone cost effective measures to prevent environmental degradation.”^{21,30} Critics of the Precautionary Principle often cite the lack of attention paid to the “cost” component of the principle, complaining that devotees stifle economic growth and prosperity with unfounded fears rather than reasoned consideration of known data. This principle is commonly extended to potentially harmful situations other than the environment. A common criticism of the Precautionary Principle is the degree to which alternative actions have been evaluated for safety. As an example, concern about thimerosal safety (as a vaccine preservative and source of ethylmercury exposure) in young children led many parents to forego childhood vaccinations. Vaccine manufacturers have removed the thimerosal preservative from most routine childhood vaccines. Although this process was accelerated by the theoretical—and, ultimately, unfounded—concerns regarding this source of mercury exposure in young children, the cost of delayed or omitted vaccination was a number of real and preventable infectious diseases that occurred, including hepatitis B.^{5,6,11}

Although the Kehoe and Precautionary Principles originated as policy approaches to public health issues, they underlie the automatic or subconscious biases that each individual brings to his or her own personal risk assessment or tolerance. The response to uncertain situations is derived from one’s framing of belief systems and assumptions about life, justice, and eternity.^{3,10,14} These underlying world views should be explicitly recognized and addressed in a formal risk assessment. Table 130–1 lists the components of a risk assessment.

TABLE 130–1. Components of Risk Assessment

Hazard Identification

Name and amount of suspected xenobiotic (or general use category if the xenobiotic is unknown)

Exposure Pathway

Proposed route of exposure

Consistency with the nature of the xenobiotic (eg, water-soluble liquid)

Modifying Factors

Environmental factors that would influence systemic availability of the xenobiotic

Patient characteristics (susceptibility or resistance factors), such as:

Chronic medical conditions

Possible xenobiotic–drug or other interactions

Genetic polymorphisms in hepatic or other metabolic pathways

Toxicity Assessment

Compare and contrast organ effects expected from the particular xenobiotic with existing symptoms

DIFFERENTIATING PUBLIC HEALTH FROM INDIVIDUAL RISK ASSESSMENT

It is difficult to translate public health risk assessment done for populations by entities such as the EPA to the individual level. Simplistically, the iterative process of adjusting known noncancer adverse exposure outcome limits in an animal model (eg, lowest observed adverse effect level {LOAEL} or no observed effect level {NOEL}) to a safe level of exposure for all humans (including so-called “sensitive subpopulations”) has been arbitrarily set at repetitive multiplicative factors of 10 for each of these extrapolations. These are called “uncertainty factors” and are used in the

absence of specific information about human exposure to identify a conservative human “safe dose.” This would be set at 0.001 times the animal model LOAEL, reflecting a 10-fold reduction in dose for extrapolation from LOAEL to NOEL, another 10-fold reduction for extrapolation from animal to human, and another 10-fold reduction for potentially “sensitive” human populations. These “uncertainty factors” are actually safety factors for the adverse effect of interest. When individuals exceed these limits, they remain protected by very robust safety factors, and are not—as it is often portrayed—exposing themselves to a defined harm. An example of this is the dietary guidelines (also known as “fish health advisories”) for fish consumption based on concern about exposure to methylmercury and polychlorinated biphenyls. These dietary recommendations are based on epidemiologic studies that suggest subtle neuropsychiatric abnormalities in maternal–fetal pairs (in at least some populations) from levels of fish consumption 10 to 100 times that of the “usual” American diet. Clinical mercury toxicity requires still higher levels of consumption. Although it seems reasonable (precautionary) for pregnant women to limit their intake of certain high mercury-containing fish species, it is inappropriate to avoid fish and the nutrients contained therein because of a misplaced fear of mercury exposure. Furthermore, these risk assessments do not apply to nonpregnant women, children, or men, although they are often generalized to all humans.²

The public health modeling concept for cancer health effects risk assessment is even more complex and often misunderstood. In this setting, modeling assumes a linear, no-threshold carcinogenic effect from exposure to a given xenobiotic. Cancer risks from exceedingly small exposures are extrapolated from data in cancer-prone animal models with exposures so large that they are only likely in the experimental setting. This experimental construct ignores the moderating impact of incremental dosing of small amounts over a protracted period of time, and potential metabolic and self-repair mechanisms in humans. The “acceptable risk” in this setting is then taken as “one excess cancer in a population of 1 million exposed individuals.” Although a limitation of this model is explicit in the statement that this estimate represents “a plausible upper bound estimate of risk at low dose where true risk may be lower, including zero,”¹² this important caveat is rarely communicated, resulting in the common response by individuals that “an extra cancer may be acceptable for you, but not when it is my child.”

As this brief review of the principles of regulatory approaches to noncancer and cancer effects demonstrates, risk assessment is often imprecise. Risk characterization for the individual should avoid unfamiliar statistical concepts, aiming instead to communicate the likelihood of significant risk for the exposure actually experienced. The CDC has codified this approach for a community using such escalating terms as “no public health concern,” “public health concern,” “public health threat,” and “immediate risk.” Although there is debate about the general use of these terms in isolation (without explicit explanations), a similar approach with an individual could summarize the risk assessment using the phrases “safe,” “no adverse effects are expected,” “may be of concern—we will need to do some follow-up testing,” and “this might be (or is) a problem—let’s do the following studies or treatments.”

RISK COMMUNICATION

Risk communication consists of an exchange of facts and opinions that allow an individual or a group to make an informed decision regarding a course of action or treatment. Practically, risk communication is a way of translating incomplete knowledge so that individuals can achieve informed decision-making. During a one-on-one interaction with a poisoned individual and his or her family or a caller to the poison center, there is a need to gain the fullest attention or cooperation of the individual. After this has occurred, the discussion is usually focused on the risks and benefits of various treatment options (eg, gastrointestinal decontamination) or possible diagnostic modalities (eg, observation versus neuroimaging versus antidote administration). The group dynamics of environmental exposure risk communication at a public meeting are very different. Federal agencies that interact with communities in “Superfund” sites (eg, the EPA and the ATSDR) have promulgated principles and practical recommendations for risk communication in this setting. [Table 130–2](#) summarizes general principles of risk communication.

TABLE 130–2. Principles of Risk Communication⁷ and Applicability to the Poison Center

<i>Principle</i>	<i>Applications</i>
Accept and involve the individual as a partner	The caller must be involved to obtain the best information possible
Plan carefully and evaluate your efforts	There is a very short time to establish rapport with the caller; do not increase the caller's anxiety by asking irrelevant questions or arguing Monitor your tone; ask for repetition of key information or recommendations
Listen to the individual's specific concerns	Why did the person call? Was it for information, treatment recommendations, or reassurance? Make sure the underlying reason has been addressed
Be honest, frank, and open	If there is uncertainty or there are unknowns, indicate that uncertainty while providing a workable plan
Work with other credible sources	Involve medical toxicology backup and other consultants, particularly for questions regarding chronic exposure or effects
Meet the needs of the media	If calls involve media notification or contact, make sure the critical information is stated frequently, provide a human context, and avoid sensationalism
Speak clearly and compassionately	Remember that the caller was concerned enough to initiate the contact; make sure the call is completed with a clear plan; provide follow-up appropriate to the situation

Although some of these recommendations are more applicable to longer-term deliberations and interactions, much of the individual communication done by the poison center and medical toxicologists succeeds or fails based on these same principles (Table 130–2). Lacking the opportunity for repeated interactions over time to identify and discuss assumptions and biases, toxicologists need to establish credibility, listen to concerns and empathetically respond, admit areas of insufficient knowledge, and commit to follow-up interactions to convey effectively a risk characterization for an individual based on the available knowledge and experience. The scientific terms, rationale, and any extrapolation from modeling (eg, animal data or case series) should be conveyed in an understandable manner to show that appropriate safety factors are incorporated into areas of uncertainty as a risk-diminishing step. The patient or audience should leave the interaction with a clear understanding of the difference between a short-term risk of symptoms that will resolve or result in serious illness and the degree of certainty about the potential for a long-term consequence.

An example of poor risk communication can be found in the immediate aftermath of the World Trade Center disaster in September 2001. The mass rescue and recovery response was largely voluntary and heroic; however, inadequate attention was paid to the importance of respiratory protection against the heavy particulate and alkaline dust in the early hours after the towers collapsed. The high incidence and persistence of cough and other respiratory symptoms in responders have been attributed to this exposure. Communication of the real risk of respiratory symptoms to early responders would have emphasized the critical importance of appropriate use of personal protective equipment. This would have been balanced against the time-limited possibility of saving lives of those potentially trapped in largely inaccessible locations. Since 2001, a proliferation of other associations to World Trade Center dust exposure (including low birthweight) are reported, which are of doubtful validity.³¹ Appropriate risk communication to people concerned about these reports should emphasize the important role of confounders, the investigational nature of the study hypothesis, and the lack of relevant risk to any given individual.

Effective risk communication must therefore address several questions. After the best information has been obtained about the identification of the xenobiotic and the nature of the exposure, the following must be conveyed:

- Likely **magnitude** of the risk: This includes information on the process by which the person would be exposed (ie, the exposure pathway), such as airborne inhalation or drinking water delivery via a contaminated plume in the ground water and dose–response, such as: “Does the reported exposure to a particular xenobiotic (amount and duration)

approach the exposure amounts reported to cause symptoms?”

- **Urgency** of the risk must also be conveyed along with practical recommendations for simple actions consistent with the level of urgency.
- The **applicability** of a risk characterization might also need to be addressed. Are the animal data applicable to humans? Is the exposure something of concern for an individual?
- **Uncertainties** of the risk assessment: This could include a “worst-case scenario” approach to unknown exposures or uncertainties in the quantity of an absorbed dose. The need for continued observation or follow-up for clinical changes would be expressed here. Individual risk tolerance may vary greatly. The same information may be interpreted differently by risk-averse versus risk-tolerant people. A variety of comparisons or communication techniques may be used to provide an adequate characterization of risk. It is important to remember that the public and even medical professionals have limited ability to understand and incorporate data that rely on numbers and statistics. This health numeracy limitation is even more prevalent than is limited health literacy ([Chap. 135](#)).¹⁵
- **Management options**: In addition to follow-up and repeated evaluations by a medical toxicologist, the range of choices, associated with their relative benefits or risks, should be presented to the individual or group of individuals. A summary recommendation or opinion from the presenter should emphasize specific steps people can take to decrease exposure or potential toxicity if indicated by the level of risk. This last step is important because uncertainty significantly impacts the ability of an individual to take appropriate action. People should not leave the meeting or interaction with the impression that “no one knows what is going on or what we should do.”

APPLICATION OF RISK ASSESSMENT AND COMMUNICATION PRINCIPLES TO TOXICOLOGY

Although it has long been recognized that many home-initiated poison center calls concern nontoxic or minimally toxic xenobiotics potentially ingested by children,²⁴ the frequent lack of documented ingestion raises the possibility of under-triage based on misplaced confidence that relies on prior experience. It is generally assumed that the sheer volume of calls provides some reassurance regarding the accuracy of our risk assessment of these xenobiotics, but we should remain cautious in our interpretation of poison center data^{5,17,27} ([Chap. 136](#)). Moreover, even calls about nontoxic xenobiotics require communication between the caller and CSPI beyond simple substance identification. The importance of risk assessment and communication principles can be seen in the joint position statement²² on the prehospital management of “minimally toxic substances” crafted by the American Association of Poison Control Centers (AAPCC), the American Academy of Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT). According to the position statement, a CSPI can make a risk assessment that an exposure is benign or minimally toxic only if the following characteristics are true²²:

- “The information specialist has confidence in the accuracy of the history obtained and the ability to communicate effectively with the caller.”
- “The information specialist has confidence in the identity of the product(s) or substance(s) and a reasonable estimation of the maximum amount involved in the exposure.”
- “The risks of adverse reactions or expected effects are acceptable to both the information specialist and the caller based on available medical literature and clinical experience.”
- “The exposure does not require a health care referral because the worst potential effects are benign and self-limited.”

The position statement further notes that patient disposition decisions can be altered by many additional factors, including intent, environment, presence of symptoms (possibly unrelated to the xenobiotic in question), and ongoing review of current recommendations in the face of more data.²² These points emphasize both the dependence of the CSPI on information derived from the caller and his or her confidence in the level of comprehension of the caller. The caller should understand that his or her exposed child is safe; the conversation with the toxicology experts should alleviate concern as the nature of the assessment process is explained to whatever degree is necessitated by the caller’s risk tolerance.

In the case of a symptomatic patient or a hospital-or physician-initiated contact to a poison center or medical toxicologist, the caller should expect more than just xenobiotic-related information; he or she also expects knowledge and expertise that will provide reassurance or direction for improving the patient’s health status. However, merely relaying information regarding the diagnosis, course, and predicted outcome is insufficient. There is often another underlying reason for the call. This could be anxiety, uncertainty, or misinformation established by an individual’s previous experiences or knowledge base. A sense of guilt may underlie a parent’s call for an inadvertent exposure occurring when a child was unsupervised. A health care professional may have previously had significant difficulties in the management of a poisoned patient. If these issues are not addressed, then the caller may continue seeking reassurance by repeated calls to the poison control center or by seeking additional input from other sources, such as family, friends, primary physicians, other health care providers. Any variance in the information obtained from these sources may be construed as inconsistencies between supposed experts rather than differences in emphasis with regard to the same information, leading to further uncertainty for

the caller. Of further concern, the Internet has become a common source of second opinion for health care. Although many sites are useful, there is no quality control or filter to sort good information from bad or even harmful advice.¹³ Table 130–3 lists some barriers to effective risk assessment and communication.

TABLE 130–3. Factors That Affect Appropriate Risk Assessment and Effective Risk Communication

Nature of previous encounters with poison center or health care field
Lack of prior patient–health care professional relationship
Incomplete or inadequate response to a prior question
The provision of information contrary to “popular understanding” or media representation
Loss of credibility
Lack of appreciation of individual or cultural differences in the perception of risk or the applicability of data
Incomplete or limited comprehension of scientific or statistical principles

INTERPRETING PUBLIC HEALTH CONCERNS FOR THE INDIVIDUAL

CSPIs and medical toxicologists frequently encounter callers or individuals at community events or interact with the media regarding public health–related issues, such as heavy metal exposures involving mercury, lead, or arsenic or concerns about “toxic mold,” plasticizers, and other environmental xenobiotics. Often these people are concerned that their symptoms or future personal or family health may be adversely impacted by such exposures. Such supposed exposures are usually poorly documented, sometimes also driven by popular media descriptions or litigation, and the risk is virtually impossible to ascertain during a short telephone or personal interaction. In these situations, the individual is best served by referral to a primary care physician with toxicology consultation or directly to a medical toxicology clinic. The data and perceptions can be completely reviewed and a more appropriate risk assessment communicated in those settings. These interactions are very difficult because they are often emotionally and politically charged.²⁵

In general, the communication of and response to information depend on a preexisting world view and prevailing circumstances. The same possible outcome will be perceived as more or less severe depending on factors other than the nature of the outcome itself. Several authors have characterized the perceived tolerance to different risks, stratified by features such as familiarity and personal control^{10,30} (Table 130–4). The emotional response of individuals confronted with these risks is sometimes characterized as “outrage.” One communications specialist has posited that “risk = hazard + outrage.”²⁸ He characterizes situations in which there is a significant hazard but little outrage as requiring “precaution advocacy,” essentially informing the relevant parties of the need for more action or involvement to reduce risk. On the other end of the spectrum is a situation with little hazard but significant outrage, which requires “outrage management” to address fear or anger that is dissociated from the actual hazard posed by the situation. The greater the degree of familiarity with the particular exposure situation and the greater the voluntary nature of the exposure, the less fear or outrage will be expressed for a given adverse outcome, whether this is an appropriate response or not. Although not necessarily applicable to the initial “fight-or-flight” response to an emergency, these concepts are certainly applicable to the aftermath of these events. Of note, although risk communicators use analogies to place exposures into a context familiar to their audience, one must be careful to avoid equating voluntary and involuntary risk assumption or equating those exposures or risks assumed by one segment of the population unequally. An example of this is the use of a smoking risk analogy when talking to a nonsmoker.

TABLE 130–4. Factors That Alter the Acceptability of Perceived Risk¹⁰

<i>More Acceptable</i>	<i>Less Acceptable</i>
Natural	Human made
Associated with a trusted source	Not associated with a trusted source
Familiar	Unfamiliar
Voluntary	Involuntary
Potentially beneficial	Limited or absent potential benefit
Statistical (low harm likelihood)	Catastrophic (high harm likelihood)
Fairly distributed or shared by all	Unfairly distributed (“injustice”)
Affects adults	Affects children

Risk communication has become very important in the setting of preparedness for terrorism. Although a great deal of attention and money have been directed to improvement of public health infrastructure, reporting and surveillance

mechanisms, and response to perceived and actual terrorist acts, less attention has been directed to the process of communicating risk to the individual.^{8,20} Although some countries practice public health emergency drills regularly, the United States has concentrated on development of organizational structures and lines of authority, with attention to the importance of outcome-based exercises only recently emphasized.

Maintaining readiness for catastrophic terrorist events (or natural occurrences such as pandemic influenza or storm related flooding) should use the same risk assessment and communication techniques appropriate for other urgent public health matters. Unfortunately, many factors affect the characterization of risk other than the facts. The importance of presentation style, perception, or the role of the communicator's own biases is exemplified by these two composite articles describing the same events:

1. Unknown assailants have infiltrated the mail delivery system, resulting in severe illness and death of children, healthy adults, and elderly people throughout the country. The initial symptoms can be nonspecific but rapidly progress to death if treatment is not begun early. The medical community routinely fails to diagnose the conditions early, and the government has no system in place to detect this threat after it occurs. The long-ignored public health system is not prepared to deal with the huge burden of preventing illness in those who may have been or will be exposed. Anyone who receives regular mail may be at risk. Tens of thousands of our citizens are taking prophylactic antibiotics "just in case." If you receive any unusual packages or see collections of powder that do not have an obvious explanation, call the police. If you develop a fever, cough, chest pain, or unusual rash, which may not be painful, seek medical attention at once. Tune in to your local news station for more information on this burgeoning threat to our nation's security.
2. A small number of individuals in isolated exposure settings have developed illnesses after bioterrorism events. Most people have survived these exposures, particularly with early and proper medical care. The government has developed a case definition, and medical experts have disseminated information to assist the medical community and public in the early recognition of symptoms and signs that are consistent with this exposure. Prophylactic treatment within days of exposure of those in high-risk professions, such as mail handlers at major postal sorting facilities, prevents illness. Unfortunately, there have been a large number of hoaxes and false alarms about possible terrorist events and a lot of understandable fear in the community about nonspecific symptoms. For more information, contact your local health department or use the CDC Web site: <http://www.bt.cdc.gov/agent/anthrax/needtoknow.asp>.

Both of these paragraphs describe the 2001 anthrax bioterrorism events within the United States, during which a total of 22 people become ill, of whom five died from anthrax exposure. The first communication suggests that everyone is at risk and the situation is dire; the communication in the second paragraph is that the risk is isolated (a single individual died who was not in what was recognized as an at-risk setting from the seven identified mailings) and there is a plan and process being developed to respond to the threat. Whereas the first is sensationalistic, imparting a helpless victim role to the reader, the second provides a framework in which to assess one's personal risk and access to sources of reliable information. Both types of reports were prevalent after the 2001 anthrax attacks. Which report seems more complete, accurate, or useful is determined by the assumptions and perspectives of the reader in addition to the message the author wishes to deliver or response desired. Some would say that communicating a high degree of risk is important to gain the attention of the reader and to ensure that no one ignores a warning. However, the lack of a risk perspective prevents the reader from placing this information in context with the myriad other risk communication messages conveyed on a daily basis. In general, risk communication messages that do not provide a context or comparison to generally familiar activities or risks are more prone to misinterpretation or misapplication. As biopreparedness moves from public health infrastructure development and surveillance improvement to planning and response drills, appropriate message development and risk communication to the public need to be emphasized.

SUMMARY

- High quality risk assessment and effective risk communication are the hallmarks of a successful interaction between the public and poison centers and between a toxicologist and an individual patient, the media, or the public health community.
- Adherence to general principles includes obtaining the best information possible regarding potential exposures and conveying in an understandable fashion a risk characterization of the hazard, likelihood of a completed exposure pathway (thus, the likelihood of an actual exposure), possible health effects, and treatment options.
- It is important to clarify the difference between public health standards and individual exposure risks, with an understanding of the many psychosocial issues that influence perception.
- Information should be provided in a context that allows the individual to prioritize his or her response based on a factual and balanced presentation with respect to his or her health literacy and health numeracy.

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131 Hazardous Materials Incident Response

Bradley J. Kaufman

A hazardous material (hazmat) can be any xenobiotic (solid, liquid, or gas) with the potential to harm. Typically, we are most concerned about xenobiotics that can harm people, although a hazardous material may also harm other living organisms, the environment, or property. Outside of the United States, hazardous materials are often referred to as dangerous goods.

A “hazmat incident” implies that there was an unplanned or uncontrolled release of, or exposure to, a hazardous material. These terms are also used interchangeably; here we will use hazardous materials. Although there are no specific requirements for an event to be considered a hazardous materials incident, typically there must be the potential for many people or a large area to be affected; otherwise, all toxicologic exposures would fall into this category. Therefore, a hazardous materials incident falls within the larger disaster management framework within a community.

Hazardous materials include chemical, biologic, and radiologic xenobiotics. In fact, a single event could provide exposure to multiple xenobiotics. Complicating matters, the incident response required for chemical, biologic, or radiologic xenobiotics may differ substantially depending on many factors. For instance, an envelope containing a white powder suspicious for containing anthrax spores that is opened in an office might require decontamination of the exposed people and environment. However, the release of the same anthrax spores surreptitiously at multiple sites may not be recognized until days later because of the delayed onset of symptoms. Certainly, a very different emergency response would be required. Emergency managers and health care professionals must consider all possibilities and adjust the incident response based on the specific xenobiotics involved, the route of the exposure and other variables such as time. This chapter discusses the basic principles used for a confined and quickly identifiable hazardous materials incident.

In general, a hazardous materials incident response focuses on the care of patients exposed to xenobiotics in the prehospital setting, prepares for multiple casualties, and emphasizes patient decontamination while at the same time trying to prevent exposure and contamination of first responders and health care professionals.

Every emergency response has the potential to involve hazardous materials and therefore first responders must always appreciate this possibility. A simple motor vehicle collision often releases gasoline into the environment. A victim pulled from a burning building may have carbon monoxide poisoning. A terrorist may contaminate an explosive device with radioactive material (eg, dirty bomb). The early identification that an event involves a hazardous material will allow for better patient care.

DISASTER MANAGEMENT AND RESPONSE

Preparedness requires the planning of actions to be taken when a disaster occurs, as well as the practicing with mock exercises of these actions. Preplanning is critical to limit damage from an event, and numerous such hazardous materials incident response plans exist. The recovery phase occurs after the immediate needs and threats to human life are addressed in the response phase and entail the restoration of property, infrastructure, and the environment.

The response phase includes the mobilization of appropriate resources and the coordinated management of the incident. A hazardous materials incident response must include the containment of the xenobiotic followed by neutralization, removal, or both. Typically, such a response includes multiple trained professionals from various agencies, often including the emergency medical services (EMS), fire departments, police departments, environmental protection agencies, and other first responder emergency services personnel. In fact, major hazardous materials events, especially those considered purposeful or the result of a terrorist act, may have responders from multiple federal, state, and local agencies, each with equipment and vehicles, and hundreds of personnel at the scene. These events can be chaotic until control and coordination are achieved.

Disaster management has four phases: planning, response, mitigation, and recovery. Mitigation measures are plans and efforts that attempt to prevent or reduce the effects of a potential hazard from becoming a disaster or minimizing the effects of a disaster if it has already occurred. One example of a mitigation measure is to use a secure container to prevent leakage of a chemical that is to be stored.

Initial disaster management is provided by local resources and agencies with progressive escalation to county, state, and federal agencies as necessary. The US Federal Emergency Management Agency (FEMA) within the US Department of

Homeland Security is the lead federal agency for emergency management in the United States.

Medical professionals are a necessary part of all hazardous materials incident responses because patient assessment and treatment are typically the highest priority. However, as with all mass casualty events, physicians, and other health care professionals, even those highly trained in emergency medicine, toxicology, or hazardous materials response, must not respond to the location of the event unless they are part of a planned response team that has been requested to respond to the incident. Unsolicited medical personnel at the scene of a hazardous materials incident, although well intentioned, may actually harm the coordinated response and interfere with lifesaving efforts.

Limiting the loss of life is dependent on all responding agencies and personnel working efficiently and effectively together. The coordination of federal, state, and local governments is mandated by a National Incident Management System (NIMS).¹⁰ Interoperability and compatibility among on-scene assets are dictated by the Incident Command System (ICS), which consists of an organizational hierarchy and defines the necessary management components of the overall incident, including mechanisms necessary for controlling personnel, operations, and communications.

The request for mobilization, management, and utilization of volunteer medical personnel at the scene of a disaster should be planned for in advance for those events that might benefit from these resources.³⁰ Unsolicited medical professionals lack the communications equipment necessary to work within a multiagency coordinated operation. They often function outside the organized ICS. They may lack or be unaware of the necessary personal protective equipment (PPE). The medical treatments they provide may lack the oversight and protections required for the provision of medical care. These environments are, by definition, hazardous, and freelance medical personnel may in turn become patients themselves, thereby adding to the burden of on scene rescuers. Furthermore, although a patient affected by a specific hazardous material may have the same physical findings and treatment indications whether at the hazardous materials scene or at the hospital and although the same toxicologic principles apply, these differences in location often require variation in the medical decisions made and the actual care provided. Typically, disaster plans incorporate the utilization of local medical assets such as hospitals and clinics. Therefore, communities are best served if medical providers respond to their respective institutions during an incident.

RESPONSE COMPONENTS

After the release of a hazardous material, there must be a notification to emergency response personnel. Typically, someone witnesses the incident itself, such as a motor vehicle collision in which a tanker trailer is breached, or some resultant effects of the release, such as a fire, and the individual then activates the emergency response system by calling 9-1-1. Alternatively, an established detector may activate an emergency response to a hazardous materials incident even before there are easily observable results of the release.

The first responders may not be aware that an incident is hazardous materials related when responding. For instance, they may be assigned to respond to an unconscious patient, unaware that the cause of the medical emergency was a chemical exposure. Although every emergency response cannot be assumed to have a hazardous materials etiology, emergency responders must always remain vigilant for such situations.

Extensive knowledge, training, and judgment are required for all emergency personnel who respond to hazardous materials incidents. There are some basic paradigms followed for a hazardous materials response. Personnel should approach the scene from uphill and upwind if possible. They should not rush in to try to help patients because the rescuer may become an additional victim if exposed. It is important to establish a perimeter to secure the scene while evacuating those not contaminated, thereby preventing additional people from being exposed or contaminated. The identification of material, establishment of containment or safety zones, wearing of PPE, decontamination, and medical management of patients are discussed later. Other considerations include hazardous materials resources available, the need for escalation to other emergency response agencies, weather conditions, terrain, confinement of the release, intentionality, and the need for rapid rescue and evacuation of casualties.

Identification of Hazardous Materials

If the identity of the xenobiotic(s) is known before arrival at the scene, then research can begin while the responders are still en route with reviews of the physical, chemical, and toxicologic properties of the xenobiotic. If the xenobiotic is not known before arrival at the scene, then efforts to obtain this information should begin as soon as safely possible.

The identification of the specific xenobiotic(s) involved is of highest priority because many of the response components depend on the properties and potential health effects of the xenobiotic itself. Whether the incident involves a transportation element such as a rail car or road trailer or is at a fixed location such as a factory or medical facility, all available information must be used toward material identification, including placards, container labels, shipping documents, material safety data sheets (MSDS), detector devices, knowledgeable persons at the scene, patient signs and symptoms, and even odors at the scene such as the rotten egg smell of hydrogen sulfide.

Because many hazardous materials are transported via rail car or road trailer, emergency response personnel must

always maintain a high index of suspicion when responding to a transportation incident. In the United States, first responders are required to be familiar with the use of the Emergency Response Guidebook, which is an aid for quickly identifying the hazards of the material(s) involved in a transportation incident.⁴⁴

Hazardous materials may be categorized in various ways, often grouped by their harm-causing property. For instance, hazardous materials may be radioactive, flammable, explosive, asphyxiating, pathogenic, and biohazardous.

The xenobiotics most commonly encountered at hazardous materials incidents vary from one locale to another and are predominately determined by the major industries in a particular area.^{47,48} For example, pesticides are the most commonly encountered class of hazardous materials in Fresno County, California, whose major industry is agribusiness.⁴⁸ Although most hazardous materials incidents involve only one hazardous material, more than one hazardous material may be encountered at a given incident. One study described 107 hazardous materials incidents involving a total of 156 materials.⁴⁸

The vast majority of consequential hazardous materials incidents are caused by gases, vapors, or aerosols. In one study, four of the five most commonly encountered individual chemicals were ammonia, phosphine, sulfur oxides, and hydrogen sulfide.⁹ The important implication for decontamination is that gases do not usually contaminate people secondarily because they do not adhere to patients. Therefore, patients exposed only to gases generally do not require skin decontamination to prevent secondary contamination, and much greater efficiency is possible in patient care at gas, vapor, and liquid hazardous materials incidents. Inhalation is the most common route of exposure at hazardous materials incidents and was the route of exposure at 73% of the hazardous materials incidents, accounting for 76% of the exposed patients described in one study.^{8,9}

Because the number of hazardous materials is so large, it is efficient to group hazardous materials according to their toxicological characteristics. Various classification systems have been devised. The International Hazard Classification System (IHCS) is the most commonly used system (Table 131-1).^{44,47} Individual hazardous materials studies commonly use their own classification systems, emphasizing the toxicodynamic effects of hazardous materials such as systemic asphyxiants or highlighting individual chemicals such as ammonia or chlorine or general classes of chemicals such as acids, bases, or volatile organic compounds.^{8,9}

TABLE 131-1. International Hazard Classification System

Class 1: Explosives

- Division 1.1: Mass explosion hazard
- Division 1.2: Projection hazard
- Division 1.3: Predominantly a fire hazard
- Division 1.4: No significant blast hazard
- Division 1.5: Very insensitive explosives
- Division 1.6: Extremely insensitive detonating articles

Class 2: Gases

- Division 2.1: Flammable gases
- Division 2.2: Nonflammable compressed gases
- Division 2.3: Poisonous gases
- Division 2.4: Corrosive gases (Canada)

Class 3: Flammable/combustible liquids

Class 4: Flammable solids

- Division 4.1: Flammable solid
- Division 4.2: Spontaneously combustible materials
- Division 4.3: Dangerous when wet materials

Class 5: Oxidizers and organic peroxides

- Division 5.1: Oxidizers
- Division 5.2: Organic peroxides

Class 6: Poisonous materials and infectious substances

- Division 6.1: Poison materials
- Division 6.2: Infectious substances

Class 7: Radioactive substances

Class 8: Corrosive materials

Class 9: Miscellaneous hazardous materials

Chemical Names and Numbers. Chemical compounds may be known by several names, including the chemical,

common, generic, or brand (proprietary) name^{5,6} A chemical may be the sole substance in a given hazardous material or one of several compounds in a mixture

The Chemical Abstracts Service (CAS) of the American Chemical Society numbers chemicals to overcome the confusion regarding multiple names for a single chemical. The CAS assigns a unique CAS registry number (CAS#) to atoms, molecules, and mixtures. For example, the CAS# of methanol is 67–56–1.^{35,36} These numbers provide a unique identification for chemicals and a means for crosschecking chemical names. Identifying a chemical by name and CAS# is critical because one must be as specific as possible about the hazardous material in question. Trade or brand names can be misleading. The MSDS describing a product usually lists the chemical name, the CAS#, and the brand name.²⁹

Vehicular Placarding: UN Numbers, NA Numbers, and PIN. Substances in each hazard class of the IHCS (Table 131–1) are assigned four-digit identification numbers, which are known as United Nations, North American, or Product Identification Numbers, and are displayed on characteristic vehicular placards. This system is used by the US Department of Transportation in the Emergency Response Guidebook⁴⁴ The IHCS assigns a chemical to a hazard class based on its most dangerous physical characteristic, such as explosiveness or flammability. Other potential hazards of a xenobiotic, such as its ability to cause cancer or birth defects, are not considered. This system provides very little guidance in treating poisonings caused by hazardous materials

National Fire Protection Association 704 System for Fixed Facility Placarding. Fixed facilities, such as hospitals and laboratories, use a placarding system that is different from the vehicular placarding system. The National Fire Protection Association (NFPA) 704 system is used at most fixed facilities³¹ The NFPA system uses a diamond-shaped sign that is divided into four color-coded quadrants: red, yellow, white, and blue. This system gives hazardous materials responders information about the flammability, reactivity, and health effects, as well as other information, such as the water reactivity, oxidizing activity, or radioactivity

The red quadrant on top indicates flammability; the blue quadrant on the left indicates health hazard; the yellow quadrant on the right indicates reactivity; and the white quadrant on the bottom is for other information, such as OXY for an oxidizing product, W for a product that has unusual reactivity with water, and the standard radioactive symbol for radioactive substances.

Numbers in the red, blue, and yellow quadrants indicate the degree of hazard: numbers range from 0, which is minimal, to 4, which is severe, and indicate specific levels of hazard.

Similar to all placarding systems, this one also has limitations. It does not name the specific hazardous substances in the facility and gives no information about the quantities or locations of the materials.

United Nations. Recognizing that the transport of chemicals often occurs internationally and that the labels and MSDS often have different information in different countries, the United Nations developed a chemical classification system in an attempt to harmonize an approach to classification and labeling. The Globally Harmonized System of Classification and Labelling of Chemicals classifies substances and mixtures by their health, environmental, and physical hazards

CHEMTREC is a service of the Chemical Manufacturers Association providing continuous essential chemical information with regard to shippers, products, and manufacturers. CHEMTREC is available at 800–424–9300 or at <http://www.chemtrec.org> at no charge, 24 hours a day. Details of an incident are relayed to the shipper's or manufacturer's 24 hour emergency contact, and they in turn are linked to hazardous materials incident responders. Technical data are available on handling the substance(s) involved, including the physical characteristics, transportation, and disposal.

A regional poison center is another valuable source of information. Other information sources include local and state health departments, the American Conference of Governmental and Industrial Hygienists, Occupational Safety and Health Administration (OSHA), National Institutes of Occupational Safety and Health (NIOSH), Agency for Toxic Substances and Disease Registry, and Centers for Disease Control and Prevention.^{1,2,3,35,36,38}

Exact identification is desirable but not always possible. Hazardous materials responders may be able to classify the hazardous material into one of several major toxicologic classes by identifying a hazardous materials toxidrome that allows them to reasonably treat the patients and protect themselves and others. For example, do patients have irritation of the mucous membranes and upper airway caused by a highly water-soluble irritant gas? Do the patients exhibit signs of asphyxia with major central nervous system (CNS) or cardiopulmonary signs and symptoms? Do patients exhibit signs of cholinergic excess caused by organic phosphorus compounds or carbamate poisoning? Do patients exhibit chemical burns compatible with corrosives? Do patients have the odor of solvents with signs of CNS depression and cardiac irritability compatible with exposure to hydrocarbons or halogenated hydrocarbons?

Also, even when the exact identity of the hazardous material is not known, what is usually known is the physical state of the material, that is, solid, liquid, or gas. Airborne xenobiotics potentially mean many more victims. Airborne xenobiotics include not only gases and vapors but also the liquid suspensions (fog, aerosols, and mists) and the solid suspensions (smoke, fumes, and dusts).

Exposure and Contamination

A person may have received an external exposure to hazardous materials and may be at risk for the resultant health

consequences even though he or she may not be contaminated by the hazardous materials. For instance, a person may be temporarily irradiated by an exposure to a radioactive source. After exposure, a hazardous material may remain on a victim (external) or within a victim (internal). For instance, if radioactive materials (usually in the form of dust particles) are on the body surface or clothing (ie, contamination has occurred), and the person will continue to have exposure until decontamination occurs.

Primary contamination is contamination of people or equipment caused by direct contact with the initial release of a hazardous material by direct contact at its source of release. Primary contamination may occur whether the hazardous material is a solid, a liquid, or a gas. Secondary contamination is contamination of health care personnel or equipment caused by direct contact with a patient or equipment covered with adherent solids or liquids that have been removed from the source of the hazardous material spill.

The state of matter will help health care professionals determine whether the hazardous material presents a significant risk of secondary contamination and whether decontamination of the skin and mucous membranes is necessary. Secondary contamination generally occurs only with solids or liquids. In general, patients or equipment covered with adherent solid or liquid hazardous materials, including chemical, biologic, or radiologic agents, should be decontaminated before transportation to prevent downstream contamination of health care professionals and equipment. An exception to the principles of limited need for cutaneous decontamination for those exposed to gas is a patient whose sweaty skin was exposed to a highly water-soluble irritant gas such as ammonia that dissolves in sweat to produce corrosive ammonium hydroxide. In this case, the primary purpose of decontamination is to prevent or treat the patient's chemical burns caused by the caustic action of aqueous ammonium hydroxide on perspiring skin rather than to prevent secondary contamination of rescuers. Aerosols are airborne xenobiotics that are not gases. Aerosols are suspensions of solids or liquids in air, such as solid dusts or liquid mists, that can cover victims with these adherent solids or liquids, which can effect secondary contamination. These patients require decontamination to prevent secondary contamination.

Emergency personnel and equipment can become contaminated at hazardous materials incidents.^{12,20,21,22,47,48,51} For example, in one study, contamination occurred to one ambulance that drove through a puddle of liquid organic phosphorus pesticides that had spilled from a crashed exterminator truck. This ambulance was responding to a call for a "motor vehicle crash."⁴⁸

Hazardous Materials Site Operations

Limiting dispersion of the hazardous material is critical to prevent further ill consequences. The physical state of a material determines how it will spread through the environment and gives clues to the potential route(s) of exposure for the material. Unless moved by physical means such as wind, ventilation systems, or people, solids will usually stay in one area. Solids can cause exposures by inhalation of dusts, by ingestion, or rarely by absorption through skin and mucous membranes. Solids that undergo sublimation, changing directly from a solid into a gas without passing through the liquid state, can give off vapors that may cause airborne exposure. Only two commonly encountered solids sublime, dry ice (CO₂) and naphthalene. A vapor is defined as a gaseous dispersion of the molecules of a substance that is normally a liquid or a solid at standard temperature and pressure (STP), that is, 32°F (0°C = 273°K) and 1 atm (760 torr = 760 mm Hg = 14.7 psi). Uncontained liquids will spread over surfaces and flow downhill. Liquids may evaporate, creating a vapor hazard.

The vapor pressure (VP) is useful to estimate whether enough of a solid or liquid will be released in the gaseous state to pose an inhalation risk. VP is defined essentially as the quantity of the gaseous state overlying an evaporating liquid or a subliming solid. The lower the VP, the less likely the xenobiotics will volatilize and generate a respirable gas. Conversely, the higher the VP of a chemical, the more likely it will volatilize or generate a respirable gas. Water has a VP of approximately 20 mm Hg at 70°F (21°C), and acetone has a VP of 250 mm Hg at the same temperature. Therefore, acetone evaporates more rapidly than water and poses more of an inhalation risk. Standard reference texts (eg, NIOSH Pocket Guide to Chemical Hazards Merck Index) list VPs for commonly encountered chemicals.^{35,36,44}

Hazardous Materials Scene Control Zones. Scene management is a fundamental feature at a hazardous materials incident. It is almost always necessary to isolate the scene, deny access to the public and the media, and limit access to emergency response personnel to prevent needless contamination. Three control zones are established around a scene and are described by "temperature," "color," or "explanatory terminology" [Table 131–2](#) and [Fig. 131–1](#)). NIOSH, the US Environmental Protection Agency (EPA), and most US prehospital and hospital health care professionals use the temperature terminology system³⁶

TABLE 131–2. Nomenclatures of the Hazardous Materials Control Zones

<i>Temperature Terminology System^a</i>	<i>Color Terminology System</i>	<i>Explanatory Terminology System</i>
Hot zone	Red zone	Exclusion or restricted zone
Warm zone	Yellow zone	Decontamination or contamination reduction zone
Cold zone	Green zone	Support zone

^aFrom the National Institutes of Occupational Safety and Health and the Environmental Protection Agency.

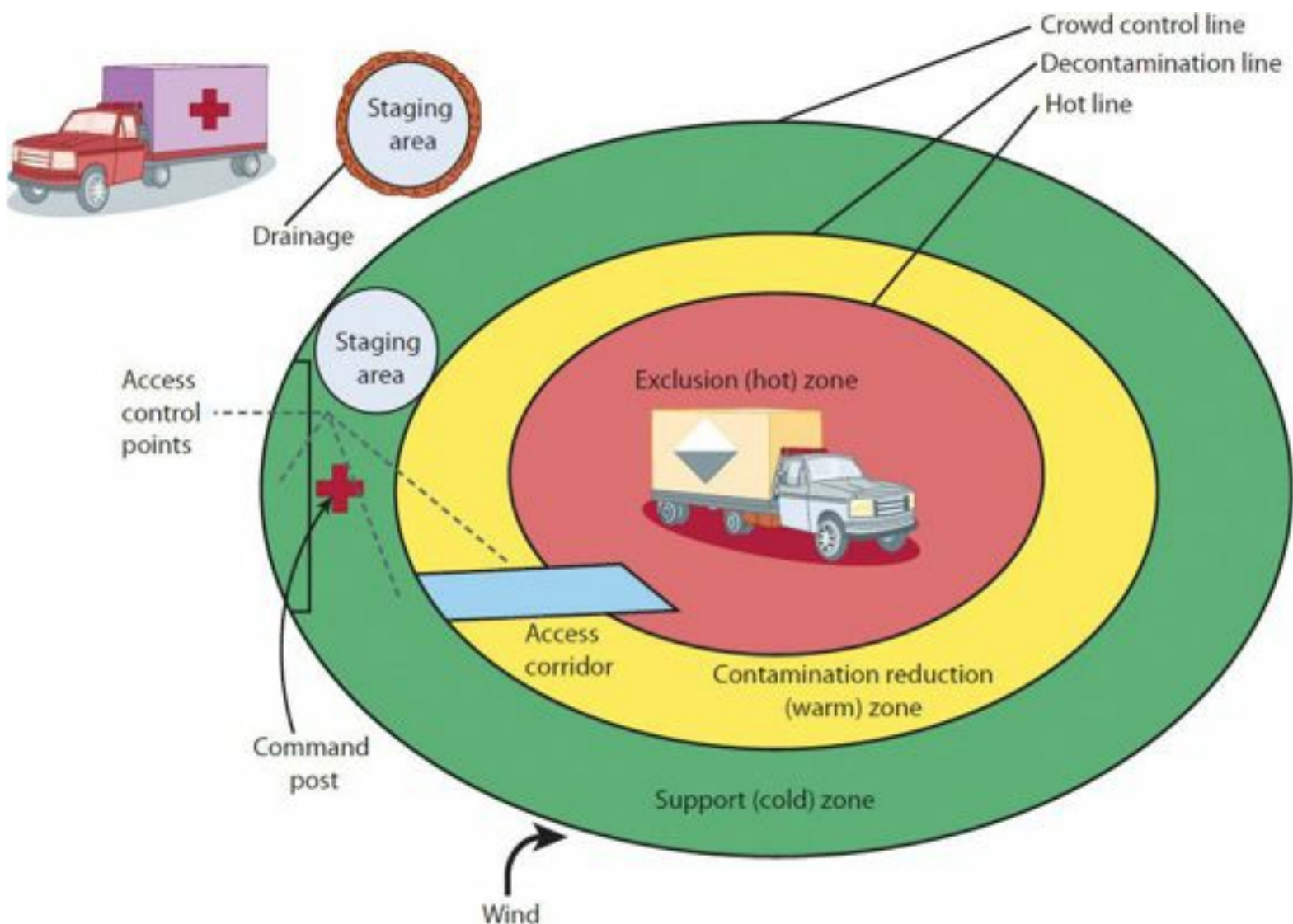


FIGURE 131-1. NIOSH/OSHA recommended hazardous materials control zones.

The hot zone is the area immediately surrounding a hazardous materials incident. It extends far enough to prevent the primary contamination of people and materials outside this zone. Primary contamination may occur to those who enter this zone. In general, evacuation—but no decontamination or patient care—is carried out in this zone, except for opening the airway and placing the patient on a backboard with spine precautions. This is because rescuers are generally hazardous materials technicians who wear level A or B suits that severely limit their visibility and dexterity. In specific situations, antidotes may be administered via autoinjectors as in the case of nerve agent antidotes.

The warm zone is the area surrounding the hot zone and contains the decontamination or access corridor, where victims and the hazardous materials entry team members and their equipment are decontaminated. It includes two control points for the access corridor. Many consider initiating therapy at this stage, particularly for chemical weapons, events where multiple casualties are involved.

The cold zone is the area beyond the warm zone. Contaminated victims and hazardous materials responders should be decontaminated before entering this area from the warm zone. Equipment and personnel are not expected to become contaminated in this zone. This is the area in which resources are assembled to support the hazardous materials emergency response. The incident command center is usually located in the cold zone, and there is greater ability to provide patient care there. Care provided in this zone includes the primary survey and resuscitation with management of airway (with

cervical spine control), breathing, circulation, disability, and exposure with evaluation for toxicity and trauma (ABCDE). Definitive care also includes antidotal treatment for specific poisonings.

Personal Protective Equipment

A critical goal of hazardous materials emergency responders is protecting themselves and the public. Safeguarding hazardous materials responders includes wearing appropriate PPE to prevent exposure to the hazard and prevent injury to the wearer from incorrect use of or malfunction of the PPE equipment.^{26,37}

PPE can create significant health hazards, including loss of cooling by evaporation, heat stress, physical stress, psychological stress, impaired vision, impaired mobility, and impaired communication. Because of these risks, individuals involved in hazardous materials emergency response must be trained regarding the appropriate use, decontamination, maintenance, and storage of PPE. This training includes instruction regarding the risk of permeation, penetration, and degradation of PPE. PPE with a self-contained breathing apparatus (SCBA) with a fixed supply of air significantly limits the amount of time the wearer can operate in the hot zone, usually about 20 minutes.

Levels of Protection. The EPA defines four levels of protection for PPE: levels A (greatest protection) through D (least protection). The different levels of PPE are designed to provide a choice of PPE, depending on the hazards at a specific hazardous materials incident ([Table 131–3](#))

TABLE 131–3. Personal Protective Equipment

Level ^a	Protects Skin and Eyes From			Protects Respiratory System From	
	Select Vapors and Aerosols	Gases, Vapors, and Aerosols	Oxygen-Deficient Atmospheres	Liquids and Solids	Gases and Vapors
D					
C	+			+	
B	+		+	+	+
A	+	+	+	+	+

^aLevel A is a self-contained breathing apparatus (SCBA) worn under a vapor-protective, fully encapsulated, airtight, chemical-resistant suit. Level B is a positive-pressure supplied-air respirator with an escape SCBA worn under a hooded, splash-protective, chemical-resistant suit. Level C is an air-purifying respirator worn with a hooded, splash-protective, chemical-resistant suit. Level D is regular work clothing (offers no protection).

Level A provides the highest level of both respiratory and skin (clothing) protection and provides vapor protection to the respiratory tract, mucous membranes, and skin. This level of PPE is airtight, fully encapsulating and the breathing apparatus must be worn under the suit.

Level B provides the highest level of respiratory protection and skin splash protection by using chemical-resistant clothing. It does not provide skin vapor protection but does provide respiratory tract vapor protection. Some hospitals have specially trained health care professionals who wear level B PPE when decontaminating patients presenting to the hospital. However, the majority of hospitals are training their frontline emergency department (ED) health care professionals to wear level C PPE when decontaminating contaminated patients who present to the hospital.

Level C protection should be used when the type of airborne xenobiotic is known, its concentration can be measured, the criteria for using air-purifying respirators are met, and skin and eye exposures are unlikely. Level C provides skin splash protection, the same as level B; however, level C has a lower level of respiratory protection than levels A and B.

Level D is basically a regular work uniform. It should not be worn when significant chemical respiratory or skin hazards exist. It provides no respiratory protection and minimal skin protection. Level D was specifically developed to show what not to wear for chemical protection.

Personal Protective Equipment Respiratory Protection. Personnel must be fit tested before using any respirator. A tiny space between the edge of the respirator and the face of the hazardous materials responder could permit exposure to an airborne hazard. Contact lenses cannot be worn with any respiratory protective equipment. Corrective eyeglass lenses must be mounted inside the face mask of the PPE. The only exception to these general rules are the use of hooded level C powered air purifying respirators (PAPRs) that do not require fit testing and allow individuals to wear their own eyeglasses within the hooded PAPR. This is the reason that most US hospitals prefer hooded PAPRs for their ED personnel who must decontaminate patients

Level A PPE mandates the use of a SCBA. A SCBA is composed of a face piece connected by a hose to a compressed

air source. An open-circuit, positive-pressure SCBA is used most often in emergency response and provides clean air from a cylinder to the face piece of the wearer, who exhales into the atmosphere. Thus, a higher air pressure is maintained inside the face piece than outside. This affords the SCBA wearer the highest level of protection against airborne hazards because any leakage will force air out of the face piece and not allow airborne hazards to enter against the higher pressure within the face piece. Disadvantages of the SCBA include its bulkiness and heaviness and a limited time period of respiratory protection because of the limited amount of air in the tank.

A supplied-air respirator (SAR) may be used in level B PPE and differs from SCBA in that air is supplied through a line that is connected to a source located away from the contaminated area. Only positive-pressure SARs are recommended for hazardous materials use. One major advantage of SARs over SCBA is that they allow an individual to work for a longer period. However, a hazardous materials worker must stay connected to the SAR and cannot leave the contaminated area by a different exit.

An air-purifying respirator (APR) may be used in level C PPE and allows breathing of ambient air after inhalation through a specific purifying canister or filter. There are three basic types of APRs: chemical cartridge, disposable, and powered air (PAPR). Although APRs afford the wearer increased mobility, they may be used only where there is sufficient oxygen in the ambient air. The chemical cartridges or canisters purify the air by filtration, adsorption, or absorption. Filters may also be used in combination with cartridges to provide increased protection from particulates such as asbestos. Powered devices reduce the work of breathing which can significantly limit an individual's performance while wearing PPE.

Decontamination

A major goal of the initial hazardous materials response is the decontamination of contaminated victims. Not only does decontamination reduce the health consequences for the victim (by reducing absorption or exposure time) but also prevents secondary contamination. Decontamination of equipment, the environment, and the entire area (ie, hot zone) may also be necessary but is secondary to the decontamination of victims.

An estimated 75% to 90% of contaminants may be removed simply by removing the victim's clothing and garments. Subsequent decontamination is most commonly accomplished by using water to copiously irrigate the skin of a victim, thereby physically washing off, diluting, or hydrolyzing the xenobiotic. However, the water solubility of a hazardous material must be considered to determine whether water alone is sufficient for skin decontamination or whether a detergent must also be used. The general rule regarding solubility is that "like dissolves like." In other words, a polar solvent, such as water, will dissolve polar substances such as salts. For example, the herbicide paraquat is actually a salt—paraquat dichloride—that is miscible in water. Therefore, if a patient's skin is contaminated with paraquat, copious water irrigation is sufficient for skin decontamination. A mild liquid detergent is acceptable but is not necessary. On the other hand, a nonpolar solvent, such as toluene, is not water soluble and is immiscible.^{35,36} Therefore, if a patient's skin is contaminated with toluene, water irrigation alone may be insufficient for decontamination, and a mild liquid detergent is also necessary.^{35,36} Furthermore, copious water may not be available at the site, thereby requiring rescuers to ration the supply and minimize irrigation using the least amount of water necessary. Some solid chemical contaminants may react with water and thereby cause an increased hazard if water used for decontamination. Such xenobiotics may be better removed mechanically by physically wiping it from the skin while avoiding smearing the xenobiotic or abrading the skin. Some contaminants may be chemically "inactivated" by applying another chemical, such as a 0.5% hypochlorite solution.

When performing decontamination, close attention should be paid to all exposed skin, particularly, the skin folds, axillae, genital area, and feet. Lukewarm water should be used with gentle water pressure to reduce the risk of hypothermia. Water should be applied systematically from head to toe while the patient's airway is protected.

Exposed, symptomatic eyes should be continuously irrigated with water throughout the patient contact, including transport, if possible. Remember to check for and remove contact lenses.

Removal of internal contamination is often much more problematic. In some cases, specific medications may be administered to enhance elimination or inactivate the hazardous material. For instance, Prussian blue can trap radioactive cesium in the intestine so that it can be eliminated from the body in the stool rather than be reabsorbed.

Scene Triage. Victim decontamination and movement from a scene requires an organized methodology for categorization of medical severity. The most common triage method used is the Simple Triage and Rapid Treatment system (START)⁴ although many others exist. This system follows a simple algorithm that allows for a color categorization based upon the victim's respirations, perfusion, and mental status: immediate (red), delayed (yellow), walking wounded/minor (green), and deceased/expectant (black). Victims may be initially triaged in the contaminated zone and then re-triaged after decontamination.

HAZARDOUS MATERIALS INCIDENT RESPONSE RULES AND STANDARDS

OSHA and the NFPA have developed rules and guidelines, respectively, regarding hazardous materials incident response.^{24,31–34,40,45} OSHA rules are mandated as law and must be followed.^{24,40,45} Meeting NFPA guidelines will ensure OSHA compliance.^{24,31,32,34,37,40}

The Superfund Amendments and Reauthorization Act of 1986 (SARA) required OSHA to develop and implement standards to protect employees responding to hazardous materials emergencies. This resulted in the Hazardous Waste Operations and Emergency Response standard, 29 CFR 1910.120, or HAZWOPER.⁴⁵

NFPA 471, Recommended Practice for Responding to Hazardous Materials Incidents, outlines the following tactical objectives: incident response planning, communication procedures, response levels, site safety, control zones, PPE, incident mitigation, decontamination, and medical monitoring.³²

NFPA 472, Standard on Professional Competence of Responders to Hazardous Materials Incidents, helps define the minimum skills, knowledge, and standards for training outlined in HAZWOPER for three types of responders.³³

Prehospital Hazardous Materials Emergency Response Team Composition, Organization, and Responsibilities

First Responder at the Awareness Level. First responders at the awareness level could be first on the scene at an emergency incident involving hazardous material. They are expected to recognize the presence of hazardous materials, protect themselves, secure the area, and call for better trained personnel. They must take a safe position and keep other people from entering the area. They must recognize that the level of mitigation exceeds their training and call for a hazardous materials response team. Most basic curricula of emergency medical technicians include this level of first responder training

First Responder at the Operational Level. These individuals are trained in all competencies of the awareness level and are additionally trained to protect nearby persons, the environment, and exposed property from the effects of hazardous materials releases. Operational level certified individuals are expected to assume a defensive posture, control the release from a safe distance, and keep the hazardous material from spreading. Operational level individuals are trained to perform absorption of liquids, containment of the spill, vapor suppression, and vapor dispersion. They do not operate within the hot zone

Hazardous Materials Technician. Hazardous materials technicians respond to hazardous materials releases, or potential releases, for the purpose of controlling the release. They are trained in the use of chemical-resistant suits, air-monitoring equipment, mitigation techniques, and the interpretation of physical properties of hazardous materials. Technicians are capable of containing an incident, making safe entry into a hazardous environment, determining the appropriate course of action, victim rescue, and cleaning up or neutralizing the incident to return the property to a safe and usable status, if possible. These individuals are trained to operate within the hot zone to mitigate the incident. This certification level includes knowledge of hazardous material chemistry, air-monitoring equipment, tools used within the hot zone, and more

Advanced Hazardous Materials Components

Advanced Hazardous Materials Providers. Paramedics should be trained in the recognition of signs and symptoms caused by exposure to hazardous materials and the delivery of antidotal therapy to victims of hazardous materials poisonings²⁴

The inclusion of such training into a hazardous materials response team is beneficial, not only for the needs of the public but also to protect hazardous materials technicians who make entry into hazardous atmospheres.²⁴ Ideally, hazardous materials technicians' entry into hazardous atmospheres should not be performed until appropriately trained paramedics are on the scene with resuscitative equipment in place, including a drug box containing essential antidotes for specific hazardous materials.²⁴

Patient Care Responsibilities of the Prehospital Decontamination Team and the Hazardous Materials Entry Team. Hazardous materials responders should identify the entry and exit areas by controlling points for the access corridor (decontamination corridor) from the hot zone, through the warm zone, to the cold zone (Fig. 131–1). This corridor should be upwind, uphill, and upstream from the hot zone, if possible. Hazardous materials technician entry team members should remove victims from the contaminated hot zone and deliver patients to the inner control point of the access (decontamination) corridor. Hazardous materials decontamination team members decontaminate patients in the decontamination (access) corridor of the contamination reduction (warm) zone^{11,14,18,19,24,27,28,42}

The primary responsibility of the prehospital hazardous materials medical sector is the protection of the hazardous materials entry team personnel. This is accomplished by researching and recording clinically pertinent information about the hazardous material, remaining available on scene for medical treatment, and assessing individuals before entry into and on exit from a hazardous environment.²⁴ Documentation of each assessment should be recorded on a prepared form and compared with the exclusion criteria defined by NFPA 471.^{24,32}

In some systems, the hazardous materials entry team may include specialized providers who have the ability to provide lifesaving patient care within the hot zone. The ability to perform triage or cardiopulmonary resuscitation or to provide any medical care is greatly limited by the PPE being worn. Therefore, only immediately lifesaving procedures should be considered, such as intubation/ventilation or antidote administration using an autoinjector.

Patient Care Responsibilities of Emergency Medical Services Providers at Hazardous Materials Incidents. EMS providers who are not part of the hazardous materials team should report to the incident staging area and await direction from the incident commander. They should approach the site from upwind, uphill, and upstream, if possible

EMS providers should remain in the cold zone until properly protected hazardous materials incident responders arrive, decontaminate, and deliver patients to them for further triage and treatment. Then EMS providers should evaluate each patient, triage as appropriate, and move the patient to the appropriate casualty collection point or rapidly transport to the hospital as resources allow. Exposed victims who are initially asymptomatic should continue to be observed and reassessed for the delayed development of symptoms, and the EMS provider should be prepared to upgrade the triage category for the patient. All EMS systems should have protocols in place that direct operations at hazardous materials scenes. Ideally, the EMS response matrix for such events includes the response of an EMS physician or contact with online medical control who will coordinate appropriate care with the regional poison center, toxicologists, and hospitals.

Transportation of patients from the hazardous materials incident is ultimately under the control of the incident commander but is usually delegated to the prehospital hazardous materials medical sector and EMS providers. In general, no victim with skin contamination should be transported from the hazardous materials site without being properly decontaminated. Before transportation, EMS should notify the receiving hospital of the number of victims being transported and their toxicologic history, patient assessments, and treatment rendered.

Hospital Responsibilities for Hazardous Materials Victims

Ideally, the local or regional ED physicians and personnel will receive advanced notification about a hazardous materials incident before any victims arrive at the hospital. This notification to the hospital should occur as early in the event as possible to allow for maximum “ramp-up” time. The notification should include, if known, information regarding the event, hazardous materials involved, number and condition of casualties to be transported to the hospital, as well as information regarding the decontamination completed. Assistance of a poison center and a toxicologist is generally recommended.

Victims may leave an incident scene and subsequently present to a hospital. The hospital must have a preestablished protocol by which hospital response teams will decontaminate patients who arrive at the hospital if they have not been previously decontaminated or if field decontamination is believed to be insufficient.^{7,15,16,17,23,25,39,41,43,46,49,50} Hazardous materials patients who require skin decontamination should be denied entry to the ED until they are decontaminated by an appropriately trained and equipped hazardous materials response team. The emergency physician will determine when the patient is safe to enter the ED after carefully assessing the risks and benefits to the decontaminated patient, the other patients in the ED, and the ED health care personnel.

SUMMARY

- Hazardous materials incident response is an integrated, interdisciplinary approach involving prehospital, hospital, poison center, and public health professionals.
- Most patients at hazardous materials incidents are exposed through inhalation of a gas, a solid, or a liquid aerosol.
- Prehospital and hospital health care professionals must use appropriate PPE when caring for patients who have not been decontaminated.
- Decontamination is critical to alter absorption for patients and to prevent secondary contamination of downstream health care professionals and equipment.
- The general principles of toxicology apply regardless of whether a patient is at a hazardous materials incident in a prehospital or hospital setting. Although patient care resources vary among these treatment settings, the fundamental principles of patient care remain the same. All patients should receive a primary survey and resuscitation, emphasizing airway, breathing, and circulation.

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132 Chemical Weapons

Jeffrey R. Suchard

HISTORY AND EPIDEMIOLOGY

The first well documented intentional use of chemicals as weapons occurred in 423 B.C. when Spartans besieging Athenian cities burned pitch soaked wood and brimstone to produce sulfurous clouds.⁸² Chemical weapons were sporadically used, or their use considered, up through the nineteenth century.⁴⁶

Large-scale chemical warfare began in World War I when the Germans released chlorine near Ypres, Belgium, killing hundreds and forcing 15,000 troops to retreat.^{19,46} Both sides rapidly escalated the use of toxic gases, released from cylinders or by artillery shells, including various pulmonary irritants, lacrimators, arsenicals, and cyanides.

The Germans first used sulfur mustard in 1917, again near Ypres, and caused more than 20,000 deaths or injuries.⁴⁶ Unlike prior chemical weapons, mustard was persistent in the environment and vesicated the skin in addition to injuring the lungs and mucous membranes. The Allies soon responded in kind. Sulfur mustard was unequalled in its ability to incapacitate opponents.¹⁰ Injuries far outweighed fatalities, tying up manpower and resources to care for the wounded. By the end of the war, chemical weapons had caused more than 1.3 million casualties and approximately 90,000 deaths.¹⁹

Only one major chemical weapon event occurred during World War II. German planes bombed American ships carrying chemical munitions docked in the harbor of Bari, Italy, releasing the contents of 2000 mustard bombs and causing more than 600 Allied military and an unknown number of civilian casualties.^{10,46}

Germany began producing nerve agents just before World War II. Tabun was developed in 1936 by Gerhard Schrader when conducting insecticide research for IG Farbenindustrie,^{29,73} but was abandoned as an insecticide because of its overwhelming human toxicity. Sarin was synthesized in 1938, and named after its developers: Schrader, Ambrose, Rudringer, and Van der Linde.²⁹ Between 10,000 and 30,000 tons of tabun and 5 to 10 tons of sarin were produced during World War II. Soman was synthesized in 1944, but no large-scale production facilities were developed. When the Allies discovered these nerve agents at the end of the war, code names were designated based on the order of their development. Tabun was called GA (the letter G standing for German), sarin was GB, and soman was GD.²⁹

In 1952, the British synthesized an even more potent nerve agent while searching for a dichlorodiphenyltrichloroethane (DDT) replacement. This substance was given to the United States for military development, and was named VX. A VX leak killed 6000 sheep near a military base in Skull Valley, Utah in 1968.^{29,41,73} The Russians developed a similar nerve agent, variably referred to as VR or “Russian VX.”³⁷ The United States used defoliants and riot control agents in Vietnam and Laos. Iraq used sulfur mustard, tabun, and soman during its war with Iran in the 1980s, and may have also used cyanide against the Kurds.⁴⁶

Terrorist groups have also begun to employ chemical weapons. Sarin was released twice by the Aum Shinrikyo cult in Japan. The first release occurred in Matsumoto in 1994, killing seven and injuring more than 600.⁴⁸ A more highly publicized sarin attack occurred in the Tokyo subway system in 1995, killing 12 and resulting in more than 5000 persons seeking medical attention.⁷⁰ Cult members have also used VX in assassinations.⁴⁷ Chemical weapons may particularly appeal to terrorist groups, in that the technology and financial outlay required to produce them is much less than for nuclear weapons, although the potential morbidity, mortality, and societal impact remain high (Table 132–1).

TABLE 132–1. Unconventional Weapons: Definitions and Acronyms

Chemical warfare	Intentional use of weapons designed to kill, injure, or incapacitate on the basis of toxic or noxious chemical properties
Biologic warfare	Intentional use of microorganisms or xenobiotics derived from living organisms to cause death, disability, or damage in humans, animals, or plants
Terrorism	The unlawful use of force against persons or property to intimidate or coerce a government, the civilian population, or any segment thereof, in furtherance of political or social objectives
CW	Chemical warfare, or chemical weapon
BW	Biological warfare, or biological weapon
CBW	Chemical and/or biological warfare, or weapons
NBC	Nuclear, biological and/or chemical; usually in reference to weapons
CBRNE	Chemical, biological, radiological, nuclear, and explosive; usually in reference to weapons
WMD	Weapon of mass destruction; nuclear, radiologic, chemical, or biological weapon intended to produce mass casualties

Chemical weapons clearly fall within the purview of medical toxicology. Indeed, unlike the diverse xenobiotics widely studied by toxicologists that may incidentally cause poisonings, chemical weapons are specifically designed to kill, injure, or incapacitate. Some compounds generally considered nonlethal, such as tear gas and pepper spray, are therefore also considered chemical weapons. Biologic weapons share some characteristics with chemical weapons ([Table 132–2](#)) and are covered in [Chap. 133](#), although the issues common to both chemical and biologic weapons are discussed in this chapter.

TABLE 132–2. Chemical versus Biological Weapons: Comparison and Contrast²⁶

<i>Similarities</i>		
Xenobiotics most effectively dispersed in aerosol or vapor forms		
Delivery systems frequently similar		
Movement of xenobiotics highly subject to wind and weather conditions		
Appropriate personal protective equipment prevents illness		
<i>Differences</i>	<i>Chemical Weapons (CWs)</i>	<i>Biological Weapons (BW)</i>
Rate at which attack results in illness	Rapid usually minutes to hours	Delayed usually days to weeks
Identifying release	<i>Easier:</i> Rapid clinical effects Possible chemical odor Commercially available chemical detectors	<i>Harder:</i> Delayed clinical effects Lack of color, odor, or taste Limited development of real-time detectors
Xenobiotic persistence	Variable Liquids semipersistent to persistent Gases nonpersistent	Generally nonpersistent most BW xenobiotics degraded by sunlight, heat, desiccation (exception: anthrax spores)
Victim distribution	Near and downwind from release point	Victims may be widely dispersed by the time disease is apparent
First responders	EMTs, hazard materials teams, firefighters, law enforcement officers	Emergency physicians and nurses, primary care practitioners, infectious disease physicians, epidemiologists, public health officials (but may be same as CW if release is identified immediately)
Decontamination	Critically important in most cases	Not needed in delayed presentations; less important for acute exposures
Medical treatment	Chemical antidotes, supportive care	Vaccines, antibiotics, supportive care
Patient isolation	Unnecessary after adequate decontamination	Crucial for easily communicable diseases (eg, smallpox, pneumonic plague); however, many BW agents are not easily transmissible

This chapter focuses on the acute and long-term clinical effects of exposure to chemical weapons, their mechanisms of toxicity, and the medical treatment of individual casualties, based on published human case experience. There are many other potential subtopics related to chemical (and biologic) weapons that are not specifically reviewed here, including disaster incident command ([Chap. 131](#)), CBW agent detection, provision of medical care in a chemically contaminated environment, and the ever-growing body of evidence accumulated from in vitro and ex vivo models of chemical warfare agent poisoning.

GENERAL CONSIDERATIONS

Physical Properties

The term war gas is generally a misnomer. Sulfur mustard and nerve agents are liquids at normal temperatures and

pressures, and many riot-control agents are solids. These weapons are most efficiently dispersed as aerosols, which probably leads to the confusion with gases. Some chemical weapons (eg, chlorine, phosgene, hydrogen cyanide) are truly gases, and although they are generally considered obsolete for battlefield use, they might still be used as improvisational agents, especially in terrorist attacks.

Liquid chemical weapons have a certain degree of volatility and may evaporate into poisonous vapors. Volatility is inversely related to persistence, the tendency to remain in the environment. Persistent agents, such as mustard or VX, can contaminate an area for prolonged periods, denying the enemy free movement and use of contaminated material. The toxic hazard from semipersistent agents like sarin or nonpersistent agents like hydrogen cyanide dissipates more rapidly.

Aerosols, gases, and vapors are highly subject to local atmospheric conditions. Less dispersion occurs with atmospheric inversion layers and in the absence of wind, as typically occurs at night or in the early morning. Enclosed spaces also prevent wind dispersion and even simple dilution. Except for hydrogen cyanide, CW gases and vapors are all denser than air and will pool in low-lying areas.

As a practical example, consider the 1995 sarin release in the Tokyo subway system. The number of fatalities could have been much higher had it been effectively aerosolized instead of simply allowed to evaporate. Photos from the attack show severely affected or deceased victims in very close proximity to mildly affected, ambulatory individuals. Presumably, sarin concentrations decreased so rapidly as distance from the source increased that few victims were significantly contaminated. After removal from high-concentration areas, the victims' bodies posed less threat to bystanders because of dilution and improved ventilation. Even so, some health care professionals were secondarily exposed, as the victims were not disrobed prior to entering the hospitals. Up to 46% of hospital staff in areas with poor ventilation reported symptoms consistent with mild acute poisoning, although cholinesterase levels were not reported.^{52,53,56} About one-third of rescue workers in the 1994 Matsumoto sarin incident also developed mild toxicity. Rescuers arriving at the scene later were less likely to develop symptoms,⁴⁹ suggesting that the vapor had dissipated over time.

Preparation for CBW Incidents

A rational medical response to CBW events differs from the common response to isolated toxicologic incidents. Health care professionals must learn about these unconventional weapons and the expected “toxicodromes” that may occur.¹ In addition, health care professionals must protect themselves and their facilities first, or ultimately no one will receive care. New medicolegal and ethical considerations will arise in CBW mass-casualty events that otherwise infrequently occur. The greatest good for the greatest number of victims may preclude heroic interventions in a few critical patients. Charges of negligence may later arise regarding delays in treatment or failure to diagnose subtle signs of disease, even if such actions were unavoidable at the time. Even if physicians become well versed in the appropriate response to CBW incidents, the question remains as to how many will be willing to continue working in the presence of an actual public health disaster.³⁰

The responses to chemical and biologic weapons will also differ.²⁶ Chemical weapons, like conventional explosives, generally produce clinical effects within seconds to hours, making a “scene” or “hot zone” evident. The first responders for a chemical event will be fire and police authorities, hazmat teams, and emergency medical services. Patients will be brought to local health care facilities and the disease process, although perhaps not the specific etiology or diagnosis, will be recognized rapidly. With biologic weapons, the victims will not all present for care at the same time in the same place. First responders will be local and distant emergency departments (EDs) and primary care offices, highlighting the need for training in these specialties.

Recommendations for sustained health care facility domestic preparedness include improved training to promptly recognize CBW mass casualty events, efforts to protect health care professionals, and establishing decontamination and triage protocols.⁴⁰ Table 132–3 lists some specific recommendations. Several facets of the response to a CBW event are still being refined, such as the optimal choice of personal protective equipment, determining who needs decontamination and by what means, and what is to be done with wastewater produced by mass decontamination.^{36,40} On a tactical level, communication can be severely impaired by personal protective gear, which points out the need for loudspeakers or other forms of public address.^{40,81}

TABLE 132–3. Recommendations for Health Care Facility Response to Chemical and/or Biological Warfare or Weapons Incidents

- Immediate access to personal protective equipment for health care professionals
- Decontamination facilities that can be made operational with minimal delay
- Triage of victims into those able to decontaminate themselves (decreasing the workload for health care providers) and those requiring assistance
- Decontamination facilities permitting simultaneous use by multiple persons and providing some measure of visual privacy
- A brief sign-in process where patients are assigned numbers and given identically numbered plastic bags to contain and identify their clothing and valuables

- Provision of food, water, and psychological support for staff, who may be required to perform for extended periods
- Secondary triage to separate persons requiring immediate medical treatment from those with minor or no apparent injuries who are sent to a holding area for observation
- Providing victims with written information regarding the agent involved, potential short and long term effects, recommended treatment, stress reactions, and possible avenues for further assistance
- Careful handling of information released to the media to prevent conflicting or erroneous reports
- Instituting postexposure surveillance

Individual clinicians and hospitals caring for victims of known or suspected CBW incidents should contact their local department of health, which may in turn report the incident to outside agencies such as the US Federal Bureau of Investigation and the Centers for Disease Control and Prevention (Table 132–4).

TABLE 132–4. Chemical and/or Biological Warfare or Weapons Phone Numbers/Contacts

CDC Emergency Preparedness and Response:

<http://emergency.cdc.gov>

Emergency Response Line: (770) 488–7100

CDC Division of Bioterrorism Preparedness and Response: (404) 639–0385

US Army Medical Research Institute of Chemical Defense Emergency Response Line: (410) 436-3276 or (410) 322-6822

Federal Bureau of Investigation (FBI):

Find your local FBI field office at:

<http://www.fbi.gov/contact-us/field/field-offices>

National Response Center:

For reporting releases of hazardous substances: www.nrc.uscg.mil/

(800) 424–8802, or (202) 267-2675

CDC = Centers for Disease Control and Prevention; FBI = Federal Bureau of Investigation.

Decontamination

Decontamination serves two functions: (1) to prevent further absorption and spread of a noxious substance on a given casualty, and (2) to prevent spread to other persons. Chemical weapons that are exclusively gases at normal temperatures and pressures such as chlorine, phosgene, or hydrogen cyanide only require removing the victim from the area of exposure. Isolated aerosol or vapor exposures, as from volatilized nerve agents or sulfur mustard, are also terminated by leaving the area and may require no skin decontamination of the victims.^{46,71} Japanese experience with sarin suggests that clothing should be removed from victims of nerve agent vapor exposure and placed in airtight receptacles, such as sealed plastic bags. Some of the secondary exposures to sarin were thought to have occurred as nerve agent that had condensed on the victims' clothing revaporized into the ambient air, and this caution probably holds true also for sulfur mustard vapor exposures.

Chemical weapons dispersed as liquids present the greatest need for decontamination. Because nerve agents are highly potent and have rapid onset of effects, some victims with significant dermal contamination may not survive to reach medical care.⁷¹ Liquid-contaminated clothing must be removed, and, if able, victims should remove their own clothing to prevent cross-contamination.

Decontamination should be done as soon as practicable, to prevent progression of disease, and should occur outside of health care facilities to prevent contamination of the working environment and secondary casualties. Decontamination near the incident scene would be ideal in terms of timeliness, although logistically this will not be possible in many situations. Field decontamination prior to transport will also help to avoid loss of vehicles from being contaminated and taken out of service. Evidence supports the likelihood that contaminated victims will present at health care facilities on their own, or be transported for care without decontamination.³⁶ In mass-casualty incidents, decontamination efforts may benefit from separating victims into those who can remove their own clothing and shower themselves with minimal direction and assistance, and the more seriously affected who will require full assistance. The degree of protective gear required by the decontamination personnel cannot be predicted in advance, and may be difficult to objectively determine at the time of the incident. Level C personal protective equipment may be sufficient for most hospital settings when the source is defined (eg, receiving and decontamination areas); however, if health care professionals begin to develop symptoms, then level B gear with supplied air would become necessary⁵⁴ (Chap. 131). When the source of the contamination is not yet known, level B gear should be used. Chemically contaminated victims presenting to a health care facility should, if possible, be denied entrance until decontaminated. Patients who have already entered a health care facility and are only later determined to be a contamination hazard present a more difficult problem. If the situation allows, such patients should be taken outside for

decontamination before returning, and the previous care area cordoned off until any remaining safety hazard has been assessed and eliminated. However, in a mass-casualty disaster, such efforts at remediation may not be practical.

Nerve agents are hydrolyzed and inactivated by solutions that release chlorine, such as household bleach, or solutions that are sufficiently alkaline. To avoid potential dermal and mucous membrane injury, a 1:10 dilution of household bleach in water (producing a 0.5% sodium hypochlorite solution) is recommended, not only for nerve agents, but also for sulfur mustard and many biologic agents.^{40,44,73} Alternatives include regular soap and water or copious water alone. Rapid washing is more important than the choice of cleaning solution because 15 to 20 minutes is necessary for hypochlorite solutions to inactivate chemical agents.⁴⁰ Care should be taken to clean the hair, intertriginous areas, axillae, and groin.⁷³

Decontamination after sulfur mustard exposure is more problematic than for nerve agents. First, it is more likely that significantly contaminated victims will survive to reach medical care, and they may remain asymptomatic for several hours. In addition, the biochemical damage becomes irreversible long before symptoms develop. Decontamination within 1 to 2 minutes is the only effective means of limiting tissue damage from mustard.⁷⁵ However, the actual means of mustard decontamination are identical to those for nerve agents. Victims must be disrobed and thoroughly showered. Dilute hypochlorite solutions (eg, 0.5% sodium hypochlorite, a 1:10 dilution of household bleach) are advocated to inactivate mustard, but copious water irrigation will also suffice.⁴⁶ Symptomatic victims of mustard exposure should still be decontaminated, although it is unlikely to benefit that particular individual it can prevent the spread of mustard to others.⁷⁵ Lewisite and phosgene oxime must also be decontaminated quickly, although they produce immediate symptoms, making it more likely that victims will present promptly when decontamination is most effective.

Water irrigation is generally recommended for riot control agent exposures because hypochlorite solutions may exacerbate skin lesions.⁴⁶ Inadequately decontaminated patients exposed to lacrimators can produce secondary cases among health care professionals, so any contaminated clothing should be removed and bagged.

Significant issues remain regarding decontamination measures. The number of people potentially requiring decontamination may easily outstrip capacity. Incidents with hundreds or thousands of victims may necessitate communal showers, selective decontamination, or both. Decontamination wastewater should ideally be contained and treated, but few facilities have the capability or funds to do this. However, wastewater may be a minor issue, since with large scale chemical weapons events the wastewater represents only a small percentage of the total environmental impact.⁴⁰

Risk of Exposure

The actual release of chemical or biologic weapons can be characterized as a low-probability, high-consequence event. Potential sources for civilian exposure include terrorist attacks, inadvertent releases from domestic stockpiles, direct military attacks, and industrial events. Terrorists may sabotage military or industrial stockpiles or directly attack the populace. Experience has shown that physicians are much more likely to encounter hoaxes,¹³ isolated cases,⁶² or limited incidents with a modest number of casualties.⁸⁰ Riot control agents are exceptions, in that treating riot control agent and pepper spray victims is a routine occurrence in many urban EDs.

Technical and organizational obstacles decrease the chance of major CBW terrorist events. Obtaining or producing chemical or biologic weapons, although simpler than for nuclear weapons, is only part of the process. Effective dissemination is difficult if the goal is to maximize casualties. Proper milling of biologics to produce stable, respirable aerosols requires technical sophistication probably only attainable with governmental research support. Low-technology attacks such as food contamination, poisoning of livestock, and enclosed-space weapons dispersal appear more likely to occur than attacks resulting in hundreds, thousands, or millions of casualties. Smaller attacks, or merely threatening use of chemical or biologic weapons, may be equally consequential from a terrorist's perspective if they exert comparable political influence with significant psychosocial impact.

The chemicals most likely to be used militarily appear to be sulfur mustard and the nerve agents. A "low-tech" terrorist attack could involve the release of toxic industrial chemicals, such as chlorine, phosgene, or ammonia gas as chemical "agents of opportunity."

Psychological Effects

Either the threat or the actual use of CBW agents presents unique psychologic stressors. Even among trained persons, a CBW-contaminated environment will produce high stress through the necessity of wearing protective gear, potential exposure to agents, high workload intensity, and interactions with the dead and dying. Disorders of mood, cognition, and behavior will be common among exposed or potentially exposed victims as a result of the uncertainty, fear, and panic that may accompany a CBW incident, even a hoax. The psychological casualties will probably outnumber victims requiring medical treatment. Civilians without training, including some health care professionals, are likely to confuse somatic symptoms with true exposure. Medical resources may easily be overwhelmed unless triage can identify those who will benefit most from appropriate counseling, education, and psychologic support. Psychiatrists and other disaster mental health personnel should be enlisted in plans to manage CBW incidents for their expertise in treating anxiety, fear, panic,

somatization, and grief.¹⁵

In Israel during the Gulf War, anxiety-related somatic reactions to missile attacks were reported in 18% to 38% of persons surveyed,¹¹ and more than 500 people sought medical attention in EDs for anxiety.⁵⁹ Among 5510 people seeking medical attention after the Tokyo subway sarin release, only about 25% were hospitalized.⁷⁰ Some of the “victims” presented days or even weeks after the incident, apparently feeling unwell and thinking they were exposed.^{53,57} Civilian survivors of chemical attacks in the 1980–1988 Iran–Iraq war report increased symptoms of depression, anxiety, and posttraumatic stress disorder compared to those exposed to low-intensity conventional warfare.²³ In one longitudinal study of American Persian Gulf War veterans, 4.6% reported their belief that they were exposed to CBW agents, despite the lack of any convincing evidence of deliberate exposures, nor of unintended exposure to any significant levels of chemical agents. Greater combat stress was associated with a higher incidence in belief in such exposures.⁷⁶ Another study reported a 64% incidence in belief of CBW agent exposure among Gulf War veterans.⁹ Reported indicators supporting these beliefs included receiving an alert, having physical symptoms, and being told to use protective gear. Belief in exposure to biologics correlated with having received an alert about chemicals, suggesting that CW alerts can spread misinformation and confusion among recipients.

Uncontrolled release of information may compound terror and increase psychologic casualties. Imagine the influx of patients resulting from a news report suggesting that anyone with dizziness or nausea be checked for nerve agent toxicity, or that fever and cough indicate infection with anthrax.

Israeli Experience during the 1990–1991 Gulf War

Israel is probably one of the best prepared countries for CBW disasters. In late 1990, the civilian population was supplied with rubber gas masks, atropine syringes, and Fuller’s earth decontamination powder.⁵⁹ Major Israeli hospitals conduct chemical practice drills every 3 to 5 years.⁸¹ These drills identify several key lessons, including designating specific hospitals for chemical casualties, blocking hospital access to a single guarded entrance to prevent internal contamination, and extending nurses’ authority to initiate treatment by established protocols. The Israeli plan provides two tiers of triage. The first triage occurs outside of the hospital by protected medical personnel who perform only life-saving interventions, such as intubation, hemorrhage control, and antidotal therapy. Patients are then decontaminated and enter the hospital. Afterward, patients are triaged again according to severity of illness into separate areas in which dedicated health care teams provide the appropriate interventions.^{64,81}

Thirty-nine ballistic missiles with conventional warheads were launched against Israel from Iraq in early 1991, with only six missiles causing direct casualties. Many more “injuries” resulted from CBW defensive measures and psychologic stress than from physical trauma. Out of 1060 injuries reported from EDs during this time period, 234 persons were directly wounded in explosions (most injuries were minor), and there were only two fatalities from trauma.^{32,59} More than 200 people presented for medical evaluation after self-injection of atropine, a few requiring admission to the hospital.^{3,32,59} About 540 people sought care for acute anxiety reactions. Some suffocated from improperly used gas masks, fell and injured themselves when rushing to rooms sealed against CBW agents, or were poisoned by carbon monoxide in these airtight rooms.^{32,59} Increased rates of myocardial infarction and cerebrovascular accidents were also observed.⁵⁹ A survey of hospital staff members found that only 42% would report for duty following a chemical weapon attack.⁶⁵

Special Populations

Pregnancy does not appear to be a significant factor in the treatment of women victims of chemical weapons. In the Tokyo subway sarin attack, five victims were identified at one hospital as being pregnant. These women were only mildly affected and were admitted for observation. All had healthy babies, the first one born 3 weeks after the incident.^{53,55,57} In Israel, no obstetric complications occurred among women wearing gas masks during labor and delivery.^{18,59}

Children differ substantially from adults with regard to chemical weapons effects and decontamination efforts. Children breathe at a lower elevation above the ground and at a higher rate than adults. Because nearly all chemical weapon gases and vapors are heavier than air, children will be exposed to higher concentrations than adults in the same exposure setting, and will likely exhibit symptoms earlier.^{5,61,86} Children may also be more susceptible to vesicants and nerve agents than adults with equivalent exposures.^{60,86} Children have thinner and more delicate skin, allowing for more systemic absorption and more rapid onset of injury with sulfur mustard. The blood–brain barrier of a child may also be less resistant than in adults and the activity of endogenous detoxifying enzymes, such as paraoxonase, is less, allowing for greater toxicity with nerve agents. Additionally, children with organic phosphorus compound poisoning less frequently exhibit a muscarinic toxic syndrome than adults, and often present with isolated central nervous system (CNS) depression.⁶⁰

The decontamination of children is another feature that requires an age-adjusted approach. Children have a larger surface area-to-mass ratio and may be more likely to carry a toxic or fatal dose of a chemical weapon on their skin. Most children will need assistance and supervision during decontamination procedures; keeping a mother or other adult guardian

with a child should help with both decontamination and thermoregulation.⁶¹

NERVE AGENTS

Physical Characteristics and Toxicity

Nerve agents are extremely potent organic phosphorus compound cholinesterase inhibitors, and are the most toxic of the known chemical weapons (Fig. 132–1).⁴⁶ For example, sarin is 1000-fold more potent in vitro than the pesticide parathion.⁷¹ Aerosol doses of nerve agents causing 50% human mortality (LD₅₀) range from 400 mg/minute/m³ for tabun down to 10 mg/minute/m³ for VX, compared with 2500 to 5000 mg/minute/m³ for hydrogen cyanide. Dermal exposure LD₅₀s for nerve agents range from 1700 mg for sarin down to only 6 to 10 mg for VX.^{46,71} Pure nerve agents are clear and colorless. Tabun has a faint fruity odor, and soman has been variably described as smelling sweet, musty, fruity, spicy, nutty, or like camphor. Most subjects exposed to sarin and VX have been unable to describe the odor.^{41,71} The G agents tabun (GA), sarin (GB), and soman (GD) are volatile and present a significant vapor hazard. Sarin is the most volatile, only slightly less so than water. VX is an oily liquid with low volatility and higher environmental persistence.^{41,46,71} Other G and V agents have been developed, including cyclosarin (GF) and Russian VX (VR).

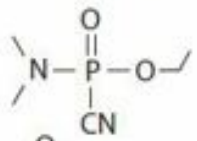
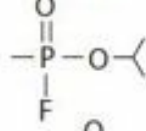
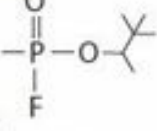
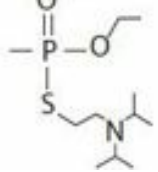
Military designation	Common name	Chemical name	Chemical structure
GA	Tabun	ethyl- <i>N,N</i> -dimethylphosphoramidocyanidate	
GB	Sarin	isopropyl-methylphosphonofluoridate	
GD	Soman	1, 2, 2-trimethylpropyl-methyl phosphonofluoridate	
VX	–	<i>O</i> -ethyl- <i>S</i> -(2-diisopropylaminoethyl)-methylphosphonothiolate	

FIGURE 132–1. Nerve agents.

Pathophysiology

The pathophysiology of nerve agents is essentially identical to that from organic phosphorus compound insecticides (Chap. 113), differing only in terms of potency and physical characteristics of the xenobiotics. The resultant toxic syndrome includes muscarinic (salivation, lacrimation, urination, defecation, GI cramping, emesis) and nicotinic (muscle fasciculation, weakness, paralysis) signs, and central effects (loss of consciousness, seizures, respiratory depression).^{29,69,73}

Clinical Effects

Nerve agent vapor exposures produce rapid effects, within seconds to minutes, whereas the effects from liquid exposure may be delayed as the agent is absorbed through the skin.⁷¹ Vapor or aerosol exposures have historically been more common, whether through experiments or from unintentional releases in the laboratory⁶⁹ or in terrorist attacks.^{48,57} Aerosol or vapor exposure initially affects the eyes, nose, and respiratory tract. Miosis is common, resulting from direct contact of nerve agent with the eye, and may persist for several weeks.^{69,73} Other ocular effects include conjunctival injection and blurring and dimming of the vision. Dim vision is often ascribed to pupillary constriction, but central neural mechanisms also play a role.⁷¹ Ciliary spasm produces ocular pain, headache, nausea, and vomiting, often exacerbated by near-vision accommodation.²⁹ Rhinorrhea, airway secretions, bronchoconstriction, and dyspnea occur with increasing exposures. With a large vapor exposure, one or two breaths may produce loss of consciousness within seconds, followed by seizures, paralysis, and apnea within minutes.⁴⁴

In the 1995 Tokyo subway sarin incident, ocular effects were most common after sarin vapor exposure, as patients

manifested miosis (89%–99% of symptomatic victims), eye pain, dim vision, and decreased visual acuity.^{29,57} Other common complaints were cough, throat tightness, nausea, headache, dizziness, chest discomfort, and abdominal cramping.^{43,78} Among 111 patients admitted to one hospital, the most common presenting signs and symptoms were miosis (99%), headache (74.8%), dyspnea (63.1%), nausea (60.4%), eye pain (45%), blurred vision (39.6%), dim vision (37.8%), and weakness (36.9%).^{53,57} Excessive secretions were less common, as rhinorrhea occurred in approximately one-quarter of patients admitted to one hospital,⁵⁷ and in none of 58 patients at another.⁷⁸ Secondary exposures occurred among emergency medical technicians (EMTs) and hospital personnel in both the Tokyo^{43,52,53} and Matsumoto^{48,49} terrorist sarin releases, apparently from evaporation of nerve agent that had condensed on the primary victims' clothing.

Liquid nerve agents can permeate ordinary clothing, allowing for percutaneous absorption and rendering the clothing of those patients' potential hazards to health care personnel prior to proper decontamination. Mild dermal exposure produces localized sweating and muscle fasciculations after an asymptomatic period lasting up to 18 hours. Moderate skin exposure produces systemic effects with nausea, vomiting, diarrhea, and generalized weakness. Substantial dermal contamination will produce earlier and more severe symptoms, often with abrupt onset. Severe toxicity from any route of exposure causes loss of consciousness, seizures, generalized fasciculations, flaccid paralysis, apnea, and/or incontinence.^{46,71,73} Cardiovascular effects are less predictable, as either bradycardia (muscarinic) or tachycardia (nicotinic) may occur.⁴⁴ In the Tokyo sarin event, tachycardia and hypertension were more common than bradycardia.^{51,78} Subtle CNS effects may continue for weeks, but typically resolve if no anoxic brain injury occurred.

Long-term effects from nerve agent exposure have mostly been limited to psychologic sequelae.⁶⁷ Neither delayed peripheral neuropathy nor the intermediate syndrome has been reliably described in humans exposed to nerve agents.^{73,74} Follow-up studies from the Japanese sarin incidents show that neuropathy and ataxia, when initially present, resolved within 3 days to 3 months.⁸⁵ The main persistent sequela is posttraumatic stress disorder, found in up to 8% of victims.^{28,85}

Treatment of Nerve Agent Exposure

Decontamination. In critically ill patients, antidotal treatment may be necessary before or during the decontamination process; but generally, decontamination should occur before other treatment is instituted.

Atropine. Atropine is the standard anticholinergic antidote for the muscarinic effects of nerve agents.¹⁷ Atropine does not reverse nicotinic effects but does have some central effects and may thus assist in halting seizure activity.^{29,41,71}

Atropine is administered parenterally, either by the intravenous (IV) or intramuscular (IM) route, and the dose is determined by titration to effect. The standard adult dose determined by the US military is 2 mg, an amount expected to produce substantial benefit in reversing nerve agent toxicity but one that should be tolerated by a healthy unexposed adult unintentionally receiving the drug.⁷¹ Current recommendations place the minimum initial dose of atropine in adults at 2 mg; dosing in children begins at 0.05 mg/kg for mild to moderate symptoms and 0.1 mg/kg for severe symptoms up to the adult dose.⁵ Severely poisoned adult patients receive an initial dose of 5 to 6 mg.^{29,71} Repeat doses are given every 2 to 5 minutes until resolution of muscarinic signs of toxicity. Therapeutic endpoints are drying of respiratory secretions and resolution of bronchoconstriction, bradycardia, and/or seizures (if initially present). Neither reversal of miosis nor development of tachycardia is a reliable marker to guide atropine therapy.²⁹ The total amount of atropine necessary to treat nerve agent poisoning is often much less than required for organic phosphorus insecticide toxicity of a similar degree. Typically, less than 20 mg is required in the first 24 hours, even in severe cases.^{29,71,73} Fewer than 20% of moderately ill patients admitted to one hospital for sarin poisoning in Tokyo required more than 2 mg atropine.⁵⁷

American troops in the 1990–1991 Gulf War were issued three MARK I kits for immediate field treatment of nerve agent poisoning. These kits are now also known as NAAKs, for nerve agent antidote kits. Each kit contains two autoinjectors: an AtroPen containing 2 mg of atropine in 0.7 mL diluent, and a ComboPen containing 600 mg of pralidoxime chloride (pyridine-2-aldoxime, 2-PAM) in 2 mL diluent.⁷¹ These autoinjectors permit rapid IM injections of antidote through protective clothing and are given in the lateral thigh.¹⁷ Treatment algorithms guided the number of MARK I kits to administer. In general, conscious casualties not in severe distress self-administer one kit (2 mg atropine), moderate to severe cases receive three kits (6 mg atropine) initially, and all receive additional doses as necessary, every 5 to 10 minutes.^{17,46,71} A combination atropine (2.1 mg) plus pralidoxime chloride (600 mg) autoinjector is available that gives both drugs with a single injection (Antidotes in Depth: A32).

In a nerve agent mass casualty incident, a hospital's intravenous atropine supplies may be rapidly depleted. Alternative sources include atropine from ambulances, ophthalmic and veterinary preparations, or substituting an antimuscarinic such as glycopyrrolate.²⁹ Atropine might also be stored as a bulk powder formulation and rapidly reconstituted for injection when needed.²⁰

Oximes. Oximes are nucleophilic compounds that reactivate organic phosphorus compound-inhibited cholinesterase enzymes by removing the dialkylphosphoryl moiety. The only oxime approved in the United States by the Food and Drug Administration is 2-PAM, a monopyridinium compound. Other pralidoxime salts are used elsewhere, such as the

methanesulfonate salt of pralidoxime (P2S) in the United Kingdom and 2-PAM methiodide in Japan. Other oximes include the bispyridinium compounds trimedoxime (TMB4) and obidoxime (toxogonin) used in other European countries^{41,57,71} Oximes should be given in conjunction with atropine, as they are not particularly effective in reversing muscarinic effects when given alone. Oximes are the only available nerve agent antidotes that can reverse the neuromuscular nicotinic effects of fasciculations, weakness, and flaccid paralysis (Antidotes in Depth: A33)

Oximes are effective only if administered before irreversible dealkylation, or “aging,” of the organic phosphorus compound-cholinesterase complex occurs. Soman has an aging half-life of 2 to 6 minutes in humans.¹⁶ It is unlikely that soman-poisoned victims will reach medical care early enough for oxime therapy to be of great benefit. For comparison, tabun has an aging half-life of about 14 hours, sarin 3 to 5 hours, and VX 48 hours.¹⁶ Pralidoxime is effective against sarin and VX in animal studies but not against tabun because of ineffective nucleophilic attack against that particular agent, and not because of aging issues. Obidoxime also is effective against sarin but not against tabun.⁴¹

The bispyridinium Hagedorn (H-series) oximes, particularly HI-6 and HLö-7, are also studied in the context of nerve agent toxicity.⁴¹ HI-6 appears beneficial against soman poisoning (possibly through direct pharmacologic action and/or reactivation of aged soman-inhibited ChE) but is not very effective against tabun. HLö-7 has reactivating activity for both soman-and tabun-inhibited ChE and may thus represent a universal oxime antidote for nerve agents. Administration of HI-6 and HLö-7 by autoinjector is difficult because they are not stable in aqueous solution.

For more details about pralidoxime administration, dosing, and adverse events, see Antidotes in Depth: A33. The ComboPen autoinjector in MARK I kits contains 600 mg pralidoxime, which produces a therapeutic maximal serum concentration of 6.5 µg/mL in average human volunteers.⁷¹ However, when possible, pralidoxime is optimally administered IV. Repeat pralidoxime dosing or continuous infusions are less likely to be needed for nerve agents than for organic phosphorus compound insecticides because severe effects are shorter-lived in properly decontaminated patients.²⁹

Anticonvulsants. Severe human nerve agent toxicity rapidly induces convulsions, which persist for a few minutes until the onset of flaccid paralysis. Diazepam is more beneficial than other anticonvulsants and simple γ-aminobutyric acid channel agonists due to its effects on choline transport across the blood–brain barrier and acetylcholine turnover.⁴¹ US military doctrine is to administer 10 mg diazepam IM by autoinjector at the onset of severe toxicity whether seizures are present or not. Thus, whenever three MARK I kits are used, a victim is also given diazepam. Additional autoinjectors are given by medical personnel as necessary for seizures.⁴⁶ The reason for the IM route of diazepam suggested above is related to timely administration under field conditions. If intravenous access is feasible, then IV diazepam in 5-mg doses IV every 15 minutes (≤ 15 mg) is recommended⁴¹ (Antidotes in Depth: A23)

Although diazepam is the most well studied benzodiazepine in the treatment of nerve agent toxicity, other medications in the same class such as lorazepam and midazolam should have similar beneficial effects. Armed service personnel of the United Kingdom have been supplied with ComboPens containing atropine sulfate (2 mg), pralidoxime mesylate (P2S; 30 mg), and avizafone (10 mg), a water-soluble prodrug of diazepam.⁸⁴

Pyridostigmine Pretreatment. The first large-scale use of pyridostigmine as a pretreatment for nerve agent toxicity occurred during Operation Desert Storm in 1991³³ Pyridostigmine is a carbamate acetylcholinesterase inhibitor that is freely and spontaneously reversible, whereas nerve agent inhibition is permanent once “aging” occurs. Toxicity from rapidly aging nerve agents such as soman (GD) can probably not be reversed by standard oxime therapy in realistic clinical situations. Almost paradoxically, then, a carbamate can occupy cholinesterase, blocking access of nerve agent to the active site, and thereby protect the enzyme from permanent inhibition. Following nerve agent exposure, pyridostigmine is rapidly hydrolyzed from acetylcholinesterase and can also be easily displaced by oximes, regenerating functional enzyme. Between 20% and 40% cholinesterase inhibition is desired to protect against nerve agents¹⁷ Doses of 60 mg of pyridostigmine bromide reduces cholinesterase activity by 28.4% in healthy individuals. Asthmatics taking 30 mg doses had a mean 24.3% reduction in cholinesterase activity without significant reductions in respiratory function or in response to inhaled atropine.⁵⁸ In animal studies, pyridostigmine confers a benefit against soman and tabun, but not against sarin or VX¹⁷ Also, it must be recognized that pyridostigmine is not an antidote, but is instead a pretreatment adjunct that greatly enhances the efficacy of atropine and oxime therapy⁷³

US troops in the 1990–1991 Gulf War took 30 mg pyridostigmine bromide orally every 8 hours when under threat of nerve agent attack. Cholinergic side effects, mostly gastrointestinal, were common but rarely required treatment.³³ Israeli soldiers taking the same dose also reported a range of mostly cholinergic symptoms but also a high incidence (71.4%) of dry mouth, which may be more related to environmental and psychological stressors.⁶⁶ Nine Israeli patients were hospitalized during the Gulf War for acute intentional pyridostigmine overdoses.² All patients recovered fully, including one patient who self-treated with atropine autoinjectors and presented with anticholinergic toxicity and another who suffered cardiac arrest, apparently from coingesting 4000 mg propranolol.

VESICANTS

Vesicants are agents that cause blistering of skin and mucous membranes (Fig. 132–2).

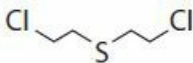
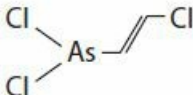
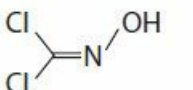
Military designation	Common name	Chemical name	Chemical structure
H, HD	Sulfur Mustard	bis-(2-chloroethyl) sulfide	
L	Lewisite	2-chlorovinyl dichloroarsine	
CX	Phosgene Oxime	dichloroformoxime	

FIGURE 132–2. Vesicants.

Sulfur Mustard

Sulfur mustard is bis(2-chloroethyl) sulfide, a vesicant alkylating compound similar to nitrogen mustards used in chemotherapy. Nineteenth-century scientists described the compound as smelling like mustard, tasting like garlic, and causing blistering of the skin on contact. The Allies of World War I called it Hun Stoffe (also called “German Stuff”), abbreviated as HS and later as just H. Distilled, nearly pure mustard is designated HD. The French called it Yperite, after the site where it was first used, and the Germans called it LOST after the two chemists who suggested its use as a chemical weapon, Lommel and Steinkopf. It was also called “yellow cross” after the markings on German artillery shells filled with mustard.^{10,14,75} Sulfur mustard caused over one million casualties in World War I,²¹ and was later used by the Italians and Japanese in the 1930s, by Egypt in the 1960s, and by Iraq in the 1980s.⁴⁶ About 100,000 Iranians from both military and civilian backgrounds were exposed to chemical warfare agents during the latter years of the Iran–Iraq war (1984–1988), many of whom are still suffering long-term effects.²² Nonbattlefield exposures have also occurred among Baltic Sea fishermen while recovering corroding shells dumped after WWII, and to persons unearthing or handling old chemical warfare ordinance.^{21,50,62,75}

Physical Characteristics

Sulfur mustard is a yellow to brown oily liquid with an odor resembling mustard, garlic, or horseradish. Mustard has relatively low volatility and high environmental persistence. Nonetheless, most historical mustard injuries occurred from vapor exposure, a danger that increases in warmer climates. Mustard vapor is 5.4 times denser than air. Mustard freezes at 57°F (13.9°C), so it is sometimes mixed with other substances, including chemical weapon agents like chloropicrin or Lewisite, to lower the freezing point and permit dispersion as a liquid.^{14,46,75}

Pathophysiology

Sulfur mustard toxicity occurs through several mechanisms. First, mustard is an alkylating agent. Mustard spontaneously undergoes intramolecular cyclization to form a highly reactive sulfonium ion that alkylates sulfhydryl (–SH) and amino (–NH₂) groups.^{10,14,46,75} The most important acute manifestation is indirect inhibition of glycolysis. Sulfur mustard rapidly alkylates and crosslinks purine bases in nucleic acids (Fig. 132–3). DNA repair mechanisms are activated, including the activation of the enzyme poly(ADP-ribose) polymerase,⁴² depleting NAD⁺, which, in turn, inhibits glycolysis, and ultimately leads to cellular necrosis from adenosine triphosphate depletion.¹⁰ Other mechanisms are probably involved, since the inhibition of glycolysis only partially correlates with the depletion of NAD⁺; sulfur mustard may also inhibit glycolysis directly through undetermined mechanisms.⁴² Mustard also depletes glutathione, leading to loss of protection against oxidant stress, dysregulation of calcium homeostasis, and further inactivation of sulfhydryl-containing enzymes.⁷⁵ Sulfur mustard is also a weak cholinergic agonist.^{46,75}

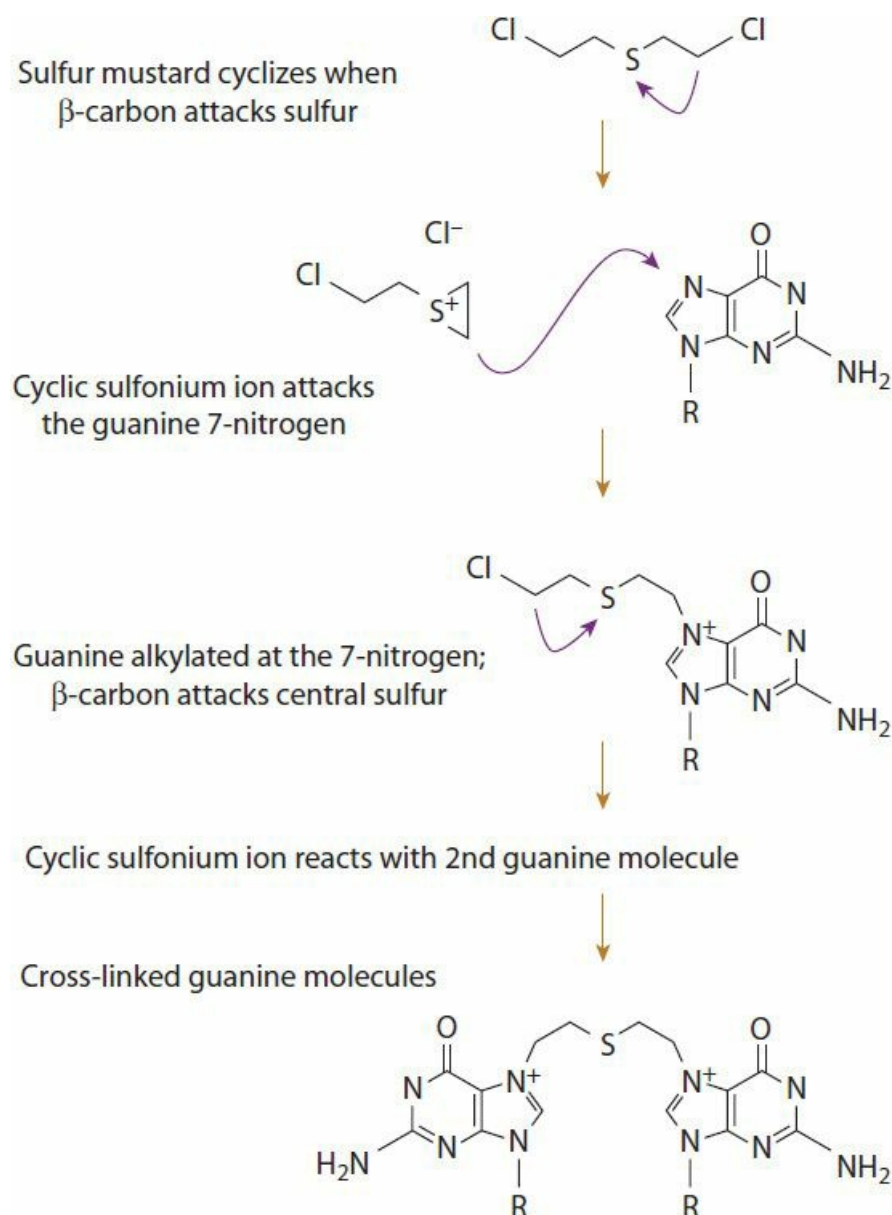


FIGURE 132–3. Mechanism of sulfur mustard toxicity: alkylation and DNA crosslinking.

Clinical Effects

The organs most commonly affected by mustard are the eyes, skin, and respiratory tract. During WWI, 80% to 90% of American mustard casualties had cutaneous lesions, 86% had ocular involvement, and 75% had airway injury. Iranian soldiers had more airway (95%) and ocular injuries (92%), and 83% had cutaneous lesions, probably because of the more extensive vaporization occurring in the warmer environment.^{10,75} Incapacitation may be severe in terms of number of lost man-days, time for lesions to heal, and increased risk of infection. In contrast, mortality is rather low. In WWI, only 2% to 3% of British mustard casualties and fewer than 2% of American casualties died. Fatality rates of 3% to 4% were reported from the Iran–Iraq War.¹⁰ Most deaths occur several days after exposure, either from respiratory failure, secondary bacterial pneumonia, or bone marrow suppression.

Dermal exposure produces dose-related injury. After a latent period of 4 to 12 hours, victims develop erythema that may progress to vesicles and/or bullae formation and skin necrosis. Warm, moist, and thin skin is at increased risk of mustard injury, in particular the perineum, scrotum, axillae, antecubital fossae, and neck. The vesicle fluid does not contain mustard because all chemical reactions are complete within a few minutes. If decontamination is not performed immediately after exposure, injury cannot be prevented. However, later decontamination may limit the severity of lesions and further spread of the agent. Skin exposure to vapor typically results in first- or second-degree burns, although liquid exposure may result in full-thickness burns.⁷⁵ Mustard easily penetrates normal clothing and uniforms, and many soldiers received gluteal, perineal, and scrotal burns from sitting on contaminated objects.

Latency of several hours also occurs following ocular and respiratory tract exposures. Ocular effects include pain, miosis, photophobia, lacrimation, blurred vision, blepharospasm, and corneal damage. Permanent blindness is rare, with recovery generally occurring within a few weeks. Inhalation of mustard results in a chemical tracheobronchitis. Hoarseness, cough, sore throat, and chest pressure are common initial complaints. Bronchospasm and obstruction from sloughed membranes occur in more serious cases, but lung parenchymal damage occurs only in the most severe inhalational exposures. Productive cough associated with fever and leukocytosis is common 12 to 24 hours after exposure, and

represents a sterile bronchitis or pneumonitis. Nausea and vomiting are common within the first few hours. High-dose exposures may also cause bone marrow suppression.^{10,46,75}

Various long-term sequelae are associated with sulfur mustard. Factory workers chronically exposed to mustard have increased risk of respiratory tract carcinomas, although the carcinogenic risk from battlefield exposures is more controversial.^{21,22,74} Respiratory sequelae include chronic bronchitis, emphysema, tracheobronchomalacia, and bronchiolitis obliterans.²² Mustard victims may also develop a delayed and often recurrent keratitis.^{21,68} Chronic dermatologic complications include scarring, pigmentation changes, and chronic, neuropathic pain, and pruritus.^{21,68} Among approximately 34,000 Iranians with confirmed exposure to sulfur mustard during the war with Iraq, chronic pulmonary sequelae were noted in 42.5%, ocular lesions in 39.3%, and dermatologic lesions in 24.5%.³⁵

Treatment

Decontamination is essential in treating the sulfur mustard exposures, even among asymptomatic victims. Further treatment is largely supportive and symptomatic.^{10,46,75} Victims may become blinded because of a combination of blepharospasm and corneal edema, which is temporary and completely resolves in most cases.

Several xenobiotics have been investigated as treatments for sulfur mustard injury. Antiinflammatory and sulphydryl-scavenging agents have shown benefit in animals as prophylactic therapy or if given immediately after exposure.⁷⁵ N-acetyl cysteine appears to be a promising therapeutic agent in cell culture and animal studies, although most of the evidence for its use relates to inhalational aerosol exposures to mustard.⁸ Neutropenia from bone marrow suppression can be treated with granulocyte colony-stimulating factor.⁴⁵

Lewisite. Lewisite (2-chlorovinyl-dichloroarsine) was developed as a less persistent alternative to avoid some shortcomings in the use of sulfur mustard in World War I. Lewisite was never used in combat because the first shipment was en route to Europe when the war ended, and it was intentionally destroyed at sea. British anti-Lewisite (BAL, dimercaprol) was developed as a specific antidotal agent and remains in use for chelation of arsenic and other metals.^{41,75}

Pure Lewisite is an oily, colorless liquid. Impure preparations are colored from amber to blue-black to black and have the odor of geraniums. Lewisite is more volatile than mustard and is easily hydrolyzed by water and by alkaline aqueous solutions such as sodium hypochlorite. These properties increase safety for offensive battlefield use, but make maintaining a potent vapor concentration difficult.

Lewisite toxicity is similar to that of sulfur mustard, resulting in dermal and mucous membrane damage, with conjunctivitis, airway injury, and vesiculation. An important clinical distinction is that Lewisite is immediately painful, whereas initial contact with mustard is not. Other differences are faster onset of inflammatory response and healing of lesions from Lewisite, less secondary infection of Lewisite lesions, and less subsequent pigmentation changes.⁷⁵ The mechanisms of Lewisite toxicity are not completely known, but appear to involve glutathione depletion and arsenical interaction with enzyme sulphydryl groups. Nevertheless, Lewisite toxicity is qualitatively and quantitatively different from the arsenic it contains. Treatment consists of decontamination with copious water and/or dilute hypochlorite solution, supportive care, and BAL. BAL is given parenterally for systemic toxicity and is also used topically for dermal or ophthalmic injuries. Alternative metal chelators that may be used as Lewisite antidotes include dimercaptopropane sulfonate and succimer (2,3-dimercaptosuccinic acid).⁴¹

Phosgene Oxime. Although classified as a vesicant, phosgene oxime (dichloroformoxime, or CX) does not cause vesiculation of the skin. CX is more properly an urticant or “nettle” agent, in that it produces erythema, wheals, and urticaria likened to stinging nettles. Phosgene oxime produces immediate irritation of the skin and mucous membranes. CX has never been used in battle, and little is known about its mechanism or effects on humans.^{46,75}

CYANIDES (CHEMICAL ASPHYXIANTS)

Several cyanides have been used as chemical weapons. During World War I, the French used hydrogen cyanide (HCN) and cyanogen chloride (CNCl), designated as agents AC and CK, respectively, without great success; the Austrians introduced cyanogen bromide (CNBr). Cyanide weapons are relatively ineffective because of rapid dispersion and their “all or nothing” biologic activity. An exposed individual either rapidly succumbs to cyanide toxicity, or will rapidly recover with minimal sequelae. Mass casualty events from cyanide CW are reported during the Iran–Iraq War and from Iraq’s suppression of the Kurds.^{6,46}

The clinical effects and treatment of cyanide toxicity are covered elsewhere ([Chap. 126](#)) and do not differ significantly if used as a weapon. Hydrocyanic acid gas persists for only a few minutes in the atmosphere, because it is lighter than air and rapidly disperses. Cyanogen chloride additionally causes ophthalmic and respiratory tract irritation and can produce delayed acute lung injury in victims who are not rapidly killed.^{6,46}

PULMONARY IRRITANTS

Both chlorine and phosgene were used as war gases in World War I. Chlorine, phosgene, various organohalides, and nitrogen oxides belong to a group of toxic chemicals designated “pulmonary irritants” because they can all induce delayed ARDS from increased alveolar-capillary membrane permeability.^{41,46,82} Although pulmonary agents have not been used militarily since 1918, the risk of chlorine and phosgene exposure remains because of their extensive use in industry, or possibly as a terrorist weapon (Chap. 124), for clinical details, as the remainder of this section highlights mass-casualty issues regarding these irritants.

When released on the battlefield, chlorine forms a yellow-green cloud with a distinct pungent odor detectable at concentrations that are not immediately dangerous. Phosgene is either colorless or seen as a white cloud as a result of atmospheric hydrolysis. Phosgene, which is reported to smell like grass, sweet newly mown hay, corn, or like moldy hay, accounted for about 85% of all World War I deaths attributed to chemical weapons.^{10,41} Phosgene produces injury by hydrolysis in the lungs to hydrochloric acid and by forming diamides that cross-link cell components (Fig. 132–4). Similar cross-linking reactions may occur with hydroxyl and thiol groups. Battlefield exposure triggers cough, chest discomfort, dyspnea, lacrimation, and the peculiar complaint that smoking tobacco produces an objectionable taste. World War I phosgene fatalities were noted to develop a mushroom-shaped efflux of pink foam at their mouths from pulmonary edema fluid. Prolonged observation after phosgene exposure is the rule, as some casualties initially appeared well and were discharged, only to return in severe respiratory distress a few hours later.^{41,46,82} Exercise appeared to precipitate ARDS in phosgene casualties.⁶³ For American soldiers in World War I, the average time spent recovering away from the front was 60 days for chlorine and 45.5 days for phosgene.¹⁹

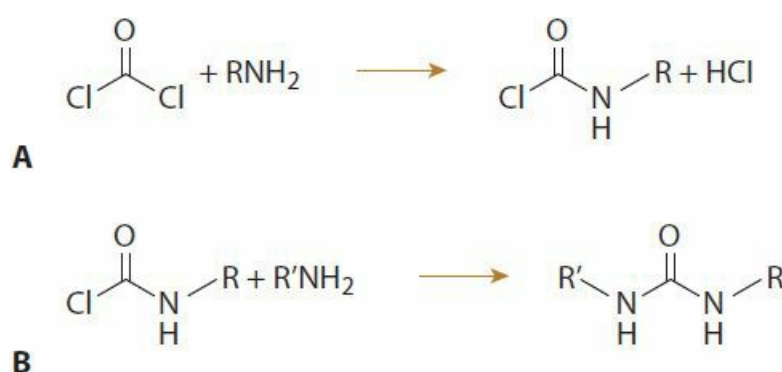


FIGURE 132–4. Proposed mechanism of phosgene toxicity. (A) Phosgene reacts with amine group to form an amide, releasing hydrochloric acid. (B) A second reaction crosslinks two amine equivalents, forming a diamide.

RIOT CONTROL AGENTS

Riot control agents (Fig. 132–5) are intentionally non-lethal chemicals that temporarily disable exposed individuals through intense irritation of exposed mucous membranes and skin. These agents are also known as lacrimators, irritants, harassing agents, human repellents, and tear gas. They are solids at normal temperatures and pressures, but are typically dispersed as aerosols or as small solid particles in liquid sprays. Common characteristics include rapid onset of effects within seconds to minutes, relatively brief duration once exposure has ceased and the victim is decontaminated, and a high safety ratio (lethal dose vs effective dose).^{41,46,72}


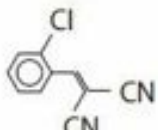
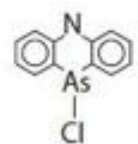
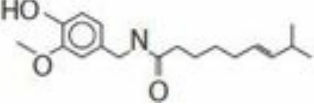
Military designation	Common name	Chemical name	Chemical structure
CN	Chemical mace	1-chloroacetophenone	
CS	Tear gas	o-chlorobenzylidene malononitrile	
DM	Adamsite	diphenylaminechlorarsine	
OC	Capsaicin pepper spray	<i>trans</i> -8-methyl- <i>N</i> -vanillyl-6-noneamide	

FIGURE 132–5. Riot control agents.

Chloroacetophenone (CN) is the active ingredient in the Chemical Mace brand nonlethal weapon.⁷⁷ *o*-Chlorobenzylidene malononitrile (CS) has largely replaced CN because of its higher potency, lower toxicity, and improved chemical stability.^{38,72} When used for crowd control, both CN and CS are disseminated as aerosols or as smoke from incendiary devices. Exposed persons develop burning irritation of the eyes, progressing to conjunctival injection, lacrimation, photophobia, and blepharospasm. Mucous membranes of the upper aerodigestive tracts can also be involved. Inhalation causes chest tightness, cough, sneezing, and increased secretions. Dermal exposure may cause a burning sensation, erythema, or vesiculation, depending on the dose. Victims generally remove themselves from the offensive environment (which is the primary purpose of their use as “riot control” agents) and recover within 15 to 30 minutes. Deaths are rare, and typically occur from respiratory tract complications in closed-space exposures where exiting the area is impossible.^{41,46,72}

The biologic mechanism whereby riot-control agents exert their effects is less well described than for other chemical weapons. CS and CN are SN_2 alkylating agents (versus sulfur mustard, an SN_1 alkylator) and react with sulfhydryl-containing compounds and enzymes. For instance, CS reacts rapidly with the disulfhydryl form of lipoic acid, a coenzyme for pyruvate decarboxylase. Tissue injury may be related to inactivation of certain enzyme systems. Pain in the absence of tissue injury may be bradykinin mediated.⁴⁶

Personal protective devices dispensing lacrimator substances also cause chemical injuries in the absence of war or civil unrest. Law enforcement agencies and private citizens may have access to products containing CS, CN, and/or (oleoresin capsicum {OC}, also known as pepper spray). OC is the essential oil derived from pepper plants (*Capsicum anuum*), which contains capsaicin (*trans*-8-methyl-*N*-vanillyl-6-noneamide), a naturally occurring lacrimator. Capsaicin activates heat-dependent nociceptors, explaining why exposures are experienced as “hot.”¹² Severe respiratory tract injuries and fatalities are occasionally reported from exposures to these devices, typically only with prolonged or highly concentrated exposures. A synthetic capsaicinoid, pelargonic acid vanillylamide (PAVA) in spray form has recently been approved as an incapacitant for police use in the United Kingdom.⁴ PAVA is believed to be safer than CS, but no published medical experience with this agent is yet available. A capsaicin-containing riot control device called Pepperball Tactical Powder has caused severe localized skin injuries.²⁵ This device is a pellet of powdered capsaicin (and carrier substances) pressurized within a thin plastic shell fired as a munition.

Chloropicrin (trichloronitromethane, or nitrochloroform) is another lacrimator that occasionally causes human toxicity through its use as a fumigant and soil insecticide.⁷⁹ 10-chloro-5,10-dihydrodiphenarsazine (or diphenylaminearsine {DM}) is a vomiting agent. Clinical effects are delayed for several minutes after exposure, by which time the victim may have absorbed a significant amount. In addition to upper respiratory and ocular irritation, diphenylaminearsine causes more prolonged systemic effects with headache, malaise, nausea, and vomiting.^{46,72}

The primary treatment for all riot control agents is removal from exposure. Contaminated clothing should be removed and placed in airtight bags to prevent secondary exposures.³⁸ Skin irrigation with copious cold water is used for significant dermal exposures.^{7,38,39} Symptomatic treatments, such as with topical ophthalmic anesthetics, nebulized bronchodilators, or oral antihistamines and corticosteroids, are indicated as appropriate in more severely affected victims.⁷ Capsaicin-induced dermatitis has been treated variably with immersion in water or oil, vinegar, bleach, lidocaine gel, and topical antacid suspensions.^{27,31,77} Cold water produces earlier symptomatic relief, but oil immersion has longer-lasting benefit.³¹

INCAPACITATING AGENTS

3-Quinuclidinyl benzilate (BZ or QNB; Fig. 132–6) is an antimuscarinic compound that was developed as an incapacitating CW agent. BZ is 25-fold more potent centrally than atropine, with an ID_{50} (dose that incapacitates 50% of those exposed) of about 0.5 mg. Clinical effects are characteristic for anticholinergics, with drowsiness, poor coordination, and slowing of thought processes progressing to delirium. BZ takes at least 1 hour to produce initial manifestations, peaks at 8 hours, continues to incapacitate for 24 hours, and takes 2 to 3 days to fully resolve.³⁴ During the recent Balkan Wars of the 1990s, allegations were made that Bosnian Serbs used BZ against civilians, who reported hallucinations associated with attacks by artillery shells emitting smoke.²⁴

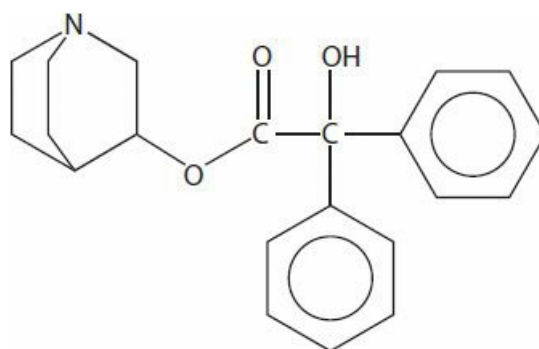


FIGURE 132–6. Incapacitating agent BZ (3-quinuclidinyl benzilate {QNB}).

Ultrapotent opioids may also be used as incapacitating CW agents. In 2002, Russian security forces used a fentanyl derivative (possibly carfentanil or remifentanyl) to end a 3-day standoff with terrorists in a Moscow theater in which Chechen rebels held more than 800 hostages.⁸³ A “gas” was introduced into the theater ventilation system, which quickly subdued the occupants. More than 650 of the hostages were hospitalized, and 128 died. Initial news reports suggested the use of BZ, although the clinical findings were more consistent with a CNS depressant. Within a few days, Russian officials stated that the agent used was a fentanyl derivative and was not expected to cause fatalities. The relatively high case fatality rate could be because of multiple factors, including variability in dose, displacement of oxygen by rapid introduction of gas into the building, failure to adequately notify health care teams and supply them with antidotes, and poor physical condition of the hostages.

Lysergic acid diethylamide (LSD) has also been investigated as an incapacitating agent.³⁴ Although effective at very low doses, battlefield use of LSD is impractical since intoxication will not reliably prevent a soldier from participation in combat.

Table 132–5 describes the various toxic syndromes that may be seen from use of CW agents.

TABLE 132–5. Chemical Weapons Toxic Syndromes

Chemical/Weapon	Organ System							
	Onset	Eyes	Upper Airways and Mucous Membranes	Lungs	Skin	CNS	GI Tract	Other
Nerve Agents								
Tabun (GA), Sarin (GB), Soman (GD), VX								
Aerosol/vapor (Mild/moderate exposure)	Rapid (seconds–minutes)	Miosis, eye pain, dim or blurred vision	Rhinorrhea, ↑ secretions	Dyspnea, cough, wheezing, bronchospasms	—	Headache	Nausea, vomiting, abdominal cramps	—
Dermal exposure (Mild/moderate exposure)	Delayed (minutes–hours)	—	—	—	Localized sweating	—	Nausea, vomiting, diarrhea, cramping	Subjective weakness, local muscle fasciculations
Severe exposure (any route)	As above (by route)	Miosis	↑ Secretions	Apnea	—	Sudden collapse, seizures	Incontinence	Generalized fasciculations, weakness, flaccid paralysis
Vesicants								
Sulfur mustard (H, HD)	Delayed (hours)	Conjunctivitis, eye pain, blurred vision, blindness (temporary)	Irritation, hoarseness, early cough, sinus tenderness, tracheobronchitis	(More severe exposures) Productive cough, pseudomembrane formation, airway obstruction	Erythema, vesicles, bullae, necrosis	—	Nausea, vomiting	Bone marrow suppression (in severe exposures)
Lewisite (L)	Immediate irritation Delayed vesication	Pain, blepharospasm, conjunctivitis, lid edema	(Same as Sulfur Mustard)	(Same as Sulfur Mustard)	Erythema, vesicles	—	—	Shock (in severe exposures)
Phosgene oxide (CX)	Immediate irritation Delayed irritation	Pain, corneal damage	Irritation	ARDS	Pain, blanching, erythema, urticaria, necrosis	—	—	—
Pulmonary Agents								
Phosgene (CG)	Immediate irritation	Irritation	Irritation, strike (Chlorine)	Dyspnea, cough, ARDS	—	—	—	Chlorine effects more rapid than phosgene
Chlorine (CL)	Delayed ARDS							
Cyanides								
Hydrogen cyanide (AC)	Rapid (seconds–minutes)	—	—	Hyperpnea then apnea	—	Anxiety, agitation, sudden collapse, seizures	—	—
Cyanogen chloride (CK)	Rapid (seconds–minutes)	Irritation	Irritation	Hyperpnea then apnea	—	Anxiety, agitation, sudden collapse, seizures	—	—
Riot Control Agents								
Lacrimators (CN, CS) Capsaicin (OC)	Immediate	Pain, lacrimation, blepharospasm, conjunctivitis	Irritation	Cough, chest pain	Burning pain, erythema Vesiculation (severe exposures)	—	Nausea, itching (may occur with CN/CS)	—
Adamsite (DM)	Rapid (minutes)	Irritation	Irritation, sneezing	Cough, chest pain	—	Headache	Nausea, vomiting, abdominal cramps	—
Incapacitating Agent								
3-quinacridinyl benzoate (BZ)	Delayed (hours)	Mydriasis	Dry mouth	—	—	Anticholinergic delirium	—	—
Ultra-potent opioids	Rapid (seconds–minutes)	Miosis	—	Hypoventilation	—	CNS depression	—	—

SUMMARY

- CBW agents are appealing to terrorist groups because the impact in terms of death, disability, economic losses, and panic remains high.
- The psychological impact of CBW terrorism may well exceed that for conventional or nuclear weapons.
- Although the probability of incidents resulting in widespread public health disasters appears low, the consequences are high, and substantial preparations must be made in advance.
- Early decontamination is often critical for victims exposed to chemical warfare agents.
- Nerve agents are potent organic phosphorus compound acetylcholinesterase inhibitors. Toxicity produces cholinergic toxicity, which is treated with antimuscarinics, particularly atropine, and oximes.
- Vesicant chemical weapons induce blistering of the skin and damage to other tissues in contact, such as the eyes or respiratory tract. Sulfur mustard has no specific antidote, but the arsenic containing Lewisite can be treated with BAL, a chelator.
- Exposure to chlorine, phosgene, ammonia and some other gases can produce delayed ARDS. Although used on the battlefield in World War I, it is expected that intentional use of these pulmonary irritant gases is now more likely to occur from their use by terrorists as “agents of opportunity.”

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133 BIOLOGICAL WEAPONS

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Expertise in dealing with biological weapons requires specific knowledge from the fields of infectious disease, epidemiology, toxicology, and public health. Biological and chemical warfare agents share many characteristics in common, including intent of use, some dispersion methods, and initial defense based on adequate personal protective equipment and decontamination (Tables 132–2 and 132–3). However, key differences between biological and chemical weapons involve a greater delay in onset of clinical symptoms after exposure to biological weapons; that is, the incubation period for most bioweapons (BW) is greater than the latent period for most chemical warfare agents. Decontamination is less crucial for victims exposed to BWs than to chemical warfare agents. Additionally, a few BWs can reproduce in the human host and cause secondary casualties, and disease following exposure to several of these agents can be prevented by the timely administration of prophylactic medications.

BWs may be bacteria, fungi, viruses, or toxins derived from microorganisms. Some fungi are listed as potential BWs; however, none are known to have been developed into weapons to date.⁶⁹ Because toxin weapons are not living organisms, some authorities classify them as chemical, rather than biological weapons. For the purpose of discussion in this chapter, toxin weapons derived from microorganisms will be considered BWs. Most of the bacterial BWs exert their effects by elaborating protein toxins.

Many diseases caused by biological weapons are either infrequently encountered in modern clinical medicine, such as anthrax and plague, or no longer occur naturally, such as smallpox. Therefore, health care personnel require specific training in recognizing and managing biological warfare victims. Potential BWs are categorized by their risk of causing mass-casualty outbreaks.¹⁴ The high-risk BWs are more easily disseminated or transmitted and may cause high mortality and potential public health disasters; these BWs include smallpox, anthrax, plague, botulism, tularemia, and several hemorrhagic fever viruses. The moderate-risk agents include Q fever, brucellosis, the equine encephalitis viruses, ricin, and staphylococcal enterotoxin B, all of which are briefly discussed in this chapter.

HISTORY

Biological warfare has ancient roots. Missile weapons poisoned with natural toxins were used as early as 18,000 years ago (Chap. 1). Other uses of biological warfare prior to the modern era relied mainly on poisoning water supplies with natural toxins, or spreading naturally occurring epidemic infections to the enemy by hurling infected corpses over battlements or through the intentional transfer of disease-contaminated goods (eg, smallpox blankets).

During World War I, Germany was the only combatant nation with an active BW program; however, by World War II many nations had BW research programs, including Japan, the Soviet Union, Germany, France, Britain, Canada, and the United States. The Japanese program included field trials with bubonic plague and conducted BW experiments on prisoners of war and civilians.³⁵ The American program was founded at Camp Detrick, Maryland, in 1942. Fort Detrick, as it is now known, remains the home of the United States Army Medical Research Institute of Infectious Diseases (USAMRIID). Anthrax and botulinum toxin were the foci of American BW development during World War II. The British program was established at Porton Down in 1940, but most of their field testing of anthrax occurred on Gruinard Island off the northern coast of Scotland, resulting in long-term soil contamination with anthrax spores.

In London, in 1978, the Bulgarian exile Georgi Markov was assassinated with a tiny metal pellet fired from a gun designed to appear like an umbrella. He was originally thought to have died from sepsis until the pellet was found at autopsy.²³ After the fall of the Soviet Union, government officials confirmed that the KGB used umbrella guns firing ricin pellets to assassinate Markov and others.

In 1979, an outbreak of human anthrax caused at least 66 fatalities in the Russian city of Sverdlovsk. Autopsies revealed that the deaths were from inhalational anthrax, and epidemiologic investigation demonstrated that almost all the cases occurred downwind from a military facility. These data are consistent only with a release of aerosolized anthrax, which has since been confirmed by Russian authorities.⁵¹

In the late 1970s and early 1980s, many reports came from Southeast Asia and Afghanistan that Soviet-supported troops were using a biological weapon known as Yellow Rain.⁶⁸ Some samples of Yellow Rain were found to contain trichothecene mycotoxins, although controversy remains as to whether this represents intentional biological warfare or was

a naturally occurring phenomenon.⁶⁰

During the 1990s, concern arose regarding the use and possible stockpiling of weapons of mass destruction (WMD) in Iraq.⁴⁵ Iraq had an active BW research program, investigating at least five bacteria, one fungus, five viruses, four toxins, and a variety of dispersion methods.^{61,71} Thousands of liters of anthrax spores, botulinum toxin, and aflatoxin were produced and weaponized into bombs and as payloads for SCUD missiles.

Biological terrorism and the threat of bioterrorism are now recognized as worldwide, growing public health concerns.³⁶ In 1984, a large outbreak of salmonellosis was traced to intentional contamination of restaurant salad bars by the Rajneeshee cult in Oregon.⁶⁶ The Aum Shinrikyo cult based in Japan investigated the use of cholera and Q fever, unsuccessfully released anthrax spores and botulinum toxin, and even sent members to Africa to obtain the Ebola virus.^{55,64} The mere threat of a BW release can terrorize a city. At the end of the 1990s, there was a huge increase in false anthrax threats, which paralyzed Los Angeles and cities in Indiana, Kentucky, and Tennessee, among many others.¹³

In 2001, closely following the September 11, 2001, attack on New York and Washington, DC, a bioterrorist attack occurred in the United States resulting in several cases of inhalational and cutaneous anthrax, with five fatalities. After years of investigation, suspicion regarding the culprit for this event was directed toward Bruce Ivins, a microbiologist who worked at USAMRIID, and would therefore have had potential access to weaponized anthrax spores. No direct evidence linked Dr. Ivins to the incident, and he had not yet been formally charged with any crime, when he died from a suicidal acetaminophen overdose in 2008.

GENERAL CONSIDERATIONS

Differences Between BW Incidents and Naturally Occurring Outbreaks

Because the clinical effects of BWs are often delayed for several days after exposure, it may be difficult to differentiate occult BW releases from naturally occurring disease outbreaks. Several epidemiologic criteria are proposed to aid in such determinations,⁵⁴ many of which should be identifiable in a BW incident (Table 133–1).

TABLE 133–1. Epidemiologic Clues Suggesting Biological Weapon Release

- Large epidemic with unusually high morbidity and/or mortality
- Epidemic curve (number of cases vs. time) showing an “explosion” of cases, reflecting a point source in time rather than insidious onset
- Tight geographic localization of cases, especially downwind of potential release site
- Predominance of respiratory tract symptoms because most bioweapons are transmitted by aerosol inhalation
- Simultaneous outbreaks of multiple unusual diseases
- Immunosuppressed and elderly persons more susceptible
- Nonendemic infection (“impossible epidemiology”)
- Nonseasonal time for endemic infection
- Organisms with unusual antimicrobial resistance patterns, reflecting BW genetic engineering
- Animal casualties from same disease outbreak
- Absence of normal zoonotic disease host
- Low attack rates among persons incidentally working in areas with filtered air supplies or closed ventilation systems, using HEPA masks, or remaining indoors during outdoor exposures
- Delivery vehicle or munitions discovered
- Law enforcement or military intelligence information
- Claim of bioweapon release by belligerent force

To avoid early detection, terrorists might choose to release a BW causing endemic infection, or a disease that mimics an endemic infection, during its season of peak incidence. In some areas of the United States, for example, a few cases of bubonic plague would not attract notice until, perhaps, dozens or hundreds of cases were identified. An outbreak of inhalational anthrax during the influenza season may similarly be hidden among patients with shared early symptoms until an unusually high mortality was evident.¹⁹ By the time the BW outbreak was recognized, the perpetrators could dispose of any physical evidence and flee the area. Alternatively, even a single case of smallpox (anywhere in the world), or Ebola virus disease or Congo-Crimean hemorrhagic fever (in nonendemic areas) should immediately raise suspicion of a BW attack.

Preparedness

Many BWs initially produce nonspecific symptoms, and diseases that rarely, if ever, occur in clinical practice. Inhalational

anthrax and pneumonic plague, for example, could easily be misdiagnosed as influenza or acute bronchitis. Providers in emergency departments (EDs) and primary care medicine must be educated to recognize the signs, symptoms, and clinical progression of diseases caused by BW.⁵⁹ Clear identification, isolation, and aggressive treatment early after exposure within the first 24 to 48 hours are the best and only means of reducing mortality and, in the case of smallpox or plague, preventing secondary or tertiary cases.²⁷ However, in spite of increasing awareness and educational opportunities, many physicians remain inadequately prepared.

Decontamination

Bioweapons are most effective when dispersed by aerosol. Shortly after a known or suspected release of bioaerosols, decontamination is a relatively minor concern because aerosols sized to reach the lower respiratory tract ($< 5\text{-}\mu\text{m}$ particles) produce little surface contamination. However, simple removal of clothing will eliminate a high proportion of deposited particles, and subsequent showering with soap and water will probably remove 99.99% of any remaining organisms on the skin.⁴⁴ Thus, decontamination after BW aerosol exposure, when needed, is achieved through disrobing and showering with soap and water. This can be done onsite or in the victims' homes and away from health care facilities, thereby reducing strain on disaster response manpower and material in multiple-victim exposures.^{27,36,44,59} When there is gross, visible evidence of skin exposure to a BW, the patient should be decontaminated by thorough irrigation, and, if available, sterilizing the skin with a sporicidal/bactericidal solution (eg, 0.5% sodium hypochlorite), and a final water rinse.^{44,59} After an occult BW release, victims are identified late after exposure; decontamination will obviously not be helpful and may only serve to delay care.

BIOLOGICAL WARFARE AGENTS

Bacteria

Anthrax. Anthrax is caused by *Bacillus anthracis*, a Gram-positive spore-forming bacillus found in soil worldwide (Figs. 133–1 and 133–2). *B. anthracis* causes disease primarily in herbivorous animals. Human anthrax cases generally occur in farmers, ranchers, and among workers handling contaminated animal carcasses, hides, wool, hair, and bones³²



FIGURE 133–1. Anthrax Gram stain.

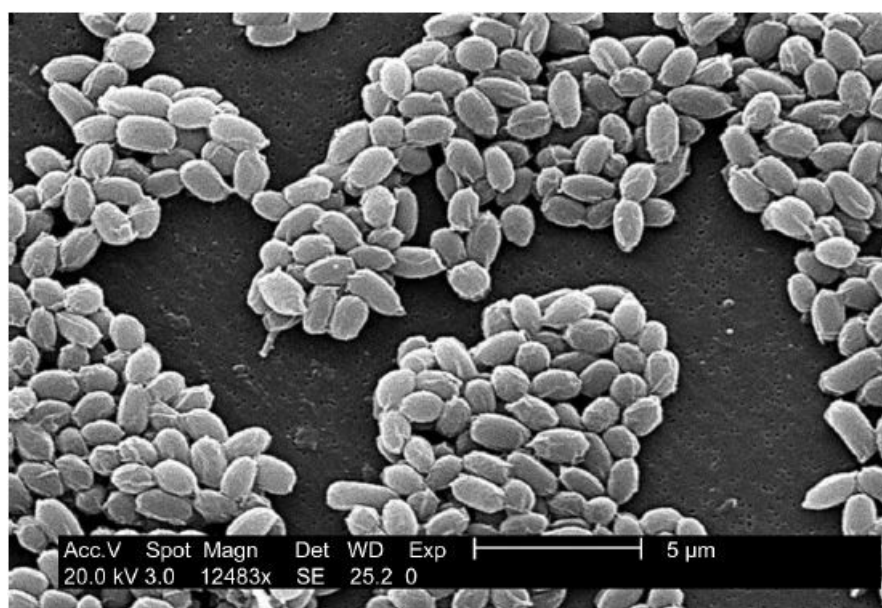


FIGURE 133–2. Anthrax spores.

Clinical manifestations. A few clinically distinct forms of anthrax may occur, depending on the route of exposure. Cutaneous anthrax results from direct inoculation of spores into the skin via abrasions or other wounds and accounts for about 95% of endemic (naturally occurring) human cases. Patients develop a painless red macule that vesiculates, ulcerates, and forms a 1-to 5-cm brown-black eschar surrounded by edema.⁴⁸ The eschar color gave rise to the name anthrax, from the Greek word *anthrakos* meaning “coal.” Most skin lesions heal spontaneously, although 10% to 20% of untreated patients progress to septicemia and death. When treated with antibiotics cutaneous anthrax rarely results in fatalities. Anthrax is not transmissible among humans.

Gastrointestinal (GI) anthrax results from ingesting insufficiently cooked meat from infected animals. Patients develop nausea, vomiting, fever, abdominal pain, and mucosal ulcers, which can cause GI hemorrhage, perforation, and sepsis. Mortality from GI anthrax is at least 50%, even with antibiotic treatment.³²

Inhalational anthrax results from exposure to aerosolized *B. anthracis* spores. Although this form of anthrax is very rare, it is so closely associated with occupational exposures that it is called “wool-sorter’s disease.” Inhalational anthrax is also likely to be the form that occurs in a BW attack, because the anthrax spores would be most effectively disseminated by aerosol. After an incubation period of 1 to 6 days, the patient develops fever, malaise, fatigue, nonproductive cough, and mild chest discomfort, which may be easily mistaken for community acquired pneumonia.¹⁹ The initial symptoms may briefly improve for 2 to 3 days or the patient may abruptly progress to severe respiratory distress with dyspnea, diaphoresis, stridor, and cyanosis. Bacteremia, shock, metastatic infection such as meningitis, which occurs in about 50% of cases, and death may follow within 24 to 36 hours. Prior to the 2001 bioterrorist outbreak, mortality from inhalational anthrax was expected to be nearly 100%, even with antibiotics, once symptoms develop.^{30,32} With appropriate antibiotic therapy and supportive care, 5 of 11 patients with inhalational anthrax in 2001 died, and although this is still a high mortality rate, it is less than that previously predicted.⁴⁰

Pathophysiology. Inhalational anthrax causes a mediastinitis. Diagnostic imaging typically shows mediastinal widening from enlarged hilar lymph nodes and pleural effusions, although pulmonary parenchymal infiltrates may also be seen.⁴⁰ Inhaled spores are taken up into the lymphatic system where they germinate and the bacteria reproduce. *B. anthracis* produces three toxins: protective antigen, edema factor, and lethal factor. Protective antigen (PA) is so named because antibodies against it protect the individual from the effects of the other two toxins. PA forms a heptamer that inserts into plasma membranes, facilitating endocytosis of the other two toxins into target cells (Fig. 133–3). Edema factor is a calmodulin-dependent adenylate cyclase. Increased intracellular cyclic adenosine monophosphate (AMP) upsets water homeostasis, leading to massive edema and impaired neutrophil function. Lethal factor is a zinc metalloprotease that stimulates macrophages to release tumor necrosis factor α and interleukin-1 β , contributing to death in systemic anthrax infections.²⁵ The combination of PA plus edema factor is called edema toxin, while PA plus lethal factor is lethal toxin.³⁴

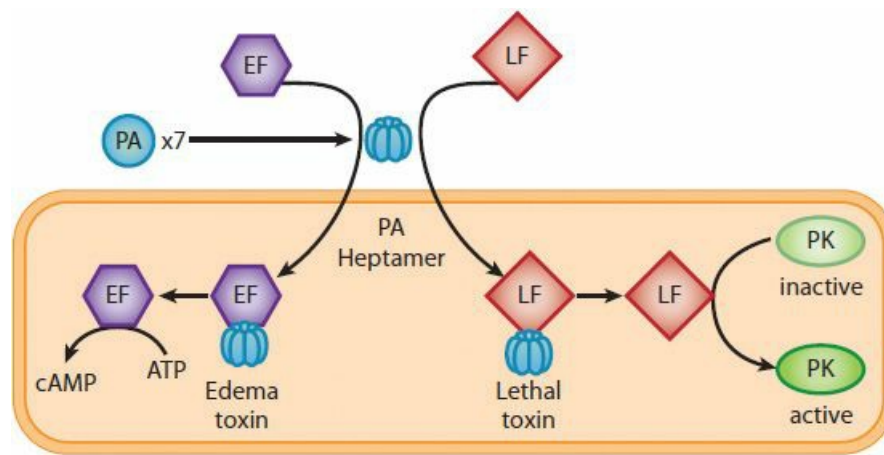


FIGURE 133–3. Model of action of anthrax toxins. EF and LF are unable to enter cells until they complex with a PA heptamer, forming edema toxin and lethal toxin, respectively. Once intracellular, release from PA allows EF and LF to exert their intracellular effects. Antibodies against PA confer resistance to the toxic effects of anthrax. EF = edema factor; LF = lethal factor; PA = protective antigen; PK = protein kinase.

Treatment. The primary antibiotics recommended to treat anthrax are ciprofloxacin and doxycycline. Although other fluoroquinolones would be expected to have similar activity against anthrax, only the manufacturer of ciprofloxacin applied for and received a US Food and Drug Administration (FDA)-approved indication for use in this infection. In a mass-casualty setting or for postexposure prophylaxis, adults should be treated with ciprofloxacin 500 mg orally (PO) every 12 hours. Alternate therapies are doxycycline 100 mg PO every 12 hours, or amoxicillin 500 mg PO every 8 hours, if the anthrax strain is proven susceptible⁴⁰ The recommended duration of therapy is 60 days, stemming from case experience in Sverdlovsk where some patients developed disease several weeks (6–7 weeks) after the spore release⁵¹ Children can also be treated with ciprofloxacin (15 mg/kg; maximum 500 mg/dose) or amoxicillin (80 mg/kg/d divided every 8 hours; maximum 500 mg/dose). The relative pediatric contraindication to fluoroquinolones is outweighed by the risk of potentially fatal disease. Cutaneous anthrax is treated with the same drugs and doses as for postexposure prophylaxis

Inhalational anthrax should be treated initially with intravenous antibiotics. Adults should receive ciprofloxacin 400 mg intravenously (IV) or doxycycline 100 mg IV every 12 hours, along with one or two additional antibiotics with in vitro activity against anthrax (eg, rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin). Children should be given ciprofloxacin 10 mg/kg IV (maximum 400 mg/dose), or doxycycline 2.2 mg/kg IV (maximum 100 mg/dose), and additional antibiotics, as indicated above.⁴⁰ However, in a true mass-casualty event, when resources are strained and inpatient care is not available for every victim, oral therapy, as described above, may be instituted. When clinically appropriate, PO antibiotic therapy can be substituted for IV forms, with total treatment duration of 60 days. Some patients in the 2001 outbreak were specifically treated with additional antibiotics that inhibit protein synthesis in attempts to reduce bacterial production of toxins.

Anthrax vaccine. An effective vaccine against anthrax is available^{33,50,72} In the United States, the Bioport Corporation (formerly Michigan Biologic Products Institute) is licensed by the FDA to produce anthrax vaccine adsorbed (AVA). The vaccine consists of a membrane-sterilized culture filtrate of *B. anthracis* V770-NP1-R, an avirulent, nonencapsulated strain that produces protective antigen, adsorbed to aluminum hydroxide, formulated with benzethonium chloride (preservative) and formaldehyde (stabilizer)⁷² In human and animal experiments, the vaccine is highly effective in preventing all forms of anthrax, and the vaccine is recommended for workers in high-risk occupations. As with any vaccine, local reactions to AVA occur in some recipients (up to 20% with mild, local reactions), and self-limited systemic reactions occur more rarely (< 1.5%). Women have more frequent injection-site reactions and other adverse events, although this sex difference is also noted with other common vaccines³⁴ Serious adverse events are very rare, with only 22 potentially related cases of serious adverse events from over 1 million doses administered to US armed forces³³ The dosage schedule for AVA is 0.5 mL subcutaneously at 0, 2, and 4 weeks and 6, 12, and 18 months, followed by yearly boosters. Preclinical studies have also been conducted on a human monoclonal antibody against protective antigen, which has been developed as an antitoxin for use in the treatment of inhalational anthrax

2001 bioterrorist anthrax outbreak. Starting on September 27, 2001, a 63 year-old Florida man developed malaise, fatigue, fever, chills, anorexia, and diaphoresis. He was admitted to a local hospital on October 2, after presenting with additional complaints of nausea, vomiting, and confusion. Chest radiography showed cardiomegaly, a left perihilar infiltrate, small left pleural effusion, and a prominent superior mediastinum. Lumbar puncture revealed hemorrhagic meningitis with many Gram-positive bacilli *Bacillus anthracis* was isolated from the cerebrospinal fluid after only a 7-hour incubation and from blood cultures within 24 hours. The patient had progressive clinical deterioration and died on hospital day four^{10,42}

On October 4, the US Centers for Disease Control and Prevention (CDC) released a public health message regarding

this case, which initially appeared to be an isolated, perhaps naturally occurring sporadic event.¹⁵ Nevertheless, the rarity of inhalational anthrax especially outside of a high-risk occupation, combined with increased suspicion in the wake of the September 11, 2001, attacks led to intense investigation of a potential bioterrorist event. Within days, epidemiologic investigation suggested workplace exposure to anthrax spores, and personnel working in the same building were started on prophylactic ciprofloxacin.¹⁶ On October 12, a case of cutaneous anthrax was reported in New York associated with a suspicious letter opened on September 25.¹⁷ Anthrax cases and environmental contamination were also soon detected in Washington, DC, and in a New Jersey postal facility. The public response to the reports of these serious and fatal cases included misuse and hoarding of antibiotics, purchasing gas masks (often with inappropriate filtering mechanisms for BW), reporting numerous miscellaneous powdery substances, and perpetrating or reporting copycat hoaxes.

By November 7, 2001, a total of 22 cases of anthrax were reported: 10 inhalational and 12 cutaneous.¹⁸ One additional death from inhalational anthrax occurred on November 21, 2001,⁴ and a case of cutaneous anthrax also occurred in a laboratory worker analyzing samples obtained during the investigation.²⁰ In two of the fatal cases, no contact with contaminated letters could be established.^{4,53} One infant hospitalized in New York with cutaneous anthrax was initially misdiagnosed as suffering from a brown recluse spider envenomation.³¹ The total number of medical victims of anthrax by Spring 2002 was 23:11 cases of inhalational anthrax (with five fatalities), and 12 cases of cutaneous anthrax (eight confirmed and four suspected).²⁰

Although the overall number of individuals infected by this bioterrorist event was relatively low, the psychosocial-economic impact was exceptionally high. Several hundred postal and other facilities were tested for *B. anthracis* spore contamination, and public health authorities recommended antibiotic prophylaxis be initiated for approximately 32,000 persons.¹⁸ Additional indirect costs and effects are more difficult to quantify, including the number of persons self-initiating antibiotic treatment without an evident indication, lost production and wages, environmental and biological sample testing, decontamination efforts, and an international sense of unease.

Published estimates of tens of thousands of deaths from a military-style anthrax attack⁴³ depend on efficient BW dispersion. The technically easier anthrax letter has clearly proven itself to be a “weapon of mass disruption.” As predicted, the psychological impact far exceeded the actual medical emergency, and events with a modest number of medical patients are probably more likely than true mass-casualty BW incidents. On the other hand, prior assumptions regarding the clinical aspects of anthrax were not as reliable. The mortality rate among the 11 cases of inhalational anthrax was 45%, considerably lower than expected and probably because of earlier diagnosis, improved supportive care measures, and a wider choice of antibiotics, compared to historic controls. Presentation with fulminant illness, such as sepsis, still appears to be predictive of a fatal outcome, yet the initial phase of illness does not necessarily lead to death, if treated with appropriate antibiotics.^{6,42,46} Pleural effusions were the most common radiographic abnormality, rather than a widened mediastinum, and pulmonary parenchymal infiltrates were seen in seven patients, whereas earlier teaching had been that pneumonia does not commonly occur with inhalation anthrax.^{32,42}

Plague. *Yersinia pestis* is a Gram-negative bacillus (Fig. 133–4) responsible for more than 200 million human deaths and three major pandemics in recorded history.^{48,49} Naturally occurring plague is transmitted by flea vectors from rodent hosts, or by respiratory droplets from infected animals or humans. Bubonic plague could result from an intentional release of plague-infested fleas. Plague is a particularly frightening BW because it can be released as an aerosol to cause a fulminant communicable form of the disease for which no effective vaccine exists. Antibiotics must be initiated early after exposure because once symptoms develop, mortality is reportedly extremely high

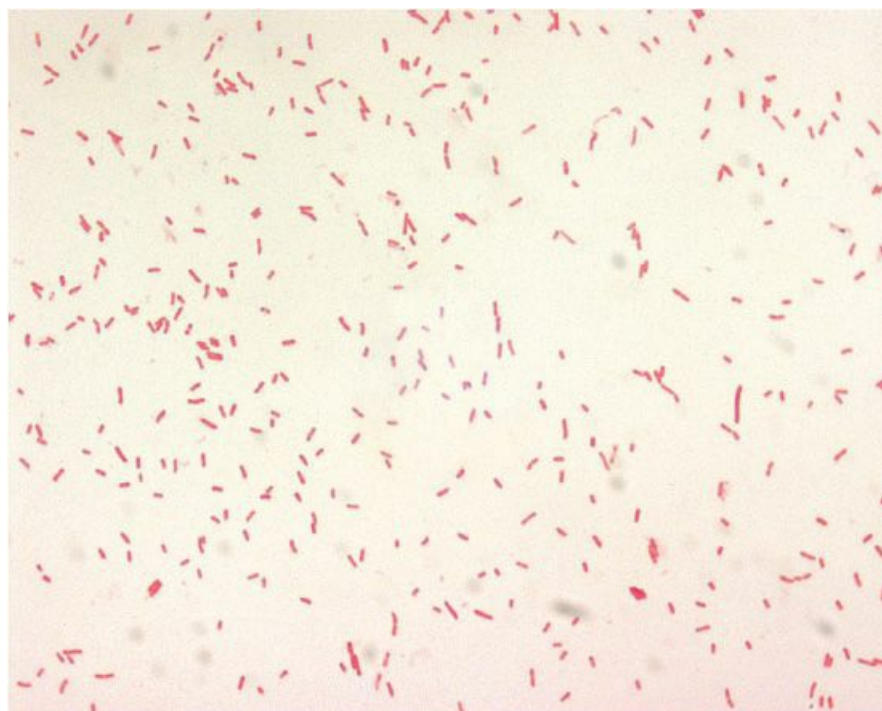


FIGURE 133–4. Plague.

Clinical presentation. Plague occurs in three clinical forms: bubonic, septicemic, and pneumonic. Bubonic plague has an incubation period of 2 to 10 days followed by fever, malaise, and painful, enlarged regional lymph nodes called buboes. The inguinal nodes are most commonly affected, presumably because the legs are more prone to flea bites, although cervical or axillary buboes are more common in children⁵⁸ In the United States, 85% to 90% of human plague patients have the bubonic form, 10% to 15% have a primary septicemic form without lymphadenopathy, and about 1% present with pneumonic plague. Secondary septicemia occurs in 23% of patients presenting with bubonic plague⁴⁹ Various skin lesions at the site of inoculation (pustules, vesicles, eschars, or papules) occur in some patients, although the petechiae and ecchymoses that occur in advanced cases may resemble meningococcemia⁴⁸ Distal gangrene may occur from small artery thrombosis, explaining why plague pandemics are sometimes called the Black Death. If left untreated, bubonic plague carries a 60% mortality rate⁴⁸

Pneumonic plague is an infection of the lungs with *Y. pestis*. Between 5% and 15% of bubonic plague patients develop secondary pneumonic plague through septicemic spread of the organism.⁴⁹ Primary pneumonic plague occurs from inhalation of infected respiratory droplets or an intentionally disseminated BW aerosol. The incubation period of pneumonic plague is 2 to 3 days after inhalation. The onset of disease is acute and often fulminant. Patients develop fever, malaise, and cough productive of bloody sputum, rapidly progressing to dyspnea, stridor, cyanosis, and cardiorespiratory collapse. Plague pneumonia is almost always fatal unless treatment is begun within 24 hours of symptom onset.³⁰

Diagnosis and treatment. Plague can be diagnosed by various staining techniques, immunologic studies, or by culturing the organism from blood, sputum, or lymph node aspirates. When gram stained *Y. pestis* appears as a Gram-positive safety pin-shaped bipolar coccobacillus^{30,58} Chest radiographs in patients with pneumonic plague reveal patchy or consolidated bronchopneumonia. Leukocytosis with a left shift is common, as are markers of low-grade disseminated intravascular coagulation (DIC) and elevations of unconjugated bilirubin and hepatic aminotransferases³⁰

Antibiotic treatment options are similar to those for anthrax. In a mass-casualty setting or for postexposure prophylaxis, adults are treated with doxycycline 100 mg PO twice daily or ciprofloxacin 500 mg orally twice daily. Children receive doxycycline 2.2 mg/kg or ciprofloxacin 20 mg/kg, up to a maximum of the adult doses. Chloramphenicol 25 mg/kg orally four times daily is an alternative. The duration of treatment is 7 days for postexposure prophylaxis and 10 days for mass-casualty incidents.³⁹ Patients with pneumonic plague need to be isolated to prevent secondary cases. Respiratory droplet precautions are necessary in pneumonic plague until the patient has received antibiotics for 3 days.³⁰ In a contained-casualty setting, pneumonic plague is treated with parenteral streptomycin or gentamicin; alternative antibiotics include doxycycline, ciprofloxacin, and chloramphenicol.³⁹ A killed whole-cell vaccine effective against bubonic plague is available, but does not reliably protect against pneumonic plague in animal studies.^{48,50}

Tularemia. *Francisella tularensis* is a small, aerobic, Gram-negative coccobacillus (Fig. 133–5) weaponized by the United States and probably other countries as well. Tularemia occurs naturally as a zoonotic disease spread by blood-sucking arthropods or by direct contact with infected animal material. Tularemia in humans may occur in ulceroglandular or typhoidal forms, depending on the route of exposure. Ulceroglandular tularemia is more common, occurring after skin or mucous membrane exposure to infected animal blood or tissues. Patients develop a local ulcer with associated lymphadenopathy, fever, chills, headache, and malaise. Typhoidal tularemia presents with fever, prostration, and weight

loss without adenopathy. Exposure to aerosolized bacteria, as employed in BW, will most likely result in typhoidal tularemia with prominent respiratory symptoms such as a nonproductive cough and substernal chest discomfort. Diagnosing tularemia is often difficult, as the organism is hard to isolate by culture and the symptoms are nonspecific. Chest radiography may demonstrate infiltrates, mediastinal lymphadenopathy, or pleural effusions^{24,28,30,50}

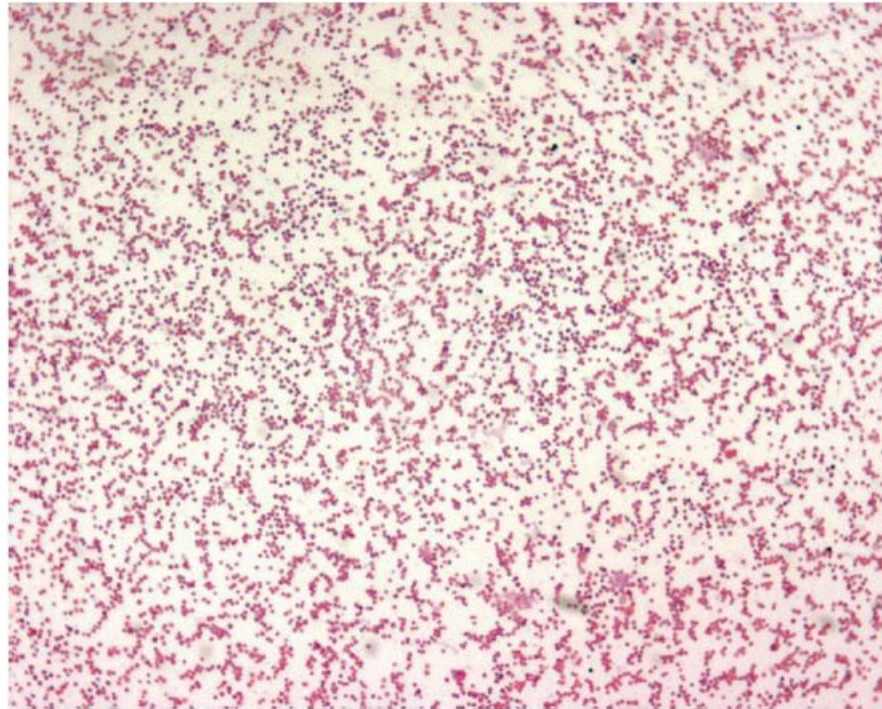


FIGURE 133–5. Tularemia.

Antibiotic treatment options are similar to those for anthrax and plague. In mass-casualty settings, or for postexposure prophylaxis, adults are treated with doxycycline 100 mg twice daily or ciprofloxacin 500 mg PO twice daily for 14 days. Pediatric dosing for doxycycline is 2.2 mg/kg or ciprofloxacin 15 mg/kg (maximum = adult dose) twice daily. When dealing with a limited number of casualties, the preferred antibiotics are streptomycin 1 g intramuscularly (IM) twice daily, or gentamicin 5 mg/kg IM/IV once daily. Alternatives include parenteral doxycycline, chloramphenicol, and ciprofloxacin.²⁴

Brucellosis. Brucellosis could potentially be used as an incapacitating BW, because it causes disease with low mortality but significant morbidity. Brucellae (*Brucella melitensis*, *abortus suis*, and *canis*) are small, aerobic, Gram-negative coccobacilli (Fig. 133–6) that generally cause disease in ruminant livestock. Humans develop brucellosis by ingesting contaminated meat and dairy products or by aerosol transmission from infected animals. The United States weaponized *B. suis* and other countries are also believed to have developed *Brucella* bioweapons. Brucellosis commonly presents with nonspecific symptoms such as fever, chills, and malaise, with either an acute or insidious onset. Because brucellae are facultative intracellular organisms that localize in the lung, spleen, liver, central nervous system (CNS), bone marrow, and synovium, organ-specific signs and symptoms may occur. Diagnosis is made by serologic methods or culture. Because single-drug treatment often results in relapse, combined therapy is indicated. Treatments of choice (adult doses) are doxycycline 200 mg/day PO, plus rifampin 600 to 900 mg/day PO for 6 weeks, or doxycycline 200 mg/day PO for 6 weeks, with either streptomycin 15 mg/kg twice daily IM or gentamicin 1.5 mg/kg IM q8h for the first 10 days^{30,38,50}

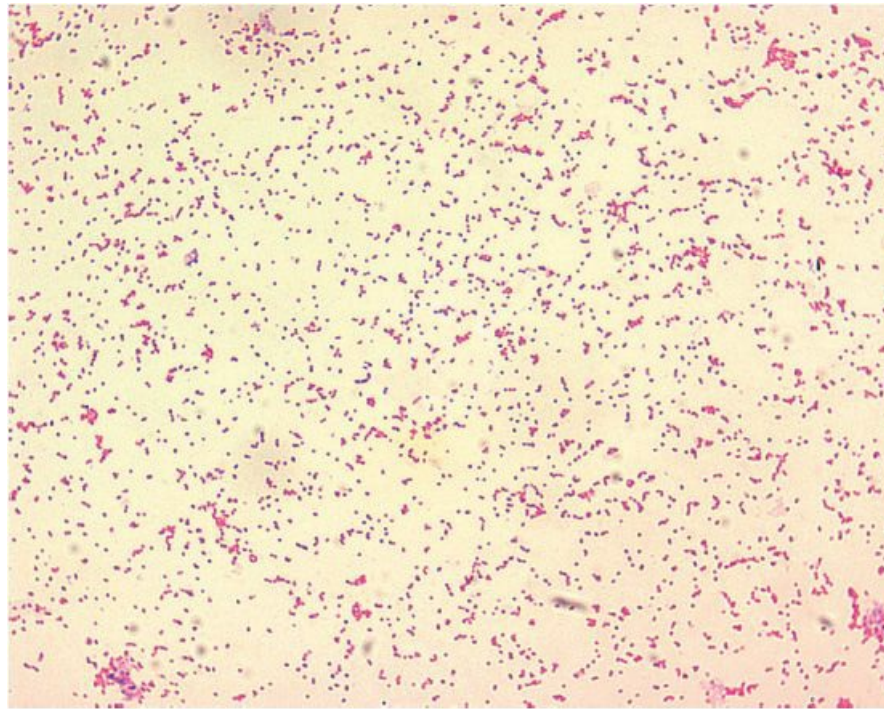


FIGURE 133–6. *Brucella*.

Rickettsiae. Features of rickettsiae favoring their use as BW include environmental stability, aerosol transmission, persistence in infected hosts, low infectious dose, and high associated morbidity and mortality. Rickettsiae that have been weaponized include *Coxiella burnetti*, the causative organism of Q fever, and *Rickettsia prowazekii*, the causative organism of louseborne typhus. Release of *R. prowazekii* into a crowded louse-infested population might induce a typhus outbreak with rapid transmission and high mortality³

Q Fever. Q fever was first described in 1937, and was given its name—Q for “query”—because the causative organism was not then known. Q fever occurs naturally as a self-limited febrile, zoonotic disease contracted from domestic livestock. Q fever is now known to be caused by *Coxiella burnetti*, a unique rickettsialike organism that can persist on inanimate objects for weeks to months and can cause clinical disease with the inhalation of only a single organism. These features are of obvious benefit for use as a potential BW. After a 10- to 40-day incubation period, Q fever manifests as an undifferentiated febrile illness, with headache, fatigue, and myalgias. Patchy pulmonary infiltrates on chest radiography that resemble viral or atypical bacterial pneumonia occur in 50% of cases, although only half of patients have cough and even fewer have pleuritic chest pain. Uncommon complications include hepatitis, endocarditis, meningitis, encephalitis, and osteomyelitis. Patients are generally not critically ill, and the disease can last as long as 2 weeks. Treatment with antibiotics will shorten the course of acute Q fever and can prevent clinically evident disease when given during the incubation period. Tetracyclines are the mainstay of therapy, and either tetracycline 500 mg PO q6h or doxycycline 100 mg PO q12h should be given for 5 to 7 days^{11,30}

Viruses

Smallpox. Smallpox is caused by the variola virus, a large DNA orthopoxvirus (Fig. 133–7) with a host range limited to humans. Prior to global World Health Organization (WHO) efforts to eradicate naturally occurring smallpox by immunization, recurrent epidemics were common and the disease carried roughly a 30% fatality rate in unvaccinated populations^{37,47} Smallpox is highly contagious (Fig. 133–8). Outbreaks during the 1960s and 1970s in Europe often resulted in 10 to 20 secondary cases per index case. One German smallpox patient with a cough, isolated in a single room, infected persons on three floors of a hospital³⁷ However, the overwhelming majority of secondary infections occur among close family contacts, especially those sleeping in the same room or even in the same bed²⁶

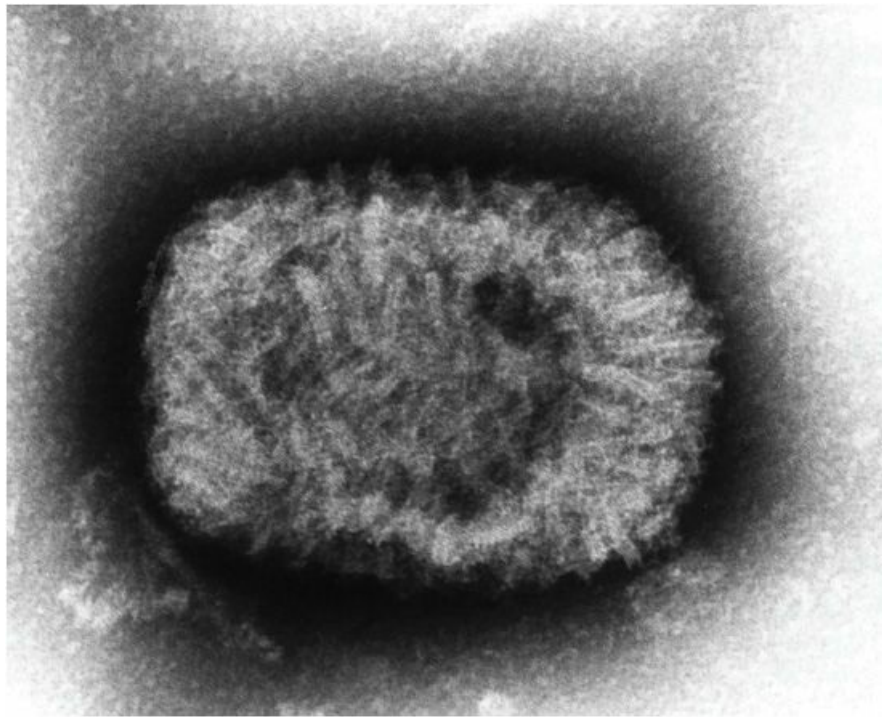


FIGURE 133–7. Variola virus.



FIGURE 133–8. Smallpox rash.

In 1980, the United Nations' WHO certified that smallpox had been eradicated from the world, and recommended ceasing vaccinations and either destroying or transferring remaining stocks of variola virus to one of two designated biosafety level 4 facilities: the CDC in Atlanta or the Russian State Research Center of Virology and Biotechnology.⁹ All remaining known variola stocks were scheduled for destruction in 1999; however, before this was done, a WHO resolution called for a delay based on an Institute of Medicine report concluding that live virus should be retained to develop new antivirals or vaccines to protect against any potential future release of smallpox.⁶² The Soviet Union is known to have weaponized smallpox, and other countries are believed to maintain stocks of variola virus. In addition to the known stockpiles of smallpox vaccine, several types of new vaccines are being produced.^{56,70} Smallpox vaccination for military personnel was reinstated in 2002 and was made available for some civilians in 2003.^{21,22}

Pathophysiology. Transmission of smallpox typically occurs through inhalation of droplets or aerosols, but may also occur through contaminated fomites. The infectious dose is not known, but is probably only a few virions. After a 12-to 14-day incubation period, the patient develops fever, malaise, and prostration with headache and backache. Oropharyngeal lesions appear, shedding virus into the saliva. Two to three days after the onset of fever, a papular rash develops on the face and spreads to the extremities. The fever continues while the rash becomes vesicular and then pustular. Scabs form from the pustules and eventually separate, leaving pitted and hypopigmented scars. Deaths usually occur during the second week of the illness. Vaccination before exposure, or within 2 to 3 days after exposure, provides almost complete protection against smallpox. The disease most likely to be confused with smallpox is chickenpox (varicella). Although the individual lesions of smallpox and varicella are physically indistinguishable, the person infected with smallpox may still be differentiated clinically. The lesions of smallpox should all appear at the same stage of development (synchronous), whereas chickenpox lesions occur at varying stages (asynchronous). Smallpox lesions tend to be found in a centrifugal distribution (face and distal extremities), whereas chickenpox lesions are more centripetal and tend to appear first on the trunk.

Two antivirals commercially available in the United States, cidofovir and ribavirin, are effective in vitro against variola.⁵⁰ However, current evidence suggests that although cidofovir may prevent smallpox when given within 1 or 2 days of exposure, it is unlikely to be effective once symptoms develop.³⁷ Even a single case of smallpox should be considered a potential international health emergency and immediately reported to the appropriate public health authorities.

Smallpox vaccination. Rapid postexposure vaccination confers excellent protection against smallpox. The smallpox vaccine employs a live vaccinia virus (derived from cowpox vaccine) rather than the actual variola virus that causes smallpox. Although contracting smallpox from the vaccine is impossible, other adverse reactions may occur. The two most serious reactions are postvaccinal encephalitis and progressive vaccinia. Postvaccinal encephalitis occurs in about three cases per million primary vaccinees. Forty percent of cases are fatal, and some survivors are left with permanent neurologic sequelae. Progressive vaccinia can occur in immunosuppressed individuals and is treated with vaccinia immune globulin (VIG; Fig. 133–9).⁷⁰ Another historically common complication of smallpox vaccination was ocular vaccinia, which typically occurred among health care personnel administering vaccine when it was inadvertently placed in the eye. Ocular vaccinia is also treated with VIG. Because smallpox was eradicated before the emergence of HIV, there is limited clinical experience with smallpox vaccination in patients with AIDS who theoretically are at increased risk of progressive vaccinia.^{37,47} However, among 10 individuals with undiagnosed HIV at the time of recent smallpox vaccination, none developed complications.⁶⁵ Routine vaccination is contraindicated in the immunosuppressed, persons with a history or evidence of eczema and other chronic dermatitis, close household or sexual contacts of patients with these contraindications, and during pregnancy. Because the vaccine is a live virus, it can be transmitted from the vaccinee to close contacts. Thirty secondary and tertiary cases of vaccinia were reported resulting from recent US military vaccinations.²¹ The number of serious adverse events from modern smallpox vaccination is very low²²; however, rare cardiac complications not reported in previous decades were noted with the recent reinstitution of smallpox vaccination in the early 2000s. More than 1 million military vaccinations given by 2006 resulted in 120 cases of myopericarditis, while 21 cases of myopericarditis occurred among nearly 40,000 civilian vaccine recipients between 2002 and 2003.⁵⁶ The number of cardiac ischemic events among vaccinees was not significantly higher than age-matched controls. After a true exposure to variola, most authorities would agree that the only absolute contraindication to smallpox vaccination is significant impairment of systemic immunity. Concomitant administration of vaccinia immune globulin would be recommended for pregnant women and persons with eczema.⁴⁷



FIGURE 133–9. Progressive vaccinia.

Viral Hemorrhagic Fevers. Several taxonomically diverse RNA viruses produce acute febrile illnesses characterized by malaise, prostration, and increased vascular permeability that can result in bleeding manifestations in the more severely affected patients. Viral hemorrhagic fevers (VHFs) are all highly infectious by the aerosol route, making them candidates for use as BW. These include the viruses causing Lassa fever, dengue, yellow fever, Crimean-Congo hemorrhagic fever, and the Marburg, Ebola virus, and Hanta viruses. Hanta virus is endemic to North America; occasional natural epidemics of human infection occur, which may initially be difficult to differentiate from a BW release. Clinical features, such as the extent of renal, hepatic, and hematologic involvement, vary according to the specific virus, but they all carry the risk of secondary infection through droplet aerosols. Ribavirin is used for some VHFs, but supportive care is the mainstay of therapy^{7,30,41}

Viral Encephalitides. Three antigenically related α viruses of the Togaviridae family pose risks as BWs: western equine encephalitis (WEE), eastern equine encephalitis (EEE), and Venezuelan equine encephalitis (VEE). Birds are the natural reservoir of these viruses, and natural outbreaks occur among equines and humans by mosquito transmission. Eastern equine encephalitis infections are the most severe in humans, with a 50% to 70% fatality rate and high incidence of neurologic sequelae among survivors. WEE is less neurologically invasive, and severe encephalitis from VEE is rare, except in children. Adults infected with VEE usually develop an acute, febrile, incapacitating disease with prolonged recovery. The equine encephalitides have many properties helpful for weaponization, in that they can be produced in large quantities, they are relatively stable and highly infectious to humans as aerosols, and a choice is available between lethal or incapacitating infections⁶³

Venezuelan equine encephalitis is considered the most likely BW threat among the viral encephalitides. After a 1-to 5-day incubation period, victims experience the sudden onset of malaise, myalgias, prostration, spiking fevers, rigors, severe headache, and photophobia. Nausea, vomiting, cough, sore throat, and diarrhea may follow. This acute phase lasts 24 to 72 hours. Between 0.5% and 4% of cases develop encephalitis, with meningismus, seizures, coma, and paralysis, which carries up to a 20% fatality rate. The diagnosis is usually established clinically, although the virus can sometimes be isolated from serum or from throat swabs, and serologic tests are available. The white blood cell count often shows a striking leukopenia and lymphopenia. Treatment is supportive. Person-to-person transmission can theoretically occur from droplet nuclei. Recovery takes 1 to 2 weeks.^{30,63}

Toxins

Several toxins derived from bacteria, plants, fungi, and algae could theoretically be used as BW, if produced in sufficient quantities. Because of their high potency, only small amounts would be needed to kill or incapacitate exposed victims. Fortunately, obstacles in manufacturing weaponizable amounts limit the number of toxins that are practical for use as biological weapons. Discussion here is limited to those toxins known or highly suspected to have been weaponized. Toxins themselves are not living organisms and therefore cannot reproduce; for this reason, they are arguably equivalent to chemical weapons. But because toxin weapons are derived from living organisms, they are categorized here as biological weapons.

Botulinum Toxin. Botulinum toxin has been developed as a biological weapon in the United States and other countries^{1,55,61,71} The two most likely means of employing botulism are by food contamination or by aerosol. Either method would result in the clinical syndrome of botulism ([Chap. 41](#)), characterized by multiple bulbar nerve palsies and a symmetric descending paralysis, ending in death from respiratory failure. Inhalational botulism from laboratory incidents

has occurred rarely in humans and has also been investigated in animal experiments⁵²

Ricin. Ricin is derived from the castor bean plant (*Ricinus communis*) and is the only biological toxin to exist naturally in more than microscopic quantities, comprising 1% to 5% of the beans by weight.⁸ Its easy accessibility, relative ease of preparation, and low cost may make ricin an attractive BW for terrorists or poor countries. Although ricin has never been used in battle, it has attracted the attention of domestic extremists and terrorists and has been used in politically motivated assassinations.^{2,23,29} Ricin is a glycoprotein lectin (or toxalbumin) composed of two protein chains linked by a disulfide bond. The B chain facilitates cell binding and entry of the A chain into cells. The A chain inhibits protein synthesis, inactivating eukaryotic ribosomes by removing an adenine residue from ribosomal RNA.²

Clinical toxicity from ricin will vary depending on the dose and route of exposure. Inhalation of aerosolized ricin results in increased alveolar-capillary permeability and airway necrosis following a latent phase of 4 to 8 hours. Ingestion causes gastrointestinal hemorrhage with necrosis of the liver, spleen, and kidney. Intramuscular administration produces severe local necrosis with extension into the lymphatics. In the absence of specific immunologic testing, differentiating ricin poisoning from sepsis may be difficult, because of the presence of leukocytosis and fever. Vaccination of laboratory animals with an investigational toxoid (a modified toxin that does not cause disease, but still induces an antibody response) is protective.²⁹

Staphylococcal Enterotoxin B. Staphylococcal enterotoxin B (SEB) is one of seven enterotoxins produced by *Staphylococcus aureus*. SEB is recognized as a “superantigen,” because of its profound activation of the immune system on exposure to even minute quantities. As a BW, SEB could be ingested through contaminated food or water, resulting in acute gastroenteritis identical to classic staphylococcal food poisoning. If inhaled as an aerosol, SEB produces fever, myalgias, and a pneumonitis after a 3-to 12-hour latent period. SEB inhalation can be fatal, but more often would simply be incapacitating for several days to weeks. Treatment is supportive.⁶⁷

Fungi and Other Fungal Toxins

Fungi may at first appear to be ideal BW, given their relative ease of handling, dissemination, and resistance of spores to physical stressors.¹² The only fungi to be included on lists of microbes with potential use as biological weapons are *Coccidioides* species, probably based on the high incidence of symptomatic infection in endemic areas. Nevertheless, the risk of serious disease is low, limiting the utility of *Coccidioides* as an effective weapon.^{12,57}

Fungal toxins considered to have potential use as BWs include trichothecene mycotoxins, aflatoxins, and amanita toxins. Although α -amanitin is extremely potent, water soluble, and heat stable, its use as a weapon would be limited by difficulties in mass production.⁵⁷ Aflatoxin would be ineffective on the battlefield, since its acute toxicity is uncertain and the carcinogenic potential is a delayed phenomenon.⁵ However, both of these toxins may still be effective as terror agents.

Trichothecene Mycotoxins. The trichothecene mycotoxins are low-molecular-weight (250–500 Da), nonvolatile compounds produced by filamentous fungi (molds) of various genera, including *Fusarium*, *Myrothecium*, *Phomopsis*, *Trichoderma*, *Tricothecium*, and *Stachybotrys*.^{5,68} Trichothecene mycotoxins are unusual among potential BW in that toxicity can occur with exposure to intact skin. Naturally occurring trichothecene toxicity results from ingesting contaminated grains or by inhaling toxin aerosolized from contaminated hay or cotton. Outbreaks of ingested trichothecene toxins result in a clinical syndrome called alimentary toxic aleukia, characterized by gastroenteritis, fevers, chills, bone marrow suppression with granulocytopenia, and secondary sepsis—a syndrome clinically similar to acute radiation poisoning. Survival beyond this stage is characterized by the development of GI and upper airway ulceration, and intradermal and mucosal hemorrhage. Trichothecene toxins are potent inhibitors of protein synthesis in eukaryotic cells, producing widespread cytotoxicity, particularly in rapidly proliferating tissues; different trichothecene toxins interfere with initiation, elongation, and termination stages of protein synthesis.⁵ Exposure to any mucosal surface results in severe irritation. Dermal exposure can produce inflammatory lesions lasting for 1 to 2 weeks, vesiculation, and, in higher doses, death.⁶⁸

Several reports from the 1970s and 1980s suggested that Soviet-supported forces were using trichothecene mycotoxins, particularly the toxin T-2 (Fig. 133–10), as BW. Aerosol and droplet clouds called Yellow Rain were associated with mass casualty incidents in Southeast Asia.⁶⁸ Such incidents would involve multiple routes of exposure, with skin deposition likely being the major site. Early symptoms included nausea, vomiting, weakness, dizziness, and ataxia. Diarrhea would then ensue, at first watery and then becoming bloody. Within 3 to 12 hours victims would develop dyspnea, cough, chest pain, sore mouths, bleeding gums, epistaxis, and hematemesis. Exposed skin areas would become intensely inflamed, with the appearance of vesicles, bullae, petechiae, ecchymoses, and frank necrosis.⁶⁸

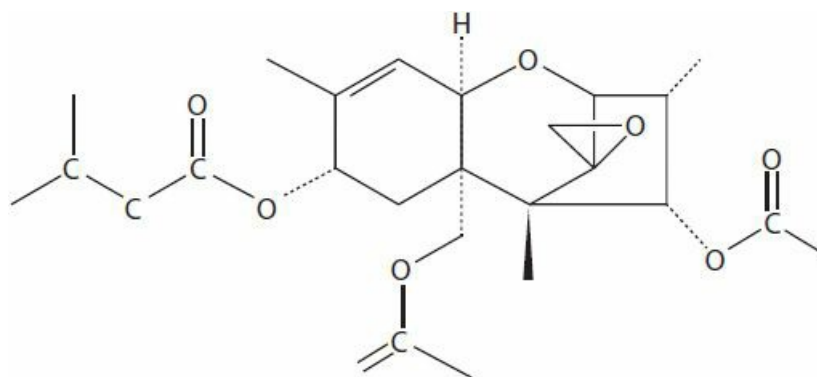


FIGURE 133–10. T-2, a trichothecene mycotoxin.

Nonetheless, evidence that trichothecene mycotoxins were used as BWs was mostly circumstantial. Although T-2 toxin was found in victims' blood and urine, it was also found in samples from unexposed individuals, probably from baseline ingestion of contaminated foods. Environmental samples containing Yellow Rain droplets were inconsistently found to contain mycotoxins. Eyewitness accounts of Yellow Rain attacks varied widely (including various descriptions of the alleged agent's color), and, despite the large number of such attacks, no contaminated ordinance or dispersal device was ever recovered.⁶⁰ It was also discovered that Yellow Rain droplets were composed mostly of pollen grains. Supporters of the Yellow Rain as BW theory retorted that pollen grains would be an ideal carrier for biotoxins, given that their size is ideal for aerosolization. However, the pollen in Yellow Rain samples did not contain protein, similar to pollen that has been digested by bees. Further, the distribution of pollen species found in Yellow Rain was indistinguishable from the contents of feces of the Asian honeybee, and mass bee defecation resulting in showers of yellow droplets has been observed.⁶⁰ The Yellow Rain "bee feces theory" assumes that any mass-casualty incidents were from endemic disease outbreaks, other chemical or biological agents not yet identified, or a combination of both.

SUMMARY

- Many BWs are pathogenic bacteria, viruses, or toxins produced by microorganisms.
- BWs share many features with chemical weapons, including that the most effective method of dispersal to cause mass casualties will be via aerosolization. Disease after exposure to many BWs includes respiratory signs and symptoms.
- Victims of BWs exposure may present in a delayed fashion due to the incubation period of the disease. However, with proper identification of the agent, postexposure prophylaxis with antibiotics and/or vaccination may be possible.
- With typical universal precautions, ill victims from BWs exposure generally do not pose an infection risk to health care providers and others. Notable exceptions include pneumonic plague, smallpox, and the viral hemorrhagic fevers.

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134 Radiation

Joseph G. Rella

Although the theory of atomism originated with the Greeks in the fifth century BC, it has been only a little more than a century that scientists could describe and measure atoms and the other particles of radiation. Today we utilize radiation and radionuclides for a vast array of purposes, ranging from mundane household uses such as smoke detection to powering satellites, cancer treatment, and examining the physical properties of individual molecules. Unfortunately, as our knowledge of how to use radiation has expanded so too has our awareness of radiation as a toxin. Indeed, for each of the last three editions of this text, there has been a significant radiation event that captured the world's attention and demonstrated clearly just how much more we need to know. The particles of radiation, their sources, and the mechanisms by which they pose a health risk are the subjects of the following discussion.

HISTORICAL EXPOSURES

Soon after x-rays were discovered in 1895, a deepening understanding of radiation and radionuclides led to their wider use and their resulting injuries. In the early days of radiation, exposures were small and of low energy, which nevertheless created injuries for a relatively small number of individuals. Clarence Dally was the first known radiation-induced death in 1904 following repeated exposures to Thomas Edison's early fluoroscopes. By 1927 nearly 100 women employed to create illuminated instrument dials became ill or died after exposure to radium-containing paint. Efforts to protect workers such as those by the British Roentgen Society were hampered by limitations on measurement of radiation despite the development in 1908 of the Geiger counter that could detect but not quantify radiation. Much later in 1984 and again in 1987, lack of proper remediation of closed radiation treatment centers led to scavengers releasing sources of ^{60}Co and ^{137}Cs , respectively. In the cobalt incident beginning in Juarez, Mexico, thousands of tiny metal pellets were spilled in a scrapyard and melted with other metals into table legs later shipped throughout Mexico and the United States. In the cesium incident in Goiânia, Brazil, scavengers were fascinated by the bluish glow of the material. Ultimately, 250 individuals were contaminated, 46 patients were treated with a chelator, and 4 died the month following the initial exposure with another dying several years afterward from radiation-induced injuries.

With the advent of the nuclear age, said to have begun with the first detonation of an atomic bomb in New Mexico in July 1945, suddenly the risks of radiation exposure grew to many thousands at once. Following the use of the two atomic bombs in Japan at the end of World War II, estimates of dead and injured for both cities were well over 200,000. Most of the deaths were from the bomb blast, but many thousands died from acute radiation syndrome (ARS) and others subsequently from radiation-induced cancers. In addition to the people of those cities who were victims of the bombs, many thousands of military personnel assigned to cleanup tasks or to attend nuclear weapons testing over the following 20 years were also exposed to radiation resulting from nuclear explosions. One relatively well-studied group, the British Nuclear Tests Veterans Association (BNTVA), found two-thirds of its study group died from neoplasms at ages 50 to 65 years, irrespective of the individual's age at the time of the witnessed explosion.

More recently in the post-nuclear testing era, large radiation incidents have occurred at the sites of nuclear reactors. In 1986, the Chernobyl nuclear reactor, built without a hard containment vessel, experienced a series of explosions releasing an enormous cloud of radioactive material. Thirty-one people died of ARS in the first few weeks following that event and an unknown number of millions potentially suffered other long-term sequelae in the surrounding geographic area.

And on March 11, 2011, a powerful earthquake off the east coast of Japan triggered a destructive tsunami that struck the Fukushima Daiichi nuclear power plant complex, knocking out its own electrical power and disabling the ability to cool its nuclear material. Over the following week, a series of explosions released an amount of radioactive material second only to the Chernobyl incident; however, no reports have suggested that anyone was injured from radiation exposure, although investigations are continuing.

In the realm of health care, radiologists of the early twentieth century used a thorium-containing contrast agent called Thorotrast in the initial development of angiography. Unfortunately, this xenobiotic accumulated in hepatic tissue resulting in malignancies and its eventual discontinuance in 1952. More recently the steadily increasing use of computed tomography (CT) has led to increased concerns over their safety and potential for stochastic effects. One retrospective study suggests there is a small but measurably increased risk for certain neoplasms in children following the accumulated radiation dose of several CT scans. This topic will be discussed in more detail later.

PRINCIPLES OF RADIOACTIVITY

Dating from the fifteenth century, radiation is defined as energy sent out in the form of waves or particles. Although considered by physicists as incomplete, the particle-wave theory remains a useful model by which to understand the toxic aspects of radiation. Despite the strong nuclear force that holds the basic building blocks of atoms together, many isotopes are unstable. Various influences such as quantum fluctuations and the weak nuclear force can tip the balance toward instability to transform an isotope. This process may be intentional, as with the criticality events in a nuclear reactor or nuclear bomb, but mainly occurs spontaneously in nature as the process called radioactive decay.

Radioactive Decay

In 1900, Marie Curie discovered that unstable nuclei decay or transform into more stable nuclei (daughters) via the emission of various particles or energy. Radioactive decay occurs mainly through five mechanisms: emission of γ -rays, α -particles, β -particles, positrons, or by capture of an electron. The emission of these various particles makes radioactive decay dangerous because these particles form ionizing radiation. Each radioisotope has a specific decay energy signature. That is, the emitted particles from a given radioisotope have known energies, which make identification of radiation sources possible.

The half-life ($t_{1/2}$) is the period of time it takes for a radioisotope to lose half of its radioactivity. Every radioisotope has a characteristic half-life, some lasting millionths of a second while others last billions of years. In every case, the activities of radioactive isotopes diminish exponentially with time (Table 134–1).

TABLE 134–1. Physical Properties of Radioisotopes

Isotope	Half-Life	Mode of Decay	Decay Energy (MeV)
Radioisotopes of Medical Examinations			
^{131}I	8 days	β^-	0.97
^{201}Tl	73 hours	EC	0.41
$^{99\text{m}}\text{Tc}$	6 hours	IT	0.14
^{133}Xe	5.27 days	β^-	0.43
^{67}Ga	78 hours	EC	1.00
^{18}F	109 months	β^- , EC	1.65
Military Radioisotopes			
^3H	12.26 years	β^-	0.02
^{235}U	7.1×10^8 years	α , SF	4.68
^{238}U	4.51×10^9 years	α , SF	4.27
^{210}Po	138 days	α	5.307
^{239}Pu	24,400 years	α , SF	5.24
^{241}Am	470 years	α , γ	5.14/0.02

EC = electron capture; IT = isomeric transition from upper to lower isomeric state; SF = spontaneous fission; MeV = megaelectron volts.

Photons are elementary particles that mediate electromagnetic radiation. Depending on their energy the radiation has different names ranging from extremely long radio waves to high-energy γ -rays.

X-rays and γ -rays are high-energy photons and are only distinguishable by their source. γ -Radiation is emitted by unstable atomic nuclei via radioactive decay and will have a fixed wavelength depending on the energy that formed it. X-rays come from atomic processes outside the nucleus. For example, an x-ray machine generates x-rays by accelerating electrons through a large voltage and colliding them into a metal target. The rapid deceleration of electrons in the target generates x-rays and in general, the higher the voltage, the greater the energy of the x-rays. Because of their nature, high-energy γ -and x-rays can penetrate several feet of insulating concrete.

β -Particles are also called electrons. They are emitted during β -decay from an unstable radionuclide. Positrons are positively charged electrons and may also be emitted during decay processes. Electrons have less penetrating ability than γ -radiation but may still pass several centimeters into human skin. β -Particles may also cause health problems chiefly through incorporation, or internalization into living organisms.

α -Particles are helium nuclei (two protons and two neutrons) stripped of their electrons and are emitted during α -decay. These particles are the most easily shielded of the emitted particles mentioned and may be stopped by a piece of paper, skin, or clothing. Unlike β -particles, α -particles principally cause health effects only when they are incorporated.

Neutrons are primarily released from nuclear processes although high-energy photon beams used in radiotherapy may also produce them. The natural decay of radionuclides does not include emission of neutrons, which is mainly a health hazard for workers in a nuclear power facility or victims of a nuclear explosion. Unique among the particles of radioactivity, when neutrons are stopped or captured they can cause a previously stable atom to become radioactive in a process known as neutron activation.

Cosmic rays complete the group of various kinds of radiation to which an individual may be exposed. Cosmic rays are streams of electrons, protons, and α -particles thought to emanate from stars and supernovas. They rain down on the earth from all directions only to give up their energy as they strike the nuclei of oxygen and nitrogen in the upper reaches of the Earth's atmosphere. By the time they reach the earth, the energy of cosmic radiation is reduced by several orders of magnitude. Traveling or living at altitude where the atmosphere shields relatively less cosmic radiation naturally means greater exposure to cosmic rays but in general is not considered a significant threat to humans.

Isotopes and nuclides are very closely related terms and most experts in the field use them interchangeably. An isotope is a set of nuclides with the same number of protons (eg, ^{123}I , ^{125}I , ^{127}I , ^{131}I). Nuclide is a more general term that may or may not be isotopes of a given element, such as fissile nuclides or primordial nuclides. Radioisotopes are isotopes that are radioactive, that is, they spontaneously decay and emit energy. Of the iodine nuclides listed previously, ^{123}I , ^{125}I , and ^{131}I are radionuclides. The nuclide ^{127}I is stable. Finally, radionuclides are simply nuclides that are radioactive.

Ionizing Radiation Versus Nonionizing Radiation

Ionizing radiation refers to any radiation with sufficient energy to disrupt an atom or molecule with which it impacts. In this interaction, an electron is removed or some other decay process occurs, leaving behind a changed atom. Depending on the specifics of the interaction, the chemical bonds become altered producing ions or highly reactive free radicals. Hydroxyl-free radicals, formed by ionizing water, are responsible for biochemical lesions that are the foundation of radiation toxicity.

The space between collisions of ionizing radiation and their target molecules varies with the particle type and its energy. A charged particle, such as an α particle, loses kinetic energy through a series of small energy transfers to other atomic electrons in the target medium, such as tissues. Most of the energy deposition occurs in the infratrack, a narrow region around the particle track extending about 10 atomic distances. The energy loss per unit length of particle track is called the linear energy transfer (LET), which is expressed in kiloelectron volts per micrometer (keV/ μm). Heavy charged particles, such as α -particles, are referred to as high-LET radiation, whereas x-rays, γ -rays, and fast electrons are low-LET radiation.

Because of its large size, collisions along the path of an α particle are clustered together, limiting its ability to penetrate tissue. By comparison, collisions along the path of γ -rays are spread out, increasing their ability to penetrate tissue. It is this ability to penetrate tissue and transfer energy that accounts for the relative dangers of the forms of radiation and tissue susceptibility.

For a source of radiation to pose a threat to tissue, the ionizing particle must be placed in close proximity to vital components of tissue to inflict damage. High-energy photons penetrate deeply and so pose a similar risk whether they come from an external source or from an incorporated source. As noted previously, α -particles have much more limited tissue penetration. Thus, α -emitters, radionuclides that radiate these particles, must first be incorporated to pose a threat to tissue. β -particles similarly have limited tissue penetration and usually are incorporated before damage may occur, although a large external exposure to β -emitters may cause serious cutaneous injury that could be life threatening, as discussed next.

Nonionizing radiation spans a wide spectrum of electromagnetic radiation frequencies. Generally, nonionizing radiation consists of relatively low-energy photons and is used safely in cell phone and television signal transmission, radar, microwaves, and magnetic fields that emanate from high-voltage electricity and metal detectors. Although these are all considered radiation in that they are all energies released from a source, these photons lack the necessary energy required to cause ionization and cellular damage.

Radiation Units of Measure

The amount of radiation to which an object is exposed, that is, the amount emitted from a source that falls on an object, is given in units called roentgens (R), a term that is now considered obsolete. A roentgen is a unit for measuring the quantity of γ -or x-radiation by measuring the amount of ionization produced in air. As an example, an individual standing at a given distance from the x-ray-generating tube of a particular x-ray machine is exposed, on the skin, to a particular number of roentgens of x-rays (Fig. 134-1).

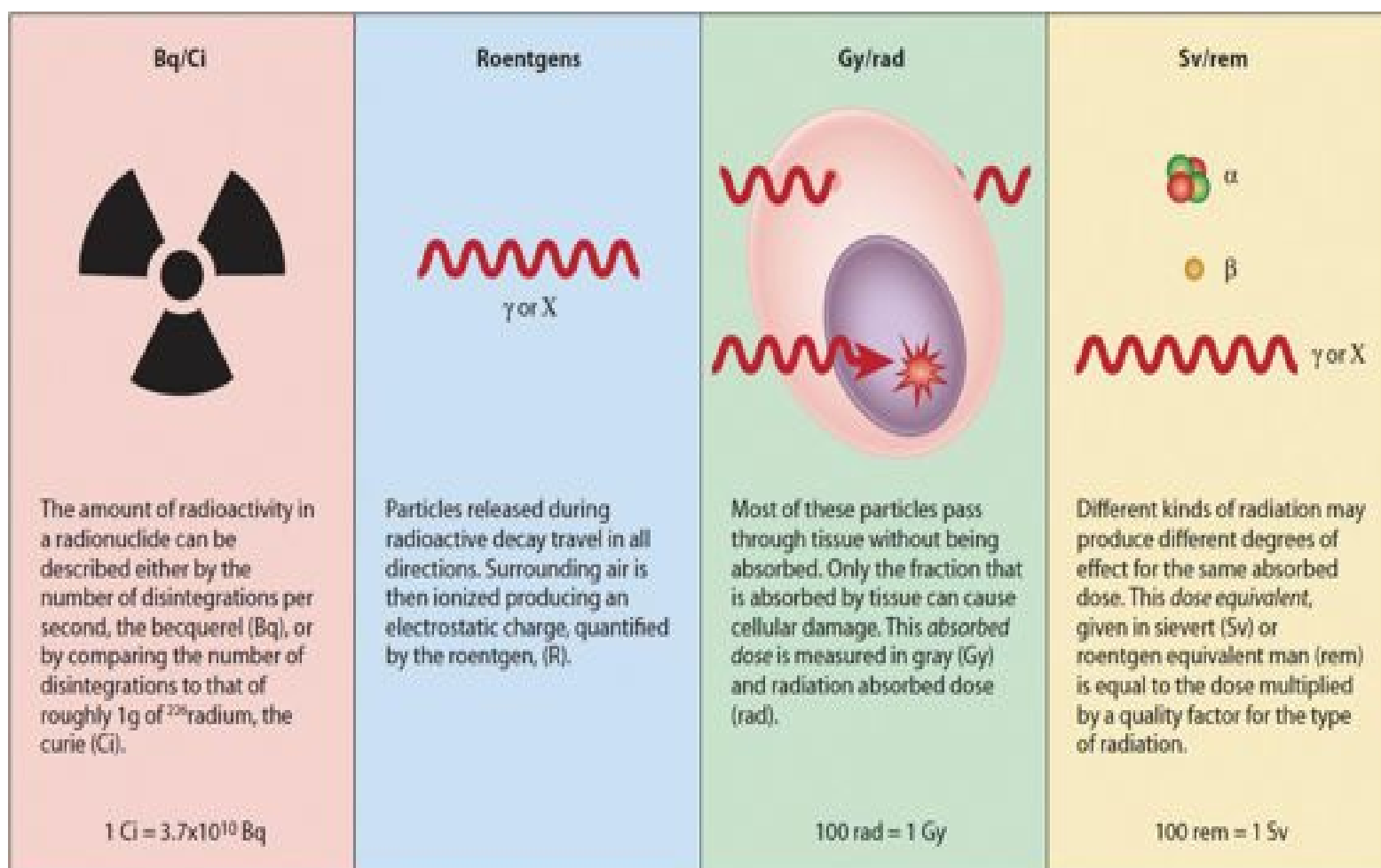


FIGURE 134–1. The definitions associated with radiation. Both curie and becquerel describe a quantity of radionuclide in terms of the number of disintegrations rather than mass. Roentgens describes the amount of air ionized by either γ -or x-rays, which indirectly quantifies the amount of radiation in the air around a source. Rad and gray (Gy) describe the fraction of radiation that actually interacts with cellular material and potentially causes injury. Roentgen equivalent man (rem) and sievert (Sv) calculate the effective dose taking into account the different particles. For example, a 100 keV α -particle causes more damage to cellular material than a 100 keV β -particle.

Not all radiation to which an individual is exposed poses a risk for cellular damage. Much of the radiation passes through the body and causes no harm. Only the fraction that is absorbed by the tissue has a chance of causing cellular damage. The International System (SI) unit that describes absorbed radiation is the gray (Gy), which has replaced the rad (radiation-absorbed dose). One Gy equals 100 rad.

To measure the risk of biologic damage regardless of the type of radiation, the effective dose is given in sievert (Sv), which has replaced the rem (roentgen equivalent man). One Sv equals 100 rem. This calculation, known as dosimetry, takes into account the type of exposure (external or internal, partial or total), the particle or particles involved (eg, α , β , γ), and the radiosensitivity of the organ or organs exposed. The effective dose is calculated according to the following equation:

$$E = D \times W_R \times W_T,$$

where E is the dose in sieverts, D is the absorbed dose in gray, W_R is the radiation weighting factor, also called Q, and W_T is the tissue weighting factor indicating the radiosensitivity of each organ.

In 1910, the curie (Ci) became the unit describing the amount of radioactivity in a source. One curie equals 3.7×10^{10} disintegrations per second based on the decay of 1 g of radium. The curie was replaced by the SI unit the becquerel (Bq) where 1 Bq is equivalent to 1 disintegration per second. Thus, 1 Ci is equivalent to 3.7×10^{10} Bq. For example, following the Chernobyl incident, 1.2×10^{19} disintegrations per second of radioactive material was released into the atmosphere. By comparison, the radioactive source of ¹³⁷Cs in Goiânia contained 50.9×10^{12} Bq (13.7×10^5 mCi) of cesium. A thallium stress test uses 111×10^6 Bq (3 mCi) of ²⁰¹Tl, and the average indoor concentration of ²²²Rn in the United States is 55 Bq/m³ (14.8×10^{-6} mCi).

Protection From Radiation

Shielding refers to the process by which one may limit the amount of unwanted ionizing radiation in a given setting. Placing a specific material between a radiation source and a target will limit the amount of ionizing radiation that will interact with

the target. When a particle of ionizing radiation is incident on a material, there exists some probability that it will interact with the material and be attenuated. What happens as a result of this interaction is dependent upon several factors, including the type of particle, its energy, and the atomic number of the target material. The photoelectric effect for photons, Bremsstrahlung for β -particles, and elastic scattering for neutrons are several examples of specific interactions. The shielding equation below allows calculation of the efficacy of shielding.

$$I = I_0 e^{-\mu x},$$

where I is the radiation intensity after shielding, I_0 is the radiation intensity before shielding, μ is the linear attenuation coefficient, and x is the thickness material in centimeters. The linear attenuation coefficient is defined as the fraction of photons removed from the radiation field per centimeter of absorber through which it passes. Examples of shielding materials are Lucite, lead, and concrete.

Distance is an important safety factor in limiting radiation exposure. Because of their mass and electric charge, α - and β -particles have a high probability of interacting with matter, such as the atmosphere. The result is that these particles do not travel more than a few centimeters through air and, in general, moving a few feet from the source of this kind of radiation is enough protection by distance. However, x-rays and γ -rays are uncharged and have no rest mass, greatly reducing their probability of interacting with matter resulting in an unlimited range in space. Photon radiation that is emitted from a point source diverges from that source to cover an increasingly wider area. The intensity of this radiation follows the inverse square law:

$$\frac{I_1}{I_2} = \frac{(r_2)^2}{(r_1)^2},$$

where I_1 is the initial intensity, I_2 is the final intensity, r_1 is the initial distance from the source, and r_2 is the final distance from the source. For example, if the intensity of radiation 1 m from a source is 1 Gy, its intensity would be 0.11 Gy at 3 m from the source.

Time of exposure is another important safety factor in limiting radiation exposure. Obviously the longer a person is exposed to radiation the greater the exposure. The US federal and state regulations based on National Council on Radiation Protection and Measurement (NCRP) and US Food and Drug Administration (FDA) recommendations specify the limits of occupational exposure as well as exposure to patients designed to limit the potentially damaging effects of radiation.

Irradiation, Contamination, and Incorporation

An object is irradiated when it is exposed to ionizing radiation. One may be irradiated when handling radioactive isotopes, undergoing medical diagnostic imaging such as x-ray or CT, and rare exposures to criticality events. These sources of ionizing radiation generate particles that can penetrate tissue well and possibly cause tissue damage. Whole-body irradiation is one in which the entire body is exposed at once. However, more commonly shielding devices such as lead aprons, and collimation techniques used in radiotherapy limit the amount of exposed tissue to the intended target. The risk of tissue damage depends on the total amount of radiation and the tissue type because different tissue types have their own intrinsic resistance to radiation damage. An irradiated object does not become radioactive itself, unless exposed to neutrons and therefore irradiated individuals pose no risk to others.

The FDA approved irradiation of wheat and flour in 1963. They concluded from 40 years of study that irradiation is a safe and effective process for many foods to control bacteria such as *Escherichia coli*, *Salmonella* spp, and *Campylobacter* spp. Irradiation does not make food radioactive, compromise nutritional quality, or noticeably change the taste, texture, or appearance of food, as long as it is applied properly to a suitable product. Organizations that support irradiation of food include the American Medical Association (AMA), the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO).

Contamination occurs when a radioactive substance covers an object completely or in part. Several examples include a laboratory or industrial worker who unintentionally spills a radionuclide on clothing or skin or a victim of a radiologic dispersing device, a “dirty bomb,” in which a radionuclide is packaged with a conventional explosive and the resultant explosion disperses the radionuclide. In these similar cases, the source of radiation is the nuclide undergoing its normal decay process, and the individual is exposed to particles such as those mentioned in [Table 134–1](#). The risk for tissue damage from the radiation particles is usually quite low, assuming that the contamination is detected and appropriate measures for decontamination are instituted.

Incorporation occurs when a radionuclide is taken up by tissue via some route that permits the radionuclide to enter the body. This principle is used in many diagnostic and therapeutic procedures such as a thallium stress test, gallium scan, or thyroid ablation therapy. Depending on the dose and type of radionuclide, incorporation may lead to tissue damage, as was the situation for several people following the event at Goiânia.

EPIDEMIOLOGY

Everyone is exposed to radiation in one form or another each day (Table 134–2). In the United States, the estimated annual dose equivalent of radiation is now considered to be 6.2 mSv, a number revised sharply upward by the National Council on Radiation Protection and Measurements (NCRP) in 2009.²⁵ Although there are naturally occurring sources of radiation in the Earth's crust that make a significant contribution to our overall radiation exposure, the contribution from man-made sources of radiation, specifically medical exposures, has increased greatly over the last few decades, as discussed next.

TABLE 134–2. Annual Estimated Average Effective Dose Equivalent in the United States

Source	Dose ^a		
	mSv/year	mrem/year	% of total dose
Natural			
Cosmic	0.27	27	5
Internal	0.31	31	5
Radon ^b	2.29	233	37
Terrestrial	0.19	19	3
Subtotal	3.10	310	50
Man-Made			
Consumer products	0.12	12.4	2
Nuclear medicine	0.74	74.4	12
Occupational	< 0.01	0.62	0.1
Medical procedures	2.23	223.2	36
Subtotal	3.10	310	50
Total	6.20	620	100

^aAll doses are averages and contain some variability within the measurement. ^bAverage effective dose to bronchial epithelium.

mSv = millisieverts; mrem = millirem.

Data from Reference 25.

Exposures to man-made sources of radiation are not required to be reported to poison centers. Historically, those that have been reported have not resulted in significant morbidity. The American Association of Poison Control Centers National Poison Data System reported a total of 4203 exposures to radiation and radioactive isotopes over the last 14 years. Of the 267 exposures reported in 2010, 73% were unintentional, and 6% involved children younger than 6 years of age. There have been no deaths reported to poison centers from exposure to radioisotopes although three patients experienced a major effect, meaning either life-threatening or significant residual disability³ (Chap. 136).

Natural Sources of Radiation

A wide variety of natural sources expose humans on a daily basis to ionizing radiation. Terrestrial sources of radiation originate from radionuclides in the Earth's crust that move into the air and water. These primordial radionuclides, so named because their physical half-lives are comparable with the age of the Earth, include uranium, actinium, and thorium. Geographic areas vary regarding the content of these radionuclides.

Radon, a radioactive noble gas, accounts for most of the human exposure to radiation from natural sources. This gas, a natural decay product of uranium and thorium, enters homes and other buildings from the building materials themselves or through microscopic cracks in the building's structures. With a relatively short half-life of 3.82 days, ²²²Rn poses a health risk if decay occurs while in the respiratory space and one of its solid daughter isotopes deposits on respiratory tissue. These radon daughters emit α -particles as they decay and are the principle causes in the associated increased incidence of lung cancer in those exposed to radon. The risk of lung cancer is further increased in heavy smokers who additionally expose their lungs to as much as 200 mSv from ²¹⁰Po, a radon daughter that is naturally found in tobacco smoke. The US Environmental Protection Agency (EPA) has recommended household-level intervention when ambient radon concentrations exceed 147 Bq/m³ (4 pCi/L). Individuals can test their own homes for radon with either short-term (< 90 days) or long-term (> 90 days) commercially available measurement devices.

The second largest natural source of radiation originates from ingested radionuclides, of which ⁴⁰K, a naturally occurring isotope is the most abundant. Potassium is the seventh most abundant element in the earth's crust, and ⁴⁰K

represents about 0.012% of this naturally occurring element. With a half-life of 1.3 billion years, ⁴⁰K decays via β emission and electron capture. Since it is part of the environment, the average amount of ⁴⁰K in the body is about 3700 Bq (0.1 μ Ci), delivering about 0.18 and 0.14 mSv to soft tissue and bone, respectively. The lifetime cancer mortality risk has been calculated for ⁴⁰K to be 4 in 100,000 from external exposure compared with one in five from the group predicted to die of cancer from all other causes per the US average.

Man-Made Sources

The 2009 publication of the NCRPs sharply increased the estimated annual dose of radiation exposure due to man-made sources of radiation largely from the steeply rising use of CT (Table 134–3).²⁵ Evolving contemporaneously with the computer, CT technology has become extremely user friendly, contributing to the estimate that more than 70 million CT scans were performed in the United States during 2005 and 2006 compared with about 3 million scans in 1980, accounting for more than one-half of the man-made collective dose.^{2,23,38} Concern over potential cancer risks stemming from this new volume of exposure centers on children where doses are higher despite increasing practice to tailor scans to the size of the patient, and also because their relatively longer lives makes children more likely to manifest a slowly developing cancer. One retrospective study conducted in Great Britain through the National Health Service over 7 years examined data for more than 175,000 young patients each in two groups with certain leukemias and brain tumors.²⁷ Based on typical machine settings and estimated absorbed doses, this study found an increased relative risk of these cancers resulting from accumulated doses of just a few CT scans. Importantly, this was one of very few studies that did not rely on extrapolated data from atomic bomb survivors.²⁷

TABLE 134–3. Diagnostic Imaging Procedures: Type and Amount of Radionuclide or Radiation

<i>Test</i>	<i>Radionuclide</i>	<i>Amount MBq / mCi</i>		<i>Effective Dose mSv mrem</i>	
Thyroid scan	¹²³ I	25	0.68	1.9	191
Cardiac stress-rest test	²⁰¹ Tl	185	5	40.7	4070
Lung perfusion	^{99m} Tc	185	5	2.0	200
Lung ventilation	¹³³ Xe	740	20	0.5	50
Bone	^{99m} Tc	1110	30	6.3	630
Gallium	⁶⁷ Ga	150	4.05	15	1500
Tumor (PET)	¹⁸ F	740	20	14.1	1410
Plain Radiographs					
Posteroanterior and lateral study of the chest				0.1	10
Abdomen				0.7	70
Pelvis				0.6	60
Lumbar spine				1.5	150
Endoscopic retrograde cholangiopancreatography				4.0	400
Computed Tomography					
Head				2	200
Cervical spine				3	300
Chest				7	700
Chest for pulmonary embolism				15	1500
Abdomen				8	800
Pelvis				6	600
Coronary angiography				16	1600

MBq = megabecquerel; mCi = millicuries; mSv = millisievert; mrem = millirem.

Data from Reference 22.

Overall use of other non-CT radiologic studies has increased greatly over the last decades as well. Estimates show 377 million radiologic procedures in the United States in 2006, not including more than 500 million dental radiologic examinations, although these examinations are not thought to contribute significantly to the overall accumulated dose. Nuclear medicine scans, particularly in the field of cardiology diagnostics, increased sharply as well and accounts for 4% of all radiologic procedures and 26% of the total collective dose.²¹

Nuclear Occupational Exposure. Estimates of the annual number of workers occupationally exposed to radiation worldwide are several million.³³ On average, those occupations with the highest exposures (about 4 mSv/year) are uranium miners and millers. Overall, as of 1994 the average annual effective dose to monitored workers in the nuclear fuel industry dropped from 4.1 to 1.8 mSv, mainly due to a large decline in underground mining. Despite the many factors that play a role in occupational exposure at more than 1200 nuclear reactors worldwide, the estimated annual effective dose to measurably exposed workers fell to 2.7 mSv.

Medical occupational exposure principally includes physicians, nurses, x-ray technologists, and laboratory workers who receive an additional annual effective dose of about 0.5 mSv, which is down from about 1 mSv 25 years ago, possibly due to efforts to improve protection practices. Exposures have been studied in emergency physicians, orthopedists, and interventional cardiologists.^{15,35} Each of these fields uses different modalities of radiation, which pose different risks to the individual performing the procedure. Although older studies suffered from various limitations, small sample sizes, and unreported compliance with recording devices, several recent studies support the older conclusions that while physicians in the emergency department are exposed to radiation from conventional radiography the doses are typically on the order of 0.5 mSv (50 mrem) per year. These doses are well below the upper limits of exposure set by the Nuclear Regulatory Commission (NRC).^{9,11,12,37} Future exposures may actually decline due to increased use of CT for trauma patients in which physicians are in the control room while scanning is in progress. Thus, although the number of CT scans performed continues to rise, the radiation exposure to staff remains low due to collimation and low scatter, as well as proper shielding in properly designed facilities.

Fluoroscopy constitutes less than 10% of all examinations in the United States but remains the largest source of occupational exposure in medicine. Studies of physician exposure to radiation by fluoroscopy used in various procedures including interventional cardiology, nephrolithotomy, vertebroplasty, extremity nailing, biliary tract, and others report effective doses ranging from 1 to 100 μ Sv (0.1–10 mrem). Depending on the procedure, doses to the hands, brain, lens of the eye, and thyroid could be much higher placing physicians at greater risk of stochastic effects than is suggested by the effective dose.^{15,35} Estimated whole-body exposures to these procedures were considered not to exceed the limits established by the Occupational Safety and Health Administration (OSHA) of 50 mSv per year. Although the likelihood of exceeding established radiation limits is low regardless of the procedure, and even assuming a reasonable increase in the number of procedures performed, appropriate shielding and safety training are emphasized to minimize the risk of exposure.

Worldwide, nearly 500,000 workers are monitored for exposures during dental x-ray, but the annual effective dose averaged over 5 years has declined to 0.05 mSv. Well over 100 million nuclear medicine procedures are performed annually in the laboratory, but the exposures of this type are quite small.²¹

Depleted uranium (DU) is used by the US military and by several other governments. Uranium ore mined from the earth is about 99% ^{238}U and 1% ^{235}U . Enrichment involves separating the isotopes—for example, via high-speed gas centrifuge—so that ^{235}U can be used as nuclear fuel and the leftover ^{238}U can be used in munitions. Consequently, although DU is radioactive, it is 40% less so than naturally occurring uranium. External exposure to solid ^{238}U is considered to be negligible although currently many studies are investigating the potential link between DU and the incidence of leukemias, other cancers, and birth defects.¹ The Depleted Uranium Follow-Up Program has surveyed exposed veterans since 1994 has not discovered any consistent, clinically significant differences in uranium-health parameters, which includes hematopoiesis, neuroendocrine, and renal function.^{20,32}

EXPOSURE LIMITS

The NRC has established the “Standards for Protection against Radiation,” which regulates radiation exposures using a twofold system of dose limitation: doses to individuals shall not exceed limits established by the NRC, and all exposures shall be kept as low as reasonably achievable (ALARA). The total effective dose equivalent may not exceed 50 mSv/year to reduce the risk of stochastic effects (see Stochastic vs. Deterministic Effects of Radiation). The dose to the fetus of a pregnant radiation worker may not exceed 5 mSv over 9 months and should not substantially exceed 0.5 mSv in any 1 month.

REGULATION AND REPORTING

The use of ionizing radiation, radiation sources, and the byproducts of nuclear energy are among the most heavily regulated

processes worldwide. Regulations for medical use of radiation derive from multiple international and national organizations. Among the international groups are the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), International Commission on Radiological Protection (ICRP), Biological Effects of Ionizing Radiation (BEIR) Committee, International Commission on Radiological Units and Measurements (ICRU), Radiation Effects Research Foundation (RERF), and International Radiation Protection Association (IRPA). Since international organizations do not have the authority to enforce their recommendations worldwide, most countries have their own regulatory groups that cooperate internationally. In the United States, the NCRP reviews recommendations from the ICRP and makes recommendations. The NCRP issues BEIR reports that have direct standards for ionizing radiation use. For medical imaging standards, recommendations from the NCRP are considered to be guidelines with which all radiology departments must comply. The goal is to foster a radiation protection program that prevents deterministic effects. Additionally, the Conference of Radiation Control Program Directors (CRCPD) suggests state regulations for control of radiation.

National regulatory agencies include the NRC, EPA, OSHA, and the FDA. The NRC also runs an Agreement State Program, which is where states have had the authority to regulate transferred to them by the NRC. The US Department of Transportation (DOT) regulates transport of hazardous materials including radioactive material.

The NRC, the EPA, and many state governments share the responsibility of licensing and regulating radionuclides in the United States. The Oak Ridge Institute for Science and Education's (ORISE) supports the NRC by maintaining the NRC's Web site for Radiation Exposure Information and Reporting System (REIRS) and the database of radiation exposure from NRC licensees (<http://www.reirs.com/>). Individual states regulate radioactive substances that occur naturally or are produced by machines, such as linear accelerators or cyclotrons. The EPA oversees the general area of environmental monitoring of radiation. The FDA regulates the design and manufacture of electronic products, inspects diagnostic x-ray equipment, and establishes specific operational standards for x-ray equipment. The NRC regulates medical, academic, and industrial uses of nuclear materials generated by or from a nuclear reactor. OSHA regulates occupational exposure to radiation, oversees regulations for training programs and "right to know" regulations.

ORISE's Radiation Emergency Assistance Center/Training Site (REAC/TS) and the International Atomic Energy Agency (IAEA) both maintain radiation incident registries that track US and foreign radiation incidents. Information for the REAC/TS registries is gathered from many sources, including the WHO Radiation Emergency Medical Preparedness and Assistance (REMPAN), IEAE, state health departments, and medical and health physics literature.

PATHOPHYSIOLOGY

Ionizing radiation causes damage to tissue by several mechanisms called direct or indirect effects. Direct effects are when particles physically damage the DNA in a cell, which can occur at the sugar phosphate backbone, hydrogen bonds, or base molecules. Although any type of radiation may cause this damage, high LET radiation is more likely to cause direct effects owing to its greater probability of interacting with DNA. When this kind of damage occurs a mutation may arise, which may then result in alteration of a germ line, development of a neoplasm, or cell death. The risk of these consequences overall, however, is low because of the relative paucity of DNA within a cell, the even smaller percentage of active DNA within a given cell, and the ability of DNA to repair itself.

While DNA represents a low probability target for radiation, the rest of the cell media represents a higher probability target. Indirect effects are when radiation impacts a molecule and creates a reactive species, which then chemically reacts with organic molecules in cells altering their structure or function. These radiation-induced ions are unstable, however, and usually convert to free radicals. Water, which is in great abundance within cells may transform into a hydroxyl radical ($\text{OH}\cdot$) following interaction with incident radiation. The hydroxyl radical diffuses only a short distance through the cell because of its highly reactive nature and itself causes molecular damage. Indirect effects are predominantly caused by low LET radiation (x-rays, γ -rays, and fast electrons).

The bystander effect refers to cellular damage in unirradiated cells that neighbor irradiated cells. As early as the 1940s, there were reports of inactivation of cells by ionization of the surrounding medium. Recently, the use of a single-particle microbeam (a device that can fire a predefined exact number of α -particles through a particular cell nucleus) demonstrated that cultured cells that were not hit by radiation showed increased chromosome damage, rearrangement, and rate of death. In one experiment, when 10% of cells on a dish were exposed to two or more α -particles, the resulting frequency of induced oncogenic transformation was indistinguishable from that when all the cells on the dish were exposed to the same number of α -particles.²⁴ Studies demonstrate the bystander effect for proton beams, x-rays, and low LET radiation.²⁸

Genomic instability is a single mutation followed by a cascade of further mutations altering the fidelity of genomic replication. This modification can be found in cell progeny many generations after irradiation and may have unpredictable outcomes in succeeding generations. Although many hypotheses have been suggested, it appears most likely that the instability is due to irreversible regulatory change in the network of cellular gene products.^{10,13,19}

Although any molecule may be damaged in a variety of ways that may lead to cell injury of varying severity, double-stranded breaks in DNA are the type of damage most likely to cause chromosomal aberrations or cell death. The

radiosensitivity of the cell is directly related to its rate of proliferation and inversely related to its degree of differentiation.

Thousands of these types of lesions occur daily in the human body. There are several mechanisms by which the body can affect its own repair, which forms the basis of fractionated radiation therapy, taking advantage of less efficient repair mechanisms of tumor cells. However, there is evidence that DNA damage induced by radiation is chemically different and more complex from DNA damage that occurs spontaneously, which contributes to a higher rate of mutation than that resulting from spontaneous damage. Dose-response relationships for mutation are approximately linear down to about 25 mGy, the statistical limit of these studies. Although repair mechanisms reduce substantially the radiation risk of mutation, there is no evidence yet that these mechanisms eliminate those risks at low doses, although some question this conclusion.¹⁶

STOCHASTIC VERSUS DETERMINISTIC EFFECTS OF RADIATION

The radiation damage just described has two consequential results: it kills cells or it alters cells and causes cancer. Injuries that do not require a threshold limit to be exceeded include mutagenic and carcinogenic changes to individual cells where DNA is the critical and ultimate target. This is the stochastic effect of radiation. Theoretically, there is no dose of radiation too small to have the potential of causing cancer in an exposed individual.

Whereas the stochastic effects of radiation may follow less severe exposures, the deterministic effects of radiation usually follow a large whole-body exposure, such as a Chernobyl-type event. In terms of cell death, a relatively large number of cells of an organ system must be killed before an effect becomes clinically evident. This number of killed cells constitutes a threshold limit that must be exceeded, and this is what is known as the deterministic or nonstochastic effects of radiation.

To illustrate the differences between stochastic and nonstochastic effects, consider a single α particle from ^{210}Po incorporated following exposure in a radon-contaminated household may impact an active segment of DNA in a patient's respiratory tract, ultimately giving rise to a cancer—the stochastic effect. In Tokaimura, Japan, following exposure to a criticality event, the most severely injured worker received 17 Sv of neutron- and γ -radiation and experienced so much cell death across so many systems in his body that he died well before any injured yet surviving cells could develop into a cancer—the deterministic effect.

ACUTE RADIATION SYNDROME

The US Army Medical Corps first described ARS in 1946 when victims of the explosions at Hiroshima and Nagasaki were admitted for treatment at Osaka University Hospital.¹⁴ Understanding the features of ARS is essential for managing a patient who is exposed to massive whole-body irradiation, generally considered to be 1 Gy (160 times the average annual exposure) or more. In many cases, a reliable estimate of the radiation dose is difficult making it more practical to focus on the clinical features of radiation injury and their prognostic utility.

ARS involves a sequence of events that varies with the severity of the exposure.³⁶ Generally, more severe exposures lead to more rapid onset of symptoms and more severe clinical features. Four classic clinical stages are described, which begin with the early prodromal stage of nausea and vomiting. These symptoms begin anywhere from hours to days postexposure. Although the time to onset postexposure is inversely proportional to the dose received, the duration of the prodromal phase is directly proportional to the dose. That is, the greater the dose received, the more rapid the onset of symptoms, and the longer their duration, except in cases in which death follows rapidly. The latent period follows next as an apparent improvement of symptoms, during which time the patient appears to have recovered and has no clinically apparent difficulties. The duration of this stage is inversely related to dose and may last from several days to several weeks. The third stage usually begins in the third to fifth week after exposure and consists of manifest illness described in subsequent paragraphs. If the patient survives this stage, recovery, the fourth stage, is likely, but may take weeks to months before it is completed. Those exposed to supralethal amounts of radiation may experience all the phases in a few hours prior to a rapid death.

These four stages describe the clinical manifestations that may be observed as a result of massive exposure, but the various systems of the body manifest their own injuries, which constitute several subsyndromes. These subsyndromes are not mutually exclusive of one another and may overlap as cell death or damage progresses. Once these subsyndromes are manifest, they may be irreversible.

The cerebrovascular syndrome describes the manifestations of injury to the central nervous system following massive irradiation. This syndrome, following exposure to doses of about 15 to 20 Gy or greater, is characterized by rapid or immediate onset of hyperthermia, ataxia, loss of motor control, apathy, lethargy, cardiovascular shock, and seizures. The mechanism of this injury may be a combination of radiation-induced vascular lesions and free radical-induced neuronal death and cerebral edema.

Despite autopsy evidence of some radiation-induced inflammatory changes to the heart, animal experiments demonstrate that the heart is relatively resistant to high doses of radiation. Cardiovascular shock is more likely because of systemic

vascular damage, which may later compound shock resulting from other subsyndromes should the patient survive to that point. A “vascular radiation subsyndrome” might be considered to help explain the hemodynamic changes a patient experiences following a massive dose of radiation.

The pulmonary system is not spared injury from irradiation. Pneumonitis may occur within 1 to 3 months following a dose of 6 to 10 Gy. This may lead to respiratory failure, pulmonary fibrosis, or cor pulmonale months to years later.

The gastrointestinal syndrome begins following an exposure to about 6 Gy or more when gastrointestinal mucosal cell injury and death occur. Findings and effects include anorexia, nausea, vomiting, and diarrhea. As the mucosal lining is sloughed, there is persistent bloody diarrhea, hypersecretion of cellular fluids into the lumen, and a loss of peristalsis, which may progress to abdominal distension and dehydration. Destruction of the mucosal lining allows for colonization by enteric organisms with ensuing sepsis.

The hematologic changes that occur following an exposure to about 1 Gy or greater are called the hematopoietic syndrome. Hematopoietic stem cells are highly radiosensitive, in contrast to the more mature erythrocytes and platelets. Lymphocytes are also radiosensitive and can die quickly from cell lysis following an exposure. This contrasts with granulocytes, which endure radiation better. In addition to stem cell death and white cell depletion with immunodeficiency, platelets are consumed in gingival and gastrointestinal microhemorrhages. The main effect of radiation-induced hematopoietic syndrome is pancytopenia leading to death from sepsis complicated by hemorrhage. The lymphocyte nadir typically occurs 8 to 30 days postexposure, with higher doses achieving earlier nadir.

The cutaneous syndrome, a local radiation injury, may develop early after exposure or may take years to manifest fully. Target cells include all layers including epidermis, hair follicle canals, and subcutaneous tissue. Signs and symptoms may include bullae, blisters, hair loss, pruritus, ulceration, and onycholysis. Skin injury ranges from epilation beginning at doses of 3 Gy to moist desquamation at about 15 Gy, to necrosis at 50+ Gy.

DOSE ESTIMATION

Determining the dose received by an individual who was irradiated is important in providing appropriate therapy and establishing a prognosis. Estimating the dose received is difficult for a number of reasons, such as the absence of a radiation-monitoring device, exposure to radiation of mixed form (such as γ and neutron radiation), and partial shielding of various body parts.

Biodosimetry is the use of physiological, chemical, or biological markers to reconstruct radiation doses to individuals or populations. Today there are numerous tools available on the Internet to assist with dosimetry, including the Biological Assessment Tool available at the Armed Forces Radiobiology Research Institute’s Web site, guidelines from the International Atomic Energy Agency, and the Radiation Emergency Medical Management Web site. Key elements of dose estimation include time to onset of vomiting, lymphocyte depletion kinetics, and chromosomal assays.

Postincident vomiting can be a sign of the ARS prodrome. Unfortunately, the incidence of vomiting in patients with significant exposure is not 100% and may also be a sign of psychological stress contributing to inaccurate estimation, especially at low doses. Fortunately, for the purposes of dosimetry lymphopenia is common following an exposure to 1 Gy or more. The observed predictability of lymphopenia has led to the development of several models for biodosimetry. Although dosimetry models are validated and account for potential modifiers such as trauma or burns, discrepancies between models suggest that more than one element of dosimetry be used whenever possible. Combining emesis and lymphopenia in a triage tool developed at REAC/TS helps to distinguish patients exposed to high dose from those exposed to less than 1 Gy.

$$T = N/L + E,$$

where T is the triage score, N/E is the neutrophil/lymphocyte ratio, and E is whether emesis has occurred. E equals 0 if no emesis and E equals 2 if emesis. Based on cases from the REAC/TS registry, for times longer than 4 hours postevent, if T is greater than 3.7, then the patient is deemed at risk to high dose exposure and should receive a further evaluation.

The broad ranges of radiation doses that correlate with lymphocyte count are described in the classic Andrews nomogram of 1965. Again, using historic data from exposed patients, a lymphocyte depletion constant was calculated using the equation

$$L(t) = L_0 e^{-K(D)t},$$

where L(t) is the lymphocyte count at time t, L_0 is the lymphocyte count prior to the exposure—the population mean taken as 2.45×10^9 cells/L—K is the rate constant for a given dose of radiation, and D is the dose of radiation. Solving for K(D) will allow for an accurate estimate of a rapidly delivered, whole-body exposure.

Although there are still other methods of biodosimetry, such as interphase aberrations assessment and electron spin resonance of dental enamel, measurement of chromosomal aberrations has become the gold standard. Introduced in 1966,

this technique analyzes the number of dicentric chromosomes that occur following a whole-body exposure to radiation. An exposure to radiation can cause breakage of the DNA molecule in two nonhomologous chromosomes and produce “sticky ends” that recombine end-to-end. In metaphase, these appear as a single chromosome with two centromeres and are called dicentric. The number of dicentrics in lymphocytes correlates reliably with a given dose of radiation. This assay conforms to International Organization for Standardization (ISO) but suffers from several drawbacks including reduction of cells for assay in the setting of proliferative cell death, and migration of lymphocytes into tissue and the lymphatic system, both limiting the time available to perform an accurate test. Other methods include the cytokinesis-block micronucleus (CBMN) assay where other unstable aberrations form but disappear over time, and premature chromosome condensation assay where chromosomes are stimulated to condense prematurely for evaluation of radiation-induced damage. This assay can detect higher doses than dicentric analysis but has yet to be validated and standardized. The translocation assay uses fluorescence in situ hybridization (FISH) chromosome-painting technique and is used primarily for estimating doses of historical exposures. Unlike dicentrics, complete translocations persist in cell Division and enable dose estimation over years following exposure. In fact, when this technique was employed to evaluate the radiation dose experienced by clean-up workers at Chernobyl, the authors concluded that it was likely that recorded doses for these cleanup workers overestimate their average bone marrow doses, perhaps substantially.¹⁷ Unfortunately, these techniques are not widely available, require incubation times of 48 to 72 hours, and cannot assess for doses greater than 5 Gy.

CARCINOGENESIS

Radiation was recognized as a carcinogen soon after it was initially discovered in 1895. Following decades of research including animal models, epidemiologic studies, and the life-span studies of Japanese nuclear bomb survivors, radiation was shown to be a “universal carcinogen” able to induce tumor in nearly every tissue type in nearly every species at all ages. In fact, radiation’s ability to induce cancer is so well established that the last three decades of research has used radiation-induced tumors to focus on DNA damage and repair mechanisms.

Double-stranded breaks are the biologically important lesion for inducing tumors. Although radiation can induce point mutations, it can also induce deletions, sometimes of an entire gene. Research on transcription-coupled repair, where the transcribed strands of expressed genes are more rapidly repaired than the rest of the genome, were shown to be repaired most often by an illegitimate recombination process that is error-prone. This loss of heterozygosity suggests that radiation-induced carcinogenesis may more likely result from inactivation of a tumor suppressor gene than activation of a proto-oncogene.¹⁸

COMMONLY ENCOUNTERED RADIONUCLIDES

Most patients who come to medical attention are not exposed to large, whole-body irradiation but rather to small spills in the laboratory or inadvertent exposures from one of many products that are commercially available. With the notable exception of a well-known case of massive americium contamination in Oak Ridge, Tennessee, and the cesium exposure in Goiânia, Brazil, the vast majority of these types of cases are not reported in the medical literature.

Americium (symbol Am, atomic number 95, and atomic weight 243) was discovered in 1944 in Chicago during the Manhattan Project. Its most stable nuclide, ²⁴³Am, has a half-life of more than 7500 years, although ²⁴¹Am, with a half-life of 470 years, was the first americium isotope to be isolated. It decays by α and γ emission and will accumulate in bone if incorporated. It is used to test machinery integrity, glass thickness, and in smoke detectors (about 0.26 μ g per detector), where it ionizes the air between two electrodes and generates an electric current that soot may impede. α -Particles from these detectors are easily absorbed within a few centimeters of the surrounding air and pose little risk. One gram of americium dioxide provides enough americium for more than 5000 smoke detectors. In 1976, a worker at the Hanford Plutonium Finishing Plant suffered a large ²⁴¹Am contamination in an explosion at the site. The patient was contaminated with 100 g or 70 MBq (500,000 smoke detectors’ worth) in the explosion. He was treated with long-term pentetic acid (DTPA) and, despite some leukopenia from the radiation, he survived for 11 years before dying from unrelated cardiac disease.

Cesium (symbol Cs, atomic number 55, and atomic weight 132) was discovered by Bunsen in 1860. It decays by β and γ emissions and tends to follow the potassium cycle in nature. It is used as a radiation source in radiation therapy and as a radionuclide source for atomic clocks. Cesium, the radionuclide of the Goiânia incident, comes in the form of a powder, which would make dispersal relatively easy if used in a dirty bomb. Insoluble Prussian blue is the FDA-approved chelator for patients contaminated with cesium (Antidotes in Depth: A28).

Iodine (symbol I, atomic number 53, and atomic weight 126.9) was discovered by Courtois in 1811. Of the 23 isotopes of iodine ¹²⁷I is the only one that is stable. ¹²⁹I and ¹³¹I are fission products that may be released into the environment during an event. These isotopes will accumulate in thyroid tissue if incorporated and can cause local damage to thyroid tissue. It is this potential for incorporation that prophylaxis with potassium iodide (KI) is indicated in the event of a large exposure.

Polonium (symbol Po, atomic number 84, and atomic weights range from 192 to 218) was discovered by Marie Curie

while searching for the cause of radioactivity of pitchblende (uranium ore). It was named after her native country of Poland. Po has 27 isotopes, the most isotopes of all the elements and all are radioactive. Po is a very rarely occurring natural element where only 100 µg is found in a ton of uranium ore. Po is chiefly manufactured by bombarding ^{210}Bi with neutrons in nuclear reactors, and it exhibits several properties that make it extremely dangerous. The short half-life of ^{210}Po and high specific activity of 4490 Ci/g means it emits a great deal of high-energy α -particles (5.3 MeV) that produce 140 W/g. For example, a capsule containing 500 mg of ^{210}Po reaches a temperature of 932°F (500°C). It also demonstrates a high volatility where 50% vaporizes in 45 hours at 131°F (55°C) and can contaminate a relatively large area even when left alone. Although only a small fraction of absorbed ^{210}Po accumulates in tissue, cumulative doses of radiation can lead to organ systems failure and death. Animal data estimate an LD₅₀ of 1.3 MBq/kg, and that various mammalian species die within 20 days following ingestion of 1 to 3 GBq. Because of the extreme specific activity of ^{210}Po , this corresponds to a dose of about 0.01 µg/kg. Currently there are no specific chelating agents for ^{210}Po . While there are limited data regarding the effects of ^{210}Po on humans, Alexander Litvinenko's death within 22 days of his poisoning with polonium is similar to animal survival data.

Radon (symbol Rn, atomic number 86, and atomic weights range from 204 to 224) was discovered in 1900 by Dorn and is the heaviest noble gas. ^{222}Rn decays by α and γ emissions. Exposure of radon gas to the pulmonary epithelium is associated with an increased incidence of lung cancer in both uranium miners and in those who dwell in residences with increased concentrations of radon. Damage to bronchial epithelium results from the α emissions of radon and radiation from radon daughters that precipitate as solids and remain in the lungs. Good enclosed space ventilation, abstinence from cigarette smoking, and monitoring of radon concentrations help to minimize this risk.

Technetium (symbol Tc, atomic number 43, and atomic weight 98.9) was discovered in 1937 and was the first element to be produced artificially. Unusual among the lighter elements, Tc has no stable isotopes and is therefore found on earth as a product of spontaneous uranium fission. The majority of technetium is extracted from nuclear fuel rods and is used in nuclear medicine for imaging. $^{99\text{m}}\text{Tc}$ (the m is for metastable referring to an intermediate energy state) emits γ -rays of similar energy to diagnostic x-rays for easy detection and has a brief half-life of 6 hours. The daughter isotope, ^{99}Tc , has a half-life of 2.1×10^5 years and allows the isotope to be eliminated before it decays. Most human contact with Tc is in medical scans where Tc has a biological half-life of about one day. There are no reports of adverse effects resulting from overdose with Tc, and no specific therapy is recommended in that event.

Thallium (symbol Tl, atomic number 81, and atomic weight 204) was discovered by Crookes in 1861. ^{201}Tl is used for cardiac imaging, has a half-life of 73 hours, and decays by electron capture and γ emission. Pharmaceutical ^{201}Tl is created in a cyclotron by bombarding thallium with protons creating ^{201}Pb and is shipped in this form, which decays into ^{201}Tl . Since the radioactive decay process is continual, it is recommended to administer the ^{201}Tl close to its calibration time to minimize the presence and effects of other radionuclidic contaminants. Chelation can be accomplished with Prussian blue (Antidotes in Depth: A28).

Tritium is an isotope of hydrogen whose nucleus contains one proton and two neutrons, and its symbol is ^3H . Tritium decays by β activity and is used in basic science research as a radioactive label, for luminous dials, and self-powered exit signs, which may contain as much as 9.3×10^{11} Bq (25Ci). Tritium has a half-life of 12.3 years. Tritium emits very weak radiation in the form of 18.6 KeV β -particles, which are easily stopped by thin layers of material, and is safe for glow-in-the-dark watches. Tritium is not absorbed as a hydrogen gas, although, when in contact with oxygen it forms tritiated water, which can be absorbed via inhalation or transdermally. The estimated LD₅₀ is 3.7×10^{11} Bq (10 Ci) given its extreme specific activity of 9649 Ci/g. When absorbed as tritiated water, tritium tends to follow the water cycle in humans, providing a whole-body dose if incorporated. However, its biologic half-life is 10 to 12 days, which can be decreased by increasing urine output, greatly limiting its potential toxicity.

MANAGEMENT

Initial Assessment and Early Triage

The initial management of patients exposed to radiation will depend on a number of different factors, including the amount of radiation in the exposure and the number of casualties in the event. Small-scale exposures to radiation still require at least a brief evaluation for burns and trauma, depending on the circumstances surrounding the nature of the exposure. Calls to the poison center from a residence require referral to emergency services for an expert evaluation of the extent of the contamination of the site and appropriate decontamination measures. Exposures in the laboratory or nuclear medicine suites require referral to the radiation safety officer in the building for a similar evaluation.

When considering a local incident involving nuclear material, first responders will likely include a hazardous materials team (HAZMAT), local police and fire departments. Hospitals should involve their radiation safety officer (RSO) and public officials will involve a state agency such as the State Department of Environmental Protection. As part of its primary

mission for the US Department of Energy, REAC/TS offers consultation with anyone on a 24/7 basis on questions regarding radiation exposure. Its emergency phone number is 865-576-1005 (ask for REAC/TS). For large incidents, other federal agencies will be involved led by the Federal Emergency Management Agency. Additional radiation expertise can be provided via the Department of Energy, and if applicable the Federal Bureau of Investigation will protect against further threats.

In a mass-casualty event, established prehospital plans should be followed to provide the best management for the large numbers of variously injured given that the radiation exposure may also be accompanied by an explosion of potentially catastrophic size. First responders must use universal precautions and should assume that all victims are contaminated; most events will only require C-or D-level protection ([Chap. 131](#)). Field triage protocols tailored to the kind of event in question will designate patients as minor, delayed, immediate, or deceased and should not be altered because of radiation exposure.

Preliminary decontamination, including removal of clothing and washing the victim, should be performed before transportation to a medical facility taking care not to contaminate prehospital providers or equipment. Uninjured patients who are contaminated should be relocated upwind of the incident site for further care.

Initial Emergency Department Management

It is not considered a medical emergency to have been irradiated or contaminated; even highly irradiated patients take days to die, which is why standard protocols regarding trauma and other medical complaints continue to be followed, even in mass casualty events. In the event of a radiation incident, there will likely be little warning of these patients arriving and information will be incomplete. Ideally, the emergency department is divided into clean and dirty areas where the dirty area is covered by plastic or butcher's paper. Staff should don surgical scrubs, gowns, surgical caps, masks, and booties, as well as a face shield. Two sets of gloves should be worn with the inner set taped to the gown. Tape should also close the back of the gown and trousers to the booties. Dosimeters should be worn at the neck for easy access by the RSO and staff should be reminded that medical personnel have never received a medically significant acute radiation dose when caring for an exposed patient.

Due to the complex nature of radiation and contamination, it will be necessary to call upon the various consultation services, who will likely be a part of the hospital medical response team, that can lend their expertise. These services include burn specialists, dermatology, nuclear medicine, radiation oncology, hematology, toxicology, and the RSO.

When patients arrive to the emergency department (ED) it is critical to follow an algorithm that takes into account issues of irradiation or contamination and includes data collection specific to biodosimetry. One such algorithm is the REAC/TS patient treatment algorithm at <http://orise.orau.gov/files/reacts/radiation-patient-treatment-algorithm.pdf>. Important patient history includes their location during the incident, duration of the exposure, time interval between exposure and clinical evaluation, occupation of the victim, and also whether the patient has had a recent nuclear medicine procedure. Physical examination, in addition to airway, breathing, and circulation should focus on vital signs, skin (erythema, blisters, desquamation), gastrointestinal symptoms (abdominal pain and cramping), neurologic findings (ataxia, headache, motor or sensory deficits), and hematologic signs (ecchymoses or petechiae). Vomiting very early after exposure is considered a sign of the central nervous system (CNS) subsyndrome and is a poor prognostic indicator.

Initial laboratory testing should include baseline complete blood count (CBC) with differential (including an extra sample in a heparinized tube for cytogenetics), serum amylase (increased from specific salivary gland inflammation and degeneration), urinalysis, baseline radiological assessment of urine, and begin a 24-hour urine collection. Other laboratory tests, if possible, may include blood FLT-3 ligand levels, blood citrulline, interleukin-6, quantitative granulocyte colony-stimulating factor (G-CSF), and C-reactive protein. Nasal swabs, emesis, and stool may be collected for radiological monitoring. For patients with persistent vomiting erythema or fever, obtain a repeat CBC with differential every 4 to 6 hours. If a patient should require surgery, the Armed Forces Radiobiology Research Institute recommends that surgery proceed immediately because of the delayed and impaired wound healing associated expected decreases in leukocytes and platelets.

Decontamination

Once a patient is medically stable decontamination may proceed. Patients who were not decontaminated prehospitally but who are grossly contaminated should be fairly easily detected as such by a quick look with an appropriate instrument. As a first step all clothing should be removed gently by cutting and not tearing as is typically done for trauma patients. Rolling supine patients allows contaminated clothes to be carefully gathered and bagged and marked. Bagged clothes and other contaminated articles should be removed from the ED to a site designated by the RSO so as not to present another source of radiation. A portable dosimeter should assist in external decontamination. After clothing removal, re-monitor the patient for contamination paying attention to exposed areas such as hair. Contaminated hair should be washed with soap and water before washing the body to avoid trickledown contamination. For patients with contaminated wounds, decontamination should prioritize the wound first, then body orifices around the face, then intact skin. Always wipe gently away from the wound. Irrigate gently to reduce splashing. Care must be taken not to abrade skin by too vigorous scrubbing or shaving of

hair. Contaminated nares can be cleared often by having the patient blow his or her nose. Ideally, all irrigating fluids are collected for analysis but this will be limited by resources and event details. There should be no eating, drinking, or smoking at the scene of decontamination.

For patients with smaller exposures to radionuclides, such as laboratory workers, decontamination is often the only management technique required to limit injury. Portable dosimeters will identify contaminated areas, which may be sealed off to limit spread of exposure, especially if the radionuclide is in gaseous form. As with larger exposures, contaminated clothing must be removed and collected. Contaminated skin must be washed with lukewarm soap and water, repeatedly if needed.

In evaluating an area in which a spill of radioactive material has occurred, a judgment must be made regarding the severity of the incident so that appropriate steps are taken. If a major incident has occurred involving large amounts of radioactive material, a large contaminated area, airborne radioactivity, or spread of radiation outside an authorized area, evacuation, notification of the radiation safety officer in an institutional setting, and calling local or regional emergency response personnel are recommended. Minor incidents involve small amounts of radioactive material where the individual knows how to clean the site, has appropriate decontamination material on hand, and can clean the area in a reasonably short time. Several different decontaminating agents are commercially available from general stores and many scientific suppliers. These agents come in the form of concentrated detergents or foaming sprays where a small spill is quickly wiped clean and disposed of in an appropriate container.

Medical Decision Making

Exposure to radiation can lead to a complex spectrum of organ damage that can be difficult and confusing for physicians when creating a treatment plan. Establishment of guidance in the form of a response category (RC) helps clarify a medical plan and disposition (Table 134–4). Following exposure to radiation, quantitative and semiquantitative criteria can be used to describe different degrees of injury to affected organ systems. Combining descriptions of the patient’s severity among categories of hematopoietic, cutaneous, gastrointestinal, and neurovascular subsyndromes allows assignment of a grade of injury. For example, a patient with a third-degree cutaneous injury but only first- or second-degree injuries to the other systems would be given an RC grade of 3, giving the cutaneous injury the greatest weighting since its severity would then carry the worst prognosis. This RC grade then suggests a certain level of care whether ambulatory versus inpatient versus intensive care unit, as well as use of specific treatments such as blood transfusion versus colony-stimulating factors (CSFs) versus bone marrow transplantation. (For specific suggestions, refer to the interactive version of this assessment tool at the Radiation Emergency Medical Management Web site at www.remm.nlm.gov.) It is essential to remember that following a mass-casualty event, response assets from facilities to medications to personnel may be diminished significantly and that recommendations using this system may be modified in accordance with other recommendations concerning crisis standards of care.^{6,7}

TABLE 134–4. Grading System for Organ System Dysfunction and Response Category for Disposition

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
Neurovascular System				
Anorexia	Able to eat	Decreased	Minimal	Parenteral
Nausea	Mild	Moderate	Severe	Excruciating
Vomiting	1/day	2–5/day	6–10/day	> 10/day
Fatigue	Able to work	Impaired	Assisted ADL	No ADL
Fever	(< 38°C)	(38°–40°C)	(> 40°C) < 24 hours	(> 40°C) > 24 hours
Headache	Minimal	Moderate	Severe	Excruciating
Hypotension (blood pressure, mm Hg)	> 100/70	< 100/70	< 90/60	< 80 systolic
Cognitive deficits	Minor	Moderate	Major	Complete
Neurological deficits	Barely detectable	Easily detectable	Prominent	Life threatening
Hematopoietic System (all counts $\times 10^9/L$)				
Lymphocytes	1.5–3.5	0.5–1.5	0.25–1	0.1–0.25
Granulocytes	4–9	< 1 ^a	< 0.5 ^a	0–0.5
Platelets	150–350	50–100	0–50	Very low ^b
Gastrointestinal System				
Diarrhea				
Frequency (/day)	2–3	4–6	7–9	≥ 10
Consistency	Bulky	Loose	Loose	Watery
Bleeding	Occult	Intermittent	Persistent	Large, persistent
Abdominal cramps/pain	Minimal	Moderate	Severe	Excruciating
Cutaneous System				
Erythema	Minimal	< 10% BSA	10%–40% BSA	> 40% BSA
Edema	Asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Blistering	Rare, sterile	Rare, bloody	Bullae, sterile	Bullae, bloody
Desquamation	Absent	Patchy, dry	Patchy, moist	Confluent, moist
Ulceration/necrosis	Epidermal	Dermal	Subcutaneous	Muscle/bone
Hair loss	Absent	Partial	Partial	Complete
Response Category				
	1, Some 2	2	3	4
	Ambulatory		Hospitalization	
General supportive care, usually no specific therapy		Supportive care, blood products	Blood products, CSFs ICU	Blood products, CSFs, SCT Specialized hospitals ^c

^aAn absolute rise in cell counts begins between days 5 and 10, which lasts about 8 to 12 days. Afterward, cell counts decline slowly reaching a nadir around day 20. ^bCell counts decline faster reaching lower nadir for more severe exposures at about days 22, 16, and 10 for grades 2 to 4. ^c"Specialized hospitals" refers to those with experience in all areas of intensive care medicine, particularly allogeneic SCT.

ADL = activities of daily living; BSA = body surface area; ICU = intensive care unit; CSFs = colony-stimulating factors; SCT = stem cell transplantation.

Data from References 6 and 7.

Medical Management

Supportive care quality will determine the extent of the morbidity and mortality. The majority of patients with ARS who succumb usually do so from fluid loss, infection, or bleeding. Irradiated patients may require treatment for nausea and vomiting, diarrhea, pain, and fluid and electrolyte losses. Vomiting is thought to occur as a result of serotonin release from damaged gut tissue. The 5-HT₃ antagonists, such as ondansetron (0.15 mg/kg intravenous {IV}) or granisetron (10 µg/kg IV), are the most effective medications to control vomiting. Prolonged antiemetic treatment is usually not necessary since emesis often resolves within 72 hours. Loperamide, anticholinergics, or aluminum hydroxide can be utilized to treat diarrhea. Mild pain may be managed with acetaminophen, but aspirin and nonsteroidal drugs are not recommended as they may exacerbate gastric bleeding. An opioid is recommended for the management of more severe pain.

Probiotics is the introduction of selective nonpathogenic strains of *Lactobacillus* and *Bifidobacteria* into the gastrointestinal tract to suppress the number of pathogens. Experimentally, this technique increased survival in canine and

rodent models. Probiotics was used to help care for three men exposed at the incident at Chernobyl, whose survival time was prolonged, although it was not statistically significant when compared, respectively to case controls.^{4,34}

Intravenous access should be established and maintained with care as they are prone to infection. If the patient is expected to become neutropenic, then consider establishing central venous access or placement of a peripherally inserted central catheter. Fluid replacement may begin with crystalloid solution with the goal of replacing gastrointestinal losses. The infusion rate will be modified by recorded inputs and outputs and assessment of surface area burns.

Prevention of infection includes attention to several aspects of care. Maintain the patient in a clean environment and institute reverse isolation for patients with at least moderate exposure or when neutrophil counts decline below 1000/ μ L. Prophylactic antibiotics and antifungals should be considered for neutropenic patients, as well as acyclovir or a congener for herpes simplex virus positive patients. If neutropenic patients become febrile, follow Infectious Disease Society of America (IDSA) guidelines for antibiotic choices. Consider broad-spectrum prophylactic antibiotic coverage, including anaerobic coverage for patients with burns.^{6,8}

Cutaneous injuries are cared for depending on the nature, location, and extent of the wounds. Care ranges from use of soothing agents or topical steroids, to drying agents and debridement, to skin grafting. Use of pentoxifylline may assist with healing. Surgical consultation or referral to a burn center may be offered.

Cytokine therapy (colony stimulating factors {CSFs}) use in radiation-exposed patients is based on demonstrated enhancement of neutrophil recovery in patients with cancer, a perceived benefit in a small number of radiation-incident victims, and several prospective trials using different animal models involving radiation exposure. These last studies demonstrated not only neutrophil recovery but also a survival advantage. The best outcomes were demonstrated when started less than 24 hours postradiation suggesting CSFs should be started as soon as possible for patients exposed to a survivable dose of radiation who are at risk for hematopoietic syndrome, that is, more than 3 Gy. Additionally, patients at extremes of age, that is, those younger than 12 years and the elderly, are considered to be more susceptible to radiation and may benefit from CSFs when exposed to lower threshold doses.⁸

Use of blood products is required for patients with significant blood loss or for those experiencing radiation-induced aplasia. This latter complication usually begins several weeks following exposure allowing for time to identify potential donors. Use of leukoreduced and (ironically) irradiated blood products should be the rule to prevent transfusion-associated graft-versus-host disease. This hyperacute complication may be further complicated by its similarity to radiation-induced organ injury, including fever, pancytopenia, rash or desquamation, diarrhea, and hyperbilirubinemia.

Stem cell transplantation (SCT) may be used to treat patients with severe bone marrow injury, but appropriate use of this therapy is complicated by a number of issues. Currently, it is believed that with aggressive supportive care and early use of CSFs, patients merely suffering from hematopoietic syndrome may survive a radiation dose of 7 to 8 Gy, but doses greater than 10 Gy are likely to be fatal, providing a narrow window of opportunity, even if an appropriate match could be found. Additionally, there are complicating factors including the manner in which exposed dose was estimated, and other potentially significant concurrent organ injuries such as burns and acute respiratory distress syndrome, which historically have accounted for 70% of radiation deaths.⁶ When caring for the severely exposed patient, consultation with a hematologist is likely the best course when considering SCT.

Management of Internal Contamination

Internal contamination is assessed differently from external doses. First, internal doses are not measured but calculated. Calculations are performed by a health physicist on samples such as nasal swabs, urine, or stool to estimate how much activity entered the body. Doses are termed committed doses defined as the doses received that last more than 50 years due to the internal deposit of the radionuclide. That is, the radionuclide dose is protracted and remains until it decays or is eliminated via normal kinetic processes. These doses are compared with the annual limits on intake (ALIs) provided by the EPA as a benchmark for medical decision making. Interpretation of committed doses from contaminated wounds requires special conversion factors provided by the NCRP.

Management of internal contamination is isotope dependent. There are more than 8000 isotopes, thus making identification of the particular isotope in question critical. Although both radioactive decay and biologic elimination contribute to an even shorter effective half-life, medical treatment is directed at one of several categories including reduction of gastrointestinal absorption, blocking uptake (as with potassium iodide), isotopic dilution (water for tritium), chemical manipulation (sodium bicarbonate for uranium), excision of shrapnel, and chelation. Both NCRP reports 65 and 161 provide comprehensive information regarding decorporation of radionuclides; however, for the few isotopes of particular concern for industry, the military, and academic and medical centers, potassium iodide and pentetic acid (DTPA) would be the most commonly applicable chelators (Antidotes in Depth: A43 and A44).

PROGNOSIS

The prognosis of those exposed to radiation varies with the amount of the exposure, the type of medical care received, and

the number of casualties in a given exposure scenario. Survival is inversely proportional to the radiation dose absorbed, and even the relatively radioresistant cell types can be killed by high amounts of radiation. Historically, the mean lethal dose required to kill 50% of humans at 60 days ($LD_{50/60}$) was about 3.5 Gy without supportive care. The addition of antibiotics and blood products support increases that mean to 6 to 7 Gy. This dose may be even higher for those treated early with CSFs in a specialized hospital. Coexisting traumatic injuries or burns will decrease the $LD_{50/60}$. An acute dose of 20 Gy or more is considered supralethal. Historically, those who were exposed to greater than 10 Gy died despite care including one worker at Tokaimura who was exposed to 17 Gy who died 3 months postexposure, and 20 of 21 workers who were exposed to radiation in the 6-to 16-Gy range at Chernobyl. Some authors suggest that those exposed to 10 Gy or greater be given supportive and comfort care only because their survival is considered to be unlikely.^{5,36}

CONSIDERATION OF THE DECEASED

Contaminated bodies should be placed in a temporary morgue that is refrigerated. Use of the hospital morgue may lead to contamination there. These bodies should not be cremated since this will only redistribute the nuclear material, which is not destroyed by fire. Respect should be paid to the religious beliefs of family members of the deceased for whom cremation may be the custom.

PREGNANCY AND RADIATION

When exposure to radiation via medical examination is possible, pregnant women and physicians have exhibited great concern over possible injury to the fetus. In general, radiation effects to an embryo or fetus are dependent on its stage of development and the dose received. The medical decision to perform imaging or a diagnostic procedure that may expose any patient to radiation is always based on a risk–benefit analysis with a given patient’s situation.

In the normal course of events, uncertainty exists regarding the normal viability of the fertilized ovum where the baseline risks of birth defects and miscarriage are 3% and 15%, respectively, for women with normal genetic and reproductive history. Very early in a pregnancy before implantation the embryo is in an “all-or-none” period of development where the greatest risk from radiation is miscarriage, but not greater than baseline risk. Older than this, the fetus is next at greatest risk between 8 to 15 weeks where major neuronal migration takes place.

The NCRP considers risk to the fetus to be negligible compared with other risks of pregnancy when the dose to the fetus is less than 50 mGy (5 rad) which corresponds to 50 mSv from x-ray examination, compared with about 6 mSv effective dose from a CT examination of the pelvis. The risk of malformation is increased only at doses above 150 mSv. As mentioned earlier, special attention must be paid to pregnant or potentially pregnant patients when deciding if an examination or procedure involving radiation is considered. Effective doses from various examinations and procedures are known to range from 0.1 mSv from posteroanterior and lateral x-ray of the chest to 15 mSv from CT angiogram of the chest, to 40.7 mSv from cardiac stress test with ^{201}Tl . The vast majority of routine diagnostic imaging procedures imparts less than 5 mSv to the fetus, increasing baseline risk by about 0.17%, and so is considered to be of negligible risk, but consideration should always be given to the potential maternal benefit of the radiologic procedure and the potential risk to the fetus.

PEDIATRICS AND RADIATION

The use of CT scanning in children has markedly increased over the last 30 years. Estimates include data that, commensurate with the 20-fold increase in use of CT scans in the United States, the use of CT for pediatric patients has increased by about eight times. The reasons for this increase are many including greater availability, greater use as a primary diagnostic tool, and an increased perception that the risk of being wrong about a diagnosis is high.^{2,23} Other estimates calculate an increased risk of lifetime mortality in the range of 0.04% for a head CT for a young female patient (1 in 2500) compared with a normal cancer mortality risk of 20% (1 in 5). This excess relative risk was supported by a large retrospective study of a pediatric population that found increased incidence of certain leukemias and certain brain tumors attributed to CT scans over a 23-year period.²⁷

Although radiation is considered to be a weak carcinogen and radiographic studies should continue to be ordered in the best interest of the patient, it is likely that the number of scans performed could safely be diminished without compromising care. Reports on this topic commonly include problems with ordering unnecessary multiple CTs, follow-up CT scans, and CT scans that occur simply due to a lack of communication between patient, health care professional, and technician. These problems, compounded by inappropriate CT protocol for pediatric patients, suggest that the medical community could be more proactive in reducing the health risk of those in our charge.

SUMMARY

- Ionizing radiation injures humans through the disruption of cellular structure and function that can lead to cell death and or mutagenesis.
- Fortunately, large exposures of radiation to the general population are rare outside of the setting of an armed conflict and most contaminations that occur are small and easily controlled.
- Recognition of the exposure and thorough decontamination are the critical steps to minimizing the potential toxicity of an exposure.
- Prognosis is based on dose which can be estimated on a number of clinical and laboratory grounds.
- Although consequential, neither contamination nor incorporation should take precedence over the highest priorities of emergency care and urgent surgery.

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A43 ANTIDOTES IN DEPTH

Potassium Iodide

Joseph G. Rella

INTRODUCTION

Potassium iodide is the antidote to radioactive iodine that may be released into the atmosphere following a nuclear incident. It is approved as a specific blocker of thyroid uptake of radioiodine to reduce the risk of thyroid cancer in susceptible populations. The indications for its use are complex and initiation and maintenance of therapy require great attention to the details of the circumstances of the exposure to limit harm that may result from either undertreatment or overtreatment.

HISTORY

Following the study of thyroid cancers in Pacific Islanders who were subjected to fallout from nuclear testing, scientists concluded in 1957 that potassium iodide (KI) could effectively protect the thyroid from radioactive iodine. The National Council on Radiation Protection and Measurements (NCRP) reported in 1977 that the sudden release of radionuclides, including radioiodine, could affect large numbers of people following a nuclear incident (Fig. A43–1). The following year the US Food and Drug Administration (FDA) requested the production and storage of KI for the purpose of blocking the effects of radioiodine on the thyroid gland when needed.



FIGURE A43–1. The decay pathway that describes how ^{131}I is derived from nuclear fuel (whether in a bomb or a reactor) and ultimately decays to stable xenon. s = seconds; m = months; d = days.

PHARMACOLOGY

Chemistry

Iodine is a chemical element, symbol “I,” atomic number 53. Its name derives from the Greek *iodes* meaning violet, owing to the violet color of elemental iodine vapor. Like other halogens, iodine occurs mainly as a diatomic molecule I_2 . Although it is considered a relatively rare element, it is the heaviest essential element used widely in biologic functions. Of 37 iodine isotopes, only ^{127}I is stable. The term iodide refers to the ion I^- , which forms inorganic compounds with iodine that is in the oxidation state -1 , such as potassium iodide.

Mechanism of Action

Neonates, children, and adolescents are particularly susceptible to the toxic effects of radioactive iodine. During the growth periods for these groups there is increasing growth of the thyroid gland, as well as an increase in thyroglobulin and iodothyronine stores. Thyroid tissue also accumulates a larger percentage of exogenously ingested iodide and more efficiently reuses iodine from degraded hormone. This increased activity during these growth periods explains the greater risk for developing thyroid cancer in children compared to adults following exposure to radioactive iodine. During pregnancy, the maternal thyroid gland is stimulated and takes up more iodine compared to other adults, thus increasing susceptibility in pregnant women to the toxic effects of radioiodine.

Exposure to radioactive iodine may occur via inhalation or via ingestion of contaminated food, as occurred following the Chernobyl incident. Radioiodine may be rapidly absorbed from either the digestive or respiratory tracts. Once incorporated into the thyroid gland, radioiodine exposes thyroid tissue to β and γ emissions, potentially leading to genetic alterations and cancer.³ This is the stochastic effect of radiation (Chap. 134).

Because the chemical properties of radioactive iodine are unchanged from stable iodine, prophylaxis with KI is effective via isotopic dilution. That is, KI competes with radioactive iodine for the active iodine transport system to reduce or dilute the concentration of radioiodine in the serum making the uptake of radioiodine much less likely, essentially blocking it.

Evacuation and Food Interdiction. KI is not a panacea for radiation exposure. Even if appropriately used during a release of ^{131}I , KI will not protect against direct radiation exposure or against other radioactive elements that may be included in fallout (ie, cesium and strontium). Depending on radiation levels, communities may be evacuated from areas surrounding a nuclear power plant experiencing a release of radioactive material. Evacuation is most effective if implemented before the passage of a radioactive plume, but this should be guided by dose estimates provided by public health authorities.

The FDA and World Health Organization (WHO) both recommend food interdiction and food control as the principal means to limit public exposure to contamination. Contaminated food that is subsequently canned may ultimately pose no risk to the population if it is stored for sufficient time to allow the radioactive iodine to decay completely. The WHO considers food control to be preferable to iodine prophylaxis and the removal of milk from the diet of some populations to be unfortunate but acceptable.^{5,16}

Pharmacokinetics

Dietary iodine is well absorbed from the small intestine under normal conditions. It distributes selectively into the thyroid gland, but also to a lesser extent into salivary glands, choroid plexus, and gastric mucosa. Iodine has a volume of distribution of 0.3 L/kg. During pregnancy and lactation, iodine distribution to mammary glands and ovaries increases.

Iodide that is not concentrated in the thyroid is excreted 80% in urine and 20% in feces, although additional losses via sweat can occur and can become an important route of loss in warmer climates. Urine iodine concentrations reflect plasma concentrations and have been used for years as a means to assess dietary iodine intake.

Pharmacodynamics

Iodine, or its ionic form iodide (I^-), is an essential nutrient present in humans in minute total body amounts of 15 to 25 mg. Iodine is required for the synthesis of the thyroid hormones L-triiodothyronine (T_3) and L-thyroxine (T_4), which in turn regulate metabolic processes and determine early growth of most organs, especially the brain. Iodide is actively transported with sodium into thyroid follicular cells, where it is concentrated 20 to 40 fold compared with its serum concentration. It is then transported into the follicular lumen where it iodinates thyroglobulin to form T_3 and T_4 (Chap. 56). Thyroid hormones are metabolized in hepatic and other peripheral (meaning extrathyroid) tissues by sequential deiodination.

ROLE IN RADIOACTIVE IODINE EXPOSURE

Studies have shown over the last 50 years that radioactive iodine uptake can be effectively blocked by KI supplementation.² In nuclear radiology, administration of iodine containing contrast media can deliver up to 45 times the recommended daily intake of free iodine and delay the uptake of therapeutic ^{131}I for several weeks.^{7,15} Following the incident at Chernobyl, the Polish government distributed nearly 18 million doses of KI to the people in its most affected provinces (in addition to food interdiction), while none was distributed to affected areas of Ukraine and Belarus. Studies of these differently treated populations who were exposed to the radioactive plume clearly demonstrated not only a dose-response relationship between radiation dose and the relative risk of thyroid cancer, but also a threefold reduction of this risk via KI supplementation.^{3,9} Although some controversy exists regarding increased numbers of detected thyroid cancers possibly due to improved screening, other studies bear out the true increase in these tumors, and also distinguished by genetic analysis radiation-induced cancers from sporadic papillary cancers.^{1,10}

After the Fukushima incident, the Japanese government gave orders to distribute KI at evacuation sites, but this did not occur. Data on the aftermath of this event are still forthcoming. Interestingly, a shortage in the United States of commercially available KI existed at the same time.¹¹ Chernobyl remains the largest experience of KI distribution following a release of radioactive material from a nuclear incident from which data and recommendations are derived.

ADVERSE EFFECTS AND SAFETY ISSUES

Thyroidal Effects

Extensive experience with treating goiter and the use of nutritional supplements in the form of iodized salt has shown that both hyper- and hypothyroidism may result from supplementation with KI.¹³ Specifically, treatment with KI is linked to

occasional hyperthyroidism, and iodized salt programs have been associated with subsequent hypothyroidism and thyroid autoimmunity. Both the prevalence of goiter and subclinical hypothyroidism can increase when iodine intake is chronically high. The Wolff-Chaikoff effect, where high concentrations of iodine inhibit the synthesis of thyroid hormones, may be devastating to fetal neurologic development in pregnant women treated with KI, which is why both the FDA and WHO advise against repeat dosing of KI for pregnant women if possible.^{5,16}

A large study in Poland following the Chernobyl incident investigated the risks and benefits of KI prophylaxis. Of the thousands of men, women, and children who were studied, the vast majority of whom received a single dose of KI, no statistical differences were found between treated and untreated groups when thyroid stimulating hormone (TSH) concentrations were measured among all populations. Additionally, among adults with thyroid disease, no cases of thyrotoxicosis or exacerbation of preexisting thyroid conditions were found. Although pregnant women were not mentioned per se, children born in 1986 and examined in the second and third years of life showed no difference in thyroid status compared with those born after radioiodine was gone from the environment. In newborns, 12 of 3214 treated on the second day of life showed transient decreases in serum free T₄ but had no clinical sequelae.⁸ Another systematic review of studies reporting adverse effects of iodine used for thyroid blocking, which also did not mention pregnant women, concluded that KI supplementation seemed not to induce severe adverse effects, but also that scientifically sound studies of this subject are scarce and provide only weak evidence.¹³

Extrathyroidal Effects

Many extrathyroidal effects of KI are described. Sialadenitis, or iodide mumps, is an inflammation of the salivary glands and appears to be unpredictable. Iododerma is a rare and reversible acneiform eruption related to iodine ingestion that may result from nonspecific immune stimulation.¹¹ Other reactions reported in association with KI use include gastrointestinal disturbances, fever, and shortness of breath.

Although some reports use imprecise definitions when attributing adverse reactions to iodine or iodide-containing medications, “allergy” refers to a specific immune response to target proteins via an immunoglobulin E (IgE) triggered release of cell mediators, such as histamine. There are no studies that demonstrate IgE antibodies to small molecules such as iodine or iodide.

“Allergy” to radiocontrast media is actually an anaphylactoid response to the high osmolality of these xenobiotics. Anaphylactoid responses manifest by release of similar mediators to anaphylactic response but via non-IgE-mediated pathways. An anaphylactoid response to iodine-containing medications or iodinated contrast materials may be predicted in patients with asthma, allergic rhinitis, and food allergies to chocolate, eggs, and milk. While seafood may contain iodine, allergy to fish or shellfish is due to specific marine proteins and not sensitivity to iodine. Patients manifesting allergic contact dermatitis resulting from iodine containing cleaning preparations such as povidone-iodine do not react to patch testing with KI. Therefore, when physicians consider the safety of KI dosing in the event of radioactive iodine exposure, reactions to radiocontrast media, seafood, and povidone-iodine should not be interpreted as an allergy to KI. Physicians must also consider that there are inactive ingredients or diluents of the KI formulation.

PREGNANCY AND LACTATION

Potassium iodide is listed in pregnancy category D and readily crosses the placenta and distributes into milk. Both the FDA and WHO support the use of KI for pregnant women when instructed to do so by public health authorities.^{5,16}

DOSING AND ADMINISTRATION

After reviewing data from Chernobyl regarding estimated doses and cancer risks in exposed children, the FDA provided recommendations for KI supplementation for various populations, depending on their relative risks (Table A43–1).^{5,16}

TABLE A43–1. Threshold Radiation Exposure Doses and Recommended Potassium Iodide KI Doses for Different Risk Groups

	Predicted Thyroid Exposure		KI Dose (mg)	Number of 130 mg Tablets	Milliliters of Oral Solution, 65 mg/mL
	Gy	rad			
Adults > 40 years of age	≥ 5	≥ 500	130	1	2
Adults 18–40 years of age	≥ 0.1	≥ 10	130	1	2
Pregnant or lactating women	≥ 0.05	≥ 5	130	1	2
Children and adolescents 3–18 years of age ^a	≥ 0.05	≥ 5	65	1/2 ^a	1
Children 1 month–3 years of age	≥ 0.05	≥ 5	32	Use KI oral solution ^b	0.5
Children birth to 1 month of age	≥ 0.05	≥ 5	16	Use KI oral solution ^b	0.25

^aAdolescents approaching adult size (70 kg) should receive a full dose of 130 mg. ^bFor smaller, more precise dosing, a KI oral solution is available with a dropper marked for 1, 0.5, and 0.25 mL dosing.

Source: FDA website.¹

Adults older than 40 years of age face a near-zero risk of developing thyroid cancer from exposure to radioactive iodine. For this group, the complications from iodide supplementation, such as goiter or Graves disease, would likely outweigh any benefit in the setting of relatively mild exposure. However, if public health experts determine that exposure dose may be 5 Gy (500 rad) or greater, which is only likely to occur for those living within a 10 mile radius of a nuclear power plant release, KI is recommended.

Adults 18 to 40 years of age are at risk of developing thyroid cancer that is approximately equal to the risks of side effects of a single dose of iodide supplementation, although it should be understood that both risks are very small. The decision to treat should be based upon the threshold criteria used as well as the risks of iodine supplementation, such as iodine reactions, or a history of past thyroid disease.

Lactating mothers should take KI when instructed to do so by public health authorities. KI is secreted in breast milk and will offer some protection to a neonate, but the risks of treatment are much higher in these patients requiring greater attention to monitoring, as discussed below.

Pregnant women have increased thyroid uptake of iodine, especially in the first trimester, compared with other adults. The developing fetus has increased iodine uptake during the second and third trimesters. Because iodine crosses the placenta, the fetus may potentially be exposed to radioactive iodine, thus supplementation with KI is only recommended at appropriate exposure thresholds.

Children 1 month to 18 years of age are at high risk of thyroid cancer from exposure to radioactive iodine and are at low risk of side effects from supplementation with KI. Therefore, supplementation for children in this age group should begin promptly following official notification of a potential radioactive iodine release.

Neonates are at significantly increased risk from exposure to radioactive iodine because of a marked increase in uptake of iodine resulting from neonatal body cooling in the immediate postdelivery period. At the same time, neonates are susceptible to functional blocking by overloading with stable iodine. Therefore, when supplementation is indicated, KI should promptly be given to neonates with critical attention to dosing. The WHO recommends the KI solution be available for maternity wards in the precise dosing for newborns. Since the most critical time period for thyroid blockage is within the first postpartum week, dosing neonates who are older than one week may be performed at home via dividing, crushing, or suspending tablets in milk, formula, or water.

Timing of Administration

For full blocking effect, KI should be administered shortly before exposure or as soon as possible afterward. Some models describe the blockade of only 50% of iodine uptake when there is a delay of several hours following an exposure.⁶ Depending on the duration and type of risk, administration of KI months after an exposure may also partially reduce thyroid cancer risk.^{6,17}

Daily Versus Single Dosing

The protective effect of potassium iodide lasts for about 24 hours, so it should be dosed daily for those groups in whom an ongoing risk is perceived. Depending on the dosing estimates for exposure, this group is primarily children aged 1 month to 18 years. Groups in whom a single dose is recommended include pregnant women and neonates, where there is a significant risk of causing harm to the fetus via impaired cognitive development. For lactating women, stable iodine will be delivered to the nursing newborn and may cause functional blocking of iodine uptake by an overload of iodine. Therefore, the FDA recommends that lactating mothers not receive repeated doses except during continuing, severe contamination, which would generally be defined by health officials.

As mentioned previously, Chernobyl is the most significant massive release of radioiodine in history and nearly all of our experience and recommendations in this type of setting derive from this one event. Although distribution of radioiodine was uneven in Poland, the air concentration of radioiodine had decreased fourfold one week after the first explosion. Therefore, KI prophylaxis was not repeated. It is perhaps based on this experience that it is generally thought that no more than one or two doses of KI would be needed following release of a single radioactive plume, during which other protective measures such as food interdiction or sheltering measures are implemented. While the possibility exists that many repeated releases of radioactive gas might require prolonged prophylaxis, repeat dosing for days to weeks may not be necessary.

Monitoring

Normal thyroid function is critical for proper brain development in a fetus. Just as a fetus and newborn is susceptible to radioiodine uptake, they are also at risk for development of hypothyroidism from repeat dosing of KI. All neonates who are treated with KI in the first weeks of life should be monitored for changes in thyroid stimulating hormone (TSH) and free T₄. Likewise when a lactating mother requires repeat doses of KI, the nursing infant should also be monitored for the development of hypothyroidism.

FORMULATION AND ACQUISITION

Several manufacturers formulate potassium iodide and market them as nonprescription, FDA approved products with a shelf life of 7 years. Longevity studies over many years have demonstrated the active ingredients of KI to be very stable. Recognizing that many state and local governments maintain stockpiles of KI for use in the event of a radiation emergency (KI is a part of the US Strategic National Stockpile (SNS), which consists of a large quantities of medications and supplies ready for use in a public health emergency), the FDA has developed guidelines for shelf life extension that manufacturers may use to extend the shelf lives of their products in increments of 2 years.⁴ Tablets are available in both 130 mg and 65 mg doses, as well as an oral solution in a concentration of 65 mg/mL. Iodide containing products not considered useful in radioiodine protection include iodized salt, seaweed, and tincture of iodine.

SUMMARY

- KI is a safe and effective means of blocking the uptake of ¹³¹I following a nuclear catastrophe.
- Firm reliance on the evaluation of health officials of the risk of exposure is vital since the overall likelihood of exposure to the critical radiation threshold is very low, except for those living within 10 miles of a nuclear reactor.
- Exposed persons should strictly adhere to dosing guidelines to minimize the potential risks of KI dosing, especially in pregnant women and newborn children.
- “Iodine allergy” is not a contraindication to KI administration in the setting of a confirmed release of radioactive iodine.
- Food interdiction and environmental evacuation or avoidance of the radioactive plume are preferable to KI prophylaxis in the event of a potential exposure and may obviate the need for KI completely.

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A44 ANTIDOTES IN DEPTH

Pentetic Acid or Pentetate (Zinc or Calcium) Trisodium (DTPA)

Joseph G. Rella

INTRODUCTION

Pentetate zinc trisodium and pentetate calcium trisodium (zinc or calcium diethylenetriaminepentaacetate; Zn-DTPA and Ca-DTPA, respectively) are chelators for certain heavy metals and radionuclides. They are approved for the treatment of internal contamination with plutonium, americium, and curium that may occur following unintentional exposure to these metals or following exposure resulting from a radiation dispersal device or “dirty bomb.”

HISTORY

First synthesized in 1954, these chelators were used investigationally to enhance elimination of transuranic elements ([Chap. 12](#)).³ DTPA has been used for the extraction of metals from soil and as a treatment for iron overload and lead toxicity.^{2,8,21} DTPA and its derivatives have also been used to help with imaging and diagnostics and more recently in chemotherapeutics. Over the last decades, hundreds of human exposures to radionuclides as well as numerous animal studies helped to define the best practices for the use of these chelators, culminating in their approval by the US Food and Drug Administration (FDA) in 2004.

PHARMACOLOGY

Chemistry

Pentetic acid is a synthetic polyaminopolycarboxylic acid with a molecular weight of 393 Da; the calcium trisodium salt weighs 497 Da, and the zinc trisodium salt weighs 522 Da. It is slightly water soluble and bonds stoichiometrically with a central metal ion through the formal donation of one or more of its electrons.

Related Xenobiotics

Several xenobiotics are used in clinical practice to chelate metals. Among these are deferoxamine, dimercaptol (British anti-Lewisite), dimercapto-propane sulfonate, edetate calcium disodium (ethylenediaminetetraacetic acid), penicillamine, Prussian blue, succimer (dimercaptosuccinic acid), and trientine hydrochloride. However, none of these are effective chelators for transuranic (elements with atomic numbers > 92) metals.

DTPA is used to convey gadolinium contrast in magnetic resonance imaging and technetium in nuclear medicine imaging. Other xenobiotics have modified the DTPA molecule in conjunction with a monoclonal antibody directed toward specific antigens found on neoplasms, allowing an attached isotope, such as ¹¹¹In, to deliver site directed radiation treatment. These related xenobiotics include tiuxetan, pendetide, and pentetreotide.¹⁷

Mechanism of Action

The conjugate base of pentetic acid has a high affinity for metal cations. Pentetic acid wraps itself around the metal forming up to eight bonds, exchanging its calcium or zinc ions for a metal with greater binding capacity ([Fig. A44–1](#)). Remaining water soluble, the chelated complex is then excreted by glomerular filtration into the urine. DTPA has specific stability constants for the various elements that it chelates, which presumably explains the different binding efficacies of the calcium and zinc salts.

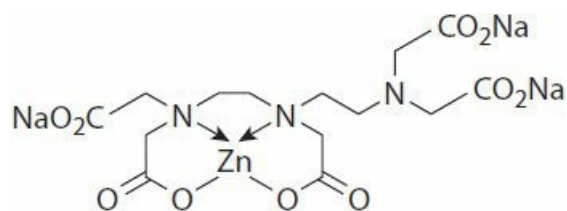


FIGURE A44-1. Trisodium zinc diethylenetriaminepentaacetate, where a transuranic element (Am, Pu, Cm) is substituted for Zn forming a stable chelate.

Pharmacokinetics

DTPA is rapidly absorbed via intramuscular, intraperitoneal, and intravenous routes, but animal studies indicate that DTPA is poorly (< 5%) absorbed by the gastrointestinal tract. Absorption via the lungs is about 20% to 30%. Its volume of distribution is small (0.14 L/kg in humans) and it is distributed throughout the extracellular space. It does not penetrate erythrocytes or other cells such as bone. The plasma half-life is 20 to 60 minutes, although a small fraction is bound to plasma proteins with a half-life of more than 20 hours. DTPA undergoes minimal, if any, metabolism. Only a minimal release of acetate has been demonstrated, and splitting of ethylene groups has not been detected. Elimination is via glomerular filtration, with more than 95% excreted within 12 hours, and 99% by 24 hours. While there are no specific data regarding dosing or clearance changes when chelating patients with kidney disease, individuals with kidney disease who receive ^{99m}Tc -DTPA or Gd-DTPA for imaging purposes demonstrate an increased elimination rate of these chelates with hemodialysis. This suggests that hemodialysis might augment transuranic chelate elimination in contaminated patients with kidney disease.^{12,22} Fecal excretion is less than 3%.

Pharmacodynamics

DTPA increases the urinary elimination rate of certain chelated metals. Animal data show that when treatment is begun within an hour of internal contamination, Ca-DTPA resulted in 10 fold greater rate of urinary elimination of plutonium as compared with Zn-DTPA. The greatest chelating capacity occurred immediately and for the first 24 hours following contamination while the metal was still circulating and available for chelation. Following the initial dose of Ca-DTPA, similar rates of elimination of radionuclide resulted from subsequent treatment with either Ca-DTPA or Zn-DTPA, although continued treatment with Ca-DTPA was associated with much greater toxicity, as described in adverse effects below. Animal studies showed that inhalational Ca-DTPA followed by a month-long regimen of Zn-DTPA reduced lung deposits of aerosolized plutonium to 2% of that compared with untreated animals.¹⁸

ROLE IN RADIONUCLIDE CONTAMINATION

DTPA is indicated and FDA approved for suspected contamination via inhalation, dermal, or wound exposure from plutonium, americium, and curium, with the goal of mitigating radionuclide incorporation and local tissue irradiation. Inhaled metals, such as might be experienced following an explosion, may be treated with nebulized DTPA. Depending on the chemistry of the metal (eg, uranium concentrates in renal tissue), this irradiation could possibly lead to development of a malignancy later in life. Chelation is indicated to increase elimination of the radionuclide and decrease cancer risk. This latter has only been demonstrated in animals. Increased urinary excretion of transuranic elements is a clinically meaningful endpoint for efficacy of DTPA. Administration of these chelators is not recommended following ingestion of americium, curium, or plutonium, because they will increase gastrointestinal absorption.

A report published by the Radiation Emergency Assistance Center/Training Site (REAC/TS) reviewed data from 685 transuranic element exposures, most of which were plutonium, curium, and americium. Most of these exposures (63.5%) were by inhalation, typically a breach of a confined area where workers access the radioactive material via arm-length gloves reaching into a protective box. Ages of the exposed ranged from 10 to 64 years of age. From the 18 patients with the most complete urine bioassay data, the average increase in urine elimination of radionuclide was 39 times the baseline rate after the first dose of DTPA.¹⁸ By 24 hours, postexposure soluble plutonium and americium are deposited in bone, theoretically rendering DTPA ineffective (in the absence of bone remodeling).⁷ Historic data concerning contaminated workers at nuclear materials production facilities, which included those who received both prolonged and delayed treatments, demonstrated greatly increased urinary excretion of radioactive material.^{1,9-11,19,20}

Other more limited data suggest that DTPA may also be effective in increasing urinary elimination following exposure to californium and berkelium, and some experts recommend DTPA for chelation of these elements. Animal data suggest the potential utility for chelating cobalt, einsteinium, lanthanum, nickel, promethium, scandium, strontium, yttrium, and yttrium. Pentetic acid salts are not effective in removing antimony, beryllium, bismuth, gallium, lead, mercury, neptunium, niobium, platinum, thorium, or uranium.

DTPA is neither recommended nor approved for treating patients contaminated with uranium or neptunium for several

reasons. DTPA mobilizes uranium from tissue stores but does not increase urinary elimination.^{5,14} Chelating incorporated neptunium is problematic because it forms very stable complexes with transferrin, making it very difficult to decorporate.^{6,13}

ADVERSE EFFECTS AND SAFETY ISSUES

A review of the clinical data by REAC/TS reported three deaths in patients with severe hemochromatosis who were treated with up to 4 g of Ca-DTPA per day. Three other patients experienced severe symptoms with similar dosing, including obtundation and lethargy, oral mucosal ulceration, stomatitis, dermatitis, and loss of lower extremity sensation. These reactions resolved upon cessation of Ca-DTPA administration. Injury was attributed to zinc depletion-induced impaired DNA synthesis in organs with rapid cell turnover.¹⁸ Caution is advised when treating individuals with severe hemochromatosis.

No serious toxicity has been reported among humans after more than 4500 Ca-DTPA administrations at recommended doses.³ Reported adverse reactions include nausea, vomiting, diarrhea, chills, fever, pruritus, and muscle cramps. Transient anosmia was observed in one individual after repeated treatments with Ca-DTPA, also possibly related to zinc depletion, although the specific mechanisms for these adverse reactions remain undefined.

Mice administered 60 times the recommended dose of Ca-DTPA developed severe injuries to kidneys, liver, and the intestines, and deaths occurred.⁵ Toxicity was correlated to the total dose and dosing schedule. Fractionated doses increased mortality compared to similar doses given as a single injection. The injuries were believed to result from significant depletion of Zn and Mn, since the same toxicity did not occur when Zn-DTPA was given at the same dose and schedule. These mice data were interpreted to suggest that Zn-DTPA is approximately 30 fold less toxic than Ca-DTPA. Acutely lethal doses of Zn-DTPA were estimated to be 10 g/kg in the adult male mouse.

Safety

Due to the renal excretion of the radioactive chelate, the kidneys are exposed to potentially higher doses of radiation than other organs, which theoretically may lead to increased risk of malignancy. Additionally, because urine is radioactive during chelation there are recommendations to use toilets instead of urinals and to flush several times. Any spilled urine or feces should be cleaned promptly and completely, accompanied by thorough hand washing. Patients being chelated should take special care to dispose of any expectorant or breast milk carefully. After nebulization treatments, patients should be cautioned not to swallow any expectorant. Nebulized treatment is associated with asthma exacerbations.

DOSING AND ADMINISTRATION

If the contamination route is mixed or unknown, then Ca-DTPA should be administered intravenously. The intravenous dose of Ca-DTPA is 1 g in adults and 14 mg/kg up to the adult dose in children under 12 years up to a maximum of 1 g, administered either undiluted over 3 to 4 minutes, or diluted in 100 to 250 mL D₅W, Ringer lactate, or 0.9% sodium chloride, over 30 minutes. On the basis of animal studies, it should not be given more slowly.⁴ Maintaining normal volume status and frequent voiding should be encouraged to dilute the radioactive chelate and minimize exposure to the bladder. If contamination occurred only via inhalation, then Zn-DTPA may be diluted 1:1 with sterile water or 0.9% sodium chloride and administered via nebulization.¹⁶

Although Ca-DTPA is recommended as the initial chelator, Zn-DTPA should be used after the first 24 hours. Although animal studies show a 10 fold increased rate of elimination of Pu with Ca-DTPA compared with Zn-DTPA, trace metals, such as zinc, are excessively removed with continued treatment with Ca-DTPA. After this period, Zn-DTPA given daily at the same dose is recommended for any continuing therapy because of its relatively diminished depletion of trace metals and the absence of liver, kidney, and intestinal injury.

Timing of Administration and Duration of Therapy

Administration of DTPA is recommended to begin as soon as possible, preferably within the first hour following contamination. Historically, about 55% of all patients treated with DTPA required only one dose. The decision to continue therapy should be based on radioassay data. This assessment should include collection of 24-hour urine samples, whole body or chest counting, and close consultation with the hospital radiation safety officer. Assistance is also available from REAC/TS at 865-576-1005; ask for REAC/TS. Current recommendations are to continue chelation until the deposition of contaminant is less than 5% of the maximum permissible body burden for a given contaminant.³

If continued therapy is indicated, then a regimen of Zn-DTPA may begin the day following initiation of therapy. Dosing regimens may include Zn-DTPA 1 g intravenously daily up to 5 days per week for the first week. If continuing chelation therapy is indicated, then a twice a week regimen should be initiated until the excretion rate of the contaminant does not

increase with Zn-DTPA administration.^{15,16} As with the decision to initiate DTPA therapy, any continued treatment must be coordinated with a radiation safety officer. For all patients, data regarding vital signs, adverse effects, and bioassay studies should be reported to the drug manufacturer and also to REAC/TS.

Monitoring

A complete blood count with differential, blood urea nitrogen, serum chemistries and electrolytes, urinalysis, as well as blood and urine radioassays should be obtained prior to initiating treatment. Daily zinc, manganese, and magnesium monitoring should occur as well as supplementation with zinc. During treatment, repeated blood, urine, and fecal radioassays should be run to monitor elimination.

Patients with Chronic Kidney Disease

Although dose adjustment is currently recommended for patients with chronic kidney disease, kidney disease will impair chelate elimination from the body. Hemodialysis might be used to increase the rate of chelate elimination in these patients. Since dialyzed radionuclides will contaminate dialysis fluid, care must be exercised during the procedure as well as in discarding fluid and preparing the machine for subsequent patient use. Consultation with the radiation safety officer (RSO) is recommended to assist with discarding waste material, as well as with the overall chelation treatment of the contaminated patient.

PREGNANCY AND LACTATION

Ca-DTPA is listed as FDA pregnancy category C based on animal data. Mouse studies involving doses up to 10 times the recommended dose for Ca-DTPA did not produce harmful effects, but doses of greater than 20 times the recommended dose produced teratogenicity and fetal death. Zn-DTPA is listed as FDA pregnancy category B, also based on mouse data. Doses up to 31 times the recommended dose were not demonstrated to impair fertility or harm to the fetus. There are no human pregnancy outcome data from which to draw conclusions regarding the risk of DTPA. Contaminated pregnant women are recommended to begin any treatment with Zn-DTPA due to perceived risk for adverse reproductive outcome. However, for pregnant patients with severe internal contamination where the risk to mother and fetus is considered to be high, Ca-DTPA may be considered for a first dose in conjunction with mineral supplements that contain zinc. These chelators do not cross the placental barrier.

There are no studies regarding DTPA excretion in breast milk. However, radiocontaminants are excreted in breast milk. Thus, women with known or suspected contamination should not breast feed. Likewise, there are no data regarding safety in lactating women, and data regarding the use in children are extrapolated.

FORMULATION AND ACQUISITION

DTPA is available as Ca-DTPA or Zn-DTPA as a sterile solution in 5 mL ampules containing 200 mg/mL (1 g per ampule) for intravenous use. It should be stored in a cool, dry place with an ambient temperature of between 59°F (15°C) and 86°F (30°C) away from sunlight. Several manufacturers formulate DTPA for intravenous administration. Five mL ampules are available singly and in 10 packs. Both chelators are maintained in the Strategic National Stockpile.

SUMMARY

- DTPA is a safe and effective means of chelating americium, curium, and plutonium in a contaminated patient.
- Rapid consultation with a radiation safety officer is recommended to determine the type and degree of contamination, as well as the need and duration of any treatment.
- In most cases, Ca-DTPA should be started as soon as possible after a contamination followed by the use of Zn-DTPA if continued treatment is needed.
- Regular monitoring and supplementation of zinc, magnesium, and manganese during therapy is recommended, although the risk of clinically significant depletion is low at therapeutic doses.
- Hemodialysis may be used to increase renal elimination when chelating contaminated patients with kidney disease, although specific data for this use are limited.

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SECTION II

POISON CENTERS AND EPIDEMIOLOGY

CASE STUDY 12

History A 60 year-old man with a history of hypertension, coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease was admitted to the hospital following an emergency department (ED) presentation for shortness of breath. Because no bed was available on the inpatient service, he was boarded in the ED for many hours. The ED physician who is no longer caring for the patient received a call from the laboratory that the patient's serum potassium was 6.8 mEq/L in a nonhemolyzed specimen. A call was placed to the patient's care team, but after several minutes there was no response.

Physical Examination A brief examination was performed, and the following vital signs were obtained: blood pressure, 166/92 mm Hg; pulse, 84 beats/minute; respiratory rate, 22 breaths/minute; temperature, 99.2°F (37.3°C); oxygen saturation, 93% on 4 L oxygen/minute via nasal cannula. The patient was awake and alert with a normal neurologic evaluation, and the chest examination revealed some wheezing and rhonchi and a regular heart rhythm with an S3 gallop. Electrocardiography (ECG) was obtained (Fig. CS12–1).

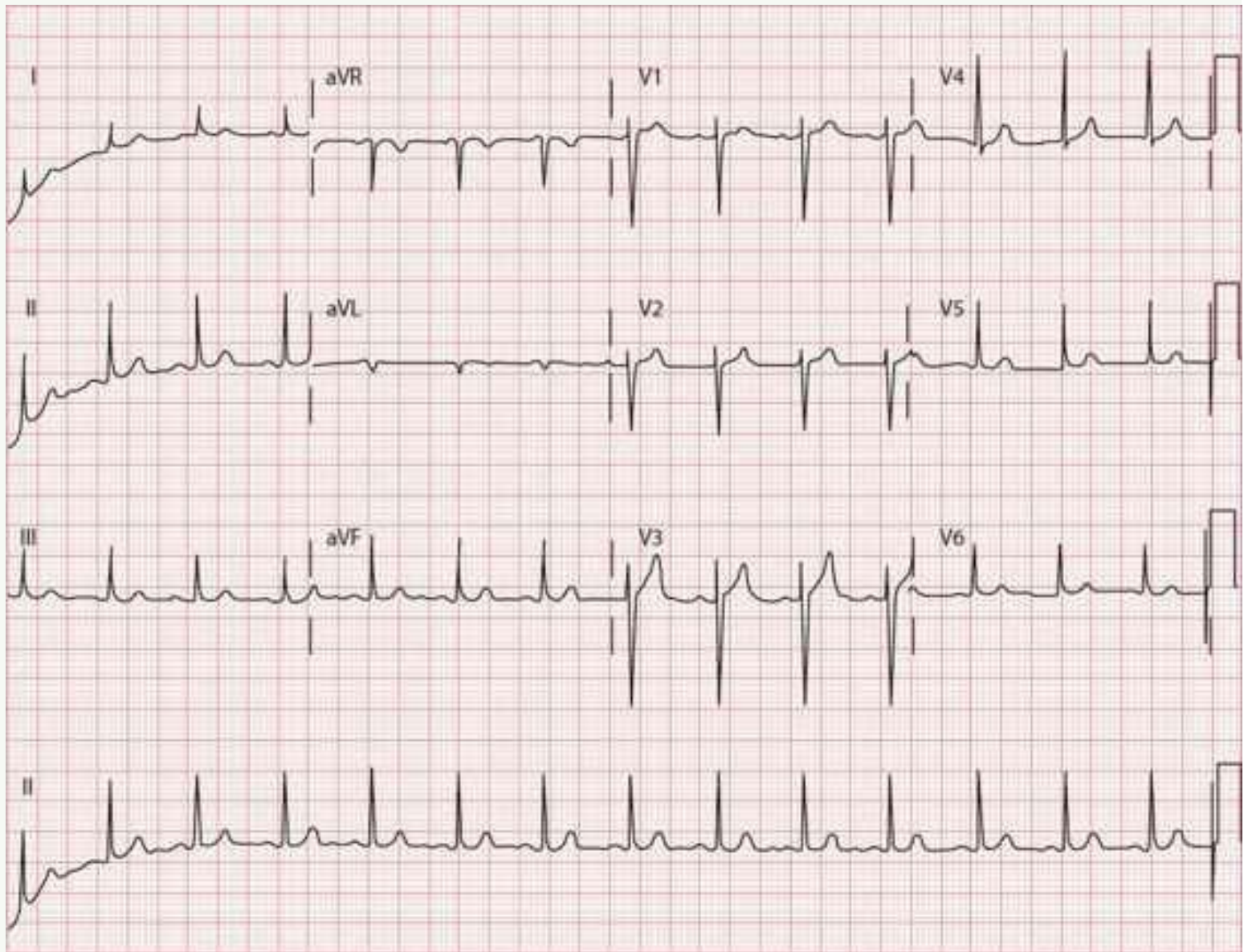


FIGURE CS12–1. Electrocardiography obtained at the time the serum potassium was reported to be elevated. The ECG shows a sinus rhythm with a rate of 90 beats/min, with normal axis and intervals. Findings consistent with hyperkalemia (Chap. 16) are absent.

Immediate Management The ED physician ordered calcium gluconate (1 g), regular insulin (10 units), and dextrose (25 g) all to be given via the intravenous (IV) route to treat hyperkalemia. Shortly after the nurse administered the medications, the patient was noted to have a generalized seizure and lost consciousness. His pulse was noted to decrease and his QRS complex widened (Fig. CS12–2). The patient's permanent pacemaker captured intermittently, and his blood pressure fell to 80/50 mm Hg. A bolus of 1 L of 0.9% sodium chloride was ordered and the patient was placed on 100% oxygen via a nonrebreather mask. A rapid reagent glucose was obtained and reported as 98 mg/dL.

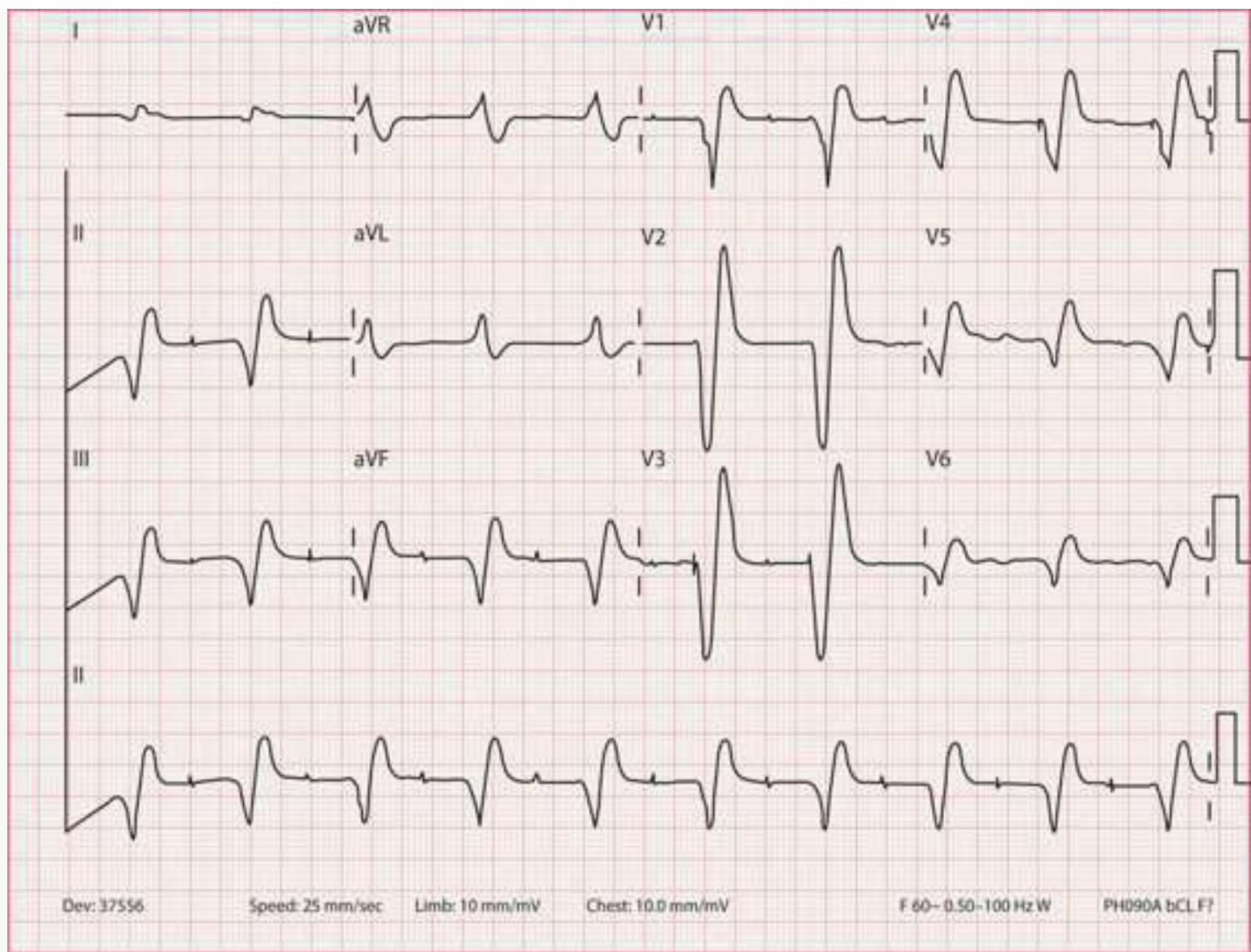


FIGURE CS12–2. Electrocardiography obtained shortly after the patient had a generalized seizure and loss of consciousness. The ECG demonstrates a wide-complex dysrhythmia with a rate of 75/min, a QRS duration of 160 msec, and an overall morphology suggestive of an idioventricular rhythm. Although pacemaker spikes are seen at a rate of 80/min it is unclear if this impulses captured.

What Is the Differential Diagnosis? The toxic syndrome that is characterized by a rapid onset of a seizure, hypotension, and a wide-complex dysrhythmia was highly suggestive of Na^+ channel blockade. Common Na^+ channel blockers are listed in [Table CS12–1](#) and discussed in [Chaps. 16, 48, 64, and 71](#). None of the ordered medications typically produce this effect. Additional considerations were that the administered xenobiotic would have to be available in an intravenous form and could be potentially confused with hypertonic dextrose since the patient’s glucose was not elevated as would have been expected following a bolus of D_{50}W (Antidotes in Depth: A12).

TABLE CS12–1. Common Xenobiotics That Block Cardiac Sodium Channels

Antidepressants	Antipsychotics
Heterocyclics	Mesoridazine
Tricyclics	Thioridazine
Bupropion	Carbamazepine
Antidysrhythmics	Cocaine
Class IA	Diphenhydramine
Class IB	Lamotrigine
Class IC	Potassium
	Hyperkalemia

Further Diagnosis and Treatment While the nurse was asked to review the medications given, the physician labelled

and saved the syringes used to deliver the original medications and administered a bolus of 2 ampules (44 mEq each) of hypertonic sodium bicarbonate. Within 1 to 2 minutes the ECG returned to baseline, his hemodynamic parameters improved, and his mental status slowly normalized.

The nurse reported that the drawer in the automated medicine dispenser was filled with lidocaine instead of dextrose and, and that the vials looked similar (Fig. CS12–3). The patient may have received a bolus of lidocaine. This was confirmed with a serum lidocaine concentration of 4.9 mg/L taken about 1 hour after the event. Full disclosure was made to the patient and the pharmacy was informed of the error.

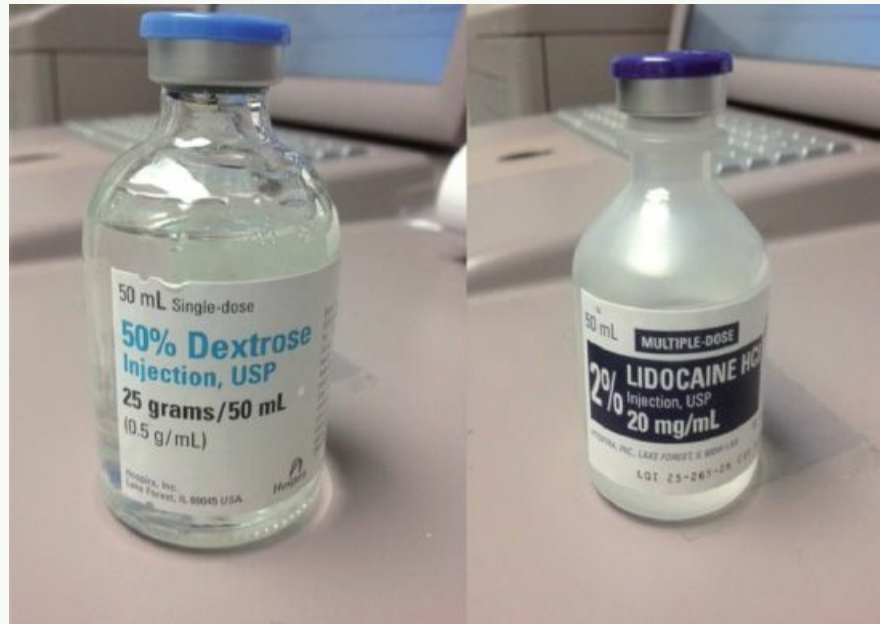


FIGURE CS12–3. Bottles of lidocaine and dextrose that were confused with each other.

How Do Medication Errors Occur? Chapters 135 to 141 deal with many issues of poison prevention and safety. This case highlights some of the key issues. System errors such as hospital and ED overcrowding that result in boarding of patients in busy areas remote from their primary care providers where teams turn over at relatively short intervals increase the likelihood of errors. Cognitive errors such as the urgency to treat a critically abnormal laboratory value (hyperkalemia), even in the absence of any characteristic ECG or clinical findings, may have been contributory. Improper filling of the storage device and purchasing of look alike medication vials added to the confusion. Finally, in this case, a simple error of not confirming that the medication that was ordered was the medication delivered, including proper dose and route, was nearly fatal. Fortunately, immediate recognition of the error and appropriate intervention proved to be life saving.

135 POISON PREVENTION AND EDUCATION

Lauren Schwartz

Unintentional poisonings are a global health concern. According to the World Health Organization (WHO) Global Burden of Disease Project, in 2004 approximately 3,346,000 people died worldwide from unintentional poisoning.⁸⁰ Nearly 1 million people die each year as a result of suicide. Approximately 350,000 deaths result from the deliberate ingestion of pesticides. In addition, an estimated 5 million snakebites occur annually.⁸⁰ The WHO has undertaken initiatives in many countries, including the Bahamas, China, Ghana, Lebanon, Myanmar, Senegal, and Trinidad and Tobago to establish Poison Centers (PCs) and raise awareness about poison prevention. Worldwide, data on nonfatal poisoning rates are currently not available, although the increase in poison centers globally may result in improved research and surveillance programs.⁵⁴ This chapter focuses on programs in North America that aim to prevent unintentional poisonings and improve access to PC services.

Healthy People 2020 is a US federal program that outlines the health goals for the nation. These overarching goals are to attain high quality longer lives, achieve health equality and eliminate disparities, create social and physical environments that promote good health and promote quality of life, healthy development, and healthy behavior across all life stages. Two objectives in the Injury and Violence Prevention section relate to poison prevention. Objective IVP-9 is to reduce poisoning deaths and Objective IVP-10 is to reduce nonfatal poisonings.²⁵ Community based public education programs at PCs are designed to help meet these other public health objectives.

LEGISLATION AND POISON PREVENTION

Since the first PC was established in 1953, a number of legislative efforts have improved poison prevention and awareness and reduced the number of unintentional poisonings in children. Public education programs at PCs have been influenced by these federal measures.⁷¹

National Poison Prevention Week

In 1961, President Kennedy signed Public Law 87–319, designating the third full week of March as National Poison Prevention Week (PPW) to raise awareness of the dangers of unintentional poisonings. Each year, during PPW, PCs and other organizations around the country organize events and activities to promote poison prevention.

Child-Resistant Packaging Act

In 1970, the Poison Prevention Packaging Act was passed. This law requires that the Consumer Product Safety Commission (CPSC) mandate the use of child-resistant containers for toxic household xenobiotics. In 1974, oral prescription medications were included in this requirement. A review of mortality data in children younger than 5 years of age shows a significant decrease in deaths after enforcement of the child-resistant packaging legislation.^{61,71,75}

Taste-Aversive Xenobiotics and Poison Prevention

Nontoxic taste-aversive xenobiotics are frequently added to products such as shampoo, cosmetics, cleaning products, automotive products, and rubbing alcohol to discourage ingestion.²⁴ This is done primarily to prevent poisoning in children except in the case of rubbing alcohol, where adults are also targeted. The most common taste-aversive xenobiotics are the denatonium salts, particularly denatonium benzoate (Bitrex, benzyldiethyl [(2,6-xylylcarbamoyl)methyl] ammonium benzoate), one of the most bitter-tasting xenobiotics known. The bitter taste of denatonium benzoate can be detected at 50 parts per billion (ppb). This aversive xenobiotic is used in concentrations of 6 to 50 parts per million (ppm), typically 6 ppm in cosmetic products and ethanol-containing household products and 30 to 50 ppm in methanol and ethylene glycol.^{8,53} Only limited data are available on the usefulness of taste-aversive xenobiotics for prevention of poisoning. Studies using denatonium benzoate added to liquid detergent and orange juice demonstrate that it can decrease the amount ingested by children.^{6,67} However, the degree of taste aversion is not universal. In one study, some children were noted to take more than one sip of denatonium benzoate-containing orange juice.⁶⁷ Taste aversion is partially a learned response. Frequently

young children do not find a bitter taste as offensive as do adults.⁷ It seems unlikely that taste-aversive xenobiotics will eliminate unintentional ingestions in children, because ingestion is required for aversive effects to occur. Taste-aversive xenobiotics may be most beneficial in the prevention of poisoning by toxic and nonaversive xenobiotics, such as ethylene glycol, methanol, paraquat, certain pesticides, acetonitrile, and bromate-containing cosmetics, where more than one or two sips of the product must be ingested to cause significant toxicity. In 1995, Oregon became the first state to mandate the addition of an aversive xenobiotic to ethylene glycol-or methanol-containing car products in its 1995 Toxic Household Products statute. Analysis on the incidence and severity of ethylene glycol and methanol exposures before and after the mandate could not demonstrate any difference in children under 6 years of age.⁴⁹ Taste-aversive xenobiotics should therefore not be substitutes for other poison prevention modalities.

Toll-Free Access to Poison Centers

In 2000, the Poison Control Center Enhancement and Awareness Act (PL 106-174) was enacted with a goal of nationwide access to PCs. A toll-free number (1-800-222-1222) was established in 2001 for all US PCs.⁷⁸ Callers are connected to a regional PC based on the area code and telephone number exchange. **Figure 135–1** displays the national logo incorporated into educational efforts.



FIGURE 135–1. National toll-free number logo.

ROLE OF PUBLIC EDUCATORS IN POISON CENTERS

Poison Center educators encompass a range of educational backgrounds including nurses, pharmacists, health educators, and teachers. The role of the public educator is based on social marketing concepts and encompasses two objectives: health promotion to change behavior, and marketing of the PC.⁶⁹ Public education programs at PCs teach poison prevention techniques (primary prevention) and raise awareness about available services should a poisoning occur (secondary prevention). Education programs may utilize primary or secondary teaching or a combination of both.^{5,27,32,39} Public educators at PCs provide a range of community based programs ranging from workshops and health fairs to producing print materials, videos and or DVDs, and awareness campaigns through public service advertising using radio, television, print, and mass transit venues. Social media in health promotion offers an opportunity to further expand the dissemination of health information to diverse audiences through enhanced communication.⁴⁷ Since underserved groups use mobile handheld devices frequently to access information, cell phones, mobile technology, and online resources provide new ways that educators can disseminate health messages to those in need.

Educators also participate in community health coalitions, working in conjunction with other injury prevention groups such as National Safe Kids, and collaborate with a wide range of community health agencies. Caregivers of children younger than age 6 have often been the most important group to reach with education programs. Educators often work with national programs for families including Women, Infant and Children (WIC), Head Start, and the Red Cross.

By contrast, older adults (individuals older than 65 years of age) have not been a priority population for PC education resources. However, this group represents a large number of fatalities reported nationally to PCs, primarily due to medication errors.^{10,27} Programs for older adults offer an educational opportunity to reach this high risk population. Collaborative programs with the American Association of Retired Persons (AARP), senior centers, and Departments for the Aging offer an opportunity to provide collaborations focusing on poison prevention and medicine safety programs through educational interventions conducted in senior centers, community agencies, and other groups that serve independently living older adults.

The membership of the American Association of Poison Control Center's Public Education Committee (PEC) includes

the educators from PCs across the United States and Canada. The mission of the PEC is to provide poison prevention awareness programs in an effort to reduce morbidity and mortality associated with poisoning. Each year, the PEC provides educational sessions at the North American Congress of Clinical Toxicology. PEC workshops focus on program development, evaluation, grant writing, strategic planning, and other topics of interest to PC educators.²⁷

NEEDS ASSESSMENTS

To develop successful poison education programs, educators must first analyze demographic data, call volume rates, cultural and language issues, and barriers to calling a PC. Geographic information systems (GIS) software offers a way for PCs to map demographic data. The use of this type of software is increasing in public health and can be applied to PC efforts. The coordination of data retrieval from various data entry programs and the use of GIS software by PC staff provides access to call rates by zip codes, counties, census tracts, or congressional districts to be used for planning programs. Health and social services for the targeted community may also be presented using GIS maps. Using GIS for population based programs is recommended for developing social marketing campaigns, health education programs, outreach efforts, and coalition building.⁶⁰ The study of geographic areas with low call rates enhances the potential for targeted and focused educational programs.

Focus groups, surveys, and interviews provide useful qualitative methods for PC educators to identify the perceptions of parents and caregivers about calling the PC. Barriers regarding PC utilization include not knowing the PC number, preference for calling 9-1-1 rather than the PC, fear of being reported to child welfare agencies, concerns with regard to confidentiality, language difficulties, lack of in person contact with health care providers, low self-efficacy, and concerns regarding the cost of the call.^{1,4,9,28,29,65,73} Each of these barriers must be considered and creatively addressed when planning new programs for reaching caregivers of young children. In one study, 51% of caregivers interviewed in a low income urban pediatric clinic said that they would immediately take their children to the emergency department (ED) after a possible poisoning exposure.⁶³ In a separate study, focus group participants stated they would not call the PC in the case of a poison emergency. Their responses ranking was (1) call the pediatrician, (2) go to the ED, (3) read the label, and (4) call a friend after a poisoning exposure.²⁸ A focus group with parents provided information to refine a telephone survey concentrating on hazardous household materials and health risks. Feedback from caregivers resulted in a more concise instrument with more targeted questions. In addition, perceptions of the PC and suggestions for future educational interventions were also gathered from participants.²⁸ Involving the target audience in the development and testing of information is demonstrated to have improved outcomes when disseminating information.⁷²

Follow-up surveys provide a way to analyze factors related to PC access. English-and Spanish-speaking caregivers in Texas were contacted after an ED visit related to a poisoning exposure in a child. Findings showed that more than half had spoken to PC staff prior to the hospital visit. Of those who did not call the PC, 68% claimed prior knowledge of the PC, yet failed to use it. Significant demographic variables associated with a failure to call the PC were Hispanic (schooling in Mexico) and African American ethnicities.³¹ Findings from an ethnographic study of 50 Mexican-American mothers with children younger than 5 years of age demonstrated that none had the PC number in their home.⁴⁶

In person interviews were conducted with parents in the pediatric clinic about poison prevention strategies and awareness of the poison center.^{16,20} A pilot study to determine predictors of storage included acculturation, age, gender, and education among parents found that less acculturated parents were more likely to store medicines and cleaning products unsafely in the home.¹⁶ Another study conducted with 216 parents and caregivers reported that 80% were aware of the poison center services. However, none knew the 800 number specifically, although many stated they had the number in their home. Of the 42 participants (20% of the sample) unaware of the PC services, 57% were non-English speakers.²⁰

In order for educators to plan effective programs with older adults a needs assessment of the perceived barriers and benefits for this target group related to accessing the PC is required. Focus groups conducted with older adults show that most do not perceive the PC as an appropriate service for their concerns, but rather as a service for children and parents. Additionally, the participants expressed a very narrow view of what was considered a poison such as bleach and household products. Similar to caregivers of children, older adults repeatedly state that they would call 9-1-1 in an emergency.¹¹

POISON EDUCATION PROGRAMS

Over half of the 2 million annual calls to PCs nationally involve children younger than 6 years of age.¹⁰ As a result, programs to teach caregivers about primary and secondary prevention techniques have been the major aim of education efforts. Typically, these programs focus on teaching poison prevention (Table 135–1) and raising awareness of PC services. Poison education programs designed to address barriers to accessing the PC through community interventions are reported in the literature. In one study, parents at two WIC centers reported an increased comfort level with calling the PC after a video based intervention.³⁰ Interventions have demonstrated an increase in knowledge about PC messages and

poison prevention in the study groups.^{30,38}

TABLE 135–1. Poison Prevention Tips

- Identify poisons inside and outside the home
- Keep poisons out of reach of children in a locked cabinet
- Keep products in their original containers
- Never keep food and nonfood items together
- Install carbon monoxide detectors in sleeping areas
- Keep plants out of reach of children and pets
- Use child-resistant containers
- Post the poison center number on all telephones and in all cell phones

Interventions Targeting Health Behavior

Unintentional poisonings frequently happen when children are left unattended for a brief period of time (< 5 minutes) and a toxic product in use or recently purchased is left within reach of the unattended child.⁵¹ A qualitative study conducted of 65 parents, some whose children had experienced an unintentional poisoning, showed that poison prevention strategies were not consistently implemented in the home. Recommendations included ongoing parent education to reemphasize that “child resistant” is not “childproof,” and reinforce safe storage of potentially toxic products, particularly those that are often used.²² When knowledge and behavior were measured through telephone surveys conducted 3 months after a poison prevention packet was mailed to families of young children who had experienced a poisoning, caregivers were more likely to have the PC number posted in the home.^{30,79}

The ED presents an opportunity for poison education programs to work with families to prevent further poisoning exposures.¹⁷ An injury prevention program provided to caregivers of young children after a home injury was effective, particularly regarding retention of poison prevention information and the use of safety devices.⁵⁶ The use of a computer kiosk in an ED to provide personalized child safety information including specific advice of poison storage for parents showed increased knowledge scores on follow-up telephone surveys.²³

The effectiveness of poison prevention education for families who called the PC following a potential exposure in a young child was also studied. Poison prevention instructions, telephone stickers, and a cabinet lock were sent to the family one week after the initial call. Follow-up telephone interviews showed that intervention group recipients reported a higher use of the cabinet lock (59%) and were significantly more likely to post the telephone number for the PC (78%) than those in the control group who did not receive any poison prevention materials within 2 weeks of the incident.⁷⁹

Poison education programs developed to address caregiver barriers have also been evaluated. An educational video targeting low income and Spanish speaking mothers was developed and evaluated. Results showed increased knowledge about the services, staff, and appropriate use of the PC compared with a control group that attended the regularly scheduled WIC class.³⁰

Instructor training programs have been designed by a number of PCs to reach leaders or educators of community based organizations to incorporate poison education into their roles for the general population. An evaluation of the “Be Poison Smart” program showed an increase in knowledge and behavior change among service providers after a standardized training session. These reported changes included having the PC number visibly posted and keeping hazardous products out of reach.⁵⁵ Working with community based services such as WIC presents an opportunity to reach the target population. Pretests and posttests administered to WIC staff and public health nurses showed increased understanding about poison prevention and increased awareness of PC services.⁵⁷ Community health workers (promotoras) are involved in health promotion particularly in hard to reach communities. A train-the-trainer model evaluation demonstrated increased knowledge and behavior for teaching healthy homes promotion in the community setting.⁴⁰

Focus group participants identified pediatricians as a trusted source of health information for parents.^{28,65} The AAP includes a poison prevention counseling recommendation as part of The Injury Prevention Program (TIPP). TIPP is a safety education program for parents of children newborn through 12 years of age. The TIPP age related safety sheets include poison prevention advice for parents of children aged 6 to 12 month, 1 to 2 years, and 2 to 4 years.² Each safety sheet encourages parents to call the toll-free number for PCs if the child ingests a potentially poisonous product. It is important that the AAP continues its support for efforts by PCs to prevent childhood poisonings.³⁹ In another study, family practitioners and pediatricians were surveyed with respect to poison prevention counseling for parents. Although more than 80% of both groups reported that this was an important topic, family practitioners were less likely than pediatricians to provide poison information during a visit.²¹

Education programs are designed for school-age curricula. The effectiveness of MORE HEALTH, a program to teach kindergarten and third-grade students about poison prevention, was studied.³⁸ Posttests administered 1 to 2 weeks after the intervention showed increased knowledge in the intervention group of children. Parents of children in the intervention group also self reported that their homes were more likely to be “poison-proofed.”

Recommendations have been made to develop programs targeting older adults, particularly about potential problems with medication use and storage.^{27,36,68} Efforts to teach nursing home staff about potential poisoning exposures are also recommended.³⁶ There has been a shift in the priority of poison education programs to address this target population. An ED study of older adults showed that seniors had poor knowledge of their current medications. In addition, patients taking more medications were less likely to know the proper dose, name, and purpose of the medications.^{14,76}

Community-Wide Interventions

A review of pediatric literature focusing on community based poisoning prevention programs showed that only four studies could be found using poisoning rates as the outcome measure. Additional creative studies to measure community based poison prevention efforts will be essential to determine the importance of these efforts.⁵⁰

In general, mass mailing of poison information is generally not an effective means to increase call volume for poison exposure or information requests nor is it cost effective.^{19,34} Similarly, a distribution of textbook covers with the national logo and PC information to elementary and secondary schools in low PC utilization counties was not an effective method for increasing PC calls.⁸² A hospital mailing that combined primary (poison prevention tips) and secondary (telephone stickers) messages were included in an established family health promotion magazine distributed widely in the PC regional area. This effort resulted in an increased call volume in areas where at least 5% of the residents received the information.³² In addition, another study result in that overall call volume increased by 11.2% after more than 1 million pieces of literature containing the toll-free number were distributed at sites including emergency departments, doctor offices, schools, and pharmacies.³³

An increased number of information calls to the PC was attributed to a campaign developed to raise community awareness.⁷⁰ Media provide a venue for conducting educational activities. Direct mail, radio, television, newspapers, and magazines were incorporated into a media campaign developed to raise awareness in a particular Latino community. A telephone survey conducted pre-and post-media campaign showed an increase in awareness about the PC.¹ Although developing this type of program is often costly compared with other education efforts, the potential audiences are vast. Mass media campaigns are powerful tools used in health promotion and disease prevention efforts.⁵⁸ Research shows that a multilevel approach of media campaigns combined with community-based interventions and health education materials influence health behaviors and raise awareness. Additional factors that contribute to successful mass media campaigns include influencing the information environment to maximize exposure, using social marketing strategies, creating a supportive environment for the target audience to make health changes, and theory based process analyses to permit changes mid-campaign and assess outcomes and subsequent strategies in an iterative manner.⁵⁸ Radio and television news stations often provide a way to broadcast poison prevention messages during PPW and during periods associated with perceived increased risks to a community. Social media is viewed as a communications tool rather than a factor in behavior change. Therefore, a process evaluation strategy is appropriate for measuring reach, context, delivery, and fidelity of application.⁴⁷

Multilingual Populations

Language and culture must be addressed when planning community-based programs. Quantitative and qualitative research examining Latino communities and calls to the PC have been conducted. The findings from interviews with 206 Latino parents at a WIC site showed that 62% had not heard of the local PC and 77% did not know the PC services were free and offered in Spanish.⁷⁴ Two other studies examined the call rates in communities with significant Latino populations. These areas had lower call rates than comparable areas based on demographic and socioeconomic factors.^{15,73} Furthermore, a number of studies demonstrate that Spanish speaking caregivers are less likely to call the PC because of concerns including confidentiality and language barriers.^{1,4,15,29,46} In a study conducted with 100 Mexican-American mothers of children younger than 5 years of age, 32% reported that a doctor or nurse would be the initial contact for health advice.⁴³ Other sources include friends and family (29%), mother, grandmother, mother-in-law (21%), and spouses (17%). Most of the mothers (81%) acknowledged the use of home remedies to treat their childrens' illnesses.⁴³ New immigrant families from Mexico and Latin America are at high risk for poisoning exposures. PC education programs should target populations in communities where the impact has the potential to be consequential.⁶⁶ Caution should be used when planning programs based on census data for demographic information as this data may not reflect the specific population or characteristic under study in community based programs. When ethnicity information is not collected from callers who contact the PC, there are severe limitations to the value of the data.¹⁵

Qualitative research can help to identify cultural issues when planning targeted education efforts. Monolingual Spanish

speaking mothers were more likely to report poor storage of household products and lack of protective placement of plants.¹ Mexican-born mothers of children younger than 5 years of age were interviewed in their homes about poison prevention techniques. Safe storage was clearly a problem in these homes with 64% of homes having bleach stored within reach of children. The presence of multiple families living in the same home further impedes safe storage practices. In this study, families stored all personal products including medications and household cleansing agents with them in their bedrooms rather than in common areas such as the bathroom.⁴⁶

It is important to consider employment of bilingual staff as public educators when attempting to expand public awareness. The benefits of a bilingual educator include the ability to provide programs directly to an audience and eliminate the need for a translator. A lack of bilingual providers was the most significant barrier identified for Spanish speaking women interviewed about injury prevention techniques.²⁶ Recommendations for more effective outreach to Latino populations include television advertisements and distribution of written information at schools, churches, and doctor offices.⁷⁴ Health education programs including mass media campaigns, designed to accurately reflect the cultural identity—language, beliefs, roles—of the targeted population are more likely to be accepted. Storytelling has also been a recommended strategy for health education among many cultures.⁴⁴ When asked to provide suggestions for poison prevention education, responses included Spanish radio and video programs as well as brochures that incorporate culturally appropriate values. Including messages into widely recognized media such as telenovelas should also be considered when developing information dissemination channels. Most parents reported interest in learning from PC staff, doctor, or a teacher.¹⁶

Field testing concepts and materials are important for the development and distribution of appropriate information for multicultural populations. Further work is needed to examine cultural beliefs related to poison prevention use of and access to the PC. It is important to address cultural beliefs related to use of herbal and other complementary medicines.³⁰ New education programs are needed to reach multilingual and multicultural targeted populations communities across the country. Programs may be more successful if individuals trust and view a source as credible, particularly when cultural attitudes and beliefs closely resemble their own.^{16,35,44} In addition, promotoras or community health workers should be considered to deliver primary prevention information in the Hispanic community for building relationships with parents and overcoming cultural barriers.^{16,40}

Health Literacy/Numeracy

Health literacy is defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”⁷² Health literacy encompasses the ability to read, understand, and discuss medical information. Research from the US Department of Education shows that only 12% of US English speaking adults have proficient health literacy skills.⁷² Older adults, Hispanic adults, immigrants, those with less than a high school degree or GED, and low income individuals are at highest risk for low health literacy.³⁷ People with low functional health literacy abilities are less likely to understand written and verbal health information, medicine labels, and appointment information.³⁷ This type of health information is often written at reading levels of at least tenth grade or higher.¹⁸ The recommended reading level for written information is sixth grade. Most Americans are able to understand medical information at this level.⁷² In addition to reading level, use of graphics, font style, color, type size, and layout are important components when developing print material.^{18,72} Recommendations for nonprint methods for communicating health information include visuals (posters, fotonovelas, pictographs), action-oriented activities (role-play, theater, storytelling), audiovisuals (videos, DVDs), and improving patient–provider communication.^{16,18,52,72}

Warning and medication labels are often difficult to understand. The inability to read these warning labels in English presents a barrier for safe storage and safe use of medication and products.⁴⁶ Identification of products often includes brand recognition.⁴⁵ Instructions for proper use and warnings may not be understood from the label independent of language.

In order to address medication safety issues, particularly with medication labels, a number of studies have evaluated ways to simplify the information provided. New recommendations for standardized prescription medicine labels incorporate four specific time periods (morning, noon, evening, and bedtime) and plain language techniques on the container.^{76,77} Similarly, recommendations for nonprescription medicine labels have been developed.⁸¹

The effects of health numeracy as a distinct component of health literacy are presented in the literature.^{48,64} Numeracy is an element of health literacy and involves the ability to use numeric information to make effective health decisions in daily life.³ This also includes concepts of risk, probability, and the communication of scientific evidence.^{48,62,64} Health-related tasks including measuring medications, scheduling appointments, and refilling prescriptions rely on applied numeracy skills.^{62,64} Patients managing multiple prescription and nonprescription regimens will lead to potential medication errors.⁷⁶ Educators need to understand the importance of interventions that accurately assess numeracy levels and appropriately address health outcomes. Recommendations for techniques to improve understanding of numeric information include simplifying concepts, using plain language strategies, and utilizing “teach-back” patient understanding strategies.^{3,72}

Applying Health Education Principles to Poison Education Programs

Health education involves planning, implementing, and evaluating programs based on theories and models. These models offer direction for educators with health promotion planning.⁴² There is a need to increase the number of poison educational programs incorporating health education principles. This includes educational efforts designed to reach individuals through community based programs and media campaigns.

Both the Health Belief Model (HBM) and Social Cognitive Theory (SCT) incorporate the concept of “self-efficacy” and are applicable when designing poison prevention interventions and mass media campaigns. Self-efficacy is the individual’s belief that he or she will be able to accomplish the task requested.^{13,18,41,58} Many health educators believe that self-efficacy is necessary to enable behavior change. The SCT suggests that individuals, the environment, and behavior are intimately and inextricably interrelated.⁴¹ The HBM suggests that individuals are more likely to make health behavior changes based on perceived risk susceptibility, severity, potential barriers, and self-efficacy. These decisions are made when actions are seen as potentially more beneficial to the individual than the perceived risks associated with surmounting the current barriers.¹³

In one study, the HBM approach was used as a framework for poison prevention and for the assessment of barriers to PC use. Questions for focus group participants were developed based on the principles of HBM—that is, perceived susceptibility, severity, benefits, barriers, and self-efficacy related to the health action requested. Most of the mothers viewed poisoning as an emergency and felt it was a health concern for their children. Cues to action are also a component of the model and involve discussions about poison prevention or related information. Participants recommended using community based venues and culturally appropriate information to expand awareness about poison prevention and the poison center.⁹

The HBM and SCT approaches were used to develop the questions for focus groups in both English and Spanish. These questions addressed issues related to poison prevention (severity and susceptibility), the services of the PC (including barriers), and suggestions for education. Focus group participants suggested the use of modeling to reinforce real life scenarios in which a mother handles the poisoning emergency with the staff at the PC with a positive outcome.²⁹ As a result, a video was developed addressing these ideas. Two poisoning situations in which a mother calls the center are depicted. One involves home management (ingestion of bleach) and the second involves taking the child to the emergency department (swallowing grandmother’s antihypertensive pill). The video and correlated teaching guides are available in English and Spanish.³⁰

It is important to develop questionnaires that will be accepted and understood by the target population. A Spanish language instrument that addresses home safety beliefs using the HBM framework was developed and tested. Low income, monolingual, Spanish speaking mothers of children younger than 4 years of age were interviewed about perceived susceptibility, severity, barriers, and self-efficacy factors affecting unintentional home injuries including poison prevention measures. Barriers identified include literacy skills and access to bilingual health information.²⁶

The HBM supports the idea that a “teachable moment” may be the ideal opportunity to present poison prevention interventions.^{23,56} People may be more open to health information after experiencing a traumatic experience.¹² Events such as an unintentional poisoning exposure may motivate individuals to behavioral change. Applying HBM principles suggests that individuals will make changes in terms of poison prevention when or if they view the severity and susceptibility of a poisoning to be high in the home. Many languages are enriched by cultural variations that must be incorporated into poison education programs and best practices for outreach. Our goal as educators is to provide efforts using models that have been tested and evaluated for addressing focused community efforts in each population served by the PC.

SUMMARY

- Poison center public education efforts must encompass needs assessments, program development, implementation, and evaluation.
- Focus groups with caregivers of young children conducted across the country have consistently identified barriers to calling poison centers. These include calling 9-1-1, fear of being reported to child welfare agencies, and lack of confidence in handling poisoning emergencies.
- Using health education theories and models, programs should be developed that address these barriers and encourage caregivers to use the services of the PC appropriately.
- Education programs focusing on the needs of older adults and promoting using the poison center as a resource for medicine safety should be designed.
- Cultural, health literacy, health numeracy, and language needs of target populations are important considerations when planning poison education programs.

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136 POISON CENTERS AND POISON EPIDEMIOLOGY

Robert S. Hoffman

HISTORY

In 1950, the American Academy of Pediatrics created a Committee on Accident Prevention to explore methods to reduce injuries in young children. A subsequent survey by that committee demonstrated that injuries resulting from unintentional poisoning were a significant cause of childhood morbidity. Simultaneously came the realizations that a source of reliable information on the active ingredients of common household xenobiotics was lacking and that there were few accepted methods for treating poisoned patients. In response to this void, the first poison center was created in Chicago in 1953.¹⁰² Although initially designed to provide information to health care professionals, both the popularity and the success of this center stimulated a poison center movement, which rapidly spread across the country. The myriad of new poison centers not only offered product content information to health care professionals, but also began to offer first aid and prevention information to members of the community.

In the 60 years that have since passed, countless achievements have been realized by a relatively small group of remarkably altruistic individuals. Throughout this time, poison services have remained free to the public, highlighting their essential role in the American public health system. Many of the legislative and educational accomplishments, which are chronicled in [Chap. 1](#), have directly reduced the incidence and severity of poisoning in children.^{98,110,116} Concurrently, the number, configuration, and specific role of poison centers have shifted in response to public and professional needs.^{50,125}

Modern regional poison centers are staffed by highly trained and certified health professionals who are assisted by extensive information systems. Support is provided by 24 hour access to board certified medical toxicologists and consultants from diverse medical disciplines, the natural sciences, and industry. The role of the current American poison center can be best summarized as follows:

- Maintaining and interpreting a database of xenobiotics
- Reducing health care costs related to poisoning through:
 - Providing information and advice to the public to prevent unnecessary hospitalizations following exposure
 - Providing information and advice to health professionals to improve the diagnosis and care of patients who present to health care
- Collecting epidemiologic data on the incidence and severity of poisoning
- Integrating epidemiologic data as part of the public health surveillance system
- Educating health care professionals on the diagnosis and treatment of poisoning
- Contributing to the science of toxicology

In the past, poison centers were evaluated based on number of incoming calls and measures of community awareness. Current emphasis should be placed on evaluating health outcomes such as admissions to the intensive care unit, length of stay in hospitals, and total health care expenditures. One crucial test of the utility of modern poison centers will be their ability to help reverse the current trend in the United States of increasing adult mortality from prescription drug poisoning.⁶⁷ This chapter explores some of the critical roles of US poison centers and attempts to offer a vision of the future. An overview of the composition of poison centers worldwide can be found elsewhere.⁹⁶ Unique issues facing poison centers in other countries are discussed in [Chap. 137](#).

MAINTAINING AND INTERPRETING A DATABASE OF XENOBIOTICS

The first toxicology database created in the United States was a set of cumbersome 5 × 8-inch index cards produced in the 1950s by the US National Clearinghouse of Poison Control Centers.¹⁰² When it grew to include more than 16,000 cards, the sheer volume of space required to store this information, and the extensive time necessary to manually search these cards, created the necessity of a central repository, such as a poison center. As available information grew, a rapid expansion of

information technology occurred, and the unwieldy index card database was privatized and transformed into microfiche. Although this resource was physically smaller, specialized equipment was required, and a search was still time consuming. Numerous encyclopedic and clinical textbooks were written to supplement the database and provide resources for the office or the bedside. With the growth of the computer age and the Internet, the computer program known as POISINDEX was established to replace the microfiche format as the major source of data on the contents of innumerable household and industrial products, drugs, and plant and animal xenobiotics. POISINDEX also provides uniform management strategies for many potentially toxic exposures. Over the years many proprietary competitors to POISINDEX such as TOXINZ and TOXBASE have gained recognition as valuable tools. Additionally, open source programs such as WIKITOX provide free information to both health care professionals and members of the public.

With this evolution of information technology, poison centers are no longer perceived as the sole guardians of toxicology information. Although these services are still essential for the public at large, and those professionals away from their computers or smart phones, a predictable decline in poison center utilization has paralleled this growth in availability of information. A 1991 study in Utah demonstrated that 82.6% of emergency physicians who had POISINDEX available in their institutions no longer routinely consulted the poison center.²⁷ A similar 1994 New York study suggested that 76% of physicians who had POISINDEX in their emergency departments (EDs) perceived that this decreased their own use of their poison center.¹²¹ These studies suggest that poison centers were more likely to be called for patients with acute and symptomatic overdose and less likely to be contacted for chronic toxicity, asymptomatic patients, and adverse drug reactions.

An initial analysis might suggest that this is an acceptable trend for health care professionals in that it both allows physicians to respond more rapidly to patient needs and for poison centers to be more available to those individuals, especially non-health care professionals, who do not have access to this information system. In fact, one regional poison center model demonstrated that an integrated voice response (IVR) system effectively reduced human interactions for medication identification by more than one-half.⁷⁵ By extension, it might be suggested that both the public and health care professionals can easily access the same information as poison specialists, making the human interaction nearly obsolete. However, this practice of “not calling” not only undermines the efforts of poison centers to gather epidemiologic data (see later) but also creates an understanding gap. In other words, the interpretation of the data is as essential (or more essential) than the data itself. For example, some commonly used sources of toxicology information such as the Physicians’ Desk Reference and material safety data sheets occasionally provide information that may be inaccurate, potentially misleading, or severely limited.^{19,56,87} Likewise, reviews of drug interaction programs designed for mobile devices demonstrated significant variability between individual programs and superiority of larger online resources.^{5,37,94,97} Although POISINDEX routinely provides more accurate information regarding overdose, it is only updated quarterly, cannot be expected to adapt to ongoing epidemiologic trends such as regional variations in substance use, and is incapable of judging adequacy or communications or the subtleties contained in natural language.

The best source for essential new information is skilled professionals who specialize in poisoning. In addition, because most databases are designed to provide information about known entities, they perform poorly when dealing with unknown and unclear scenarios—especially long and complicated differential diagnoses. For example, consider the case of a clinician caring for a lethargic child whose only medication is Zantac syrup. After the other causes of altered mental status have been excluded, the clinician considers drug toxicity. Consultation with standard references suggests that altered consciousness would not be expected with use of this medication. However, a certified poison specialist at a regional poison center recognizes the potential for drug error, has the physician review the syrup bottle in question, and then calls the pharmacy where the drug was provided. The poison specialist learns that although the prescription was written for ranitidine (Zantac), the bottle actually contains cetirizine (Zyrtec syrup), which could account for the child’s symptoms.

Thus, although originally designed as providers of information, poison centers are in reality valued consultants, with staff members who not only provide content information but also interpret clinical material and link both to appropriate management strategies. This goal can only be achieved through rigorous training and certification and recertification criteria designed to provide valued up to date interactions with health care professionals. Access to computer programs can never be considered a substitute for a thoughtful human analysis. Computers do not recognize anxiety, inappropriate questions, and other subtle issues that can only be appreciated with human interactions.

Another illustrative example of the value of poison centers can be drawn from the use of flumazenil for benzodiazepine overdose (Chap. 74 and Antidotes in Depth: A22). Although it may easily be determined by anyone capable of using a resource that flumazenil is an antidote for benzodiazepine overdoses, many subtle characteristics of the patient or the overdose often contraindicate its use. A prospective study determined that when flumazenil was used before consultation with the poison center, contraindications were present in 10 of 14 (71%) cases, resulting in one serious adverse event.²² In the study mentioned earlier, although physicians with access to POISINDEX were less likely to call the poison center, 86.7% still felt that using the poison center to gain access to a physician toxicologist was a valued resource.²⁷ Many poison centers are linked with centers for poison treatment, which are health care facilities that can provide both bedside consultation and unique diagnostic and therapeutic interventions for a subset of patients with severe or complex poisoning.¹ The benefits of consultation are discussed later in Health Care Savings.

PROVIDING INFORMATION AND ADVICE TO THE PUBLIC AND TO HEALTH PROFESSIONALS

In 2011, poison centers in the United States interacted with the public and health professionals more than 3.5 million times.¹⁸ While the financial value of these interactions will be discussed in the section on health care savings below, two major limitations to the success of poison centers were highlighted by recent studies. The first, which should be intuitively obvious, stems from the fact that poison centers are remote from the patient and can, therefore, only make decisions based on the information provided to them. Although poison information specialists are highly skilled and use a variety of communication styles to obtain the most accurate information,⁴⁸ the quality of the information impacts on the utility of their recommendations. The greatest concern often is the estimation of the actual dose of an exposure. In a 3.5 year study of all children referred by a poison center to a health care facility for the determination of the presence of either a methanol or an ethylene glycol blood concentration because of the history of an exposure, only 21 of 102 children had a measurable concentration.⁷⁸ While this has serious limitations on the interpretation of poison center data,⁶² the implications for clinical care are even greater. Likewise a human volunteer study demonstrated that adults are totally incapable of determining residual volumes in containers or describing the actual volume of semiquantitative descriptors such as “a small mouthful” or “a gulp.”⁶¹ Because critical decisions are made based on the history of ingestion or amount ingested, a clear challenge for poison centers is to develop methods to improve the accuracy of this information. Digital imagery may provide a useful method of assisting caregivers with determination of residual container volumes by allowing specialists to clarify container sizes and residual volumes.

The second challenge involves the gap that exists between recommendations that are made by poison centers and those that are accepted. Two recent papers highlight this concern. In a 7 year analysis of poison center recommendations for the administration of high dose insulin and glucose therapy, the recommended treatment was actually administered only 50% of the time.⁴⁹ Similarly, in a 5.5 year study of calcium channel blocker and β -adrenergic antagonist overdoses at a different poison center, high dose insulin and glucose therapy was only started in 42% of cases where it was recommended, and intravenous fat emulsion was only given in 33% of cases where it was recommended.⁴¹ Because both these therapies are considered effective and potentially life saving (Antidotes in Depth: A17 and A20), poison centers need to evaluate the reasons these recommendations are not accepted and explore methods to improve communication with providers. The use of on-site medical or clinical toxicology faculty liaisons may help reduce these gaps.

COLLECTING POISON EPIDEMIOLOGY DATA

In 2007, the US Centers for Disease Control and Prevention (CDC) reported that poisoning fatality surpassed both motor vehicle crashes and firearms to become the leading cause of injury related fatalities.⁹³ This trend has continued and is largely influenced by an epidemic of prescription opioid abuse.⁶⁷ Understanding the evolving trends in poisoning is essential to the development of enhanced surveillance, prevention, and education programs designed to improve medication prescribing, drug safety, and to reduce unintentional poisoning. Although data can be analyzed from numerous sources, such as death certificates, hospital discharge coding records, and poison centers, it is essential to recognize the biases that are inherent in each of these reports. Because not all significant poisonings result in either hospitalization or fatality, data from poison centers appear to offer a unique perspective.

Unfortunately, the term “poisoning” is often defined differently and therefore may be confusing. In this text, “poisoning” is used to denote any exposure to any xenobiotic (drug, toxin, chemical, or naturally occurring substance) that results in injury. Yet the data collected and disseminated by poison centers are defined by the term “exposures.”^{13-18,76,117-119} Many exposures are of limited toxicologic consequence either because of the properties of the xenobiotic involved, the magnitude or duration of the exposure, or the uncertainties regarding whether an actual exposure has occurred. Therefore, data collected by poison centers represent a limited and ill-defined measure of poisoning.

The situation is further confounded by multiple biases that are introduced by the actual reporting process, which first and foremost is voluntary and passive. Because most calls concern self reported data from the home and are never subsequently confirmed, a significant percentage of the data generated to date may actually represent only potential or possible exposures, which can introduce large statistical errors into the database. This is highlighted by the 21 of 102 children who tested positive for a toxic alcohol discussed above.⁷⁸ Despite the fact that only those 21 children were definitively exposed and potentially poisoned, all 102 were entered into the database as exposures. If these figures are representative of the rest of the data set, then they suggest that an actual ingestion does not occur in the vast majority of reported unintentional exposures in children. However, they do emphasize that in all of the cases a toxin was in an unacceptably close proximity to a child. Also, current events, hoaxes, and media awareness campaigns all may influence self-reporting rates.⁸¹ Furthermore, to report a possible exposure a caller must have a telephone, probably speak English, and have some degree of health literacy and numeracy.^{80,115} Although telecommunications devices for the hearing impaired and translation services exist, they are rarely used. Enhancement of technology to facilitate the accurate exchange of

information between poison specialists and either hearing impaired callers or those who do not speak English is essential to the success of poison centers. While text message is an interesting option, preliminary data suggest that text messaging encounters take way too long to be productive.⁹⁹ Another would be to entertain more active reporting systems automatically triggered directly by hospital laboratory values. Such a system would explore cognitive behavior of clinicians around reporting and develop a true understand of the epidemiology.

Under the present passive system, when hospitals report exposures to the poison center, a comparison of the hospital chart with the poison center record shows good agreement, demonstrating an accurate exchange of information.⁶⁴ Unfortunately, a reporting bias similar to that described above is well recognized regarding professional utilization of poison centers and has been called the Pollyanna phenomenon.⁵⁷ For example, in the spring of 1995, poison centers in the northeast United States began to receive numerous reports of severe psychomotor agitation and other manifestations of anticholinergic syndrome in heroin users. In the initial phase of the epidemic, most of the callers requested assistance in establishing a diagnosis, determining possible etiologies, and raised questions regarding treatment with physostigmine.⁵⁸ Although the epidemic continued for many months, once the media announced that the heroin supply was tainted with scopolamine, and clinicians became familiar with the indications and administration of physostigmine, call volume decreased. Stated simply, health care professionals are less likely to call the poison center regarding issues with which they are familiar, are of little clinical consequence, or are not recognized as being related to a poison. Thus, a bias is introduced that results in a relative over reporting of new and serious events and a relative underreporting of the familiar or very common, unrecognized poisoning, and those exposures or poisonings that are apparently inconsequential. Numerous comparisons support this contention. Investigators who rely on published data from poison centers as a sole source of epidemiologic information demonstrate a failure to understand the complexity of poisoning data and the aforementioned consequential limitations of poison center–derived data.

Fatal Poisoning

A 4 year study compared deaths from poisoning reported to the Rhode Island medical examiner with those reported to the area poison center.⁷⁹ Not surprisingly, the medical examiner reported many more deaths: 369 compared with 45 reported by the poison center. Although most of the cases not reported to the poison center were victims who died at home, were pronounced dead on arrival to the hospital, or those in whom poisoning was not suspected until the postmortem analysis, 79 patients who subsequently became unreported fatalities were actually admitted to the hospital with a suspected poisoning. In 10 of these cases, the authors concluded that a toxicology consultation might have altered the outcome. Examples of interventions that, if recommended and performed, might have resulted in a more favorable outcome included the proper use of antidotes such as naloxone for an opioid overdose, N-acetylcysteine for acetaminophen (APAP) poisoning, the cyanide antidote kit, sodium bicarbonate for a cyclic antidepressant overdose, hyperbaric oxygen for carbon monoxide poisoning, hemoperfusion for a theophylline overdose, and hemodialysis for a lithium overdose. While the xenobiotics may have changed since this study was performed, the fundamental principles highlighted remain relevant.

Likewise, when medical examiner data were analyzed in Massachusetts, more than 47% of poison fatalities had not been reported to the poison center.¹⁰⁷ A California study evaluating 358 poisoning fatalities reported to the medical examiner showed that only 10 poison center fatalities were reported over a similar time period, demonstrating an even more consequential reporting gap.⁷ Once again in this study, whereas the majority of underreporting was with respect to prehospital deaths (68%), only 5 of 113 hospitalized patients who ultimately died were reported to the poison center. Additionally, a cross-sectional comparison of national mortality data with poison center data for agricultural chemical poisoning demonstrated a similar trend of underreporting to poison centers of seriously poisoned admitted patients who became fatalities.⁷² Furthermore, when data for an entire year from the National Center for Health Statistics were compared with the same year of data from the American Association of Poison Control Centers (AAPCC), it was apparent that the AAPCC data captured only about 5% of annual poison fatalities.⁶³

More recent analyses have highlighted a remarkable trend. When 11 states evaluated trends in poison-related mortality from 1990 to 2001, an average increase of 145% was noted.¹⁰⁶ A more comprehensive investigation of the National Vital Statistics System accessed via the CDC's Web-based Injury Statistics Query and Reporting System database demonstrated a 5.5% increase in injury related mortality from 1999 to 2004. Mortality from poisoning accounted for 61.9% of the increase in unintentional injury, 28% of the increase in suicide, 81.2% of the increase in death from undetermined intent, and more than half of the total increase injury-related mortality.⁹³ As of 2004, death from poisoning surpassed firearms and became the second most common cause of injury-related fatality. While most of the fatalities are in adults, a review of the entire 2010 AAPCC database only found 74 reported fatalities in children.²³ Focusing on poison center data alone would produce the erroneous assumption that poisoning-related fatalities were not a significant public health concern. In actuality, poisoning is a significant concern in that other programs designed to reduce deaths from motor vehicle crashes and firearms have been largely successful whereas decades have gone by without a major intervention targeting poison related fatality.

It is logical to assume that similar disparities exist regarding the reporting of nonfatal poisonings. The resultant gap in public health data needs to be addressed through improved definitions, epidemiology, reporting, and analysis of poison-

related data systems. This inequity has developed through a long-standing tradition of poison centers to focus attention and concentrate on the largely benign exposures in children. The emphasis needs to be redirected toward seriously ill poisoning, utilization of the intensive care unit, and other markers of actual poisoning rather than health care utilization for benign events. The necessary data for such an evaluation may already exist, but the challenge will be in linking the data sets to provide a meaningful analysis.

Nonfatal Poisoning

An outreach study in Massachusetts determined that hospitals geographically close to a poison center reported their cases almost twice as often as hospitals remotely located (46% vs. 27% of total cases).²⁸ Additionally, the authors noted that private physicians were less likely to report cases than residents in training. A one year retrospective review demonstrated that only 26% (123 of 470) of poisoned patients who were treated in a particular ED were reported to the poison center.⁵⁹ Interestingly, only 3% of inhalational exposures were reported, compared with 95% of cyclic antidepressant ingestions. The authors also noted, as suggested above, that reporting decreased when comparable exposures occurred over a short period of time. Finally, in the physician survey study cited earlier, physicians reported that they would “almost never” contact the poison center for asymptomatic exposures (62.9%), chronic toxicity (50.4%), or simply to assist in establishing a reliable database (90.2%).²⁷ This statement is most likely accurate even in jurisdictions in which the reporting of all or select exposures is incorporated into public health laws.

Occupational Exposures

Xenobiotic exposure occurs commonly in the workplace. As a result of the long-recognized association between occupational exposure and illness, several federal and state government funded agencies, such as the National Institute for Occupational Safety and Health, Occupational Safety and Health Act, and the Agency for Toxic Substances and Disease Registry (ATSDR), exist to prevent occupational illness, to educate the public, and to collect data on exposures to occupational xenobiotics. Legislation provides for mandatory reporting in some instances and offers workers job protection for voluntary reporting. Poison centers also provide information on occupational exposures and collect data. Once again, there are discrepancies between the poison information data and the data collected by governmental agencies. A six month survey in California noted that only 15.9% of the occupational cases reported to the poison center were captured by a state occupational reporting system.⁹ The most common occupational toxicologic illness—dermatitis—was even further underrepresented in these cases. A follow-up study by the same authors demonstrated that more than one-third of calls came directly from the individual worker, 70% of whom were unaware of the link between their occupation and their symptoms.⁸ Although these data suggest that poison centers can provide substantial assistance following occupational exposures, one author expressed concern, noting in a follow-up study that the poison center failed to provide an adequate epidemiologic assessment in that it did not identify an average of 12 other people per workplace who were also potentially exposed in addition to the index case.¹¹ A 1999 survey of poison centers concluded that “responses to work-related calls are inadequate” and suggested that written protocols might be helpful.¹²

Adverse Drug Events and Xenobiotic Errors

Although the actual numbers are a source of controversy, data suggest that a striking number of adverse drug events (ADEs) occur each year in the United States, with many resulting in death.^{20,31,77} The ease of 24 hour telephone access, combined with the ability to consult with a health professional, make poison centers ideal resources for reporting of ADEs.³⁰ Yet, more than 76% of physicians surveyed stated that they would “almost never” contact the poison center regarding adverse drug events.²⁷ Moreover, 30 of the 56 (53.6%) poison centers surveyed stated that they had not submitted any of their ADE data to the US Food and Drug Administration’s MedWatch program.³⁴ Many of the other centers reported only partial compliance with the MedWatch system.³⁴ Biases may lead to disproportionate reporting of adverse events related to newer drugs skewing the interpretation of the data. For example, although bleeding may occur from both coumadin and dabigatran, it is easy to believe that reports would be more likely to be generated for the newer drug.

Prescription drug errors are another source of potential poisoning. Retrospective review of poison center data suggests that many of these errors are reported. In one report, the poison center provided valuable feedback to pharmacists and physicians about these errors. Ideally, reporting to the state board of pharmacy would assure that proper surveillance and counseling continue. The poison center would seem to be ideally suited to perform this function.¹⁰⁴ Unfortunately, while pharmacists are ideally positioned to identify prescribing errors, data suggest that pharmacist utilization of poison centers is poor.²

Drugs of Abuse

Poison centers also collect data on exposures to drugs of abuse and misuse. These data consist largely of calls for

information from the concerned public and reports of overdose requiring health care intervention. Although ethanol, tobacco, and caffeine are the most common xenobiotics used in society, these cases are rarely reflected in poison center data, with the exception of unintentional exposures in children. In fact, because most substance abuse does not result in immediate interactions with the health care system, other databases such as the National Institute of Drug Abuse Household Survey (now referred to as the Monitoring the Future Study) might better reflect substance abuse trends. Yet even this database has significant limitations.^{6,54} Because poison centers are more focused on immediate health care effects of exposures, it could be argued that only those cases in which health care interaction is required are of value in the database. Since poison centers collect data in real time, centers are ideally positioned to report on emerging trends and sentinel events. Recent examples include poison center experiences with trends opioid abuse in teenagers,^{51,111} bath salts,⁸⁸ synthetic cannabinoid receptor agonists,⁸⁹ and adulterated cocaine.¹¹²

Grossly Underreported Xenobiotics

As discussed previously, there is little doubt that ethanol and tobacco are the most common xenobiotics intentionally used in our society. Although their toxicologic manifestations can be acute and severe, chronic subclinical poisoning often goes unnoticed for many years. Similarly, more than 500,000 American children have lead concentrations above 10 µg/dL and polychlorinated biphenyls can be found in countless adults and children. We must remain cognizant of these large-scale exposures, such as bisphenol A, when we read that plants, cleaning products, and cosmetics comprise the most common exposures to xenobiotics¹⁸ are the most commonly “reported” exposures.

Integrating Epidemiologic Data as Part of the Public Health Surveillance System

With the current limitations of the poison center data, it should be clear that neither the numerator nor the denominator of the actual number of poisonings can be easily appreciated. However, analysis of these data for trends may be more useful because the inherent biases involved in poison center reporting are probably consistent over many years. Increasingly, poison center data are being used as part of surveillance and prediction models,^{46,123} often that extend beyond poisoning to other public health concerns.¹⁰⁵ Rapid reporting in collaboration with the CDC highlights an essential partnership.^{38,55,89} Efforts should be directed to encourage reporting to poison centers by such enhanced access methods as Web-based forms for passive reporting, a direct interface between laboratory and hospital databases that actively transmits data to poison centers, and linkages to other agencies that collect reports of poisoning such as state and local health departments. Additional resources should be directed at improved case definitions (distinguishing asymptomatic exposure from poisoning) and integration with other essential databases such as MedWatch, the National Vital Statistics System, and the National Center for Health Statistics.

Despite its limitations, poison center data have significant utility. It is often an exposure rather than an actual poisoning that provides the impetus for contact with health care. For those exposures that are unlikely to be consequential, the poison center can intervene to prevent potentially harmful attempts at home decontamination and costly unnecessary visits to health care professionals. Interaction with parents at a time of perceived crisis also provides a “teachable moment” (Chap. 135) that may help prevent a more consequential exposure in the future. For those exposures that may result in poisoning, the period of time immediately following exposure is an ideal moment to initiate first aid measures designed to prevent or lessen the severity of poisoning. For both of these reasons the cost, benefits, and efficacy of poison centers especially regarding home calls must be measured in terms of exposures and not poisonings.

HEALTH CARE SAVINGS

When visits to pediatric EDs for acute poisoning were analyzed, one study demonstrated that 95% of parents had not contacted the poison center before coming to the hospital and 64% of those children required no hospital services and could have therefore profited from a poison center interaction.²⁹ By contrast, when parents called the poison center first, fewer than 1% sought emergency services afterward. When 589 callers to one poison center were surveyed, 464 (79%) stated that they would have used the emergency care system if the poison center were unavailable.⁶⁹ In a similar study, 36% of callers would have selected a more costly alternative if the poison center were unavailable.¹⁰ Likewise, when primary care givers were surveyed, over 80% said that they would activate 9-1-1 if there were no poison center.³ Poison center data confirm that approximately 75% of reported exposures that originate outside of health care facilities can be safely managed onsite with limited telephone follow-up. Suggesting simple techniques or reassurance can successfully reduce hospital visits for patients who typically call poison centers which, as defined, may only represent a potential exposure. The use of established protocols, especially for unintentional exposures in children clearly reduces emergency department referral rates.⁶⁰ These interactions can be followed by distribution of simply written prevention literature to improve use and retention. Unfortunately, this approach is less applicable to adults and the population as a whole.

Limited data suggest that direct bedside consultation and care help reduce length of hospital stay and health care

costs.³⁶ Yet poison centers operate remotely. In one assessment, consultation with a poison center reduced length of stay by nearly 3 days.¹¹⁴ Similarly, when the poison center was consulted for patients already in the hospital, length of stay and costs were reduced by 1.9 days and nearly \$5000.²¹ This experience has been replicated outside the United States where poison center consultation resulted in a decreased length of stay of more than 3 days, respectively.⁵² Strongly encouraged or mandated interactions with poison centers might help reduce the cost of health care, hospital overcrowding, and access to limited resources such as antidotes and hemodialysis.

The national average cost to the poison center for a single human exposure call is on the order of \$35.¹²⁵ A federally funded study concluded that, in one year, poison centers reduced the number of patients who were treated but not hospitalized by 350,000 and reduced hospitalizations by an additional 40,000 patients, for a cost savings of more than \$3 million in 1996 dollars.⁸⁶ Each call to a poison center prevented at least \$175 in subsequent medical costs, providing strong theoretical evidence to support the cost efficacy of poison centers. In fact, two natural experiments support these calculations. In 1988, Louisiana closed its state sponsored poison center. During the year that followed, the cost of emergency medical services for poisoning in Louisiana increased by more than \$1.4 million. This additional expenditure represented a greater than threefold increase above the operating cost of that center.⁷¹ Similarly, because of financial disputes in California, direct access to the San Francisco poison center was electronically restricted for one major county, with a telephone recording referring callers instead to the county 9-1-1 system for assistance.⁹⁵ The result of each blocked call was to increase health care costs by approximately \$33. Moreover, these calculations cannot account for the unmeasured benefits to society from poison center interventions that reduce waiting times for ambulance availability and hospital treatments because of lower volumes, money saved by the prevention or reduction of injury from early intervention, or lives saved by enhancing access to or utilization of the health care system for seriously poisoned patients. In El Paso TX, cooperation between emergency medical services and the poison center was able to reduce ambulance dispatches by 1750 over 5 years.⁴ Overall estimates place the rate of return for poison center funding between 11 and 36:1.^{66,108}

However, many barriers prevent a person from calling a poison center, including lack of familiarity with its available services, intellectual and cultural factors, language difficulties, and confidentiality concerns.^{35,70,80,115} Epidemiologic studies demonstrate that areas of increased population density, such as major urban communities, with high percentages of minority inhabitants have lower utilization of poison center services.¹¹³ Additional barriers include the absence of caregiver comfort with the extensive personal contact provided by the health care system and a concern regarding implications of child abuse or neglect when reporting to agencies such as poison center, many of which have governmental ties.¹⁰³ Data demonstrate that public educators can help overcome some of these barriers.¹⁰⁹ One good example of an effort to overcome reporting barriers was the institution of a single national toll-free number for poisoning (1-800-222-1222). Although it is clear that this intervention improved access and increased total calls to the poison center,⁷⁴ it has yet to be determined if this has altered the patterns of use.

PROVIDING EDUCATION FOR THE PUBLIC AND HEALTH PROFESSIONALS

Poison center staff work closely with physicians, community health educators, community support groups, and parent–teacher associations to develop poison prevention activities.⁸² Table 136–1 lists common strategies advocated to prevent poisoning. Poison centers are also actively involved in enhancing training programs for paramedics,⁴⁷ medical students,⁶⁸ pharmacy students,⁴⁰ and resident physicians,^{40,91,122} and are an integral part of postgraduate training programs in medical toxicology fellowships.

TABLE 136–1. Common Strategies Advocated to Help Prevent Poisoning

All xenobiotics should be kept in their original containers. Food and drink containers should never be used for the excess of a xenobiotic.
Never store xenobiotics in unlocked cabinets under the sink. Apply locks to medicine cabinets that are within the reach of a child.
In the absence of a lock, the more toxic xenobiotics should be stored on the highest shelves.
Xenobiotics should never be left in the glove compartment of the family car.
Parents should buy or accept medication only if it is in a child-resistant container.
Medication should be considered as medicine, not a plaything and certainly not candy.
Adults should not take their medications in front of children:
This will limit exposure to drug-taking role models that may become objects of imitative behavior.
Unused portions of prescription medications should be discarded in a manner consistent with local environmental

protection guidance.
Activated charcoal should be readily available in the home for use if directed by a poison specialist or clinician.
Children who have ingested a poison will do so again within a year. These children should receive an enhanced level of supervision.

As stated previously, there is an inherent risk in both enhanced public and professional education programs. Currently, the decreased telephone utilization of a poison center could be both the result of a decrease in the incidence of exposures or poisonings or an enhanced understanding of the prevention, diagnosis, and treatment of poisoning. Although education should never be viewed as detrimental, programs must include an emphasis on the continued use of poison centers to assure access to most current information in a rapidly changing discipline that only develops through an ongoing dialog between health care professionals and poison specialists. In actuality, as a result of the ongoing analysis of incoming calls, the knowledge base has the potential to change as rapidly as the calls are reported. This is far more rapid than can occur in any published literature or electronic database. Thus, additional emphasis should be applied to routine utilization of the poison center as a public health tool to improve the accuracy of epidemiologic data. Reporting of rare or suspected events can serve as sentinel efforts that help identify consequential adverse drug opportunities long before normal postmarketing surveillance tools identify areas of concern.

On the other hand, outreach programs that advise the public to access free services for inconsequential events can easily overwhelm an already stressed system of responding to incoming calls by demanding an immediate response to the less serious calls in an appropriate time frame. Public education and public health must both be considered to assure that poison centers are staffed with the appropriate number of skilled individuals to respond not only to daily events, but also to address surges in calls that may be the result of true epidemics or responses to media announcements. Increasing calls to demonstrate increased utilization offers no public health advantage if the utilization is inappropriate or if seriously ill or potentially ill callers lose access to timely responses.

DEVELOPMENT OF FUTURE PUBLIC HEALTH INITIATIVES

The initial public health efforts of poison centers focused on attempts to alter product concentration and to enhance product labeling and packaging. These clearly beneficial endeavors should continue and must evolve. However, current events have also increased poison center activities in preparedness for mass gatherings and disasters resulting from radiological, biological, and chemical terrorism.^{53,73} Additional links with governmental agencies such as the CDC and ATSDR will expand the role of medical toxicology in community health. The need for 24 hour rapid access to centralized information, existing data entry and retrieval systems, and links to experts in medical toxicology and emergency medicine helps to place poison centers in critical roles in both local and national initiatives. Important contributions have included development of triage and treatment protocols^{24-26,32,33,39,43,60,83-85,90,92,100,101,120,124} and assessments of antidote supplies.^{42,44,45} Table 136-2 summarizes initiatives that require creation or enhancement to improve poisoning epidemiology data. Many of these are discussed extensively in a report from the Institute of Medicine.⁶⁵

TABLE 136-2. Goals for Improving Poisoning Epidemiologic Data^a

- Identify and remove barriers to reporting
- Create multiple methods of reporting:
 - Telephone, instant messaging, facsimile, Internet based, or e-mail
- Simplify communications devices for the hearing impaired
- Allow rapid access to translation services
- Enhance awareness of the public health role of poison centers
- Enhance education of caregivers and health care professionals
- Establish public health legislation requiring professional reporting of exposures
- Distinguish possible exposures from actual exposures to improve the integrity of the database
- Create a category for unconfirmed exposures in the database and encourage its use
- Divide confirmed exposures by certainty:
 - Confirmed by history
 - Confirmed by physical examination
 - Confirmed by quantitative and qualitative laboratory analysis
- Integrate the American Association of Poison Control Centers database with other databases (such as the ICD and “E” code systems) and utilize a standardized data collection instrument
- Automatically interact with hospital and commercial laboratories
- Uplink pharmacy adverse drug event reports, hospital discharges, public health department reports (similarly available with lead screening programs), fire departments and hazardous materials responders, industry workplace exposures,

death certificates, and drug abuse monitoring systems
Provide real-time analysis of incoming data to identify emerging trends
Enhance the speed of data collection and reporting
Mandate the use of accepted epidemiologic and statistical analyses of data
Provide rapid and regular feedback to primary reporters
Issue timely analyses and reports

^aSome of these efforts are either completed or partially completed, but may need refinement over time.

SUMMARY

- Public education efforts help reduce the likelihood of exposure.
- Provision of basic management advice helps to diminish the consequences of a poisoning once an exposure has occurred.
- Reassurance and proper basic management help to curtail unnecessary utilization of expensive health care.
- Interactions with health care professionals streamline the care of poisoned patients saving hospital days and health care expenditures.
- Collaboration with public health authorities will identify, inform, and help mitigate the consequences of ongoing toxicologic events.
- Data on exposures have been effective to create legislation to further limit poisoning by altering contents or improving packaging or labeling.

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137 INTERNATIONAL PERSPECTIVES ON MEDICAL TOXICOLOGY

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Poisoning is a worldwide problem, but the major effects are felt in the developing world. At least 250,000 to 350,000 people die every year from acute pesticide poisoning,⁷² and an estimated 20,000 to 94,000 humans die each year from snake bites,⁹⁷ the vast majority of whom lives in rural farming areas of lower and middle income countries. Hundreds of thousands of people are affected by groundwater arsenic contamination in Bangladesh and India,¹⁴⁹ and outbreaks of poisoning from contaminated food⁴⁰ and environmental pollution from poorly regulated industrial activity^{49,135} affect whole communities throughout the developing world.

The resources for dealing with these problems are limited in many countries. Public health education about poisons and infrastructure limiting access and exposure to the most highly toxic chemicals are practically absent in much of the developing world. Access to medical care is often limited for financial, cultural, and geographic reasons. Medical toxicology is frequently not a recognized specialty and patients are evaluated by general physicians with little training—although often with great experience. Diagnostic facilities are few, effective treatment options even more rare. Where antidotes exist, there is rarely enough knowledge or experience to use them effectively.³⁰ Intensive care beds for invasive monitoring and long-term ventilation are scarce. This chapter outlines some of the major poisoning risks and challenges for medical toxicology in the developing world.

POISONING AND THE GLOBAL BURDEN OF DISEASE

The World Health Organization (WHO) has ranked injury, including poisoning, among the top 15 causes of death worldwide for persons aged 5 to 44 years.^{114,174} Recent reanalysis of data from the Global Burden of Disease project estimated that acute and chronic exposure to chemicals caused over 4.9 million deaths and 86 million disability-adjusted life years (DALYs) worldwide in 2004—more than cancer, sexually transmitted diseases, or diabetes.^{135,179} Children younger than 15 years of age bore more than one half of this burden.

Tremendous regional disparities in the health impact of poisoning are apparent. The global mortality burden from poisoning is disproportionately shouldered by lower and middle income countries. Overall, as much as 75% or more of all poisoning related deaths occur in the developing world,⁸¹ and an estimated 95% of children who die each year from acute poisoning live in low-and middle-income countries.¹⁷⁴ Children living in Sub-Saharan Africa are at highest risk, with an estimated annual mortality rate of four children per 100,000 population. This is double the global average and higher than that in any other region.¹⁴²

These figures are striking, yet most likely underestimate the contribution of poisoning to the global burden of disease and disability. Much of the existing data on poisoning epidemiology from lower income countries reflects the experience in larger hospital centers. By contrast, most of the population lives in rural areas, and many patients with poisoning may never reach such facilities for a variety of financial, cultural, or geographic reasons. For example, logistical difficulty with accessing health care facilities was responsible in part for the high mortality from snakebite noted in one community-based study in Nepal.¹⁴⁶ Social or economic barriers often contribute to “healer shopping” within traditional or spiritual systems, with allopathic medical care delayed or avoided in many African countries.^{52,86,128}

Unintentional poisoning risks from occupational, environmental, food, or medication sources may also be poorly recognized in communities, or by health care workers.¹²³ The diagnosis of poisoning may not be suspected if a clear history of exposure is not given, because symptoms can mimic infectious or other processes and few medical centers have ready access to laboratory tests for specific poisons. When poisoning is suspect, many countries lack detailed injury surveillance systems or other standardized reporting mechanisms. The WHO has undertaken several initiatives to improve global poisoning surveillance, including support for poison center (PC) development in under represented regions worldwide, and the international efforts of the IPCS/INTOX programs to harmonize data collection and reporting terminology represent an important step toward this goal. However, the interpretation of PC data as evidence of epidemiologic trends must be approached with some caution (Chap. 136).

COMMON XENOBIOTICS AND PATTERNS OF POISONING

Agents commonly involved in acute poisoning differ substantially between communities, both within and among countries. For example, a comparison of poisoning cases seen at a major public teaching hospital in New York City with two large rural hospitals in Sri Lanka found striking differences in the classes of xenobiotics involved. A total of 70% of the patients in New York City were poisoned with pharmaceuticals, and 90% of patients in the Sri Lankan cohort were poisoned with nonpharmaceuticals, primarily pesticides and botanicals, such as yellow oleander, with a 10 times higher case fatality rate.⁸¹ A study comparing poisoning epidemiology in district (rural) and regional (urban) hospitals in Zimbabwe found that poisoning from pesticides was equally common in both settings, but animal envenomation was seen nearly twice as often at the district facilities compared to regional centers, and poisoning with pharmaceuticals was a problem seen uniquely at the regional hospital.¹⁵⁶

Understanding the local patterns and specific risks for poisoning in particular communities is of critical importance since it provides an evidence base for designing and prioritizing strategies to prevent or limit harm. This section reviews some of the more common xenobiotics implicated in poisoning in developing countries worldwide.

Pesticides

A systematic review suggested that at least 250,000—but more likely 350,000—deaths occur each year from acute pesticide self-poisoning around the world.⁷² The WHO now considers pesticide poisoning to be the single most important means of suicide, accounting for more than one-third of all suicides worldwide.²⁵ Most of these deaths occur in Asia, particularly in China and India.⁷² The annual number of deaths from occupational or unintentional pesticide poisoning is unknown but was estimated 20 years ago at 20,000.⁹⁰

While many classes of pesticides are implicated ([Chap. 113](#)), organic phosphorous (OP) pesticides appear to be responsible for the majority of pesticide-related deaths in the developing world.⁵⁶ Deliberate self-poisoning with OP pesticides puts a high cost on the health care system. In one study examining the experience in Sri Lanka, OP pesticide poisoning was responsible for 943 of 2559 (36%) admissions to a secondary hospital for poisoning.⁶⁰ The case fatality for OP poisoning was 21%, and pesticide poisoned patients occupied 41% of all medical intensive care beds. Similar situations have been reported from across the world.⁵⁶ In all likelihood, such studies underestimate the mortality associated with intentional pesticide ingestion as most are hospital based and do not include patients who die prior to hospital presentation.²

Factors contributing to the high mortality of self-poisoning with pesticides in the developing world include the intrinsic lethality of many pesticides, and health care systems that are poorly prepared to handle such critically ill patients ([Table 137-1](#)). Pesticides are often easily available in highly concentrated preparations in rural communities throughout the developing world. The ease of drinking liquid pesticides is also a factor facilitating massive intentional ingestions, as are inadequate pesticide storage systems.⁹⁹ Outbreaks of unintentional poisoning from contaminated flour or old pesticide containers used to store food still occur in rural areas.⁵⁴ The extraordinarily high human, economic, and social costs of pesticide-related mortality worldwide reinforce the importance of developing simple, economical, and evidence based strategies specifically designed to care for acutely poisoned patients in resource limited environments.^{26,32}

TABLE 137-1. Factors Contributing to High Mortality from Self Poisoning with Pesticides in the Developing World

1. Ease of access to pesticides in rural, agrarian households
2. Poor storage practices
3. Inadequate labeling of lethal pesticide products
4. High potency of pesticides
5. Lack of evidence based practice guidelines appropriate for resource poor areas
6. Lack of clear guidelines
7. Distance from and time to health care facilities and resources available at health care facilities

Envenomation

Envenomation by snakes and other animals represents another significant cause of morbidity and mortality in the developing world. Few countries mandate the reporting of animal bites, making it difficult to estimate global incidence, severity, and outcome. Current data estimates that about 20,000 to 94,000 deaths occur globally each year from snakebite.⁹⁷ The vast majority of deaths and serious envenomations occur in the developing world, with less than 100 snakebite deaths per year estimated to occur in Europe, the United States, Canada, and Australia combined.^{42,97}

Because most rural people in the developing world may first consult traditional healers, hospital based studies of

mortality and morbidity associated with snakebites likely underestimate the scope of the problem.^{42,150} For example, a study of rural Philippine rice farmers found that only 8% of cobra (*Naja philippinensis*) bite victims reached a hospital in the 1980s.¹⁷⁰ However, changes in treatment seeking can occur. Studies over the last decade in Sri Lanka have shown that patients have started going to the hospital rapidly after common krait (*Bungarus caeruleus*) snakebite, bypassing traditional healers.¹⁰³ A study in Ghana found that the incidence of snakebite victims at a district hospital increased significantly after the introduction of a new treatment protocol, possibly reflecting increased confidence in the ability of the health care system to manage these cases.¹⁶⁸

Snakebites are most commonly occupational hazards in the rural tropics. Victims are just as likely to be women as men, reflecting rural farming practices. Working in large plantations and subsistence farms places rural people in frequent contact with venomous snakes. With simultaneous changes in global climate and expansion of human settlements, it is likely that the range of venomous snakes will enlarge to include urban areas and regions previously considered too temperate to support them.^{82,121} Snakebites from members of the Elapidae and Viperidae families are responsible for the majority of deaths worldwide, although several other families are also medically important (Colubridae and Atractaspididae species, in particular; [Chap. 122](#) and Special Considerations: SC8).^{169,172}

The burden of snake envenomation on local resources can be substantial. During the rainy season in Benin, snakebites account for up to 20% of all hospital admissions, with an estimated case fatality rate of 3% to 6%.⁴³ In this region, the annual incidence of snake envenomation ranges from 200 to 100,000 in rural villagers to 1300 to 100,000 in sugar cane plantation workers.⁴³ One study conducted in Nigeria in the late 1970s noted an incidence of 497 per 100,000 and a 12% case fatality (primarily due to envenomation by the carpet viper, *Echis ocellatus*).¹³⁶

After snakebites, the second most common cause of mortality and morbidity from venomous animals is scorpion stings^{88,169} ([Chap. 118](#)). Medically important scorpion species are widely distributed throughout the tropics, being particularly common causes of morbidity in North Africa, Mexico, India, and Brazil.⁴⁴ The total number of medically significant scorpion stings that occurs annually is unknown; a recent review estimated 1.2 million stings, leading to more than 3250 deaths (case fatality 0.27%).⁴⁴ Other venomous insects, such as Arachnida (spiders) and Hymenoptera (bees, ants, and wasps), are rarely sources of significant mortality on a global scale⁸⁸ ([Chap. 118](#)).

Herbal and Traditional Medicines

The use of traditional medicine (TM) to treat or prevent health problems is widespread. The WHO estimates that around 80% of the world's population consults traditional healers regularly.¹⁷⁷ Frequently cited reasons for this preference or reliance on TM include financial considerations, sociocultural preferences, beliefs about the relative safety and efficacy of TM compared to allopathic medicines, and mistrust or relative inaccessibility of doctors.^{86,128} Traditional practitioners still greatly outnumber medical professionals in many regions. For example, in 2004 there was one traditional healer but only 0.04 physicians per 500 inhabitants in Mali.⁷¹

Although TM also encompasses a variety of spiritual, religious, or physical manipulation therapies, it often includes administration of "herbal" remedies (*muti*) either orally or via enema. These are typically prepared using a combination of aqueous plant materials, sometimes mixed with insect or other animal parts, metallic salts, or both. While traditional medicinal preparations have usually been tested by generations of practitioners and the concentrations of active ingredients are generally low, both intentional and unintentional poisonings are common.^{38,94,153,157} In a 2-year retrospective review of acutely poisoned patients from South Africa, TM was the second most common cause of admission (15.8% of cases) and had the highest mortality rate (15.2%), accounting for over half of all deaths in the series.¹⁶⁷ TM was the most common cause of admission (23% of cases) for acute poisoning in another 10-year retrospective review of cases from Zimbabwe, with a 6% mortality rate.⁹⁵

The specific chemical constituents responsible for TM poisoning may vary widely between geographic and cultural areas. Laboratory analysis and ethnopharmacologic surveys in a number of countries have begun to elucidate some of the chemical constituents of commonly prescribed recipes. Interestingly, a review of 41 autopsies in South Africa for which the causative agent was presumed to be an herbal medicine found that cardiac glycosides were present in 44% of cases.¹⁰⁹ Adulterants are also implicated in poisoning from TM formulations. For example, these are common in traditional Ayurvedic medicines (particularly heavy metals⁶³ and corticosteroids⁷⁵) and Asian medicines (particularly synthetic pharmaceuticals and heavy metals³⁶ [Chap. 45](#)). A Taiwanese study of 2609 samples found that 23% were adulterated with pharmaceutical products such as caffeine, NSAIDs, acetaminophen, and diuretics.⁸⁴

Pharmaceuticals

In many lower income countries, pharmaceuticals are relatively uncommon causes of acute poisoning. However, the incidence appears to be rising in conjunction with larger global demographic shifts toward increased urbanization and industrialization. Access to a wider array of medications is relatively greater among urban dwellers than in rural ones, and

more people in urban communities may have the financial means to buy them. In a retrospective review of poisoning cases admitted to urban versus rural health centers in Zimbabwe, poisoning with pharmaceuticals was uniquely seen at the urban facilities, accounting for more than 15% of poisoning cases at regional hospitals surveyed and none of the cases presenting for care at the district level.¹⁵⁶ The relative importance of pharmaceuticals in global poisoning trends is likely to continue over the next decades as the number of therapeutic drugs available for use in lower income countries expands, and more and more societies shift toward a “dual burden of disease” pattern, including chronic illnesses that require long-term drug therapy.^{21,120}

The pharmacopeia available in low-income countries is often more restricted than in higher income countries, and this is reflected in the types of medications implicated in acute poisoning cases. The most common xenobiotics seen in the developing world are those used to treat tropical diseases. For example, self-poisoning with the antimalarial chloroquine (Chap. 59) has been widely reported in Sub-Saharan Africa,^{20,27,116,137} although this medication is now rarely used so the incidence may soon decrease. Intentional and unintentional poisoning with the leprosy drug dapsone, as well as the tuberculosis drug isoniazid (Chap. 58), are also well reported.^{132,158,159,165}

Criminal poisoning of commuters to facilitate robbery is a common problem across South Asia.^{89,117,133} In the 1970s and 1980s, drinks containing extracts of *Datura stramonium* were given to unsuspecting commuters, resulting in anticholinergic poisoning.⁹⁸ Practice has changed recently and benzodiazepines are now more commonly given for this purpose.¹⁰⁸ As many as 300 people are admitted unconscious with this problem to a single university medical unit in Dhaka each year.¹⁰⁸

A more general issue of toxicologic concern is the prevalence of poor-quality medicines in use worldwide. Although data estimating the extent of the problem and its impact on health are limited, recent estimates suggest that more than one-third of all medicines on sale in Southeast Asia and Sub-Saharan Africa are substandard or counterfeit.^{23,118,119} The major problem with these medications is an absence or subtherapeutic concentration of active ingredient, leading to treatment failures and an increase in drug-resistant pathogens where antimicrobials are involved. However, substandard medications may sometimes contain more active ingredient than stated, leading to adverse drug effects,¹⁶¹ or contain harmful adulterants or contaminants.

Epidemic poisonings from such poor quality medicines underscore the dangers of inadequate regulation and oversight of pharmaceutical manufacture and sales. Recent examples include the deaths of more than 120 patients in Karachi from exposure to a batch of isosorbide mononitrate contaminated with pyrimethamine,¹⁵ the hospitalization of more than 50,000 infants in China with melamine poisoning from adulterated formula,⁸⁷ and the numerous epidemics of diethylene glycol poisoning in multiple countries over the past few decades from contaminated glycerine, paracetamol syrups, cough syrups, toothpastes, teething mixtures, and other medications.^{22,79,125,127,140,148}

Household Products and Chemicals

Poisoning with common household products, such as fuels, cleansing products, rat poisons, insecticides, body care products, and cosmetics, is a global problem. This general category of diverse xenobiotics is consistently implicated as a significant source of unintentional childhood poisoning worldwide. The PC movement that began in the 1950s in North America grew out of an increasing recognition of the child health risks associated with exploratory household poison ingestions. Household chemicals are a similarly well recognized risk for unintentional childhood poisoning in Sub-Saharan Africa, accounting for up to 80% of all pediatric admissions for poisoning.^{21,41,45,96,126} Internationally, the specific risks are remarkably consistent, including age younger than 6 years (with toddlers younger than 3 years of age most affected), male sex, low socioeconomic status, and unsafe storage practices in the home.

Among specific household products, hydrocarbon poisoning from unintentional ingestion of kerosene (paraffin) is widely reported as the most common cause of pediatric admissions in low-income countries around the world.^{41,45,96,102,173} Kerosene is a common fuel used to power stoves and lamps in many relatively poor communities. It is pale in color with an appearance similar to water, and it is often purchased or stored in used beverage containers making it easy to misidentify (Chap. 108).⁶² In Sub-Saharan Africa, kerosene poisoning accounts for some 25% to 75% of all poisoning-related hospital visits among children younger than 6 years of age.¹²² Several studies document an increase in poisoning related admissions during the warmer months of the year, when children are more likely to become thirsty and to drink from any beverage container at hand.^{101,102}

Caustics are another group of household products frequently implicated in poisoning in the developing world. The common form of caustic ingested varies between countries. In many countries, alkaline substances are most frequently implicated, whereas in others, such as Taiwan and Morocco, poisoning with hydrochloric or sulfuric acids may be more common.^{3,105,154,180} Acute poisoning carries substantial mortality risk, usually more than 10%. If the acute phase of caustic poisoning is survived, there also is a high rate of delayed complications, primarily esophageal strictures. Delayed complications may require surgical intervention, balloon dilatation of the esophagus (bougienage), or feeding tube placement. These treatments are expensive, require significant hospital resources, and have inherent morbidity and

mortality ([Chap. 106](#)).

As with other categories of poison, patterns of self-harm using domestic products tend to demonstrate regional particularities. For example, in Hong Kong there is significant morbidity reported in association with self-poisoning using common household detergent products such as dettol (4.8% chloroxylonol, pine oil, and isopropyl alcohol) and savlon (cetrimide).^{34,37,39,46} Frequent use of potassium permanganate for self-harm has also been reported from Hong Kong.^{129,181} Fatal poisoning with hair dye (paraphenylenediamine) is known in the Middle East and North Africa.^{29,61,80,151} Barium sulfide, arsenic sulfide, and calcium oxide are contained in hair removal preparations¹⁴⁶; poisoning from ingestion of these preparations has been reported from India and Iran.⁴ Rubigine is a domestic cleansing product containing hydrofluoric acid and ammonium difluoride that is used for self-harm in the Caribbean,⁸⁵ while ingestion of sodium hydroxide is common in Malaysia.¹⁹

Plants

Poisonous plants have been used therapeutically to induce abortion, for recreational intoxication, in homicidal acts, and for self-harm throughout human history ([Chap. 121](#)). This section briefly mentions select toxic plants that are most commonly used in self-poisoning, or that have caused epidemic poisoning in the developing world.

Self-poisoning with seeds of two plants containing cardioactive steroids are important clinical problems in Asia. Yellow oleander (*Thevetia peruviana*) kills hundreds of people each year in Sri Lanka and India^{28,57} ([Chap. 65](#)). Sea mango (*Cerbera manghas*) has killed hundreds of people in Kerala, India,⁶⁸ and is a focal problem in eastern Sri Lanka.⁵⁸ Oduvan (*Cleistanthus collinus*) leaf contains the glycosides cleistanthin A and B, which produce severe hypokalemia and cardiac dysrhythmias.¹³ Self-poisoning has killed hundreds of people in Tamil Nadu, India.^{12,155} The superb lily (*Gloriosa superba*) contains colchicine alkaloids and has also been used for self harm in South Asia^{5,9,111} ([Chap. 36](#)).

Ackee tree fruit (*Blighia sapida*), which contains hypoglycin when unripe, is widely consumed as a food source. Epidemics of fatal poisoning with unripe Ackee fruit have occurred throughout the Caribbean and in Africa.^{64,92,110,112} Poisoning by castor beans (*Ricinus communis*) or other lectin containing plants such as *Jatropha* spp (African purging nut) is well reported from Africa and South Asia^{1,65,78,93} ([Chap. 121](#)).

Numerous plant species contain atropine like alkaloids, causing an anticholinergic syndrome when ingested. Reports of intentional ingestion of *Datura* species have been reported from Africa, Asia, and Latin America.^{78,143,152} Most commonly, the seeds are ingested as a recreational drug for their hallucinatory effects,^{67,138} or as part of traditional medical preparations.³⁵

Occupational and Environmental Sources

Poisoning from occupational and environmental sources is a significant global health problem, with disproportionate effects on persons living in lower income communities around the world. Exposure to “traditional” environmental health hazards, such as indoor air pollution from the combustion of solid fuels, and naturally occurring contaminants in groundwater, soil, and food, is still a major cause of morbidity and mortality in much of the world. Around 50% of the world’s people rely on solid fuels such as coal, dung, wood, or crop residues for cooking and heating.³¹ Resultant indoor air pollution was estimated to cause 1,965,000 deaths and 41,009,000 DALYs from lower respiratory tract infections, cancers, and COPD in 2004.¹⁷⁸ In Bangladesh, arsenic contaminated groundwater contributed to 9100 deaths and 125,000 DALYs in 2001.¹⁰⁷ Dental and skeletal fluorosis from excessive fluoride in drinking water is endemic in at least 17 countries worldwide.⁶⁶

Increasingly, modern environmental health hazards (MEHHs) also play a large role in global poisoning risks.^{49,124} MEHHs include outdoor air pollution from automobiles and factories, soil and water contamination by plastics, heavy metals, pesticides and other industrial chemicals and wastes, radiation hazards, land degradation, and climate change produced by rapid urbanization and industrial development in the absence of strong regulatory controls.⁴⁹ These are important sources of both occupational and environmental exposure to a wide range of toxins with acute and chronic health effects. Inadequate safeguards to control the selection, sale, and application of pesticides in parts of Africa and Asia are linked to pesticide poisoning both as an occupational hazard^{53,91} and from residues left on food.^{11,48,123} Occupational lead poisoning has largely been controlled in developed countries through improved working conditions and occupational health screens, but remains an enormous problem in developing countries where occupational and environmental health protection measures are often underdeveloped or practically nonexistent.^{164,171}

Industrial factories are often placed in urban areas, or the areas around factories are rapidly urbanized, placing large numbers of people at risk not only from pollution but from industrial errors as well. The 1984 Bhopal tragedy in which a Union Carbide pesticide plant malfunctioned, releasing isocyanate gas into the surrounding community and causing an estimated 3787 deaths and 558,125 injuries, is emblematic of such disasters.^{14,145}

Several international agreements on chemical safety provide legal frameworks to mitigate the human and environmental impact of global industrialization; however, the actual implementation of regulatory controls has lagged behind the expansion of toxic exposures. For example, at the level governance a total of 39 Sub-Saharan African countries have ratified the Rotterdam Convention on chemical safety. Yet industrial pollution is now becoming so highly concentrated in growing urban areas that the continent's pollution intensity (pollution generated per unit of production output) is now rated among the world's highest, attesting to significant regional difficulties in enforcing such regulations.¹⁶⁶

The predominance of informal sector activity in agricultural and industrial work in lower income countries poses serious regulatory challenges. Fumes and dusts from small-scale domestic businesses involved in smelting, battery recycling or manufacture, welding, pottery, ceramic production, and artisanal mining are common sources of exposure to lead and other heavy metals in developing countries, and put not only workers but whole communities at risk.¹⁶⁴ More recently, unregulated electronic waste (e-waste) recycling, in which salable metals are reclaimed from old electronics by burning, has emerged as a significant human and environmental health hazard in parts of China, West Africa, and India.^{7,104,160} Workers are often aware of the health risks, yet economic hardship and lack of alternative employment make them unwilling or unable to change.

Easy access to industrial chemicals from inadequate regulation of packaging and sales may also facilitate their use for intentional self-harm. For example, formic and acetic acids are used in the manufacture of rubber, and case series are reported from areas surrounding rubber factories in India and Sri Lanka.¹³⁹ Copper sulfate is widely used for self-poisoning in parts of South Asia, and carries a high mortality rate due to direct damage to the gastrointestinal tract, hepatorenal failure, and hemolysis^{6,144} (Chap. 95). Cyanide has become a commonly used method in Korea over the last 20 years¹⁰⁶ (Chap. 126).

REDUCING THE GLOBAL IMPACT OF POISONING

Regulatory science and the coordinated actions of agencies and programs across multiple sectors play a vital role in preventing or reducing the impact of poisoning in society. Within the health sector, significant inter-and intraregional disparities in access to health care have a major impact on poisoning outcomes. Lack of human resources to provide acute care is an enormous problem in many parts of the developing world. In Mozambique, there is only one trained medical doctor for every 33,000 individuals, compared with 1 in 390 persons in the United States. Tanzania has a nurse to population ratio of 1:2700 individuals compared with 1:107 individuals in the United States. Policies and programs encouraging sustainable and equitable health workforce development are needed foundation to improve health care access globally.⁵⁰

Beyond rectifying the raw numbers deficit, clinical training programs in many low and middle income countries must be upgraded to promote broad exposure and specialist development in clinical toxicology and acute care. Increasing local and international commitment to the growth of emergency medicine in low-and middle-income countries promises to support the dissemination of scientific knowledge and improve provider competence in advanced resuscitation techniques.^{8,16,70} Significant gaps in infrastructure and resources to provide basic critical care interventions and meet WHO minimum standards for essential emergency supplies must also be addressed.^{17,18,83}

In addition to global disparities in acute care infrastructure generally, access to antidotes for specific poisons is either lacking or inadequate in much of the world.^{10,131,176} Poor antidote availability is not unique to the developing world,⁵¹ and many antidotes may be considered either adjunctive or unnecessary therapies. However, in certain cases they can significantly reduce the need for other medical interventions, and this may be particularly important in rural or underdeveloped areas where critical care facilities are not readily available.¹³⁴ For example, the most important challenge to improving the treatment of patients with snakebite worldwide is poor antivenom availability, particularly in rural areas where it is most needed to reduce critical delays in administration.^{162,163} Currently, many available antivenoms are prohibitively expensive, ineffective, or have a high rate of adverse reactions. Equally important, some antivenoms must be refrigerated, making storage impractical in many rural areas where the need is most acute. Critical evaluation of existing antivenoms and development of new products are thus desperately needed^{24,30,76,77,105,162,163,172,175} (Special Considerations: SC8).

Where antidotes are available, knowledge and experience to know how to use them safely and effectively is often lacking.³² Input from experts in medical toxicology improves outcomes, reduces hospital stays and health care costs associated with acute poisoning,^{33,47,69} but practitioners in many parts of the world have limited or no access to consultation with such specialists. The mission of the International Union of Toxicology is to foster international scientific cooperation, ensure the development of toxicologists, and promote the dissemination of knowledge in toxicology worldwide.⁵⁵ Through the collaborative efforts of this and other regional professional societies, an increasing number of online, regional, and international forums now offer educational and professional development opportunities in clinical toxicology around the globe. More work is needed to promote awareness and the growth of the specialty in all regions.

Improving health care access and health system preparedness is only one aspect of the coordinated, multilevel, national, and international public health responses needed to reduce the global impact of poisoning. Prevention and risk reduction efforts must involve locally appropriate community level education and awareness raising, strong governance to support the design, implementation, and monitoring of regulatory controls, and the involvement of multiple stakeholders and sectors including water, waste management, energy, agriculture, transportation, industry, and civil society. Effective legislative frameworks developed in countries with more advanced public health infrastructure have been successfully disseminated in some cases. For example, between 2000 and 2004 the proportion of people with blood lead concentrations above 10 µg/dL globally decreased from 20% to 14%, largely due to the widespread phase out of leaded gasoline.¹³⁵ Other strategies, such as pharmaceutical and food safety regulations enacted through the US Food and Drug Administration, have influenced “duplicative legislation” in other countries but continue to pose significant implementation challenges in low and middle income countries that lack the necessary financing, human resources, and infrastructure to enforce them well.¹³⁰

Many public health measures with proven efficacy, such as routine lead testing during childhood, the regulation of vehicle emissions, the detection of carbon monoxide, and the incorporation of childproof containers may seem prohibitively resource intensive in many parts of the world. The development of new, low-cost technologies such as solar heating and electrical sources, chemical assays and residue detectors, and electronic devices to identify and track pharmaceuticals hold some promise to reduce global risks for unintentional poisoning. More research is needed to propose and evaluate the effectiveness, acceptability, and sustainability of new and proven poison prevention techniques in resource-limited environments.

Recognizing that self-harm from pesticide ingestion is responsible for a majority of acute poisoning deaths worldwide, public health interventions specifically designed to limit access are an important goal. A minimum pesticide list, based on the WHO essential xenobiotic list initiative, has been proposed.⁵⁹ Such a list would provide policy makers and farmers with unbiased information about relative risks. However, voluntary initiatives such as international policy statements and industry sponsored programs often suffer from a lack of resources, a shortage of political will, and nonexistent enforcement mechanisms.^{100,115} A dramatic illustration of an effective national program to reduce pesticide poisoning risks is the ban of all WHO high-risk OP insecticides and the organic chlorine endosulfan in Sri Lanka, which effectively arrested a previously exponential increase in the incidence of pesticide poisoning and halved the national suicide rate between 1995 and 2005.⁷³ This program is estimated to have saved more than 20,000 lives in 10 years.⁷³

Ironically, some programs to remove the most environmentally persistent and toxic chemicals from use have inadvertently replaced them with agents highly toxic to humans. The replacement of persistent organic chlorine compounds with carbamates in malaria control programs is an example. The opposite effect has also occurred, for example, by replacing OP insecticides with pyrethroids to reduce human toxicity.¹⁰⁰ Coordinated pesticide harm reduction strategies should take into account concerns regarding both environmental and human toxicity, and anticipate which xenobiotics will enter into use as replacements as specific chemicals are phased out.¹⁴¹ A strategy based on industrial hygiene models of a hierarchy of controls has been proposed by several authors^{115,141}(Table 137–2).

TABLE 137–2. Hierarchical Strategies to Reduce Pesticide Poisoning Mortality in the Developing World¹⁰⁸

E	Most	Eliminate the most highly toxic pesticides
F		Substitute with less toxic, equally effective alternatives
F		Reduce use through improved equipment
I		Isolate people from the hazard
C		Label products and train applicators in safe handling practices
A		Promote use of personal protection equipment
C		
Y	Least	Institute administrative controls

SUMMARY

- Poisoning is a common worldwide. Fatal poisoning is disproportionately concentrated in lower and middle income countries, where public health systems and acute care resources to detect, manage, prevent, and collect data on poisoning are often less well developed.
- Global poisoning estimates are mostly derived from health care sources in a minority of developing world countries; current data may underrepresent the true burden and distribution of injuries from poisoning.
- Efforts to develop international poisoning surveillance systems and establish harmonized definitions of poisoning cases will help generate a more complete picture to inform local, national, and international policies and interventions.
- Pesticides are the most important cause of death from acute poisoning worldwide, with a majority of cases attributable

to acts of deliberate self harm.

- Improving access to health care and health system preparedness to provide acute care is essential to reduce global disparities in poisoning outcomes.
- Randomized controlled trials and cost effectiveness research are needed to critically evaluate the utility of specific public health and treatment interventions in resource limited settings.

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138 PRINCIPLES OF EPIDEMIOLOGY AND RESEARCH DESIGN

Alex F. Manini and Kevin C. Osterhoudt

Advances in medical toxicology are achieved through the scientific method using observations, derived from cases of poisoning and nonpoisoning due to xenobiotic exposures, to generate hypotheses. Subsequent research questions are analyzed with epidemiological investigation, and preliminary studies are examined with methodological scrutiny. Initial analytical techniques are improved, and confirmatory studies are performed. Ultimately, models relating cause to effect are formulated.

To optimize patient care, it is useful to grade the quality of available scientific evidence used to justify treatment recommendations. Decisions about how strongly to recommend a medical action will be based on the careful consideration of the risks of leaving a patient untreated, the potential benefits and harms of treatment, the quality of the guiding evidence, a balanced view of resource utilization, and the values of the person to be treated. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group has provided a framework for assessing and communicating levels of scientific evidence ([Table 138–1](#)).²² An understanding of basic principles of research design and epidemiology is required to interpret published studies and to lay the groundwork for future investigation in toxicology.

TABLE 138–1. GRADE System for Evaluating Clinical Recommendations

<i>Strength of Recommendation</i>	<i>Quality of Evidence</i>
Strong	High
Weak	Moderate
	Low or very low
<i>Strength/Quality Aggregate</i>	<i>Implications</i>
Strong/high	<ul style="list-style-type: none"> • Recommendation can apply to most patients in most circumstances • Further research is unlikely to change our confidence in the estimate of effect
Strong/moderate	<ul style="list-style-type: none"> • Recommendation can apply to most patients in most circumstances • Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Strong/low	<ul style="list-style-type: none"> • Recommendation may change when higher quality evidence becomes available • Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Weak/high	<ul style="list-style-type: none"> • The best action may differ depending on circumstances or patients or societal values • Further research is unlikely to change our confidence in the estimate of effect
Weak/moderate	<ul style="list-style-type: none"> • Other alternatives may be equally reasonable • Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Weak/low	<ul style="list-style-type: none"> • Other alternatives may be equally reasonable • Any estimate of effect, for at least one critical outcome, is very uncertain

EPIDEMIOLOGIC TECHNIQUES AVAILABLE TO INVESTIGATE CLINICAL PROBLEMS

Table 138–2 lists the different study formats discussed below.

TABLE 138–2. Epidemiologic Study Designs: Types, Measurements, and Advantages

<i>Study Design^a</i>	<i>Main Measurement</i>	<i>Advantages</i>
Clinical trial	Efficacy	Gold standard for drug development
Noninferiority trial	Safety	Noninferior drugs may be better tolerated, cheaper, or easier to use
Cohort	Incidence, Risk Factors	Provides more robust evidence of association Reduced bias in exposure data Can study many outcomes simultaneously Allows direct calculation of incidence Allows direct calculation of relative risk
Case control	Association	Smaller sample required when outcome is rare Reduced bias in outcome data Can study many exposures simultaneously Allows estimation of relative risk May obviate need for long follow-up period
Analysis of secular trends	Population Trends	Examine trends in disease events over time Study across different geographic locations Can correlate them with trends in putative exposures
Cross-sectional	Prevalence	Uncover relationships for future study Highly feasible
Case series	Descriptive	Characterize new syndromes or exposures
Case report	Descriptive	Identify signals for hypothesis generation

^aStudy designs are listed in descending order from the design that offers the best epidemiologic evidence for association to that which offers the least.

Observational Design: Descriptive

A staggering array of xenobiotics are able to injure people, necessitating reliance of toxicologists on good descriptive data regarding toxic outcomes. Through 2011, the National Poison Data System (NPDS) of the American Association of Poison Control Centers (AAPCC) has amassed a database of more than 50 million human exposures ([Chap. 136](#)). Descriptive case reporting serves a valuable purpose in describing the characteristics of a medical condition or procedure and remains a fundamental tool of epidemiological investigation. A case report is a clinical description of a single patient or procedure in a unique context. Case reports are most useful for hypothesis generation. However, single case reports are not always generalizable, as the reported situation may be atypical. A number of case reports can be grouped on the basis of similarities into a case series. Case series can be used to characterize an illness or syndrome, but without a control group they are severely limited in proving cause and effect. In 1966, a case series of two patients with acute liver necrosis following overdose of acetaminophen (APAP)¹² was accompanied by a case report of liver damage and impaired glucose tolerance after APAP overdose,⁴⁰ which led to further study and the eventual creation of the Rumack-Matthew nomogram ([Chap. 35](#)). Similarly, a 1979 case report of “hypertension and cerebral hemorrhage after trimolets ingestion”²⁴ led to subsequent animal studies, experimental human studies, and epidemiologic studies culminating in the decision by the US

Food and Drug administration to remove phenylpropanolamine from nonprescription cold remedies and appetite suppressants ([Chap. 42](#)). The important role for descriptive data in guiding clinical research, focusing educational efforts, and formulating public policy are often underappreciated.

Cross-sectional studies assess a population for the presence or absence of an exposure and condition simultaneously. Such data often provide estimates of prevalence—the fraction of individuals in a population sharing a characteristic or condition at a point in time. These studies are particularly helpful in public health planning and have been extremely useful in monitoring common environmental exposures, such as childhood lead poisoning, or population-wide drug use, such as occurs with tobacco, marijuana, and alcohol. The US National Health and Nutrition Examination Survey demonstrated that the percentage of children with blood lead concentration greater than 10 $\mu\text{g/dL}$ decreased from 88.2% to 4.4% between 1976 and 1991, with the highest rates of plumbism among African American, low-income, or urban children.⁵

An analysis of secular trend is a study type that compares changes in illness over time or geography to changes in risk factors (ecological). These analyses often lend circumstantial support to a hypothesis; however, because of the ecologic nature of their design, individual data on risk factors are not available to allow exclusion of alternative hypotheses also consistent with the data. A prime example of an analysis of secular trends is the finding that reports of Reye syndrome declined between 1980 and 1985, coincident with a fall in sales of, or physician recommendations of, children's salicylate products.⁴ This investigation suggested an etiologic role of salicylate in the development of Reye syndrome but could not exclude alternative hypotheses such as a change in viral epidemic patterns.

Observational Design: Analytical

Hypotheses that are generated by theoretical reasoning or anecdotal association require analytical testing. Case-control studies and cohort studies are analytical techniques that use observational data, and each technique has its own advantages and disadvantages ([Table 138–2](#)). Case-control studies compare affected, treated, or diseased patients (cases) to nonaffected patients (controls) and evaluate for a difference in prior risk factors or exposures ([Fig. 138–1A](#)). Because participants are recruited into the study based on prior presence or absence of a particular outcome, case-control studies are always retrospective in nature. They are especially useful when the outcome being studied is rare, and they enable the investigation of any number of potential etiologies for a single disease.

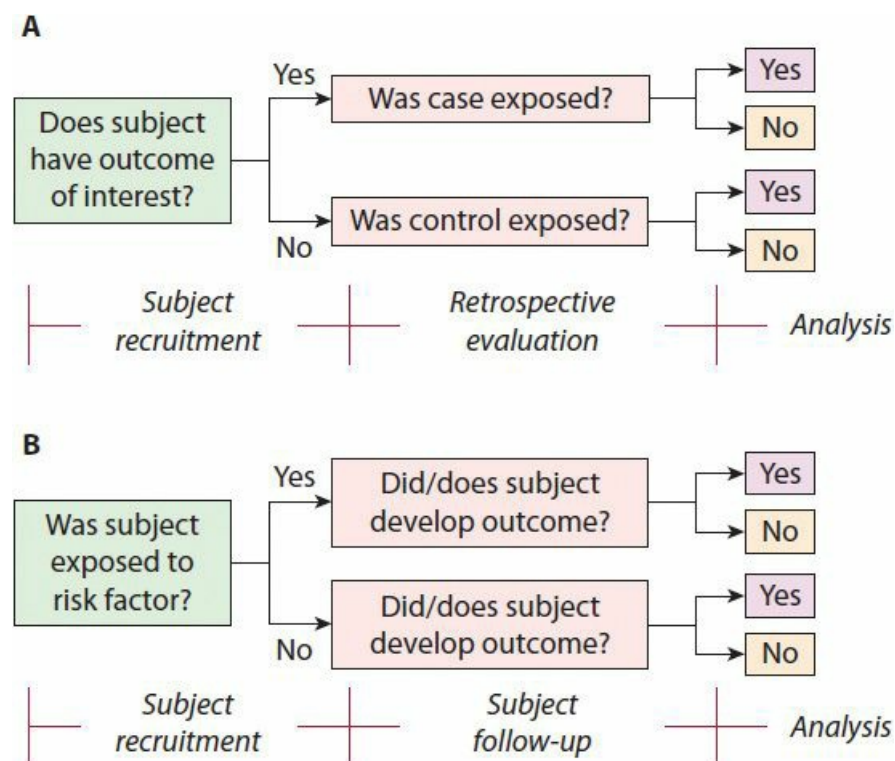


FIGURE 138–1. (A) Schematic representation of the case-control study design. Participants with an outcome or condition of interest are selected, along with control participants, and then are evaluated for previous exposure to a risk factor of interest. (B) Schematic representation of the cohort study design. Participants are recruited based on the presence or absence of a risk factor or exposure, then followed to see if they develop an outcome.

The hypothesis, derived from multiple case reports and case series, that phenylpropanolamine might increase risk for hemorrhagic stroke was well suited to case-control study. Exposure to ingested phenylpropanolamine, as an ingredient in cold remedies and appetite suppressants, was common; but hemorrhagic stroke is rare among children and young adults. Other putative risk factors such as tobacco use, hypertension history, family history, cocaine use, and contraceptive use were identifiable and could be studied simultaneously. In a case-control analysis of 702 participants with hemorrhagic

stroke and 1376 controls, the use of appetite-suppressant doses of phenylpropanolamine were found to be independently associated with the occurrence of hemorrhagic stroke.²³

Cohort studies compare patients with certain risk factors or exposures to those patients without the exposure, and then follow these cohorts to see which participants develop the outcome of interest (Fig. 138–1B). In this respect, they allow the comparison of incidence (the number of new outcomes occurring within a population initially free of disease over a period of time) between populations who share an exposure and populations who do not. They may be retrospective or prospective and enable the study of any number of outcomes from a single exposure. They are particularly well suited to investigations in which the outcome of interest is relatively common. In circumstances when an outcome of interest is very uncommon, such as the case with stroke after phenylpropanolamine use, the large number of study participants required might make a cohort study impractical. A cohort of 981 APAP overdose participants was used retrospectively to investigate whether administration of activated charcoal might be beneficial therapy for APAP poisoning.⁸ Participants were separated on the basis of whether or not they were treated with activated charcoal and were subsequently followed to see if they developed concentrations deemed toxic by the Rumack-Matthew nomogram. Perhaps the most famous cohort study was the Framingham Heart Study in which 5209 residents of Framingham, MA, aged 30 to 62 years, were followed for over 50 years. This study provided a useful tool for studying the incidence of lung cancer, stroke, and cardiovascular disease in those exposed to cigarette smoke and other hazardous xenobiotics.¹³

Experimental Design

Experimental studies are those in which the treatment, risk factor, or exposure of interest can be controlled by the investigator to study differences in outcome between the groups (Fig. 138–2). The prototype is the randomized, blinded, controlled clinical trial. Among epidemiologic study types, these provide the most convincing demonstration of causality. Clinical trials are used to measure the efficacy (the treatment effect within a controlled experimental setting) of treatment regimens and to draw inferences about the effectiveness of a treatment applied to the general population. Sometimes a trial can be designed to study drug treatments that are hampered by nonresponders to therapy, expensive drugs, or poorly tolerated regimens. Such trials are termed noninferiority trials, and operate on the null hypothesis that the new (study) drug is worse than the control (standard) drug. Thus, finding a difference between groups in a noninferiority trial means that the alternative hypothesis can be accepted that the new drug is not worse than the standard treatment.

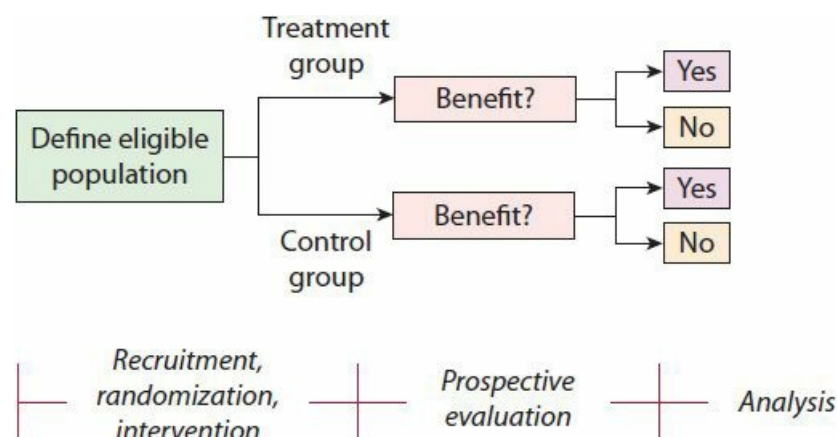


FIGURE 138–2. Schematic representation of the design of a randomized clinical trial.

Unfortunately, interventional studies are the most complex to perform, and several questions must be addressed by investigators before performing a clinical trial (Table 138–3). Human clinical trials have been especially difficult to apply to the practice of toxicology. Table 138–4 lists characteristics of poisoned patients, which hamper attempts at clinical trials. Volunteer studies, using nontoxic xenobiotics or nontoxic doses of toxic xenobiotics, are often used to circumvent many of the problems in controlling human poisoning studies; but it is typically difficult to apply results from these studies to the actual context of toxic overdoses. In an experimental, human volunteer study, activated charcoal reduced absorption of ampicillin by 57%.³⁹ Taken out of this artificial setting, a trial of single-dose oral activated charcoal was unable to prove benefit to outcome among 1479 heterogeneous participants presenting to an emergency department (ED) for possible poisoning.²⁹ Neither study was able to answer whether activated charcoal reduces morbidity from ingestion of dangerous xenobiotics if given while the xenobiotic is still in the stomach and amenable to adsorption.

TABLE 138–3. Considerations in Designing a Clinical Trial

What is the question of interest?
 What is the target patient population?
 How will the safety of subjects be assured?

What is a suitable control group?
How will outcomes be measured?
What difference in outcomes between groups is considered important?
What is the analysis plan?
How many subjects will be required?
How will randomization and blinding be achieved and maintained?
How long a follow-up period will be required?
How will loss of study subjects be addressed?
How will treatment compliance be evaluated?

TABLE 138–4. Difficulties in Utilizing Clinical Trials to Study Human Poisoning

It is unethical to intentionally “poison” subjects.
Poisoned patients represent a broad spectrum of demographic patterns.
A wide variety of xenobiotics exist.
Exposures to any single xenobiotic are usually limited.
A limited number of poisoned patients are available at any one study site.
Uncertainty often exists as to type, quantity, and timing of most xenobiotic exposures.
Poisoning typically results in a relatively short course of illness.

As toxicologists strive to find evidence for, or against, the traditions of clinical practice, several important clinical trials have been published. Among them are many important examples and lessons in epidemiologic study design. One trial attempted to evaluate whether or not corticosteroids might be beneficial in preventing esophageal strictures secondary to circumferential caustic injury of the esophagus.³ Because of the inherent difficulty in recruiting eligible patients from a single institution, only a small sample of 60 patients with esophageal injury were recruited over an 18-year period. Another study randomized hyperbaric oxygen therapy versus sham (placebo) therapy, among 152 victims of carbon monoxide poisoning, to investigate its effect on the development of neurocognitive injury.⁴² Certain concerns with the methodology and analyses of clinical studies are examined later in this chapter to illustrate epidemiologic concepts, and must be carefully considered when trying to apply the results of any clinical trial into the patient care setting.

MEASURES USED TO QUANTIFY THE STRENGTH OF AN EPIDEMIOLOGIC ASSOCIATION

The objective of analytical studies is to define and quantify the degree of statistical dependence between an exposure and an outcome. Such associations are ideally represented by the relative risk of developing an outcome if exposed in comparison to being unexposed. Thus, the relative risk can be defined as the incidence of outcome in exposed individuals compared to the incidence of outcome in unexposed individuals. The relative risk can be calculated directly from cohort or interventional studies. However, in a case-control study, an investigator chooses the numbers of cases and controls to be studied, so true incidence data are not obtained. In case-control studies an odds ratio can be calculated, and the odds ratio will provide an estimate for relative risk in situations in which the outcome is rare, such as when the outcome occurs in fewer than 10% of exposed individuals. **Figure 138–3** demonstrates the calculation of relative risk or odds ratio from analytic studies.

		Outcome	
		Yes	No
Exposure	Yes	a	b
	No	c	d

Cohort study
Relative risk = $\frac{a}{a+b} \div \frac{c}{c+d}$

Case-control study
Odds ratio = ad/bc

FIGURE 138–3. Use of a 2×2 table to calculate or estimate relative risk from analytic studies. In cohort studies, study participants are selected on the basis of exposure. In case-control studies, participants are selected on the basis of outcome. The letters a, b, c, and d represent the number of participants either exposed or unexposed to a “risk factor” or treatment, with or without the outcome of interest. The odds hazard ratios estimate the relative risk if the outcome of interest is rare.

A relative risk of 1.0 signifies that an outcome is equally likely to occur whether an individual either is exposed or is not exposed and implies that no association exists between the exposure and the outcome. A relative risk approaching 0 suggests that an exposure is a marker of protection regarding the outcome, and a relative risk approaching infinity suggests the exposure predicts a tendency toward the outcome. Among men and women using phenylpropanolamine appetite suppressants, the odds ratio for development of hemorrhagic stroke was 15.9 which suggests a strong association.²³

MEASURES USED TO QUANTIFY THE SIGNIFICANCE OF AN EPIDEMIOLOGIC ASSOCIATION

One of the essential features of research in medical toxicology is integration of the available data, whether clinical or experimental, into logical assumptions about how the overall system functions. Systems that are studied in medical toxicology research typically involve either elucidation of how a toxic insult influences normal physiology, or the mechanism and degree to which an antidote mitigates toxicity. Prior to undertaking a study, medical toxicology investigators may have no way of knowing whether their hypothesis is correct or applies at all. Thus, predictions made based on a priori hypotheses may be tested by performing experiments or by sampling observed data in an organized fashion. If the results are consistent with the predictions, then the hypothesis is retained. If they are not, then the prior hypothesis is rejected and a new hypothesis is formulated. This process is the basis of the scientific method and is also known as hypothesis testing.

Determination of whether the observed data in a toxicology investigation allow us to retain or refute our a priori hypothesis depends on our ability to gauge the certainty that the data were arrived at by chance. When observing a set of data, investigators can never be 100% certain that what they observed actually happened; it is possible that confounding factors biased what was observed, and it is possible that the observation was made simply by chance. To deal with this problem of interpretation, researchers use statistical methods to evaluate whether their data were arrived at by chance. The presence of an association between two factors in any given study has a number of possible explanations (Table 138–5).

TABLE 138–5. Types of Associations Between Exposures and Outcomes That May Be Found with a Clinical Study

No association	The outcome is independent of exposure.
Artificial association	
Chance	The association demonstrated by the study resulted from random error.
Bias	Systematic error in the study led to the noted association.
Indirect association	The association is real, but not truly cause and effect (confounding).
Causal association	The outcome is dependent on the exposure.

To differentiate between differences due to chance and potentially real differences between comparison groups,

researchers can use a philosophical trick known as the null hypothesis. The null hypothesis involves beginning experiments with the assumption that there is no difference between groups being compared. Thus, any significant deviation from observed and expected results under the null hypothesis allows the investigator to reject the null hypothesis and adopt the alternative hypothesis. The alternative hypothesis to the null is that the groups being compared are significantly different from one another (ie, not the same).

To begin, one must assign a probability percentage or P value to the likelihood that their observed results are really the case assuming the null hypothesis to be true. With some exceptions, the standard P value deemed to represent ability to reject the null hypothesis has historically been set to 5% (or $P < .05$) in medical toxicology epidemiologic science. This value is also termed the alpha (α), the significance level, the type 1 error, and can also be thought of in layman terms as the chance of falsely finding a difference between groups when one does not exist.

Because analytic studies involve only a sample of the total population, they contain two types of inherent error. Type 1 error, also referred to as an alpha (α) error, is the likelihood that an investigator may conclude that an association exists when none truly does. Type 2 error, or a beta (β) error, is the possibility that an investigator will be unable to find an association when one is really present. The most commonly reported measures of type 1 error in published toxicology studies are the P value and the confidence interval (CI). Statistical significance has customarily, but not necessarily, been defined as having less than a one in 20 chance of conducting a false-positive study. Therefore, a type 1 error of less than 5%, which corresponds to a P value of less than 0.05, is usually deemed “statistically significant.” In some cases investigators must use a significance level (P value) even lower than 0.05 when testing multiple hypotheses at once, for example, in genetic marker studies examining multiple genes across an entire genome. Such a correction is termed the Bonferroni correction, and is applied as the P value divided by the number of variables being tested at once: $P = (\text{significance level}) / (\# \text{ concurrent variables})$.³⁷ The result is a smaller (ie, more stringent) corrected significance level for studies that test multiple hypotheses at once. For example, if a study protocol uses a genetic “chip” assay to evaluate 50 markers at once for an association with a predetermined disease in a population, the Bonferroni correction would require significance at $(0.05)/(50) = 0.001$ in order to deem any association to be statistically significant.

Perhaps a more informative description of the significance of an association is provided through the CI. The CI not only provides a test of statistical significance, it also offers information pertaining to the degree (and possible range) of differences observed. In an unbiased study, the 95% CI provides a range between which, if the study could be repeated an infinite number of times, the observed point estimate would fall between the CI 95% of the time. For example, one study reported that no toddlers ingesting one or two calcium channel blocker tablets became seriously ill, but a subsequent analysis of the CI around this small set of data demonstrated that the true incidence could be as high as 18%.³² A CI around a relative risk or odds ratio is not statistically significant if it includes 1.0, and the narrower the CI the more precise the estimate of the magnitude of effect.

The likelihood that a study will find a difference if one truly exists is termed statistical power and relates to the likelihood of a false-negative study (type 2 error). Power is usually artificially set by an investigator before a study is performed and is typically set at 80% or 90% to practically limit the number of study participants needed. [Table 138–6](#) lists considerations applicable to choice of sample size. The sample size of a study is determined by the frequency of the exposure and outcome within the study population, the strength of association deemed clinically relevant, and the amount of error deemed acceptable in the study. Because power is often set relatively low, it is difficult to state that an association does not exist. It is more appropriate to state that a study was unable to reject the null hypothesis to find an association.

TABLE 138–6. Considerations in Choice of Sample Size

	<i>Sample Size</i>	
	<i>Large</i>	<i>Small</i>
Pros	<ul style="list-style-type: none"> • Able to detect associations of small magnitude • Less susceptible to some biases • More robust analysis 	<ul style="list-style-type: none"> • Less work • Less cost
Cons	<ul style="list-style-type: none"> • More work • More cost 	<ul style="list-style-type: none"> • Might not detect associations of small magnitude • More susceptible to biases associated with patient differences

The finding of a low P value indicates a statistically high level of confidence that a difference between study groups exists but offers no indication that the difference is clinically important. The interpretation of statistical versus clinical significance is often facilitated through calculation of CIs. Small actual differences between two groups can become

statistically significant if large numbers of participants are studied. Likewise, impressive associations of cause and effect can seem trivial if few participants are in a study. The clinical significance of an association is left to the judgment of the individual interpreting a study. Ideally, a working definition of clinical significance is developed before a study is performed.

METHODOLOGIC PROBLEMS FOUND WITHIN CLINICAL STUDIES

The calculation of a P value or CI does nothing to assess the adequacy of study design. These measures are used to quantify the influence of random error, or chance, on research findings. Clinical research involving patients is particularly susceptible to bias, which can be defined as systematic error in the collection or interpretation of data. Because such error can lead to an inappropriate estimate of the association between an exposure and an outcome, careful evaluation of potential biases affecting a clinical study is of paramount importance.

Selection bias refers to error introduced into a study by the manner in which participants are selected for inclusion in the study. This type of bias is most problematic for retrospective studies in which exposures and outcomes have both occurred at the time of participant recruitment. Selection bias may be introduced into a prospective clinical study if the study fails to enroll potential participants, or if potential participants refuse to participate, on a systematic basis. Selection bias may even influence the results of clinical trials. In a 1995 trial that found no difference in outcome between acutely poisoned patients treated with gastric emptying and patients from whom gastric emptying was withheld, all patients presenting to the ED after acute overdose were enrolled.³⁵ Because most patients with poisoning exposure are likely to do well with minimal support, selection of patients on this basis might be expected to bias this study to find no effect. Reasoning suggests that the patients most likely to benefit from gastric emptying are those with life-threatening toxic ingestion presenting within the first hour after overdose. Indeed, subgroup review of the results of this paper suggests clinical benefit within this group of patients, but without conclusive power.

Information bias refers to error introduced into a study as a result of systematic differences in the quality of data obtained between exposed and unexposed groups, or between those with and without the outcome of interest. Several distinct types of information bias may exist. Affected and nonaffected individuals may have differential memories regarding exposures, so recall bias is a concern in retrospective studies. The potential for recall bias may be cited as criticism of retrospective case-control studies of the association between phenylpropanolamine and hemorrhagic stroke, in which patients and families were asked to recollect their phenylpropanolamine use history. Stroke victims and their families might be more vigorous in their recall of exposures than control participants. Similarly, interviewer bias may occur if study personnel differ in how they solicit, record, or interpret information as a result of knowledge of participant status regarding exposures or outcomes.

Prospective studies may be troubled by loss to follow-up, especially if participants are lost from the study for reasons relating to either exposure or outcome such as when participants withdraw from a study because they are feeling better, or are “lost” because they die. Misclassification bias occurs when investigators incorrectly categorize participants with respect to exposure or outcome. In a retrospective study of 378 children regarding the predictability of caustic esophageal injury from clinical signs and symptoms, it was found that 11 of 80 asymptomatic children had significant burns.¹⁴ There is a possibility that these “asymptomatic” children were misclassified because of lack of rigorous written documentation of symptoms or signs within the medical charts. In addition, studies that use “cause of death” as an outcome may be vulnerable to misclassification as well. In a large study comparing 414 poison center (PC) deaths with 7050 poisonings in the corresponding Vital Statistics database, the medical examiner and a medical toxicologist adjudication panel concurred on “cause of death” in only 66%, which the authors interpreted as only fair (ie, less than good) agreement.²⁶ Thus, when investigators define “cause of death” as their study outcome, their results may be biased depending on which specialists are used to provide the “cause of death” interpretation.

Bias is best minimized through careful study design. It is important to precisely define the study question and the population at risk and to carefully define rigorous inclusion and exclusion criteria. The outcome should also be defined precisely. During data acquisition the best way to reduce bias may be to keep study personnel gathering exposure data blinded to outcome, and vice versa. Often, it may also be advisable to keep study participants unaware of their status within a study to the extent that it is ethical (thus, “double-blinded”—neither investigators nor participants are aware of the participants’ status within a study). Use of placebos or “sham treatments” is a way to facilitate blinding. One of the strongest criticisms of a 1995 trial of HBO for the prevention of delayed neurologic syndromes after CO poisoning³⁶ has been the failure to blind patients and investigators to the treatment in question,³¹ a flaw that was corrected in a follow-up study published in 2002.⁴² It is inevitable that some degree of potential bias will be present in any clinical study. Such bias should be reviewed in the analysis, and estimations of its magnitude and direction (bias toward or away from rejection of the null hypothesis) should be considered.

Unlike selection and information biases, which are errors introduced into studies primarily by the investigators or participants, confounding is a special type of problem that may occur within a study as a result of interrelationships between the exposure of interest and another exposure. Confounding is a bias wherein an observed association is not a

product of cause and effect but instead results from linking of the exposure of interest to another associated exposure. Studies pertaining to adverse effects of drugs of abuse are especially prone to confounding by variables such as concomitant caffeine use, alcohol use, tobacco use, nutritional deficiency, and/or psychiatric illness. Analytic studies may restrict characteristics of enrolled participants or match participant characteristics between comparison groups in an effort to reduce confounding. Accordingly, it has been suggested that future studies on delayed neuropsychiatric manifestations following CO poisoning control for potential confounding from depression and cyanide exposure.²⁷ During data analysis, confounding can often be controlled through stratification of data into subgroups or through multivariate analysis techniques.

Randomization is of central importance in clinical trials. It prevents selection bias and insures against unintended bias. It is also an important method to assure that unsuspected confounding factors are equally distributed between treatment groups within interventional studies. The four common types of randomization include (1) simple, (2) block, (3) stratified, and (4) unequal randomization. The simple method is equivalent to tossing a coin for each participant who enters a trial, such as heads = active, tails = placebo. Generally, a random number generator is used for this type of randomization. Block randomization is often used to guarantee balance in numbers during a clinical trial. The basic idea of block randomization is to divide potential patients into m blocks of size $2n$, randomize each block such that n patients are allocated to A and n to B, and then to choose the blocks randomly. Less common is stratified randomization to prevent imbalance in prognostic factors that may confound estimating treatment effect. Stratified randomization achieves balance within important subgroups. For example, using block randomization separately for diabetics and nondiabetics in a cardiovascular trial. And finally, unequal randomization may be used when two or more treatments under evaluation have a cost difference such that it may be more economically efficient to randomize fewer patients to the expensive treatment and more to the cheaper one.

In order to improve the reporting of clinical trials, and to improve the recognition and interpretation of biases within them, guidelines referred to as the Consensus Standards of Reporting Trials (CONSORT) have been adopted by many medical journals.³⁰ The CONSORT guidelines provide a checklist to allow authors to systematically and uniformly report data and limitations. When interpreting published studies, it is also important to consider the potential for publication bias. Publication bias refers to the tendency for researchers, editors, and pharmaceutical companies to handle the reporting of studies with positive results differently from those with negative or inconclusive results.³⁸ Many journals now require that researchers register all planned clinical trials into a registry as a prerequisite for subsequent publication.

BIASES INHERENT IN STUDIES USING THE AMERICAN ASSOCIATION OF POISON CONTROL CENTERS DATABASE

The NPDS database of the AAPCC is an ambitious effort to catalog and describe the epidemiology of poisoning in the United States and Canada. These data serve to help identify new poisoning epidemics, focus prevention and education efforts, guide demographic and economic poisoning analyses, and guide implementation of public health policies. It is a desirable goal to use this database in defining the scope of toxicity for particular xenobiotics and as a clinical research tool. In this regard, it is important to understand the biases inherent in the current database.

It has been suggested that selection bias might exist within PC data if poisoning is unrecognized as a cause of illness or if a caregiver has no questions pertaining to the management of a recognized poisoning.²² Indeed, a survey of 170 emergency physicians in Utah found that 53% admitted to using a PC for symptomatic acute overdoses, and only 10% contacted PC for the purposes of reporting cases to the national database.¹⁰ Such selection might result in a bias of PC data toward more severe cases. On the other end of the spectrum, two large investigations have found selection bias in PC data suggesting that fatal poisonings may be severely underrepresented.^{19,26} It is interesting to note that in a 2004 report of the Institute of Medicine,²¹ the estimated range of annual fatal poisonings in the United States was from approximately 1000, derived from AAPCC data, to more than 30,000, derived from other databases. A study of potential spectrum bias in PC utilization found that one ED reported 95% of cyclic antidepressant overdoses, 33% of venomous snakebites, and only 3% of inhalation exposures.¹⁷ Further complicating the interpretation of PC data are the findings that such data may also be biased regarding geographic distribution of callers,² age,³⁴ ethnicity,^{2,11,34,41} and socioeconomic status.⁴¹

Knowledge of information bias within NPDS data is less well characterized. Phone interviews of callers, many under duress, are certain to be subject to recall and interviewer bias. A comparison of rural hospital chart data to the NPDS database demonstrated deficiencies in PC reporting and in clinical information transfer to the NPDS database.²⁰ Loss to follow-up remains a problem for many PCs, and misclassification of poisonings by health care professionals inadequately trained in medical toxicology remains too common. The clinical conundrum of the unwitnessed ingestion frequently becomes an issue in PC-derived studies designed to create triage policies. Some children having never ingested a xenobiotic of concern may be misclassified as an exposure and may be improperly analyzed.²⁵

Another potential weakness of PC data involves potential misclassification of substances considered by regional consultants and caregivers. Postmortem toxicology can be a surrogate marker for the accuracy of exposure information reported to PCs in fatal cases. Previously, a putative analysis was undertaken at the New Jersey PC to characterize the

discordance between PC consultation and postmortem toxicology.¹⁶ The researchers found that in 41 of the 206 (19.9%) fatal cases receiving poison center consultation, substances were found at the time of postmortem examination that were not considered in the poison center consultation. This study highlights the potential for discordance between exposures considered and those confirmed by forensic toxicologists. The reasons for discordance may include a lack of thorough history taking or a cognitive bias to the substances initially reported.

Despite the large volume of descriptive poisoning data available, it has proven difficult to derive valid, clinically useful conclusions from either the NPDS database or from published case reports.⁶ One suggested means through which to minimize information bias in descriptive toxicology is through the use of improved data collection charts.⁷ One large data collection effort underway to address this particular issue is the Toxicology Investigators' Consortium (ToxIC), supported by the American College of Medical Toxicology, a prospectively collected data registry of patients seen by medical toxicologists at myriad hospitals and medical centers across the United States. Other researchers have found it useful in clinical studies to transform PC data collection from a passive to an active process through the use of specific research instruments.²⁸ Further efforts are required to reduce and to quantify the impact of selection, interviewer, recall, misclassification, and information biases within PC data to optimize the value of this important resource.

EVIDENTIARY CRITERIA USED TO LINK CAUSE AND EFFECT

As was illustrated in Table 138–5, association of an exposure to an illness does not necessarily equate to cause and effect. In assessing causation, it must be determined if bias is present in the selection or measurement of exposure or outcome. If a study is unbiased, then the role of chance in the occurrence of the observed association must be explored. If an association is unbiased, unlikely to result from random error, and is not subject to confounding, then assumptions regarding to causation can be derived. Table 138–7 provides a list of evidentiary criteria, first proposed by Bradford Hill in 1965,¹⁸ that are often used to support causation.

TABLE 138–7. Bradford Hill Criteria for Determining Causation

Strength	What degree of relative risk or odds ratio was demonstrated in the analysis?
Consistency	Does the cause and effect hold true in different studies, locations, and populations?
Specificity	Does the effect occur without the cause in question, or vice versa?
Temporality	Does the cause precede the effect?
Biologic gradient	Is there a dose–response effect?
Plausibility	Is the association consistent with the current understanding of the biological system?
Coherence	Is the association compatible with existing theory and knowledge?
Experiment	Was the association demonstrated in a well-designed study?
Analogy	Is there another cause–effect relationship in nature that is similar to the one in question?

In medical toxicology it is virtually impossible to prove causal relationships beyond any doubt. The goal is to build empiric evidence so that associations can be confirmed or refuted with conviction. However, many toxicologists deem clinical trials indicating a lack of benefit from gastric emptying, or indicating a therapeutic benefit of HBO therapy for CO intoxication, unconvincing because of the degree of bias present in all relevant published clinical trials. To address this issue, some consensus works (from position papers to formal consensus studies) attempt to provide guidance to clinical toxicologists regarding interventions where equipoise remains despite published clinical trials. For example, the Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument is widely used in consensus guidelines. The instrument in its present form has been updated as “AGREE II” and is composed of 23 items organized into six quality domains (scope, stakeholders, rigor, clarity, applicability, independence).¹

INFERENTIAL STATISTICAL TESTS

As discussed previously, researchers must devise an appropriate statistical test to determine whether or not their data were arrived at by chance, a process known as inferential statistics. Once the significance level has been chosen, the inferential statistical test of choice depends on the type of data that are being collected. It should be noted that using the wrong statistical test for a given set of data will invalidate the results of a study; thus, choosing the correct statistical test is of paramount importance for research study design, as well as for toxicologists who try to interpret published medical studies.

Once the significance level has been set, then the data must be classified by type. Generally, data are either: (1) categorical/nominal (≤ 2 categories of data with no intrinsic ordering, eg, presence/absence of medical comorbidities), (2) continuous/interval (data along a scale where each value is equidistant from one another, eg, dollar values), or (3) ordinal/ranked (≤ 2 categories of data with clear intrinsic ordering, eg, grade in high school). The method used to compare groups of data thus depends on whether data is categorical, continuous, or ordinal. Most commonly, categorical data are compared in terms of ratios/percentages (Chi-squared test) and continuous data are compared in terms of means (student's t-test) or medians (Mann-Whitney U test). As a general rule of thumb, an ideal analysis involves comparing interval/ratio data between groups due to the fact that this data contains more information than any of the other forms of data. Finally, the number and relatedness of the independent variables for analysis must be determined. Most commonly, two unrelated samples are compared to assess for associations. However, there are times when groups are paired or related, such as in clinical trials with before/after data in the same participants. Additionally, it is possible to use more advanced techniques to compare three or more independent variables at once (Table 138–8).

TABLE 138–8. Parametric vs. Nonparametric Inferential Tests Based on Data Type

<i>Data Type</i>	<i>Parametric Test</i>	<i>Nonparametric Test</i>
Continuous/interval		
Related samples	Paired <i>t</i> -test	Wilcoxon signed rank
Unrelated samples	Independent samples <i>t</i> -test	Mann-Whitney U
≥ 3 groups	ANOVA	Kruskal Wallis
Correlation	Pearson R	Spearman rho
Nominal/categorical		
Related samples	Chi-squared Fisher exact	McNemar
Unrelated samples	Chi-squared Fisher Exact	Mantel Haenszel trend
≥ 3 groups	Chi-squared	Cochran-Armitage
Correlation	Kappa	Spearman rho
Ordinal/Ranked		
Same scales	Not applicable (NA)	Mann Whitney U
Different scales	NA	Wilcoxon signed rank
≥ 3 groups	NA	Cochran-Armitage
Correlation	Spearman rho	NA

Inferential statistical tests are generally classified into parametric versus nonparametric techniques. This distinction is based on the fact that statistical tests make varying assumptions with regard to the population parameters that characterize the distributions for which the test is employed. Parametric tests generally make more stringent assumptions upon the data to produce valid results, while nonparametric tests make few if any assumptions about the data parameters and can thus be thought of as a “backup” test if the parametric assumptions are not met. For example, the *t*-test assumes that the two groups being compared are independent of each other, and that the dependent variable is continuous and normally distributed along a bell-shaped curve (also known as a Gaussian distribution). Similarly, the Chi-squared test assumes independent observation from a random selection of a given population with a large enough sample size such that any cell in the resultant 2×2 table is greater than five. A violation of one or more of these basic assumptions renders the test results invalid and mandates application of the nonparametric versions of these tests. A summary of common parametric and nonparametric tests based on data classifications is illustrated in Table 138–8.

EVALUATION OF DIAGNOSTIC TESTS AND CRITERIA

In clinical practice it is often useful to have a test, which may be a laboratory result or clinical paradigm, to help arrive at a diagnosis or predict an outcome. For instance, historical questionnaires, capillary blood lead concentrations, and venous blood lead concentrations might all be used to identify children at risk of neurocognitive injury from plumbism.⁹ However, each of these approaches is likely to have certain disadvantages in terms of effort, cost, discomfort, and/or accuracy. Targeting lead evaluation and therapy in children on the basis of exposure history is expected to be easy and inexpensive, but may not identify some children with significant poisoning; thus, the test may be susceptible to being falsely negative. Capillary blood testing is more costly and uncomfortable and may be susceptible to false-positive test results because of environmental lead dust present on fingertips. The possibility of false-positive or false-negative results must be considered

with any diagnostic test (Fig. 138–4).

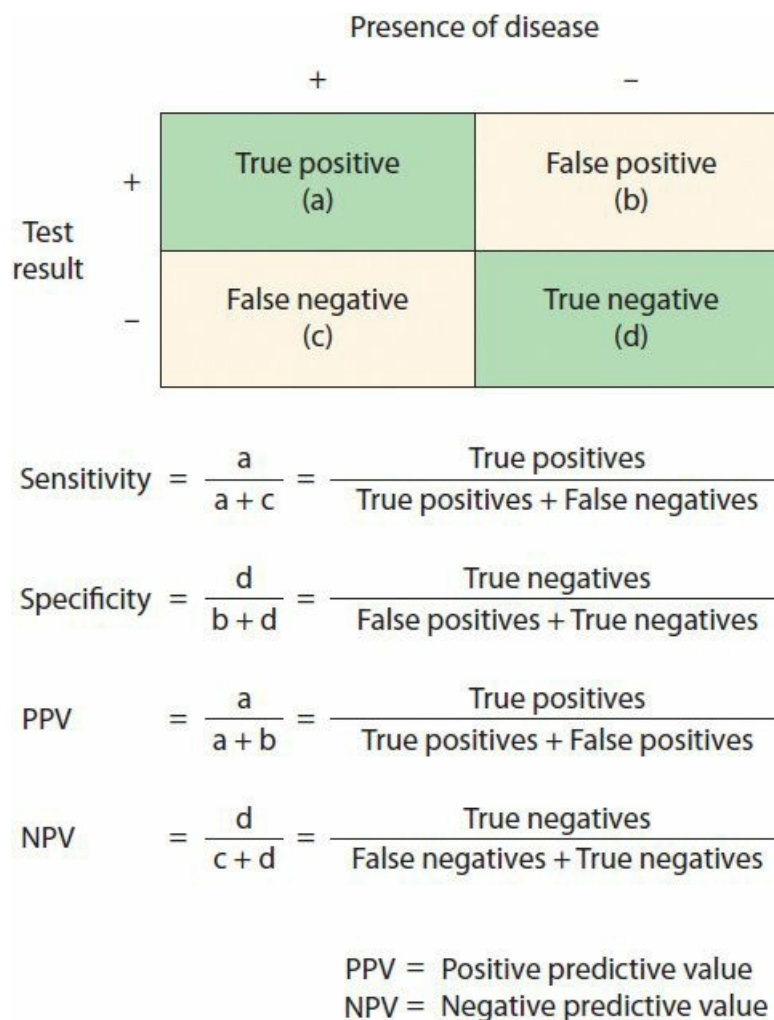


FIGURE 138–4. Possible results of diagnostic testing and the statistical characteristics used to describe the utility of diagnostic tests. The letters a, b, c, and d represent the numbers of tested individuals with or without the disease of interest.

The utility of diagnostic testing is often described in terms of sensitivity, specificity, predictive value of a positive test (PPV), and predictive value of a negative test (NPV). A cross-sectional design is often used to study diagnostic tests, as we seek to determine the prevalence of positive tests among the diseased (sensitivity), and the prevalence of negative tests among the healthy (specificity). A perfect test would be highly sensitive and specific, but this is seldom possible. A highly sensitive test (eg, D-dimer to assess for pulmonary embolism) is often used in screening programs because they rarely lead to false-negative diagnoses. Specific tests (eg, cardiac troponin to assess for acute coronary syndrome) are typically used to “rule-in” a diagnosis, as they rarely yield false-positive results. Whereas sensitivity and specificity are inherent properties of a diagnostic test applied to a given population, the probability of disease—based on the results of a test—is highly dependent on the prevalence of disease within the population being tested. The PPV is the probability of having disease in a patient with a positive test; the NPV is the probability of not having disease when the test result is negative. Numerous studies have tried to examine the utility of vomiting, leukocytosis, hyperglycemia, total iron-binding capacity, and radiographic findings in predicting toxicity after acute iron overdose. In a retrospective assessment of 40 adults with oral iron overdose, vomiting was found to predict a serum iron concentration above 300 µg/dL with a sensitivity rate of 84%, specificity of 50%, NPV of 44%, and PPV of 87%.³³ This suggested that the presence of vomiting should raise concern for iron toxicity but that the lack of vomiting was not particularly reassuring. Figure 138–4 illustrates the calculation of the sensitivity and specificity rates, as well as the PPV and NPV. It is important to remember that these calculations, too, are subject to bias and are best presented with CIs.

Galen, an influential physician from the second century, remarked of his clinical trial, “All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.” Unfortunately, error in contemporary clinical investigation of poisoning tends to be more insidious than the error in logic in Galen’s conclusion, and skillful scrutiny of published research remains an important endeavor.

SUMMARY

- Medical toxicology has embraced the vision of incorporating “evidence-based, or literature-based, medicine” into practice.

- Randomized clinical trials, although a noble goal, are rare and have proven difficult to perform within the discipline.
- As toxicologists move beyond descriptive data reporting, there remains great potential for scientific advancement in the field of toxicology via observational, hypothesis-testing, clinical research.
- Clinical investigators are charged with the imperative to perform studies based on sound epidemiologic principles.
- All studies, by nature of population sampling, are at the mercy of chance, but such random error can be quantified using statistical techniques.
- Systematic error (bias) can be limited, but not entirely excluded, through careful study design.
- Clinicians interpreting published toxicologic research need to thoroughly evaluate a study's research objectives, design, data acquisition, analysis, and conclusions before applying the results to patient care (Table 138–9).

TABLE 138–9. Questions to Consider When Evaluating a Study

Research objectives What is the study question? What is the studied population?
Study design What type of study was performed? How were participants recruited and enrolled? Why were participants excluded? What was the nature of the comparison group?
Data accrual How were the data collected? Are the exposures and outcomes clearly defined? Are the observations reliable and reproducible? Was randomization and/or blinding used? Were participants lost to follow-up?
Analysis Are the results statistically significant? Are the results clinically significant? Are potential confounding variables controlled? Was the study powered to detect important differences?
Conclusions Are the conclusions justified by data?

- Future epidemiological investigation should allow more valid conclusions to be drawn regarding the associations between exposures and outcomes, or regarding the value of treatments for poisonings, discussed in the preceding chapters of this text.

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139 DRUG DEVELOPMENT, ADVERSE DRUG EVENTS, AND POSTMARKETING SURVEILLANCE

Louis R. Cantilena

This chapter will focus on drug-induced diseases that occur as expected or unexpected adverse drug events (ADEs), as a drug–drug interaction or an ADE causing an untoward drug–disease interaction. Also included in this chapter is a discussion of an approach to the diagnosis of drug-induced disease, an overview of the new drug approval process in the United States, monitoring of drug safety postapproval, and the suggested role for the medical toxicologist in the discovery, reporting, and prevention of ADEs.

ADEs are defined as untoward effects or outcomes associated with use of a drug. In this chapter, the word “drug” will be used for a pharmaceutical product and includes prescription and nonprescription medications, and dietary supplements.

In the United States, all new prescription and nonprescription medications must be shown to be both safe and effective in order to achieve approval by the US Food and Drug Administration (FDA), a prerequisite for marketing and sale. Dietary supplements fall outside of this legal requirement ([Chap. 45](#)).

HISTORY OF THE UNITED STATES DRUG APPROVAL PROCESS

The evolution of drug product regulation in the United States has generally been reactionary; that is, most drug regulations were created in response to medicine related disasters at various times in our history. Prior to 1900, there was no requirement for a drug or medical device manufacturer to demonstrate that the product actually worked (efficacy), was safe when used as directed, or was made to be within precise manufacturing specifications. In addition, no laws existed that required labeled claims be proven valid. Any product could be sold as a company desired and it was left to the consumer or health care professional to determine if the products actually worked and were safe. Initiation of medicinal product regulation and the overall evolution of the US drug law and regulations are closely linked to specific medical product disasters that occurred during the twentieth century in the United States. Relatively recent changes in US drug approval law further changed drug review timelines and prioritization of drug application reviews. Most recently, specific provision of the FDA authorization has designated certain medication classes, such as antimicrobials, to receive extended patent protection as an incentive to develop new medications in an area where growing antibiotic resistance is on the rise and has become a public health concern.

Examples of the pre-1900—or preregulation—marketed products include aspirin containing heroin sold as cough syrup and wine with cocaine to enhance sales of the alcoholic beverage. There was no legal requirement for systematic testing of products to determine content or the presence of possible adulterants in product formulations. The Pure Food and Drug Act of 1906 required pharmaceutical manufacturers to meet a standard for the concentration and purity of the drugs they marketed. However, the burden of proof was on the FDA to show that the drug was incorrectly labeled or that the advertising or label was false or misleading. To a large extent this is the current regulatory state for dietary supplements.

The Food, Drug, and Cosmetic Act of 1938 resulted from a tragedy in which more than 100 patients (mostly children) died from poisoning by an excipient used in an oral solution of sulfanilamide, an antibiotic. Massengil, a pharmaceutical company, in an attempt to improve the palatability of a pediatric formulation of a sulfanilamide, added the solvent diethylene glycol to the formulation. Diethylene glycol is a sweet-tasting, but nephrotoxic hydrocarbon. Only after almost a full year of marketing were cases of renal failure and death reported in sufficient numbers to alert authorities to the extremely toxic nature of the product. The Food, Drug, and Cosmetic Act of 1938 accomplished the following:

- Required companies to list the ingredients on each product label
- Required companies to provide the known risks concerning use of the product to physicians or pharmacists
- Made illegal the misbranding of food or medical products
- For the first time, required companies to test their products for safety before being sold

Drugs already marketed before 1938 were exempt from the requirement ([Chap. 1](#)).

The Kefauver-Harris Amendments to the Food and Drug Act of 1962 resulted from the drug approval disaster that occurred in Europe and not in the United States. An application in the early 1960s for the approval of α -N-phthalylglutaramide (thalidomide), a sedative hypnotic already marketed in Europe at the time, was submitted to the FDA for review and approval. The sedative hypnotic had a rapid onset and short duration of action, did not affect ventilation, did not cause a morning-after effect, and was inexpensive. Dr. Frances Kelsey, a medical officer at the FDA, delayed approval by asking the sponsor to clarify several issues in the reportedly poorly organized new drug application (NDA). In the interim, an unusual teratogenic effect, phocomelia, or limb misdevelopment, was linked to the use of thalidomide in Europe. Congressional hearings on the “almost” approval for marketing in the United States resulted in the Kefauver-Harris Act of 1962, which required a drug manufacturer or sponsor to do the following:

- File an investigational new drug (IND) application prior to initiating a clinical study with a drug in humans
- Demonstrate that the drug was effective for the condition that it was being marketed to treat
- Provide adequate directions for safe usage of the drug

The act also was not retroactive and drugs that were already on the market were exempt from these new requirements. However, the Waxman-Hatch Act of 1983, among other things, incentivized companies to establish evidence in support of actual indications for an exempt drug. The effects of this incentivisation were demonstrated when a small pharmaceutical company studied the use of colchicine in gout which the company applied for, and subsequently received exclusivity leading to a 50 fold increase in the price of this ancient drug.¹⁷

Subsequent US food and drug laws that have primarily affected FDA review and approval of products include the following:

1. The Orphan Drug Act of 1983: The act provides financial incentives to drug manufacturers to develop drugs for the treatment of rare diseases and conditions (see <http://www.fda.gov/orphan/designat/list.htm> for a list of drugs that are approved under the Orphan Drug Act). A rare disease is defined as one in which there are less than 200,000 affected persons in the United States, or one affecting more people, but in which the cost of drug development is likely to exceed any potential sales of the drug (<http://www.fda.gov/orphan/oda.htm>). Some perverse outcomes due to marketing exclusivity have resulted. For example, colchicine received 7 years of marketing exclusivity after study of its use in patients with Familial Mediterranean Fever.¹⁷
2. The Prescription Drug User Fee Act (PDUFA) of 1992: The Act requires that manufacturers pay user fees to the FDA for NDAs and supplements to enable the FDA to hire additional reviewers and accelerate the review process. This Act, which has undergone several revisions (the latest in 2007), has proven to be controversial due to the new working relationships created between industry and regulators, and the concern that it may lead to compromises that are not in the best interest of public health.

The question remains as to whether or not the introduction of user fees and their associated mandate for shorter FDA review times for NDAs have had the desired impact.³⁷ A recent comparison of review times over the first four Prescription Drug User Fee Act (PDUFA) authorizations did not find a substantial improvement.⁶ Compared with European Medicines Agency (EMA) and Health Canada, the analogous agencies to FDA in those regions, the FDA already had, and has maintained, significantly shorter review times over the past decade.⁶ Additionally, some believe that the shorter review times for FDA approval appear to be associated with an increased likelihood of drug withdrawal and black box label modification of the drug label postapproval,² although others do not concur.⁴⁰ The debate on this issue intensified during the controversy involving the cyclooxygenase-2 (COX-2) inhibitor antiinflammatory drugs. This widely publicized withdrawal and press coverage of the related litigation resulted in congressional hearings on the review practices and monitoring of drug safety by the FDA. The legislation has evolved to attempt to provide FDA with regulatory authority, adequate funding, and to encourage scientific exchange between the FDA and sponsors of drug products during the drug development process with the goal of improved quality and efficiency of the development process. PDUFA V, the fifth reauthorization of the FDA covering the period of 2013 to 2017, was recently approved.

3. The Dietary Supplement Health and Education Act (DSHEA amendment) of 1994: The Act removed from FDA the authority to require proof of safety or efficacy prior to marketing of products considered dietary supplements (including herbal remedies). Only when the manufacturer of a product makes a specific health claim, such as “treats congestive heart failure,” does the FDA have premarketing approval authority. That is, the use of structure or function claims, such as “supports heart function,” obviates the need for approval. Furthermore, rather than placing on the manufacturers the burden of proof for safety and efficacy of a product, the FDA is required to determine that a product is unsafe to prevent sale and distribution in the United States. Few dietary supplements have reached that benchmark.
4. The FDA Modernization Act of 1997: Among other things, the Act allowed for an accelerated drug approval process for the treatment of life-threatening illnesses such as AIDS and cancer if the drug has the potential to address medical needs unmet by currently available drugs. Many of the accelerated drug approvals rely on efficacy results derived from surrogate markers linked to the ultimate indication for the drug. For example, the protease inhibitors were approved on the accelerated track for the treatment of AIDS based on their demonstrated ability to reduce HIV viral load in

preapproval clinical studies. Although practical, this may not be ideal and has led to additional authorities granted in later legislation (such as the Food and Drug Administration Safety and Innovation Act {FDSIA}).³²

5. The Pediatric Research Equity Act of 2003: The Act requires manufacturers to study drugs being submitted for approval for a claimed indication in children. The FDA provides incentives such as patent extension and marketing exclusivity for performing these evaluations. As a result more data from children are being provided to guide therapeutic use of medications in this patient group, at the expense of allowances for marketing exclusivity to those manufacturers who provide such data.¹⁹
6. In 2007, the Food and Drug Administration Amendments Act (FDAAA) increased FDA responsibilities and authorizations primarily aimed at improving product safety. Specified deadlines for drug application reviews were added as well as the creation of a priority for FDA review based on indication and potential benefit of the candidate drug for a disease population. Four of the provisions of FDAAA reauthorize past legislation: PDUFA, the Medical Device User Fee Amendments of 2007 (MDUFA), the Pediatric Research Equity Act of 2007 (PREA), and the Best Pharmaceuticals for Children Act of 2007 (BPCA).

FDAAA gives authorization to FDA to require postmarketing studies, primarily of drug safety, including surveillance and clinical trials, as well as the requirement that sponsors incorporate Risk Evaluation and Mitigation Strategies (REMS) in their proposed marketing activities as a prerequisite for product approval. REMS are a mechanism to allow FDA to require proactive risk surveillance for newly approved products or those in which safety signals are detected. The elements of REMS vary considerably among products, and may be applied to both safety concerns and the potential for misuse, as in the case of prescription opioids.³⁸ The impact of these new regulations remains unclear, particularly as to whether still stronger regulatory oversight is needed to protect the public health.

FDAAA also included a requirement for FDA to ensure that clinical trial information is provided to the National Institute of Health's ClinicalTrials.gov Web site. However, despite the mandate, most trials are not reported within one year of their completion.²⁹

Drug shortages, which have been present for decades, reached crisis levels in 2010. The reasons are multifactorial, but coincide with a time when an empowered FDA began enforcing high manufacturing standards at production sites around the nation and the world.¹⁶ Although many of the concerns leading to plant closure were not associated with patient harm, the proactive stance primarily affected generic drug manufacturers,³ initially mainly those producing oncology drugs that were unable or unwilling to respond to standard regulations. The shortage of important drugs had significant medical and ethical consequences including delays in care and medication errors. Furthermore, economic consequences of the use of more expensive (and potentially less effective) alternative drugs and development of a "gray" market led to higher costs.³³ Some health systems turned to compounding pharmacies, which were largely unregulated. As this practice grew, new concerns such as interstate transport of compounded medications and safety risks from lax oversight became prominent.⁷

7. In 2012, the bipartisan passage of FDSIA again reauthorized PDUFA (now PDUFA V).³¹ This law included two noteworthy new FDA responsibilities and authorities: the establishment of a user fee requirement for generic drugs and for biosimilar (genericlike) biologic products similar to what is called the innovator product for drugs, and a new category of drug application designation called the "breakthrough therapy" designation. The breakthrough designation allows FDA to assist drug developers in an expedited review and approval process of a product application when there is preliminary clinical evidence that shows the drug may be a substantial improvement over existing therapies for treatment of patients with life-threatening diseases. Other new initiatives include an active effort to include patient groups representative of the affected populations in the overall FDA review processes and some yet to be determined measures to enhance the safety of the drug supply chain. This act allowed FDA to better regulate foreign drug manufacturing facilities to help alleviate shortages, and to require pharmaceutical companies to make the FDA aware of impending drug shortages. In addition, the provisions of the BCPA and PREA were made permanent.

A complete listing of the laws and statutes enforced by the FDA is found on the FDA Web site.¹⁰

THE DRUG DEVELOPMENT PROCESS

Figure 139–1 is a schematic overview of the process for drug development of a new molecular entity (NME). The process begins with the preclinical evaluation of the candidate drug. During this evaluation, preclinical toxicologic testing is performed in more than one animal species, and other testing includes product stability, good manufacturing methods, purity, and potential carcinogenicity. Dose–response relationships in animal models and in vitro receptor binding or surrogate marker effects are often determined at this phase of the evaluation. At this time many manufacturers determine the metabolism of the drug in animal and in vitro human systems. Following this preclinical testing, the sponsor submits an IND application to the FDA for approval to initiate human testing. This application contains all relevant data concerning animal and in vitro toxicology testing, product manufacturing and purity, and a protocol for using the drug in initial human

investigation. Within 30 days, the FDA must review the IND application and either allow the proposed human study to proceed or inform the sponsor that additional data or preclinical (eg, animal) study is required before clinical testing of the candidate drug can begin.

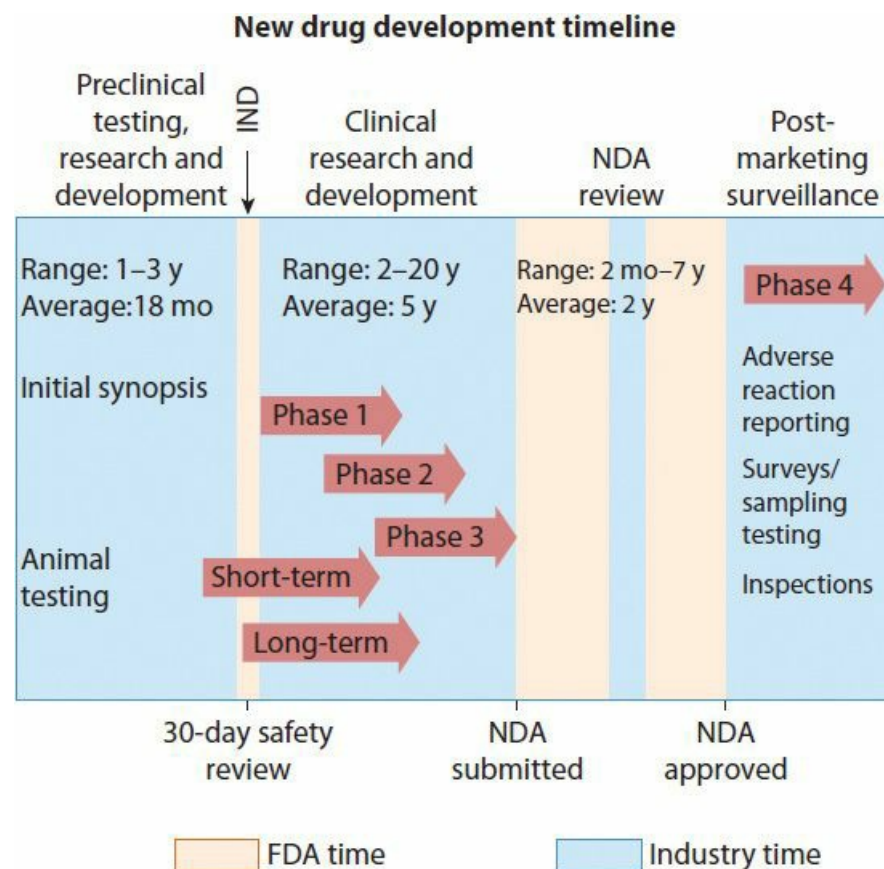


FIGURE 139–1. Schematic representation of new drug development. FDA = US Food and Drug Administration; IND = Investigational New Drug; NDA = New Drug Application. (From www.fda.gov.)

The clinical study of new candidate drugs is divided into four basic phases.

Phase 1 clinical testing involves a relatively small number of participants with the primary aim of determining the safety and toxicity of the drug. Many phase 1 studies will also determine the human pharmacokinetics and metabolism of the drug. Phase 1 studies are normally conducted in 20 to 100 healthy volunteer participants, with the notable exception of phase 1 studies for cancer chemotherapeutics, which enroll only patients with cancer.

Phase 2 clinical testing is designed to determine the potential efficacy of the drug product in humans, usually at varying levels of exposure to the drug candidate. In this phase, approximately 100 to 300 participants are usually studied. In phase 2 clinical trials, participants generally have the diseases for which the drug is intended or are capable of demonstrating the appropriate, validated, biologic surrogate marker to indicate response to the drug. An example of this would be when a drug intended for early treatment of acute coronary syndrome is tested to show that it can inhibit *in vivo* platelet function after oral dosing in human study participants.

Phase 3 clinical drug studies usually involve large scale clinical trials in the actual population for which the drug is intended for use. Typically, this phase of drug development will involve testing a treatment cohort versus a control treatment of several hundred to several thousand patients who have the target disease, depending on both the prevalence of the disease and effectiveness of the drug. The primary goal of phase 3 studies is to determine the safety and efficacy of the candidate drug in the actual intended patient population in question, under conditions similar to the anticipated medical use. At the completion of phase 3, an NDA (request for approval to market) is submitted to the FDA. A candidate drug completing phases 1, 2, and 3 can thus be approved for marketing after study in only 2000 to 4000 patients. In the setting of a fast-track approval or under the Orphan Drug regulations, substantially fewer patients will receive the drug before its approval for marketing. The relatively small number of human exposures to a new chemical or biologic entity prior to approval for marketing is an important factor that limits the sensitivity of the drug approval process to detect uncommon ADEs.

Toward the end of the review cycle, the FDA often seeks the external advice of its constituted advisory committees prior to their approval decision, especially in the setting of an uncertain risk–benefit profile of a candidate drug. FDA advisory committees generally are organized by therapeutic areas and are composed of medical professionals, primarily from academia, as well as biostatisticians, a patient representative, a consumer representative, and a nonvoting industry representative. These same advisory committees also convene to consider postapproval safety or efficacy data when FDA is considering an important change to a drug label or other postapproval regulatory action. Generally, the FDA prepares

questions for the committee members and provides an FDA briefing document containing a detailed data analysis and background of the issue from the FDA perspective as well as a briefing document prepared by the drug sponsor containing corresponding information. Committee members comment and vote on the FDA questions during the proceedings. For a new drug approval, one question generally includes a yes or no answer as to whether or not the committee member believes that the drug can be marketed with an adequate risk–benefit profile. The advisory committee vote is technically nonbinding for the FDA, but the FDA generally follows the advice of the committee. A recent issue of concern is the fact that some members of FDA advisory committees with perceived conflicts of interest are granted waivers by FDA to participate.²³ The appearance of conflict of interest on an advisory committee can have a significant impact on the drug approval process, and the FDA has begun to decrease the number of committee member waivers.

At the conclusion of the NDA review process and, at times, following an Advisory Committee meeting on the application, the FDA may issue an approval for marketing the new product. On occasion, the FDA issues an “approvable” letter, indicating that the product is potentially approvable but additional data will be needed before final approval can be granted. Examples of additional data required in this setting include further clinical study of a specific drug interaction, use of the drug in a specific patient population, or extension of the submitted drug stability testing. Once approval of the drug is given by the FDA, the next phase of drug development begins as discussed separately below.

Phase 4 Drug Development: Postmarketing Surveillance

Every drug, therapeutic biologic product, or medical device carries with it some potential risk. If society required that only “completely” safe drug products could be marketed, the drug approval process would likely take decades and few if any new drugs would be made available. Therefore, the FDA and the pharmaceutical industry rely significantly on postmarketing surveillance for further safety information regarding the toxicity of a medical product after approval. A postmarketing surveillance system is in place to monitor postapproval drug safety. These systems are intended to detect unanticipated or previously unrecognized adverse events or to identify an at-risk population in whom the safety profile differs from that which was expected prior to marketing. Individual pharmaceutical manufacturers are responsible for monitoring the safety of their products and regularly reporting any detected ADEs to the FDA. The FDA postmarketing surveillance program (MedWatch) for all medical products is a parallel system in place to monitor drug and medical device safety. This system relies on spontaneous reports by health care professionals or patients regarding the occurrence of deleterious effects associated with the use of a medical product.

Because manufacturers are also required by law to report ADEs associated with use of their products to MedWatch, the FDA database contains one complete data set called FDA Adverse Event Reporting System (FAERS), that was renamed from AERS in 2010 following its enhancement and integration of device-related data.³⁴ Because the MedWatch system is passive in nature, the estimated overall rate for adverse event reporting is estimated at only 1% to 10%. Despite this, the number of serious adverse events reported to MedWatch increased between 1998 and 2005,²⁶ although the completeness of the reports remains poor.¹³ Improved attitudes toward reporting, perhaps due to an appreciation of the risk of error and adverse drug effects, leads to better MedWatch reporting.¹² Both, the adverse event reports from MedWatch and those that are submitted from product manufacturers are entered into the FAERS database. This database is fully computerized and therefore easily searchable and contains adverse event reports from human drug and biologic products. The system contains more than 7 million reports, entered since 1969, and is growing substantially. In 2012 there were nearly 1 million reports submitted to FAERS. Approximately 95% of the total reports in the system are generated by the manufacturers and the remaining 5% are submitted via the MedWatch system.

The primary goals of the MedWatch system are the following:

- To increase awareness of drug-and device-induced disease.
- To clarify what should (and should not) be reported to the agency.
- To facilitate reporting of adverse effects by creating a single system for health professionals to use in reporting ADEs and product problems to the agency.
- To provide regular feedback to the health care community about safety issues involving medical products.⁹

Establishing causality for a specific medical product is not required before submission of a MedWatch report. The FDA is primarily interested in the reporting of serious adverse events, or an ADE previously not associated with the drug being administered, whether or not a causal relationship is established. Although any potential ADE should be reported, an event is considered serious and must be reported when the patient outcome is one of the following:

- Death: If the death is suspected to be a direct result of the adverse event
- Life threatening: If the patient was considered to be at substantial risk of dying at the time of the adverse event or the use or continued use of the product would result in the patient’s death (eg, gastrointestinal hemorrhage, bone marrow suppression, pacemaker failure, and infusion pump failure that permits uncontrolled free flow and results in excessive drug dosing)
- Hospitalization (initial or prolonged): If admission to the hospital or prolongation of a hospital stay resulted from the

adverse event (eg, anaphylaxis, pseudomembranous colitis, bleeding that causes or prolongs hospitalization)

- Disability: If the adverse event resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's body function/structure, physical activities, or quality of life (eg, cerebrovascular accidents caused by drug-induced coagulopathy, toxicity, peripheral neuropathy)
- Congenital anomaly: If there is a suspicion that exposure to a medical product before conception or during pregnancy resulted in an adverse effect on the child (eg, vaginal cancer in female offspring from maternal exposure to diethylstilbestrol during pregnancy or limb malformations in the offspring from thalidomide use during pregnancy)
- Requires intervention to prevent permanent impairment or damage if use of a medical product is suspected to result in a condition requiring medical or surgical intervention to preclude permanent impairment or damage to a patient (eg, acetaminophen overdose-induced hepatotoxicity requiring treatment with N-acetylcysteine to prevent permanent damage, burns from radiation equipment requiring drug therapy)

MedWatch reports are easily done through the MedWatch Web site, or by facsimile, telephone, or mail. Physician reports are given priority for review by the FDA in the MedWatch system. A well-documented case of a serious adverse event is a significant and useful contribution to the MedWatch system.

Reports of serious ADEs to the FDA or to the manufacturer can become an epidemiologically detectable signal that can trigger a more detailed investigation, several examples of which are provided later in this chapter. On occasion, serious ADEs detected in the AERS database have led to the withdrawal of products from the US market without conducting additional studies.

Reporting serious ADEs has periodically been encouraged by various health care groups in conjunction with the FDA. Currently, the MedWatch program is supported by more than 140 organizations, representing health care professionals and industry collaborating as MedWatch Partners to help achieve these goals. These organizations include medical societies and organizations such as the American Medical Association (AMA), the American College of Medical Toxicology (ACMT), and the American Academy of Pediatrics (AAP) that have encouraged their members to report to the MedWatch system. As a requirement for hospital accreditation, The Joint Commission mandates hospitals to collect, analyze, and report significant and unexpected ADEs to the FDA.

The primary limitation of the MedWatch system is the exclusive reliance on spontaneous reporting of ADEs. The system is passive in nature and therefore has several important limitations. Significant underreporting is known to occur in such systems. The uncertainty about the significance of a signal in the AERS database is exacerbated by the low estimated rate for adverse event reporting and the fact that the true incidence of the reported ADE is almost never precisely known because the denominator, which is the number of actual exposures to the drug, is rarely accurately known. Despite these limitations, the MedWatch system has detected significant ADEs during the postmarketing period.

Drug regulators must rely on passive surveillance systems like the AERS database to detect potential uncommon or rare but serious ADEs postapproval. This is primarily because a relatively small number of patients or participants are exposed to the drug during phases 1 to 3 prior to approval for marketing. For example, to detect an uncommon ADE occurring in approximately 1 of 5000 individuals exposed to a drug with 95% probability that the ADE resulted from exposure to that drug, approximately 15,000 patients would have to be exposed to the drug. In a balanced (equal numbers of drug and placebo recipients) placebo-controlled clinical trial, 30,000 participants would need to be enrolled. Premarketing clinical studies (phases 1, 2, and 3) are usually inadequate to detect rare ADEs, ADEs that are incorrectly diagnosed, or ADEs that result from a drug interaction that may not have been tested in the development program.

An example of a rare ADE not detected until postmarketing involves the drug felbamate, which was approved by the FDA in September 1993 and subsequently found to be associated with aplastic anemia during postmarketing surveillance. Felbamate induced aplastic anemia had not been detected during the drug development program. By July 1994, nine cases had been reported from an estimated 100,000 patients exposed to felbamate in the United States.²⁸ Most of the aplastic anemia cases occurred in patients who had taken the drug for less than 1 year. The nine cases represented an approximate 50-fold increase in aplastic anemia over the expected rate in the population with the very low background rate of two to five cases per million per year allowing the FDA to attribute this rare condition to exposure to felbamate.

The primary role of the MedWatch system is to generate a hypothesis for potential association of an ADE with a specific drug. These hypotheses are sometimes further tested in subsequent phase 4 investigations. An example of this "hypothesis generation" function of MedWatch was the question of whether phenylpropanolamine (PPA) caused hemorrhagic stroke in patients using nonprescription diet suppressants or cough and cold preparations containing PPA. In the early 1990s, the Spontaneous Reporting System (SRS; now AERS) detected a potential association of hemorrhagic stroke and nonprescription use of PPA. An industry-sponsored prospective, case-controlled study was designed to determine if such an association existed. The multicenter study demonstrated that an association did exist, especially for women aged 18 to 49 years. The Nonprescription Drug Advisory Committee (NDAC) of FDA reviewed this study and the associated MedWatch data in the fall of 2000 and decided that the evidence supported such an association. The committee advised the FDA to remove PPA from the market, which occurred a short time later. Although the entire process of signal identification from MedWatch to presentation of results from the prospective epidemiologic study required nearly a decade for PPA, the process demonstrates the value of the hypothesis-generating ability of the MedWatch system.

Potential outcomes of a safety signal detection for a marketed drug include dose reduction in all or certain high risk patient populations, restriction of the sale of the specific drug to a more medically supervised environment or the development of a patient registry to more closely monitor use, and removal of the drug from the market. These options are further discussed later in this chapter.

Other types of phase 4 safety investigations include clinical studies, comparative studies with the new drug versus a competitor, or a special population study or drug interaction study when suspicion is raised that there may exist a different risk–benefit relationship in certain clinical settings. The enhancement of safety information is the primary goal of most phase 4 studies. Other than the specific prospective study in patient subpopulations, the methods by which phase 4 safety studies are usually conducted are primarily observational and epidemiologic. Main sources of data for the postapproval monitoring of the safety of a drug are the spontaneous reports gathered by both the pharmaceutical manufacturer and FDA. The fields of pharmacovigilance and pharmacoepidemiology are typically employed in the conduct of phase 4 studies. Attributing a serious ADE to a drug solely from MedWatch reports does occur, but it is much more common for the AERS database to produce a signal, suggesting a possible drug-related safety problem.

ESTABLISHING THE DIAGNOSIS OF DRUG-INDUCED DISEASE

The recognition and diagnosis of a drug-induced disease, or an ADE, is an essential skill for all practitioners, and especially for medical toxicologists and clinical pharmacists and pharmacologists. The diagnosis of an ADE is typically established as the result of a systematic medical evaluation. One approach to establishing the diagnosis of drug-induced disease involves consideration of six related questions concerning the patient’s clinical presentation and available medical data, as shown in [Table 139–1](#).

TABLE 139–1. Questions to Consider When Establishing the Diagnosis of an ADE
1. Was the timing of the adverse event appropriate relative to the exposure to the drug?
2. Has the effect noted, which is the suspected ADE, been previously reported?
3. Is there evidence of excessive exposure to the drug?
4. Are there other more likely etiologies responsible for the condition suspected as being an ADE?
5. What is the patient’s response to cessation of a suspect drug (dechallenge)?
6. What is the patient’s response to rechallenge?

ADE = adverse drug event.

The first question concerns the timing of the onset of the adverse event in relationship to the reported exposure to the drug. Perhaps because of publicity or word of mouth, ADEs are sometimes reported to the FDA MedWatch system even when the onset of the adverse event occurs before the first exposure to the suspect drug. A careful reconstruction of the time course of drug exposure and onset of adverse effects is extremely important in assessing causality. The time course differs considerably for different adverse clinical events. An anaphylactic reaction to a drug usually occurs within minutes of exposure, whereas renal insufficiency caused by a drug is not likely to be clinically detectable for up to several days after the exposure. A drug that causes cancer (a carcinogen) may not produce a clinically detectable effect for decades. Establishing a time course is an essential first step in the process of making the diagnosis of drug-induced disease.

The second question is whether or not this adverse effect was reported previously for the suspect drug. An adverse drug effect that occurs commonly is likely to be known before the approval of the drug and therefore is typically found on the initial drug label. For example, respiratory depression and mental status changes were well known before the approval of fentanyl, an opioid agonist. Less common ADEs for drugs that have been on the market for a period of time are sometimes found in case reports in the literature, various medical databases, and in mention of safety related information. These will appear in a revised drug label for the medical product. Previous reports linking the observed adverse effect to drug exposure are very helpful to the clinician trying to establish a significant level of probability for causality in the setting of an ADE.

However, in the setting of a newly approved drug or a previously unreported possible ADE, neither previous reports/medical literature nor the drug label will help establish causality. In this setting, the clinician must rely more on what is known of the pharmacology, the pharmacokinetics, and the anticipated pharmacodynamics of the suspect drug and the timing of the appearance and observed time course of the adverse event. The known pharmacology about the drug should include “target” effects as well as “off target” effects. It is important to put “drug-induced disease” in the differential diagnosis for most patients presenting for medical care. Someone has to be the first to report what is ultimately recognized as an adverse effect. Appropriate vigilance for the possibility of a new ADE significantly increases the probability that a finding can be made early after introduction of a new drug to prevent more widespread drug-induced morbidity or mortality.

The next question to consider is: “Is there evidence of excessive exposure to the drug?” Most ADEs that occur are

predictable on the basis of the known pharmacology of the specific drug. Such ADEs are referred to as type A ADEs.⁵ For example, antihistamines such as diphenhydramine are known to cause significant anticholinergic effects. When a patient presents with mental status changes and clinical findings consistent with the anticholinergic toxidrome after significant exposure to an antihistamine-containing product, the observed effects are consistent with an ADE attributable to the antihistamine. Occasionally, proof of drug excess can come from measurement of the drug in serum. In the case of the patient with a history of atrial fibrillation who exhibits nausea, vomiting, vision changes, and ventricular dysrhythmias, the measurement of an elevated serum digoxin concentration supports the diagnosis of digoxin toxicity or an ADE attributable to digoxin perhaps as an inadvertent or intentional overdose, drug interaction, or change in patient renal function resulting in excessive circulating digoxin concentration. In any case, knowing the pharmacology of the drug is important for establishing the diagnosis of an ADE.

When an ADE is caused by an allergic mechanism or another mechanism unrelated to extent of the exposure to the drug, that is, a type B ADE, evidence of drug excess usually does not contribute to the diagnosis. In this setting, other factors such as allergy history or pharmacogenetic background are weighed more heavily to support the diagnosis of an ADE. Patients are usually not aware of their genetically determined ability to metabolize or react to medications but most patients will recall a previously experienced allergic reaction.

The next issue to address in considering possible causality is whether there are other more likely etiologies that could be responsible for the observed effects. Although it is important to be appropriately vigilant for possible ADEs, it is equally important not to miss an alternative cause for the patient's condition. There are certain clinical settings in which establishing an ADE becomes a diagnosis of exclusion. For example, in the case of persistent fever, the assignment of the diagnosis "drug fever" should not be made until a complete search for infectious causes has excluded this etiology.

A very important factor to consider in contemplating a diagnosis of ADE is "What is the patient's response to cessation of a suspect drug (dechallenge)?" In this case, the pharmacokinetics of the drug and the timing of resolution of the specific condition must be carefully considered. In some instances, the resolution of a type A ADE closely follows the pharmacokinetics of the suspect drug. For example, in the case of acute β -adrenergic antagonist poisoning, cardiac effects resolve in association with decreasing serum concentrations of the drug in question. However, in other instances, onset and resolution of the ADE may not correlate with drug concentrations in the body, for example, in the case of a penicillin rash, which may develop within 1 or 2 days or longer after starting the medication, but may take several days to weeks to completely resolve. In this example of a type B ADE, the resolution of the condition (rash) occurs over a much longer time period than would be predicted by the pharmacokinetics of the drug. When a suspected ADE resolves after discontinuation of exposure to the offending drug, along a predictable time course, the result of this dechallenge would support the diagnosis of ADE.

Lastly, the clinician may have the opportunity or need to rechallenge the patient with the suspect drug. If the rechallenge results in the identical response or effect, this would be considered strong evidence to support a causal relationship for the suspect drug and the adverse event. In the setting of a serious or life-threatening adverse event, it is too dangerous to perform a rechallenge with the suspect drug, in which case the response to rechallenge will not be known. In this setting, the weight of evidence previously discussed will then be the only factors available to assign the probability of causality.

FDA REGULATORY ACTIONS REGARDING SAFETY

When new information about a safety issue for an already marketed drug raises concern at FDA, several regulatory options are available to either attempt to improve the safety of the drug or remove the drug from the US market. The most common regulatory action taken by the FDA is modification of the drug label. These modifications can include restrictions as to whom should receive the drug, what doses should be given for which indications or to which patient populations, what type of monitoring should be performed during therapy, and how long treatment should be administered. When potentially life-threatening safety information is discovered, and the FDA believes that the risk-benefit relationship remains in favor of continued availability of the drug, the FDA can require that a boxed warning (sometimes called a "black box" warning) be carried in the label. A black box warning is the most serious warning placed in the label of a prescription medication. If a black box warning is established, then health care professional advertisements regarding product availability are no longer permitted. Additionally, the manufacturer is required in most cases to send a "Dear Doctor" letter to potential prescribers informing them of the new black box warning. Dear Doctor letters may also be required when the FDA requires that prescribers be notified about a significant change in the drug label warning. An example of current medications with recently added black box warnings is antidepressant medication that now must warn about the increased risk of suicidality if children and adolescents are prescribed antidepressants. The antipsychotic medication clozapine currently has five black box warnings in its drug label for the following attributed ADEs: agranulocytosis, myocarditis, seizures, "adverse cardiovascular and respiratory effects," as well as increased mortality in elderly patients with dementia-related psychosis.

Another option employed by the FDA is the implementation of restricted availability measures to permit continued availability of the drug but only with specified restrictions. For example, use of the drug isotretinoin (Accutane) requires compliance with a multiple component REMS program called iPLEDGE that includes informed consent, prescriber and dispensing pharmacy registration, serial pregnancy testing if applicable, documentation of patient education, and

completion of risk management programs by patients who will receive the medication.³⁶ This option is more commonly used today when there is concern about “off-label” use. The FDA authority to require companies to submit, prior to drug approval, and execute, postapproval, an effective risk management plan is intended to improve both the monitoring and prevention of postapproval adverse drug events and their consequences.

When the FDA believes that a drug can no longer be safely used despite modification of the drug label or any of the aforementioned restrictions, the regulatory threshold is reached to initiate removal of the drug from the market. This occurs when an acceptable risk–benefit relationship for continued availability of a drug product is no longer possible. Table 117–2 in the seventh edition of Goldfrank’s Toxicologic Emergencies contains a compilation of products that were withdrawn or removed from the market in the United States for reasons of safety or efficacy. Some recent additions to that list of drugs include valdecoxib (marketed as Bextra) and rofecoxib (marketed as Vioxx), withdrawn because of recognition of elevated cardiovascular risk associated with their use.¹¹ In the case of the COX-2 inhibitor withdrawals, the precipitating factor for withdrawal was the findings of a strong safety signal for excess cardiovascular mortality and morbidity during the conduct of efficacy studies for other potential therapeutic indications for these drugs. The postmarketing surveillance system did not serve as the initial, precipitating data set for regulatory action in this instance.^{20,27} The manufacturers voluntarily withdrew these COX-2 inhibitors and the majority of the drugs deemed unsafe by FDA from the US market. In many cases, the manufacturer ceases marketing the specific drug after notification by the FDA that regulatory action is being initiated to remove their drug from the market. Only very rarely has the FDA itself actually removed a drug from the market. One example where the FDA did implement removal is the drug phenformin, which was removed by the FDA after due process was completed. In the case of ephedra-containing dietary supplements, the FDA removed these products from the market based on their analysis of safety data obtained from the medical literature and from analysis of cases reported to the MedWatch system. In some cases, the pharmaceutical manufacturers file suit against the FDA to fight or delay the planned regulatory action against the product. The manufacturer’s legal action generally prolongs the time the product remains on the market because the drug usually continues to be sold, while the legal proceedings and appeals proceed through the courts.

Some feel that approval of a drug by FDA should preempt legal action for safety issues identified in the drug labeling. However, the FDA decision-making process regarding drug approval is largely reliant on efficacy and safety data provided by the manufacturer or in the publicly available medical literature. Plaintiff actions, taken against drug and device manufacturers, are sometimes a source of significant publicity and confidential disclosures regarding questionable behaviors practiced by companies that market medicinal products. The patient’s right to tort action against a product’s manufacturer provides an important mechanism to assure drug safety following approval and marketing.⁵ Recent US Supreme Court appeals have challenged this position seeking to reinforce the legal position of federal preemption. In the case of *Wyeth v. Levine*, the manufacturer appealed to the US Supreme Court to uphold the federal preemption status for FDA approved drugs.¹⁸ On March 4, 2009, the US Supreme Court ruled that federal law does not preempt this particular plaintiff from seeking and obtaining a judgment from the product manufacturer because the product was approved by the FDA. The case provided the opportunity to debate the extent of protection afforded by the FDA approval status and the issue of product liability litigation as a part of postmarketing surveillance of drug products in the United States. At the current time, medical devices are governed under a distinct statute in which FDA approval does preempt many forms of litigation.

In recent years, there have been highly publicized drug withdrawals for risk of cardiovascular ADEs such as the COX-2 inhibitors and the recent market withdrawal for rosiglitazone and its subsequent relabeling and reauthorization of marketing for the product for the past two decades. Until recently, the most common reasons for FDA initiated drug withdrawals in the United States have been prolongation of the QTc interval followed by drug-induced hepatotoxicity. These ADEs, as well as the propensity to cause significant drug–drug interactions, are still the primary reasons for drug–safety-related regulatory action in the United States.

Prolongation of the QT Interval

Three significant drug withdrawals in the mid-to late 1990s exemplified a serious drug safety issue with regard to drug related prolongation of the QT interval when administered alone or as the result of increasing plasma concentrations due to inhibition of its metabolism by other medications. The three examples in this category are terfenadine (Seldane), astemizole (Hismanal), and cisapride (Propulsid). Several deaths were reported to the MedWatch system for patients taking these medications. In the case of terfenadine, the initial publication of a case report for polymorphic ventricular tachycardia in the setting of routine use of this nonsedating antihistamine with the self-administration of a known inhibitor of drug metabolism led to FDA funded small prospective clinical studies to confirm a previously unrecognized ability of terfenadine to dramatically alter cardiac repolarization, which can lead to torsade de pointes. The drug was marketed in 1985, cardiac toxicity was detected in clinical use in 1990,²⁵ the FDA funded clinical cardiac safety research performed in 1991,¹⁵ and, ultimately, the drug was withdrawn from the market in 1998. The medicolegal course of the other two drugs is similar except that prospective controlled studies to document the extent of QT prolongation were not performed before regulatory action was taken. These early experiences led to new rigorous regulatory requirements and significant

preclinical screening by manufacturers of all drugs worldwide.

These three drug withdrawals demonstrated that the preapproval assessment of cardiac repolarization effects at that time was incapable of detecting even the most potent dysrhythmogenic drugs during their respective development and FDA review. Based on this dramatic systematic failure, FDA (as well as the European and Japanese drug regulatory agencies) now requires a thorough QT study (tQT) for all new molecular entities.²⁴ These studies are designed to detect as little as a 5-millisecond increase in the corrected QT interval in healthy volunteer participants and must include a positive control to demonstrate the sensitivity of the study to detect this low-level change reliably. Since this new requirement was put in place, no newly approved drugs have subsequently been removed from the US market for QT safety reasons, although questions remain about its cost effectiveness.¹

Significant Drug–Drug Interactions

Removal of mibefradil (Posicor) from the US market is an example of a drug withdrawn from the US market because of postmarketing discovery of a plethora of drug–drug interactions. Mibefradil, a pharmacologically unique calcium channel blocker, was approved by the FDA for the treatment of patients with hypertension and chronic stable angina. The FDA approved mibefradil for marketing in 1997 with the knowledge that the compound possessed the ability to inhibit certain hepatic CYP enzymes; these facts were included on the drug label. The initial labeling for mibefradil specifically listed three drug–drug interactions: astemizole, cisapride, and terfenadine (CYP3A pathway interactions). During the one year that mibefradil was marketed, information accumulated regarding drug–drug interactions with many other drugs and CYP pathways. As the in vitro and in vivo drug interaction data continued to accumulate for mibefradil, the FDA made labeling changes and issued a public warning for these potential drug interactions within 5 months of its initial approval. Additionally, the sponsor distributed a letter to health care professionals warning of drug–drug interactions. In the face of a growing and significant list of drug–drug interactions, and a 3 year international study demonstrating no clinical benefit of mibefradil over placebo for congestive heart failure, the FDA initiated regulatory action. In an unprecedented step for a drug with numerous drug interactions, the FDA requested that it be withdrawn from the market approximately a year after it was approved.³⁰ The FDA felt that the extensive drug–drug interactions could not be addressed by standard drug label instructions and additional public warnings.

Drug-Induced Hepatotoxicity

Another category of ADE of recent concern is those drugs that cause hepatotoxicity. In June 1998, the manufacturer of the NSAID bromfenac sodium (Duract) withdrew this agent from the US market.¹⁴ The NDA was submitted for review to the FDA in 1994 and after 28 months of review was approved. The drug was withdrawn approximately 11 months later after postmarketing discovery of significant hepatotoxicity. Although no cases of serious liver injury were reported during premarketing clinical trials, after introduction to the market, a higher incidence of liver enzyme elevation was found in patients who were being treated with the drug. Postapproval exposure of patients to bromfenac generally resulted in longer periods of treatment than that of the participants in the clinical trials. Because of a preapproval concern by the FDA that long-term exposure to bromfenac could cause hepatotoxicity, bromfenac labeling specified that the product was to be used for 10 days or less. This dosing limitation appeared to be inconsistent with the initial approved drug indication for treatment of a chronic condition (eg, osteoarthritis). Information concerning elevated hepatic enzymes was actually included in the original product labeling. The postmarketing surveillance of this product identified rare cases of hepatitis and liver failure, including some patients who required liver transplantation, among those using the drug for more than 10 days specified on the label. In February 1998, approximately 6 months after approval for marketing, the FDA added a black box warning indicating that the drug should not be taken for more than 10 days. Nonetheless, severe injury and death from long-term use of bromfenac sodium continued to be reported, and ultimately, the sponsor agreed to voluntarily withdraw bromfenac sodium from the market. The withdrawal of bromfenac sodium raised several important questions concerning interpretation of “safety laboratory testing,” such as liver enzymes during the drug development program, and also raised questions concerning the effectiveness of drug labeling.

The FDA has issued specific guidance on how to evaluate drug-induced liver injury (DILI) during drug development.⁸ As with many other adverse drug effects, severe DILI is uncommon so despite extensive study, few cases will be found prior to, and even after, marketing. Properly evaluated for evidence of lesser injury, drug databases may be able to offer insight into the potential for more severe liver injury. One of the common guidelines utilized by FDA is Hy’s law, which states that severe liver injury is predicted by laboratory assessment that includes an alanine aminotransferase of more than three times the upper limit of normal and a bilirubin of more than twice the upper limit of normal in a patient with no other reason for such an abnormality.²² Although imperfect, this is effective in preventing new drugs from obtaining approval and having others withdrawal from the market.

Other Examples of Postmarketing Safety Problems Leading to Drug Withdrawal

One voluntary withdrawal of two separate drugs used in combination serves as an important example of the discovery and

publicizing of an unusual adverse event occurring years after individual drug approval but after a significant increase in the prescription use of the combination product. The drug fenfluramine was approved in 1973 after an FDA review period of 75 months. A significant increase in prescription use of a combination product of fenfluramine with phentermine, for weight loss (referred to as “fen-phen”), began in the 1990s when clinical data suggested that this drug combination was effective in a weight loss program.³⁵ However, use of the fen-phen drug combination was never fully approved by the FDA and was therefore considered an “off-label” guideline usage of the product. The number of prescriptions for the drug combination soared in the mid-1990s. In July 1997, research from the Mayo Clinic reported 24 cases of an unusual form of cardiac valvular disease causing aortic and mitral regurgitation in patients using the fen-phen combination.⁴ The publicity surrounding the potential linkage of this drug combination to an unusual adverse event led to a significant increase in reports of possible adverse events associated with this drug combination. The FDA issued a public health advisory and initiated further epidemiologic studies to ascertain its prevalence. The FDA also encouraged echocardiographic studies of valvular diseases in patients taking fenfluramine or dexfenfluramine either alone or in combination with phentermine. Although at the onset the FDA, the product manufacturers, and the medical community did not expect valvular lesions to be associated with either fenfluramine or dexfenfluramine, the epidemiologic evidence suggested a possible association, leading the FDA to conclude that these agents should be removed from the US market. The potential association of valvular heart disease with these agents is an example of the use of a case-control study to explore a possible causal relationship between drug exposure and an ADE. In this case, it is unclear what the strength of the MedWatch signal was for the possible association of cardiac valvular disease with exposure to the fen-phen combination. The association between cardiac valvular lesions and exposure to the drug combination serves as an example of elucidation of a rare, unexpected ADE as the result of a dramatic increase in the number of exposed patients using a product.

ROLE OF THE TOXICOLOGIST IN THE DETECTION AND PREVENTION OF ADVERSE DRUG EVENTS

Toxicologists can play an extremely important role in ADE diagnosis and prevention, through efforts in patient care, education, and administrative functions. In patient care, it is common for the medical and clinical toxicologists to be the first medical specialists to be consulted for a patient with a potential ADE. Perhaps more than any other medical specialty, medical and clinical toxicologists are likely to include a thorough medication history that also includes prescription and nonprescription products, as well as dietary supplements. The medical toxicologist’s active involvement in the clinical arena, especially in settings in which the initial diagnosis of ADEs can be made, also serves to provide an important role model: the medical toxicologist as an educator to promote the detection and prevention of ADEs often in the academic setting of a medical school and affiliated teaching hospitals. Here, the academic toxicologist can champion the inclusion of education in therapeutics in the curriculum for medical and pharmacy students and house officers, and take an active role in the implementation of the instruction. Assuring that the curriculum in therapeutics includes recognition and prevention of ADEs and medical errors that lead to ADEs could have a significant beneficial impact on the ultimate outcome of the education process toward reduction of preventable ADEs. In addition to making sure that quality information is presented in the curriculum for trainees, the medical toxicologist can often create a special teaching opportunity for this type of education by establishing an elective or, in some cases, required experience in the curriculum for training in therapeutics. Participation in a quality learning experience can significantly impact the graduates’ knowledge of and attitudes toward therapeutics and risk reduction in patient care. Although the Institute of Medicine report on medical errors²¹ did not focus on education initiatives in its main recommendations for reduction of medical errors in the United States, it seems logical that education be considered an important (yet incomplete) tool to improve medication use and prevent ADEs and medical errors with therapeutic agents.

The growth of the discipline of medication safety has provided new venues for involvement of toxicologists. Creation of interdisciplinary teams at many medical centers has allowed a system-oriented approach to the detection, mitigation, and prevention of adverse drug events. These take the form of pharmacy and therapeutics, medication safety, and quality improvement committees, and provide important opportunities to impact on the drug-induced disease problem. Interventions may be proactive and include targeted education programs, system modifications to reduce error rates, or a limitation of a specific drug usage to certain units of the organization or by certain specialties.

A well-documented, complete report to MedWatch made by a health care professional is given priority review by the FDA. The toxicologist is likely to encounter a significant number of drug induced disease cases from a diagnostic and management standpoint, therefore practitioners of the specialty can make a significant impact on ADE reporting. All staff, including medical and clinical toxicologists and their trainees, should always submit an adverse event report locally for appropriate cases they encounter. Hospitals generally do not mandate or request that the reported event be “serious” as a requirement. The FDA MedWatch system requests that the reported events must be serious in nature or not previously associated with the medication involved. Other organizations that collect data on medication errors, such as the Institute for Safe Medication Practices, provide valuable insight and support to the drug safety community. They maintain a database, as do poison centers, and reporting is voluntary but important. In addition to reporting of the ADE, the medical toxicologist

should promote publication of case reports of all new adverse events or adverse events occurring with newly approved products. Such publication often stimulates appropriate reporting of ADEs from other practitioners and generally raises awareness concerning a new ADE.

An additional and very important role for toxicologists who work with poison centers is to facilitate the accurate reporting of poison center data to the National Poison Data System. Poison center data are invariably considered in the overall safety evaluation of approved and marketed drug. This is especially true for drugs with the potential for abuse and misuse. Accurate information and causality assignment for fatalities by the medical and managing directors of PCs can greatly aid regulatory decisions and guide efforts to improve drug safety at the national and international levels.

SUMMARY

- Drug-induced disease is common in both inpatient and outpatient settings.
- Despite significant advances in medical science applied to drug development and regulation, ADEs continue to occur and will continue to do so for the foreseeable future. ADEs have a significant impact on patient mortality and morbidity in addition to producing a significant burden on the health care system.
- ADEs caused by newly approved drugs and ADEs resulting from a previously unrecognized association with drugs with a long marketing history continue to be a significant cause of mortality and morbidity.
- The rapidly expanding number of approved drugs requires that the medical and clinical toxicologists and other practitioners have a continuing commitment to reduce the risk for ADEs in medical practice.
- Active participation in clinical, teaching, and administrative roles that can improve ADE detection, analysis, and accurate reporting at the local and national levels by medical and clinical toxicologists has led to important advances in patient safety.
- Maintaining a high level of commitment to these tasks as individuals and as a specialty will ultimately improve patient safety and benefit society.

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MEDICATION SAFETY AND ADVERSE DRUG
EVENTS

Brenna M. Farmer

HISTORY AND EPIDEMIOLOGY

Patient safety is of great interest to many regulatory groups, such as The Joint Commission, hospital administrations, health care professionals, and the general public. The interest has continued to grow since the publications of two reports by the Institute of Medicine. The first report, in 1999, focused on all medical errors and introduced measures necessary to ensure a safer health care system.⁸⁵ The second report, in 2006, focused on reducing medication errors and adverse drug effects.⁸³ These reports and others reveal that medications errors represent up to 25% of all medical errors.⁴⁹ Many health care institutions address medication safety through their pharmacy and therapeutics (also commonly called drug and formulary), medication safety, patient safety, and quality improvement committees. Table 140–1 shows a timeline of some important developments in medication safety.

TABLE 140–1. Critical Events in the Evolution of Medication Safety

1820	United States Pharmacopoeia (USP) is established in Washington, DC
1906	The Pure Food and Drugs Act is passed by Congress
1927	The Bureau of Chemistry is re-formed into Food, Drug, and Insecticide Administration and the Bureau of Chemistry and Soils
1930	The Food, Drug, and Insecticide Administration was renamed the Food and Drug Administration (FDA)
1962	Kefauver-Harris Drug Amendments passed to ensure drug efficacy and greater drug safety President Kennedy proclaims the Consumer Bill of Rights, which includes the right to safety, right to be informed, and right to choose
1963	Representatives from FDA, USP, American Medical Association (AMA), and American Pharmacists Association form the US Adopted Names Council to establish drug nomenclature
1968	The FDA is placed in the Public Health Service after reorganization of the federal government health program
1970	The FDA requires the first patient package insert
1975	The Institute of Safe Medication Practices's (ISMP) work officially begins with a continuing column in <i>Hospital Pharmacy</i>
1987	The first ISMP list of dangerous drug abbreviations is printed in <i>Nursing '87</i>
1989	Agency for Health Care Policy and Research (AHCPR) is established as an agency in the Public Health Service in the Department of Health and Human Services
1991	Institute for Healthcare Improvement is founded as a not-for-profit organization to aid in improvement of health care quality USP and ISMP create Medication Error Reporting Program (MERP)
1993	A consolidation of several adverse reaction reporting systems is launched as MedWatch, the FDA voluntary reporting system for problems associated with medical products
1996	The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) is formed
1997	National Patient Safety Foundation is established with patient safety as its sole purpose ISMP founds a subsidiary, Medical Error Recognition and Revision Strategies (Med. E.R.R.S.), to work with drug companies to predict problems with names, labels, and packaging
1998	USP launches MEDMARX, an Internet-accessible medication errors reporting system for hospitals Founding members of The Leapfrog Group meet to discuss ways to purchase health care to influence its quality and affordability ISMP publishes a list of high alert medications
1999	The Institute of Medicine (IOM) <i>Report To Err is Human: Building a Safer Health System</i> ¹⁷ is published The Leapfrog Group founding members establish the reduction of preventable medical errors as their initial focus The National Quality Forum is created as the President's Advisory Commission on Consumer Protection and Quality in the Health Care Industry Agency for Health Care Policy and Research is renamed Agency for Healthcare Research and Quality
2006	IOM <i>Report Preventing Medication Errors</i> ¹⁸ is published
2007	USP and Quantros, a company that collects data on health care quality, patient safety and accreditation, partner to run MEDMARX

Studies of medical errors, including those involving medications, are of a highly variable quality and usefulness. This occurs in large part because they address diverse populations, the definitions utilized vary, and a variety of data collection techniques, including observational studies and voluntary reporting, are employed.

One study estimates that 180,000 people die each year of medical errors,⁶⁴ and 60% of these injuries are probably preventable.¹⁷ The Institute of Medicine estimates that an additional 44,000 to 98,000 people die each year from medical errors.⁸⁵ However, despite having methodologic differences, both studies establish that medical errors cause thousands of deaths each year. Studies like these illustrate the “Swiss Cheese Model of Error,”⁹² that is, multiple errors must align with an initial error to lead to harm.

More than 1.5 million preventable adverse drug events (ADEs) may occur each year.⁸³ An ADE is an untoward event or outcome associated with the use of a drug. The definition of ADEs includes medication errors as well as adverse reactions to a drug and drug interactions. A medication error is “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.”⁸¹ An adverse drug reaction is a sign or symptom related to use of a medication that results in unpleasant effects when an error has not occurred. An adverse drug reaction is also an ADE.⁵ Those ADEs and medication errors with serious effects lead to 3.1% to 6.2% of all hospital admissions.⁶²

In 1997, the cost of a single ADE was estimated to be \$2000 to \$5000 at academic medical centers.^{10,22,23} Similarly, in 2012, a retrospective multi-center study of community hospitals estimated an increased cost of \$3000 to overall care and increased length of stay of 3 days above expected when an ADE occurs.⁴⁶ Other studies estimated that the annual cost of ADE morbidity and mortality was greater than \$77 to 177 billion in the ambulatory care setting,^{33,50} \$2 billion in hospitals,^{10,23} and \$4 billion in nursing homes.¹⁶ These costs exclude legal or other costs that accrue to the patient or their families.

Deaths from Medication Errors and ADEs

Although medication errors are the most common cause of iatrogenic patient injury, less than 2% result in injuries. Nevertheless, the incidence of ADEs in hospitalized patients is estimated to range from 2% to 20%²² resulting in 7000 deaths annually in the United States.⁸⁵ A retrospective review of hospital death certificates by ICD 9 and ICD 10 codes from 1983 to 2004 revealed an increase of 361% in fatal medication errors and a 33% increase in deaths from ADEs occurring in a patient's home.⁹¹ The hospital death certificate review also revealed an increase in fatal medication errors 32 times higher when prescription medications were combined with alcohol and or illicit xenobiotics.⁹¹ According to voluntary MedWatch reports to the US Food and Drug Administration (FDA), 17% of reported ADEs were associated with death, 7% were associated with permanent disability, and many others had serious complications. Women and elderly patients were at the highest risk.⁷⁸

National Coordinating Council for Medication Error Reporting and Prevention Taxonomy

A useful medication error taxonomy, developed by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), classifies medication errors according to severity of outcome (Fig. 140–1).⁸¹ Importantly, the categories of least severity (A and B) describe circumstances or events in which the potential to cause error exists, or the error occurs but does not affect the patient. These “near misses” are so frequent that they serve as a critical source of information related to systems problems and education about medication error, but are typically underreported and underappreciated. In one study of 154,816 errors reported by hospitals and health systems to MEDMARX from 1999 to 2001, most of the errors were in category C (47%) and resulted in no patient injury, whereas there were 19 errors in category I, contributing to or resulting in patient death, comprising 0.01%.⁹⁶ See Fig. 140–2 for a comparison of errors in the inpatient versus the emergency department (ED) setting based on the NCC MERP classification.

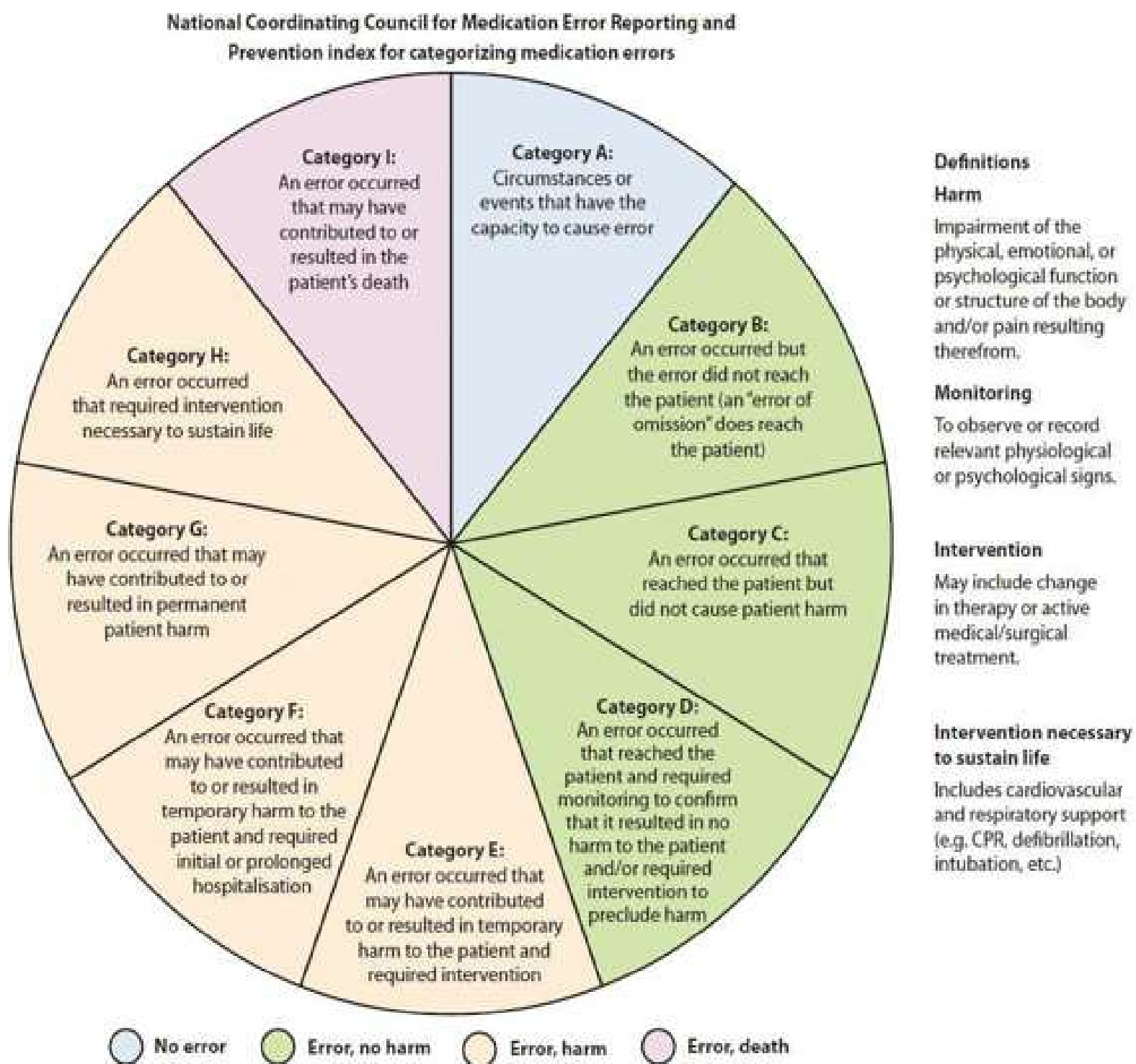


FIGURE 140–1. Diagram showing National Coordinating Council for Medication Error Reporting and Prevention categories of medication errors, ranging from fatal to errors with no impact on patient care. (© 2001 National Coordinating Council for Medication Error Reporting and Prevention. All rights reserved.)

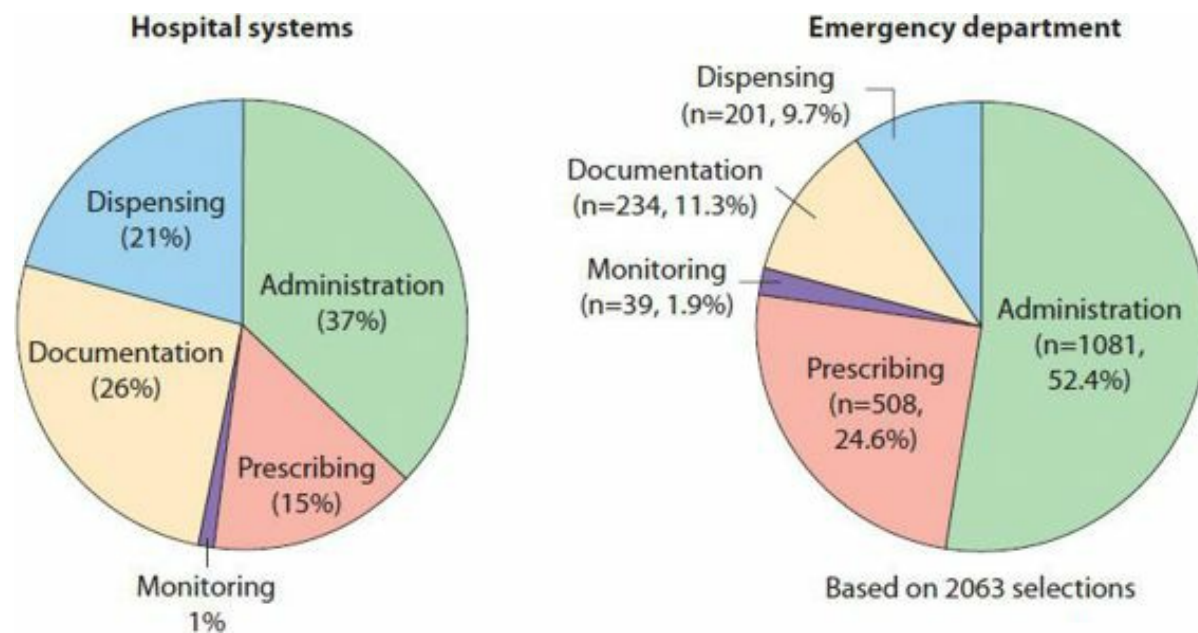


FIGURE 140–2. Diagram showing MEDMARX data for (A) hospital systems and (B) specifically for the Emergency Department. (Adapted from United States Pharmacopeial Convention, www.usp.org.)

Medications Involved

FDA reports suggest that opioid analgesics and immune modulators are the most common medications in which errors resulted in death.⁷⁸ The medications most frequently involved in errors and ADEs reported to MEDMARX were insulin, anticoagulants, morphine, and potassium chloride.⁹⁶ These medications are considered high alert drugs according to the sentinel event alert system of The Joint Commission. Recently, The Joint Commission has focused more on all opioids (not just morphine) in order to promote safe use in the hospital setting.¹⁰⁵ Identifying characteristics of high-risk drugs include low therapeutic index, pharmacokinetic interactions, inherent undesirable effects, newly approved or “off-label” use, and direct-to-consumer promotion.¹³ Table 140–2 lists medications commonly reported and their classes of errors.

TABLE 140–2. Medications or Classes Commonly Responsible for Medication Errors

Acetaminophen	Electrolyte replacement
Albuterol	Potassium chloride
Antibiotics	Fluid replacement therapies
Amoxicillin	Furosemide
Cefazolin	Insulin, other antidiabetics
Cephalexin	Opioids
Levofloxacin	Fentanyl
Penicillin	Meperidine
Vancomycin	Methadone
Anticoagulants	Morphine
Heparin	Opioid-acetaminophen combinations
Warfarin	Oxycodone
Aspirin	Sedatives
Cardiovascular	Benzodiazepines
Clopidogrel	
Digoxin	
Inotropes	
Vasopressors	
Chemotherapeutics	

The Medication Process

The Medication Process comprises the five stages in the sequence of ordering a medication to its delivery to the patient.

The stages are prescribing, transcribing, dispensing, administering, and monitoring.⁶ For patients discharged from the ED or hospital, discharge, and follow-up is the sixth stage.²⁸ Although the medicating process has only six stages, there are multiple steps within each stage. The potential for error is high, increasing proportionately as the number of steps and their complexity increase. Figure 140–3 describes typical errors that occur at each stage in the process, along with prevention strategies.

Stage	Error producing conditions	Medication error reducing strategies
Prescribing	Incomplete knowledge of medication Incomplete knowledge of patient	Readily available medication reference systems Increased pharmacist availability Take a thorough medication/medical/allergy history Physicians order entry Computerized decision support Pediatric patients: Determine accurate weight in kilograms Be alert for calculation/decimal point errors Caution with "off-label" prescribing Geriatric patients: Consider co-morbidities and drug-drug interactions in particular Consider possibility of falls with new medications Consider renal, hepatic and thyroid function Follow Beers criteria Potentially pregnant patients: Rule out pregnancy Careful evaluation of risk/benefit
Transcribing	Verbal orders Poor penmanship Abbreviations, symbols	Avoid verbal orders except in emergencies Write legibly; print if necessary Avoid acronyms or prohibited abbreviations Electronic order transcription Team communication errors Indicate decimal point clearly No trailing zeros Avoid apothecary terms Include physician phone number/pager
Dispensing	Dispensing by nurses Dispensing by physicians Patient ID	Nurses dispense to another nurse and not themselves No dispensing by physicians Automated dispensing Check with physician if any ambiguity in order Check correct placement of decimal points Check weight is correct in kilograms Always check for allergies to medication class Doubly confirm patient identification; bar-coding Double-check arithmetic
Administration	Multiplicity of medications Potency of medications Multiple patients Parenteral administration Medication incompatibilities Physician administration	Be prepared to challenge orders Clarify any ambiguity or doubt concerning medication order Consistent consultation with reference materials Consultation with hospital pharmacist if available Call back verbal orders Implement systematic safety checks Avoid physician administration of medication whenever possible
Monitoring	Potent medications Parenteral administration Emergent procedures Complex procedures	Ensure adequate monitoring technology Ensure adequate monitoring personnel Clear protocols for conscious sedation or rapid sequence intubation Ensure adequate monitoring time following drug administration
Follow-up	Patients leaving hospital or other healthcare facility, and especially medicated patients	Reconcile all medications No verbal discharge instructions to patients given amnestic drugs Provide written information on any new medication to patient if possible Advise patients of any necessary follow-up Consider effect of medication if patient driving home

FIGURE 140–3. Stages in the ordering and delivery of a medication and typical errors associated with each stage. (Based

on data from Bates DW. Using information technology to reduce rates of medication errors in hospitals. *BMJ*. 2000; 320:788–91. Peth HA. Medication errors in the emergency department: a systems approach to minimizing risk. *Emerg Med Clin North Am*. 2003;21:141–58.)

The greatest number of errors resulting in preventable ADEs (medication errors) occurs at the first prescribing stage.⁷ In a study of serious medication errors, 39% were found to occur at the prescribing stage, 12% at transcription, 11% at dispensing, and 38% at administration.⁶⁵ In one study of 17,808 inpatient and ED medication orders, 6.2% of orders written involved a prescribing error and 30% of these were likely to harm the patient if they were not discovered.¹⁵ Another recent prospective study suggests that up to 43.8% of medications orders on hospital wards had a prescribing error discovered by ward-based pharmacists, despite the level of prescriber experience.⁹⁸ In the ED, most errors occurred in either the prescribing or administration phase.⁸⁹

Transcribing errors usually involve poor communication due to illegible handwriting, the use of trailing zeroes, or inappropriate abbreviations. Poor handwriting can also lead to confusion, particularly with regard to look-alike and sound-alike medications.⁹⁰ All information, whether printed, spoken, or otherwise communicated, must be transmitted in a clear, unambiguous, and timely fashion with avoidance of abbreviations. In its 2004 National Patient Safety Goals, The Joint Commission developed a minimum list of five sets of dangerous abbreviations, acronyms, and symbols that should not be used, and proposed preferred terms.¹⁰⁴ The Institute for Safe Medication Practices (ISMP) also published a comprehensive list.⁴⁸ By not using these abbreviations, the hope is that communication will be improved and that there will be no misinterpretation of poor physician handwriting.

Dispensing errors are most commonly due to substitution and labeling errors.⁹⁹ Errors at the stage of administering medications include incorrect drug, incorrect dose, incorrect route, and a drug given to the wrong patient. Computerized provider order entry (CPOE) was introduced to improve the medication process from prescribing to administering but has introduced new problems. See the Information Technology section for further discussion.

Monitoring and discharging with follow up are associated with fewer errors. This phase involves attention to liver and kidney function, checking xenobiotic concentrations, and attention to and evaluation of drug interactions and pharmacokinetic interactions.²⁸ Monitoring must be an ongoing process that begins when the patient receives the medication, regardless of where the patient is in the health care system, and continues as long as the individual continues to have the medication prescribed. In the acute stages of treatment, such as in the hospital or ED, the process is especially important and requires optimal three-way linkage between the pharmacy, laboratory, and physician.⁹⁷ This process must be maintained throughout the individual's continued relationship with the health care system. In the outpatient setting, providers must be aware of signs and symptoms related to adverse drug effects while they are monitoring and following up patients. In a study of 661 patients in four primary care practices, patient reports of medication side effects to their physicians led to changed therapies in 76% of cases. A failure to identify medication-related symptoms and change therapy resulted in 21% ameliorable and 2% preventable ADEs. Ameliorable ADEs were defined as those in which "the severity or duration could have been reduced substantially had different actions been taken."¹¹²

SPECIAL AT-RISK POPULATIONS

Important medication safety issues exist for children and older adults, a problem that is exacerbated by their underrepresentation or exclusion from clinical trials. It is estimated, for example, that only a third of the medications used to treat children have been adequately tested in this population.²⁵ Similar concerns apply to medications used in older adults and those individuals with specific underlying medical conditions that would have excluded them from trials.⁴⁷

Pediatric Considerations

Pediatric adverse events involving medications may occur from the prenatal period and throughout childhood from the neonatal period through maturation. Errors may occur in all settings: the home, in ambulatory care, the ED, hospital floor, pediatric intensive care unit (PICU), and neonatal intensive care unit (NICU), and by all caregivers. Approximately 1 in 6.4 pediatric orders results in an error that reaches the child.⁷² Because of the greater need for dose calculations to allow for weight-based dosing, dose-related errors are more likely to occur in children.⁵² Errors also occur in the home environment with nonprescription medications, but the true incidence is unknown. In one survey, the errors associated with home antipyretic use were estimated at almost 50%.⁷³ These errors were typically associated with underdosing, which is generally of little immediate harm.⁹⁵ In the ambulatory care setting, the incidence is unknown but one study identified "numerous" errors in prescription writing in a pediatric clinic.¹¹⁰ In the ED setting, the error rate was estimated at 10% of all pediatric charts.⁵⁷ There may be an increased risk of errors in children cared for in nonacademic or rural EDs compared with academic or pediatric EDs.⁵⁵ A retrospective chart review of 177 pediatric charts in four rural EDs identified 84 different medication errors in 69 of the 135 patients who received medications. The outcomes of these errors were in NCC

MERP categories A to D (Fig. 140–1).⁷¹ A study of 18 pediatric ED voluntary event/incident reporting data showed that 19% of all incidents were related to medication events. A total of 94% were medication errors and 6% were ADRs. Errors included using incorrect weights, duplicate dosing, and miscalculations. Human factors contributed to 84% of the medication errors in this study.¹⁰⁰ See the Factors Affecting Human Performance section for further discussion.

Hospitalized children experience up to three times the rate of medication errors and potential ADEs as do adults.⁵³ The incidence of medication errors of hospitalized children is estimated at about 6% for all orders written; the majority (74%) of these occur at the prescribing stage and approximately 20% are classified as potentially harmful based on a 4-point Likert scale developed by the researchers instead of the NCC MERP classification previously described.³⁸ Pharmacists based on pediatric hospital wards, discovered that 5.9% of orders contained a prescribing error and were able to intervene through the order entry system.³⁰ Generally, children in the intensive care unit appear to be at higher risk for errors compared to adults and hospitalized children not in the ICU, presumably reflecting the increased complexity of disease and the medications used.⁵⁵ Incorrect dosing, especially with the intravenous route, is the most commonly reported error. Dosing of antimicrobials and intravenous fluids are the most common medications involved.^{29,36,53} Errors and discrepancies found in hospital discharge instructions, with lack of complete medication reconciliation, could lead to patient harm⁵¹ (Chap. 32).

Geriatric Considerations

Medication errors in older adults also occur throughout the health care continuum: the home, ambulatory care, in nursing homes, in the assisted-living setting, and in the hospital (Chap. 33). Adults older than 65 years of age have a relative risk of 2.37 for drug complications and 4.12 for medication errors compared to adult patients younger than 65 years of age.¹⁷ The incidence of medication error at home with nonprescription medications is unknown but, for reasons outlined below, would be expected to exceed that of the younger adult population. Using a variety of methodologies, ADEs were evaluated for a 12 month period in a multispecialty ambulatory care practice in a cohort of 27,617 Medicare enrollees, equivalent to more than 30,000 person-years of observation. Extrapolating their findings, to the estimated 38 million Medicare enrollees (those ≤ 65 years), would predict nearly 2 million ADEs annually, of which more than 25% would be considered preventable and about 180,000 fatal or life threatening.⁴³ A recent study estimates that there are about 265,802 ED visits in patients older than 65 years of age for ADEs and 99,628 of these patients require admission to the hospital. In the same study, patients older than 80 years of age constituted half of those admitted to the hospital. Medications or classes of medications involved in two-thirds of the hospitalizations were diabetic and antithrombotic medications.¹⁹

There are more than 1.5 million nursing home residents in the United States. The average such resident uses six different medications, and 20% use ten or more.¹⁴ Extrapolating the findings of a study of 18 community-based nursing homes in Massachusetts over a 1 year period predicts 350,000 ADEs annually, more than one-half of which would be preventable.⁴² Fatal or life-threatening ADEs would represent 20,000 of these predicted events of which 80% would be preventable. Approximately one million other seniors live in assisted-living facilities, and are vulnerable to medication errors for a variety of reasons, including inadequate physician support, inadequately trained staff, and staffing shortages. ADEs cause 10.5% of hospital admissions for geriatric patients and are the most common type of adverse event occurring in hospitalized elderly patients.^{66,114} These drugs result in nearly 50% of ADE-related visits to the ED but are only prescribed during 9.4% of outpatient visits.²⁰

Addressing these issues is becoming ever more important as the US Census Bureau predicts a rise of 62 million in the number of Americans 65 years of age or older by the year 2025 and a 68% increase in the 85 years of age or older population that may be at an even higher risk.⁴ Advancing age brings with it several important considerations from the point of view of medication safety. Medical comorbidity increases with age, and therefore an increasing likelihood of receiving multiple medications. With more medications, the number of potential errors and interactions increases. Frailty and cognitive decline in older adults may result in errors following self-administration. Alterations in medication absorption, metabolism, distribution, and elimination may all affect the efficacy of the medication (Chaps. 9 and 33).

Criteria were developed in both the United States (Beers)^{11,12,35} and Canada⁷⁴ to determine appropriateness of medication prescribing for nursing home residents. Forty eight medications or classes of medications to avoid, and medications to avoid in the presence of 20 diseases/conditions were identified.³⁵ The prevalence of inappropriate medication use in older adults is estimated to be in the 12% to 40% range.¹⁰² One in five prescriptions given to elderly individuals are considered inappropriate based on Beers criteria, with diphenhydramine and amitriptyline being the most common medications prescribed inappropriately.⁸⁷ Older adult patients medicated with benzodiazepines, for example, have a four-fold increase in falls (Chap. 33).

RESPONSE TO MEDICATION ERROR

One of the leading causes of medication errors is human performance deficit. Almost invariably a human action will

precede the ADE, and this temporal contiguity of action and consequence typically generates a tendency to blame someone. In most cases the blame will fall on the last person to have had contact with the patient. In recent years, however, a consensus has emerged that blaming people for errors is counterproductive. The number of ADEs that result from egregious behavior is very small, and more often than not an explanation for the fault will be found within the system that allowed the error to occur. Attempts to understand the nature of these faults, and to correct them, while being sensitive to the potential for unintended consequences, is the most appropriate response. Several processes can be used to respond to errors or system-problems. These include root cause analysis, clinical incident analysis, failure mode and effect analysis, and Lean Six Sigma (LSS).

Root cause analysis (RCA), a term originally used to investigate major industrial events, is a technique that provides a structured, process-oriented analysis of sentinel events. The Joint Commission in accredited hospitals mandated its use in 1997. It is a time-consuming process requiring multidisciplinary teams with specialized training, and is subject to bias and methodologic limitations.¹⁰⁸ Nevertheless, a judiciously conducted RCA may provide insights into systemic failures underlying the ADE, and identify areas that require change. An alternative approach, a clinical incident analysis protocol, was developed that more appropriately shifts the emphasis from the individual to the system.¹⁰⁷ The clinical incident analysis protocol utilizes seven factors as the basis for an investigation. Some organizations have developed a hybrid combining these two approaches. Both RCA and clinical incident analysis are conducted retrospectively, and therefore subject to retrospective bias

An alternative approach is failure mode and effect analysis (FMEA), which proactively attempts to identify potential errors, to initiate preventive measures. A multidisciplinary group is utilized in the FMEA approach to identify a process or subprocess that needs analysis, to identify the steps of the process and determine the risk/likelihood/severity of failure of each step. Once this phase is accomplished, the team prioritizes a high-risk step and conducts an RCA to make recommendations on redesigning the step. The establishment modifications are analyzed in their performance to determine change and decrease in risk. This process is designed as a quality control and assurance to protect the proceedings from legal investigation.³

Other processes are being introduced into the health care industry to improve quality of care and safety and reduce costs. Two such approaches are Lean and Six Sigma, sometimes utilized together as LSS. Both were initially described in the Toyota Production System and have been adapted to health care. Define, measure, analyze, improve, and control are all steps related to LSS. It involves defining the process that needs evaluation, determining how to measure the process, analyzing the data collected based on the determined measures, forming an improvement plan based on the analysis, and putting a new process in place with the goals of developing a lasting culture regarding the newly improved process with elimination of waste.^{1,116} Each of these steps has principles to guide the use of LSS. The Agency for Healthcare Research and Quality has made specific forms to aid health care facilities when adopting these approaches to safety and improvement.⁶³

REDUCING ERRORS

To reduce medication errors, each hospital should simplify, standardize, and stratify processes and communication. The medication process should be carefully automated with computer order entry and bar coding as extensively as the system will permit. While these information technology solutions will aid the medication process, nothing is perfect and each change introduces new problems. See the Information Technology section later. Limitations of attention and vigilance should be understood and the reporting of errors in a nonpunitive environment should be encouraged.⁶⁵ Improving information access, error proofing, reducing reliance on memory, enhanced training, and the use of buffers or redundancy in an attempt to prevent errors should also be encouraged.⁶⁴ Each time a medication is given, the focus should be “right drug, right dose, right route, right patient, at the right time.”

In 2003, the American Academy of Pediatrics Committees on Drugs and on Hospital Care developed a position statement regarding the reduction of medication errors in the pediatric population. The recommendations can be adapted to all hospital settings and to patients of all ages. These recommendations include appropriate staffing, utilization of the resources in the pharmacy, standardization of hospital equipment and protocols, and the development of a nonpunitive, barrier-free system to report and easily track errors.¹⁰³ Other more recent groups also encourage reduction of medication errors and participation in medication safety. The American College of Medical Toxicology encourages medical toxicologists to use their expertise and training to aid health care systems in reduction of errors and other pharmacy and therapeutics issues.²

For older adults, prescribers should review medication indications and avoid age bias. Polypharmacy should be limited, with medications prescribed only as necessary. Dosing should be adjusted, as needed based on renal and hepatic function. Medication review by pharmacists can aid in decreasing the use of potentially inappropriate medications and in decreasing the number of medications prescribed (polypharmacy).⁷⁶ In the hospital, outside of the emergency department and emergent situations, pharmacists review all medication orders, when available, and verify the medication as

appropriate prior to it being dispensed. Pharmacists can also aid in medication reconciliation at transitions of care and upon hospital discharge to prevent complications of polypharmacy.^{40,59}

FACTORS AFFECTING HUMAN PERFORMANCE

Human factors lead to many medication errors. In fact, it is not surprising that human performance deficits are the primary causes of medication errors in such an extremely complex medical environment. A performance deficit means that the individual making the error had the prerequisite knowledge to avoid the error but failed to do so. There are numerous variables that contribute to performance deficit, including many ergonomic issues such as workload, distractions, resource limitations, and staff shortages. This environment is both burdened and enriched by many inherited properties. Human factors and ergonomics theory draws on a variety of disciplines, including industrial engineering, industrial psychology, cognitive psychology, and information technology. Much can be done to optimize the interface between humans and the work environment and to ensure that systems operate more efficiently. As a general principle, it would be preferable if the dominant purpose in designing medical devices and processes was that they fit human users, and not the converse. Table 140–3 lists some of the more common human performance deficits. Such errors often manifest as simple slips of action, or execution failures, arising from distraction by something other than the task at hand.⁹² Vigilance is better maintained in individuals who are well rested and working without interruption or distraction in a well-designed environment. Fewer medication errors occur in optimally designed environments.⁶⁵

TABLE 140–3. Common Factors That May Adversely Affect Human Performance ^{27,96}	
Attentional capture	
Diminished motivation/morale	
Distractions	
Fatigue	
Fragmentation, transitions of care	
Inadequate resource availability (Resource Availability Continuous Quality Improvement	
Trade-Off)	
Increased work acuity/cognitive load	
Inexperience	
Interruptions	
Poor workplace ergonomics	
Sleep deprivation/debt	

Human performance deficits such as diminished memory, sleep deprivation, depression, and distractions contribute to errors. Resident physician mood and lack of sleep are also factors in performance deficits. Depressed residents made 6.2 times as many medication errors as nondepressed residents.³⁴ Sleep deprivation and improper supervision were highlighted initially after the Libby Zion case, in which a patient on phenelzine developed fatal serotonin toxicity following the administration of meperidine by a sleep-deprived and inadequately supervised intern. Interns working a traditional schedule of call every third night with extended work shifts (36 hours) made 35.9% more serious medical errors than those with the current reduced work schedule.⁶⁰ In particular, there were 20.8% more serious medication errors during the older work schedules compared with the current reduced hour schedule.⁶⁰ In 2008, an Institute of Medicine study addressed resident work hours and patient safety. This report recommended residents be provided with designated sleep time during each day and rest periods each week in order to decrease the risk of fatigue-related medical errors.⁸⁴

A particularly important goal for human performance deficit is the reduction of cognitive load and distractions. Many medication errors originate from cognitive failings because of interruptions, distractions, inexperience, or simple overloading—referred to as performance deficit. In the ED, increased cognitive load such as related to increased number of boarding patients, increased number of medication orders, and increased number of medications to be administered all lead to increased medication errors.⁸⁹ Further efforts must be directed at strategies to reduce cognitive failure. The adoption of some very simple strategies based on human factors engineering principles will reduce error, such as simplification of the number of steps involved, reducing reliance on memory, applying cognitive forcing strategies,²⁷ and using cognitive aids. Research into reducing distractions during medication administration has focused on adapting principles from the airline industry, “the sterile cockpit principle.”³⁷ This principle limits interruptions and distractions that could interfere with proper performance of a critical task or tasks. In the airline industry, the use of this principle occurs during takeoff, taxi, and landing. In medication administration, this principle involves the use of “do not disturb” signs or vests worn by the nurse administering medications, no conversations to disrupt the medication nurse during this important task, and the other nurses on the unit answering phone calls or patient/family questions. This approach reduces medication

administration errors by improving human performance.^{37,93} One particularly useful aid to reduce cognitive load is the color-coded Broselow-Luten system, for pediatric medication dosing.⁶⁹ This approach has the potential for further development to improve the safety of nonprescription medications and other potentially dangerous products used in the home.

Another factor that contributes to errors is the assignment of a new role to a provider such as asking physicians to dispense or administer medications. Pharmacists are the only professional group formally trained and experienced in dispensing medication, and not surprisingly, their presence is associated with a lower medication-dispensing error rate.^{58,67} Nurses administer medications because they receive such training and the administration should be restricted to them except during specific circumstances such as procedural sedation.²⁸

KNOWLEDGE DEFICITS

The two most common factors contributing to prescribing errors are related to knowledge deficits. These deficits include lack of knowledge about the drug and about the patient.^{65,68} Knowledge deficits about medications are likely due to the number new medications, dosage formulations, and indications. With the large number of medications prescribed and the continuing and frequent release of new medications, it is difficult to know all of the relevant clinical pharmacology of each medication, including interactions, side effects, and contraindications. Decision support, most commonly in electronic format, should be contemporaneously available to health care professionals to assist in decreasing prescribing errors.⁹⁰ However, electronic pharmacopeias, as a form of decision support, can have errors and omit warnings, such as recently discussed with extended-release or long-acting opioids.⁶¹

Knowledge deficits may also affect dosing calculations and drug ordering. This may be related in part to the lack of formal education regarding the medication process during medical school training. Only 10% of medical students answered dose calculation questions correctly.¹¹³ However, students in their final year of training performed much better than students in the lower years.¹¹³ It is unclear where, when, and how the students obtained the knowledge in the higher years. Specific training is needed in both of these areas of calculation and order writing. Improvements have been demonstrated following a short educational intervention,⁸⁶ but it is unclear how long this knowledge is retained. Generally, there appears to be a tacit assumption that these skills will be acquired during clinical training, but this study suggested that this knowledge might not be acquired independently and that specific training is indicated.

The prevailing emphasis in physician training is on knowledge acquisition. Less time is spent inculcating critical thinking skills and/or teaching reasoning, the assumption being made that these are passively acquired during the process of training. Although this is partially true, it does not exclude opportunities to improve these cognitive faculties by direct intervention.²⁶

COMMUNICATION

Improved team communication should result in fewer medication errors. Orders should be written clearly, or CPOE (discussed in detail in the Information Technology section) should be used. Orders should optimally include the indications for the medication. Both generic and trade names should be included in orders so that confusion with look-alike/sound-alike drugs may be avoided. Abbreviations should have limited use and trailing zeros should be eliminated. Verbal orders should be used sparingly due to the high risk of sound-alike medications and confusion with dosing.⁹⁰ If a verbal order is necessary, then it should be restated immediately to the ordering clinician to ensure that it is correct and restated from the physician to the nurse in a “closed loop” communication process.

Communication theory should receive more emphasis in health care training. Good communication skills both within and among disciplines and especially between practitioners and their patients will limit errors. As patients are admitted, transferred within, and discharged from health care facilities, it is essential that precise communication as to what medications, strengths, and doses the patient is receiving occur. This process is known as medication reconciliation. Any changes that have occurred must be accurately recorded. This effort was adopted by The Joint Commission in 2005 and continues to be an important National Patient Safety Goal. As with other aspects of patient safety, these issues should be formally introduced into the education curriculum. Studies have shown that pharmacists are an integral part of optimal medication reconciliation.^{40,59}

INFORMATION TECHNOLOGY

Information technology (IT) in health care has been ponderously slow to develop compared with its use in other organizations, but it is now gathering momentum and has obvious potential to improve patient safety.^{8,82} On the other hand, as considerable gains may be made, new technology can also be expected to introduce new types of errors.^{21,115} The US

Pharmacopeia announced in 2004 that nearly 20% of 235,159 medication errors reported to MEDMARX involved computerization or automation.⁹⁶ One study evaluating CPOE in a tertiary care hospital found that the system actually facilitated a wide variety of medication error risks.⁴⁴ Common errors associated with order entry include wrong medication selection and input of incorrect data (patient weight, creatinine clearance).¹⁰⁶ Another study identified 24 different types of failures associated with CPOE but suggested that many could be easily corrected, in particular by concentrating on organizational factors.⁵⁶ However, more detailed insights have been offered into why process-supporting IT systems fail.¹¹¹ Much of the data involved in the medication process are relatively straightforward, amenable to rapid and efficient processing, including crosschecking with patient medication history and evaluating for drug interactions (an example of decision support). A study reviewing 28 trials of point-of-care decision support report showed a 4.2% improvement in patient care with a trend toward better improvement in care when a response was required from prescriber¹⁰¹

Past studies demonstrate that computerized order entry with decision support reduces the incidence of serious medication errors by 50% to 55% once the transitional instability has passed.^{9,70} This approach mainly reduces errors at the prescribing stage of the medication process and, while likely to prevent 80% of prescribing errors that led to no patient harm, the errors most likely to cause patient harm may not be as amenable to reduction as these errors may be related to dispensing, administration, or monitoring.¹⁵

In high-risk populations, CPOE reduces medication errors. In children, CPOE with substantive decision support reduced ADEs (including medication errors) and potential ADEs in an inpatient pediatrics ward.⁴⁵ It also decreased the rate of nonintercepted medication errors by 7% although there was no change in the rate of patient harm.^{53,109} In the NICU, CPOE eliminated all calculation errors as decision support included an automatic dosage calculator.²⁴ However, these decisions support systems cannot improve human errors due to entering incorrect weights, incorrect units of weight (kilograms versus pounds), or medications entered on the wrong patient.¹⁰⁶ In geriatric medication errors, CPOE resulted in less potentially inappropriate medication prescribing through decision alerts, which led to a pharmacist call to the prescriber that offered alternative choices of medications if possible.⁷⁷ Decision support in CPOE can also lead to too many alerts when orders are placed, causing alert fatigue and resulting in providers entering an answer to proceed past (or “blow-by”) the alert without reading or comprehending the alert. A study reviewing an alert about critical drug–drug interactions with warfarin found that only 19% of providers and 9.7% of pharmacists responding appropriately to the alert and changed the medication order.⁷⁵

Use of barcoding for dispensing and administration of medication ensures that the correct drug is given to the intended patient at the dose intended. Barcoding significantly decreased the relative risk of targeted, preventable ADEs by 47% to 50% in an NICU.⁸⁰ The risk of opioid related ADEs were also reduced when barcode medication administration was implemented.⁷⁹ This technique decreases the amount of time nurses spend administering medications in the ICU, allowing them to reallocate that time to other direct patient care activities.³¹ As with all technology, new problems arise with the implementation of barcoding and can lead to errors. Such problems range from inability of the scanner to read the barcode on the medication or on the patient identification band, downtime processes, mismatch of barcodes due to new manufacturer barcode, or new or aging scanners, and many more.³²

Unit dose dispensing systems, usually in association with CPOE and barcoding of medications, reduced monthly errors from five to none in the inpatient setting.³⁹ The package sent from pharmacy is prepared to administer to a specific patient at the appropriate dose, eliminating the need for the nurse to draw up medications resulting in fewer errors. Other dispensing systems, like automated dispensing cabinets (ADCs), have also been linked to CPOE, barcoding, and can allow for a pharmacist to verify correct drug, correct dose, patient allergies, and use of the medication prior to a drug being dispensed from the cabinet. These ADCs can decrease dispensing errors. However, errors can occur when using ADCs. One such problem, “drug override,” can occur, particularly in an emergency situation or as a work-around. This allows a drug to be dispensed prior to pharmacist verification. Another error, look-alike medication errors, can occur due to the small screens on the ADCs. Errors have also been known to occur when the ADCs are stocked such that an incorrect drug is placed in an incorrect bin of the ADC.⁴¹

SERVICE-BASED CLINICAL PHARMACISTS

Clinical pharmacists are now employed in high risk areas such as the ICUs, the pediatrics services, and EDs to identify and prevent medication errors. In one ICU study, the input of a clinical pharmacist during rounds saved an estimated \$270,000 annually in costs of rehospitalization due to ADEs.⁶⁷ The involvement of a clinical pharmacist in work rounds of an adult ICU reduced preventable ADEs by 66%.⁶⁷ The introduction of clinical pharmacists in pediatric services is credited with a 94% reduction of potential ADEs and medication errors.⁵³ In particular, the addition of pharmacists in the PICUs reduced the serious medication error rate by 80%.⁵⁴ One study showed that pharmacists in three EDs identified 2200 interventions with an estimated savings of \$488,000. This savings came from lower-cost medications, reduced length of stay, and fewer

readmissions.⁹⁴ Another study showed that there were 16 errors per 100 medication orders in the control group (without a pharmacist), while the intervention group (pharmacist present in the ED) only had five errors per 100 medication orders, resulting in a 67% reduction.¹⁸ A recent study suggests that the availability of ED pharmacists has even more impact on reducing errors by their assistance for questions, discussion, and consultation rather than in the review of medication orders.⁸⁸ And, as previously discussed, hospital pharmacists have been able to improve medication reconciliation across the continuum of care for patients.⁵⁹

However, fiscal restrictions will inevitably mitigate against the expansion of service pharmacists as cost-benefit arguments will be applied. An unintended consequence of having a clinical pharmacist present may be that nurses, residents, and attending physicians will always defer to them and consequently spend less time developing and maintaining their own skills for off-hour periods when such help may not be available.

ROLE OF THE TOXICOLOGIST

Clinical and medical toxicologists are in a unique position to investigate causes and help decrease the incidence of both medication errors and ADEs in the institutions where they work. With their specialized knowledge and training in pharmacology, poisoning, and clinical medicine, both physicians and pharmacists with advanced training in toxicology can also aid in the prediction, identification, and management of ADEs. Medical toxicologists should optimally be involved in Pharmacy and Therapeutics and Medication Safety committees (or related efforts) at their institutions. They should educate the providers at their hospitals as to means to reduce errors and encourage diligent reporting of medication errors to the hospital and the national databases such as MedWatch at the FDA. They should also encourage drug manufacturers to be diligent in alerting physicians with regard to identified problems.²

SUMMARY

- Medications are the principal commerce of modern medicine, and medication safety is of paramount importance to health care systems. The delivery of medications safely to patients is a complex process and is particularly important in pediatrics and geriatrics.
- Health care professionals should be aware as to why errors occur and how they can be prevented in order to improve patient and medication safety.
- Information technology holds promise for significant improvement in medication safety. Focus should be on CPOE, barcoding, unit dose dispensing, avoidance of look-alike/sound-alike medications, and education.
- Use of clinical pharmacists and updated electronic-based literature should be encouraged.
- Communication and nonpunitive local and national reporting must be encouraged in order to learn from errors.
- Patient safety requires a collaborative effort particularly with the medication manufacturer, but also with federal regulation authorities, independent research organizations, error theorists, hospital administrators and managers, information technologists, nurses, cognitive psychologists, human factors ergonomists, and chronobiologists and all of the health care professionals involved in patient care.
- Clinical and medical toxicologists have a significant role in medication safety.

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141 RISK MANAGEMENT AND LEGAL PRINCIPLES

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The number and diversity of toxicologic emergencies faced by emergency department (ED) staff have increased steadily since the early 1970s and continue to rise today. This chapter discusses the medical–legal management of patients who are exposed to xenobiotics that may alter their ability to think. It also addresses the legal and ethical dilemmas routinely encountered by emergency medicine practitioners.

Patients with toxicologic emergencies require immediate care, and yet are often unable to give consent because their impaired consciousness prevents them from making informed decisions. Treating patients who present with an acute organic impairment manifested by confusion, irrational thought, or even dangerous behavior is very challenging. Emergency practitioners must recognize the medical–legal problems created when the impaired patient refuses treatment and insists on leaving against medical advice. The issue is further complicated by the variations in relevant state laws. Emergency practitioners must become familiar with the legal requirements of informed consent and the essential management necessary to avoid liability for negligence and abandonment within the state that they practice. Of particular concern are the risk management and liability issues that relate to impaired patients attempting to leave the ED before medical care is complete. The legal requirements of informed consent in emergency settings, the duty to treat, medical malpractice, battery, and negligence, are examined here. Guidelines based on generally accepted common law principles are suggested for developing appropriate patient care plans and departmental policies. These issues and principles are best illustrated by case examples.

INFORMED CONSENT

Patient 1

An 18 year-old college student was brought by ambulance to the ED after a friend reported seeing her in the bathroom with slit wrists and an empty bottle of acetaminophen (APAP). In the ED, the patient was alert and oriented to person, place, and time. Vital signs were: blood pressure, 120/65 mm Hg; pulse, 95 beats/min; respiratory rate, 16 breaths/min; and temperature, 99.1°F (37.3°C). A rapid bedside glucose concentration was 120 mg/dL. The patient stated that she ingested the APAP approximately 5 hours earlier. The health care team wished to measure an APAP concentration to determine whether N-acetylcysteine should be administered. The patient refused venipuncture and stated that she would refuse any medications. The physicians informed the patient that she might suffer irreparable damage to her liver and possibly die if not treated immediately.

Medically treating patients against their will poses a difficult problem. Forcible treatment violates a patient's autonomy and their right to privacy. However, harm may be caused to the patient if the appropriate evaluation and treatment is not performed. As an example, in the case above, the patient gives a history of ingesting a large amount of APAP, which may cause hepatotoxicity and even death if not treated ([Chap. 35](#)). Her refusal for this evaluation highlights the important issue of whether a physician is ever justified in performing an assessment of someone who is alert and oriented, yet poisoned, and who refuses treatment. Do most patients suffering from a mental illness such as depression need to be treated against their will? If the harm that faces the patient is not immediate, but certain in the near future, does the physician have the authority to treat? General principles of patient autonomy and informed consent will be elucidated here.

A patient's right to choose the course of medical treatment was first recognized in the early twentieth century in a landmark case decided by the New York State (NYS) Court of Appeals in *Schloendorff v Society of New York Hospital*.²⁴ Mary Schloendorff was admitted for abdominal pain and was found to have a mass on physical examination. Her physicians offered her a more thorough examination under anesthesia and the option for surgery. Although she consented only to the exploratory surgery, during the procedure the mass was removed. Postoperatively, Schloendorff developed an infection and gangrene, and several fingers were amputated. She sued the hospital. In its decision, the Court upheld Schloendorff's right to self-determination, and the right to refuse treatment. It stated:

Every human being of adult years and sound mind has a right to determine what shall be done with his own body and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages, except in cases of emergency in which the patient is unconscious and it is necessary to

operate before consent can be obtained.²⁴

This decision became the foundation for the “Doctrine of Informed Consent.” Informed consent serves to protect a patient’s autonomy, and creates the concept that each individual has the right to choose a personal course of medical treatment.³⁶ This includes the right to refuse care, and the right to terminate care already in process. In a nonemergent situation, it is the responsibility of the physician to obtain approval from the patient or surrogate before rendering treatment.

Generally accepted components to the informed consent process consist of (1) an explanation of the treatment or procedure, (2) alternative choices to the proposed intervention, and (3) relevant risks, benefits, and uncertainties associated with each alternative. This discussion must take place whether the patient is consenting to a procedure, or refusing a recommended procedure. A patient does not automatically assume the risks of rejecting the recommendations of the physician if the patient has not been fully apprised of the consequences of his or her decision.²⁹ Furthermore, it is the duty of the physician to assess how well the patient understands the above information. Before a physician may accept a patient’s approval or refusal of care, the patient must demonstrate adequate understanding of the information discussed.

State courts may apply one of two standards to determine if the information communicated by the physician was sufficient. The reasonable person standard requires a physician to disclose information that a reasonable person in the same position as the patient would need to make an informed decision.¹⁰ The alternative is the reasonable physician standard, which requires a physician to reveal information that a reasonable physician in a similar circumstance would disclose.¹⁰ States vary on which standard they apply.

Courts recognize that the requirement for informed consent is not absolute, and that there are exceptions in which a physician does not need to obtain permission before rendering treatment. In *Schloendorff v. Society of New York Hospital*, the Court recognized that consent is not required in emergency situations. Situations are generally considered emergent if care of the patient would be compromised if there were a delay in treatment. In New York, an emergency is defined as a situation that includes both the immediate endangerment of life or health and the need for the immediate alleviation of pain.²⁷ Physicians need to determine the specific requirements of informed consent in their respective states.

Often well-intended efforts of the physician to communicate treatment information to an impaired patient prove ineffectual and present the practitioner with a medical–legal dilemma. The physician may be unable to discuss in a meaningful way the implications of the proposed treatment with the patient. Nevertheless, there is a duty to treat the patient who presents with a life-threatening condition or the potential for permanent disability. In these situations, consent is considered to be implied, and emergent treatment should be provided. The principle of implied consent is a general tenet of tort law.²¹

Risk Management Consideration and Documentation

Patient 2

A 28 year-old woman was brought to the ED by police who believed she might be a “body stuffer” (an individual who swallows drugs to avoid arrest and prosecution). The triage nurse helped the patient onto a stretcher and brought her to the treatment area and recorded normal vital signs. The patient became combative and uncooperative as the physician initiated the examination and he verbally ordered that the patient be restrained. The patient was given 40% oxygen via face mask, cardiac monitoring was begun, and an intravenous line was started with 0.9% sodium chloride at 125 mL/h, then a bolus of 100 mL of D₅W and 100 mg of thiamine were administered intravenously (IV). Orogastric lavage was then performed, and 50 g of activated charcoal (AC) was administered.

One hour after arrival the patient’s vital signs were: blood pressure, 120/70 mm Hg; pulse, 82 beats/min; and respiratory, rate 24 breaths/min. The patient was noted to be stable and transferred to an observation unit. Oxygen and cardiac monitoring were discontinued. No further orders were: written, and the patient remained restrained. Three hours later the vital signs were: blood pressure, 110/60 mm Hg; pulse, 92 beats/min; and respiratory rate, 18 breaths/min. A nursing note stated the patient was resting comfortably.

Forty-five minutes later, the initial physician completed his shift at midnight and informed his replacement that the patient was stable and resting in the holding area.

At 4:20 am the patient was found unresponsive and hypotensive, with agonal respirations and a weakly palpable pulse. She felt very hot to the touch and had a rectal temperature of 108°F (42.4°C). Resuscitative efforts were initiated but were unsuccessful. Thirty minutes later the patient was pronounced dead.

Several important risk management questions frequently arise in medical malpractice litigation involving the ED. To prove that a case constitutes medical malpractice, a plaintiff’s attorney must show clear and convincing evidence of a departure from good practice by the physician. The attorney must further demonstrate that the negligent act or omission by the physician proximately caused the patient’s injury. Courts have held that where “there is substantial probability that the [defendant physician’s] negligent conduct caused the resulting injury, that sufficient evidence has been developed against [the] physician.”³⁵

The problems associated with an improperly documented ED record are numerous, but they can be minimized if the practitioner is cognizant of risk management principles. When the attorney for the patient (plaintiff's attorney) introduces evidence to prove the case, the central document in the medical malpractice trial is likely to be the ED record. Thus, every entry in that record is scrutinized with great care by both parties (plaintiff and defendants), and the importance of completing it with knowledge of risk management implications should be a concern for all health care professionals.

The physician is required to write a medical record that will amply support the basis for the medical judgments exercised. When a physician chooses to write only a summary statement on the record without noting supporting clinical data or patient history, claims alleging failure to diagnose will be extremely difficult, if not impossible, to defend. One of the basic elements of the defense in a medical malpractice case is that the physician's judgment was appropriate, given the clinical facts and the patient's history available at that time. Therefore, physicians who do not record supporting clinical data and history deprive themselves of a strong "medical judgment" defense.

Inappropriate entries or markings on the medical record can weaken the defense in a liability case. For example, in attempting to correct an error in entering a PO₂ value, if the physician or nurse totally obliterates the number, an attorney representing a patient may suggest to the jury that the obliteration was done intentionally to conceal clinical data harmful to the position of the defense. If a physician must correct a prior entry made on the record, then the preferable method is to draw a single line through the value or word to be changed, insert the correct information directly above, and initial the correction. Timing and dating the correction also precludes potentially difficult questions of chronology and responsibility in a courtroom setting. By following these suggestions, the physician can avoid any accusations of intentionally concealing an error in judgment (Fig. 141-1).

Preferable				Unacceptable			
Example 1				Example 2			
ABG #1	pH	7.31		ABG #2	pH	7.31	
PCO ₂	45			PCO ₂	45		
PO ₂	38	58 md	4/22/94	PO ₂			

FIGURE 141-1. Examples of the preferred and an unacceptable procedure for correcting an error in the medical record.

A frequent claim is that the patient was abandoned or improperly monitored. For the above patient, although the chart appears to document repeated vital signs at appropriate intervals, no temperature is included after the first set until the patient is moribund, nor is any mention made again of the continued use of restraints, the continued need for these restraints, or any adverse effects developing from the use of restraints. Additionally, documentation of physician assessment of the patient's medical condition is incomplete. For example, there is no mention in the physician's notes of the possible cause of the patient's change in mental status. Likewise, there is no documentation regarding the police officers' concerns that the patient was a "body stuffer." Body stuffers quickly ingest a drug to avoid detection, which can result in life-threatening toxicity (SC 5). Documentation of the physician's review of this concern is necessary.

Quality assurance reviews of ED records often demonstrate inadequate charting by physicians and nurses monitoring patients who remain in the department for prolonged periods of time. Under any circumstances, a lapse of documentation of the patient's clinical condition for 4 hours or more after the initial physician and nursing assessment creates a potential risk management problem. In a lawsuit, the plaintiff's attorney would undoubtedly use such a record to develop the theory that no care whatsoever was given to the patient during this time interval, and that the patient was abandoned.

Monitoring notations in the medical record are considered inadequate when they do not offer insight into the patient's clinical status. Thus, any monitoring note for a patient who must be restrained in the ED for a lengthy period of evaluation, observation, or until an inpatient bed becomes available must include specific clinical data and observations (laboratory results, radiographic findings, hemodynamic changes, and infusion of medications and solutions). All of these deficiencies would undoubtedly be noticed and highlighted at trial by a plaintiff's expert, who frequently is a board-certified physician in the same specialty.

Documentation supporting the restraint of an impaired patient against his or her will must include a clinical description to support such a forcible impediment to the patient's right to liberty and freedom of movement. Such a clinical description should specifically describe any manifestation of agitation and uncooperative behavior. The record should refer to the specific uncooperative acts of the patient and, most importantly, should comment on the difficulties in providing care to the patient because of the patient's actions.

Physicians who order restraints for patients must exercise extreme caution in the language used to describe such patients. A judgmental note stating that a patient is "a chronic drunk and obnoxious" could undermine the support for the use of restraints. Poorly written notes can become an issue in a medical malpractice action, with the plaintiff's attorney focusing on the derogatory nature of such a statement and suggesting a less than caring attitude by the doctor toward the

patient. A plaintiff's appeal that criticizes the ethical and social consciousness of the physician could very likely be seized upon by a jury, resulting in a punitive verdict against the physician. As a general rule, all health care professionals should depict a compassionate and professional manner when describing patient behavior and lifestyles in objective and concrete terms. An alternative and more appropriate description of a patient comparable with the one above would note that the patient had a "history of alcohol dependence and was agitated and or combative."

To summarize, a well documented ED record consistent with the accepted risk management principles set forth is the best course for the physician managing a difficult overdose situation in which legal principles may appear to present problems in providing proper medical management.

FORCIBLE RESTRAINT OF THE IMPAIRED PATIENT

Patient 3

A 31 year-old woman was found unresponsive on the street and brought to the ED by ambulance. Friends on the scene reported that the patient used methadone. In the ED she was unresponsive and apneic. Oxygen was immediately administered by bag-valve mask and intravenous access was obtained. Naloxone was administered, and shortly thereafter the patient regained consciousness. After 20 minutes of care in the ED, the patient became fully alert and oriented, with no evidence of hypoxia or other clinical signs to suggest impaired judgment. The patient stated that she had taken methadone and demanded to be discharged immediately.

The right of a hospital to retain and physically restrain a person who has an altered level of consciousness for evaluation and emergency intervention is generally well supported by states and case law.¹¹ Reasonably clear guidelines for the management of such impaired patients have evolved from legal precedents governing appropriate medical assessment, from risk management considerations, and from the predictability of patient injury in the event of premature discharge.

A staff decision to allow a treated or partially treated patient with a drug overdose who subsequently becomes alert to return to the community must be based on an assessment of several factors. The initial concern is the capacity of the patient to comprehend. Before the patient can be permitted to leave the hospital, a determination would have to be made that the patient is capable of understanding the information presented and has neither a medical nor a psychiatric problem preventing such a voluntary decision. The next consideration is that of medical stability. Has the initial process that caused the clinical scenario completed its course? The history of drug use in this patient is cause for concern that the underlying toxic metabolic process is not yet resolved, and alteration in mental status, significant respiratory compromise, or other medical symptoms may recur when the naloxone is metabolized, again placing the patient at risk.

Common ED practice and sound legal principles suggest that both the hospital and its staff have a duty to prevent such a person from leaving if the duration of the effect of the involved xenobiotic is longer than that expected for the antidote. Because the duration of effect for naloxone is considerably shorter than that of methadone, the physician can predict with reasonable certainty that coma or apnea will reoccur in the near future. The physician has the duty to inform the individual of the life-threatening nature of the condition, and then to retain, with restraints if necessary to retain, the patient in the hospital until medically stable.

Liability in this situation is further reduced when the chart substantiates the medical judgment that was the basis for the decision to retain the patient and, if applicable, the use of restraints. Such documentation should specifically note the likely relapse of the patient into a symptomatic state and that this occurrence could place the patient in a life-threatening situation. When documented in a clear manner, legal challenges to the decision to restrain the patient have a limited chance of success. Sound risk management principles support treatment and detainment. Conversely, prematurely releasing a patient with a significant overdose exposes both the physician and the hospital to a claim of negligence on the grounds of failure to foresee a likely and harmful event.

BLOOD ALCOHOL CONCENTRATION AND EVIDENCE COLLECTION

Patient 4

A 41 year-old man who was a driver involved in a motor vehicle collision was taken to the ED by ambulance. Two motorists in another vehicle were killed. The patient had no physical complaints, but was brought to the hospital for medical clearance. On arrival, he was alert and oriented, responded appropriately to all commands, and demonstrated normal motor function and had a normal gait. Police officers suspected that he was driving while intoxicated, but he refused a breath alcohol test at the scene.

The police officers informed the ED staff that he was arrested and might be charged with vehicular homicide. The officers then requested that the emergency physician draw a blood specimen to determine the blood alcohol concentration. The patient stated that he would not allow the ED staff to draw blood for a determination of an alcohol concentration.

In 2010, there were 10,228 people who died in alcohol-related motor vehicle crashes, which was 31% of all traffic

related deaths in the United States.⁹ This number has declined in recent years and has decreased 4.9% from 2009. In the United States, an alcohol-related motor vehicle crash kills someone every 51 minutes.⁹ In 2010, crashes resulting from alcohol-induced impairment were responsible for 17% of fatalities in children younger than 14 years who were killed in motor vehicle crashes.⁹ Alcohol-impaired motor vehicle crashes cost more than \$37 billion every year.⁸ Drugs other than alcohol (eg, marijuana and cocaine) are involved in about 18% of motor vehicle driver fatalities.¹⁵ The judicial system has historically been one of the most effective tools to combat drunk driving, and its effectiveness depends on the ability to identify and punish individuals who violate the law. It is essential, however, that the collection of evidence does not violate the rights afforded by the US Constitution. Does forced phlebotomy for patients suspected of driving while intoxicated violate these protected rights? This has long been debated in the courts, and issues specifically brought into question include the Fourth Amendment,³⁰ the right against unreasonable search and seizure; the Fifth Amendment,³¹ the right against self-incrimination, and the Due Process clause of the Fourteenth Amendment.³² Past decisions on these issues help guide current laws and practices.

Every state, and the District of Columbia, has driver “implied consent” laws. When a person obtains a driver’s license, he or she consents at the time of acquisition to a chemical alcohol test if suspected of driving while intoxicated. Under implied consent laws, when a person suspected of driving while intoxicated refuses to take an alcohol test, a penalty is imposed. Specific penalties for refusals vary from state to state. At a minimum, the refusal results in suspension or revocation of a driver’s license. Some states assign additional fines and penalties for this action. A few states allow the refusal itself to be submitted at trial in support of the prosecution, making it possible to be convicted of an intoxication charge without chemical evidence.³ Certain states (eg, Texas, Illinois) allow blood tests to be performed on patients as ordered by an officer of the law, when there is probable cause of driving while intoxicated resulting in severe injury.^{20,28} Other states, such as New York and California, allow forced blood samples with a warrant issued by a judge.^{5,18} State laws regarding the approach to this situation vary and it is important that the ED staff be familiar with the specific requirements of the law of that state.

How much force may be used to collect chemical evidence? Does a physician violate human dignity and privacy in obtaining evidence for the State? These issues were addressed by the United States Supreme Court. In *Rochin v California*,²³ the Court overturned a conviction of drug possession based on violation of the Fourteenth Amendment. In this case, police were informed that Rochin was selling drugs. While entering the home of the defendant, the police witnessed the defendant swallow two pills that were lying on the night stand. When the officers failed to recover the pills on the scene, the officers took Rochin to the ED, where they directed the physician to administer an emetic through a nasogastric tube. The capsules were recovered from the vomit, and Rochin was convicted by the trial court for possessing morphine.^{1,23} The Supreme Court reversed this decision, based on the Fourteenth Amendment, “nor shall any State deprive any person of life, liberty or property, without due process of law....”³⁶ The term due process is vague, and is defined on a case-by-case basis, but it essentially means that states must use fair legal procedures when depriving an individual of life, liberty, or property. In *Rochin*, the court concluded that forced emesis by a physician was believed to violate Due Process, stating:

This is conduct that shocks the conscience. Illegally breaking into the privacy of the petitioner, the struggle to open his mouth and remove what was there, the forcible extraction of stomach contents—this course of proceeding by agents of government to obtain evidence is bound to offend even hardened sensibilities. They are methods too close to the rack and the screw to permit constitutional differentiation.²³

The Supreme Court revisited the issues presented in *Rochin* 4 years later in *Breithaupt v Abram*.⁴ *Breithaupt* was the driver of a truck who killed three occupants of another vehicle. In the ED, a police officer requested that a blood alcohol concentration be drawn. The blood, drawn while the patient was unconscious, was above the legal limit for alcohol and the patient was convicted of involuntary manslaughter. *Breithaupt* argued that the blood draw, as in forced emesis in *Rochin*, violated due process as he did not consent to its collection. Justice Clark disagreed, stating “the distinction rests on the fact that there is nothing ‘brutal’ or ‘offensive’ when done, as in this case, under the protective eye of a physician” and that the “blood test procedure has become routine in our everyday life.”^{3,4} Phlebotomy while the patient is unconscious and unable to give consent was determined not to violate the due process clause of the Fourteenth Amendment.

The Supreme Court continued to expand the scope of permissible phlebotomy in *Schmerber v California*.²⁵ *Schmerber* was involved in a motor vehicle crash in which the police officer suspected he was intoxicated. Unlike in *Breithaupt*, *Schmerber* was conscious, and a physician drew a blood sample at the officer’s request despite the patient’s verbal refusal. The attorney for *Schmerber* asserted that forced phlebotomy violated several constitutional rights. Specifically, it violated the Fourth, Fifth, and Fourteenth Amendments of the US Constitution. He alleged that forced phlebotomy denied him due process of the law, it violated his privilege against self-incrimination, and it violated his right against unreasonable search and seizure.^{3,25}

The Supreme Court rejected all of these arguments. The phlebotomy did not violate the due process clause because “the extraction was made by a physician in a simple, medically acceptable manner in a hospital environment. ... We cannot see that it should make any difference whether one states unequivocally that he objects or resorts to physical violence in protest or is in such condition that he is unable to protest.”²⁵ Furthermore, the forced blood draw did not violate the Fifth

Amendment's Privilege Against Self-Incrimination because the Fifth Amendment only protects evidence of a "testimonial or communicative nature," such as writings or speech. Finally, there was no violation of the Fourth and Fourteenth Amendments' protections against unreasonable search and seizure as the delay necessary to obtain a warrant threatened the destruction of evidence. Considering the "totality of the circumstances" in *Schmerber*, the blood alcohol test fell under the Court's exigent circumstances exception to the general requirement of a warrant.

The percentage of alcohol in the blood begins to diminish shortly after drinking stops, as the body functions to eliminate it from the system. Particularly in a case such as this, where time had to be taken to bring the accused to a hospital and to investigate the scene of the accident, there was no time to seek out a magistrate and secure a warrant.

To ensure compliance with standards set forth in *Schmerber*, the states have tailored laws and regulations governing the seizure of blood for the purpose of blood alcohol testing. Laws generally require the procedure be (1) performed in a reasonable, medically approved manner, (2) incident to a lawful arrest, and (3) based on the belief that the arrestee is intoxicated. It should be remembered that the issues raised by any one case are complex, and the application in real situations is difficult. Laws and regulations governing blood draws for alcohol testing vary from state to state and are the subject of frequent restructuring and amendment. Medical staff should review with hospital counsel the local laws and regulations that pertain to these issues. However, physician and patient safety must always be the priority. The benefits of determining a patient's blood alcohol concentration must be weighed against the risks of the procedure. For example, drawing blood in an agitated patient may place the staff at risk for a needle stick and the patient at risk of vascular injury.

It should also be noted that the US Supreme Court in *Missouri v. McNeely* restricted the holding of *Schmerber* for warrantless blood alcohol testing.¹⁷ In *McNeely*, the State of Missouri argued that the metabolism of alcohol over time, by itself, was justification to obtain warrantless blood alcohol testing in the hospital. The US Supreme Court rejected this argument. While the dissipation of alcohol from the blood stream over time is one of the factors to consider when evaluating the "totality of the circumstances," it does not meet the exigency exception to the warrant requirement by itself. The majority opinion held that "when officers in drunk driving investigations can reasonably obtain a warrant before having a blood sample drawn without significantly undermining the efficacy of the search, the Fourth Amendment mandates that they do so." This does not suggest that a physician should insist on a warrant when an officer requests a blood alcohol test, as this is a protection that is afforded retrospectively by the courts. Familiarity with local regulations is necessary to properly manage requests for blood alcohol testing.

CONFIDENTIALITY

Patient 5

A 32 year-old woman was fired from her job as a high school mathematics teacher. The school board called for her termination after learning that she had a history of alcohol dependence and had a previous hospitalization for detoxification at the local community hospital. A parent on the school board was also employed as a nurse at the hospital, where the teacher had received therapy. The school board member (and nurse) had inadvertently accessed the medical record of the teacher while caring for a patient with the same last name.

The Health Insurance Portability and Accountability Act (HIPAA) was enacted by Congress in 1996 and signed by President Clinton. Initially, the purpose of HIPAA was to increase the portability of health insurance, and allow employees to maintain insurance when they changed jobs. The Act called for the establishment of several provisions, among them an electronic database designed to facilitate the exchange of information between health care professionals, insurance companies, and those involved in financial and administrative transactions.¹⁶ However, the idea of developing an electronic database brought to light already growing concerns regarding the maintenance of patient privacy. For the first time, medical records would be accessible to an unlimited number of people working in health care, from bill processors to pharmacists to clinicians. Could the right to privacy be jeopardized by a system designed to increase efficiency?

Prior to HIPAA, individual hospitals or physician offices designed their own methods for maintaining confidential patient information. Records were maintained on computers in some circumstances and on paper in others. Accessibility to that information was largely regulated by state laws, and supported by some federal regulations and ethical codes of conduct. During the 1990s, however, the weaknesses of the existing systems gained attention as multiple high profile breeches of confidentiality surfaced. For example, the medical records of a congresswoman were released to the media during her campaign, making her history of depression and a past suicide attempt public knowledge.²⁶ There were also several cases of the medical records of hospital employees being read by staff members not involved in the employees' care, health insurance companies releasing health care information to employers without permission, and physicians releasing information to pharmaceutical companies that subsequently solicited the patient.³⁷ These breaches of ethics were each a testament to the fact that the right to privacy needed more stringent regulation. If these examples could occur in the previous systems for recording information, then it could be assumed that further violations would occur with increased access through an electronic database.

The Privacy Rule of HIPAA has become the most well-publicized aspect of this Act among health care personnel. The

Privacy Rule governs the use and disclosure of protected health information in the hands of health care professionals, health plans, and health care clearinghouses.¹⁶ The terminology used in the Privacy Rule is extensively defined. The following is a brief summary of the terms used.

Protected Health Information

Protected health information includes any individually identifiable information concerning the past, present, or future health of an individual; medical information pertaining to assessment and treatment of an individual; in addition to payment and billing information. All forms of information, written, oral, or electronic, are protected by this rule. Deidentified data are not considered protected health information.

Covered Entities

The term “covered entities” includes any person or business that provides health-related services or products. All those providing health-related services, for example, clinicians, pharmacists, medical equipment providers, and other health care professionals, are considered covered entities. Companies that provide disability insurance, car insurance, or casualty insurance are not included in the rule.^{16,33}

Health Care Clearinghouses

Health care clearinghouses are entities that compile health care information, such as billing companies or data processing centers.

Institutions are required to provide all individuals with written notice of their privacy policy when they first seek medical care. Patients must be informed of how the institution may use and disclose information. The notice must also describe patients’ rights, including the right to access their medical information and their right to file a complaint if they believe their rights are violated. The notice must be written in plain language, and the patient must be written acknowledgment of receipt of the information in the notice.

The Privacy Rule of HIPAA was not intended to impede health care. There are several exceptions to the rule. A covered entity is permitted to use and disclose protected health information for the purposes of evaluation and treatment. Physicians have the freedom to consult with each other, both within and outside their own institution in order to provide clinical care. Additionally, there are several specific exceptions to the Privacy Rule listed within the document—situations in which protected health information may and often must be disclosed, and may be done without an individual’s permission. For example, activities related to public health, such as reporting communicable diseases, information necessary to report actual or suspected abuse, neglect or domestic violence, or information pertaining to cadaver organ or tissue donation are specifically exempt from the Privacy Rule.¹²

The HIPAA Privacy Rule specifically addresses consultations with poison centers. It states:

We consider the counseling and follow-up consultations provided by poison control centers with individual providers regarding patient outcomes to be treatment. Therefore, poison control centers and other health care professionals can share protected health information about the treatment of an individual without a business associate contract.¹²

Violations of the Privacy Rule are subject to penalties, the severity of which is dependent on the type of infraction. Simple noncompliance may result in financial penalties. Moreover, significant or intentional disclosures of information may incur steeper fines in addition to criminal charges and potential imprisonment.³⁷ In 2009, as part of the economic stimulus, the Health Information Technology for Economic and Clinical Health Act (HITECH) under the American Recovery and Reinvestment Act (ARRA) was passed.²² This Act was primarily created to encourage the use of electronic health records and supporting technology. However, it also widened the scope of privacy and security protections defined by HIPAA. Several notable changes are the increase in civil penalties for willful neglect extending up to \$250,000 for a single violation, and as high as \$1.5 million for repeated or uncorrected violations. Furthermore, HIPAA provisions now apply to business associates. Business associates are defined as persons who, on behalf of a covered entity, perform or assist in performing a function or activity that involves the use or disclosure of individually identifiable health information.

OTHER LEGAL CONSIDERATIONS FOR POISON CENTERS AND POISON SPECIALISTS

Patient 6

The Poison Center received a call from a concerned mother that her daughter might have ingested one of the grandmother’s diabetes medications. The mother stated that the child was acting normally all day at the grandmothers’ house, but when the family returned home, the child had become drowsy. When contacted, the grandmother had confirmed that one pill was missing from her purse although she did not know the name of her medication. The poison center advised that the parents

give the child juice and closely observe her for the next 6 hours. Approximately 2 hours later, while sleeping, the child had a seizure. The child continued to seize in the hospital, where medical evaluation revealed hypoglycemia. The patient subsequently suffered permanent neurologic damage. The medication was later identified as glyburide. Action was brought against the poison center, alleging inappropriate advice and failure to recommend transport to a hospital.

As a general rule, any physician who decides to treat a patient enters into a physician–patient relationship that creates well established legal duties. Courts have ruled that the physician–patient encounter need not be a face-to-face interaction to have legal consequences. For example, the absence of physical contact between a physician and patient as in the practice of radiology and pathology does not preclude a patient from asserting that a duty of care exists.⁶ More particularly and quite relevant to the practice of a poison center, a New York State court ruled that an initial telephone call from a patient to a physician can be sufficient basis to hold that physician responsible for inappropriate advice or a significant error in judgment.¹⁹ Given the legal precedents previously stated, it is eminently clear that contact with a poison information specialist is a sufficient foundation for a subsequent legal action if inappropriate advice was given.

STANDARDS OF CARE APPLICABLE IN POISON CENTERS

Standards of care applicable to toxicologists are examined under the same legal framework as other medical specialists. The basic medical malpractice concepts are universal with some variations from state to state. Generally, for patients to prevail in medical malpractice cases, they must demonstrate “by a preponderance of the evidence: (1) that the doctor’s treatment fell below the ordinary standard of care expected of a physician in his [or her] medical specialty, and (2) the existence of a causal relationship between the alleged negligent treatment and the injury sustained.”³² While standard of care is recognized not to be one of perfection, what constitutes the “ordinary standard of care” has much room for interpretation.

In the nineteenth century, courts determined what the “ordinary standard of care” was by introducing testimony from physicians practicing in the community where the event occurred. This was known as the strict locality rule.³⁴ The strict locality rule was intended to prevent the inequities of comparing rural physicians working with limited resources and under exigent conditions from physicians working in large urban hospital settings.¹⁴ In many jurisdictions, however, the strict locality rule was rejected because (1) it was difficult to find an expert witness in a small community to testify against another physician in the community, and (2) the strict locality rule permitted some small medical communities to set unacceptably low standards of care.³⁴ In response, some states adopted the modified locality rule, which compares the physician in question with physicians practicing “in similar localities.”³⁴ Over time, the basis for the modified locality rule was also questioned. Advances in transportation, communication, and education continued to minimize the disparity between rural and urban medical practice. Many states abandoned the locality rule altogether, permitting evidence of nationwide medical practices, as described by one court:

[A] physician must exercise that degree of care, skill, and proficiency exercised by reasonably careful, skillful, and prudent practitioners in the same class to which he [or she] belongs, acting under the same or similar circumstances. Rather than focusing on different standards for different communities, this standard uses locality as but one of the factors to be considered in determining whether the doctor acted reasonably.²

While there is movement toward reviewing nationwide medical practices, depending on the jurisdiction where the event occurs, any one of the above rules may apply. In New York, courts allow evidence from the specific locality where the event occurred, from statewide practice, or from nationwide practice.¹³

A discussion of standard of care for poison control specialists should also mention several operational aspects of poison centers. Poison information specialists are required to have rapid and accurate access to a standard information resource system that contains both basic information and recommendations to deal with most toxic exposures. If a patient were to bring an action, then the negligence theory against the poison center might rely on deviations from the standard recommendations in these resources.

It would be inaccurate to suggest, however, that the duty of care owed by a poison information specialist can be measured only by how closely the advice given compares with these standard resources. Frequently, a poison specialist may encounter situations that cannot be managed in accordance with an information system alone, and may seek counsel from a clinical pharmacist or a medical toxicologist working with the poison center. If this were to occur, then any subsequent legal proceeding would also review carefully the content of the information given to the consultant regarding accuracy and appropriateness of treatment for the underlying toxicologic problem.

STATE STATUTES LIMITING LIABILITY OF POISON CONTROL CENTER CONSULTANTS

A comprehensive review of state-enacted legislation providing additional liability protection to poison center consultants is outlined elsewhere.⁷ These state statutes provide either immunity from malpractice claims or indemnity for a successful

claim against a poison center consultant. The statutes are state specific and poison center consultants should review them with local counsel, particularly if the statute has not been challenged in the jurisdiction in question.

Several states have enacted laws granting immunity to poison center consultants. Immunity is an affirmative defense to medical malpractice liability. In other words, even if a lawsuit were to meet all of the criteria for a successful malpractice claim, the lawsuit would not lead to compensation for injuries sustained because of this state-conferred protection. Examples of states that have enacted statutes providing immunity include Arkansas, California, Florida, Louisiana, Ohio, Tennessee, and Washington.¹ These statutes are not absolute protections from liability. State statutes granting immunity usually stipulate that the poison center consultant act in good faith while performing the duties required. In some instances, the poison center consultant must have been providing information in accordance with protocols established by the poison center. These laws do not protect against gross negligence, nor do they provide protection against intentional misconduct by the poison center consultant.

Other states have enacted laws that require the state to indemnify poison center consultants in the case of a successful malpractice claim. In other words, a patient may bring a medical malpractice claim against a poison center consultant, but if the claim is successful, the state itself compensates the patient rather than the poison center consultant. States that have enacted indemnity statutes, including Illinois and Texas.³⁹ Statutes providing state indemnification for medical malpractice claims are also limited in that they do not provide protection in the case of gross negligence, nor do they provide indemnity in the case of intentional misconduct.

In addition to state statutes that specifically limit liability for poison center consultants, it has been argued that some states may hypothetically provide protections under common law or general “public immunity” statutes.³⁸ Neither poison centers nor poison center consultants are specifically named under these state laws, but may be afforded immunity protection. States with general common law or “public immunity” statutes include North Carolina, Missouri, Illinois, Connecticut, and Georgia. Finally, many states have sovereign immunity statutes that afford liability protection to any entity created, funded, and operated by the state. Poison centers and their staff may be considered such an entity, and therefore, granted the protection.

PRACTICES OF REGIONAL POISON CENTERS THAT CAN REDUCE POTENTIAL LIABILITIES

There are some inherent risks of potential liability for a poison center. To minimize such risk and the risk of civil actions against a poison center, quality assurance and risk management programs should be a regular function. Daily audits or monitoring of the advice given by poison information specialists should be done. Such interactions enhance care and ensure patient safety for the individual and establish a higher general standard.

The medical toxicologists and clinical pharmacists responsible for supervising the poison information specialists must be able to adequately assess the competence and capabilities of the staff and to make recommendations, take corrective actions, and provide suggestions for improvement to involved members. This process is facilitated by such actions as audiotaping calls made to the poison center and the subsequent advice given, and reviewing written records maintained by the information specialist on each particular case. Documentation is extremely important, because in the event of a lawsuit, the most likely area of dispute will be what was actually said to the patient.

SUMMARY

- The risk management and legal issues of an ED with patients exposed to xenobiotics, often with impaired judgment, are complex. The substantial practical challenges in administering emergent treatment to an individual unable to provide proper informed consent may vary depending on individual state laws with respect to initiating that treatment.
- Medical care is further complicated by the difficulties inherent in documenting these interactions with our patients.
- Furthermore, both forcible restraint (often desired by the physician) and evidence collection (requested by law enforcement) have significant potential ramifications for the care provider.
- Maintaining patient confidentiality outside the ED, despite circumstances often visibly volatile within, may seem futile, yet legal obligations to protect patient privacy have become more stringent, not less.
- A well organized hospital is dependent on a close working relationship among the legal, risk management, and medical personnel. Only in this manner can they learn, cooperate, and meet the needs of the ever-evolving clinical dilemmas they confront.

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Normal Vital Signs by Age^a

Age	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats/min)	Respiration (breaths/min) ^b
Adult	120	80	60–100	16–24
16 years	120	80	80	16–30
12 years	119	76	85	16–30
10 years	115	74	90	16–30
6 years	107	69	100	20–30
4 years	104	65	110	20–30
2 years	102	58	120	25–30
1 year	100	55	120	25–30
6 months	90	55	120	30
4 months	90	50	145	30–35
2 months	85	50	145	30–35
Newborn	65	50	145	35–40

^aThe normal rectal temperature is defined as 15° to 100.4° (33°–38°C) for all ages. For children 1 year of age or younger, these values are the mean values for the 50th percentile. For older children, these values represent the 90th percentile at a specific age for the 50th percentile of weight in that age group. ^bThese values were determined in the emergency department and may be environment and situation dependent.

Common Equations

<u>Temperature</u> $^{\circ}\text{C} = (^{\circ}\text{F} - 32) \times 5/9$ $^{\circ}\text{F} = (^{\circ}\text{C} \times 9/5) + 32$	<u>Weight</u> $\text{lbs} = \text{kg} \times 2.204$ $\text{kg} = \text{lbs} \times 0.454$	<u>Anion Gap (mEq/L)</u> $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$	<u>Calculated Osmolarity (mOsm/L)</u> $2\text{Na}^+ + \frac{\text{BUN}}{2.8} + \frac{\text{Glucose}}{18} + \frac{\text{EtOH}}{4.6}$	<u>SI Units from Conventional</u> $\text{mmol} = \text{mg} \div \text{MW}$ $\text{mEq} = \text{mmol} \times \text{charge}$
<u>Serum Concentration</u> $C_p = \frac{S \times F \times \text{Dose}}{(\text{Vd(L/kg)} \times \text{Wt(kg)})}$	<u>Half-Life</u> $t_{1/2} = \frac{0.693}{K_e}$ where $K_e = \frac{(\ln C_1 - \ln C_2)}{t_1 - t_2} = \frac{Q}{\text{Vd}}$	<u>A-a Gradient (on room air)</u> $150 - \text{PO}_2 - (1.25 \times \text{PCO}_2)$		
<u>Body Mass Index (BMI) (kg/m²)</u> $\frac{\text{Wt (lbs)} \times 703}{\text{Ht (in)}^2}$ or $\frac{\text{Wt (kg)}}{\text{Ht (m)}^2}$	<u>Body Surface Area (m²)</u> $\sqrt{\frac{\text{Ht (in)} \times \text{Wt (lb)}}{3131}}$ or $\sqrt{\frac{\text{Ht (cm)} \times \text{Wt (kg)}}{3600}}$	<u>Creatinine Clearance (mL/min)</u> $\left(\frac{(140 - \text{age}) \times \text{Ideal Body Wt (kg)}}{72 \times \text{Cr}_{\text{min}}} \right) \times (0.85 \text{ for women})$		

Toxic Syndromes

Group	Vital Signs								
	BP	P	R	T	Mental Status	Pupil Size	Peristalsis	Diaphoresis	Other
Anticholinergics	-/↑	↑	±	↑	Delirium	↑	↓	↓	Dry mucous membranes, skin flush, urinary retention
Cholinergics	±	±	-/↑	-	Normal to depressed	±	↑	↑	Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative-hypnotics	↓	↓	↓	-/↓	Depressed	±	↓	-	Hyporeflexia, ataxia, nystagmus
Opioids	↓	↓	↓	↓	Depressed	↓	↓	-	Hyporeflexia
Sympathomimetics	↑	↑	↑	↑	Agitated, disoriented, hallucination	↑	-/↑	↑	Tremor, seizures
Withdrawal from ethanol or sedative-hypnotics	↑	↑	↑	↑	Agitated, disoriented, hallucination	↑	↑	↑	Tremor, seizures
Withdrawal from opioids (abstinence-related; antagonist precipitated withdrawal may mimic sympathomimetics)	-/↑	-/↑	-	-	Normal, anxious	↑	↑	↑	Vomiting, rhinorrhea, piloerection, diarrhea, yawning

↑ = increase, ↓ = decrease, ± = variable, - = (strongly) unlikely, BP = blood pressure, P = pulse, R = respirations, T = temperature

Selected Emergency Antidotes with Common Initial Doses^a

Antidote	Indication and Dose	Page
N-acetylcysteine	Acetaminophen: Adults: IV: 150 mg/kg in 200 mL D ₅ W infused over 60 minutes, followed by 50 mg/kg in 500 mL D ₅ W over 4 hours, then 100 mg/kg in 1000 mL D ₅ W over 16 hours. Oral: 140 mg/kg, followed by 70 mg/kg every 4 hours for 17 doses. NOTE: Special IV dilution required for children. www.acntadote.com/dosecalc.php	465
Atropine	Cholinesterase inhibitors: Adults: 1–2 mg (mild) or 3–5 mg (severe) IV, doubled every 3–5 minutes until bronchospasm resolves. Children: 20 µg/kg up to adult dose IV, doubled as for adults. Also for other cholinergics in similar dosing.	1425
L-Carnitine	Valproic acid–induced hyperammonemia or valproic acid–induced elevated AST/ALT: Clinically ill: 100 mg/kg (up to 6 g) infused IV over 30 minutes, followed by 15 mg/kg infused over 30 minutes every 6 hours. Clinically well: 100 mg/kg/day given orally in divided dose every 6 hours up to 3 g/day.	657
Deferasuxime	Iron: Begin continuous IV infusion at 5 mg/kg/h, titrate to 15 mg/kg/h as tolerated with a total dose of 6–8 g/day.	623
Digoxin-specific antibody fragments (Fab)	Digoxin: Known concentration: # of vials = wt (kg) × concentration (µg/mL) / 100 rounded up to nearest vial. Empiric dosing: Acute: 10–20 vials. Chronic: Adults: 3–6 vials; Children: 1–2 vials. Usually given as IV infusion over 30 minutes. An IV bolus is acceptable for cardiac arrest. NOTE: For nondigoxin cardioactive steroids, use empiric dose.	904
Dimercapitol (BAL)	Lead encephalopathy: 75 mg/m ² (~4 mg/kg) deep IM every 4 hours. First dose to precede edetate calcium disodium (CaNa ₂ EDTA) by 4 hours. Contraindicated if peanut allergy.	1181
Edetate calcium disodium (CaNa ₂ EDTA)	Lead encephalopathy: 1500 mg/m ² /day (~50–75 mg/kg/day) as a continuous IV infusion (conc. ≤0.5%); maximum dose 3 g/day; reduce dose if impaired kidney function. NOTE: BAL should be administered 4 hours prior to starting this dose.	1241
Fomepizole	Methanol or ethylene glycol: 15 mg/kg diluted in 100 mL 0.9% NaCl or D ₅ W infused IV over 30 minutes; after 12 hours give next 4 doses at 10 mg/kg every 12 hours; additional doses at 15 mg/kg every 12 hours if needed. Adjust dose during hemodialysis.	1364
Glucagon	β-Adrenergic antagonists or calcium channel blockers: IV infusion over 1–2 minutes. Adults and Children: 50 µg/kg. Repeat in 10 minutes for 1–2 doses as needed. Dose may be increased up to 10 mg in an adult. Consider continuous infusion at 1–5 mg/h. Emesis may occur.	870
Hydroxocobalamin	Cyanide: Adults: 5 g reconstituted with 200 mL 0.9% NaCl (invert for 60 seconds) and infuse IV over 15 minutes. Children: 70 mg/kg up to 5 g. Repeat second dose as needed.	1618
Insulin (High dose insulin [HIE] therapy)	Calcium channel blockers or β-adrenergic antagonists: 1 unit/kg IV bolus regular human insulin. Follow with infusion of 1 unit/kg/h. Use 10 units/mL insulin concentration. Titrate to 2 units/kg/h if no improvement in 15 minutes and titrate up to 10 units/kg/h as needed. If glucose <300 mg/dL, give 0.5 g/kg D ₅ W bolus. Start 0.5 g/kg/h dextrose infusion. If glucose >300 mg/dL, hold glucose. Monitor glucose every 5–30 minutes until stable then every 1–2 hours. Maintain glucose 100–250 mg/dL. Monitor K ⁺ frequently. Give K ⁺ if <2.8 mEq/L.	851
Intravenous Fat Emulsion (IFE) 20%	Cardiac arrest from lipid soluble xenobiotic (CCB, TCA, local anesthetics): IFE 20% 1.5 mL/kg over 1 minute. Follow with infusion at a rate of 0.25 mL/kg/min (15 mL/kg/h) for 30–60 minutes while continuing chest compressions. Repeat bolus for severe persistent symptoms.	931
Leucovorin (Folinic acid)	Methotrexate: 100 mg/m ² infused IV over 15–30 minutes every 3–6 hours for several days or until methotrexate serum concentration <1 × 10 ⁻⁶ M in the absence of bone marrow toxicity.	693
Methylene blue	Methemoglobinemia: 0.1–0.2 mL/kg of 1% methylene blue IV over 5 minutes followed by a 30 mL fluid flush of 0.9% sodium chloride.	1631
Naloxone	Opioid-induced respiratory depression: Adults: 40–50 µg (0.04–0.05 mg) IV titrated upward to reversal, avoid opioid withdrawal, provide manual ventilation. Children: not receiving chronic opioids 0.01 mg/kg IV titrated as for adults.	510
Nitrites and sodium thiosulfate	Cyanide: Adults: (1) Sodium nitrite: 300 mg (10 mL of a 3% conc) infused IV over 2–5 minutes. (2) Sodium thiosulfate: 12.5 g (50 mL of a 25% conc) infused IV over 10–30 minutes or as a bolus. Children: (1) Sodium nitrite: 6–8 mL/m ² (0.2 mL/kg) of a 3% conc (max 300 mg) infused IV over 2–5 minutes. (2) Sodium thiosulfate: 7 g/m ² (0.5 g/kg) (max 12.5 g) infused over 10–30 minutes or as a bolus. NOTE: In both adults and children, avoid sodium nitrite when carboxyhemoglobin is expected to be elevated.	1612
Octreotide	Sulfonylurea-induced hypoglycemia: Adults: 50 µg SQ every 6 hours. Children: 1.25 µg/kg (max 50 µg) SQ every 6 hours.	738
Physostigmine	Anticholinergic syndrome: IV infusion over 5 minutes. Adults: 1–2 mg. Children: 20 µg/kg (max 0.5 mg). The dose can be repeated in 5–10 minutes if an adequate response is not achieved and cholinergic effects are not noted.	677
Pralidoxime	Cholinesterase inhibitors: Adults: 30 mg/kg (up to 2 g) over 15–30 minutes followed by a maintenance infusion of 8–10 mg/kg/h (up to 650 mg/h) for sickest patients. Children: 30 mg/kg (max 2 g) infused IV over 15–30 minutes and then 10–20 mg/kg/h (max 650 mg/h).	1429
Pyridoxine	Isoniazid: 1 g for each gram of isoniazid up to 70 mg/kg (max 5 g) infused IV at 0.5 g/min until seizures stop, with the remainder infused IV over 4–6 hours. Empiric dose: Adults: 5 g. Children: 70 mg/kg (max 5 g) at specific dosing rate. May repeat dose if needed.	797
Succimer	Lead poisoning: Adults and Children >5 years old: 10 mg/kg orally every 8 hours for 5 days followed by every 12 hours for 14 days. Children <5 years old: 350 mg/m ² orally as for adults.	1235

^aConsult pages listed for complete information regarding dose, route, duration of therapy, adverse effects, safety issues, contraindications, and other considerations. For up-to-date information, contact your regional poison center at 800-222-1222 or a medical toxicologist.

Common Toxicology Laboratory Concentrations (serum unless otherwise noted)					
	Conventional	SI		Conventional	SI
Acetaminophen	10–30 µg/mL	66–199 µmol/L	Lithium	0.6–1.2 mEq/L	0.6–1.2 mmol/L
Arsenic (blood)	<1 µg/L	<0.0665 µmol/L	Mercury (blood)	<10 µg/L	<50 nmol/L
Arsenic (urine)	<50 µg/L	<0.665 µmol/L	Mercury (urine)	<20 µg/L	<100 nmol/L
Caffeine	1–10 µg/mL	5.2–51 µmol/L	Methanol	<25 mg/dL	<2.8 mmol/L
Carbamazepine	4–12 mg/L	17–51 µmol/L	Methemoglobin	<1%	<3%
Carboxyhemoglobin (blood)	<2%	<2%	Phenobarbital	15–40 mg/L	65–172 µmol/L
Cyanide (blood)	<1 µg/mL	<38.5 µmol/L	Phenytoin	10–20 mg/L	40–79 µmol/L
Digoxin	0.8–2 ng/mL	1.1–2.6 nmol/L	Salicylates ^a	15–30 mg/dL	1.1–2.2 mmol/L
Ethanol	80 mg/dL	17.4 mmol/L	Thallium (blood)	<2.0 µg/L	<9.78 nmol/L
Ethylene glycol	<25 mg/dL	<4 mmol/L	Thallium (urine)	<5.0 µg/L	<24.5 nmol/L
Iron	80–180 µg/dL	14–32 µmol/L	Theophylline	5–15 µg/mL	27.8–83 µmol/L
Lead (blood)	<10 µg/dL	<0.48 µmol/L	Thiocyanate	<10 µg/mL	<100 µmol/L
Lidocaine	1.5–5 µg/mL	6.4–21.4 µmol/L	Valproic acid	50–120 mg/L	347–832 µmol/L

This table provides generally accepted normal or toxication concentrations as listed. Please see the appropriate chapter for details regarding specific situations. Normal ranges may vary by laboratory.

^aThe therapeutic concentration of digoxin for heart failure is 0.5 to 0.9 ng/mL, but toxicity is usually considered only when the concentration is > 2 ng/mL. ^bThis value is the “per se” concentration for ethanol above which motor vehicle operators are considered legally impaired in the United States. ^cConcentration must be interpreted with respect to the patient’s serum pH and clinical status. ^dSee acetaminophen monograph (page 451).

Common Standard Blood/Serum Laboratory Concentrations

	Conventional	SI		Conventional	SI
Ammonia	10–80 µg/dL	6–47 µmol/L	PCO ₂ (art)	35–45 mm Hg	4.7–6.0 kPa
Bicarbonate	18–24 mEq/L	18–24 mmol/L	PCO ₂ (ven)	45–55 mm Hg	6.0–7.33 kPa
BUN	7–18 mg/dL	2.5–6.4 mmol/L	pH (art)	7.35–7.45	7.35–7.45
Calcium	8.4–10.2 mg/dL	2.10–2.55 mmol/L	pH (ven)	7.33–7.40	7.33–7.40
Chloride	98–106 mEq/L	98–106 mmol/L	PO ₂ (art)	90–100 mm Hg	12–13.3 kPa
Creatinine	0.6–1.2 mg/dL	0.053–0.106 mmol/L	PO ₂ (ven)	30–50 mm Hg	4.0–6.67 kPa
Glucose	60–110 mg/dL	3.3–6.1 mmol/L	Phosphorus	3–4.5 mg/L	1–1.4 mmol/L
Lactate	<10 mg/dL	<2 mmol/L	Potassium	3.5–5.0 mEq/L	3.5–5 mmol/L
Magnesium	1.3–2.1 mEq/L	0.65–1.05 mmol/L	Sodium	135–145 mEq/L	135–145 mmol/L

art = arterial; ven = venous.

Clinical and/or Laboratory Findings in Poisoning and Overdoses	
Agitation	Anticholinergics, ^a ethanol and sedative-hypnotic withdrawal, hypoglycemia, phencyclidine, sympathomimetics ^b
Alopecia	Alkylating agents, radiation, selenium, strontium, thallium
Ataxia	Benzodiazepines, carbamazepine, carbon monoxide, ethanol, hypoglycemia, lithium, mercury, nitrous oxide, phenytoin
Blindness or decreased visual acuity	Caustics (direct), cocaine, cisplatin, mercury, methanol, quinine, thallium
Blue skin	Amiodarone, FD&C #1 dye, methemoglobin, silver, sulfhemoglobin
Constipation	Anticholinergics, ^a botulism, lead, opioids, thallium (severe)
Deafness, tinnitus	Aminoglycosides, cisplatin, metals, loop diuretics, opioids, quinine, salicylates
Diaphoresis	Amphetamines, cholinergics, ^c ethanol and sedative-hypnotic withdrawal, hypoglycemia, opioid withdrawal, salicylates, serotonin toxicity, sympathomimetics ^b
Diarrhea	Arsenic and other metals/metalloids, boric acid (blue-green), botanical irritants, cathartics, cholinergics, ^c colchicine, iron, lithium, opioid withdrawal, radiation
Dysesthesias, paresthesias	Acrylamide, arsenic, ciguatera, cocaine, colchicine, <i>n</i> -hexane, thallium
Gum discoloration	Arsenic, bismuth, hypervitaminosis A, lead, mercury
Hallucinations	Anticholinergics, ^a dopamine agonists, ergot alkaloids, ethanol, ethanol and sedative-hypnotic withdrawal, LSD, phencyclidine, sympathomimetics, ^b tryptamines (eg, AMT)
Headache	Carbon monoxide, hypoglycemia, monoamine oxidase inhibitor/food interaction (hypertensive crisis), nitrites, serotonin toxicity
Metabolic acidosis (elevated anion gap)	Cyanide, ethylene glycol, ketoacidosis (diabetic, starvation, alcoholic), iron, isoniazid, metformin, methanol, paraaldehyde, phenformin, protease inhibitors, salicylates, toluene, uremia
Miosis	Cholinergics, ^c clonidine, opioids, phencyclidine, phenothiazines
Mydriasis	Anticholinergics, ^a botulism, methanol, opioid withdrawal, sympathomimetics ^b
Nystagmus	Barbiturates, carbamazepine, carbon monoxide, ethanol, lithium, monoamine oxidase inhibitors, phencyclidine, phenytoin, quinine
Purpura	Anticoagulant rodenticides, doxipogrel, corticosteroids, heparin, pit viper venom, quinine, salicylates, warfarin
Radiopaque ingestions	Arsenic, "body packer," chloral hydrate, enteric coated tablets (variable), halogenated hydrocarbons, metals (eg, iron, lead)
Red skin	Anticholinergics, ^a boric acid, disulfiram-ethanol interaction, hydroxocobalamin, scombroid, vancomycin
Rhabdomyolysis	Carbon monoxide, doxylamine, HMG CoA reductase inhibitors, sympathomimetics, ^b <i>Tricholoma</i> mushrooms
Salivation	Arsenic, caustics, cholinergics, ^c ketamine, mercury, phencyclidine
Seizures	Bupropion, camphor, carbon monoxide, cyclic antidepressants, ethanol and sedative-hypnotic withdrawal, <i>Gyromitra</i> mushrooms, hypoglycemia, isoniazid, theophylline
Tremor	Antipsychotics, arsenic, carbon monoxide, cholinergics, ^c ethanol, lithium, mercury, methyl bromide, sympathomimetics, ^b thyroid hormones
Weakness	Botulism, diuretics, magnesium, neuromuscular blockers, paralytic shellfish, steroids, toluene
Yellow skin (jaundice)	Acetaminophen (late), <i>Amanita</i> mushrooms, β -carotene, dinitrophenol, pyrrolizidine alkaloids

Anticholinergics: eg, antihistamines, atropine, cyclic antidepressants, scopolamine. ^aSympathomimetics: eg, amphetamines, β -adrenergic agents, cocaine, ephedrine, methylxanthines. ^bCholinergics: eg, muscarinic mushrooms, organic phosphorus compounds, and carbamates, including Alzheimer drugs and physostigmine and pilocarpine, and other direct acting cholinergics.

Periodic Table of the Elements

IA																					0
1	2																				18
1	2	IIA											IIIA	IVA	VA	VIA	VIIA				18
3	4	5	6	7	8	9	10	11	12				13	14	15	16	17	18			18
11	12	13	14	15	16	17	18	19	20				21	22	23	24	25	26	27	28	29
23	24	25	26	27	28	29	30	31	32				33	34	35	36	37	38			38
39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
87	88	89	90	91	92	93	94	95	96	97	98	99	101	102	103	104	105	106	107	108	109
137	138	139	140	141	142	143	144	145	146	147	148	149	151	152	153	154	155	156	157	158	159
167	168	169	170	171	172	173	174	175	176	177	178	179	181	182	183	184	185	186	187	188	189
223	224	225	226	227	228	229	230	231	232	233	234	235	237	238	239	240	241	242	243	244	245
287	288	289	290	291	292	293	294	295	296	297	298	299	301	302	303	304	305	306	307	308	309